Physical Activity and the Abdominal Viscera

*Physical Activity and the Abdominal Viscera* is the first book to examine the response of the visceral organs to acute and chronic physical activity, in cases of both health and disease. Bringing together a previously disparate body of research, Professor Roy Shephard sets out the physiology, function during exercise, pathology of disease, and role of physical activity in preventing and managing disease in the visceral organs.

Working systematically through the viscera, the book first identifies the response to exercise and pathologies of the liver, gall bladder and biliary tract, then goes on to examine the function of the kidneys and bladder, and finally covers issues including the spleen, sickle cell disease and prostate cancer.

Providing a clear and well-structured guide to the relationship between the visceral organs and physical activity, *Physical Activity and the Abdominal Viscera* is a vital reference text for academics and upper-level students in sports medicine and clinical exercise physiology, and for health professionals in preventive medicine.

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The *Routledge Research in Physical Activity and Health* series offers a multi-disciplinary forum for cutting-edge research in the broad area of physical activity, exercise and health. Showcasing the work of emerging and established scholars working in areas ranging from physiology and chronic disease, psychology and mental health to physical activity and health promotion and socio-economic and cultural aspects of physical activity participation, the series is an important channel for groundbreaking research in physical activity and health.

**Physical Activity and the Gastro-Intestinal Tract**  
Responses in health and disease  
*Roy J. Shephard*

**Technology in Physical Activity and Health Promotion**  
*Edited by Zan Gao*

**Physical Activity and the Abdominal Viscera**  
Responses in Health and Disease  
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Physical Activity and the Abdominal Viscera
Responses in Health and Disease

Roy J. Shephard
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Preface

In the early 20th century, sports scientists began their investigations with a cycle ergometer or a motor driven treadmill, and an interest in establishing the energy expenditures of athletes by the technique of indirect calorimetry. Many reports appeared on the maximal oxygen consumption developed by various classes of competitor, along with information on their peak levels of ventilation, heart rate and cardiac output. During the 1960s, it was recognized that vigorous aerobic activity made a valuable contribution to population health, helping to counter the growing epidemics of cardiovascular disease and obesity. A vast literature thus developed on the responses of the muscles and the cardio-respiratory system to acute and chronic physical activity.

The muscles certainly provide the immediate motive force for an active individual, and the cardio-respiratory system plays an essential role in delivering oxygen and nutrients to the working muscles. However, sustained physical activity would be impossible without the contribution of the viscera to maintaining the constancy of the milieu intérieur. The fluid needed to dissipate heat, the energy provided by ingested fats and carbohydrates, and the essential amino acids needed for muscle hypertrophy are all delivered to the body via the gastro-intestinal tract. Critical steps in the provision of the prime energy source of glucose to the active muscles (glycolysis and gluconeogenesis) depend upon metabolic processes within the liver, and the regulation of fluid balance and the excretion of the unwanted by-products of metabolism depend upon the healthy functioning of the kidneys and urinary tract. A clear understanding of the impact of exercise upon the viscera is thus important in optimizing athletic performance, in developing tactics to prevent chronic disease and in enhancing the individual’s overall health.

substantive mention of gastro-intestinal function, the liver or the kidneys. I had planned to provide a brief overview of the topic for the Year Book of Sports Medicine, beginning in 2013,[8] but this initiative was thwarted when this particular Year Book ceased publication. Nevertheless, the time was ripe to summarize existing knowledge on the physiology of the gut and the abdominal viscera and its application to preventive medicine. A first volume, looking at physical activity and the function of the gastro-intestinal tract was thus published.[9] The present text complements this volume with information on physical activity and the abdominal viscera.

Each chapter considers first the normal physiological responses to exercise, and then examines how these responses are modified by repeated exercise sessions, whether the moderate bouts of activity typical of the community fitness centre or the intensive programmes of the international competitor. Implications for health promotion and preventive medicine are also reviewed. It is recognized that although moderate physical activity typically enhances health, excessive exercise can impair both competitive performance and health. Adverse effects are particularly likely if a competitive athlete pushes exercise to the point where most of the cardiac output is directed to the claims of the muscles (for nutrients and oxygen) and the skin (for heat dissipation), leaving the viscera dangerously deprived of their normal blood supply. It is important to define the tipping point where exercise begins to have adverse effects, relating this threshold to the individual’s age, fitness and health. Further, the potential benefits of moderate activity will not be realized unless people persist with their prescribed activity, so there is also a need to document factors affecting compliance with exercise programmes in various types of visceral disorder.

Our narrative begins with the liver. Here, the chemical processing of carbohydrate, fats and protein takes place. These vital biochemical reactions are substantially modified by acute and chronic physical activity, and excessive physical activity can adversely affect function. Further, habitual physical activity can reduce the risk of various pathologies, including the metabolic syndrome, non-alcoholic fatty liver disease, hepatic inflammation, cirrhosis and hepatocellular carcinoma. This chapter is followed by a discussion of the gall bladder and biliary tract, noting that function can be modified by both acute physical activity and aerobic training, and that an active lifestyle can modify the risks of developing gallstones, cholecystitis and gall bladder cancer.

The next section of the text addresses the excretion of waste products via the kidneys and urinary tract. It considers the significance of temporary manifestations of renal dysfunction (exercise-induced microproteinuria and microhaematuria), as well as the potential for developing acute renal failure during exhausting exercise. It points also to the danger of chronic renal damage from an excessive intake of creatine and non-steroidal anti-inflammatory drugs. Further, it explores the place of rehabilitation programmes for patients undergoing dialysis or receiving renal transplants, and it discusses the role of regular physical activity in reducing the risk of renal cancer and kidney stones. A specific chapter examines the risks of contact sport for an athlete with a single kidney. A chapter on the bladder looks at the
influence of impact sports upon stress incontinence; it also directs attention to exercise haematuria and considers the possible value of habitual physical activity in relation to cancer of the urinary bladder.

The final section of the book looks at the spleen and the prostate gland. Changes in splenic volume with exercise are reviewed and their practical significance for circulatory and immune function are considered. Subsequent chapters explore the clinical issues of restriction of exercise participation in those affected by infectious mononucleosis and sickle cell disease. The final two chapters consider the practical significance of physical activity in the prevention and management of chronic prostatitis, benign prostate hyperplasia and prostate cancer.

Two areas that are not discussed in detail are the fat stores and immune function. Both body fat and the immune system might well be considered as “internal organs”. Interactions between habitual physical activity and fat accumulation are certainly very important in the context of the prevention of obesity, diabetes, hypertension and other forms of chronic disease, and there is growing evidence that exercise can cause a favourable modulation of immune function. The topic of physical activity and the metabolic syndrome receives brief discussion in the context of hepatic function (Chapter 1) and the impact of physical activity upon the immune system is noted in the context of changes in splenic volume (Chapter 7). However, the effects of physical activity upon obesity and immune function are both large topics, and have already been covered in some detail by other books, so that in the interests of providing a compact account I have not allocated space to a detailed discussion of these issues.

As the writing of this book has progressed, I myself have learned much about a badly neglected area of exercise science and health promotion, with relevance not only to the maximizing of human performance, but also the prevention and clinical management of some major clinical problems. I hope that this will also be your experience.

Roy J. Shephard,
Brackendale, BC, Canada, 2017

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1 Responses of liver to acute and chronic physical activity

Introduction

With a mass of between 1.4 and 1.7 kg, the human liver is the largest of the viscera. Galen considered it the most important organ in the body, responsible for the formation of three of the body’s four “humours”, the blood, yellow bile and black bile.\[1\] It has a wide range of biological functions, including not only the secretion of bile, but also the synthesis of various proteins, amino acids, glycogen, cholesterol, triglycerides, hormones and vitamins, the metabolism of proteins, fats and carbohydrates, the storage of iron and copper, the regulation of glycogen storage and blood volume, and the elimination of various toxins from the body by a combination of metabolism and excretion. It also ensures an adequate blood level of the metabolites needed to maintain vigorous physical activity and to allow the synthesis of new muscle and brain tissue.\[2–5\] However, major consensus texts on physical activity, fitness and health\[6, 7\] have provided little information as to how its function is modified by either an acute bout of physical activity or by regular endurance training. The main focus of available literature has been upon physical activity in the context of pathologies such as acute hepatitis and fatty liver (steatosis).\[8\]

The present chapter considers the physiological and pathological responses of the liver to acute and chronic physical activity. The text spans the population spectrum from very sedentary individuals to elite endurance athletes, assessing the level of physical activity that promotes optimal hepatic function, and examining possible dangers of excessive physical activity. In the interests of simplicity, the reader is referred to a recent review for details of the complex biochemical and molecular processes underlying these responses.\[9\] Specific clinical issues relating to the metabolic syndrome, non-alcoholic fatty liver disease, hepatic inflammation, hepatic cirrhosis and hepato-cellular carcinoma are deferred to Chapter 2.

Acute hepatic responses to moderate endurance activity

In the healthy individual, the liver makes an important contribution to maintaining the constancy of the body’s internal environment (what the classical
French physiologist Claude Bernard\textsuperscript{[10]} termed the “milieu intérieur”). We will here look at the favourable changes in carbohydrate, lipid, and protein metabolism that are induced by an optimal volume of moderate endurance activity, and will consider briefly biochemical triggers and molecular processes underlying the hepatic responses.

**Carbohydrate metabolism**

Under resting conditions, the human liver normally contains 100–150 g of glycogen. This store is important to performance, providing a reserve of carbohydrate that can stabilize blood glucose levels during a prolonged bout of physical activity. Studies using stable isotopes have demonstrated an increased output of glucose from the liver during exercise.\textsuperscript{[11]} The resulting rise of blood glucose contributes to an increase in the rate of glucose oxidation during physical activity. It also causes a temporary suppression of appetite, an important tactic for the clinician who includes regular exercise as a component of any weight-loss programme.

The rate of glucose usage is closely matched to the individual’s work-rate,\textsuperscript{[12, 13]} but during moderate and vigorous physical activity (50–85\% of an individual’s maximal oxygen intake, VO\textsubscript{2max}), liver-derived glucose contributes less to the body’s total energy requirement than oxidation of the larger glycogen reserves found in skeletal muscle.\textsuperscript{[12]} The breakdown of hepatic glycogen (glycolysis) may initially lead to an outflow of lactate from the liver, but subsequently an increased glucose output is the main manifestation. As activity continues, the liver takes up lactate produced by the skeletal muscles,\textsuperscript{[14]} glycerol and amino acids (released from skeletal muscle through the action of cortisol), using these substances as substrates to synthesize glucose (the process of gluconeogenesis).\textsuperscript{[15–17]} The hepatic metabolism of lactate is important not only in providing a fuel for gluconeogenesis, but also in controlling the decrease of blood pH that inhibits performance as the muscle production of lactate increases.

Depending upon a person’s recent diet and training status, liver and muscle glycogen reserves together suffice for 90–180 minutes of vigorous aerobic exercise.\textsuperscript{[18]} The athlete can increase these resting glycogen stores both by endurance training and by the ingestion of a high carbohydrate diet for several days (the process of “carbohydrate loading”). For the first hour or more of physical activity, blood glucose levels are maintained predominantly by the breakdown of hepatic glycogen.\textsuperscript{[3]} However, as activity continues, there is a progressive increase in the relative contribution of hepatic gluconeogenesis. During very prolonged activity, there is still a substantial rate of hepatic gluconeogenesis,\textsuperscript{[19]} but this is no longer sufficient to maintain homeostasis. Once hepatic and muscle glycogen reserves have been exhausted, the blood glucose concentration falls, unless the work-rate is reduced.\textsuperscript{[11]}

The glycogen reserves of the liver must be replenished following exercise. Storage is regulated by the hormone insulin. This acts on the hepatocytes, up-regulating the enzyme glycogen synthase to increase the rate of glycogen
synthesis. The process is dependent upon GTPase ADP-ribosylation factor-related protein 1 (ARFRP1). This protein regulates the secretion of insulin-like growth factor-1 and sorting of the glucose-transporter GLUT-2, contributing to both normal tissue growth and the glycogen synthesis needed to rebuild liver glycogen stores.\[20\]

**Lipid metabolism**

The influence of exercise upon hepatic lipid metabolism is important to the understanding and prevention of fatty infiltration of the liver. Hormonal responses to endurance exercise, particularly the secretion of catecholamines, cause a mobilization of free fatty acids (FFAs) from fat depots in various parts of the body, and there is also a reduction of hepatic re-esterification of fatty acids, thus increasing the net availability of FFA in the circulation.\[21, 22\] Given that much of the total blood flow is redistributed from the viscera to the working muscles during vigorous physical activity, the majority of circulating FFAs are redirected to the contracting muscles, and the liver rapidly loses its dominant role in clearing circulating fatty acids from the blood stream. Muscular oxidation of the circulating FFAs accounts for most of the whole-body fat that is metabolized during physical activity, although during intense exercise triglycerides already stored within the muscle fibres also make a small contribution to the total energy expenditure.\[12\]

Under resting conditions, the liver accounts for about 40% of circulating fatty acid uptake, substantially exceeding the uptake by skeletal muscle (~15%).\[23, 24\] A portion of the fatty acid uptake is oxidized by the liver,\[25, 26\] and a part is re-esterified to triglycerides.\[27, 28\] The latter are either stored in the liver, or are secreted as very low density lipoprotein triglycerides (VLDLs). During physical activity, the hepatic uptake of FFAs drops sharply, now accounting for less than a quarter of the total FFA that is cleared from the circulation.\[22\] If the oxygen supply to the working muscles is good, the VLDL particles could in principle be oxidized by skeletal muscle.\[29\] However, one report found that the hepatic release of VLDL triglycerides was unchanged during 90 minutes of exercise at 58% of VO$_{2\text{max}}$\[30\] and in another study 60 minutes of cycle ergometry at 60% of VO$_{2\text{max}}$ had no influence upon the release of VLDLs in sedentary women.\[31\] Thus, the current consensus is that hepatic VLDL triglycerides make only a trivial contribution to whole-body fat metabolism during exercise.\[32\]

Animal data suggest that the ability of the liver to synthesize triglycerides is decreased during exercise. One study was performed on obese Zucker rats, an inbred species that has a high rate of fat synthesis; this investigation found a decrease in hepatic fatty acid synthase mRNA and thus of the enzyme needed for fatty acid synthesis in response to a bout of exhausting exercise.\[33\] A second report used Sprague-Dawley rats which had been starved and then refed;\[34\] treadmill running to exhaustion again decreased hepatic fatty acid synthase activity in these animals. However, a review of animal experiments concluded that laboratory exercise had no significant effect upon the liver content of total
lipids, phospholipids or cholesterol in normally fed rats; presumably, an excessive intake of food is also a factor in fatty infiltration of the liver.

Following a bout of vigorous physical activity, a combination of persistently high concentrations of circulating fatty acids and an up-regulation of the hepatic enzymes involved in triglyceride synthesis tends to replenish the fat content of the liver. Thus, Johnson et al. noted that endurance-trained men showed small but significant increases in proton magnetic resonance spectroscopy estimates of hepatic triglyceride content both 30 minutes and 4 hours after 90 minutes of cycle ergometry at 65% of \( \dot{V}O_2 \text{peak} \). Likewise, Hu et al. observed that in mice, high levels of circulating fatty acids were induced by a prolonged (60–90 min.) period of exercise, and this led to an increase of hepatic triglycerides three–four hours following exercise. Again, a single four-hour bout of swimming up-regulated hepatic stearyl CoA desaturase, with a resultant increase in hepatic triglyceride content.

### Protein metabolism

Sustained physical activity can augment the hepatic synthesis of a number of proteins, including albumin and insulin-like growth factor binding protein (IGFBP). This response is important to the anabolic response to regular exercise. The IGFBP binds IGF-1, allowing growth hormone to act continuously upon nearby cells in the liver, and thus to produce more IGF-1, in what is termed a paracrine action.

Isotope infusion studies in humans have demonstrated increases in both the fractional (6%) and the absolute synthesis (16%) of albumin six hours after completing a session of vigorous interval exercise. In rats, an increase in hepatic IGFBP-1 mRNA expression was also observed for up to 12 hours following vigorous treadmill running. This response likely reduces blood levels of IGF-1, and thus curtails muscle glucose uptake immediately post-exercise, preventing hypoglycemia, although it also has the paracrine effect of augmenting hepatic synthesis of IGF-1, as noted above.

If muscle and liver glycogen reserves have been depleted by very prolonged physical activity, the liver plays an important role in sustaining the glucose supply by forming glucose from amino acids. The necessary amino acids are released from skeletal muscle in response to the action of catabolic hormones such as cortisol. One study found that arterial concentrations of the amino acid alanine rose 20–25% with mild exertion, and by 60–95% at heavier work rates; 8–35% increases were also seen in the arterial concentrations of other amino acids, including isoleucine, leucine, methionine, tyrosine and phenylalanine. From differences in blood concentrations between the hepatic artery and the hepatic vein, it can be deduced that even during mild and moderate physical activity, humans increase the splanchnic blood stream uptake of alanine by 15–20%. The use of these amino acids in gluconeogenesis is evidenced by increased concentrations of urea nitrogen in the sweat.
Triggers of hepatic responses to physical activity

The relative importance of blood-borne factors (changes in the temperature and volume of blood flow, circulating hormones, cytokines and metabolite concentrations) and direct influences (for example, local hypoxia and a depletion of high energy phosphates) in triggering acute hepatic responses to physical activity remains unclear. If the dominant trigger could be determined, it might become possible to tailor the exercise stimulus to cause a selective modification of this factor, and thus maximize hepatic adaptations either to improve physical changes in liver metabolism performance or to enhance liver health. For instance, if a decrease in hepatic blood flow was found to be a primary determinant, a short bout of high-intensity exercise might be recommended rather than a prolonged period of low-to-moderate-intensity activity.

There seems no fundamental reason why triggers of altered hepatic metabolism should differ between humans and laboratory animals, but one issue in interpreting current evidence is that much of the available research has been conducted on rodents, where resting hepatic glycogen reserves are relatively much larger than in humans. The classical view has been that the exercise-induced stimulation of hepatic glucose metabolism is largely a consequence of an altered hormonal milieu, with an attenuated secretion of insulin and rising glucagon concentrations. The latter hormone stimulates hepatic glucagon receptors, and if physical activity continues for longer than 60–90 minutes, responses can be accentuated by a combination of declining plasma glucose concentrations and depletion of hepatic glycogen reserves. A rising glucagon concentration boosts the liver’s extraction of glucose precursors from the blood, speeds the conversion of these precursors into glucose and also stimulates glycolysis. The underlying biochemical sequence is a stimulation of hepatic glucagon receptors that increases concentrations of cyclic adenosine monophosphate (cAMP), with an activation of protein kinase A and an extracellular signal-regulated kinase (ERK) that acts as an “on/off” switch. Glucagon also amplifies adenosine monophosphate kinase (AMPK) signalling, thus inhibiting processes that use the energy stored in the ATP molecule, while at the same time stimulating processes that increase stores of ATP.

Somewhat surprisingly, moderate physical activity does not cause much change in peripheral venous glucagon levels. However, this may be because the concentrations measured in blood collected from the arm veins do not necessarily reflect hepatic glucagon levels. During vigorous exercise, catecholamine secretion may also contribute to the increase in gluconeogenesis, either by providing the liver with additional substrate from adipose tissue lipolysis and increased peripheral lactate formation, or by activating hepatic catecholamine receptors and thus the ERK on/off switch. Against this last hypothesis, hepatic glucose output does not seem to be greatly affected by adrenoreceptor blockade.

Some correlate of glycogen depletion, albeit changes in concentration of a metabolic substrate, a derivative of substrate oxidation, an energy-storing compound such as ATP, or an associated alteration in cell volume might also trigger
a metabolic response more directly by acting on the hepatic afferent nerves. In support of this hypothesis, studies in rats show that if glucagon secretion is suppressed by infusion of the hormone somastatin, an increased activity of the hepatic sympathetic nerves can be detected in terms of an augmented output of epinephrine and norepinephrine. However, hepatic glucose release is unaffected by hepatic denervation alone, and section of the hepatic nerves does not curtail the increase of blood sugar seen in rats during a brief bout of exercise.

Some of the changes of liver function that are seen during physical activity may occur independently of either hormones or the autonomic nerve supply. One possible trigger is the cytokine interleukin-6; this is released from muscle during exercise and appears to play an important role in regulating carbohydrate metabolism. A number of pointers suggest an action of IL-6 upon the liver. IL-6 stimulation of hepatoma cells increases their glucose production and the injection of IL-6 into mice induces a small increase of hepatic phosphoenolpyruvate carboxykinase (PECPK), an enzyme involved in gluconeogenesis. Exercised mice also show an increase of CXCL-1, a hepatic chemokine that attracts neutrophils and is involved in inflammation and wound healing. Muscle-derived IL-6 seems the trigger for secretion of this chemical messenger; the full range of functions of CXCL-1 are unclear, but given its anti-inflammatory actions, it could well be responsible for some of the beneficial health effects associated with an adequate programme of habitual physical activity. Finally, IL-6 may mediate a very large increase of hepcidin, a hormone that inhibits iron uptake and causes a trapping of iron in hepatic cells and macrophages; an increase of hepcidin and a resulting anaemia is a problem encountered in some athletes following a prolonged and strenuous bout of training.

Physical activity might also modify liver function through an increased generation of reactive oxygen species, as in skeletal muscle. Vigorous and prolonged physical activity (particularly if performed under hot and humid conditions) significantly restricts visceral blood flow, temporarily depriving the liver of an adequate oxygen supply, and this could favour an increased formation of reactive oxygen species (ROS). The secretion of heat shock proteins is linked to the production of ROS, and the exercise-induced up-regulation and accumulation of heat shock proteins, as seen in several rat studies following an hour of exhausting treadmill running might seem to support this hypothesis. However, other researchers have found little evidence of oxidative stress in the liver lipids and proteins of the rat following either acute or chronic exhausting exercise, with no clear changes in the activity of various antioxidant enzymes such as metallothionein-1, heme oxygenase-1 and superoxide dismutase following a non-exhausting 60 minute run.

Thus, there remain several competing hypotheses as to what triggers the observed hepatic adaptations to physical activity: an alteration in the hormonal milieu (changes in the concentrations of insulin, glucagon and/or epinephrine), an effect uponafferent nerves through some correlate of glycogen depletion, a response to secretion of a cytokine such as IL-6 or an effect of oxidant stress.
Molecular changes in the liver with acute physical activity

Information on the molecular changes induced by acute exercise is based almost exclusively on studies of normally inactive rodents (Table 1.1). The changes are complex and details can be found elsewhere.[9, 81] Manifestations, all of which seem favourable to performance, include an up-regulation of enzymes involved in carbohydrate metabolism, a decreased expression of fat synthesizing enzymes and an up-regulation of systems protecting the liver cells against genetic mutation and heat shock. An analysis of the transcriptome (the total of RNA messengers) in mice hepatocytes following 60 minutes of moderate intensity exercise showed that while 352 transcripts were up-regulated, 184 were down-regulated. Many of the changes in messenger RNA affected the activity of genes of recognized importance for glycolysis, gluconeogenesis and fatty acid metabolism.[87] Physical activity also activated some of these same genes in skeletal muscle, but the response was generally more marked in the liver. The effect was transient, disappearing within a few hours of ceasing a given bout of physical activity.[74, 81]

An acute bout of exercise consistently leads to an up-regulation of gluconeogenic and metabolic enzymes such as glucose-6-phosphatase, pyruvate dehydrogenase and phosphoenolpyruvate carboxykinase (PEPCK),[58, 74] a down-regulation of fat-synthesizing enzymes[33, 34] and the induction of metabolic regulators such as insulin receptor substrate.[74] Cortisol is normally implicated in the activation of hepatic PEPCK transcription. Thus, responses to physical activity are greatly attenuated in adrenalectomized animals and are absent in transgenic mice bred with deletion of the normal glucocorticoid regulatory unit.[77]

Hepatic responses to high-intensity and prolonged physical activity

High intensities of physical activity can reduce hepatic blood flow, and if exercise is prolonged, there is evidence of temporary derangements of hepatic function. However, recovery is rapid, and the changes usually have little clinical significance. We will look at the extent of reductions in local blood flow, and will review markers of impaired liver function that include histological changes, impaired pharmokinetics, markers of oxidative stress and altered blood levels of hepatic enzymes (Table 1.2). Long-lasting or permanent changes might deter athletes from participation in ultra-endurance events, but information to date suggests that liver function is typically normalized within a few days even after an event such as an ultra-marathon run.

Hepatic blood flow

Human hepatic blood flow is commonly estimated from the circulatory clearance of intravenously injected indocyanine dye. This technique suggests decreases of ~ 20% during brief vigorous effort and a much larger reduction of blood flow if
<table>
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<th>Author</th>
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<th>Biological effect</th>
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<tr>
<td>Anthony et al.[39]</td>
<td>Increased IGFBP-1 mRNA expression</td>
<td>May help to limit hypoglycaemia post-exercise</td>
</tr>
<tr>
<td>Banzet et al.;[58]</td>
<td>Up-regulation of glucose-6-phosphatase, pyruvatedehydrogenase,</td>
<td>Increase of gluconeogenesis</td>
</tr>
<tr>
<td>Dohm et al.;[73]</td>
<td>phosphoenol pyruvate carboxylase</td>
<td></td>
</tr>
<tr>
<td>Hoene et al.;[74]</td>
<td>Increased peroxosome</td>
<td>Increased levels of protein that regulates mitochondrial biogenesis</td>
</tr>
<tr>
<td>Nizielski et al.[75]</td>
<td>Increase of peroxosome</td>
<td></td>
</tr>
<tr>
<td>Banzet et al.;[58]</td>
<td>proliferator-activated receptor coactivator PGC-1</td>
<td></td>
</tr>
<tr>
<td>Helmrich et al.;[76]</td>
<td>Reduced expression of lipogenic enzymes</td>
<td>Less fat synthesis</td>
</tr>
<tr>
<td>Hoene et al.[74]</td>
<td>Induction of insulin-receptor substrate</td>
<td></td>
</tr>
<tr>
<td>Ropelle et al.[78]</td>
<td>Regulation of gluconeogenesis</td>
<td></td>
</tr>
<tr>
<td>Gonzalez and Manso[69]</td>
<td>Increased synthesis of heat shock protein molecular chaperones</td>
<td>Protection of proteins against stressors</td>
</tr>
<tr>
<td>Haase et al.[79]</td>
<td>Increased mRNA and cytochrome c protein</td>
<td>Improves oxidative potential</td>
</tr>
<tr>
<td>Hansen et al.[80]</td>
<td>Increased production of follistatin</td>
<td>Inhibits myostatin, facilitates muscle hypertrophy</td>
</tr>
<tr>
<td>Hoene et al.[74]</td>
<td>Induction of insulin-receptor substrate</td>
<td>Increases insulin binding, facilitates gluconeogenesis</td>
</tr>
<tr>
<td>Hoene and Weigert[81]</td>
<td>Changes in 352 gene transcripts</td>
<td>Many of the genes active in glycolysis, gluconeogenesis and fatty acid metabolism</td>
</tr>
<tr>
<td>Huang et al.[82]</td>
<td>Increase of adiponectin receptor 1, decrease of adiponectin receptor</td>
<td>Regulation of gluconeogenesis</td>
</tr>
<tr>
<td>Kelly et al.[83]</td>
<td>Increased hepatic AMP-activated protein kinase activity</td>
<td>Regulation of carbohydrate and lipid metabolism; effect less in IL-6 knock-out mice</td>
</tr>
<tr>
<td>Khanna et al.[84]</td>
<td>Increased hepatic content of bound form of alpha-lipoic acid</td>
<td>Co-factor for many mitochondrial proteins active in metabolism</td>
</tr>
<tr>
<td>Lavoie et al.;[85]</td>
<td>Increased blood levels of insulin binding growth factor binding protein</td>
<td>Helps glucose regulation by neutralizing insulin-like effects of insulin-like growth factor-1; also counters apoptotic effect of p53</td>
</tr>
<tr>
<td>Leu and George[86]</td>
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activity is prolonged or is undertaken in a hot environment.\textsuperscript{[88, 89]} For any given duration of effort, there appears to be an inverse dose-response relationship between visceral blood flow and the intensity of physical activity, with indocyanine clearance decreasing by ~ 80% as the intensity of activity approaches the individual’s \(\dot{V}O_2\text{max}\).

The elimination of indocyanine depends upon both hepatic blood flow and the continued ability of the liver cells to excrete the dye in a normal fashion.\textsuperscript{[90]} Thus, it has been argued that during heavy physical activity, in doycyanine-based inferences regarding hepatic blood flow may be confounded because of impairments in the excretory capacity of the liver cells. Nevertheless, major exercise-related decreases in hepatic blood flow have been corroborated by other techniques. Thus, clearance of intravenous injections of sorbitol have indicated hepatic blood flow reductions of ~ 40% when exercising at 40% of \(\dot{V}O_2\text{max}\)\textsuperscript{[91]} of 60–70% at 60–70% of \(\dot{V}O_2\text{max}\)\textsuperscript{[92]} and of 83% during near-maximal exercise.\textsuperscript{[93]} Further, Fojt et al. demonstrated dramatic drops of oxygen saturation in the hepatic vein during prolonged physical activity,\textsuperscript{[94]} much as would be expected if the oxygen extraction due to hepatic metabolism was unchanged, but local blood flow was greatly reduced. Nevertheless, the magnitude of changes remains somewhat contentious, particularly during short periods of vigorous exercise. Thus, using a radionuclide technique, Flamm et al.\textsuperscript{[95]} found only a 25% decrease in hepatic blood content during brief but intense cycle ergometry (5 minutes at 75% and 5 minutes at 100% of maximal aerobic effort). Likewise, Froelich et al.\textsuperscript{[96]} noted only a statistically non-significant 14% reduction of hepatic blood content during a short progressive cycle ergometer test to voluntary exhaustion.

The indocyanine and sorbitol-based human estimates of hepatic blood flow seem confirmed by animal studies where para-aminomphiphuric acid and sulphobromthalein were injected into a mesenteric vein, and blood samples were drawn from both portal and hepatic veins,\textsuperscript{[97]} with the hepatic arterial blood flow calculated as the difference between these two readings. Further, application of an electromagnetic flow-probe to the portal vein of rats showed that there was a large

\begin{table}
\centering
\begin{tabular}{lll}
\textbf{Author} & \textbf{Change} & \textbf{Biological effect} \\
Ochiai and Manso\textsuperscript{[37]} & Up-regulation of hepatic steryl CoA desaturase & May protect against insulin resistance \\
Peeling\textsuperscript{[61]} & Increase of hepcidin & Inhibition of iron uptake; could contribute to athlete’s anaemia \\
Roecker et al.\textsuperscript{[62]} & & \\
\end{tabular}
\end{table}

Notes: AMP = adenosine monophosphate. Co A = conezyyme A. IGFBP-1 = insulin-like growth factor binding protein 1. mRNA = messenger ribonucleic acid. PGC = perioxosome gamma co-activator. PECPK = phosphoenolpyruvate carboxykinase
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<tr>
<td>Bürger- Mendonça et al. 121</td>
<td>6 male athletes</td>
<td>Half-triathlon</td>
<td>Comparison of blood samples before and after race; significant change in AST and ALP but not ALT</td>
<td>Moderate temperatures. All enzyme values remained within normal limits</td>
</tr>
<tr>
<td>De Paz et al. 122</td>
<td>13 male runners, mean age 36 years</td>
<td>100 km race</td>
<td>Post-race increases in ALT +42%, AST+193%, GGT +56%, CK +2,000%</td>
<td>Cool conditions; serum bilirubin +106%. Also decrease of serum haptoglobins</td>
</tr>
<tr>
<td>Fallon et al. 123</td>
<td>7 male, 2 female</td>
<td>1,600 km ultramarathon</td>
<td>Increases of ALT, AST, GGT, LDH, CK; ALT remains high when AST and CK falling</td>
<td>Temperatures 11–32 °C</td>
</tr>
<tr>
<td>Holly et al. 124</td>
<td>6 male, 3 female triathlon competitors</td>
<td>Hawaiian Ironman competition</td>
<td>ASAT +700%, SGPT +262%, LDH +222% immediately after competition</td>
<td>Initial resting values high normal; enzymes marginally increased 5–6 days later</td>
</tr>
<tr>
<td>Kratz et al. 125</td>
<td>32 male, 5 female runners, average age 49 years</td>
<td>Boston marathon</td>
<td>AST +265%, ALT +37%, CK +2,343% increased after race, 24 h &gt; 4 h</td>
<td>Cool environment; bilirubin increased 60%, serum urea nitrogen increased 29%</td>
</tr>
<tr>
<td>Lippi et al. 126</td>
<td>15 healthy males</td>
<td>21 km half-marathon</td>
<td>AST, LDH, CK increased 0–24 h following run</td>
<td>ALT not measured</td>
</tr>
<tr>
<td>Long et al. 127</td>
<td>10 athletes</td>
<td>Short triathlon (10 km run, 20–40 km cycle, 1.0–1.5 km swim)</td>
<td>Modest increases of AST (30%) and LDH(53%)</td>
<td>Moderate temperatures; ALT not measured</td>
</tr>
<tr>
<td>Mena et al. 128</td>
<td>Professional cyclists</td>
<td>800 km/6 days and 2,700 km/20 days with overnight rests</td>
<td>Increases of ALT, AST, ALP and (in longer race) LDH; partial return to normal with overnight rest</td>
<td>Cumulative increase of serum enzyme concentrations over race</td>
</tr>
<tr>
<td>Authors</td>
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<tr>
<td>Nagel et al.</td>
<td>55 runners</td>
<td>1,000 km in 20 days</td>
<td>AST increased 500%, ALT 300%, GGT 600%, CK 2,000%; ALT remains high when AST and CK falling</td>
<td>Decreases in serum albumin and choline esterase (could reflect decreased synthesis or increase of IL-1)</td>
</tr>
<tr>
<td>Noakes and Carter</td>
<td>13 athletes</td>
<td>160-km run</td>
<td>Increases of LDH 241%; AST 821%; CPK 1,732% in those completing event</td>
<td>Temperatures not stated; total bilirubin also increased twofold; ALT and GGT not determined</td>
</tr>
<tr>
<td>Noakes and Carter</td>
<td>18 experienced, 5 novice competitors</td>
<td>56 km ultramarathon</td>
<td>Greater rise of AST and CPK in novices, despite slower running speed</td>
<td></td>
</tr>
<tr>
<td>Rama et al.</td>
<td>7 well-trained male distance runners, mean age 37 years</td>
<td>100 km road race</td>
<td>GGT +19%, CK +3,121%</td>
<td>Cool conditions; ALT not measured</td>
</tr>
<tr>
<td>Richards et al.</td>
<td>43 successful runners (28 M, 16 F) vs. 10 who collapsed (9M, 1F)</td>
<td>14 km Sydney city to surf run</td>
<td>Casualties showed higher values for blood urea nitrogen, serum creatinine, uric acid and bilirubin</td>
<td></td>
</tr>
<tr>
<td>Shapiro et al.</td>
<td>26 untrained men</td>
<td>110 km march in 2 days</td>
<td>Increases in CK, AST and aldolase</td>
<td>Midday temperatures 30°C; ALT not measured. Increased enzyme levels only seen in those marching at 6 km/h</td>
</tr>
<tr>
<td>Smith et al.</td>
<td>27 male, 7 female runners, aged 18–65 years</td>
<td>Marathon run</td>
<td>Significant increases in CK, AST, LDH immediately following event</td>
<td>ALT not determined; climate not specified</td>
</tr>
<tr>
<td>Suzuki et al.</td>
<td>9 well-trained male triathletes</td>
<td>Ironman triathlon</td>
<td>Significant increases immediately and especially 24 h after race: ALT 185%; AST 759%; CK 2,680%; GGT −20%</td>
<td>Moderately warm conditions</td>
</tr>
</tbody>
</table>
Table 1.2 continued

<table>
<thead>
<tr>
<th>Authors</th>
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<tbody>
<tr>
<td>Van Rensburg et al. [137]</td>
<td>23 male athletes, average age 33 years</td>
<td>Triathlon competition</td>
<td>Significant increases of AST, CK and LDH immediately post-race</td>
<td>ALT not measured; 4.5% decrease of body mass over event</td>
</tr>
<tr>
<td>Waskiewicz et al. [138]</td>
<td>14 male runners, mean age 43 years</td>
<td>24 h ultra-marathon</td>
<td>Increased enzymes 24 h after run; ALT 350%, AST 1,354%, CK 1,204%, no change of GGT</td>
<td>Cool conditions</td>
</tr>
<tr>
<td>Wu et al. [139]</td>
<td>10 males, 1 female</td>
<td>24-h marathon</td>
<td>Blood enzymes tested immediately, 2 and 9 days after event. AST 1,344,630, −8%; ALT 237,259, 44%; LDH 286,205, 59%; no significant change of GGT</td>
<td>Moderately warm conditions; bilirubin increased immediately post-race</td>
</tr>
<tr>
<td>Other forms of exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apple and McGue [140]</td>
<td>2 male runners</td>
<td>6 weeks of training for a marathon</td>
<td>ALT increased in ó subjects; large increases of LDH and CK</td>
<td></td>
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<tr>
<td>Beard et al. [141]</td>
<td>2 joggers with heat stroke</td>
<td></td>
<td>Reduced level of clotting factors produced by liver</td>
<td></td>
</tr>
<tr>
<td>Bunch [142]</td>
<td>6 runners</td>
<td></td>
<td>Clinically “abnormal” levels of hepatic enzymes</td>
<td></td>
</tr>
<tr>
<td>Fojt et al. [94]</td>
<td>6 male volunteers</td>
<td>Cycle ergometer exercise at 70–85% of maximal oxygen intake to exhaustion (26–60 min)</td>
<td>Hepatic vein shows increased content of ALT and other liver enzymes</td>
<td></td>
</tr>
<tr>
<td>Hammouda et al. [143]</td>
<td>18 male football players</td>
<td>30 sec Wingate test</td>
<td>Small increases of CK 11%; AST 10%; ALT 16%; LDH 13%</td>
<td></td>
</tr>
<tr>
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<td>Comments</td>
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<tr>
<td>Kayashima et al. [101]</td>
<td>14 soldiers aged 24–36 years</td>
<td>80-km trek on limited diet over 4 days</td>
<td>Enzymes sampled immediately and after 8 days. Increases: AST 177, 152%; ALT 39, 234%; LDH 66, 8%; CK 208, −68%</td>
<td>Associated leucocytosis and bilirubinaemia immediately after exercise</td>
</tr>
<tr>
<td>Malinoski[144]</td>
<td>3 soldiers</td>
<td>Several days of strenuous training</td>
<td>Increases of ALT, AST and CK</td>
<td></td>
</tr>
<tr>
<td>Nathwani et al. [145]</td>
<td>4 prison inmates</td>
<td>3 undertook vigorous squatting; 1 a long-distance run</td>
<td>Increases of AST, ALT, CPK and LDH</td>
<td>Liver damage unlikely since normal serum bilirubin and prothrombin times</td>
</tr>
<tr>
<td>Ohno et al. [146]</td>
<td>7 sedentary male students</td>
<td>Running 5 km, 6 times/week for 10 weeks</td>
<td>50% decrease of resting GGT</td>
<td></td>
</tr>
<tr>
<td>Pettersson et al. [147]</td>
<td>15 healthy men not used to weight-lifting</td>
<td>1 h of weight-lifting</td>
<td>AST, ALT, LDH, CK all remained elevated for 7 days post-exercise</td>
<td>Laboratory conditions</td>
</tr>
<tr>
<td>Takahashi et al. [148]</td>
<td>7 male rugby players, average age 21 years</td>
<td>2 successive Rugby sevens matches of 10 min duration, with 4-h inter-game interval</td>
<td>Increases of CK 42%; LDH 25%; AST 13%; but not ALT</td>
<td>Cool conditions</td>
</tr>
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</table>

**Animal data**

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<tr>
<td>Litvinova and Viru [149]</td>
<td>Male Wistar rats aged 10–12 weeks</td>
<td>10-h swimming with loading 10% of body mass</td>
<td>103% increase in hepatic 14C urea content</td>
<td>Effect decreased by adrenalectomy</td>
</tr>
</tbody>
</table>

Notes: ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; CK = creatine kinase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; LDH = lactate dehydrogenase; SGFT = serum glutamic pyruvic transaminase, also known as alanine amino transferase
and progressive decrease of flow when animals exercised for 40 minutes at an oxygen consumption of 70 ml/(kg.min).[98]

Recovery of the normal hepatic blood flow is quite rapid even following heavy physical activity, and ultrasound studies suggest that for a few hours the local flow may even rise above normal levels. This response may reflect inflammation of the liver. Arguably, it also serves to replenish glycogen reserves and to speed normalization of circulating FFAs following exercise.[99]

**Histological changes with physical activity**

Histological changes associated with vigorous and/or exhausting physical activity could point to adverse effects of excessive physical activity, but studies have been conducted mainly in animals, and the findings are controversial. Sixty minutes of moderate intensity treadmill running has little effect upon the morphological characteristics of hepatic tissue.[100] However, this activity is enough to cause an acute inflammatory response, with an increase in the peripheral white cell count.[101] Moreover, the hepatocytes show a greater decrease in cell volume than can be attributed simply to glycogen depletion;[100] possibly, cell size is reduced due to a glucagon-induced decrease in cytoplasmic potassium ion content.

Rowell[17] suggested that activity of sufficient intensity to cause hepatic hypoxia predisposed to central lobular necrosis. Based on an extracellular fluid shift and a decrease of serum amino acids observed during a 23-hour ultra-marathon, Lehmann et al.[102] hypothesized that a decrease of intracellular volumes served as a signal leading to a catabolic degradation of various body cells, including the adverse changes in hepatocytes that others had reported.

A study of rats running for 60 minutes at 75% or 90% of $\text{VO}_{2\text{max}}$ purported to show not only increased blood levels of hepatic enzymes, but also oedema and necro-inflammation of the liver tissue.[103] However, this conclusion was based upon only 24 animals divided between six controls and four other treatment groups. Moreover, only two of the four treatment groups showed necrotic changes, and interpretation of the liver histology was not conducted in a “blinded” fashion. The same criticism of a lack of “blinded” evaluation applies to other reports. Mitochondrial swelling in hepatocytes surrounding the hepatic venules was reported when rats ran for 100 or more minutes to exhaustion,[104] and 60–90 minutes of running to exhaustion was said to induce cancerous changes, necrosis and apoptosis of the hepatocytes.[105]

**Impaired hepatic drug clearance**

One practical measure of the extent of any activity-related changes in hepatic function is to monitor the clearance of drugs normally eliminated by the liver. Test agents fall into two basic categories: “low clearance” drugs such as acetaminophen, antipyrine, diazepam, amylobarbitone and verapamil, where elimination depends largely upon hepatic enzyme activity and biliary excretion,[106] and “high
clearance” drugs such as indocyanine, bromsulphthalein, sorbitol and lidocaine, where elimination reflects mainly hepatic blood flow.[89, 107]

The elimination of low-clearance drugs clearance in humans is largely unaffected by either moderate exercise[108–112] or by prolonged low to moderate intensity activity such as six–nine hours of marching,[113, 114] although there remains a need for further observations on very prolonged events such as ultra-marathon runs. In contrast, given the dramatic changes of blood flow noted above, it is not surprising that vigorous and/or prolonged physical activity reduces the elimination of high clearance substances.[111, 115]

Oxidant stress

Oxidant stress impairs the ability of the hepatocyte endoplasmic reticulum to fold and assemble proteins correctly. It can be caused by severe exercise and by aging. Significant oxidant stress may develop after rather than during physical activity,[64] and in order to determine the extent of such changes it is important to continue the search for markers of oxidant stress into the recovery period. As in skeletal muscle, oxidant stress is not always an “adverse” phenomenon; on occasion, it provides valuable signals, inducing adaptations of the liver to regular physical activity.[81]

Some[116–118] but not all human studies[119] have demonstrated transient oxidant stress following prolonged and/or vigorous exercise. However, human studies have not examined changes within the liver itself. Thus, Pinho et al.[116] found a variety of circulatory markers of such stress (increases of thiobarbituric reactive substances [TBARS], lipid hydroperoxide and protein carbonylation), along with up-regulation of superoxide dismutase and catalase, the enzymes breaking down reactive products, following participation in an Ironman triathlon. Neubauer et al.[117] made observations not only immediately after a triathlon, but also 1, 5 and 19 days later. They found that markers of oxidative stress had normalized within five days. Turner and associates[118] examined athletes after participating in a 223 km race. Their investigation noted DNA damage in peripheral blood mononuclear cells immediately after the run, with increased protein carbonylation persisting for seven days. Further, levels of the anti-oxidant reduced glutathione were still depressed at 28 days. In contrast, Margaritis et al.[119] found evidence of inflammation, including increased leucocyte counts, but no signs of oxidative stress following participation in a triathlon event.

Animal studies have provided more direct evidence that exhausting exercise can indeed cause oxidative stress within the liver tissue. As in the human study of Turner et al.,[118] the hepatic glutathione levels of rats fell following a bout of exhausting exercise, reflecting a large increase in oxidative metabolism and reduced stores of the normal buffer to reactive oxygen species.[120] Increased blood levels of malondialdehyde (MDA, a marker of lipid peroxidation), NOx and xanthine oxidase were seen in mice following 15 maximal sprints of 30 seconds. Temporary muscle damage was suggested by large increases in serum amino-transferases and lactate dehydrogenase (LDH), but there were no changes in
levels of TBARS, superoxide dismutase or glutathione peroxidase in liver samples.\textsuperscript{150} Relative to control animals, liver samples of aging rats that ran to exhaustion at 70–75\% of their maximal oxygen intake showed increased neutrophil infiltration, along with higher levels of myeloperoxidase (an enzyme that is a marker of neutrophil infiltration) and MDA, with (paradoxically) reductions in levels of the anti-oxidant enzymes catalase and glutathione peroxidase.\textsuperscript{151} Other studies of rats have found significant increases in measures of hepatic lipid peroxidation, with a substantial increase of MDA following 30 minutes\textsuperscript{152} or 80 minutes of swimming to exhaustion.\textsuperscript{153}

There is also a substantial rise in the temperature of hepatic tissue during exhausting exercise, and rodent studies have demonstrated an associated increase in concentrations of 70 kDa and 72 kDa heat shock proteins.\textsuperscript{69, 70}

\textit{Serum enzyme levels}

Clinicians frequently evaluate human hepatic function in terms of serum enzyme levels. Short periods of physical activity usually have little or no effect upon such indices,\textsuperscript{143, 148} but in the hours following a marathon or triathlon competition, many investigators have found increased serum concentrations of aminotransferases, often accompanied by increased bilirubin levels and markers of inflammation such as IL-6 and C-reactive protein. Such findings have also been observed in laboratory animals after prolonged and vigorous physical activity.\textsuperscript{103} However, the cause of these changes (hepatic injury, haemolysis or muscle injury) and their clinical significance has remained unclear. Confirmation of hepatic malfunction has been sought in a decreased synthesis of proteins such as albumin and choline esterase,\textsuperscript{129, 139} although any reduction in the circulating concentrations of these substances could also reflect the influence of increased serum concentrations of the cytokine interleukin-1.\textsuperscript{129}

By catheterizing the hepatic vein, it is possible to show that the liver rather than muscle is the source of increased enzyme levels during exhausting exercise. Thus, Fojt et al.\textsuperscript{94} noted that after 25–60 minutes of cycle ergometry at 70–85\% of maximal oxygen intake, concentrations of enzymes such as lactate dehydrogenase, succinate dehydrogenase and creatine phosphokinase were greater in hepatic venous blood than in arterial blood. Moreover, local ischaemia was demonstrated by a hepatic venous oxygen saturation that dropped from a typical resting level of 75\% to as low as 5\% during the exercise bout.

\textit{Other measures of impaired liver function}

Several pieces of biochemical evidence suggest that any exercise-induced disturbances of liver function are usually short term and of relatively minor clinical significance. Nagel et al.\textsuperscript{129} saw decreases in serum albumin and choline esterase over a 1000 km event, likely reflecting some transient decrease in hepatic synthesis of these proteins, and Beard\textsuperscript{141} observed a decreased hepatic production of clotting factors in two runners who suffered from heat stroke. However, many
investigations have noted an increase of bilirubin synthesis during and following competition. Thus, De Paz et al. reported a substantial increase in bilirubin levels following a 100 km race,[122] Noakes et al.[130] noted a large increase of bilirubin over a 160 km run, Wu et al.[139] observed an increase of bilirubin following a 24-hour marathon and Kratz et al.[125] found an increased excretion of both bilirubin and urea following participation in the Boston marathon. Nathwani et al.[145] also commented on the normality of prothrombin times in their subjects following a bout of vigorous exercise.

Conclusions

Vigorous and/or prolonged physical activity can cause an inflammatory response in animal livers, but possible histological evidence of more permanent damage to the hepatocytes requires confirmation by blinded observations. Vigorous physical activity causes a slowing in the elimination of markers dependent on hepatic blood flow, but little change in the clearance of markers dependent on normal liver function. There is some evidence of oxidative stress in both humans and animals, and a transient appearance of hepatic enzymes in the serum with exhausting exercise. However, these changes are reversed within a few days. There is little evidence of either depressed protein synthesis or permanent hepatic damage; indeed, some of the changes that have been observed may be a necessary component of normal and positive hepatic adaptations to vigorous physical activity.

Chronic effects of moderate endurance activity

Carbohydrate metabolism

Strenuous endurance training increases an athlete’s ability to sustain a higher work-rate during prolonged activity and to exercise for a longer time before the onset of fatigue. One factor contributing to this change is an improved ability to maintain blood glucose levels during prolonged effort. This is in part a consequence of an increased capacity for skeletal muscle to store glycogen and to oxidize fat at the expense of glucose. However, further adaptations likely include an increased storage of glycogen in the resting liver, and slower rates of both glycolysis and gluconeogenesis at any given absolute intensity of effort. Thus, Murakami et al.[154] found that after 12 weeks of treadmill training, the glycogen content of rats livers was increased by about 30%. Coggan et al.[155] required human volunteers to cycle for 45–90 minutes per day at 75–100% of peak oxygen intake, and at the end of 12 weeks they observed a substantially reduced rate of glycolysis and some reduction of gluconeogenesis at any given intensity of exercise. This probably reflected mainly a lesser secretion of epinephrine and norepinephrine during what had become a less challenging test exercise, but there were also higher insulin and lower glucagon concentrations, as also noted by Galbo et al.[156] Further, the availability of gluconeogenic precursors (lactate and glycerol) was reduced at any given intensity of exercise.[155]
Rodent investigations have shown some differences from human studies, probably because whereas gluconeogenesis accounts for some 20% of glucose production when humans undertake moderate exercise, in rats the figures range from 40–70%. Most but not all\cite{157} rodent studies have observed increased activity of the enzymes and signalling molecules involved in carbohydrate and lipid metabolism following aerobic training.\cite{158,159} For example, Khanna et al.\cite{84} trained rats by running them to exhaustion up a 10% grade at 2.1 km/h; this induced an increase in the hepatic content of the bound form of alpha-lipoic acid (lipoyl-lysine), an important co-factor in lipid metabolism. Both glycolytic and gluconeogenic responses to a given concentration of glucagon were also enhanced following training.\cite{172,173} Mechanisms underlying the increased response to glucagon apparently include an adjustment in the ratio of inhibitory to stimulatory guanine-nucleotide binding protein (G protein) and a resultant increase in activity of the “second messenger” adenyl cyclase.\cite{172} The increased capacity for gluconeogenesis allows the trained animal to sustain higher work-rates and to maintain blood glucose levels for longer during a sustained bout of activity.\cite{174} Moreover, the liver has an increased absolute capacity to metabolize lactate\cite{175} and alanine,\cite{176} with an associated increase of gluconeogenesis.\cite{176,177}

**Lipid metabolism**

The enhanced ability of the exerciser to metabolize fat following training is largely a function of enzymatic adaptations in skeletal muscle, and there is little evidence that the liver contributes to this response. Nevertheless, regular exercise is associated with alterations in lipid/lipoprotein metabolism and appears to reduce the storage of triglyceride in the liver.

The limited effect of training upon the hepatic metabolism of fat is perhaps understandable, given the apparently trivial contribution of the liver to fat oxidation during physical activity.\cite{32} The hormones that contribute to the lipolysis of depot fat include epinephrine, norepinephrine, ghrelin, growth hormone, testosterone and cortisol, and plainly training blunts the response of several of these hormones to exercise. After training, the action of the growth hormones is countered by increasing circulating concentrations of insulin and insulin-like growth factor binding protein-1.\cite{178} Blood glycerol and FFA concentrations are also lower at a given absolute exercise intensity,\cite{246} thus reducing the available substrate for hepatic synthesis of triglycerides.

A substantial number of studies have examined associations between regular physical activity, liver fat content and liver mass. In general, liver fat content has been lower in more active individuals, but it is difficult to be certain exercise was responsible, since many studies have had no control group, and interventions have often included alterations of diet as well as increases of physical activity. Liver fat content has generally been determined by proton magnetic resonance spectroscopy, ultrasound, CT scan or biopsy, but habitual physical activity has usually been assessed by questionnaires of dubious validity, rather than by objective techniques, and when comparisons have been made, large discrepancies
have been seen between subjective and objective estimates of habitual physical activity.\[165\]

### Cross-sectional associations between habitual physical activity and amount of liver fat

Of 12 cross-sectional studies, 6 samples, often quite large, involved healthy individuals, and 6 smaller subject-groups had fatty livers (Table 1.3). Nine investigations relied on questionnaire assessments of habitual activity, but there were also studies using a Sense-wear arm-band\[161\] an accelerometer\[162\] and a pedometer.\[168\] All reports except that of Kang et al.\[165\] found less fat accumulation and fewer pathological changes in the livers of individuals who engaged in greater amounts of physical activity, with benefit being seen with both aerobic and resistance exercise.\[171\] The negative report of Kang et al.\[165\] measured habitual physical activity using the Paffenbarger questionnaire, and they observed comparable levels of physical activity in those with and without evidence of the metabolic syndrome.

### Cross-sectional associations between aerobic fitness and amount of liver fat

Eleven studies (mostly with relatively small samples, and some deliberately including obese subjects or individuals with fatty livers) have related aerobic fitness (generally measured as the peak effort attained on a treadmill or cycle ergometer test) to liver fat content (Table 1.4). All except two investigations with small sample sizes\[183, 188\] found less hepatic fat in individuals with higher levels of aerobic fitness.

### Physical activity interventions and amount of liver fat

At least 36 studies have examined the impact of physical activity interventions upon liver fat content (Table 1.5). Unfortunately, many of the studies have lacked controls, and sometimes the interpretation of data has been compromised by the inclusion of dieting and other lifestyle measures as a part of the intervention. All 12 controlled investigations showed a reduction of liver fat in response to a physical activity programme, although in some cases the benefit was no greater than that which was obtained by a dietary intervention.

### Animal studies of exercise training and amount of liver fat

Investigations of exercise and hepatic fat accumulation have often used animals that were fed high-fat diets or were genetic variants prone to obesity (Table 1.6). A further limitation of many animal studies is that controls have lived unnatural lives of physical inactivity and over-eating relative to their natural state. In consequence, differences in hepatic tissue mass between sedentary and exercised...
## Table 1.3 Influence of regular physical activity on fat content of human liver, as seen in cross-sectional comparisons

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Methodology</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bae et al. [160]</td>
<td>72,359 Korean adults</td>
<td>Ultrasound, self-reported physical activity</td>
<td>Risk of fatty liver 0.53–0.72 if exercise for 30 min, 3 times/wk for 3 months</td>
<td>Active individuals also had reduced AST and ALT levels</td>
</tr>
<tr>
<td>Fintini et al. [161]</td>
<td>Children with fatty livers (n = 40) vs. obese (n = 30) vs. lean peers (n = 41)</td>
<td>Physical activity questionnaire &amp; Sense-ware arm bands</td>
<td>Those with fatty livers devoted more time to sedentary pursuits, engaged in less physical activity</td>
<td>Questionnaire data did not agree well with Sense-ware data</td>
</tr>
<tr>
<td>Gerber et al. [162]</td>
<td>3,056 participants in the US NHANES survey of 2003–2006 aged &gt;20 years</td>
<td>Fatty liver index based on BMI, waist circumference, triglycerides and GGT, accelerometer</td>
<td>Individuals with fatty liver index &gt;60 units had lower accelerometer readings (29 counts/ min per day), and spent less time at all levels of activity</td>
<td></td>
</tr>
<tr>
<td>Hattar et al. [163]</td>
<td>Hispanic children, aged 12.1 years; 20 fatty liver, 20 obese, 17 controls</td>
<td>Liver biopsy, retrospective physical activity questionnaire</td>
<td>Sedentary score &gt;2 associated with stage 2–3 hepatic fibrosis</td>
<td>15% of children with fatty livers performed light exercise, vs. 35% of obese and 59% of non-obese children</td>
</tr>
<tr>
<td>Hsieh et al. [164]</td>
<td>3,331 adult Japanese men</td>
<td>Ultrasound, physical activity questionnaire</td>
<td>Fatty liver less prevalent in those exercising regularly &gt;2 days/week than in sedentary men</td>
<td>Dose–response relationship (sedentary vs. those active 1, 2 and 3 days/week)</td>
</tr>
<tr>
<td>Kang et al. [165]</td>
<td>39 M, 52 F with fatty liver, age 48 years</td>
<td>Liver biopsy, physical activity questionnaire</td>
<td>No difference of histology with reported physical activity</td>
<td></td>
</tr>
<tr>
<td>Kistler et al. [166]</td>
<td>302 men, 511 women with fatty liver</td>
<td>Liver biopsy, self-reported physical activity</td>
<td>Neither moderate nor total exercise associated with stage of hepatic fibrosis; however, those meeting recommended vigorous activity had reduced odds of fatty liver</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Sample</td>
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<tr>
<td>Leskinen et al.</td>
<td>16 same-sex middle-aged twin pairs discordant for activity</td>
<td>Proton magnetic resonance spectroscopy, physical activity questionnaire</td>
<td>Inactive twins had 3 times as much liver fat as active peers</td>
<td>Inactive twins also had greater body mass, fat mass, visceral fat and lower fitness</td>
</tr>
<tr>
<td>Newton et al.</td>
<td>36 M, 36 F (36 with fatty liver, 36 controls)</td>
<td>Liver biopsy, pedometer</td>
<td>Those with fatty liver took 20% fewer steps/day</td>
<td></td>
</tr>
<tr>
<td>Perseghin et al.</td>
<td>114 M, 77 F aged 19–62 years</td>
<td>Proton magnetic resonance spectroscopy, physical activity questionnaire</td>
<td>Hepatic fat &gt;5%) 25% in least active quartile, 2% in most active quartile</td>
<td>Association attenuated by adjustments for age, sex, BMI, insulin sensitivity and adiponectin</td>
</tr>
<tr>
<td>Tiikkainen et al.</td>
<td>27 women with previous gestational diabetes</td>
<td>Proton magnetic resonance spectroscopy, physical activity questionnaire</td>
<td>Women with low fat exercised for 30 min 5 times/week, those with &gt;5% liver fat only 3 times/week</td>
<td>Fatty liver associated with insulin resistance</td>
</tr>
<tr>
<td>Zelber-Sagi et al.</td>
<td>375 Israeli men and women, mean age 51 years</td>
<td>Abdominal ultrasound, physical activity questionnaire</td>
<td>Hepatic fat related to sports participation (odds ratio 0.66) and resistance exercise (0.61).</td>
<td>Hepatic fat only related to resistance exercise if adjusted for BMI; relationship non-significant if also adjusted for leptin or waist circumference</td>
</tr>
</tbody>
</table>

Note: ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; GGT = gamma-glutamyl transferase
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<tr>
<th>Author</th>
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<th>Results</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Church et al.</td>
<td>218 men aged 33–73 years</td>
<td>CT scan, peak treadmill endurance time</td>
<td>Treadmill endurance time and BMI independently associated with fatty liver</td>
<td>Associations attenuated if abdominal fatness included in model</td>
</tr>
<tr>
<td>Hannukainen et al.</td>
<td>Nine male monozygotic twin-pairs differing in habitual physical activity</td>
<td>Proton magnetic resonance spectroscopy, maximal oxygen intake on cycle ergometer</td>
<td>20% less visceral fat in more active twins</td>
<td>Hepatic uptake of free fatty acids lower in active twins</td>
</tr>
<tr>
<td>Haufe et al.</td>
<td>Overweight and obese subjects (31 M, 108 F aged 40–50 years)</td>
<td>Proton magnetic resonance spectroscopy, peak oxygen intake on cycle ergometer</td>
<td>Negative correlation between aerobic fitness and hepatic fat, M &gt; F</td>
<td>In men, correlation independent of visceral adipose tissue</td>
</tr>
<tr>
<td>Kantartzis et al.</td>
<td>70 M, 100 F (50 with fatty liver)</td>
<td>Proton magnetic resonance spectroscopy, peak oxygen intake on cycle ergometer</td>
<td>Initial peak oxygen intake strongest predictor of reduction in hepatic fat with diet and physical activity</td>
<td>Authors conclude cardio-respiratory fitness determines liver fat content</td>
</tr>
<tr>
<td>Krasnoff et al.</td>
<td>19 M, 18 F, average age 45.9 years</td>
<td>Liver biopsy, symptom-limited peak oxygen intake on treadmill</td>
<td>No relationship between peak oxygen intake and fatty liver</td>
<td></td>
</tr>
<tr>
<td>Kuk et al.</td>
<td>86 lean pre-menopausal women</td>
<td>CT scan, peak treadmill endurance time</td>
<td>Treadmill endurance lower in those with fatty liver</td>
<td>Liver fat not related to other metabolic risk factors</td>
</tr>
<tr>
<td>Leskinen et al.</td>
<td>16 same-sex middle-aged twin pairs discordant for activity</td>
<td>Proton magnetic resonance spectroscopy, peak oxygen intake on cycle ergometer</td>
<td>Inactive twins had 3 times as much liver fat</td>
<td>Inactive twins also had greater bodymass, fat mass, visceral fat and lower aerobic fitness</td>
</tr>
</tbody>
</table>
animals have varied widely between investigations. In the study of Yiamouyiannis et al., rats that were fed ad libitum and given free access to a running wheel also ate more than controls, thus presenting with larger livers and increased values for total liver protein, mitochondrial and cytosolic protein tissue. Because of liver hypertrophy, the total activity of several enzymes involved in the breakdown of foreign chemical substances was also increased, although the activity per gram of liver or per gram of hepatic protein remained unchanged.

The physical activity intervention adopted in animal experiments has usually been enforced treadmill running or swimming, although two studies have examined the effects of resistance exercise. Of 19 studies, 18 showed lower hepatic fat in the exercised group, the one exception being Yasari et al. In terms of fat reduction, resistance exercise seemed as effective as aerobic activity, and perhaps because peak intensities of effort were higher, intermittent activity had a greater effect than continuous effort.

Impact upon circulating lipids

Table 1.4 continued

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Methodology</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>McMillan et al.</td>
<td>293 men aged 29–78 years</td>
<td>CT scan and peak treadmill endurance time</td>
<td>Peak treadmill time weakly correlated with liver fat ($r = -0.24$)</td>
<td>Probable overlap of sample with McMillan et al.</td>
</tr>
<tr>
<td>Nguyen-Duy et al.</td>
<td>161 men aged 33–72 years</td>
<td>CT scan and peak treadmill endurance time</td>
<td>Peak treadmill time weakly correlated with liver fat ($r = -0.26$)</td>
<td>Relationship eliminated by introduction of waist circumference</td>
</tr>
<tr>
<td>O’Donovan et al.</td>
<td>50 men aged 34–56, both obese and lean</td>
<td>Proton magnetic resonance spectroscopy, peak oxygen intake on cycle ergometer</td>
<td>Liver fat was greater in unfit</td>
<td></td>
</tr>
<tr>
<td>Seppala-Lindroos et al.</td>
<td>30 middle-aged men (15 with fatty liver)</td>
<td>Proton magnetic resonance spectroscopy, maximal oxygen intake</td>
<td>No significant difference of maximal oxygen intake between high and low fat groups [35.6 vs. 33.5 ml/(kg min)]</td>
<td>High liver fat defined as &gt;3%, so that some relatively normal individuals included in high fat group</td>
</tr>
</tbody>
</table>
### Table 1.5 Effects of regular physical activity on fat content of human liver, as seen in longitudinal studies of exercise training

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample Description</th>
<th>Methodology</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albu et al. [189]</td>
<td>58 obese subjects, average age 59 years</td>
<td>CT scan, 175 min moderate aerobic exercise/week + moderate energy restriction</td>
<td>18% decrease in hepatic fat</td>
<td>No control group</td>
</tr>
<tr>
<td>Bacchi and Moghetti et al. [190]; Bacchi et al. [191]</td>
<td>31 overweight or obese individuals</td>
<td>Magnetic resonance imaging, 4 month programme; 60 min aerobic exercise at 60–65% heart rate reserve 3 times/week vs. 60 min resistance exercise at 70–80% 1RM 3 times/week</td>
<td>Hepatic fat reduced 33% (aerobic) vs. 26% (resistance programme)</td>
<td>No control group</td>
</tr>
<tr>
<td>Bonekamp et al. [192]</td>
<td>45 adults with type 2 diabetes mellitus, age 53 years</td>
<td>Proton magnetic resonance spectroscopy, 45 min of moderate aerobic exercise plus weight lifting, 3 times/week for 6 months, vs. controls</td>
<td>2.5% reduction in hepatic fat, effect persisted if adjusted for BMI or visceral fat</td>
<td>Dietary policy unclear</td>
</tr>
<tr>
<td>Chen et al. [193]</td>
<td>54 M and F Taiwanese with fatty livers, age 38–40 years</td>
<td>Ultrasound, 10 week diet + exercise (high-intensity cycle ergometry, 1 h twice/week) vs. exercise alone vs. control</td>
<td>Liver fat decreased by either exercise or diet</td>
<td></td>
</tr>
<tr>
<td>de Piano et al. [194]</td>
<td>58 obese adolescents, with or without fatty liver average age 16.5 years</td>
<td>Ultrasound, 1-year lifestyle intervention with aerobic (60 min at ventilatory threshold, 3 times/week) or aerobic + resistance (3 sets of 6–20 reps for main muscle groups) training</td>
<td>Combined aerobic + resistance exercise more effective than aerobic exercise alone</td>
<td>No non-exercise control group</td>
</tr>
<tr>
<td>Devries et al. [195]</td>
<td>41 men and women, aged 38–40 years; half of sample lean, half obese</td>
<td>CT scan, 3 months cycle ergometer training, 60 min/day, 3 times/week, progressing to 65% of maximal oxygen intake in women and 70% in men</td>
<td>Training did not alter liver attenuation on CT scan</td>
<td>No control group</td>
</tr>
<tr>
<td>Author</td>
<td>Sample</td>
<td>Methodology</td>
<td>Results</td>
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<tr>
<td>Eckard et al.</td>
<td>56 adults aged 18–70 with fatty liver</td>
<td>Liver biopsy, 6 month programme; moderate exercise (30–60 min, 4–7 times/week, tracked by exercise log and pedometer) vs. exercise + low fat or moderate fat + low processed carbohydrates vs. standard care</td>
<td>All intervention groups improved, with no significant inter-group differences</td>
<td></td>
</tr>
<tr>
<td>Fealy et al.</td>
<td>13 obese subjects aged 58 years, sex not specified</td>
<td>Proton magnetic resonance spectroscopy, 1 week of walking, 60 min/day at 85% of maximal heart rate</td>
<td>Reduced markers of apoptosis, mediated through increase doxidative capacity and greater insulin sensitivity</td>
<td>No control group</td>
</tr>
<tr>
<td>Finucane et al.</td>
<td>100 healthy older people (50 served as controls)</td>
<td>Proton magnetic resonance spectroscopy, 12 week cycle ergometer exercise, 60 min, 3 times/week vs. control group</td>
<td>Significant reduction of liver fat in intervention group</td>
<td>Increased predicted maximal oxygen intake, no change of body mass</td>
</tr>
<tr>
<td>Franzese et al.</td>
<td>41 M, 34 F obese children aged 9.5 years</td>
<td>Ultrasound, 6 months of diet + exercise</td>
<td>Liver fat decreased with loss of weight</td>
<td>No control group</td>
</tr>
<tr>
<td>Goodpaster et al.</td>
<td>130 severely obese adults (101 completed trial)</td>
<td>CT scan, 6 months, diet + exercise vs. diet</td>
<td>Both groups lost weight, exercised group lost more liver fat</td>
<td></td>
</tr>
<tr>
<td>Grønbæk et al.</td>
<td>117 obese children, average age 12.1 years</td>
<td>Ultrasound, 10 week period at a weight loss camp with daily hour of varied aerobic exercise</td>
<td>Reduction of fatty liver</td>
<td>No control group</td>
</tr>
<tr>
<td>Hallsworth et al.</td>
<td>19 sedentary adults with fatty livers, aged 52 years experimental, 62 year controls</td>
<td>Proton magnetic resonance spectroscopy, 8 week resistance exercise (n = 11) vs. standard treatment (n = 8); physical activity monitored by Sense-wear arm band</td>
<td>13% reduction of liver fat with no change in body mass, total fat mass or visceral fat volume</td>
<td>Lipid oxidation, glucose control and insulin resistance all improved. Controls older</td>
</tr>
<tr>
<td>Author</td>
<td>Sample</td>
<td>Methodology</td>
<td>Results</td>
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<tr>
<td>Hickman et al.</td>
<td>35 men and women (21 with hepatitis C virus), aged 44 years</td>
<td>Liver biopsy, 15 month programme of diet plus encouraging 150 min aerobic</td>
<td>14 patients biopsied after 3–6 months of exercise showed lessening of</td>
<td>No control group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>exercise per week</td>
<td>liver fat</td>
<td></td>
</tr>
<tr>
<td>Jin et al.</td>
<td>120 potential liver donors with fatty livers</td>
<td>Hepatic biopsy, dietary restriction + 10 weeks of exercise (3 x 20 min sessions of jogging or walking per week)</td>
<td>Histological improvement in 103 of 120 subjects</td>
<td>Improvement of steatosis with weight reduction &gt;5% and cholesterol reduction &gt;10%, No control group</td>
</tr>
<tr>
<td>Johnson et al.</td>
<td>19 sedentary obese men and women</td>
<td>Proton magnetic resonance spectroscopy, 4 weeks of aerobic cycle ergometer exercise (30–45 min, 3 times/week) at intensity rising to 70% of peak oxygen intake</td>
<td>21% reduction of hepatic triglycerides</td>
<td>No control group</td>
</tr>
<tr>
<td>Kawaguchi et al.</td>
<td>35 adults with fatty liver resistant to lifestyle counselling (12 trained, 23 controls)</td>
<td>Ultrasound, hybrid training (voluntary and electrical contraction of quadriceps and hamstrings, 19 min 2 times/week for 12 weeks)</td>
<td>Liver fat decreased</td>
<td>Associated reduction of insulin resistance and small decrease of body mass, No control group</td>
</tr>
<tr>
<td>Koot et al.</td>
<td>144 obese children, mean age 14.1 years</td>
<td>Ultrasound, 6 month programme, with 3 x 1 hour sessions of unspecified exercise/week plus changes in eating behaviour</td>
<td>Prevalence of fatty liver decreased from 31 to 12%</td>
<td>Changes related to decreased insulin resistance and 12% decrease of body mass, No control group</td>
</tr>
<tr>
<td>Author</td>
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</tr>
<tr>
<td>Larson-Meyer et al. [208]</td>
<td>46 overweight men and women</td>
<td>Proton magnetic resonance spectroscopy, CT scan, 6-month study: dietary restriction + exercise (structured to increase energy expenditure 12.5%) vs. dietary restriction vs. low-calorie diet vs. control</td>
<td>Liver fat reduced in all 3 experimental groups</td>
<td></td>
</tr>
<tr>
<td>Lazo et al. [209]</td>
<td>96 men and women with diabetes mellitus, aged 45–76 years, divided between lifestyle and education/support group</td>
<td>Proton magnetic resonance spectroscopy, weekly meetings to encourage dieting and progression to 175 min of moderate exercise per week for 1 year</td>
<td>Decrease in fatty liver 50.8% (intervention) vs. 22.8% (controls)</td>
<td></td>
</tr>
<tr>
<td>Lee et al. [210]</td>
<td>48 obese adolescent boys divided into 3 groups</td>
<td>Proton magnetic resonance spectroscopy, 3 month trial, 3 sessions/week 60 min aerobic exercise (50% rising to 60–75% of maximal oxygen intake) or resistance exercise (60% of initial 1RM) or controls</td>
<td>Both types of exercise reduced hepatic lipids</td>
<td>Subjects instructed to follow weight maintenance diet; only resistance exercise increased insulin sensitivity</td>
</tr>
<tr>
<td>Nobili et al. [211]</td>
<td>37 boys, 16 girls, aged 5.7–18.8 years (plus 33 drop-outs)</td>
<td>Liver biopsy, diet plus physical activity for 24 months</td>
<td>Improvements of liver histology</td>
<td>No non-exercise control group</td>
</tr>
<tr>
<td>Oza et al. [212]</td>
<td>67 cases of fatty liver, only 22 completed treatment</td>
<td>CT scan, 6 month home-based diet + exercise (target of 23 MET-h/week physical activity + 4 MET-h/week of exercise</td>
<td>19/22 showed decreases of visceral fat</td>
<td>Poor compliance, no control group</td>
</tr>
<tr>
<td>Author</td>
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<td>Methodology</td>
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<tr>
<td>Promrat et al. [213]</td>
<td>Overweight or obese subjects randomized to lifestyle (20) or education (10) groups</td>
<td>Liver biopsy, 48-week intervention; weekly, then biweekly counselling aiming for 7–10% weight loss, exercise and altered behaviour</td>
<td>Histology improvement &gt;3 points in 14/20 of intervention vs. 3/10 of control subjects</td>
<td>Improvements in hepatic condition associated with weight loss</td>
</tr>
<tr>
<td>Santomauro et al. [214]</td>
<td>36 obese children with fatty livers</td>
<td>Ultrasound, 1 year lifestyle approach, focusing on dieting and increased physical activity</td>
<td>Reduction or disappearance of fatty liver linked to increased physical activity and associated weight loss in 12 of 36 children</td>
<td>Weight loss main variable accounting for reduction of liver fat. No control group</td>
</tr>
<tr>
<td>Schäfer et al. [215]</td>
<td>48 with impaired glucose tolerance, 133 normal subjects</td>
<td>Proton magnetic resonance spectroscopy, 24-month diet + exercise at anaerobic threshold (Polar heart rate monitor)</td>
<td>Liver fat decreased 28%, visceral fat 8% in those with impaired glucose tolerance</td>
<td>Body mass decreased 3% in both groups. No non-exercise control group</td>
</tr>
<tr>
<td>Shah et al. [216]</td>
<td>18 obese subjects &gt;65 years</td>
<td>Proton magnetic resonance spectroscopy, diet vs. diet + exercise (thrice weekly 90-min sessions of aerobic, resistance, flexibility and resistance training, with diet adjusted to achieve a similar energy deficit)</td>
<td>Both treatments reduced liver fat and insulin resistance to similar extent, but added exercise improved physical function</td>
<td>Body mass decreased 9–10% in both groups. No non-exercise control</td>
</tr>
<tr>
<td>Shojaee-Moradie et al. [217]</td>
<td>17 initially sedentary men (7 of 17 served as controls)</td>
<td>Proton magnetic resonance spectroscopy, exercised for 6 weeks. 60–85% of maximal aerobic power for 20 min, 3 times/week</td>
<td>No change of liver fat content, but decrease in hepatic insulin resistance</td>
<td>No control group</td>
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<tr>
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<tr>
<td>Slentz et al.</td>
<td>155 overweight adults aged 18–70</td>
<td>Computed tomography, 8 month training 3 days/week: aerobic (running 19 km/week at 75% aerobic power) vs. resistance vs. combined aerobic + resistance training</td>
<td>Aerobic training decreased hepatic fat 5.6%. No benefit from resistance training alone, combined therapy similar to aerobic training alone</td>
<td>No non-exercise controls</td>
</tr>
<tr>
<td>Sullivan et al.</td>
<td>18 obese adults with fatty livers, average age 48 years</td>
<td>Proton magnetic resonance spectroscopy, 16-week exercise (45–55% peak oxygen intake, 30–60 min/day, 5 times/m week, n = 12) vs. control (n = 6)</td>
<td>Exercise reduced liver fat 10%, but no change in body mass or % body fat</td>
<td>No change in hepatic VLD secretion or VDL apoB-100 secretion</td>
</tr>
<tr>
<td>Tamura et al.</td>
<td>14 patients with</td>
<td>Proton magnetic resonance spectroscopy, 2 week comparison, diet or diet + exercise (walking 60–90 min/day for an increase in energy expenditure of about 0.7 MJ/day)</td>
<td>Hepatic lipids decreased in both groups, but no added effect of exercise</td>
<td>Diet + exercise group younger than diet alone group</td>
</tr>
<tr>
<td>Thamer et al.</td>
<td>48 M, 64 F, average age 46 years</td>
<td>Proton magnetic resonance spectroscopy, diet + 3 h/week aerobic exercise monitored by Polar pulse-counter, average follow-up of 264 days</td>
<td>33% decrease of liver fat, despite little change in overall body fat</td>
<td>Decrease of liver fat associated with improved insulin sensitivity. No control group</td>
</tr>
<tr>
<td>Thomas et al.</td>
<td>10 obese adults, age not stated</td>
<td>Proton magnetic resonance spectroscopy, diet + pedometer monitored recommendation of 10,000 steps/day</td>
<td>40% decrease of liver fat</td>
<td>Changes associated with body fat. No control group</td>
</tr>
<tr>
<td>Ueno et al.</td>
<td>25 obese (10 served as controls)</td>
<td>Liver biopsy, restricted diet and walking or jogging for 3 months</td>
<td>Reduction of liver fat</td>
<td>No control group</td>
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exercise sessions may contribute to some of the observed improvements in lipid and lipoprotein concentrations that have been attributed to training. Cross-sectional research shows that high density lipoprotein cholesterol (HDL-C) levels are higher in regular exercisers than in their inactive counterparts, and circulating concentrations of HDL-C increase with exercise training. Similarly, exercise training can reduce circulating triglycerides and the secretion of hepatic VLDL triglycerides. These benefits are associated with a decreased activity of hepatic lipase and alterations in the levels of other hepatic enzymes that are involved in HDL-C remodelling (including cholesteryl ester transfer protein and lecithin cholesteryl acyl transferase). Inter-individual human differences in the response of hepatic lipase to training programmes have been traced to a polymorphism in the hepatic lipase gene LIPC –514C-T.

Rodent investigations have provided insights into the molecular changes underlying training-induced changes in lipid and lipoprotein metabolism. Training reduces the hepatic levels of two enzymes central to the synthesis of fatty acids: acetyl-coenzyme A carboxylase and fatty acid synthase and alters the levels of other hepatic enzymes that are involved in HDL-C remodelling (including cholesteryl ester transfer protein and lecithin cholesteryl acyl transferase). Inter-individual human differences in the response of hepatic lipase to training programmes have been traced to a polymorphism in the hepatic lipase gene LIPC –514C-T.

Table 1.5 continued

| Author                      | Sample                        | Methodology                                           | Results                                                        | Comments                          |
|-----------------------------|-------------------------------|-------------------------------------------------------|                                                               |                                   |
| van der Heijden et al.[225] | 15 obese and 14 lean adolescents | Proton magnetic resonance spectroscopy, 12 week aerobic programme (30 min sessions, 2 or 4 times/week at 70% of maximal oxygen intake) | Hepatic fat reduced in obese but not in lean subjects          | No control group. Exercise increased hepatic and peripheral insulin sensitivity |
|                             | Obese adolescents (6 M, 6 F)  | Proton magnetic resonance spectroscopy, 12 week resistance exercise (twice/week, all major muscle groups) | Hepatic fat content unchanged, but insulin sensitivity increased 24% | No control group. Body mass increased 2.6 kg |

Notes: BMI = body mass index; CT = computed tomography
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<tr>
<td>Botezelli et al.</td>
<td>Male Wistar rats initially aged 28 weeks fed on 60% fructose diet</td>
<td>Swimming 1 h/day at anaerobic threshold, starting at 28 or 90 days</td>
<td>Liver lipids reduced by either early or late onset training</td>
<td>Swimming improved insulin sensitivity. No control group</td>
</tr>
<tr>
<td>Cameron et al.</td>
<td>Male Wistar rats fed high-fat/high carbohydrate diet or corn starch</td>
<td>8 weeks of treadmill running, 20 min/day increasing to 30 min/day, 5 days/week; 1 km/h, 0% incline</td>
<td>Liver mass and hepatic fat decreased in experimental group</td>
<td>Exercise decreased body fat, abdominal fat and blood glucose, improved blood lipid profile</td>
</tr>
<tr>
<td>Charbonneau et al.</td>
<td>Female Sprague–Dawley rats initially 10 weeks old, fed high-fat diet</td>
<td>Treadmill exercise progressing to 60 min/day at 26 m/min, 10% slope</td>
<td>28% gain of hepatic fat with high-fat diet was completely reversed by exercise</td>
<td>Glucagon resistance of obese rats also prevented by exercise</td>
</tr>
<tr>
<td>Cintra et al.</td>
<td>Obese mice fed high-fat diet</td>
<td>8 weeks of running (50 min/day 5 days/week at 1 km/h)</td>
<td>1.7-fold reduction of liver fat</td>
<td>Associated reduction of regulatory element-binding protein-1c</td>
</tr>
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<td>Colombo et al.</td>
<td>Male diabetic fatty Zucker rats</td>
<td>5 weeks of treadmill running (1 h/day, 6 days/week, 20 m/min)</td>
<td>Liver fat decreased</td>
<td>Modification of many hepatic genes associated with lipogenesis and detoxification</td>
</tr>
<tr>
<td>Corriveau et al.</td>
<td>Three groups of ovariectomized vs. one group of sham-operated rats</td>
<td>25% dietary restriction vs. dietary restriction + resistance exercise (weighted stair climbing 5 times/week)</td>
<td>Liver lipid accumulation not stopped by dietary restriction, but reversed by resistance exercise</td>
<td>Abdominal fat also reduced by resistance exercise</td>
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<td>Gauthier et al.</td>
<td>Female Sprague–Dawley rats initially 6 weeks old, fed high-fat diet</td>
<td>Treadmill exercise progressing to 60 min/day at 26 m/min, 10% slope</td>
<td>Liver triglyceride content substantially reduced by concomitant exercise relative to sedentary controls</td>
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<tr>
<td>Gauthier et al., [232]</td>
<td>Female Sprague-Dawley rats initially 6 weeks old fed high-fat diet</td>
<td>Treadmill exercise progressing to 60 min/day at 26 m/min, 10% slope introduced from 8th to 16th week of high-fat diet</td>
<td>Exercise decreased visceral fat 30%</td>
<td>Leptin concentrations also reduced by exercise</td>
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<td>Yasari et al. [233]</td>
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<tr>
<td>Hao et al. [234]</td>
<td>12 week ovariectomized female rats</td>
<td>Treadmill running (10–18 min/day at 0% grade for 15–60 days)</td>
<td>Exercise reduced hepatic fat relative to controls</td>
<td>Associated increase in HDL/total cholesterol ratio</td>
</tr>
<tr>
<td>Leite et al. [235]</td>
<td>Adult female Wistar rats, half of sample ovariectomized</td>
<td>Sedentary vs. resistance training (weighted ladder climbing), 4–9 climbs every 3 days</td>
<td>Exercise reduced liver fat content, less in ovariectomized than in intact animals</td>
<td>Other fat depots also reduced</td>
</tr>
<tr>
<td>Marques et al. [236]</td>
<td>C57/BL6 mice fed standard chow or very high-fat diet</td>
<td>Sedentary vs. 8 weeks treadmill running (60 min/day, 5 days/week at 1 km/h)</td>
<td>Hepatic fat content reduced by exercise</td>
<td>Exercise also reduced insulin resistance, cholesterol and triglycerides</td>
</tr>
<tr>
<td>Moura et al. [237]</td>
<td>60 day alloxan-treated diabetic Wistar rats</td>
<td>Swimming 1 h/day, 5 days/week for 44 days with load 3.5% body mass (below anaerobic threshold)</td>
<td>Hepatic fat content lower in swimmers than in sedentary peers</td>
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<tr>
<td>Pighon et al. [238, 239]</td>
<td>Ovariectomized rats following 8 weeks of food restriction +</td>
<td>Normal feeding vs. food restriction vs. resistance training (weighted ladder climbing)</td>
<td>Resistance exercise and dieting both avoid regain of liver fat</td>
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<tr>
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<tr>
<td>Rector et al.</td>
<td>Hyperphagic, Otsuka Long-Evans</td>
<td>36-week voluntary</td>
<td>Exercise prevented hepatic fat accumulation (also prevented by dietary restriction)</td>
<td>Exercise group showed greater benefits, including increased hepatic mitochondrial fatty acid oxidation, enhanced oxidative enzyme function and protein content, and suppression of hepatic lipogenic proteins</td>
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<td>Tokushima Fatty rats initially aged 4 wks</td>
<td>wheel running vs. sedentary controls</td>
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<tr>
<td>Schultz et al.</td>
<td>Male C57BL/6 mice fed high-fat diet</td>
<td>Unweighted swimming progressing to 60 min/day</td>
<td>15% reduction of fatty liver relative to high-fat controls</td>
<td></td>
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<tr>
<td>Sene-Fiorese et al.</td>
<td>Male Wistar rats aged 90–120 days fed high-fat diet</td>
<td>min/day 90 swimming vs. 330 min/day swimming sessions</td>
<td>Intermittent exercise more effective than continuous in preventing hepatic fat accumulation</td>
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<tr>
<td>Takeshita et al.</td>
<td>Mice initially aged 6 weeks</td>
<td>Access to running wheel (covering 4.9 km/day) vs. sedentary control</td>
<td>Exercisers had lower liver weights and liver triglyceride content</td>
<td>Exercisers had lower plasma leptin and insulin-like growth factor-1 levels</td>
</tr>
<tr>
<td>Thylfault et al.</td>
<td>Rats selected for high (1,514 m) and low (200 m) running capacity</td>
<td></td>
<td>Less fit rats had reduced mitochondrial content, reduced oxidative capacity, increased peroxisomal activity, and fatty liver</td>
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<tr>
<td>Yasari et al.</td>
<td>Female rats given high-fat diet from 6th to 8th week</td>
<td>Treadmill running progressing to 60 min/day at 26 m/min, 10% slope</td>
<td>Liver triglyceride content not affected by exercise</td>
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Rats have shown changes in the composition of hepatic phospholipids following eight weeks of wheel training. These changes likely have implications for the membrane properties of the hepatocytes, cell signalling and gene expression, although details of such changes remain to be explored. [263]

**Protein metabolism**

An expansion of plasma volume is a well-recognized adaptation to regular physical training, and is important to the increase in aerobic performance. Increased expression of the hepatic albumin gene mRNA augments hepatic albumin synthesis, and rodent studies indicate that this can occur within as little as 12 days of the initiation of training. [264] Endurance training also increases the production of heat shock proteins in both the liver and other tissues, [265, 266] and decreases the secretion of appetite stimulating orxigenic proteins. [267] An increased synthesis of IGF-1, stimulated by action of the pituitary growth hormone, is important to the muscle hypertrophy associated with training. [266]

**Triggers of hepatic responses to training**

Changes in the concentrations of several hormones (insulin, glucagon and oestrogen) and cytokines (IL-1-b, IL-6, IL-10 and IGF-1) and altered tissue sensitivity to these agents may all contribute to the changes of hepatic metabolism that are observed following a period of aerobic training.

In terms of carbohydrate homeostasis, an increased hepatic sensitivity to insulin has been observed in some animal studies. Regular exercise training reduces the hepatic mRNA level and protein content of hepatic PEPCK, thus contributing to enhanced insulin sensitivity. [269] Human studies have usually shown an enhanced hepatic insulin sensitivity following training, although this has not always been the response. [200] Gains of overall insulin sensitivity have been observed following the aerobic and resistance training of obese diabetic patients, [270] with 16 weeks of resistance training in adolescents, [271] with progressive resistance training of older men with type-2 diabetes mellitus, [272] with resistance training of obese adolescents [273] and with high-intensity interval training of obese mice. [274]

An increased availability of glucagon seems important to the reduction of liver fat content. The hepatic glucagon receptor density and glucocorticoid receptor count are increased in exercise-trained rats, [273] and exercise does not reduce liver fat in animals that lack glucagon receptors. [276] Hepatic oestrogen receptors also influence fat accumulation; [277] ovariectomy predisposes female rats to the development of fatty livers, with an increase of inflammatory biomarkers such as inhibitor-κB kinase β and interleukin-6, an increased activity of hepatic lipogenic enzymes such as sterol regulatory element-binding protein-1c, acetyl-CoA carboxylase (ACC) and stearoyl CoA desaturase), and a decreased expression of enzymes related to fat oxidation such as carnitine palmitoyltransferase and hydroxyacyl-CoA-dehydrogenase. With the exception of increases in ACC, regular physical activity can reverse the adverse changes associated with
ovariectomy, at least in rats and mice. Carnitine, an important co-factor for the oxidation of both long-chained fatty acids and carbohydrate, may also be important to the hepatic response, with regular exercise attenuating the reduction of carnitine palmitoyltransferase I activity that is induced by a high-fat diet and up-regulating the genes involved in hepatic carnitine synthesis and uptake. Training also increases the gene expression of microsomal triglyceride transfer protein and diacylglycerol acyltransferase-2 in ovariectomized rats, further changes that lead to a reduction in hepatic triglyceride content.

In terms of hepatic protein synthesis, some investigators have observed greater serum levels of IGF following aerobic training. This could reflect either an increased hepatic production of IGF or an increased hydrolysis of the corresponding binding factor. Resistance training also causes an early and sustained release of IGF-1. However, such responses are not seen with a low fat diet; exercise training then increases serum concentrations of IGF-1 binding protein, thus decreasing circulating levels of free IGF-1, both in rats and in humans. Rodent studies have also suggested that regular aerobic exercise training may decrease levels of the inflammatory cytokines IL-6 and IL-1β and increase levels of the anti-inflammatory cytokine IL-10, with an associated decrease in hepatic apoptosis during an experimental episode of bacterial sepsis.

**Role of oxidant stress**

Most studies of mice, rats and dogs have shown moderate aerobic training as minimizing markers of oxidant stress, and concentrations of hepatic glutathione transferase S activity and reduced glutathione are increased, with enhanced gene expression of unfolded protein response markers. Further, the activities of hepatic antioxidant enzymes such as superoxide dismutase and the corresponding signalling molecules are increased. Nevertheless, a few investigators have found no change or even a decrease of anti-oxidant enzyme activity following heavy endurance training. One problem in such investigations is that (unlike early observations on isolated hepatocytes) there is sometimes little relationship between anti-oxidant enzyme levels as measured in the general circulation and local oxidant stress in the liver. In one study of rats, prolonged bouts of vigorous exercise (two hours of swimming/day for three months) led to a down-regulation of cytosolic aconitase, a key factor in cellular iron homeostasis, possibly due to an increased production of NO and oxidative stress. Another report described a decrease in the mRNA for one anti-oxidant enzyme (hepatic superoxide dismutase), although there was an increase of mRNA for another anti-oxidant enzyme, catalase.

**Physical activity and functional activity of the liver**

Ferreira found a decrease of apoptotic cells in mice livers following seven weeks of treadmill training. It is unclear from studies of serum enzyme levels and pharmacokinetics how far human liver function is enhanced by regular low to
moderate intensities of aerobic training. Nevertheless, the traditional clinical markers of impaired hepatic function (serum ALT and GGT levels) do show a negative correlation with habitual physical activity,[303–305] probably at least in part because a sedentary lifestyle predisposes to the development of a fatty liver.[306]

In terms of pharmacokinetics, some reports have shown little benefit from physical activity. Exercise training did not alter creatinine clearance in boxers,[307] nor did it change the elimination of propranolol in initially sedentary subjects.[308, 309] Likewise, cross-sectional comparisons showed no significant differences of aminopyrine metabolism, galactose elimination or indocyanine green clearance between endurance runners and relatively sedentary medical students.[310] Nevertheless, the majority of reports have suggested that hepatic function is enhanced by vigorous (but not exhausting) training.[107] Thus, the clearance of antipyrine (which depends almost exclusively on hepatic metabolism) was faster in athletes than in controls, with no difference between sprinters and endurance competitors.[311] Likewise, endurance runners had a faster clearance of antipyrine than sedentary but otherwise healthy men.[312]

Longitudinal evidence supports these cross-sectional inferences. Three months of exercise training increased the clearance of antipyrine and aminopyrine in previously sedentary students. Moreover, individual improvements in these indices correlated highly with gains in VO$_{2 max}$.[313] Three months of moderate intensity exercise (a thrice weekly mixture of aerobic and strength training) also increased antipyrine clearance in elderly women.[314]

Animal experiments generally confirm that regular moderate physical activity has beneficial effects upon hepatic function. Five weeks of training increased antipyrine clearance in mares,[315] and the livers of regularly exercised rats had a greater ability to metabolize and excrete certain chemicals not normally found in the body, such as naphthol and styrene products[247] and halothane.[316] In the study of halothane toxicity, hepatic glutathione levels were unchanged by ten weeks of treadmill exercise, and it remained unclear whether the more rapid clearance of halothane was due to enhanced anti-oxidant defence mechanisms or the associated decrease in hepatic fat.[316]

One factor that increases the liver’s ability to eliminate some substances after training is an increased secretion of biliary transporters. Chronic exercise such as swimming or running augments the hepatic production of bile acids[317] and increases the availability of bile acid transporters.[318] These changes accelerate the biliary clearance (but not necessarily the blood stream clearance) of substances such as indocyanine green,[318] acetaminophen and antipyrine.[317]

Areas for further research

There remain several competing hypotheses as to what triggers the hepatic responses to an acute bout of exercise, and further research elucidating the underlying mechanisms might enable investigators to design exercise programmes that would enhance adaptations favourable to performance and hepatic health.
The magnitude of the decrease in hepatic blood flow during a bout of prolonged and vigorous exercise remains contentious, with the indocyanine technique suggesting large and potentially harmful reductions, and other techniques apparently showing much smaller changes (although as yet only evaluated over shorter periods of exercise). There is a need to repeat radionucleide studies following periods of vigorous exercise that are as long as those used in the indocyanine research. Confirmation is also required of the single study suggesting that hepatic enzyme release is increased by prolonged exercise. If this is indeed the case, the duration of the enzyme leakage needs to be determined. Information to date suggests that liver function is normalized within a few days of ceasing a demanding bout of endurance exercise, but if such changes prove to be long lasting or permanent, sports physicians may need to reconsider the wisdom of participation in ultra-endurance athletic events.

Evidence that regular physical activity reduces hepatic fat seems convincing, underlining the role of physical activity in countering fatty liver. However, there remains scope for further studies where the reduction in hepatic fat content is related to objective rather than subjective measures of habitual physical activity, providing clearer evidence on optimal patterns of physical activity. Further, it remains important to resolve the question as to how far regular physical activity enhances overall hepatic function.

**Practical implications and conclusions**

The liver plays a vital role in maintaining the constancy of the internal environment, with particular reference to blood glucose and pH. During an acute bout of physical activity, there is a release of glucose from the liver, initially by the breakdown of local glycogen reserves and (as these reserves are depleted) by the synthesis of glucose from lactate, glycerol and amino acids. These responses help to maintain a stable blood glucose in prolonged athletic endeavours. Triggers to hepatic adjustments include changes in the levels of hormones (particularly insulin, glucagon and adrenaline), altered afferent nerve input associated with some correlate of glycogen depletion, a response to the muscular release of IL-6, or an accumulation of reactive oxygen species. Under resting conditions, the liver is a major site for fatty acid uptake. Much of the fat is repackaged and secreted as VLDLs. However, during a prolonged bout of physical activity, possibly as a consequence of reduced hepatic blood flow and/or increased fatty acid uptake by muscle, the liver adopts a more ‘passive’ role, with no measurable change in its fat content. Albumin and IGF-1 levels are increased after an acute bout of exercise; they likely have growth-promoting effects on the active muscles and contribute to maintenance of a stable blood glucose. Prolonged or exhausting physical activity causes a dramatic decrease in blood flow to the liver. There may then be a short-term inflammation, with a reduced clearance of drugs, oxidant stress, increased concentrations of heat shock proteins and a release of hepatic enzymes. However, such disturbances usually resolve spontaneously within a few days.
After training, glycogenolysis and gluconeogenesis are reduced at a given absolute work-rate, but liver glycogen storage and the hepatic capacity for glucose output are increased, thus enhancing performance potential. Training also appears to reduce the overall liver mass, with a reduction in its fat content and an increase of HDL-C levels. Hepatic concentrations of albumin and heat shock proteins increase, and levels of appetite-stimulating proteins decrease. Triggers for these changes likely include altered secretion of hormones (insulin, glucagon and estrogen) and a number of cytokines. Most cross-sectional and longitudinal research studies also suggest an improvement of hepatic function with training, as shown by a decreased fat content, reduced markers of oxidant stress and increased concentrations of anti-oxidant enzymes.

References
40 Responses of liver to physical activity


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2 Physical activity and hepatic pathologies

Introduction

The effects of physical activity upon the metabolism of the health liver were examined in Chapter 1. We here examine interactions between physical activity and some clinically important chronic hepatic disorders, including the metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), various types of hepatic inflammation and resulting fibrosis, cirrhosis and hepatic carcinoma, as well as issues of liver transplantation. We look specifically at the role of inadequate habitual physical activity in the genesis and progression of these various syndromes, and will consider appropriate exercise recommendations for the prevention and treatment of such disorders.

Physical activity and the metabolic syndrome

The metabolic syndrome is a relatively new diagnosis. It is now perhaps the commonest of the clinical disorders associated with hepatic dysfunction, and it has played a prominent role in stimulating the development of exercise-related wellness programmes. But as long as 250 years ago, the Italian physician and anatomist Giovanni Battista Morgagni (1682–1771) identified an association between visceral obesity, a high blood pressure, atherosclerosis, high levels of uric acid in the blood and frequent episodes of obstructed breathing during sleep. The distinct characteristics of male-type (android) obesity were described by the French physician Jean Vague, and he noted its association with various metabolic disorders, including diabetes mellitus and a premature onset of atherosclerosis. Another historical landmark was Reaven’s 1988 Banting lecture, where he coined the term “Syndrome X” for a clustering of glucose intolerance, hypertension, low concentrations of high density lipoprotein (HDL) cholesterol, raised serum triglycerides and hyperinsulinaemia. The term “Syndrome X” did not gain wide acceptance, but the idea of this particular clustering of risk factors persisted and soon became identified as the metabolic syndrome.

The metabolic syndrome is now found widely in most developed societies, with a prevalence ranging from 16–33%. It has been associated with an “obesity epidemic” that probably reflects, among other possible causes, a progressive...
reduction of habitual physical activity and an increased consumption of refined carbohydrates. There is a strong association between the metabolic syndrome and non-alcoholic fatty liver disease, although it is less clear which of these conditions is cause and which is effect.

**Diagnostic criteria for the metabolic syndrome**

The World Health Organization has defined the metabolic syndrome by the presence of insulin resistance (type 2 diabetes, impaired fasting glucose, impaired glucose tolerance or impaired glucose uptake when insulin levels are increased), plus two of four other factors: a blood pressure >140/90 mm Hg (or use of hypotensive medication), triglycerides >150 mg/dL, HDL cholesterol <35 mg/dl (men) or 39 mg/dL (women) and obesity (a body mass index >30 kg/m2 or a waist/hip circumference ratio >0.9 [men] or >0.85 [women]), with traces of protein in the urine.

A joint committee of the US National Heart, Lung and Blood Institute and the American Heart Association advanced slightly different criteria: abdominal obesity, atherogenic dyslipidaemia (raised triglycerides and reduced HDL cholesterol), a raised resting blood pressure, insulin resistance, a pro-inflammatory state and a prothrombotic state. Specific criteria included a waist circumference >1.02 m (men) or 0.88 m (women), triglycerides >150 mg/dL, HDL cholesterol <40 mg/dL (men) or <50 mg/dL (women), a blood pressure >130/85 mm Hg and a fasting blood glucose >110 mg/dL.

Another set of identifiers adopted in our study of a Japanese population was the presence of three or more of the following: (1) a body mass index >25 kg/m2, (2) fasting triglycerides >150 mg/dL, (3) a fasting serum HDL cholesterol <40 mg/dL (men) or 50 mg/dL (women), (4) a blood pressure >130/85 mmHg, and (5) a fasting plasma glucose >110 mg/dL) and/or a haemoglobin A1c >5.5%.

**Role of physical activity in prevention and treatment**

Many of the characteristics of the metabolic syndrome reflect a malfunction of the liver, and most can be reversed by regular physical activity. A number of investigations based upon physical activity questionnaires have demonstrated associations between development of the metabolic syndrome, a low level of habitual physical activity and a high proportion of sedentary time. Thus, a study of 1144 elderly people in Northern Italy found a highly significant inverse relationship of reported leisure activity with triglycerides, waist circumference and insulin resistance. Likewise, a four-year follow-up of 612 Finnish middle-aged men found 107 developing the metabolic syndrome; this risk was halved in those who took >3 hours/week of moderate leisure-time physical activity, and men in the upper third of the maximal oxygen intake distribution were 75% less likely to be affected by the metabolic syndrome than those who were sedentary. An analysis of data for 1626 adults from the NHANES survey of 1999–2000 found that those who engaged in >150 minutes/week of
moderate or vigorous physical activity had approximately half the risk of the metabolic syndrome relative to those who were sedentary (odds ratio 1.90 [1.22-2.97]), although data adjustments for age, sex, ethnicity, smoking and alcohol use attenuated the odds ratio to 1.46.[13] Frequent use of a computer or TV watching was also associated with an increased prevalence of the condition; risk ratios were for 1 hour, 1.41; 2 hours, 1.37; 3 hours, 1.70 and >4 hours, 2.10.[13] Likewise, in Europe, a study of 992 adults found that the risk of the metabolic syndrome was positively associated with the number of hours per day spent watching television or working at a computer screen.[14]

The Nakanojo study provided objective evidence of the inverse association between habitual physical activity (as measured by a pedometer/accelerometer over an entire year) and incidence of the metabolic syndrome in a sample of 220 Japanese aged 65–84 years.[10] The risk was 4.3 times greater in the least active quartile of this population (those taking <4700 steps/day and spending <9 min/d at an exercise intensity >3 METs) than in the most active quartile (those taking >8500 steps/day and spending >24 min/d at an intensity >3 METs).

Bankoski and associates[15] focused specifically on sedentary time, as monitored by an accelerometer. Their subjects were 1367 adults aged >60 years, participants in the 2003–2006 NHANES survey, and they noted small differences pointing to an association between sedentary time and the risk of developing the metabolic syndrome. In affected individuals, the sedentary portion of the day was greater (67.3 vs. 62.2%), sedentary bouts were longer in duration (17.7 vs. 16.7 minutes) and accelerometer counts were lower during sedentary periods (14.8 vs. 15.8 counts/minute); further, these differences in risk persisted after adjusting statistically for differences in physical activity levels, showing that sedentary time was an independent risk factor. Healy et al.[16, 17] also used accelerometers to categorize sedentary time in 169 Australians. They found that independently of moderate to vigorous physical activity, there were significant associations of sedentary time, light-intensity time and mean activity intensity with waist circumference and clustered metabolic risk. Moreover, breaks in sedentary time were associated with reductions in waist circumference and triglyceride levels and enhanced glucose tolerance, independently of total sedentary time and moderate to vigorous physical activity.[16]

There remains a need for additional longitudinal studies, but whether based on subjective or objective measures of physical activity patterns, cross-sectional investigations provide convincing evidence of an association between both an active lifestyle and a minimization of sedentary time and a reduced risk of the metabolic syndrome.

### Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) was first described in 1980.[18] It is characterized by the accumulation of fat in hepatocytes, much as seen with an excessive alcohol consumption, and it is often discovered accidentally as a rise in the serum enzymes that are used as markers of hepatic dysfunction. The healthy
liver contains some fat (triglycerides that are stored in the hepatocytes), but NAFLD is commonly diagnosed when fat stores exceed 5% of hepatic mass. NAFLD accounts for the majority of liver disease worldwide. It affects 25 to 45% of adults\cite{18–21} including most individuals who are obese.\cite{22} Moreover, its prevalence appears to be increasing.\cite{23} NAFLD even affects 2.6 to 9.6% of children, depending upon age, sex, ethnic group and habitual activity.\cite{24, 25}

**Diagnosis and patho-physiology of NAFLD**

Liver biopsy and histological assessment provide gold standards for the diagnosis of NAFLD, but in human research the liver fat content is more commonly inferred from proton magnetic resonance spectroscopy or computed tomography. In animals, the usual approach has been chemical or histological analysis of hepatic tissue at sacrifice.

Hepatic fat accumulation is an important form of liver dysfunction, and is commonly associated with obesity, cardiovascular disease and diabetes mellitus. The build-up of triglycerides could reflect an increased delivery of fatty acids to the liver, either from adipose tissue or directly from the diet, increased *de novo* hepatic lipogenesis, decreased hepatic fatty acid oxidation or a decreased exit of fatty acids from the liver in the form of VLDL triglycerides (Chapter 1). The first of these mechanisms is probably the most important.\cite{26} Studies using radioactive markers found that 59% of the fat was derived from non-esterified fatty acids, 26% from *de novo* lipogenesis and 15% from the diet.\cite{27} The increase in hepatic fat impairs insulin sensitivity by suppressing the activity of phosphatidylinositol-3-kinase, a key enzyme mediating the action of insulin on the liver.\cite{26} Adipose tissue also manifests insulin resistance in NAFLD.\cite{28} Any given secretion of insulin becomes less effective in increasing muscle glucose uptake and in suppressing the release of fatty acids from fat.\cite{29}

NAFLD can progress from a simple accumulation of fat in the hepatocytes (the condition of steatosis) through inflammation of the liver tissue (steato-hepatitis) to fibrosis, cirrhosis, liver failure and even hepatic carcinoma.\cite{30} It is not entirely clear why the condition remains a simple steatosis in some individuals but progresses to more serious complications in others. Inter-individual differences in reactions to reactive oxygen species, cytotoxic dicarboxylic acids, and hormonal balance as well as mitochondrial abnormalities may be involved.\cite{30} Progression to steatohepatitis probably reflects the combined effects of hepatic fat accumulation and oxidant stress, possibly supplemented by a fatty acid mediated apoptosis of liver cells,\cite{31} and gut barrier dysfunction with entry of endotoxins into the hepatic circulation.\cite{32} However, anti-oxidant therapy is not necessarily helpful in preventing disease progression. In one study of children, Nobili et al.\cite{33} found that provision of anti-oxidants such as alpha-tocopherol and ascorbic acid did not enhance the benefits gained from treatment with a simple combination of exercise and weight loss.

NAFLD is commonly associated with other markers of inadequate physical activity, including cardiovascular disease, metabolic syndrome and type 2
diabetes mellitus. Although body fatness is a prime determinant of whole-body insulin sensitivity, the main factor influencing hepatic insulin sensitivity seems to be the individual’s active energy expenditure.[34] A follow-up of 6003 patients with NAFLD found that 411 developed type 2 diabetes over 4.9 years. Less than 60 minutes of exercise per week and a gamma glutamyl transferase (GGT) level >109 IU/L were significant predictors of a risk of developing diabetes; for both indicators, hazard ratios averaged 1.60.[35] GGT facilitates the intracellular transport of glutathione; increases in GGT levels are thus a possible indicator of attempts to counter the oxidant stress which can predispose to diabetes.[36]

Low levels of habitual physical activity predispose to obesity, dyslipidaemia, impaired glucose tolerance and high blood pressure, and physical activity is effective in the clinical management of these problems. However, a reduction in liver fat content is also an important component of both prevention and treatment. A decrease of hepatic fat content can avert type 2 diabetes mellitus, particularly in older individuals.[37, 38] Similarly, a normalizing of liver fat content improves the insulin-induced suppression of hepatic glucose output and restores normal fasting blood glucose concentration in patients with type 2 diabetes.[39]

**Habitual physical activity, attained fitness and liver fat content**

Many reviews have pointed to the possible role of physical activity in the prevention and management of NAFLD (Table 2.1). There is general agreement on the benefits obtained from a combination of regular exercise and dieting. Some authors have suggested that these two treatment options act independently of each other, but others have found the benefits of exercise are linked rather closely to resulting reductions in body mass. The optimal intensity, duration and frequency of exercise sessions remain unclear, and in many studies poor compliance with exercise and/or dietary regimens has been a major problem with both therapy and data analysis. Some reviewers have pointed to adjuvant benefits from certain drugs and behavioural counselling, but others maintain that no drugs are useful in treating NAFLD. Despite these various uncertainties, there is good evidence, drawn from cross-sectional and longitudinal human studies as well as animal research, that regular physical activity can reduce the accumulation of fat in the liver (see also Chapter 1), and some (but not all) studies of physical activity programmes have demonstrated a reversal of the increased levels of enzymes such as alanine transaminase that were signalling hepatic dysfunction.

**Cross-sectional studies in humans**

Many cross-sectional investigations have shown associations between low levels of habitual physical activity and/or aerobic fitness and the prevalence of excessive amounts of fat in the liver (Table 1.3), usually with evidence of liver dysfunction in the form of increased hepatic enzyme levels. Most authors have used questionnaires to assess habitual physical activity, but three studies used objective activity monitors,[64–66] and one report classified subjects based upon
Table 2.1 Conclusions of published reviews concerning the role of physical activity in the prevention and treatment of NAFLD

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their obesity. The sample size of study populations has ranged from small groups to >30,000 people, and one analysis was based upon twins with dissimilar activity patterns, allowing an examination of possible genetic contributions to the disorder. In one instance, the data obtained by objective monitoring suggested

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an effect of physical activity, but (probably because of a lesser reliability and validity of the test instruments) classifications of the same individuals based upon subjective questionnaires did not.\cite{64} Collectively, cross-sectional studies have shown that habitual physical activity is an important correlate of hepatic fat content, with a possible dose-response relationship.\cite{69} However, two reports found no relationship between the severity of histological abnormalities in the liver and the volume of habitual physical activity.\cite{70, 71} Other analyses (including the twin study of Leskinen et al.\cite{68}) related hepatic fat accumulation to aerobic fitness (Table 1.4). With two exceptions,\cite{72, 73} hepatic fat levels were inversely associated with aerobic fitness, although in some studies the association was relatively weak\cite{74, 75} particularly when data were co-varied for inter-individual differences in obesity.

**Longitudinal studies in humans**

Longitudinal trials in humans have usually had only a small sample size (Table 1.5), with “usual treatment” or a dietary regimen serving as the control treatment. Interventions have ranged widely from general lifestyle recommendations to closely supervised interventions with careful control of both exercise and diet. Typically, liver fat content has decreased, often with increases in insulin sensitivity, as activity levels have been augmented. One report noted an associated improvement of histopathology in response to an exercise and weight loss programme,\cite{76} but there is as yet little evidence to support the idea that increased exercise can reverse cell damage. Beneficial effects of exercise upon serum aminotransferase levels have also been unclear, possibly because in some studies levels of this enzyme were close to normal prior to the initiation of treatment.\cite{41, 77}

Most studies have pointed to a maximization of reductions in hepatic fat content and a possible normalization of serum amino-transferases from programmes that induced a significant weight loss through a combination of physical activity and dieting, but the respective contributions of regular physical activity, dietary change and weight loss to improvements in hepatic function remain to be clarified.\cite{77} Exercise has traditionally been employed with the goal of facilitating weight loss, but some investigators have found benefits from exercise in the absence of either dieting\cite{78} or any change in body mass.\cite{79} Furthermore, in some reports benefits have persisted after statistical adjustment of data for changes in body mass,\cite{80} and at least one study found that dietary manipulation did not enhance the effects of exercise alone.\cite{81}

Nevertheless, much of the current evidence suggests that physical activity benefits the liver primarily by enhancing the effects of dieting;\cite{76} it may\cite{82} or may not\cite{37, 83} increase the insulin sensitization induced by dieting alone. A weight loss of 10% or more seems the most effective means to lower liver fat content and normalize amino-transferase levels; effects are smaller if the decrease in body mass is 5% or less.\cite{84} Several reports have suggested that although exercise brings other health benefits, including a sensitization to insulin, it does not enhance the hepatic response to dieting alone.\cite{37, 83, 85}
Although most investigators have looked at the benefits of aerobic training programmes, a few reports have examined hepatic responses to resistance training. Unfortunately, the findings have been inconsistent. A controlled three-month trial in obese adolescent boys reported that thrice weekly 60-min sessions of either aerobic or resistance exercise reduced liver fat, but only resistance exercise was effective in increasing insulin sensitivity.\[86\] Two of three comparisons between aerobic and resistance training\[47, 86\] found similar decreases of hepatic fat with both types of exercise. However, the third and largest study found no benefit from resistance training alone, and the response to aerobic training was not augmented by adding a resistance training component.\[87\] Another study of a resistance exercise found no reduction of inflammatory markers with this type of treatment,\[88\] and a 12-week trial of resistance exercise found a decrease of insulin resistance without a change of hepatic fat content.\[89\] Thus, although resistance exercise helps to correct the muscular weakness and autonomic dysfunction that is often associated with NAFLD,\[90\] it remains unclear whether it is effective in decreasing steatosis; for the present, it seems best to advocate aerobic exercise.

Longitudinal studies in animals

Animal studies of exercise and hepatic steatosis generally confirm the findings from human investigations (Table 1.6). The animal data provide growing empirical evidence that fat accumulation has adverse effects upon hepatic function, and that these changes can be reversed by a programme of sustained exercise. Further, the animal research adds helpful information on underlying cellular mechanisms.

In mice that were fed a high-fat diet, regular physical activity reduced hepatic fat accumulation, improved insulin resistance and reduced circulating levels of cholesterol, triglycerides, and aspartate transaminase and alanine transaminase.\[91\] Regimens based on dietary restriction, voluntary wheel running and imposed swimming or treadmill running have all seemed effective in preventing steatosis (Table 1.6), and in one report beneficial changes were elicited more readily by intermittent than by continuous bouts of swimming.\[92\] Yasari et al.\[93\] commented that after six weeks of detraining, rats that had run on a treadmill for four weeks had regained a similar body fat to their sedentary peers, but liver lipid infiltration had not yet increased. In contrast, Linden et al.\[94\] found that four weeks of inactivity following 16 weeks of wheel-running caused the development of hepatic steatosis in obese rats, although liver triglycerides were still 60% lower than in animals that had remained sedentary throughout.

Underlying mechanisms

Details of the mechanisms underlying the adverse effects of hepatic fat are discussed in a recent review.\[95\] Lipid accumulation appears to down-regulate phosphatidylinositol 3-kinase, a key enzyme mediating the action of insulin in hepatocytes.\[26\] Rats fed an obesity-inducing diet not only developed peripheral
insulin resistance, but also showed activation of the pro-inflammatory molecules c-jun N-terminal kinase (JNK) and nuclear factor kappa-B (NF-kB).

Cellular adaptations seen with enhanced physical activity have included increased hepatic mitochondrial fatty acid oxidation, enhanced oxidative enzyme function and protein content, and suppression of de novo hepatic lipogenesis.[96] Specific molecular mechanisms include increased hepatic mitochondrial activity and subsequent beta-oxidation of fats,[96] a decreased level of transcription factors regulating the genes involved in cholesterol and fatty acid synthesis,[97] down-regulation of a rate-limiting enzyme in the biosynthesis of monounsaturated fats[98] and a decrease of hepatic ketone synthesis.[99] Regular exercise also normalizes the catabolism of branched-chain amino acids[100] and attenuates the reduced levels of hepatic IGF-1 seen in alloxan-diabetic rats.[101]

Further, exercise training lessens endoplasmic reticular stress in the liver, as shown by decreased phosphorylation of the two major metabolic markers of this condition.[102] Moreover, the glucose stimulation of insulin secretion is decreased in rats with access to an exercise-wheel, without any deterioration in their capacity for glucose homeostasis.[103] Seven days of voluntary wheel running increased release of the hormone-like hepatic insulin sensitizing substance (HISS), thus decreasing insulin resistance.[104, 105] Finally, exercise partially reversed attenuated insulin and leptin signalling in rats with chlorpromazine-induced diabetes.[106]

One way in which aerobic exercise appears to exert a beneficial influence on hepatic function is by decreasing myostatin output.[107] This substance inhibits muscle growth, thus predisposing to obesity, hepatic insulin resistance and diabetes.[107] It may also have more direct effects upon hepatocytes.[108] Inactivation of the gene for myostatin binding increased myostatin levels, causing hepatic steatosis in mice in the absence of any change in muscle mass.[109] Moreover, injection of recombinant myostatin slowed overall growth, again without change of muscle mass.[107] Finally, normal liver function depends on an appropriate balance between cell proliferation and apoptosis; however, both mouse and human liver cell cultures have shown increased apoptosis when incubated with recombinant activin, which binds to the same receptors as myostatin.[100, 111]

Exercise training also has beneficial effects that arise outside the liver. Positive influences on insulin sensitivity include an increase in muscle mass, an alteration in muscle quality, an increase in the energy demands of skeletal muscle and a reduction of fat stores in other viscera.

Following a sudden one-week cessation of exercise, several metabolic precursors of steatosis were seen in obese rats, along with an increased appetite. Other changes included a decrease in hepatic mitochondrial oxidative capacity, an increased hepatic expression of lipogenic proteins and increased levels of hepatic malonyl CoA, a key factor in lipid synthesis.[112]

**Hepatic inflammation, fibrosis and cirrhosis**

Chronic liver inflammation, whether from NAFLD, alcohol abuse or viral infection, drives hepatic fibrosis, but the pathological process can be prevented,
stabilized or reversed by immuno-suppressive, anti-inflammatory, anti-oxidant and antiviral agents.\cite{113} Cirrhosis is a late stage in the process, where there is severe fibrotic scarring of the liver and a gross hepatic malfunction that leads to jaundice, fatigue, weakness, loss of appetite, itching and easy bruising.

Responses to exercise therapy seem relatively independent of the cause of liver inflammation. Positive influences include an increase in muscle mass, an alteration in muscle quality, an increase in the energy demands of skeletal muscle and a reduction of visceral fat stores (leading to a reduced incorporation of fatty acids into the liver). Exercise also seems to exert a direct beneficial influence on hepatic pathology beyond any reduction in liver fat content. As fibrosis develops, markers of hepatic apoptosis increase,\cite{114} but the prevalence of these changes is inversely associated with the individual’s level of habitual physical activity.\cite{115}

**Hepatitis**

About a tenth of those who have developed steatosis progress to the inflammatory stage of steato-hepatitis. Regular physical activity reduces the likelihood of developing a NAFLD hepatitis because it reduces the fat content of the liver (above). The shift from NAFLD fibrosis to cirrhosis is usually seen only in those individuals who are over the age of 50 years, and it is thought to reflect a progressive dysfunction of the hepatic mitochondria.\cite{116}

**Alcoholic hepatitis**

Alcoholic hepatitis is seen following an excessive intake of alcohol, usually repeated over the course of many years. In one biopsy survey, 20% of alcoholics showed hepatitis.\cite{117} As with NAFLD, alcoholic hepatitis is commonly marked by an accumulation of fat in the liver and increases of serum enzymes that indicate liver damage.\cite{118} The 28-day mortality of acute alcoholic hepatitis can be as high as 30–50\%.\cite{119} It has sometimes been hypothesized that regular physical activity can play a preventive role, reducing the risk to the liver from an excessive alcohol consumption, but this view is not supported by current research.\cite{120, 121} There seems to have been no systematic study of physical activity in the treatment of alcoholic hepatitis, once this is established.

**Steato-hepatitis**

Baba et al.\cite{122} had a group of 65 patients with steato-hepatitis participate in a moderate intensity exercise programme (30 minutes at 60–70\% of maximal heart rate five days/week) for three months. This regimen apparently contributed to a functional reversal of the pathology in the 44 individuals who complied with the prescribed exercise; serum amino-transferase levels were reduced in the compliant group, and there was complete normalization of hepatic enzyme levels in 20 of the 44 compliant individuals. Hickman et al.\cite{123, 124} also noted a 17\% improvement of aerobic fitness and decreased hepatic enzyme levels, but no
reversal of histological changes after six months of a progressive 15-item circuit training routine. In contrast, some studies in rats have suggested that endurance training can reverse structural damage in the liver, including mitochondrial abnormalities.[125] He et al.[126] fed rats a high-fat diet, and they noted less severe histological changes in animals that undertook vigorous swimming exercise relative to control animals.

**Viral hepatitis**

Viral hepatitis develops in about 15% of those infected with the hepatitis B virus, but is more commonly a consequence of hepatitis C infections. Prevalence of the disease is high among athletes, perhaps because of exposures through international travel and/or the sharing of water bottles. During the acute phase, there is commonly enlargement of the liver and spleen, with complaints of nausea, abdominal pain and fatigue. Some clinicians have recommended prohibiting sports participation until such findings are resolved.[127] However, there have been very few reported cases of exercise-induced hepatic rupture even during the acute phase of the disease, and such guidelines may be overly restrictive.[128]

Viral hepatitis is regarded as chronic if the disease has persisted for six months. At this stage, affected individuals are still less active than their peers.[129] Complaints of fatigue may persist, but those with mild disease tolerate exercise programmes quite well.[127, 130] Ritland et al.[131] examined nine patients with chronic active hepatitis who were receiving immuno-suppressive therapy, and they found that 12 weeks of interval training (30 minute sessions, three to four times per week, with the active component rising to 75% of maximal heart rate) yielded improvements of aerobic function (a 20% gain in Åstrand predictions of maximal oxygen intake), without any worsening of enzyme markers of liver dysfunction.

**Fibrosis**

Unfortunately, physical inactivity causes a worsening of NAFLD, and this can create a vicious cycle of fatigue that further discourages physical activity. A sedentary lifestyle is particularly likely in those who have become obese. An adequate intensity of physical activity is important in preventing disease progression. Neither the risk of steato-hepatitis nor the histological stage of fibrosis were associated with either the total volume of physical activity or the duration of moderate physical activity,[71] but in individuals who met the currently recommended weekly amount of vigorous physical activity, the odds of finding steato-hepatitis was 0.65, and in those who reported undertaking twice the recommended amount of vigorous physical activity, the odds were reduced to 0.53.[71] Others have noted little cellular repair response to modest doses of physical activity. Ueno et al.[132] found that a three-month programme of walking and jogging reduced liver fat content, but did not change the extent of hepatic fibrosis. Likewise, Krasnoff and associates[72] found no association between currently
reported physical activity and the histological severity of NAFLD, although a possible effect of exercise intensity was signalled by milder disease in those with a higher peak oxygen intake.

However, Oh et al.[133] examined the response to a 12-week exercise programme (fast walking and mild jogging for 40–60 minutes, three times/week) in 42 NAFLD patients where liver fibrosis was suspected, and they found a favourable response matching that seen with dietary restriction. There were equivalent reductions in serum alanine aminotransferase and gamma glutamyl transpeptidase levels (−20.6% vs. −16.1% and −25.7% vs −34.0%), and similar improvements of insulin resistance (−29.7% vs. −26.9%), and increases in serum adiponectin levels (+33.4% vs. +15.1%). Moreover, exercise training reduced serum levels of the markers of inflammation and oxidative stress usually associated with fibrosis: ferritin and thiobarbituric acid reactive substances (−25.0% vs. +1.1% and −33.5% vs. −10.5%). Other reports also found substantial benefits from vigorous exercise. A group of 13 obese individuals (body mass index 35 kg.m²) with NAFLD undertook one week of vigorous exercise (60 minutes/day at 80–85% of maximal heart rate)[114] despite the short duration of this trial, the intervention reduced circulating levels not only of alanine transaminase, but also of a marker of hepatic cell apoptosis (CK18 fragments), thus increasing the potential for regeneration of healthy liver tissue. We may thus conclude that vigorous exercise can attenuate the stimuli leading to hepatic fibrosis in NAFLD, and correct some metabolic markers of hepatic dysfunction, although it is less likely it will reverse fibrotic changes that have already occurred.

These conclusions are reinforced by animal experimentation. In some animal studies, not only enzyme markers, but also histological appearances have improved. In mice where hepatic fibrosis was induced by feeding a high fat diet and large amounts of fructose,[134] vigorous exercise (16 weeks of treadmill running, 60 minutes per day at speeds increasing from 15–20 m/minute) reduced histological evidence of fibrosis relative to control animals. A second animal study noted histological evidence of inflammation and steatohepatitis (macrovesicular steatosis and lymphocytosis) in sedentary rats that were fed a high-fat diet, but such findings were greatly attenuated in their peers who undertook vigorous daily physical activity (swimming for 30 rising to 90 minutes per day); alanine transaminase but not aspartate transaminase levels were also reduced in the exercised animals.[126]

Cirrhosis

Although regular physical activity can prevent the progression of NAFLD to cirrhosis, exercise programmes seem unlikely to reverse the advanced pathological changes associated with this diagnosis. The primary clinical rationale for advocating exercise therapy in hepatic cirrhosis is rather to reduce associated physical weakness and co-morbidities,[147] and to enhance survival prospects if the patient receives a liver transplant.[138, 140] Lemyze et al.[148] have pointed to multiple factors that impair physical performance in advanced hepatic cirrhosis, including
deconditioning, malnutrition, anaemia, cirrhotic cardiomyopathy and the hepato-pulmonary syndrome.

The impairment of physical capacity seems proportional to disease severity as measured by the Pugh index of liver failure, but is independent of aetiology (NAFLD, alcoholism or viral hepatitis).\cite{135, 142, 143} Even moderate physical activity (30% of peak work rate) increases pressures in the hepatic portal vein, with a danger of precipitating oesophageal bleeding,\cite{149} particularly if varices have developed in the lower part of the oesophagus.

Clinical concerns over possible oesophageal haemorrhage have led many investigators to report the anaerobic threshold, or to predict maximal oxygen intake from submaximal data rather than to assess aerobic capacity by direct measurements of peak treadmill or cycle ergometer effort (Table 2.2). Levels of anaerobic threshold, aerobic fitness and exercise tolerance are all low,\cite{77, 131, 135–138, 141–144} particularly if there is an associated accumulation of ascitic fluid in the peritoneal cavity.\cite{135, 144}

Patients with cirrhosis usually show muscular weakness,\cite{141, 143, 145, 146} probably in part because of a decrease in protein synthesis.\cite{150} Thus, Campillo et al.\cite{135} noted that individuals with cirrhosis had low levels of prealbumin (0.10 g/L, vs. norms of 0.28–0.32 g/L) and albumin (30 g/L, vs. norms of 40–435 g/L), and Wong et al. also found low albumin levels, particularly in patients who had developed ascites.\cite{144}

When exercising at three to four times resting oxygen consumption, the respiratory quotient of sedentary individuals normally indicates a roughly equal usage of fat and carbohydrate; however, Camillo et al.\cite{136} saw an almost exclusive use of carbohydrate in patients with cirrhosis who were exercising. This could reflect in part a low maximal oxygen intake—even exercise demanding four times resting oxygen consumption approaches maximal effort for some patients with cirrhosis. Over 32 minutes of moderate physical activity, Campillo et al.\cite{136} found that the patients also showed a progressive decrease of blood glucose and an accumulation of blood lactate, likely reflecting defective hepatic gluconeogenesis. DeLissio et al.\cite{137} also commented on a defective endogenous production of glucose in those with cirrhosis, although in their four subjects blood glucose levels did not fall during exercise, because (in contrast to Campillo et al.) fat usage was greater than in controls.

There have been few investigations of the effect of aerobic training in patients with cirrhosis. One investigation reported a 29% gain of predicted VO\textsubscript{2max} over 10–12 weeks of conditioning,\cite{131} and a second trial with only four subjects found an increase of VO\textsubscript{2max} in two of the four individuals following training, with an 18–20% improvement of muscle strength in these two individuals.\cite{135} Exercise that includes an element of resistance training is arguably a useful therapy for restoring muscle mass and improving fitness, strength and functional capacity, but it remains unclear whether an increase of habitual physical activity can restore liver health (and if so, the dose of activity that is needed). One major obstacle to implementing and sustaining exercise training in advanced liver disease is the initial fatigue of the patient. This has an adverse effect upon the individual’s quality of life\cite{151} and by discouraging physical activity, it progressively
<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Measurement technique</th>
<th>Findings</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Campillo et al.</td>
<td>24 cases of liver cirrhosis (? cause) in good clinical condition</td>
<td>Incremental treadmill</td>
<td>$\dot{V}O_2^{peak}$ 19.6 ml/[kg.min]</td>
<td>$\dot{V}O_2^{peak}$ inversely related to Pugh score for liver failure ($r = -0.57$), may reflect loss of muscle mass</td>
</tr>
<tr>
<td></td>
<td></td>
<td>exercise (3 min/stage) to subjective exhaustion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Campillo et al.</td>
<td>10 cases of alcoholic liver cirrhosis, 6 sedentary controls</td>
<td>32 minutes exercise at 3–4 times resting oxygen consumption</td>
<td>Patients metabolized exclusively carbohydrates, whereas controls used equal parts of fat and carbohydrate</td>
<td>Patients showed decreased blood glucose and increased lactate levels, indicating impaired gluconeogenesis</td>
</tr>
<tr>
<td>DeLissio et al.</td>
<td>4 cases of hepatic cirrhosis</td>
<td>Prediction of $\dot{V}O_2^{peak}$ from treadmill exercise at 50% of maximal effort</td>
<td>$\dot{V}O_2^{peak}$ 29.9 ml/[kg.min] vs. 49.0 ml/[kg.min] in controls</td>
<td>Lack of normal endogenous gluconeogenesis in patients, as seen from infusions of isotopically marked glucose</td>
</tr>
<tr>
<td>Dharancy et al.</td>
<td>135 cases of hepatic cirrhosis</td>
<td>Progressive cycle ergometer test with 10W/min increments of loading to exhaustion</td>
<td>$\dot{V}O_2^{peak}$ 17.2 ml/[kg.min], 61% of predicted; 54% of patients had $\dot{V}O_2^{peak}$ 60% of predicted $\dot{V}O_2$-AT also low</td>
<td>Patients with $\dot{V}O_2^{peak}$ &lt;60% of normal had decreased 1 yr survival following transplant operation (64.7% vs. 96.4%, $p = 0.0003$). MELD score of disease severity inversely related to $\dot{V}O_2^{peak}$</td>
</tr>
<tr>
<td>Epstein et al.</td>
<td>156 patients on transplant waiting list, 59 received transplants</td>
<td>Cycle ergometer test, ramp protocol to $\dot{V}O_2^{peak}$</td>
<td>6 died within 100 days of transplant had $\dot{V}O_2^{peak}$ &lt;50% predicted and $\dot{V}O_2$-AT also reduced</td>
<td></td>
</tr>
<tr>
<td>Pieber et al.</td>
<td>15 patients on transplant waiting list</td>
<td>Cycle ergometer test, 25 W increase of loading every 2 minutes</td>
<td>$\dot{V}O_{2max}-AT$ 10.3 mL/[kg/min]</td>
<td>Associated decreases in health-related quality of life</td>
</tr>
<tr>
<td>Author</td>
<td>Sample</td>
<td>Measurement technique</td>
<td>Findings</td>
<td>Comments</td>
</tr>
<tr>
<td>-----------------</td>
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</tr>
<tr>
<td>Ritland et al.</td>
<td>9 cases of hepatitis receiving immunosuppressive therapy, 5 with cirrhosis</td>
<td>Prediction of $\text{VO}_{2\text{max}}$ from submaximal test, using Astrand nomogram</td>
<td>Predicted $\text{VO}_{2\text{max}}$ 31 ml/[kg.min]</td>
<td>$\text{VO}_{2\text{max}}$-increased by interval training, 19% at 4–5 wk, 29% at 10–12 wk</td>
</tr>
<tr>
<td>Terziyski et al.</td>
<td>19 cases of hepatic cirrhosis</td>
<td>Treadmill test, Bruce protocol</td>
<td>$\text{VO}_{2\text{peak}}$ 23.9 ml/[kg.min] 72.1% of predicted</td>
<td>Patients with mild and moderate hepatic cirrhosis have reduced exercise capacity, which correlates with Child-Pugh score (p = 0.031)</td>
</tr>
<tr>
<td>Wiesinger et al.</td>
<td>12 alcoholic cirrhosis, 8 post viral hepatitis, 6 other causes of cirrhosis</td>
<td>Cycle ergometer, increased 25 W every 2 minutes</td>
<td>19 pts completed cycle ergometer test. $\text{VO}<em>{2\text{AT}}$ Child-Pugh class: A = 11.6 ml/[kg.min] (54% pred $\text{VO}</em>{2\text{max}}$) B = 10.3 ml/[kg.min] (37% pred $\text{VO}<em>{2\text{max}}$) C = 8.7 ml/[kg.min] (32% pred $\text{VO}</em>{2\text{max}}$)</td>
<td>Patients with advanced stage liver disease are stage dependently impaired in their physical capacity</td>
</tr>
<tr>
<td>Wong et al.</td>
<td>39 cases of hepatic cirrhosis</td>
<td>Exercise capacity – $\text{VO}<em>{2\text{peak}}$ – $\text{VO}</em>{2\text{AT}}$</td>
<td>$\text{VO}_{2\text{peak}}$ (ml/kg.min) (from graph): pre-ascitic 24, ascitic 13.5 controls: 28.5</td>
<td>Patients had a significant reduction in exercise capacity and an early anaerobic threshold; associated myocardial thickening and ventricular stiffness</td>
</tr>
</tbody>
</table>

**Muscle strength**

| Andersen et al. | 24 cases of alcoholic cirrhosis                                        | Isokinetic strength flexion and extension of ankle, hip, knee, elbow and wrist; abduction and adduction of shoulder | Strength reduced 29–35% in patients compared with controls LBM 35.6kg (79% of predicted) | Anthropometry                           |
exacerbates the initial loss of muscular strength. Nevertheless, regular progressive exercise can counter such fatigue, even in people with advanced fibrosis. Moreover, given adequate motivation and a progressive programme, patients with cirrhosis can tolerate quite vigorous exercise; they can maintain oxygenation of the brain and muscles even during incremental cycle ergometry to

### Table 2.2 continued

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Measurement technique</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pieber et al. [141]</td>
<td>15 patients on liver transplant waiting list</td>
<td>Isokinetic dynamometer, handgrip dynamometer</td>
<td>Peak torque of knee extensors 97 N-m, Handgrip force 524 N</td>
<td>Patients with end-stage liver disease have deficits of muscle strength</td>
</tr>
<tr>
<td>Tarter et al. [146]</td>
<td>49 alcoholic, 42 non-alcoholic cirrhosis</td>
<td>Isokinetic device, concentric and eccentric contraction force in upper and lower limbs</td>
<td>Upper limb peak concentric peak force (N): alcoholic = 50.5, nonalcoholic = 55.0, controls = 68.1. Eccentric force (N): alcoholic = 95.0, nonalcoholic = 94.6, controls = 122.2. Lower limb peak concentric force (N): alcoholic = 104.6, nonalcoholic = 108.2, controls = 140.8. Eccentric force (N): alcoholic = 187.5, nonalcoholic = 196.8, controls = 241.5</td>
<td>Psychomotor capacity correlates negatively with isokinetic strength in cirrhosis</td>
</tr>
<tr>
<td>Wiesinger et al. [143]</td>
<td>12 alcoholic cirrhosis, 8 post viral hepatitis, 6 other causes of cirrhosis</td>
<td>Isokinetic dynamometer and handgrip dynamometer</td>
<td>Knee torque depends on Child-Pugh score: Class A 149 N-m, Class B 108 N-m, Class C 89 N-m. Handgrip: Class A 680 N, Class B 569 N, Class C 451 N</td>
<td>Patients with advanced liver disease are stage dependently impaired in their physical capacity. Impairment unrelated to disease aetiology</td>
</tr>
</tbody>
</table>
and they show no evidence of hypoglycemia while undertaking 90 minutes of treadmill exercise at 50% of maximal oxygen intake.\textsuperscript{137}

We may conclude that exercise rehabilitation programmes can have favourable effects even in advanced hepatic disease, if the affected individuals can be motivated to sustain their participation in such activity.

**Hepatocellular carcinoma**

Hepatocellular carcinoma is usually a secondary complication of advanced NAFLD, hepatitis B or C infection, or alcoholic cirrhosis. In countries where viral hepatitis is prevalent, this is the dominant cause of hepatic cancer, but in North America alcoholism and NAFLD are more important antecedents.

Interactions between physical activity and hepatocellular carcinoma have had little study, although given that physical activity reduces the risk of NAFLD, some preventive value would be anticipated. A ten-year follow-up of 507,897 retired Americans found a significantly reduced risk of hepatic carcinoma (odds ratio 0.64) in those who reported regular activity (>5 times a week) versus those who exercised never or rarely.\textsuperscript{155} Likewise, a comparison between sedentary mice and those assigned to daily treadmill running for 32 weeks showed that although both groups were fed a diet that induced NAFLD, the exercisers had a lower incidence of hepatic tumours.\textsuperscript{156}

Moderate physical activity may offer palliative therapy in those with established disease. One case report noted that six weeks of supervised aerobic exercise (cycling twice per week) produced a 20% increase in peak work capacity, along with an increase in the six minute walking distance and quality of life.\textsuperscript{157}

**Liver transplants**

An increasing proportion of patients with advanced liver disease are now treated by hepatic transplantation. Maximization of physical condition is important to the success of such surgery. Patients remain at risk of NAFLD following transplants, and it is thus important to continue regular physical activity following operation. Empirical non-randomized data further suggest that those who exercise have a higher quality of life after hepatic transplantation,\textsuperscript{158} although the direction of causality in this relationship remains debatable.

**Areas for further research**

Much of the research on physical activity and hepatic pathologies has been cross-sectional in type, and there remains scope for substantial prospective trials that examine the value of various patterns of physical activity in preventing and treating disorders of liver function. The respective contributions of physical activity, dietary change and weight loss to improvements in hepatic function remain to be clarified, and there is a need to clarify whether a reduction of
sedentary behaviour will augment the benefit yielded simply by an increase of habitual physical activity.

Although regular physical activity improves effort tolerance and enhances the quality of life in advanced liver disease, often with a reversal of high levels of hepatic enzymes, it is less clear whether liver histopathology can be improved in response to a combined exercise and weight loss programme. Methods of increasing compliance with prescribed exercise also require further study.

A few reports have noted favourable responses to resistance exercise in NAFLD, although its effectiveness in management and treatment is not yet clearly established. There also remains a need to define the minimum dose of physical activity that is required for benefit, to clarify the exercise tolerance of individuals with impaired hepatic function and to determine doses of exercise that may lead to hepatic injury. Finally, there has as yet been little systematic study of the possible role of exercise programmes in the treatment of patients with alcoholic hepatitis.

**Practical implications and conclusions**

Many features of the metabolic syndrome suggest hepatic dysfunction, and there is a close association between this syndrome and the non-alcoholic fatty infiltration of NAFLD. Risks of developing the metabolic syndrome are reduced independently by both regular physical activity and the avoidance of sedentary habits. Sedentary behaviour also predisposes to steatosis and associated disorders, including atherosclerotic disease and diabetes mellitus. If untreated, simple steatosis, NAFLD, alcoholic inflammation and exposure to hepatitis B or C can all initiate a sequence of fibrosis, cirrhosis and even cancerous change in liver tissue, particularly if habitual physical activity is inadequate.

Regular physical activity and dieting can restore insulin sensitivity, counteract diabetes and steatosis, and possibly facilitate recovery from various forms of hepatitis. Optimization of functional capacity is important to quality of life and the success of liver transplantation if such treatment is undertaken. The majority of therapeutic programmes have prescribed moderate to vigorous aerobic exercise for three to five days per week. However, further information is needed on the efficacy of resistance versus aerobic exercise, on the minimum dose of activity required for benefit, on the exercise tolerance of individuals with chronic liver disease, and on the dose of exercise that may lead to hepatic injury.

Programme compliance is a problem for the obese. Fatigue (probably centrally mediated) is frequent in hepatic steatosis, and this may reduce motivation or even preclude sustained vigorous activity. The one study of NAFLD that examined predictors of exercise adoption and adherence concluded that initial confidence in the ability to exercise was often low in hepatic dysfunction, in part because of a fear of falling. Supervised exercise with similarly affected individuals can often improve self-confidence and reduce fears of falling, but if such an approach is ineffective, less conventional tactics may be needed to increase daily energy expenditures. One investigation achieved a significant
reduction of alanine transaminase through a combination of regular voluntary and electrical stimulation of the quadriceps and hamstring muscles.\textsuperscript{[161]}

References


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3 Effects of physical activity on the gallbladder and biliary tract in health and disease

Introduction

This chapter looks at the impact of acute and chronic physical activity upon biliary function in both health and disease. Although physical activity modifies the secretions and emptying of the healthy gall bladder, the responses to exercise have greater significance for the prevention of disease than for the enhancement of human performance. After considering the prevalence, economic impact and factors contributing to gall bladder disease, and taking a brief look at the resting function of the gall bladder, the text examines the impact of exercise-induced changes in gallbladder emptying upon the risks of cholecystitis, gallstones and biliary tract tumours. In particular, it attempts to distinguish the direct effects of physical activity from changes due to reductions in body fat and blood cholesterol levels.

Prevalence and economic impact of biliary tract disorders

In Classical Greece, black and yellow bile were regarded as two of the body’s four basic “humours”, and an imbalance in their secretion was considered a cause of ill-health.[1]

Today, a major segment of people in the developed world still suffers from disorders of the biliary tract. Gallstones affect perhaps 25 million Americans, at estimated annual direct and indirect costs of over US$6 billion, and as many as 500,000 Americans undergo surgical removal of the gallbladder each year. Moreover, gallstones are equally prevalent in many other developed countries.[2–8] If untreated, the stones can provoke a gallbladder infection in up to 35% of affected individuals,[9] and if combined with stasis of the bile, such infection predisposes to gall bladder cancer. There are 2.5 cases of gallbladder cancer per 100,000 of the US population each year, and gallstones are found in 80% of those with gallbladder malignancies.[10]

Factors contributing to gallbladder disease

Important factors contributing to the development of gallbladder pathologies include an excessive secretion of mucus, supersaturation of the bile with
Resting gallbladder function

Bile is a greenish-brown fluid produced in the liver. It serves as a surfactant and emulsifying agent, and is important to the intestinal digestion of fat. In its absence, fat remains largely unabsorbed and is excreted in the faeces. However, the gallbladder in itself is not essential to digestion, since the entire organ can be removed without obvious adverse effects upon the patient other than some dilatation of the bile ducts.

When a person is fasting, bile accumulates and is concentrated in the gallbladder. Here, the concentration of its constituents is 3–11 times higher than in the fluid first secreted by the liver. Bile is released into the gut after a meal, through a combination of gallbladder contraction and relaxation of the sphincter of Oddi, located where the bile duct empties into the duodenum. Contraction of the gallbladder is probably initiated by the combined action of intrinsic nerve plexuses in its walls, a weak response to vagal and alpha-adrenergic nerve fibres, and the liberation of hormones (particularly cholecystokinin) from the intestinal wall. Cholecystokinin induces gallbladder contraction via the parasympathetic nerves, serving as a neurotransmitter for this component of the autonomic nervous system. Its action can be countered by the drug loxiglumide, which blocks parasympathetic nerve receptors in the gallbladder wall.

Methods of visualizing gallbladder function include watching the emptying of a contrast medium in serial radiographs, following the excretion of radioisotopes, and the use of ultrasound. The last approach has the advantage that the subject is not exposed to radiation. Depending on age, sex and body size, the human gallbladder has a capacity of some 50 mL, but it typically contains less than 30 mL of bile. Even when fasting, the gallbladder shows both rhythmic
contractions (with a frequency of 2–6/sec) and sustained contractions that persist for 5–30 minutes. When resting, some 10–30% of the gallbladder contents are emptied every one to two hours,[38] As much as 65% of the gallbladder contents can be expelled during the first 30–40 minutes following the ingestion of a fatty meal.[39]

Table 3.1 Published reviews suggesting a possible role for regular physical activity in protecting a person against chronic gallbladder disease

<table>
<thead>
<tr>
<th>Authors</th>
<th>Conclusions of reviewers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deibert et al.[11]</td>
<td>Brief discussion of the gall bladder in the context of sport, suggesting that the risk of cholelithiasis could be reduced by physical training</td>
</tr>
<tr>
<td>de Oliveira &amp; Burini[12]</td>
<td>General review of exercise and the gastro-intestinal tract, commenting that mild to moderate intensity exercise protected against cholelithiasis</td>
</tr>
<tr>
<td>Hofmann[4]</td>
<td>Exercise was seen as allowing frequent meals without an excessive energy intake relative to energy expenditures, thus enhancing gallbladder emptying</td>
</tr>
<tr>
<td>Jeong et al.[13]</td>
<td>Emphasized the potential contribution of obesity to the development of gallbladder disorders</td>
</tr>
<tr>
<td>Khazaeina et al.[14]</td>
<td>Main focus was upon the impact of exercise upon the elimination of drugs, but noted that physical activity increased the rate of biliary excretion</td>
</tr>
<tr>
<td>Lammert and Matern[15]</td>
<td>Suggested that measures for the prevention of biliary disorders included physical activity, slow weight reduction, regular vitamin C supplementation and moderate coffee consumption</td>
</tr>
<tr>
<td>Moga[16]</td>
<td>Regular aerobic exercise was seen as an appropriate alternative to cholecystectomy</td>
</tr>
<tr>
<td>Peters &amp; de Vries[17]</td>
<td>General review of physical activity and the gastrointestinal tract. Concluded that physical activity had beneficial effect upon cholelithiasis beyond its effect in reducing body mass</td>
</tr>
<tr>
<td>Rissanen and Fogelholm[18]</td>
<td>Concluded that some (but not all) studies of gallstones have shown a protective effect of regular physical activity</td>
</tr>
<tr>
<td>Shaffer[19]</td>
<td>Physical activity is mentioned as the final item among a list of potential measures to prevent gallstones</td>
</tr>
<tr>
<td>Simrénn[20]</td>
<td>General review of physical activity and gastrointestinal tract. Concluded that physical activity seems to protect against cholelithiasis</td>
</tr>
<tr>
<td>Utter and Goss[21]</td>
<td>Concluded that aerobic exercise seemed beneficial in preventing gallstones, but the precise mechanism remained unclear</td>
</tr>
</tbody>
</table>
Most of the cholesterol found in the bile has been secreted by the liver. It remains unclear whether cholesterol is also excreted by the healthy gallbladder mucosa. However, cholesterol can accumulate in the gallbladder wall under pathological conditions. Inflammation reduces the ability of the gallbladder to concentrate bile, but it also increases its viscosity through a greatly increased secretion of mucinous material.\[40\]

**Acute effects of physical activity on the gallbladder**

An acute bout of vigorous physical activity could potentially stimulate emptying of the gallbladder by increasing the activity of vagal and sympathetic nerves, or by changing blood hormone concentrations. During prolonged endurance activity, effects might also arise from a progressive reduction in visceral blood flow. Empirical studies of acute responses are limited to one study of cholecystokinin levels and two studies of gallbladder function, one carried out on dogs and the other in healthy women (Table 3.2).

The study of dogs concluded that vigorous physical activity (4–5 h of treadmill running at an unspecified speed and slope) did not increase the quantity of bile secreted by previously sedentary animals. However, the pigment content was augmented, possibly because running increased the breakdown of red cells.\[40\] Philipp et al.\[41\] examined plasma levels of cholecystokinin in 11 male and 8 female marathon runners. Relative to control values collected a few weeks later, plasma cholecystokinin concentrations were elevated immediately before competition, apparently in anticipation of the run, and levels of this hormone showed a further modest increase immediately following completion of the event. Gallbladder function was not measured directly, but from the known effects of cholecystokinin one might anticipate an increase in emptying of the gallbladder in response to the run. Utter et al.\[38\] have made the only direct human observations on gallbladder function in relation to exercise. They examined 12 healthy

<table>
<thead>
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<th>Author</th>
<th>Subjects</th>
<th>Type of exercise</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>McMaster et al.</td>
<td>Dogs 4–5 h of treadmill running</td>
<td>4–5 h of treadmill running in previously sedentary</td>
<td>No increase in volume of bile secretion, but increase of pigment content</td>
</tr>
<tr>
<td>Philipp et al.</td>
<td>11 male, 8 female marathon</td>
<td>Competitive marathon run</td>
<td>Cholecystokinin increased in anticipation of event, further boosted</td>
</tr>
<tr>
<td>Utter et al.</td>
<td>12 healthy females 30 min of</td>
<td>30 min of recumbent cycle ergometer exercise</td>
<td>No significant effect on scintigraphic estimates of gallbladder emptying,</td>
</tr>
</tbody>
</table>

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females, injecting a technetium-99m marker and recording images at five-minute intervals. The fractional emptying of the gall bladder, the latent period to the onset of emptying and the duration of ejection following 30 minutes of recumbent cycle ergometer exercise at 65% of peak aerobic power did not differ significantly from what had been observed at rest.

Blood concentrations of other hormones known to modify gallbladder motility are affected by physical activity (for instance, there are increases in gastrin, motilin, secretin and somatostatin, and decreases in pancreatic polypeptide and vasoactive intestinal peptide), but the possible impact upon gallbladder function of such widespread changes in the hormonal milieu has yet to be examined.

**Chronic effects of physical activity on the gallbladder**

The chronic effects of physical activity upon gallbladder function have been examined in two cross-sectional comparisons of obese versus more active individuals and two longitudinal exercise interventions, all involving relatively small groups of subjects (Table 3.3).

**Table 3.3** Effects of chronic physical activity upon gallbladder function, as seen in both cross-sectional studies and longitudinal interventions

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Activity assessment</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cross-sectional studies</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mathus-Vliegen et al. [43]</td>
<td>60 obese patients entering weight-loss programme</td>
<td>Subjects questioned about their physical activity</td>
<td>No effect of physical activity on gallbladder function</td>
</tr>
<tr>
<td>Vezina et al. [42]</td>
<td>18 morbidly obese individuals, 9 tall and 9 muscular people of similar body mass</td>
<td>No specific observations on physical activity</td>
<td>Gallbladder volumes and emptying rates similar in the 3 groups</td>
</tr>
</tbody>
</table>

| **Longitudinal interventions** |                                 |                                         |                                               |
| Sari et al. [45] | 23 middle-aged obese women (no control group) | 4 weeks of a walking intervention (45 min sessions at 60–80% of maximal heart rate) 5 days/week | Intervention led to small increase in late-phase post-prandial gallbladder motility, and decrease in late-phase post-prandial gallbladder volume, independent of changes in body mass |
| Utter et al. [44] | 27 obese women (16 assigned to training programme) | 12 weeks of aerobic training that increased peak oxygen intake by 9% | Non-significant trend to increase of gallbladder ejection fraction |
Vezina et al.\cite{42} used both ultrasound and the radio-isotope \textsuperscript{99}technetium diisopropyliminodiacetic acid to make inter-individual comparisons of gallbladder volumes and emptying rates. No significant differences were found between a group of 18 individuals who were morbidly obese and 9 tall and 9 muscular subjects who had a comparable body mass, but who presumably engaged in greater levels of physical activity. Mathus-Vliegen et al.\cite{43} used ultrasonography to study inter-individual differences in the fasting and post-prandial gallbladder volumes of obese individuals who had entered a weight-loss programme. They concluded that body mass, fat-free mass, a central (abdominal) pattern of fat distribution and insulin levels were the main determinants of such functional characteristics of the gallbladder as fasting volume, ejection volume and ejection fraction. Subjects were also questioned about their habitual physical activity, but responses showed no significant association with any measures of gallbladder function.

Utter et al.\cite{44} had 16 obese women engage in 12 weeks of aerobic training (30 min/day of recumbent cycle ergometer exercise at 65\% of their individual peak aerobic power). This regimen increased their maximal oxygen intake by 9\%. The ejection fraction of the gallbladder as measured by the radio-isotope Technetium-\textsuperscript{99m} showed a tendency to increase by 15\% after training, but this trend was not statistically significant relative to control subjects (who also showed a 5\% increase in ejection fraction). In contrast to this equivocal result, Sari et al.\cite{45} looked at the effects on gallbladder volume and motility of four weeks of walking (5 days/week for 45 minutes at 60–80\% of the individual’s maximal heart rate) in 23 middle-aged obese women. This uncontrolled study showed small but significant decreases in post-prandial volumes of the gallbladder following training, accompanied by 12–25\% increases in the post-prandial ejection fraction; the main changes in response were seen 90–150 minutes after ingesting the test meal. The gain in peak aerobic power following the intervention was not specified; there was a 2.2 kg decrease of body mass, although weight changes were said to be unrelated to the changes in gallbladder function.

There is plainly some discrepancy between the significant changes of gallbladder motility observed in the uncontrolled trial of Sari et al.\cite{45} and the statistically insignificant trends of similar magnitude described by Utter et al.\cite{44} after a longer period of apparently comparable training. This issue needs to be resolved by further experimentation.

**Physical activity and chronic gallbladder disease**

Gallstone formation, cholecystitis and cholecystectomy are closely intertwined problems, and many reports have examined the influence of regular physical activity upon all three conditions. After discussing factors predisposing to gallstone formation, findings are thus analysed jointly for all three diagnoses, although a distinction is drawn between conclusions based upon cross-sectional, prospective and case-control studies and what is normally regarded as the optimal epidemiological approach of randomized controlled trials.
Factors predisposing to gallstone formation

Gallstones contain varying proportions of cholesterol, calcium and bilirubin. Factors predisposing to gallstone formation include not only biliary stasis, but also local infection, metabolic abnormalities and a failure of acidification of the bile.

A reduced motility of the gallbladder and resulting biliary stasis allows more time for crystal formation. As discussed above, there is some evidence that a reduction of biliary motility is associated with both obesity and the adoption of a sedentary lifestyle.

Under normal conditions, the gallbladder probably secretes some cholesterol. This process is stimulated by infection, and there is also an increased secretion and/or a reduced breakdown of a mucinous, protein-containing exudate,[46, 47] possibly with a reduction of bile salt concentrations. All of these changes predispose to gallstone formation.

Metabolic abnormalities of interest in the context of gallbladder disease include an increased uptake of cholesterol from the circulation, an increased hepatic synthesis of cholesterol, a reduced breakdown of cholesterol to bile salts and an increased intestinal reabsorption of cholesterol.[48] These several factors predispose to a bile that is super-charged with cholesterol and readily undergoes crystallization.[49, 50] Crystallization is associated with a decreased ratio of bile salts to cholesterol. The normal range is from 1:20 to 1:30, but stone formation occurs if the ratio drops below 1:13.[51, 52]

Failure of the diseased gallbladder epithelium to acidify an alkaline bile is a further adverse factor, leading to the precipitation of calcium carbonate,[53] an important component of gallstones.

Cross-sectional studies

Many cross-sectional studies have examined associations between habitual physical activity and some measure of gallbladder disease (often an ultrasonographic diagnosis of gallstones, but sometimes only a physician’s report of gallbladder disease or a hospital record of a cholecystectomy) (Table 3.4). Some studies have found benefit from physical activity, but conclusions in other reports have been negative or equivocal. Among problems of interpretation, subject numbers have sometimes been small, the categorization of physical activity has often been quite crude and statistical analyses have not always made adequate adjustment for other important co-variates such as obesity.

Sarin et al.[54] commented on a relationship between the level of habitual physical activity and the type of gallstone that is formed. In 200 consecutive patients where an arbitrary three-level classification of habitual physical activity had been made, they noted that cholesterol stones (94% of the total) were typical of sedentary individuals, whereas pigmented stones were more frequent in active individuals, probably reflecting a contribution of exercise induced haemolysis to stone formation.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Method of physical activity measurement</th>
<th>Indicator of disease</th>
<th>Covariates</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basso et al.</td>
<td>512 pregnant women</td>
<td>Crude 3-level classification of physical activity</td>
<td>Ultrasonographic diagnosis of gallstones</td>
<td>No covariate adjustments</td>
<td>Gallstones found in 4.5% of sample; little relationship to habitual physical activity</td>
</tr>
<tr>
<td>Chuang et al.</td>
<td>53 obese women</td>
<td>Questionnaire on sport, occupational activity and leisure activity</td>
<td>Ultrasonographic diagnosis of gallstones</td>
<td>BMI, HDL cholesterol</td>
<td>Sport participation, but neither occupational nor leisure activity associated with reduced risk of gallstones</td>
</tr>
<tr>
<td>Friedman</td>
<td>5209 adults</td>
<td>Interview</td>
<td>Combination of hospital records and self reports of gallbladder disease</td>
<td>No data provided, but population activity said to be low</td>
<td>Habitual physical activity not related to gallbladder disease</td>
</tr>
<tr>
<td>GREPCO</td>
<td>2325 Roman civil servants</td>
<td>4-item questionnaire on physical activity at leisure and work, active commuting and other walking</td>
<td>Ultrasonographic diagnosis of gallstones or history of cholecystectomy</td>
<td>Age, BMI, lipids, parity</td>
<td>Habitual physical activity showed no significant effect, even in univariate analyses</td>
</tr>
<tr>
<td>Jorgensen</td>
<td>3608 Danish adults 30–60 years of age</td>
<td>4-level classification of occupational and leisure activity</td>
<td>Ultrasonographic diagnosis of gallstones and/or cholecystectomy</td>
<td>Cigarette smoking, coffee, BMI, weight change</td>
<td>No significant relationship between gallbladder disease and habitual physical activity</td>
</tr>
<tr>
<td>Kriska et al.</td>
<td>2130 Puma Indians</td>
<td>Interview-conducted physical activity questionnaire</td>
<td>Ultrasonographic diagnosis of gallstones</td>
<td>BMI and other confounders</td>
<td>Gall stones significantly related to inactivity in cross-sectional analysis</td>
</tr>
<tr>
<td>Pagliarulo et al.</td>
<td>1337 cases of diabetic mellitus</td>
<td>3-level estimate of habitual physical activity</td>
<td>Ultrasonographic diagnosis of gallstones</td>
<td>Age, obesity, family history</td>
<td>No significant relationship between gallstones and habitual physical activity</td>
</tr>
<tr>
<td>Authors</td>
<td>Subjects</td>
<td>Method of physical activity measurement</td>
<td>Indicator of disease</td>
<td>Covariates</td>
<td>Conclusions</td>
</tr>
<tr>
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<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Sakuta &amp; Suzuki [67]</td>
<td>974 male members of Japanese defence forces</td>
<td>2-way classification of physical activity, based on reports of “sweat-producing activity”</td>
<td>Ultrasonographic diagnosis of gallstones</td>
<td>Cigarette smoking, vegetable intake</td>
<td>Gallstones related to total homocysteine levels, but not to habitual physical activity</td>
</tr>
<tr>
<td>Sarin et al. [54]</td>
<td>200 consecutive patients with gallstone disease</td>
<td>Arbitrary 3-level classification of habitual physical activity</td>
<td>Gallstones obtained at cholecystectomy</td>
<td></td>
<td>Cholesterol stones typical of sedentary individuals, pigmented stones found in more active individuals</td>
</tr>
<tr>
<td>Storti et al. [56]</td>
<td>8010 post-menopausal women</td>
<td>Modified Harvard alumni questionnaire disease</td>
<td>Self-report of cholecystectomy or gallbladder</td>
<td>Body mass and other risk factors</td>
<td>Lower 3 physical activity quartiles vs. top quartile, odds ratio of 1.57 for gallbladder disease</td>
</tr>
<tr>
<td>Utter et al. [58]</td>
<td>2088 Puma Indians</td>
<td>Interviewer administered questionnaire</td>
<td>Clinically diagnosed gallstones</td>
<td>Diabetes mellitus</td>
<td>Gradient of risk 14.2–4.7% from least to most active tertile of diabetic men. Unable to test in non-diabetic men or women</td>
</tr>
<tr>
<td>Walcher et al. [57]</td>
<td>2129 adults aged 18–65 years</td>
<td>Interviewer supervised physical activity questionnaire</td>
<td>Ultrasonographic diagnosis of gallstones</td>
<td>Age, BMI, cholesterol, Vitamin C ingestion</td>
<td>Odds ratio of physical activity &gt;2h/week vs. &lt;2h/week 0.65 (0.52–0.79)</td>
</tr>
<tr>
<td>Williams [55]</td>
<td>29,110 male, 11,953 female runners</td>
<td>Habitual physical activity and 10 km running speed</td>
<td>Self-reported, BMI and clinician-diagnosed gallbladder disease</td>
<td></td>
<td>Relative to least fit individuals, 75% reduction of risk in males running &gt;4.75 m/s, 85% in females running &gt;4 m/s</td>
</tr>
</tbody>
</table>
Table 3.4 continued

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Method of physical activity measurement</th>
<th>Indicator of disease</th>
<th>Covariates</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams and Johnston [58]</td>
<td>97 rural Canadian women</td>
<td>Energy intake, 3 level classification of habitual physical activity</td>
<td>Ultrasonographic diagnosis of gallstones and/or cholecystectomy</td>
<td>Age, skinfold thicknesses</td>
<td>Low physical activity and low range of energy intake increased risk of gallbladder disease</td>
</tr>
</tbody>
</table>

Notes: BMI = body mass index; METs = metabolic equivalents

Positive findings

The study of Paul Williams [55] is the largest to report positive findings. He examined the independent effects of physical fitness (as inferred from 10 km race speed), habitual physical activity (the reported km/day of running) and body mass index on the risks of self-reported but clinician-diagnosed gallbladder disease in 29,110 male and 11,953 female runners. In this study, women with a body mass index >22.5 kg/m² had a greater age-adjusted risk of gallbladder disease than that seen in the leanest women, and the risk accelerated sharply in those with a BMI above 27.5 kg/m². In terms of fitness, in men a running speed faster than 4.75 m/s reduced the risk by 83% (75% after adjusting for BMI and physical activity), and in women a speed >4 m/s reduced the risk by 93% (85% after adjusting for daily running distance and BMI) relative to individuals who were slower runners. The relationship of risk to habitual running distance (men: p = 0.01; females: p = 0.008) reflected largely the greater thinness of those who were running longer distances.

A second large study (Storti et al. [56]) carried out a logistic regression analysis on 8,010 post-menopausal women of average age 71 years, categorizing participants as either healthy or diseased (the latter group developing self-reported gallstones or requiring cholecystectomy). Modified Harvard questionnaire reports of habitual physical activity were divided into quartiles. Comparing the lowest two with the topmost physical activity quartile, the less active women had an odds-ratio of 1.57 (95% confidence interval 1.11–2.23) of developing gallbladder disease, after allowing statistically for the effects of body mass index and other known risk factors.

Walcher et al. [57] examined 2,129 adults. The overall prevalence of gallstones was 7.8%, and a multivariate analysis showed that the odds ratios for evidence of gallstones were 0.34 (95% CI 0.14–0.81) for those taking vitamin C supplements, 0.62 (CI 0.42–0.94) for those engaging in physical activity >2 h/week vs. <2 h/week, and 0.65 (CI 0.52–0.79) for those showing a high total cholesterol.
Finally, Williams and Johnston[58] looked at the prevalence of gallbladder disease in 97 rural Canadian women. The total daily energy intake was estimated from a four-day dietary record, and a three-level classification of habitual physical activity was made. After controlling for age, significant factors increasing the risk of gallbladder disease were skinfold thicknesses, reports of taking little physical activity and a limited range of energy intakes.

Negative findings

In contrast to the above reports, several quite large studies have failed to find significant associations between habitual physical activity and gallbladder disease. Friedman et al.[59] examined data from 5209 Framingham residents aged 30–62 years. Gallbladder disease was diagnosed from a combination of subjective reports and hospital records, and a simple classification of habitual physical activity was ascertained by interview. This investigation found no association between gallbladder disease and reported physical activity, but the authors admitted that analysis was made more difficult because there was little range of physical activity among their subjects.

Jorgensen[60, 61] made a four-level rating of both occupational and leisure activity in 3608 Danes aged 30–60 years. Body mass index (women), smoking (men only) and slimming treatment (men only) all showed significant associations with the risk of gallstones, but risk was unrelated to the simple index of habitual physical activity used in this investigation.

The Roman group for epidemiology and prevention of cholelithiasis (GREPCO)[64] undertook ultrasonographic examinations of 2325 Italian civil servants. A five-item questionnaire assessed habitual physical activity, but in a multivariate analysis, scores for this index showed no significant relationship to the risk of gallstones.

Pagliarulo et al.[66] studied risk factors for ultrasonographic evidence of gallstones in 1337 patients with diabetes mellitus. In this study, risk was linked to age, obesity and family history, but not to a three-level estimate of habitual physical activity.

Among other, smaller studies, Basso et al.[62] examined 512 pregnant women. A crude three-level classification of physical activity (“a lot”, “a little” or “none”) showed little relationship to the presence of gallstones as seen on ultrasound. Sakuta and Suzuki[67] examined risk factors for ultrasonographic evidence of gallstones in 974 male members of the Japanese defence forces. Gallstones were found in only 39 members; stones were associated with total homocysteine concentrations (but not with total cholesterol concentrations) after adjusting the data for lifestyle factors that included cigarette smoking, vegetable intake and habitual physical activity (a two-way classification, based on reports of undertaking sweat-producing activity). However, no comment was made about any association of risk with habitual physical activity.
Equivocal reports

Chuang et al.\cite{63} studied 53 obese women who were undergoing gastric by-pass surgery. After allowing for the effects of BMI and HDL cholesterol levels, sport participation but not occupational or leisure activity reduced the odds of discovering gallstones during surgery.

Utter et al.\cite{68} studied relationships among physical activity (as determined by an interviewer-administered questionnaire), diabetes mellitus and gallbladder disease in Puma Indians, a population with a high prevalence of clinically diagnosed gallstones. Among the men with diabetes, there was a clear decrease in incidence of gallstones from the least to the most active tertiles (14.1%, 6.1% and 4.7%). However, there were few gallstones among the non-diabetic men and an insufficient range of physical activity among the women to examine risks for the other categories of subject.

Longitudinal studies

Longitudinal studies have the advantage of greatly increasing the number of person-years of experience, and both habitual physical activity and the onset of gallbladder disease can often be determined more precisely. Three of four major trials have shown a substantial inverse association between physical activity and the risk of gallbladder disease (Table 3.5), and in two of the three trials, the level of physical activity was well known, since it was reassessed every two years. Banim et al.\cite{69} carried out a 14-year prospective trial on 25,639 volunteers aged 40–74 years. The risk of developing gallstones was evaluated against an initial four-level categorization of occupational and leisure physical activity. Comparing the most active quartile against the three less active quartiles, the hazard ratio for the development of gallstones was a statistically significant 0.3 at 5 years, and a non-significant 0.70 (95% CI 0.49–1.01) at 14 years. The authors speculated that after ten years, their initial classification of physical activity was probably no longer valid for many subjects, thus explaining the weakening of the association.

Leitzmann et al.\cite{70} completed an eight-year prospective study on 45,813 medical professionals, initially aged 40–75 years; 828 members of the group developed gallstones or underwent cholecystectomy over the course of the investigation. Comparing extremes of physical activity as determined by a detailed questionnaire, and allowing for multiple confounding variables that included diabetes mellitus, body mass index and the use of cholesterol-lowering drugs, the relative risk of gallbladder disease in the most active quintile (an estimated energy expenditure of 32.6 metabolic equivalents (MET)-h/week) was 0.65 in those aged <65 years and 0.75 in those aged >65 years. Risk was also independently associated with sedentary behaviour. Comparing those who watched >40 h of television per week with those who watched less than 6 h/wk, the risks of gallbladder disease for the sedentary individuals in 1.58 for younger men and 3.32 in older men.
Table 3.5  Longitudinal studies relating the onset of gallbladder disease to initial assessments of habitual physical activity

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Activity measurement</th>
<th>Diagnostic criterion</th>
<th>Covariates</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banim et al. [69]</td>
<td>25,639 volunteers</td>
<td>4-level categorization of occupational and leisure activity at entry to study</td>
<td>Medical diagnosis of biliary disease and/or ultrasoundography</td>
<td>BMI and other risk factors</td>
<td>Most active quartile vs. remaining quartiles; risk of gallstones in active quartile 0.3 at 5 years and 0.7 at 10 years</td>
</tr>
<tr>
<td>Kriska et al. [65]</td>
<td>2130 Puma Indians</td>
<td>Interviewer-conducted physical activity questionnaire at entry to study</td>
<td>Ultrasoundographic diagnosis of gallstones over 3–4 years</td>
<td>BMI and other confounding variables</td>
<td>Gallstones significantly related to inactivity, but relationship only statistically significant in those free of diabetes mellitus</td>
</tr>
<tr>
<td>Leitzmann et al. [70]</td>
<td>45,813 medical professionals</td>
<td>Detailed physical activity questionnaire, reassessed every 2 years</td>
<td>History of gallstones or cholecystectomy</td>
<td>Diabetes, body mass index, use of cholesterol-lowering drugs</td>
<td>Relative risk (most active quintile, 32.6 MET-h/wk) vs. least active quintile 0.65 if aged &lt;65 yr, 0.75 if aged &gt;65 yr. Adverse effects of TV watching (&gt;40 vs &lt;6h/wk) 1.58 (younger), 3.32 (older men)</td>
</tr>
<tr>
<td>Leitzmann et al. [71]</td>
<td>60,290 nurses initially aged 40–65 yr</td>
<td>Recreational physical activity and sedentary behaviour reassessed every 2 years for 10 years</td>
<td>Cholecystectomy</td>
<td>BMI and weight change</td>
<td>Relative risk of cholecystectomy, highest vs. lowest physical activity quintile, 0.69. Sitting time (&gt;60 h vs. &lt;6h) relative risk 2.32</td>
</tr>
</tbody>
</table>
Leitzmann et al.[71] collected reports of physical activity every two years for ten years in a study of 60,290 nurses who were initially aged 40–65 years. Using a multivariate analysis, they showed that the relative risk of cholecystectomy was 0.69 in the most active quintile relative to those in the least active quintile. The relative risk of cholecystectomy in those sitting >60 h/week vs. those sitting <6 h/week was also 2.32. Further, the risks associated with low physical activity and sedentary behaviour persisted after statistical adjustments for the effects of body mass index and changes of body mass.

Sahi et al.[72] made a prospective study of 16,785 male Harvard alumni, initially aged 15–24 years. Within this sample, body mass index and cigarette smoking but not physical activity as assessed for the period 1962–1966 were significant risk factors for self-reported, physician-diagnosed gallbladder disease as recorded in 1972 and 1977. As in the study of Banim et al.[69] it is possible that relationships with physical activity were obscured by a change of lifestyle between 1962–1966 and 1977.

Kriska et al.[65] carried out a three to four year prospective trial on 2130 American Indians who were initially free of gallstones. Ultrasonography was undertaken at follow-up, and 650 of the sample were found to have developed gallbladder disease over the course of the trial. After adjusting for confounding variables including body mass index, gallbladder disease was inversely related to habitual physical activity as determined by an interviewer-conducted questionnaire. However, this relationship was only statistically significant in those individuals who were free of diabetes (about a half of the total sample).

Case-control studies

With the exception of the investigation of Hou et al.[73], case-control studies have involved relatively small samples of subjects, with a corresponding limitation in their power to detect statistically significant benefits from a physically active lifestyle (Table 3.6).

Positive findings

Hou and associates[73] compared 8485 women with a self-reported physician diagnosis of gallstones versus 16,970 controls, matched by year of birth and age at diagnosis. Positive odds of developing gallbladder disease were associated with the highest vs. the lowest body mass index, with large waist and hip circumferences (3.82, 95% CI 2.47–5.23) and with the time spent sitting at work (p = 0.01). Negative odds were associated with questionnaire estimates of occupational (p = 0.03) and domestic (p = 0.02) physical activity, regardless of the individual’s level of adiposity.

Two other studies presented positive findings. Ortega et al.[74] compared 54 patients with gallstones against 46 matched controls. Physical activity habits were assessed from a simple questionnaire based on the time spent in activities such as vigorous walking and sleeping. The controls were substantially more active than
those with gallstones, but the two groups did not differ in body mass index. Ostrowska et al.\[75\] compared 169 patients with cholelithiasis and 203 controls. Preventive value was found in a moderate intensity of physical activity, both at work and in leisure time.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Physical activity or fitness indicator</th>
<th>Indicator of disease</th>
<th>Covariates</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hou et al.[73]</td>
<td>8485 cases, 16,970 controls</td>
<td>Questionnaire of occupational, commuting and domestic activity</td>
<td>Self-reported physician diagnosis of gallbladder disease</td>
<td>BMI, waist-hip circumferences</td>
<td>Gallstones positively related to sitting time and negatively associated with occupational and domestic activity</td>
</tr>
<tr>
<td>Ko et al.[76]</td>
<td>205 pregnant women with gallstones vs. 443 controls</td>
<td>Questionnaire and interviews</td>
<td>Ultrasonographic diagnosis of gallbladder disease</td>
<td>BMI, HDL cholesterol, insulin resistance</td>
<td>Data was co-varied for physical activity, but any influence not stated</td>
</tr>
<tr>
<td>Linos et al.[79]</td>
<td>100 cases, 290 controls</td>
<td>10-item physical activity questionnaire</td>
<td>Ultrasonographic diagnosis of gallbladder disease</td>
<td>Various constituents of diet</td>
<td>Energy expenditure of cases 7.05 MJ/d vs. 7.76 MJ/d in controls (p = 0.06)</td>
</tr>
<tr>
<td>Misciagna et al.[80]</td>
<td>101 female patients, 101 controls</td>
<td>Questions on walking time and sleeping time</td>
<td>Ultrasonographic diagnosis of gallbladder disease</td>
<td>BMI</td>
<td>Controls substantially more physically active than cases</td>
</tr>
<tr>
<td>Ortega et al.[74]</td>
<td>54 cases, 46 controls</td>
<td>Simple questionnaire on walking and sleeping habits</td>
<td>Ultrasonographic diagnosis of gallbladder disease</td>
<td>BMI</td>
<td>Controls show substantially more physical activity than those with gallstones</td>
</tr>
<tr>
<td>Ostrowska et al.[75]</td>
<td>54 patients, 46 controls</td>
<td>Physical activity inferred from total energy intake</td>
<td>“Proven gallstones”</td>
<td>BMI</td>
<td>No difference in body mass or response to physical activity questions</td>
</tr>
<tr>
<td>Sarles et al.[77]</td>
<td>396 cases of cholelithiasis, 397 controls</td>
<td>Two simple questions on habitual physical activity</td>
<td>Radiology and/or surgery</td>
<td>“Proven gallstones”</td>
<td>Trend to lower physical activity in men developing gallstones; no difference in women</td>
</tr>
</tbody>
</table>
Negative findings

Ko and colleagues\textsuperscript{76} compared 205 women who showed evidence of new gall-bladder sludge or stones during pregnancy against 443 controls. A logistic analysis showed that the effect of body mass index was attenuated after adjusting for insulin resistance. Insulin resistance was a predictor of cholelithiasis, even after adjusting for body mass index, HDL cholesterol and habitual physical activity. Although physical activity was assessed in this study, there was no discussion of its impact upon the risk of gallbladder disease; however, habitual physical activity would likely have modified both body mass index and insulin resistance.

Sarles et al.\textsuperscript{77} compared 101 female patients where cholelithiasis was found at operation or on radiography with 101 controls. The patients with gallstones had a greater energy intake than the controls, but neither physical activity (as assessed by questions such as “how active is your life?” and “do you like walking?”) nor body mass differed significantly between cases and controls.

Equivocal findings

Wheeler et al.\textsuperscript{78} compared 396 patients with clinically-proven cholelithiasis against 397 controls. The main focus of their study was upon diet, but physical activity levels were inferred from total energy intakes; there was an insignificant trend to a lower energy intake (and thus presumably a lower level of physical activity) in the men who had developed gallstones, but no differences of energy intake were found between female cases and controls.

Linos and associates\textsuperscript{79} compared 100 small-town Italians with gallstones against 290 matched control subjects. A multiple regression analysis that also included dietary characteristics showed a nearly significant trend to an association between gallstones and a lack of physical activity (as assessed by a ten-item physical activity questionnaire). Other significant risk factors were a diet rich in animal fats and refined sugars but poor in vegetables. The estimated energy expenditures for cases and controls were 7.05 and 7.76 MJ/d, respectively (\(p = 0.06\)). Misciagna et al.\textsuperscript{80} reported further details on what appear to have been the same 100 cases and 290 controls, reaching essentially the same conclusions.

Randomized controlled trials

There have as yet been only three small-scale randomized controlled trials of physical activity as a means of reducing the risk of developing gallstones in individuals who were initially free of gallbladder disease (Table 3.7). In each study, subjects in the intervention group were encouraged to increase their weekly volume of physical activity, but the change in behaviour relative to control subjects was quite modest. Moreover, given the sample sizes, even with a ten-year follow-up, the number of patients developing gallstones was too small to anticipate strong statistical evidence of health benefit.
Table 3.7 Randomized controlled trials relating physical activity to the risk of developing gallbladder disease

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Experimental approach</th>
<th>Diagnostic criterion</th>
<th>Covariates</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ko et al.</td>
<td>Pregnant women (591 intervention, 605 controls)</td>
<td>Physical activity of intervention group increased by motivational materials and small group instruction</td>
<td>Ultrasoundographic diagnosis of gallstones</td>
<td></td>
<td>No difference of sludge or stones at 18 or 36 weeks (but increases of physical activity quite modest)</td>
</tr>
<tr>
<td>Rexroad et al.</td>
<td>171 post-menopausal women, half assigned to a walking programme</td>
<td>Walking group energy expenditures 4.9 vs. 2.8 MJ/week for control group</td>
<td>Not stated</td>
<td>Age, body mass</td>
<td>10-year incidence of gallbladder disease 4.8% vs. 9.1% (n.s.)</td>
</tr>
<tr>
<td>Storti et al.</td>
<td>182 elderly women aged 74 years</td>
<td>7-year walking intervention, objective activity monitor</td>
<td>Self-report of gallbladder surgery or physician-diagnosed gallstones</td>
<td>BMI, hormone use, smoking and other risk factors</td>
<td>Odds ratio 1.13 lowest vs. highest tertile of walking activity</td>
</tr>
</tbody>
</table>

Randomized controlled trial (mice)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Experimental approach</th>
<th>Diagnostic criterion</th>
<th>Covariates</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilund et al.</td>
<td>50 gallstone-sensitive (C57/L/J) mice</td>
<td>Experimental group ran for 12 weeks, 45 min/d at 15 m/min</td>
<td>Collective weight of gallstones at euthanasia</td>
<td></td>
<td>Sedentary vs. exercised animals 143 vs. 57 g of gallstones</td>
</tr>
</tbody>
</table>

Note: n.s. = non-significant.

Rexroad et al.\[81\] carried out a ten-year follow up of 171 post-menopausal women who were initially free of gallbladder disease. Subjects were randomly assigned to a walking programme or a control group. At the end of the trial, the respective reported walking energy expenditures were 4.9 and 2.8 MJ/week. There was a statistically non-significant tendency (p = 0.27) to a difference in the number of diagnoses of gallbladder disease over the ten years (4.8% vs. 9.1%, 4 vs. 8 cases), and this difference became larger and statistically significant (p < 0.05) when a post-hoc comparison was drawn between highly active members of the intervention group vs. low active members of the control group (2.1% vs. 13.9%, 1 vs. 5 cases). Adjustment for age and body mass did not diminish these effects.
Storti et al.\[56\] carried out a randomized controlled trial of a walking intervention on 182 elderly women (average age 74 years). They followed their subjects for seven years. Women in the lowest tertile of habitual physical activity as determined by an objective electronic monitor had a higher risk of self-reported physician diagnosed gallstone disease than those in the top tertile (odds ratio 1.13, 95% confidence interval 1.01–1.28; 6 vs. 0 cases).

Ko et al.\[82\] randomized pregnant women between what was intended as a moderate exercise intervention (n = 591) and a control group (n = 605). The intervention (motivational materials and participation in small group educational sessions) produced only modest increases in reported physical activity, and the incidence of gallbladder sludge and/or stones in the experimental subjects was unchanged relative to that in the control group at either the 18th or the 36th week of pregnancy (25 vs. 20 cases).

**Animal experiments**

Animal experiments have the advantage that the daily dose of physical activity can be closely controlled. However, it is not easy to transfer the conclusions to humans. The enforced exercise is often stressful for the animal, there are substantial differences of anatomy and physiology between laboratory animals and humans, and it is difficult to evaluate effects from differences of body size and life span.

Wilund and associates\[83\] carried out a small controlled trial on a sample of 50 gallstone-sensitive (C57-L/J) mice. Animals in the experimental group ran on a treadmill for 12 weeks, 45 min/day at a speed of 15 m/min, and they were then euthanized. The pooled weight of gallstones was 2.5 times greater in the animals that had remained sedentary than in the experimental group (a total weight of 153 vs. 57 mg). However, by the end of the experiment, the sedentary animals were also more obese than those in the experimental group, and the accumulation of fat could have contributed to the greater gallstone formation in control animals.

**Overall conclusions**

The overall findings are by no means unanimous. In cross-sectional comparisons, some have seen a reduced frequency of gallbladder disease in individuals who were physically more active,\[55–58\] but others have reported equivocal findings\[65, 65, 68\] or have observed no such association.\[59–62, 64, 66, 67\] Nevertheless, studies finding a significant effect were mostly those with the largest sample size.\[55–57\] Possibly, the absence of a significant effect in other cross-sectional studies could reflect an inadequate sample size and/or a weak assessment of habitual physical activity. Longitudinal studies generally support the cross-sectional work, with three of four major investigations showing substantial benefit to the physically active group. Leitzmann et al.\[70\] concluded that the risk of gallstone disease could be reduced 34% by taking as little as 30 minutes of aerobic exercise five times/week.
Case-control studies provide further tentative support for the health benefits of regular physical activity; three reports (including by far the largest of seven studies[73]) showed positive effects, and in two other papers there were non-significant trends towards benefit. One small study with a weak measure of physical activity showed no benefit, and in the final study there was no comment on any possible effect of physical activity.

Randomized controlled trials have not to date resolved these controversies. The increases of habitual physical activity achieved by experimental interventions have been quite small, and with the sample sizes used, the number of cases developing gallstones have been too few to demonstrate a statistically significant effect. There are many differences between laboratory animals and human subjects, but a single trial in mice supports the view that regular exercise reduces the risk of gallstones.

Nevertheless, the weight of evidence seems to point towards a reduced risk of gallbladder disease in those who are active, and this seems one more reason for clinicians to urge adoption at least the minimum recommended levels of daily physical activity.

Possible mechanisms of altered risk

If indeed the risk of gallbladder disease is diminished by engaging in regular physical activity, what are the likely mechanisms of benefit? One tempting explanation is a reduction of biliary stasis, brought about by an increase of gallbladder motility[44, 84, 85] that is mediated through increased neural stimulation, cholecystokinin secretion[86, 87] and/or an increase of gastro-intestinal transit rates.[84] However, the empirical data supporting any decrease in biliary stasis are by no means conclusive. Regular exercise could also address other major risk factors, including obesity, a high serum cholesterol level and type 2 diabetes mellitus. Moreover, a focus upon individuals who adopt an active lifestyle could identify health-conscious people who have favourable dietary practices and avoid cigarette smoking. However, some published trials have controlled for such co-variates, and these studies suggest that regular physical activity reduces the risk of cholelithiasis beyond any effects attributable to the control of body mass, diet and other risk factors.[69–71] Regular physical activity speeds gastro-intestinal transit[84] and this could decrease the resorption of cholesterol from the large intestine,[84, 88] thus reducing the risk of a supersaturation of the bile.[49, 63, 87] Finally, regular physical activity could act upon the liver, modifying the synthesis of cholesterol phospholipids and bile acids and/or altering their excretion into the bile.[83]

Studies in mice bred for their susceptibility to gallbladder disease have shown that training also increases the hepatic expression of two genes (LDLr and SRB1) that are known to be involved in the clearance of cholesterol. Exercised mice demonstrate an up-regulation of the protein Cyp27 that is associated with the hepatic production of bile acids.[83] The net effect of exercise upon the intestinal reabsorption of cholesterol remains less clear. Trained animals show a reduced
expression of NPC1L1 (which would reduce cholesterol reabsorption), but at the same time there is a reduction in the expression of ABCG5 and G8 (which would have the effect of increasing cholesterol reabsorption).[83]

**Physical activity and gallbladder cancer**

Gallbladder cancer accounts for 80–95% of malignant lesions of the biliary tract. The incidence in North America is quite low (about 1.5/100,000 people). Three papers have examined associations between habitual physical activity and the risk of developing such neoplasms (Table 3.8). In order to accumulate an adequate number of cases, investigators have needed to follow very large populations for long periods, and the measures of habitual physical activity have been correspondingly weak.

Behrens et al.[89] examined data on 507,981 participants in the National Institutes of Health-Association of Aging and Retired Persons (NIH-AARP) Diet and Health Study. They looked at the association between the frequency per week of physical activity (lasting >20 min and of sufficient intensity to work up a sweat) and the risk of hepatobiliary cancer. Over a ten-year follow-up, there were 317 cases of incident biliary cancer. A multivariate analysis compared the most active (vigorously active >5/week) with the least active individuals (never or rarely engaging in vigorous activity). When data were simply adjusted for age

| Table 3.8 Prospective studies showing a possible association between habitual physical activity or fitness level and the risk of gallbladder or biliary tract cancer |
|---|---|---|---|---|
| **Author** | **Subjects** | **Measure of activity or fitness** | **Covariates** | **Conclusions** |
| Behrens et al.[90] | 507,981 individuals initially aged 50–71 years | Frequency of activity bouts lasting >20 min and of sufficient intensity to develop a sweat | Multiple variables, including BMI | 317 cases of biliary cancer in 10 year follow-up; most active quartile vs. 3 least active quartiles, relative risk 0.63 (0.33–1.21) |
| Peel et al.[91] | 38,801 men attending Cooper Aerobics Center | Treadmill endurance time | Age, smoking, alcohol consumption, diabetes, family history of cancer, BMI | 7 cases of gallbladder cancer over up to 28 years. Non-significant trend favouring fit over unfit individuals (RR 0.83, 0.09–7.74) |
| Yun et al.[90] | 444,693 men aged >40 years | 2-level classification of habitual physical activity | Dietary preferences | Almost significant reduction of risk of gallbladder cancer for those with moderate or vigorous physical activity (RR 0.81, 0.65–1.02) |
and sex, there was a suggestion of benefit (odds ratio 0.47 for the active individuals), but with a fuller multivariate analysis that included other known risk factors, somewhat favourable trends were no longer statistically significant for tumours in the extra-hepatic bile duct (0.86, 95% CI 0.45–1.65), the ampulla of Vater (0.66, 95% CI 0.29–1.48) or the gallbladder itself (0.63, 95% CI 0.33–1.21).

Yun et al.[90] made a six-year follow up of 444,693 Korean men aged >40 years, including their reported dietary preferences as co-variates in the analysis. A two-level classification of habitual physical activity yielded an almost significant reduction in the risk of gallbladder cancer among those who habitually engaged in moderate or vigorous physical activity (risk ratio 0.81, 95% CI 0.65–1.02).

Peel et al.[91] used treadmill endurance times as a measure of attained aerobic fitness and a presumed surrogate of habitual physical activity in a study of 38,801 men attending the Cooper Aerobics Center in Dallas, Texas. Over a 28-year follow-up there were only seven cases of gallbladder cancer, but these cases showed a weak non-significant trend favouring the fit over unfit individuals (relative risk 0.83, 95% CI 0.09–7.74).

Thus, all three prospective studies of habitual physical activity and biliary tract cancer showed a non-significant trend to a reduced risk of gallbladder cancer in the more active individuals. Further investigation with even larger samples and/or a meta-analytic combination of data from several studies may in the future provide a statistically more convincing proof that regular physical activity has significant value in preventing cancer of the biliary tract. If indeed the reduced risk is confirmed by further study, possible mechanisms of benefit could include not only a lesser frequency of cholecystitis, but also a reduction of body mass, an increase of insulin sensitivity, a reduction of oxidant stress and a lesser likelihood of cigarette consumption among regular exercisers.[89]

Areas for further research

There is scope for further study of cholecystokinin concentrations, coupling this data with measures of gallbladder emptying.[41] Moreover, further investigations are needed to clarify conflicting evidence concerning the effects of physical activity and gallbladder function.[44, 45]

In terms of gallbladder disease, objective pedometer/accelerometer monitoring could be used to provide more accurate information on the volume of physical activity undertaken in cross-sectional, prospective and case-control trials. Such monitors are now sufficiently inexpensive that it is possible to collect data on large population samples, particularly older individuals whose main form of daily activity is walking. There is also scope for more randomized controlled trials, both in humans and in animals. In human trials, the incidence of gallbladder disease could possibly be increased by focusing on recruiting high-risk groups, as in the animal experiments of Wilund et al.[83] A meta-analysis of closely similar trials might also serve to accumulate sufficient data to demonstrate statistically significant effects. Meta-analysis certainly seems the only approach that is likely
to yield an adequate number of cases to test the effects if physical activity upon gallbladder cancer.

**Practical implications and conclusions**

Gallstones form if supersaturated biliary fluid remains in the gallbladder for too long. Gallstones predispose to chronic infection and cancerous change in the biliary tract. Current evidence suggests that an acute bout of physical activity may increase the motility and emptying of the gallbladder, thus reducing the risk of gallstone formation and limiting exposure of the gallbladder to carcinogenic chemicals. Although many investigations have now examined the influence of acute and chronic physical activity upon gallbladder function and susceptibility to disease, the findings remain suggestive rather than conclusive. In terms of gallbladder motility and biliary stasis, one uncontrolled report suggested a modest benefit from four weeks of aerobic exercise, and a second study found a similar change following 12 weeks of roughly equivalent physical activity, but any change was not significant relative to control subjects. Many cross-sectional, prospective and case-control studies have pointed towards some reduction in the risk of gallbladder disease among physically more active individuals, but randomized controlled trials have lacked the statistical power to confirm these observations. Nevertheless, observations on gallstone-sensitive mice support the overall inference from human studies that there is indeed some benefit from regular physical activity.

The potential clinical value of exercise programmes in preventing gallstone formation could be substantial. One prospective five-year study of 25,639 adults suggested that after adjusting for other risk factors, individuals with the highest level of physical activity had a 70% lower risk of symptomatic gallstones than those who were sedentary. This particular report left unclear whether physical activity had actually reduced the risk of gallstone formation, or whether it had merely made the onset of symptoms less likely. However, other studies with ultrasonographic monitoring of gallstone formation have provided good evidence that not only are symptoms reduced, but the prevalence of gallstones is lower among individuals who engage in regular physical activity.

The practicality of encouraging greater physical activity in those who are at risk is less clearly established. The person who develops gallstones is typically an obese middle-aged woman, and it is not easy to bring about and sustain a substantial increase of physical activity in such a population. The prospective study of Banin et al. estimated that 161 patients would have to be treated in order to avert a single case of symptomatic gallstones. Possibly, programmes should be justified in part on the basis of the remaining 160 people who make substantial increases in their habitual physical activity and who thus gain important health advantages unrelated to changes in gallbladder function.

Chronic gallbladder infection also predisposes to cancer of the biliary tract, and a limited number of prospective studies suggest that regular physical activity may reduce this risk.
References

4 Physical activity and kidney function in health and disease

Introduction

This chapter examines the impact of physical activity upon the normal functioning of the kidneys, and explores such manifestations of temporary dysfunction as exercise-induced microproteinuria and microhaematuria. It also considers the potential of developing acute renal failure during a prolonged bout of exhausting exercise and the possibility of chronic renal damage in athletes with an excessive intake of creatine supplements or non-steroidal anti-inflammatory drugs (NSAIDs). Turning to issues of renal disease, it then examines the place of exercise programmes in the rehabilitation of patients who are undergoing dialysis or who have received renal transplants, and it considers the possibility that regular physical activity may reduce the risk of renal cancer. Finally, it looks at the impact of physical activity upon the endocrine function of the kidneys and the development of kidney stones. The following chapter discusses the tricky clinical issue of advice that should be given to the competitive athlete who has only a single kidney.

Physiological background

The kidneys play an important role in the maintenance of fluid and electrolyte homeostasis at rest, and this function becomes even more critical when equilibrium is challenged by the demands of athlete who engages in vigorous physical activity. An interplay between renal artery perfusion pressure and sodium excretion influences the renin-angiotensin-aldosterone system, thus making an important contribution to the regulation of systemic blood pressure. However, the impact of acute and chronic physical activity upon function of the healthy kidney has received relatively little attention in physiological texts, and even less is known about interactions between habitual physical activity and long-term renal health.

When writing The Physiology of Muscular Exercise in 1919, Francis Bainbridge[1] did not discuss renal issues. Other books on exercise physiology written from the 1930s to the 1970s[2–5] also gave scant recognition to the impact of physical activity upon the renal system, although there were some exceptions.
Sir Charles Lovatt Evans commented in a general physiology text “a small trace of albumin will often be found in the urine which is passed shortly after taking muscular exercise, but it has no pathognomonic significance”. Laurence Wesson also contributed a brief chapter on kidney function to a text on exercise and sports medicine, emphasizing the adjustments of renal plasma flow and glomerular filtration rates that were seen during a bout of vigorous exercise, and David Lamb devoted an 11-page chapter to the kidneys in his exercise physiology text.

Others have focused on such overt responses to vigorous physical activity as proteinuria, haemoglobinuria and myoglobinuria. In 1878, von Leube noted proteinuria in 14 of 119 soldiers after they had completed a strenuous 1–3 day march, and in 1910 J.H. Barach commented on microscopic haematuria in 18 of 19 marathon runners shortly after they had completed their event. Barach pointed out that runners with the highest blood pressures at the end of the race excreted the most protein. In contrast, Hellebrandt attributed albuminuria to the drop in blood pressure that commonly followed a bout of strenuous exercise. Edwards et al. observed that 13 of 13 football players had albuminuria after 45–60 minutes of play. Jundell and Fries emphasized that at any given intensity of effort, the extent of proteinuria was reduced after subjects had undergone aerobic training.

The diversion of renal plasma flow from the kidneys to the working muscles was first inferred by Edwards and colleagues on the basis of an exercise-related reduction of urea clearance, a phenomenon noticed earlier by Addis and Drury and by MacKay. The magnitude of such changes was first estimated by Barclay et al., using a diodrast clearance technique. A full-speed 400 m run caused a 45% decrease in glomerular filtration and a 39% decrease in renal blood flow. White and Rolf confirmed these observations, noting that while light jogging induced little change, heavy exercise could reduce renal perfusion by up to 80%, with a five-fold increase of renal vascular resistance. Observations by Chapman et al. and Grimby demonstrated the impact of both absolute and relative exercise intensity on the reduction of plasma flow, with persistence of the flow deficit for as long as 40 minutes following exercise. Robinson and colleagues further demonstrated that these adverse changes were exacerbated if an athlete was dehydrated or exercising in a hot environment.

In 1921, Campbell and Webster introduced the idea of measuring glomerular filtration in terms of creatinine excretion. Their attempts to determine how filtration was affected by physical activity led to inconclusive results, but subsequent authors have used both creatinine and inulin clearance techniques to demonstrate that there is a substantial decrease of glomerular filtration in response to vigorous physical activity.

Physical activity and renal blood flow

In humans, renal blood flow has commonly been estimated by the clearance of diodrast or para-amino hippurate. Other options have included thermodilution...
(using a thermistohr to measure intravascular temperature following injection of a warm solution), positron emission tomography (collecting the gamma rays as a marker perfuses the kidney), radionuclide angiography (detecting the emissions from a $^{99m}$Technetium infusion) and Doppler ultrasound. Animal experiments have commonly been based on the passage of radio-labelled microspheres through the kidneys. Other techniques used in animal research have included a thermostromuhr (a small intravascular electrical heater positioned between two thermocouples), an electromagnetic flow transducer, Doppler ultrasound and Technetium clearance (Table 4.1).

Under resting conditions, the kidneys receive about a quarter of the total cardiac output, a perfusion rate of some 4 ml/min per gram of renal tissue. Flow is directed mainly to the renal cortex, where a high flow rate persists over a wide range of systemic blood pressures. The efferent blood vessels leading from the renal glomeruli are smaller than the afferents. Thus, the hydrostatic pressure within the glomeruli is high, and this tends to force small molecules (water, glucose, amino acids, sodium chloride and urea) across the glomerular membrane from the renal capillaries into the nephrons. This process of molecular transfer is termed glomerular filtration and it is commonly evaluated in terms of creatinine clearance (the rate of creatinine excretion, divided by the plasma creatinine concentration). Some 15% of renal plasma flow is filtered into the glomeruli under resting conditions.\textsuperscript{30} However, filtration tends to fall during physical activity, as a means of enhancing muscle blood flow.\textsuperscript{31} Much of the material excreted into the glomeruli is normally reabsorbed in the renal tubules, but in very vigorous exercise, the process of reabsorption may either become over-loaded because of increased leakage of protein into the glomeruli, or it may be impaired by a local oxygen lack associated with the physical activity itself.

In humans, indirect measurements of renal plasma flow using diodrast and para-amino hippurate clearance techniques suggest that exhausting endurance exercise quickly initiates a general visceral vasoconstriction. Renal vascular resistance can increase as much as fivefold.\textsuperscript{21} Renal blood flow is reduced by 70% or more\textsuperscript{32–34} (Table 4.1), depending on the intensity of exercise,\textsuperscript{22, 35} with the extent of vasoconstriction exacerbated by heat exposure or dehydration.\textsuperscript{25} Changes seem related to the release of epinephrine and dopamine,\textsuperscript{36} and they can persist for a substantial time following a sustained bout of exercise.\textsuperscript{20, 22} One comparison of young and elderly men found little difference in flow reduction with age, but in this study the two groups had surprisingly similar levels of maximal oxygen intake,\textsuperscript{37} suggesting that the older individuals were unusually fit. The flow reduction is abolished by the vasodilator dihydralazine.\textsuperscript{38}

Most studies have involved dynamic forms of physical activity, although vigorous static muscular contractions also decrease renal blood flow.\textsuperscript{40, 41} The renal vasoconstriction of endurance exercise seems a manifestation of sympathetic nerve activity. Likewise, the vascular constriction associated with static handgrip exercise is largely absent in humans who have received kidney transplantation and thus lack a renal autonomic nerve supply.\textsuperscript{41}
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<td>402 m run reduced renal plasma flow 39%, from 736 mL/min to 447 mL/min</td>
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<td>Chapman et al.[22]</td>
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<td>Author</td>
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<td>Middlekauf et al.[40]</td>
<td>20 males, 9 females</td>
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<td>Momem et al.[41]</td>
<td>7 transplant patients (2–27 months post-op.), 11 matched controls</td>
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<td>Radigan &amp; Robinson[24]</td>
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<td>Treadmill, 4.2 km/h, 5% grade; renal blood flow decreased 39–42% when exercising in cool, fell 39% at rest in heat, and further 31% fall when exercising in heat</td>
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<td>Rowell[33]</td>
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<td>Suzuki et al.[34]</td>
<td>6 males</td>
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<td>Armstrong &amp; Laughlin</td>
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<td>6 weeks of sprint training did not change 63% renal flow reduction with exercise</td>
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</table>
Miniature swine trained to run on a treadmill show a 70% reduction of renal blood flow during vigorous physical activity.\cite{52, 53} Horses and ponies also show a 50% reduction of renal blood flow as soon as they begin to walk.\cite{31, 50} However, the response of dogs and baboons\cite{43, 45, 46, 48, 51, 54–56} apparently differs from that of humans; conscious animals of these species sometimes show an immediate decrease of renal blood flow, but resting values return as the exercise continues, even if the animal is engaged in such heavy exercise as pulling a sled or running 2.4 km at a speed of about 32 km/hr. Millard and colleagues\cite{48} suggested that in dogs, any vasoconstriction occurred in the face of blockade of the autonomic nerves, and thus was a form of auto-regulation. However, in rabbits the early reduction of renal blood flow was not seen after denervation of the baro-receptors,\cite{44} suggesting that the immediate stimulus to renal vasoconstriction was an exercise-induced rise of systemic blood pressure.

### Table 4.1 continued

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<td>7 20–30 kg dogs</td>
<td>Pulsed ultrasonic flowmeter</td>
<td>Treadmill 4.2–7.2 km/h, 12% slope produced initial drop, then return to normal renal blood flow</td>
<td>Slight decreases of renal blood flow during spontaneous activity</td>
</tr>
<tr>
<td>Sanders et al.\cite{52}</td>
<td>14 miniature swine aged 6–9 months</td>
<td>Radio-labelled microspheres</td>
<td>Exercise at 4.8–7.2 km/h, 0–10% grade; 34% flow reduction with moderate, 70% reduction with severe exercise</td>
<td></td>
</tr>
<tr>
<td>Stebbins &amp; Symons\cite{53}</td>
<td>12 miniature swine</td>
<td>Radio-labelled microspheres</td>
<td>20 min exercise at 80% of heart rate reserve reduced renal blood flow 36% (31% if treated with Losartan)</td>
<td>Losartan is an angiotensin II antagonist</td>
</tr>
<tr>
<td>Van Citters &amp; Franklin\cite{54}</td>
<td>18 sled dogs</td>
<td>Doppler ultrasound/ telemetry</td>
<td>Sledge hauling did not change renal blood flow</td>
<td></td>
</tr>
<tr>
<td>Vatner et al.\cite{55, 56}</td>
<td>9 adult baboons</td>
<td>Doppler ultrasound</td>
<td>Blood flow to kidneys showed minor reductions during spontaneous exercise in outdoor enclosure</td>
<td></td>
</tr>
</tbody>
</table>
Training reduced the renal vasoconstriction of exercise in one study of rats,[42] but another report found no difference in response after six weeks of sprint training.[49] The impact of exercise was greater in elderly than in young adult animals.[47]

**Physical activity and glomerular filtration**

Glomerular filtration is the process whereby fluid and solutes are filtered from the renal capillaries into the renal glomeruli and nephrons. It is usually measured in terms of the clearance of a marker such as inulin that is freely filtered by the kidneys, and does not undergo subsequent metabolism, secretion or reabsorption in the renal tubules. In humans, vigorous physical activity leads to a progressive drop in the glomerular filtration rate (GFR) as renal perfusion decreases.[57] Changes in both renal blood flow and glomerular filtration are apparently proportional to the intensity of effort,[23, 58, 59] and are greater in young than in older subjects.[60] GFR decreased by 18% following a half-marathon event[61] and a 230 km Alpine cycle event,[62] by 25% after a 525 km Alpine ultra-marathon ride[63] and by 30% after an 81 km Nordic ski race.[20, 64] A bout of circuit training also reduced the estimated GFR by 8–10%.[65] Values may fall to 60% of resting figures during maximal exercise, with substantial associated decreases in creatinine and urea clearance. In one of the studies cited above, the GFR had largely normalized within six hours of ceasing exercise.[61] but decreases of GFR have persisted for 24 hours following both a 21 km run[66] and two endurance cycle races.[62, 63]

The decrease in GFR is usually somewhat smaller than that for renal blood flow. Thus, the GFR per unit of blood flow (i.e. the filtration fraction) increases progressively from a resting figure of 15% to 25% or more during a severe bout of exercise.[20, 38, 67]

**Physical activity and other aspects of renal physiology**

Physical activity usually has a marked anti-diuretic effect, as the pituitary gland attempts to maintain plasma volume in the face of fluid losses in sweat by increasing plasma concentrations of anti-diuretic hormone. However, this compensatory mechanism is not always sustained during prolonged heavy exercise.[20, 30] There is also an increased secretion of the hormone aldosterone; this facilitates the reabsorption of sodium ions in the glomerular tubules, countering increases in the secretion of atrial natriuretic peptides that would otherwise have increased glomerular flow rate and sodium excretion.[58, 68] Other factors limiting the action of atrial natriuretic peptides during heavy exercise likely include greater renal sympathetic nerve activity, and increased blood levels of angiotensin II and catecholamines.[57] Urodilatin is a hormone similar to the atrial natriuretic peptides and it causes diuresis by augmenting renal blood flow. The kidneys increase the output of this substance during physical activity.[69] Further research is needed to clarify the respective contributions of urodilatin and atrial natriuretic peptides to the exercise response.
Despite large increases in plasma lactate concentrations during exhausting activity, renal mechanisms of lactate excretion quickly become saturated and urinary excretion is a minor consideration in the metabolism of lactate during exercise.\[^{78, 71}\] Only minor quantities of lactate have been found in the urine after such activities as mountain climbing\[^{72}\] or five hours of hard work.\[^{27}\] Some of the lactate entering the renal glomeruli is actively reabsorbed in the proximal renal tubules.\[^{73}\] A part is reconverted to glucose,\[^{74}\] although the gluconeogenic capacity of the renal cortex is only about a fifth of that of liver tissue. There is some evidence that the acidosis associated with vigorous exercise stimulates a doubling of the activity of the kidney enzymes involved in this process.\[^{75}\]

If the exercise has been very severe, there may be a rise of serum creatinine. Creatinine concentrations >0.3 mg/dl or >50% over baseline usually indicate acute renal dysfunction.\[^{76–78}\] although in athletes with well-developed muscles and a large muscle mass, care must be taken to interpret absolute concentrations relative to the individual’s body mass index.\[^{79}\]

Given extensive losses of sodium ions in sweat, it is important to reduce the renal excretion of sodium during vigorous physical activity. During a marathon run, the renal excretion of sodium ions decreases by 30–50%.\[^{67}\] Commonly, the change is larger than can be explained by a decrease in glomerular filtration; altered secretions of the hormones renin-angiotensin and aldosterone are probably involved, as well as a direct action of the renal sympathetic nerves.\[^{80}\]

Other changes in renal function during physical activity can include an oliguria (defined clinically as a urinary secretion in the range 80–400 mL/day) and a rise of serum potassium levels. Unless an athlete drinks large volumes of fluid during a prolonged event, urine output decreases by 50% or more. There is generally an associated increase in urinary acidity and electrolyte concentrations, although very heavy physical activity may impair a person’s ability to concentrate the urine.\[^{81, 82}\] If the antidiuretic effect of exercise is combined with an over-enthusiastic drinking of water or hypotonic fluids and exposure to a cool environment, this can potentially induce the dangerous condition of hyponatraemia;\[^{83}\] the normal lower limit of plasma sodium is 135 mE/L and symptoms are likely if the sodium ion concentration falls below 130 mE/L.

**Exercise-induced proteinuria**

Proteinuria may reflect either an increased glomerular filtration of protein molecules or a slowing in their tubular resorption.\[^{84, 85}\] The rate of protein filtration depends upon the health of the kidneys and the balance of hydrostatic and osmotic pressures across the glomerular membrane.\[^{86}\] Thus, an exercise-induced increase of systemic blood pressure can increase protein filtration. An accumulation of acids (including lactic acid) in the renal tissue may also increase protein loss,\[^{14, 87}\] and the abolition of proteinuria following administration of indomethacin suggests that prostaglandins may be involved in the process.\[^{88}\]
At rest, urinary protein excretion averaged over a 24-hour period is less than 80 mg/L, and values >100 mg/L are suggestive of a renal pathology. Alternative definitions of abnormality are a total urinary protein loss >150 mg/day or >100 mg/day and/or an albumin loss >30 mg/day. It is important to draw a clinical distinction between microalbuminuria and macroalbuminuria. Microalbuminuria is a normal phenomenon in those who engage in prolonged and vigorous physical activity. It is characterized by a protein loss in the range 30–300 mg/day, with a urinary albumin/creatinine ratio of >3.5 mg/mmol in women and >2.5 mg/mmol in men. Hohwü-Christensen and Högberg found a post-exercise proteinuria in almost all top Swedish cross-country skiers (Table 4.2), and Gardner found protein in 45% of urine specimens collected from 47 football players. Others have described proteinuria following participation in various sports with the magnitude of protein loss being proportional to the intensity of effort. Gardner coined the term “athletic pseudonephritis” for his findings, since the red cell and broad granular casts he observed in the urinary sediment had previously been considered (erroneously) as a sign of renal disease; these findings disappeared quickly after completion of the athletic season and he thus reasoned they had little clinical significance.

For most investigators, macroalbuminuria implies a protein loss >300 mg/day and values in excess of this threshold are harbingers of underlying renal disease. Cubeddu et al. noted that a protein excretion substantially smaller than 300 mg/day was sometimes still associated with various cardiac risk factors and could be corrected by reductions in obesity, hypertension and insulin resistance. They thus suggested that clinicians should set the limit of normality much lower than 300 mg/day; in their view, urinary protein losses of 10–29 mg/day were associated with an adverse prognosis.

Most urinary protein is in the form of relatively small molecules (molecular weights <200,000 Daltons). Some 20 mg consists of pre-albumin and albumin, and the residue includes transferrin (an iron carrying glycoprotein), the k and g light chains of immunoglobulin, Tamm Horsfall mucoproteins (secreted by the renal tubules) and a and g immunoglobulins (probably derived from the renal tubules). Although well-standardized laboratory assays of urinary protein are now available, assessments are commonly based on the colour changes seen during a simple urine dipstick test (Albustix). This detects albuminuria reasonably well, but is less effective in measuring the loss of low molecular weight proteins, gamma globulins and haemoglobin. Estimates of protein loss can also be compromised if urine is retained in the bladder following exercise, and rather than expressing protein loss per unit volume of urine, it is preferable to relate it to the excretion of creatinine.

Techniques involving paper electrophoresis and the use of immune antisera have allowed identification of the various proteins and thus to infer glomerular and tubular contributions to the observed protein loss. Glomerular proteinuria yields a urine with a high proportion of plasma constituents and is commonly assessed in terms of albumin loss. A normal albumin excretion but an increased excretion of alpha-1-microglobulin suggests that the disorder is of
<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alyea &amp; Parish[103]</td>
<td>Participants in various sports</td>
<td>70–100% showed albuminuria in track, lacrosse, crew, football and distance swimming</td>
<td>Red cells and casts also seen in 60–80% of athletes</td>
</tr>
<tr>
<td>Bailey et al.[94]</td>
<td>369 athletes</td>
<td>Proteinuria frequent, incidence increased with intensity of exertion</td>
<td>42 of 369 athletes had positive occult blood test</td>
</tr>
<tr>
<td>Barach et al.[104]</td>
<td>19 Marathon runners</td>
<td>18/19 developed proteinuria immediately following their event</td>
<td></td>
</tr>
<tr>
<td>Coye &amp; Rosandich[93]</td>
<td>10 football players</td>
<td>Protein content of urine increased 2–15-fold in 24 hours following a game</td>
<td>Larger increase in albumin than in globulin</td>
</tr>
<tr>
<td>Edwards et al.[13]</td>
<td>42 Harvard football players (male)</td>
<td>Incidence of proteinuria rises from 4/9 (first period) to 13/13 (final period)</td>
<td>Proteinuria estimated from turbidity in nitric acid test; average degree of turbidity rises as match continues</td>
</tr>
<tr>
<td>Gardner[84]</td>
<td>47 football players, 424 urine specimens</td>
<td>45% of samples showed proteinuria</td>
<td>Unusual formed elements in 27 of 424 samples, gross haematuria in 1 sample</td>
</tr>
<tr>
<td>Hellebrandt et al.[14]</td>
<td>Cycle ergometry, load ~120 Watts</td>
<td>Exhausting exercise gives immediate proteinuria; prolonged exercise gives proteinuria during post-exercise hypotension</td>
<td>Sulpho-salicyclic acid turbidity method</td>
</tr>
<tr>
<td>Hohwü-Christensen and Högberg[102]</td>
<td>204 top cross-country skiers</td>
<td>Almost all (92%) showed proteinuria immediately after skiing</td>
<td>Also haematuria in 28% of skiers</td>
</tr>
<tr>
<td>Javitt &amp; Miller[105]</td>
<td>5 healthy university students</td>
<td>Proteinuria peaked 5 minutes after 3–22 min vigorous treadmill runs</td>
<td>Protein loss correlated with both decreased glomerular filtration and renal acidity</td>
</tr>
<tr>
<td>Kachadorian et al.[97]</td>
<td>51 20 km runners</td>
<td>Proteinuria in 41/51</td>
<td>Proteinuria associated with cast formation</td>
</tr>
<tr>
<td>Nedbal &amp; Seliger[106]</td>
<td>41 normal young men</td>
<td>All showed proteinuria after 5 min treadmill run</td>
<td>Protein fractions show similar distribution to that in blood</td>
</tr>
<tr>
<td>Perlman et al.[98]</td>
<td>499 males, progressive treadmill test to exhaustion</td>
<td>Incidence of proteinuria (average 10.6%) increased with age to 4th decade</td>
<td>Albustix method</td>
</tr>
<tr>
<td>Poortmans &amp; Labilloy[99]</td>
<td>15 men, 100m, 400m and 3000m runs</td>
<td>5-, 25- and 18-fold increase of protein excretion</td>
<td>Protein loss influenced by intensity and thus lactate accumulation</td>
</tr>
</tbody>
</table>
Tubular proteinuria usually reflects a saturation of reabsorption mechanisms by a high rate of glomerular protein leakage, with the urine containing a large fraction of normally reabsorbed low molecular weight proteins such as lysozymes and the beta-2 microglobulins. Defects of tubular reabsorption can be demonstrated by examining the changes in proteinuria following lysine perfusion; lysine blocks the normal tubular reabsorption of protein.

Protein reabsorbed in the renal tubules may be metabolized locally, or it may be returned to the circulation as intact protein molecules, polypeptides and amino acids.

### Clinical significance of resting microglobinuria

Under resting conditions, even a low-level microglobinuria can be the harbinger of an adverse prognosis. In children, the extent of daily protein loss is, paradoxically, inversely related to the individual’s obesity. Possibly, this is because thin children have a much higher level of daily physical activity and are therefore more likely to boost their average protein excretion by periods of exercise-related proteinuria. In adults, resting microglobinuria merits a careful examination of the patient, since it is associated with an increased risk of many chronic conditions, including the metabolic syndrome, atherosclerotic heart disease, hypertension, ischaemic stroke, left ventricular hypertrophy, cardiomyopathy, cardiovascular death, all-cause mortality, diabetic nephropathy, chronic obstructive pulmonary disease, cancer (particularly bladder and lung cancer) and systemic inflammation as indicated by high blood levels of c-reactive protein.

The pathological bases for associations between resting urinary protein loss and chronic disease remain unclear. When predicting prognosis in chronic renal disease, the estimated GFR is a stronger predictor of mortality than the extent of proteinuria. Cardiorespiratory fitness also remains a significant predictor of mortality, irrespective of the individual’s GFR. The detection of exercise proteinuria has some value in indicating the likelihood of developing persistent microproteinuria in diabetes, but microalbuminuria is not usually associated with impaired insulin sensitivity or with exercise proteinuria.

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**Table 4.2 continued**

<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Todovorić et al.</td>
<td>11 male physical education students</td>
<td>Cycle ergometer exercise to heart rate of 170–180 beats/min; proteinuria in 10/11 constant effort and 11/11 variable intensity</td>
<td>Proteinuria related to lactate accumulation, greater with variable intensity effort</td>
</tr>
<tr>
<td>von Leube</td>
<td>119 soldiers</td>
<td>14/19 showed proteinuria after 1–3 day march</td>
<td></td>
</tr>
</tbody>
</table>

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Kidney function in health and disease
Physical activity and microhaematuria

Microhaematuria is defined as the presence in the urine of >3 red cells per high-power microscopic field\textsuperscript{[155, 156]} or more than 50 red cells per mL of fluid\textsuperscript{[157]}. Estimates of the prevalence of microhaematuria in the general population range from 0.19% to 16.1%\textsuperscript{[158]}. Exercise-related microhaematuria is most commonly seen in distance runners. Haematuria was found in 9 of the 50 marathoners immediately following their event, although all initially had a normal urine; the blood disappeared in all 9 individuals within 48 hours\textsuperscript{[159]}. Others have set the prevalence of microhaematuria in those running distances of 21–90 km at 20–25%\textsuperscript{[160, 161]}. Red cells are usually seen in the first specimen of urine collected after a run, and findings are apparently independent of the intensity of effort. Potential explanations include repeated impacts of the posterior wall of the bladder against its base (particularly during running on hard surfaces) and glomerular bleeding due to local hypertension, vascular spasm and hypoxic damage\textsuperscript{[160, 162, 163]}. One report suggested that haematuria could be avoided if the bladder was not completely emptied prior to a run; it was hypothesized that the residual urine provided a hydrostatic cushion, reducing impacts of the posterior bladder wall with the base\textsuperscript{[163]}. The presence of haemoglobin or myoglobin can also cause the secretion of a red-coloured urine, as in acute renal failure (below). In acute rhabdomyolysis, myoglobin may be found in the absence of haemoglobin\textsuperscript{[157]}

Although microhaematuria can be precipitated by vigorous physical activity, a careful history, physical examination and a laboratory evaluation that include an estimate of glomerular filtration rate are required to rule out both menstruation and potentially dangerous causes of haematuria such as infection, renal disease, viral illnesses, trauma and recent urological procedures\textsuperscript{[164]}. Particular concern should be shown if the haematuria does not resolve within 72 hours of ceasing exercise. The red cells should be inspected critically for abnormal cells and casts that may indicate renal disease. In individuals over the age of 35 years, cystoscopy is also advisable to check for a possible tumour in the bladder or urinary tract.

Physical activity and acute and chronic renal failure

Severe exercise, particularly if it is performed under hot conditions with an inadequate supply of fluids can occasionally lead to an acute renal failure. An excessive intake of creatine can cause chronic renal failure, but as discussed below, chronic problems more commonly arise from damage to the renal blood vessels due to diabetes mellitus or chronic high blood pressure.

Acute exercise-induced renal failure

The patho-physiology of acute, exercise-induced renal failure may involve either an exertional breakdown of muscle tissue (rhabdomyolysis), with myoglobinuria and a blockage of the renal tubules, or an excessive reduction of renal blood flow
with ischaemic damage to the kidney tissue, sometimes exacerbated by the direct toxic effects of myoglobin.\textsuperscript{165} There may also be an increase in serum creatinine.\textsuperscript{166} An acute renal failure of this type is quite rare. In the very demanding 90 km Comrades ultra-marathon race in South Africa, there have been only ten cases of acute renal failure among more than 20,000 competitors.\textsuperscript{167} One option in further reducing this risk would seem to focus on countering mechanisms that cause excessive renal vascular constriction. However, additional research is needed to determine whether the emphasis should be on reducing renal sympathetic nerve activity, increasing nitric oxide availability or countering prostaglandin release\textsuperscript{168, 169} as a means of decreasing vasoconstriction.

\textit{Adverse effects of creatine supplements and anti-inflammatory drugs}

In 1998, concerns were raised that the prolonged ingestion of large doses of creatine supplements by athletes could cause chronic renal damage.\textsuperscript{170} In theory, the conversion of excess creatine to sarcosine could lead to the formation of methylamine, with toxic end-products of formaldehyde and hydrogen peroxide.\textsuperscript{171} A watch should certainly be kept for this danger, although as yet studies have not confirmed the fear that long-term creatine supplements produce toxic levels of methylamine, formaldehyde and hydrogen peroxide.\textsuperscript{172} A large intake of anti-inflammatory drugs can also have adverse effects on the kidney, particularly in individuals whose bodies normally rely on an increased prostaglandin secretion to counter a reduced renal blood flow. Occasionally, an excessive reliance on NSAIDS may cause an acute deterioration of renal function, but provided that is detected, this can be reversed by stopping the use of such medication.\textsuperscript{173}

\textit{Physical activity and end-stage renal disease}

A Canadian survey set the prevalence of chronic renal disease at 12.5% of adults.\textsuperscript{174} The affected patient initially compensates for the diseased kidney tissue by increasing glomerular filtration in those glomeruli that are still functional. However, as the condition progresses, a growing proportion of glomeruli show a thickening of their basement membranes, and later they collapse, to be replaced by hyaline material. Cells in the renal tubules also undergo a fatty degeneration, and the loss of excretory power leads to a progressive increase in blood urea, with weakness, fatigue, loss of appetite, a high blood pressure, anaemia and impaired cardiac function.\textsuperscript{175}

End-stage renal disease is unfortunately progressive, and eventually the decrease in glomerular filtration and the rise of blood urea are such that the patient requires treatment by either regular dialysis sessions or a renal transplant. The threshold for initiating dialysis is commonly a glomerular filtration rate of less than 15 mL/min.\textsuperscript{176} At this stage, the individual’s physical condition is usually poor, and the quality of life can be improved by participation in a regular exercise programme, conveniently arranged concurrently with dialysis sessions.
Chronic exercise enhances overall body function and it may also improve renal function by its action upon other systems, inducing changes in visceral perfusion, sympathetic nerve activity and hormonal secretions at any given intensity of exercise.

Patients requiring thrice weekly dialysis typically enter treatment with a peak oxygen intake and a peak working capacity as low as 55–75% of normal (Table 4.3). Some authors have attributed the impairment of oxygen transport to a low haemoglobin level[180, 185, 189, 190] and others to cardiac dysfunction.[177, 183, 186, 187] Probably, both factors are involved. Another potential limiting factor is a generalized muscle weakness.[191] Exercise is unwise immediately before dialysis because serum potassium levels are then high, and immediately following dialysis the patient often feels too fatigued to engage enthusiastically in an exercise programme. However, patients can usefully undertake moderate cycle ergometer training to occupy their time while dialysis is proceeding.

Well-designed aerobic training can increase the working capacity of a dialysis patient by 25%[192] (Table 4.4). Exercise is thus an important component of treatment at all stages of care. Even prior to enrolment in dialysis, it can increase a patient’s maximal walking distance.[193] As treatment continues, specific efforts are needed to increase strength and endurance and to encourage incorporation of the patient into an on-going community rehabilitation programme. The effects of such conditioning can be reinforced by the administration of erythropoietin to counter the low haemoglobin level.[192] Long-term studies are still needed to demonstrate that such interventions increase longevity, but existing data show a substantial impact upon the individual’s immediate quality of life.[192]

Physical activity and renal transplantation

Exercise-induced changes in glomerular filtration rate in the transplanted kidney are very similar to those seen in a normal individual, but those with a renal transplant show a less marked exercise-induced excretion of albumin, possibly because a lack of innervation abolishes the normal increase in plasma renin activity.[194] Patients sometimes have a near normal maximal aerobic power and functional capacity following recovery from a successful renal transplantation[187, 195–197] but often a continuing lack of interest in physical activity keeps their maximal oxygen intake below the anticipated level for their age.[198, 199] Further, evaluation is not easy because weakness and a low oxidative capacity in the muscles often limit attainment of a plateau of oxygen consumption during exercise testing.[200] One study of patients over the age of 60 years found little gain of muscle strength in the year following renal transplantation.[201] In contrast, a vigorous 24-week training programme increased the maximal oxygen intake of 16 renal transplant patients from 29 to 38 ml/[kg.min], and it also yielded 25–56% gains in their isokinetic strength.[200]
### Table 4.3 Physical working capacity in patients with chronic renal disease

<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>Measure</th>
<th>Effects of chronic renal disease</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barnea et al. [177]</td>
<td>22 patients undergoing dialysis</td>
<td>Peak cycle ergometer test</td>
<td>Peak working capacity was 52% of normal</td>
<td>Poor performance attributed to lactate accumulation and early muscle fatigue</td>
</tr>
<tr>
<td>Clyne et al. [178, 179]</td>
<td>20 pre-dialysis patients</td>
<td>Maximal cycle ergometer test</td>
<td>Maximal working capacity 74% of normal</td>
<td>Loss of work capacity correlated with low haemoglobin (67% normal)</td>
</tr>
<tr>
<td>Clyne et al. [180]</td>
<td>38 men, 20 women with GFR of 3–32 mL/min</td>
<td>Maximal cycle ergometer test</td>
<td>Maximal working capacity 40–143% of expected norm</td>
<td>Working capacity correlated with total haemoglobin after allowing for sex, age and GFR</td>
</tr>
<tr>
<td>Clyne &amp; Jogestrand [181]</td>
<td>5 M, 3 F uremic patients, pre-dialysis</td>
<td>Maximal cycle ergometer test</td>
<td>Maximal working capacity 80% of normal</td>
<td>Working capacity increased to 92% normal with erythropoietin treatment</td>
</tr>
<tr>
<td>Clyne et al. [182]</td>
<td>11 uraemic patients</td>
<td>Maximal cycle ergometer test</td>
<td>Maximal working capacity 67% normal</td>
<td>Working capacity increased to 78% of normal after transplantation</td>
</tr>
<tr>
<td>Lundin et al. [183]</td>
<td>9 men, 1 woman, dialysis &gt;5 yr</td>
<td>Maximal oxygen intake (Bruce treadmill test)</td>
<td>8 of 10 patients said to be normal but max.oxygen intake averaged only 28.6 ml/[kg.min] at average age of 32.7 years</td>
<td>2/10 had cardiac enlargement, myocardial ischaemia in 1/10</td>
</tr>
<tr>
<td>Lundin et al. [184]</td>
<td>7 men, 3 women on haemodialysis</td>
<td>Maximal oxygen intake (Bruce treadmill test)</td>
<td>Maximal oxygen intake 15.1 ml/[kg.min] at average age of 44 yr</td>
<td>Max oxygen intake increased to 22.7 ml/[kg.min] with erythropoietin treatment</td>
</tr>
<tr>
<td>Mayer et al. [185]</td>
<td>13 patients on dialysis, haemoglobin 5.1–12.2 mg/100 mL</td>
<td>Maximal cycle ergometer test</td>
<td>Oxygen consumption at anaerobic threshold and maximal oxygen intake (53% of normal)</td>
<td>Decrease in both variables correlated with low haemoglobin level</td>
</tr>
</tbody>
</table>
Physical activity and the risk of renal cancer

The incidence of renal cancer varies substantially from one country to another. In British Colombia, tumours of the renal parenchyma are found in 6.5/100,000 in men and 3.2/100,000 in women, with corresponding figures of 0.6 and 0.3/100,000 for the rarer type of lesions affecting the renal pelvis. Available reports offer a tantalizing suggestion that regular physical activity may protect against renal parenchymal cancers (Table 4.5), although there does not seem

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**Table 4.4 Responses to training in patients before or during dialysis**

<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>Treatment</th>
<th>Response</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clyne et al.[202]</td>
<td>7 men, 3 women, predialytic, uraemic</td>
<td>Exercise 3/wk for 3 months vs. 9 controls</td>
<td>9.4% increase in peak work capacity in exercised group</td>
<td>No change in controls</td>
</tr>
<tr>
<td>Painter[192]</td>
<td>Patients on dialysis</td>
<td>Aerobic training</td>
<td>25% gain of working capacity</td>
<td>No erythropoietin administered</td>
</tr>
<tr>
<td>Zabetakis et al.[190]</td>
<td>5 haemodialysis patients</td>
<td>10 wk aerobic treadmill training at anaerobic threshold</td>
<td>21% increase in peak oxygen intake</td>
<td>Also increase in anaerobic threshold of experimental group</td>
</tr>
</tbody>
</table>

Note: GFR = glomerular filtration rate
<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergström et al.\textsuperscript{[204]}</td>
<td>3.28 million men, 3.35 million women, 18-year follow-up</td>
<td>4-level classification of occupational activity, RR of sedentary job 1.25 in men, no effect in women</td>
<td>Few women had active jobs</td>
</tr>
<tr>
<td>Bergström et al.\textsuperscript{[205]}</td>
<td>17,241 twin-pairs, 20 yr follow-up</td>
<td>102 cases of renal cell cancer, risk of tumours unrelated to occupational or leisure activity</td>
<td></td>
</tr>
<tr>
<td>Brownson et al.\textsuperscript{[206]}</td>
<td>17,174 male cancer patients (449 renal cases)</td>
<td>No reduction of risk of renal cancers in those with active occupations</td>
<td></td>
</tr>
<tr>
<td>Choi et al.\textsuperscript{[207]}</td>
<td>576,562 men followed for 6 years</td>
<td>92 deaths from renal cancer; hypertension gave mortality risk of 2.43; risk for exercisers 0.9 (CI 0.6–1.4)</td>
<td>Prime focus of experiment on hypertension rather than exercise</td>
</tr>
<tr>
<td>Chiu et al.\textsuperscript{[208]}</td>
<td>406 cases, 2434 controls</td>
<td>In women, OR of cancer with exercise &lt;1/month vs. &gt;1/day 2.5; no significant effect of physical activity in men</td>
<td>Substantial effect from BMI, but little interaction between physical activity and BMI</td>
</tr>
<tr>
<td>Chow et al.\textsuperscript{[209]}</td>
<td>363,392 men long-term follow up, 759 renal cell and 136 renal pelvic cancers</td>
<td>Top third of BMI distribution doubled cancer risk</td>
<td>Prime focus on obesity, not exercise</td>
</tr>
<tr>
<td>Goodman et al.\textsuperscript{[210]}</td>
<td>189 M, 79 F cases of renal cell carcinoma vs. matched controls</td>
<td>3-level leisure activity categorization and occupational activity unrelated to risk of cancer</td>
<td>BMI is associated with cancer in both sexes</td>
</tr>
<tr>
<td>Lindblad et al.\textsuperscript{[211]}</td>
<td>Structured interviews, 379 cases of renal cell cancer, 353 controls</td>
<td>Physical activity at work reduced risk in men but not in women; men showed dose-response effect, greatest if related to physical activity at age 40 years</td>
<td>Body mass and BMI weak risk factors in men, but important in women</td>
</tr>
<tr>
<td>Mahabir et al.\textsuperscript{[212]}</td>
<td>29,133 male smokers</td>
<td>210 cases of renal cell cancer seen over 12-year follow-up. Vigorous leisure activity gave relative risk of 0.46, no effect of occupational activity</td>
<td>Dose-related effect of leisure activity</td>
</tr>
<tr>
<td><strong>Author</strong></td>
<td><strong>Sample</strong></td>
<td><strong>Findings</strong></td>
<td><strong>Comments</strong></td>
</tr>
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<tr>
<td>Mellemgaard et al. [213]</td>
<td>368 cases, 396 matched controls</td>
<td>Questionnaire on activity at work and leisure. No effect of physical activity on cancer risk</td>
<td>Relative weight was an important risk factor</td>
</tr>
<tr>
<td>Menezes et al. [214]</td>
<td>Cases (173 M, 133 F) and matched controls</td>
<td>Women (highest vs. least physical activity) RR 0.41, report of strenuous recreation RR 0.40; in men, RR 0.49</td>
<td>Moderate physical activity of little benefit in women. In men, greatest effect from activity as an adolescent.</td>
</tr>
<tr>
<td>Moore et al. [215]</td>
<td>482,386 adults</td>
<td>1,238 cases of renal cancer in 8.2 yr follow-up; multivariate risk ratios (highest vs. lowest activity) 0.77 (current activity), 0.82 (as adolescent)</td>
<td>Most benefit of moderate physical activity seen with age-adjusted data but not in multivariate model</td>
</tr>
<tr>
<td>Nicodemus et al. [216]</td>
<td>34,637 women followed for 15 years</td>
<td>124 cases of renal cancer; benefit of physical activity seen with age-adjusted data but not in multivariate model</td>
<td>Central adiposity a major risk factor</td>
</tr>
<tr>
<td>Pan et al. [217]</td>
<td>810 cases, 3106 controls</td>
<td>Recreational physical activity 2 years earlier had no effect on risk of cancer</td>
<td>Large risk associated with high BMI</td>
</tr>
<tr>
<td>Paffenbarger et al. [218]</td>
<td>51,977 men, 4706 women</td>
<td>Risk of renal cancer unrelated to former participation in university sports teams</td>
<td>Only 29 cases of cancer</td>
</tr>
<tr>
<td>Pukkala et al. [219]</td>
<td>Comparison of 1449 physical education and 8619 language teachers</td>
<td>RR of renal cancer 0.29 in physical education teachers</td>
<td>Only 15 cases of cancer</td>
</tr>
<tr>
<td>Setiawan et al. [220]</td>
<td>161,126 adults, 8.3 year follow-up</td>
<td>Relative risk of renal cell cancer in obesity: 1.76 (M), 2.27 (F), with hypertension 1.42 (M), 1.58 (F), current smokers 2.3 (M), 1.7 (F)</td>
<td>Significant dose-related trend to reduction of risk with physical activity (METS/day) in women only</td>
</tr>
<tr>
<td>Tavani et al. [221]</td>
<td>767 cases, 1534 controls</td>
<td>Occupational activity reduces risk at all ages from 15–60 years (OR 0.65–0.70). No effect of leisure activity</td>
<td>Controlled for BMI, smoking and alcohol consumption</td>
</tr>
</tbody>
</table>
any information concerning the possible effects of exercise on the risk of pelvic lesions. Unfortunately, many studies have been based on relatively few cases of renal cancer, limiting the possibility of demonstrating a statistically significant benefit. Moreover, measurements of physical activity have often been weak, some samples have included few individuals who were vigorously active, either at work or in their leisure hours, and the period when activity was examined may not have coincided with the time when the carcinogenic change is likely to have occurred.

**Prospective and cohort studies**

There have been eight large-scale prospective trials. Six of the eight have found some relationship between renal parenchymal cancer and leisure or occupational activity, although the relationship has not always been demonstrated in both sexes. Setiawan et al.\(^{[220]}\) completed a prospective study of 161,126 adults over a period averaging 8.3 years. In a multivariate analysis, there were substantial relative risks of renal cell cancer associated with current smoking (2.3 [M], 1.7 [F]), obesity (1.76 [M], 2.27 [F]) and hypertension (1.42 [M], 1.58 [F]). Questionnaire estimates of physical activity (MET/day) were also significantly related to cancer risk in women (with an inverse dose-related association between habitual physical activity and renal cancer), but a physically active lifestyle conferred no benefit in men. It was suggested that the sex difference in response might reflect residual confounding of the data by effects of exercise upon obesity. Bergström et al.\(^{[204]}\) conducted an 18-year prospective study of Swedes (3.28 million men and 3.35 million women), noting diagnoses of renal cell cancer in relationship to a four-level categorization of occupational activity. A significant dose-response relationship was observed in men, disadvantaging those in the more sedentary jobs (a relative risk averaging 1.25 after adjusting for socio-economic status, area of residence and year of follow-up). However, perhaps because of lesser job demands or confounding from substantial domestic physical demands, a heavy occupation provided no protection to the women.
A 12-year follow-up of 29,133 male smokers found 210 cases of renal cell cancer.\cite{212} In a multivariate analysis, the risk was unrelated to occupational activity, but was strongly related to reported leisure activity, with a dose-related risk ratio of 0.46 favouring the most active individuals.

Nicodemus et al.\cite{216} followed 34,637 women for 15 years. Most women reported little physical activity, but nevertheless in an age-adjusted model 124 cases of renal cancer showed an inverse relationship to participation in vigorous leisure activity (RR 0.37). Relative weight was also a major risk factor, and after including this and other co-variates in the analysis, leisure activity no longer had a statistically significant effect.

Moore et al.\cite{215} questioned 482,386 adults about their current leisure activity and their physical activity as an adolescent. During an 8.2-year follow-up there were 1238 cases of renal cancer. Risk was reduced both with current leisure activity (RR 0.77) and with reported physical activity as an adolescent (0.82).

The case-cohort study of van Dijk et al.\cite{222} followed 120,852 adults for 9.3 years. There were 275 histologically confirmed cases of renal cell cancer over this period. Risk was unrelated to energy intake, but in the men there was a substantial inverse relationship to leisure activity; those taking 30–60 minutes of such activity per day had a relative risk of 0.52 relative to those who were inactive (although with no evidence of a dose-response gradient).

Bergström et al.\cite{205} followed 17,241 twin pairs for 20 years. There were 102 cases of renal cell cancer in their sample, but risk was not associated with either occupational or leisure activity. Brownson et al.\cite{206} made a general survey of occupational classifications in 17,174 male cancer cases, including 449 individuals with renal tumours. They also found no relationship between occupational classification and the renal lesions.

**Case-control studies**

Of nine case-control studies, five have shown a reduced risk of renal cancer in the more active individuals. Lindblad et al.\cite{211} conducted a case-control study that compared 379 cases of renal cell cancer with 353 controls. A structured interview found a strong inverse dose-related relationship between relative risk and a four-level classification of job activity in men, the greatest benefit being associated with vigorous activity at the age of 40 years (a risk of 0.37 relative to the least active workers); however, occupational activity had no significant impact upon the relative risk of renal cancer in women. Menezes et al.\cite{214} compared 173 male and 133 female cases of renal cancer with matched controls. After adjustment for age, BMI and smoking habits comparisons of the most active vs. the least active women yielded a relative risk of 0.41, and reports of strenuous leisure activity were also associated with a relative risk of 0.40; however, little reduction of risk was seen among those reporting only moderate physical activity. In the men, both total recreational activity and moderate physical activity yielded risk ratios of 0.49, with the greatest effects being seen from physical activity undertaken as an adolescent. The study of Chiu et al.\cite{208}
included 406 cases of renal cancer and 2434 controls. In the women, the odds of developing renal cancer for those reporting exercise <1 time/month versus those who were exercising at least once per day was 2.5; there was also a substantial risk associated with a high body mass index, but apparently little interaction between the two variables. However, in the men, no significant benefit was associated with reports of frequent physical activity.

Tavani et al.[221] studied 767 individuals with renal tumours and 1534 controls. After controlling for BMI, smoking and alcohol consumption, there was a beneficial effect from occupational activity, irrespective of the age when it was undertaken (odds ratio 0.65–0.7), but no effect of leisure activity was observed. Pukkala et al.[219] compared 1449 physical education teachers with that of 8619 (presumably physically less active) language teachers. The relative risk of renal cancer in the physical education teachers was 0.29 relative to the language teachers, although the entire study included only 19 individuals with renal cancer.

Other case-control studies reached negative conclusions. Paffenbarger et al.[218] examined relationships between renal cancer and prior membership of university sports teams. There were only 29 cases of renal cancer in this series and these incidents bore no relationship to the rather tenuous measure of habitual physical activity provided by affiliation to an athletic team as a young adult. Goodman et al.[210] made a three-level categorization of leisure activity and a categorization of occupational activity in a small sample. The risk of renal cell cancer was strongly related to body mass index, but was unrelated to either leisure or occupational physical activity. Likewise, Mellemgaard et al.[213] compared 368 histologically verified cases of renal cancer with 396 controls, finding an association between tumours and relative weight, but no relationship of cancers to physical activity either at work or in leisure time. Finally, in a comparison between 810 cases of renal cancer and 3106 controls, Pan et al.[217] found no effect from recreational activity that had been undertaken two years prior to the diagnosis of malignancy.

Conclusions

Despite the difficulties associated with this type of investigation, six of eight prospective trials and five of nine case-control studies have suggested that habitual physical activity is associated with a reduced risk of renal cancer. Possible mechanisms include a reduction in body mass and body fat, a lowering of blood pressure and reductions of chronic inflammation and oxidative stress.[223, 224]

Physical activity and prevention of renal calculi

The lifetime risk of renal stones is about 19% in men and 9% in women. To the extent that a prolonged and vigorous physical activity causes dehydration and increases urinary calcium concentrations, it can increase the immediate risk of developing renal calculi. In contrast, an eight-year follow-up of 84,225 initially healthy post-menopausal women suggested that regular moderate physical
activity decreased the overall risk of kidney stones. The threshold of protection was three hours of moderate walking per week, and the reduction of risk rose to 31% among those who engaged in >10 MET-h/wk of leisure activity. Suggested mechanisms of overall risk reduction include an activity-stimulated increase of fluid intake, a decreased sodium excretion and a decreased sympathetic nerve activity. Weight-bearing activity might also encourage the deposition of calcium in the bones, rather than its excretion in the urine. In contrast, a high body mass index is associated with an increased risk of renal stones.

**Physical activity and endocrine functions of the kidney**

An exercise training programme can have a positive effect upon health in many other parts of the body by modulating the endocrine functions of the kidney, increasing the secretion of erythropoietin, calcitro)l (which modulates the uptake of calcium from the gut and thus bone health) and renin-angiotensin (important in hypertension and congestive heart failure).

**Areas for further research**

Human studies consistently show a large reduction of renal blood flow during vigorous physical activity. In contrast, exercise may induce an initial vasoconstriction in dogs, but renal blood flow returns to its resting value as effort continues. It would be interesting to explore reasons for this species difference. Is it an expression of the greater contribution of the spleen to the maintenance of blood volume in the dog, or is it simply an artifact, due to differences in the methods used to measure regional blood flow in humans and in dogs?

A variety of mechanisms regulate renal blood flow during physical activity and there is scope to explore these control processes in greater detail. How far is the vasoconstriction related to altered levels of hormones such as urodilatin, atrial natriuretic peptides, renin-angiotensin and aldosterone, and how far does control operate more directly via the renal sympathetic nerves? This is a question that could be examined after local denervation in animals or by the study of humans with a kidney transplant. A greater understanding of control systems could help in the prevention of the acute exercise-induced renal failure associated with excessive vasoconstriction. Should the focus of preventive efforts be on reducing renal sympathetic nerve activity, on increasing nitric oxide availability or even on countering prostaglandin release?

Exercise rehabilitation certainly enhances renal functional capacity and the immediate quality of life in patients who are undergoing dialysis, but long-term studies are still needed to demonstrate whether such interventions increase longevity and/or the quality adjusted life expectancy.

Other areas meriting further investigation include the possible role of habitual physical activity in reducing the risks of urinary calculi and renal parenchymal cancer.
Practical implications and conclusions

A drastic reduction of renal blood flow may be anticipated during prolonged endurance exercise. Although this normally causes no more than a slight and rapidly reversed urinary loss of protein and red cells, in a hot environment it is important to monitor water intake and to avoid the dehydration that could precipitate acute renal failure. Further, the risk of renal failure seems to be exacerbated by the frequent administration of NSAIDs, and athletes should be advised against excessive self-medication with such drugs. In those with chronic renal failure, functional capacity is generally low; an early assessment of physical capacity is advisable in such individuals, and thereafter, they should be enrolled in a progressive rehabilitation programme. Finally, the likely relationship between sedentary living and renal parenchymal cancer is one more good reason to encourage everyone to adopt an active lifestyle.

References

2. Dawson PM. The physiology of physical education for physical educators and their pupils. Baltimore, MD: Williams & Wilkins, 1935.


171. Sale C, Harris RC, Florence J, et al. Urinary creatine and methylamine excretion following 4 x 5 g.day<sup>−1</sup> or 20 x 1 g.day<sup>−1</sup> of creatine monohydrate for 5 days. *J Sports Sci* 2009; 27: 759–766.


5 Implications of a single kidney for the young athlete

Introduction

The kidneys play a vital role in maintaining the “milieu intérieur”.\cite{1, 2} In the view of Claude Bernard, the “constancy of the internal environment (milieu intérieur) is the condition of free and independent life”.\cite{3} The previous chapter examined the reactions of the healthy kidneys to acute and chronic physical activity. In this chapter, we consider responses in the individual who has only a single kidney, looking at the advice that the clinician should offer to the young athlete with only one kidney.

Although the kidneys are normally paired organs, kidney donors typically live as long as their peers. Within two weeks of kidney removal, resting function based upon the remaining kidney is running at 70% of pre-operative levels, and eventually excretory capacity may reach 85% of that for the paired organs.\cite{4} Other causes of a unilateral kidney include a birth defect (renal agenesis, affecting between 1 in 500 and 1 in 1800 infants),\cite{5} and surgical removal of a kidney because of a neoplasm, injury or disease. Despite the generally favourable prognosis for those with a single kidney, it is important to maintain the health of the remaining organ; regular physical activity can contribute to renal health by reducing the risks of hypertension, diabetes mellitus and other kidney-damaging diseases.

The main objectives of this chapter are to weigh conflicting opinions on the risks of renal injury associated with an active lifestyle and to suggest principles that should guide the clinical management of children with a single kidney. Specific issues include (1) permissible types of physical activity for individuals who have only a single kidney, (2) the overall risk of renal injury during various types of physical activity, (3) factors modifying this risk, including the absence of one kidney, (4) a close examination of the purported dangers associated with “contact” sports, and (5) practical issues in the management of renal injuries and the communication of risk levels to anxious parents.

Current opinions on sport participation with a single kidney

There is currently a wide division of opinion among health professionals on the wisdom of sport participation by those with a solitary kidney. In Italy, an annual
medical certification is required to participate in any type of organized sport, and such certification is denied to those with a solitary kidney. In North America, also, many physicians are reluctant to recommend that such individuals participate in sport, particularly if body contact is anticipated, because of the perceived risk of trauma to the remaining kidney. It is argued that even minor cumulative damage from repeated trauma could shorten the useful lifespan of the remaining kidney, and if any one injury were severe enough to require a nephrectomy, the only option left for the patient would be to perform dialysis several times per week, with the hope that a suitable kidney donor might eventually be found. Even following renal transplantation, the patient would face on-going treatment with immune-suppressant drugs; this would cause a greatly reduced overall resistance to infectious diseases and a reduced overall quality of life.

Given these potentially serious adverse prospects, a survey of the American Society of Pediatric Nephrology found that 86% of respondents banned children with a single kidney from playing American football, although surprisingly only 5% were prohibited from cycling. A similar survey of the Urology Section of the American Academy of Pediatrics found 68% of members prohibiting all types of contact sports for individuals with a single kidney. Again, only 42% of members of the American Medical Society for Sports Medicine would allow one of their own children with a solitary kidney to practice unrestricted sports. Many review articles have appeared (Table 5.1), but unfortunately there is as yet no consensus on an appropriate policy. Moreover, decisions to date have generally been based on expert clinical opinions rather than on hard epidemiological evidence.

The American Academy of Pediatrics and the American and the Canadian Urological Associations have recently looked critically at the available statistics, suggesting that the constraints commonly applied may be excessive, and run counter to the best interests of a child’s overall health. The American Academy of Pediatrics has pointed out that the risk of renal injury in contact sports is in fact very low. It seems that many physicians continue to make cautious recommendations about sport participation more because of fears of litigation in the event of an injury than because of an objective assessment of the true costs and benefits. As Psooy has underlined, the risk of a catastrophic injury to the head is far greater than the risk of injury to a solitary kidney. Psooy has thus argued that sport should be allowed for those with a solitary kidney, after a careful and documented explanation of risks to both the participant and the next of kin and the adoption of appropriate protective measures. Other authors who have made an objective analysis of injury statistics have concluded that widely prevalent and draconian restrictions on sport participation for the child with a single kidney are unwarranted. Styn and Wan further noted that there is no evidence of an over-representation of individuals with solitary kidneys among reported cases of renal injury, although this could reflect either low risk or a restriction of sport participation by the individuals concerned.
Table 5.1 Review articles making recommendations concerning sport participation for the patient with a single kidney

<table>
<thead>
<tr>
<th>Authors</th>
<th>Information source</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td><strong>Favourable</strong></td>
<td></td>
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<tr>
<td>Bernard[6]</td>
<td>Literature review</td>
<td>Sports participation is generally safe, with very minimal risk to the remaining kidney</td>
</tr>
<tr>
<td>Grinsell et al.[7]</td>
<td>Search of medical and sports literature</td>
<td>Restricting participation of patients with a single, normal kidney from contact/collision sports is unwarranted</td>
</tr>
<tr>
<td>Johnson et al.[8]</td>
<td>National paediatric trauma registry</td>
<td>Prohibition of contact sports with a solitary kidney overly protective, needs to be re-evaluated</td>
</tr>
<tr>
<td>Psooy[9-11]</td>
<td>Nine recent articles</td>
<td>Risk of renal injury a fifth of that for head injury; most dangerous sports are bicycling, sledding, downhill skiing/snowboarding and horse-related activities</td>
</tr>
<tr>
<td>Rice[19]</td>
<td>Council on Sports Medicine &amp; Fitness, American Academy of Pediatrics</td>
<td>Athlete needs individual assessment for contact, collision and limited-contact sports. Protective equipment may reduce the risk of injury to the remaining kidney sufficiently to allow participation in most sports, providing such equipment remains in place during activity</td>
</tr>
<tr>
<td>Styn &amp; Wan[21]</td>
<td>Literature review</td>
<td>Risk of sport participation very low, but not zero. No evidence that risk of renal injury greater if solitary rather than bilateral kidneys</td>
</tr>
<tr>
<td><strong>Neutral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patel et al.[12]</td>
<td>Review of major articles</td>
<td>No consensus on participation in contact or collision sports by adolescents with one kidney</td>
</tr>
<tr>
<td>Sacco et al.[20]</td>
<td>Literature review</td>
<td>Sports responsible for 13% of genitourinary trauma, but renal trauma usually Grade I–II, not requiring surgical treatment; significant injury rare if solitary kidney</td>
</tr>
<tr>
<td>Risser; Washington</td>
<td>Am. Acad. Pediatrics, consensus report</td>
<td>Athlete needs individual assessment for contact, collision and limited-contact sports</td>
</tr>
<tr>
<td><strong>Unfavourable</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyment[15]</td>
<td>Consensus of American Academy of Pediatrics</td>
<td>No contact or collision sports should be allowed</td>
</tr>
<tr>
<td>Sharp et al.[16]</td>
<td>Survey of American Academy of Pediatrics, Urology Section</td>
<td>68% of respondents recommended no contact sport if solitary kidney, although recognizing that the risk was low (&lt;1%)</td>
</tr>
<tr>
<td>Speafico et al.[17]</td>
<td>Study of survivors of renal tumours</td>
<td>Need to avoid lifestyles and behaviours potentially dangerous to remaining kidney; but current Italian blanket prohibition of competitive organized sports seems unjustified</td>
</tr>
</tbody>
</table>
Risks of renal injury during sport and physical activity

Renal injury is in itself a rare occurrence, accounting for about 3% of all trauma, and despite the fears of some physicians, sport accounts for only a small fraction of injuries involving the kidneys. In adults, a survey of 9119 individuals with blunt renal injuries found that 63% of these were caused directly by motor vehicle collisions, and a further 4% by cars hitting pedestrians; 14% were due to falls and only 11% were attributed to sport participation. In the paediatric portion of the sample, motor vehicles caused 30% of cases directly and 13% were caused by a motor vehicle hitting the child; falls caused a further 27% of incidents and only 12% were due to sports participation. Other authors have found recreational sports responsible for 2–28% of renal injuries (Table 5.2).

Table 5.2 The incidence and severity of renal injury during sports participation

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample</th>
<th>Findings</th>
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</thead>
<tbody>
<tr>
<td>Berqvist et al.</td>
<td>1354 cases of abdominal trauma in Skaraborg County (Sweden), 1950–1979</td>
<td>59 sport-related injuries to kidneys; approximate incidence 8 per million person-years, apparently rising. Nephrectomy needed in 2 cases, hemi-nephrectomy in 1 case over 30 years of experience</td>
</tr>
<tr>
<td>Gerstenbluth et al.</td>
<td>68 children with blunt renal trauma (14 due to sport)</td>
<td>5 cycling and 1 sports injuries grade IV or V damage to kidneys</td>
</tr>
<tr>
<td>Grinsell et al.</td>
<td>American Organ Procurement and Transplantation Network</td>
<td>96,000 patients awaiting a renal transplant. None due to sport participation</td>
</tr>
<tr>
<td>Grinsell et al.</td>
<td>US National Athletic Trainers’ Association High-School injury survey, 1995–1997; 4 million athletic exposures</td>
<td>18 renal injuries, but none resulted in nephrectomy or permanent renal injury. Renal injuries in basketball 2.3 (M), 2.6 (F) per million exposures; soccer 2.5 (M), 6.0 (F) per million exposures. Risk lower than head or spinal injury</td>
</tr>
<tr>
<td>Johnson et al.</td>
<td>US national pediatric trauma registry, 49,561 cases</td>
<td>92 incidents due to cycling, 88 to sports participation (approximate incidence 8 and 7 per million children-years). Only 4 sports injuries required nephrectomy</td>
</tr>
<tr>
<td>McAleer et al.</td>
<td>San Diego trauma registry 1984–2000, 14,763 patients</td>
<td>113 renal injuries due to various physical activities (7 per year); no single-kidney cases, no nephrectomies required</td>
</tr>
<tr>
<td>Wan et al.</td>
<td>Trauma registry, 4921 injured children aged 5–18 yr, Western New York State, 1993–2000</td>
<td>Recreational kidney injury 6.9 per million children-years. Recreational injuries requiring nephrectomy 0.4 per million children-years</td>
</tr>
<tr>
<td>Wan et al.</td>
<td>National pediatric trauma registry, 81,923 cases aged 5–18 yr, 1990–1999</td>
<td>42 renal injuries due to sport, mainly in older children, 4.2 per year. No injuries required nephrectomy</td>
</tr>
</tbody>
</table>
Not only is the risk of renal trauma during sport low, but many of the recorded injuries associated with sport are only a minor bruising of the kidneys, with full and rapid recovery of normal function. Only a small fraction of those who are injured require a nephrectomy. Wan et al.\cite{26} studied 4921 children aged 5–18 years listed in the Western New York State Trauma Registry for 1993 to 2000. The total incidence of recreational kidney injuries was 6.9 per million children-years, and catastrophic injuries needing nephrectomy occurred only 0.4 times per million children-years. The same authors\cite{27} examined data from the US national paediatric trauma registry for 1990–1999. Among 81,923 incidents, they were only 42 sport-related renal injuries (a total of 4.2 per year), none of which required nephrectomy.

Johnson et al.\cite{8} had similar findings in an analysis of the US national paediatric trauma registry for the period 1995–2001. Of the 49,651 cases listed, 813 involved kidney injuries; 92 of these were associated with cycling and only 88 with participation in various types of sport. Based upon census reports for US children in 2000, the incidence of renal injuries for cycling and sports participation were approximately eight and seven incidents per million children-years, respectively, agreeing quite well with the estimates of Wan et al.\cite{26} Moreover, only four of the sports injuries reported by Johnson et al.\cite{8} required a nephrectomy.\cite{8} A further study, based upon data from the San Diego paediatric trauma registry,\cite{25} examined 14,763 incidents occurring between 1984 and 2000. The population involved was not specified, but there were a total of 113 sports-related renal injuries in this sample, a total of seven per year. None resulted in nephrectomy and none involved individuals with a solitary kidney.

The US National Athletic Trainers’ Association high school injury survey\cite{7} analysed data on 23,666 incidents among some 4 million athletic exposures from 1995 to 1997. This series included only 18 renal injuries, and none of these resulted in nephrectomy or any other known loss of renal function. The risk of any degree of renal injury for high-school students was set at 2.3 injuries per million exposures in male basketball players, and 2.6 per million exposures in male soccer players, with corresponding figures for girls of 2.5 and 6.0 injuries per million exposures. These risks were a striking two orders lower than those observed for serious incidents of head and spinal injury.

A 30-year survey from Skaraborg County, Sweden\cite{22} showed a similar experience to that in the US. There were approximately eight sport-related renal injuries per million person-years, although the authors commented that the incidence of such events appeared to be rising over the study period (1950–1979), perhaps because of the growing popularity of active recreation. Only two nephrectomies and one heminephrectomy had been required over the course of this Swedish survey.

Additional evidence on the relative safety of sport participation comes from the American Organ Procurement and Transplantation Network. In December of 2011, 96,000 patients were awaiting a renal transplant for various reasons, but not one of them had suffered a kidney injury during sports participation.\cite{7} It is plain
that the risk of any type of renal injury during sports participation is low, and that most of the injuries are minor in nature. One small study specifically examined the severity of injuries; it found that only one of eight sport-related incidents was severe (Grade IV or V), but that five of six bicycle-related injuries fell into the severe category.[23]

**Factors modifying the inherent risk of sports-related renal injury**

Factors potentially modifying the risk of renal injury during sport and active recreation include the individual’s initial renal health, age, the presence of a solitary kidney, the wearing of effective protective equipment, patterns of play and the degree of supervision of the activities that are undertaken.

**Initial renal health**

A person with two healthy kidneys usually has a substantial renal reserve, and normal function is quite well maintained even after nephrectomy. However, the functional margin is inevitably smaller for a person who begins with a single kidney, and the initial health of the kidney then becomes a significant issue. A much more cautious attitude to sport participation is required if one or both kidneys are ectopic, multicystic or for any reason show poor performance on tests of renal function.

**Age**

The kidneys are relatively larger in children than in adults, and they sometimes retain foetal lobulation. Both of these factors cause them to protrude below the rib cage, making them more vulnerable to blunt trauma. Vulnerability is further increased in children because the rib cage is less rigid than in an adult, and there is less soft tissue support of the kidneys.

**Solitary kidney**

A solitary kidney may hypertrophy until it is 50% larger than paired kidneys. It then faces a greater potential exposure to external trauma just because of its greater size and its protrusion below the rib cage, although statistics do not always reveal any consequence of this greater susceptibility, perhaps because only a small proportion of those with solitary kidneys are allowed to participate in vigorous activities. A solitary kidney also has a more than normal vulnerability to irreversible damage from heat stress, and the temperature limits that are set for prolonged bouts of endurance exercise should be observed particularly carefully in those with a single kidney.
Protective equipment

The US National Kidney Foundation and the Kidney and Urology Foundation of America have each advocated the use of protective padding as a means of protecting a solitary kidney from trauma. The equipment is custom-made, and the cost can be high (commonly more than US$350). Moreover, although the use of such equipment may appear logical, there is as yet no good evidence to show the extent to which it is effective in reducing renal injury.[10]

Patterns of play and degree of supervision

The risk of most types of physical injury, including damage to the kidneys, is influenced by the level of competition, the individual’s playing position, and the degree of supervision of a game. The simple precautions of close supervision by a coach or parent and the firm enforcement of rules of play are likely to reduce the risks of renal injury. In general, the prevalence of injuries is greater for unsupervised play than for organized sport. The practical lesson is that the incidence of renal trauma can be reduced by a rigid enforcement of rules and a careful supervision of free play.

Conclusions

When assessing the risks of sport, account should be taken of initial renal health, the child’s age, the absence of one kidney, the availability and efficacy of protective equipment, the playing position, the level of competition and the supervision of play by officials and parents. Particular care is needed for those with a solitary kidney, since this is more vulnerable to heat stress, and its hypertrophy places it at a greater risk of physical injury.

Sports and physical activities with the greatest risk of renal injury

Many physicians have considered contact sports as particularly dangerous from the viewpoint of renal injury, and available statistics show that they are responsible for a substantial proportion of injuries relative to other types of active pursuit (Table 5.3). However, because the total number of renal injuries is small and there are national and regional differences in the popularity of various sports and leisure pursuits, relative risks vary substantially from one report to another. Moreover, the data are often hard to interpret, since the reported injury percentages commonly exclude incidents that have arisen when cycling, operating all-terrain vehicles or engaging in playground recreation.

In an 18-year review of statistics for the US National Football League, Brophy et al.[31] found that the overall risk averaged 2.7 incidents of renal trauma per season. Further, all of the affected individuals were subsequently able to return to play with both kidneys intact. About a third of these patients
<table>
<thead>
<tr>
<th>Study</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total # of activity-related renal injuries</td>
<td>13,006</td>
<td>59</td>
<td>14</td>
<td>465</td>
<td>18</td>
<td>85</td>
<td>98</td>
<td>15</td>
<td>42</td>
<td>115</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Football</td>
<td>16.6%</td>
<td>7.1%</td>
<td>8.6%</td>
<td>66.7%</td>
<td>23.5%</td>
<td>6.1%</td>
<td>33.3%</td>
<td>61.9%</td>
<td>33.3%</td>
<td>10.4%</td>
</tr>
<tr>
<td>Ice-hockey</td>
<td>13.6%</td>
<td>21.4%</td>
<td>7.3%</td>
<td>18.7%</td>
<td>2.4%</td>
<td>4.8%</td>
<td></td>
<td></td>
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<tr>
<td>Soccer</td>
<td>4.9%</td>
<td>57.6%</td>
<td>7.3%</td>
<td>18.7%</td>
<td>2.4%</td>
<td>4.8%</td>
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<td></td>
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</tr>
<tr>
<td>Other sports</td>
<td>17.8%</td>
<td>11.8%</td>
<td>44.1%</td>
<td>18.7%</td>
<td>41.2%</td>
<td>49.0%*</td>
<td>20.0%</td>
<td>26.2%</td>
<td>49.6%</td>
<td></td>
</tr>
<tr>
<td>Other active pursuits</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Horse-riding</td>
<td>7.3%</td>
<td>8.5%</td>
<td>3.0%</td>
<td>6.7%</td>
<td>3.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skiing</td>
<td>11.8%</td>
<td>8.5%</td>
<td>19.6%</td>
<td>8.2%</td>
<td>13.0%</td>
<td>4.3%</td>
<td></td>
<td></td>
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<tr>
<td>Snowboard</td>
<td>8.2%</td>
<td>6.7%</td>
<td>3.5%</td>
<td></td>
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<tr>
<td>Sledge</td>
<td>14.2%</td>
<td>12.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycling</td>
<td>17.8%</td>
<td>57.1%</td>
<td>20.4%</td>
<td>27.6%</td>
<td>6.7%</td>
<td>17.4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor-cycle and ATVs</td>
<td>26.2%</td>
<td>14.3%</td>
<td>11.3%</td>
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</tbody>
</table>

Note: * Including skate-boarding, roller-blading, use of playground equipment and miscellaneous falls

required hospitalization, but none underwent any form of surgery. Incidents were ten times more prevalent during actual games (0.000005 per exposure) than during practices, but nevertheless the authors of this report argued that it may be safe for individuals with only one functioning kidney to play in the NFL. This verdict was accepted by 61% of NFL physicians, although a lower percentage of clinicians gave their assent to the idea that students with a single kidney could participate in high school (45%) or college (50%) games. A six-year study of Australian Rules football found that 13 cases of renal trauma had been admitted to one hospital, with 2 requiring nephrectomy; however, the level of risk cannot be assessed in this report, since there is no indication of the corresponding number of exposures.

Somewhat in contrast with North American experience, a study from Sweden found a predominance of renal injuries among soccer players, particularly at the start of the playing season, when they were presumably in poorer physical condition.

A survey of North American high-school students found most of the renal injuries were in football (boys) or in soccer (girls), and two surveys of trauma-centre statistics found a concentration of renal injuries among football players.

A series of 14 activity-related renal injuries in Ohio included data on cycling. This report demonstrated that the bicycle was a dangerous machine for youth; it was responsible for five of the six high-grade renal injuries (grade IV or V) seen in the study. McAleer et al. also concluded that cycling and the use of all-terrain vehicles were major causes of renal injuries. This verdict was further substantiated in a survey of 116 renal injuries from blunt trauma. The commonest source of injury in this last series was a motor vehicle collision (33 cases), with other causes including cycling (20 cases), use of all-terrain vehicles (13 cases), limited contact sports (20 cases), contact sports (12 cases), alpine sports (9 cases) and horseback riding (4 cases). The use of all-terrain vehicles was to blame for the most severe injuries that required nephrectomy. Interestingly, 2 of the 116 cases in this series were individuals with unilateral kidneys, and 3 other patients had abnormally positioned kidneys. Among football players, the greatest risk was in pick-up games, when no protective equipment was worn. One report where American football appeared more dangerous than cycling was from western New York State; possibly, cycling was not a common pursuit in this region. Johnson et al. included specific data for cycling injuries in their survey, and they also found a substantial proportion of incidents were attributable to American football. However, none of the injuries needing nephrectomy were associated with contact sports; injuries requiring renal surgery were from sledding (two cases), downhill skiing (one case) and roller-blading (one case).

Perhaps the most satisfactory evidence on risk levels comes from the large surveys of Bagga et al. and Grinsell et al. Bagga et al. underlined the importance of cycling and use of sports vehicles, which together accounted for 44% of all physical activity-related renal trauma. Nevertheless, American football and soccer together were also responsible for more than a fifth of renal...
injuries. Grinsell et al.[24] put together data on 465 renal injuries from a survey of 11 articles; this analysis also found that a substantial proportion of renal injuries were due to American football and soccer, although the totals for these sports were outweighed by the risks of cycling and skiing. In this last report, the 14 incidents requiring nephrectomy were attributed to downhill skiing (five), cycling (four), horse-back riding (two), soccer (two) and American football (one).

A number of articles have looked at the risks involved in specific forms of active recreation, including the operation of all-terrain vehicles, cycling, alpine activities and horse-back riding, although unfortunately in most of these reports the lack of exposure rates does not allow a calculation of the incidence of renal injuries. Nevertheless, it does appear that risks are greater for some personal leisure pursuits than for most forms of organized sport.

**All-terrain vehicles**

Consensus groups in both Canada and the US have concluded that the operation of all-terrain vehicles by young and inexperienced children with inadequate protection is particularly dangerous in terms of renal trauma.[35, 36] Wu et al.[33] emphasized that dirt bikes and all-terrain vehicles were the most important sources of serious recreational injuries to the kidneys.

**Cycling**

The use of a bicycle by a child or a mountain bike by a young adult is another cause of concern. A study of 107 serious cycling accidents found 30 head and neck injuries, and 18 that involved the abdomen; the 3 renal injuries in this series were caused by impact of the ends of the handlebars on the abdomen.[37] Current handlebar designs are quite dangerous. In a second report, 5 of 30 handlebar injuries involved the kidneys, and in 3 of these nephrectomy or heminephrectomy was required.[38] A further study found 40 handlebar injuries among 134,116 children admitted to a Swiss hospital; 1 of the 40 children concerned had sustained a renal rupture.[39] Another analysis of 1990 patients who had been injured when riding various types of vehicles found that 236 of these incidents (including 151 abdominal injuries) were due to the handlebars; 29 of these required a major operation (although usually for small bowel perforation or pancreatic trauma rather than renal injury).[40]

When a child loses control of a bicycle, he or she typically falls onto the end of the handlebars as the wheel rotates through 90 degrees. Possibly, the risk of major injury could be diminished by lessening the maximum potential rotation of the front wheel of the bicycle, altering the shape of the handlebars, and either padding the ends of the handlebars or making them compressible.[41–43] Other avoidable risk factors are use of an inappropriate size of bicycle by a child and the operation of stunt bicycles.
Alpine activities

Winter sports such as skiing, snowboarding and sledding are other likely causes of abdominal trauma. The incidence of skiing injuries in Austria is about one per visitor-year, with 2% of these injuries affecting the kidneys.[30] The Urology Department of an Innsbruck hospital treated 254 children for renal trauma over a 26-year period, mostly due to skiing incidents. In about a third of these patients, the renal injury was severe, but only four nephrectomies were needed.[30] The risk of abdominal injuries is higher for snowboarding than for skiing,[44, 45] the abdomen accounted for 0.7% of injuries in skiers and 1.2% in snowboarders, with renal injury accounting for 29.7% of all abdominal trauma in skiers and 68.4% in snowboarders.[44] Most of the skiing injuries were sustained in the afternoons, possibly because of a deterioration in snow conditions or fatigue of the skier. Problems were also more frequent in children, adolescents and those with low skill levels, suggesting the value of lessons that embrace safety precautions.[44–46]

In many skiers, other adverse factors were defective bindings and the use of rented equipment.[46]

Sledding is a fairly frequent source of renal injury. Factors increasing risk for sledgers include towing by a vehicle such as a snowmobile, sledding near to a road and collision with a stationary object such as a tree.[47] Five of 25 sledders who were admitted to a paediatric trauma centre had abdominal injuries, with 2 involving the kidneys; however, 11 of the same group had sustained head injuries.[47]

Horseback riding

As in other active pursuits, the head of the horseback rider is at greater risk than the abdomen. About 8% of the injuries sustained during horseback riding are abdominal (for instance, trampling by another rider after falling), whereas 38% affect the face and head. Many other injuries occur while grooming or walking beside a horse.[48] A study of 315 injuries involving horses found that eight involved the kidneys.[49] Children should ride a mount that is well-matched to their size and abilities, wear boots with heels (to minimize dragging after a fall) and stand clear of the horse’s hooves when dismounted.[50]

Martial arts

Renal contusion can occur in sports such as jujitsu, judo and aikido. De Meersman et al.[51] found that 85% of judoka who had fallen 100 times on a 2.5 cm thickness mat developed significant haematuria (>50 red cells per high-powered field), and this was considered evidence of renal trauma. However, the reported rate of renal injuries for martial arts is quite low, 1 of 5700 injuries sustained in 24,027 training years.[52] Safety in the martial arts can be enhanced by increasing the thickness of matting, and possibly by the use of spring-loaded mats.[53]
Other sports causing renal injury

Case reports have identified other occasional incidents of renal trauma during many recreational activities, including a haematoma induced under the renal capsule by exposure to paint-gun pellets.\[54\]

Conclusions

Physical activities presenting a higher than average risk of renal injury appear to include operation of all-terrain vehicles, cycling, alpine sports, horseback riding and martial arts. Individuals with single kidneys should preferably choose alternative pursuits, and particular care should be observed if they continue to be involved in such activities.

Managing risks of renal trauma for the active child

Practical management issues include the advice that clinicians should give to parents on the proportion of sport-related renal injuries that are likely to require nephrectomy, on the duration of restricted activity that should be observed following less severe renal injury, on the likelihood of a permanent impairment of renal function following renal trauma, and on the restriction of sports participation for children with a solitary kidney.

Proportion of activity-related renal injuries requiring nephrectomy

Although the overall risk of renal trauma during physical activity is low, the likelihood of adverse long-term consequences is further attenuated because injuries are often quite minor and can be managed conservatively. One report found that 6% of injuries required abdominal exploration and no more than 2% underwent only nephrectomy.\[55\] Many of those who sustain a renal injury can return to their chosen form of physical activity after as little as two weeks of rest, although severe lacerations may require several months away from competition.\[31, 56\] Minor injuries are often assessed in terms of continuing haematuria, although this does not always provide a reliable guide to the extent of renal injury.\[12, 30, 57\]

In weighing the relative risks of various types of physical activity, it is important to look at not only the total incidence of renal trauma, but also the typical severity of injuries associated with a given type of activity. Several non-contact sports such as cycling, skiing and snowboarding seem particularly prone to cause severe injuries, with a greater chance that nephrectomy will be required following injury.

Duration of restricted physical activity following injury

The typical duration of restricted activity for minor renal trauma is two to six weeks. However, vigorous physical activity should be limited until haematuria has ceased.\[6, 36\]
**Risk of permanent renal damage**

The immediate recovery of the kidney from blunt trauma is usually quite rapid and relatively complete. However, there are sometimes long-term sequelae (usually from subcapsular bleeding and pressure necrosis\(^58\)). The resulting impairment of renal function is particularly troubling for the individual with a solitary kidney.

A review of 157 patients with renal agenesis found that even in the absence of any known trauma, as adults they were at increased risk of hypertension, proteinuria and renal insufficiency.\(^59\) A three-year follow-up of 13 children with high-grade renal injuries found no signs of hypertension or other renal abnormalities.\(^60\) However, technetium-99m-dimercaptosuccinic acid renal scans have indicated that severe (Grade 5) renal trauma can ultimately cause renal scarring and a loss of kidney tissue that impairs renal function.\(^61\) Further information is needed on the extent of this risk.

**Advice to parents**

Health professionals have the responsibility of communicating the level of risk associated with sport participation to the parents of a child with a single kidney. While the need to use all possible tactics to minimize dangers should be underlined, it is also important to the overall development of a child that an excess of caution does not remove safe and interesting options for involvement in health-promoting physical activity.

Although the risk of renal injury is very low in most types of physical activity, it is not non-existent. One way of explaining the level of risk to an anxious parent is to compare the incidence of kidney and head injuries. Most types of physical activity carry at least a five times greater risk of head injury than of renal trauma.\(^9, 10\) And despite a growing public concern about concussion in American football and ice hockey, the potential risk of a head injury is not usually considered a sufficient reason to prohibit children from participating in these sports.

At the same time, there are simple precautions that can greatly reduce the risk of renal injury, as discussed above, and it is particularly important that these precautions be communicated to the parents, particularly if a child has only a single kidney.

**Areas for further research**

There remain many gaps in current knowledge concerning the dangers of an active lifestyle for the individual with a single kidney. Risks remain poorly defined because most available statistics lack critical information on the number of hours of exposure to a given type of physical activity per year. Moreover, some analyses of overall risk appear to exclude exposure to informal but relatively risky activities such as schoolyard play, cycling and the operation of all-terrain...
vehicles. A greater risk of injury might be anticipated for those with a hypertrophied single kidney, but this is not apparent in the available data. Possibly, this is because many children with a single kidney lead severely restricted lives. The use of haematuria as a means of detecting persistent renal injury seems to be unreliable, and a simple but effective tool is needed to monitor recovery following renal trauma. More information is also needed on the immediate vulnerability to heat stress and the long-term incidence of hypertension in those sustaining serious renal injuries. Finally, there is a need for more precise evaluation of the efficacy of equipment intended to protect against renal injury.

Practical implications and conclusions

Many health professionals still seem overly cautious about recommending sport participation for children with single kidneys, although sometimes permitting more dangerous pursuits such as cycling. Risks and benefits need to be weighed carefully, with recognition that there are dangers to physical, social and mental development if the life of a child with a solitary kidney is unduly restricted. Empirical evidence shows that the absolute risk of renal injury during most types of physical activity is very low, although not non-existent. For instance, there are 2.6 incidents per million exposures in male soccer players. Many of the renal injuries incurred during physical activity are minor in nature and only a small proportion require nephrectomy. Contact sports account for perhaps a fifth of physical activity-related renal injuries. The operation of all-terrain vehicles, cycling, alpine sports and horseback riding are more common sources of renal trauma, and cycle handlebars should be redesigned to make them safer. Possible factors modifying inherent risks include initial renal health, the individual’s age (children being more vulnerable than adults), careful supervision of play, choice of playing position and level of competition, and the wearing of effective protective equipment. Minor renal injuries may require only two to six weeks of restricted physical activity. Often, there are no long-term consequences to blunt renal trauma, although subcapsular haematomas can cause pressure necrosis, with later risks of hypertension, proteinuria and renal insufficiency. Health professionals should emphasize that sport participation carries greater dangers for the head than for the kidneys, and that serious renal injury is more likely from motor traffic than from participation in most sports. Moreover, they should underline the importance of continued regular physical activity to the overall health and development of the child. Nevertheless, those with a solitary kidney should probably avoid sports that involve contact or have a high risk of collisions.

References


6 Bladder function in health and disease

Physical activity and bladder control, haematuria and bladder cancer

Introduction

This chapter explores the interaction between impaired bladder control and various types of physical activity, looking at whether particular types of sport are likely to cause problems of incontinence, and examining the possible role of exercise programmes in improving bladder control. It also adds to the information on haematuria presented in Chapter 4, and it explores whether habitual physical activity has any role in the prevention or treatment of bladder cancers.

The problem of urinary incontinence

Urinary incontinence is defined by the International Continence Society as a “complaint of any involuntary leakage of urine”. Clinicians commonly distinguish a form of urinary leakage termed stress urinary incontinence, which is precipitated by physical exertion, sneezing or coughing, and is of particular concern to the athlete. However, some authors maintain that other types of incontinence can also be precipitated by repeated bouts of strenuous physical activity.

Risk factors for urinary incontinence include old age, parity (particularly if instrumentally aided delivery of a baby has been necessary), obesity, diabetes mellitus, stroke, smoking, depression, overall functional impairment, oestrogen deficiency, genitourinary surgery and the use of medications such as psychotropic agents, angiotensin converting enzyme (ACE) inhibitors and diuretics. Incontinence is also associated with eating disorders, possibly because an inadequate intake of nutrients leads to muscle weakness; this factor could contribute to incontinence in gymnasts, where anorexia is sometimes a problem. Most studies of stress incontinence in athletes have been based on nulliparous individuals, although exercise is particularly likely to induce incontinence in the first few months following pregnancy.

Prevalence, economic impact and clinical evaluation of urinary incontinence

Urinary leakage varies greatly in volume and frequency, and because the affected
individuals are often embarrassed by their condition, the problem tends to be under-reported. In the general population, 25–40% of women have some urinary leakage at least once per year, and in 10% incontinence occurs as often as once per week.[8, 9] Leakage is less frequently in men. Incontinence is often thought as affecting mainly elderly people. However, Sandvik and associates[10, 11] summarized 13 studies of women, finding urinary leakage of unspecified severity in 20–30% of young women, rising to 30–40% in middle-age and 30–50% in the elderly. Certainly, occasional incontinence is to be expected in at least 15–30% of older community-dwelling older adults, as well as 50% of nursing home residents.[4, 5, 12]

Stress incontinence is usually a social inconvenience rather than a major health issue, but it can cause medical problems such as urinary tract and perineal infections, pressure ulcers and sleep disturbances. It also reduces the individual’s quality of life[13] and discourages participation in both physical activity[14, 15] and other forms of social interaction. In 1996, the estimated costs of urinary incontinence to the US economy were $11.2 billion within the community and $5.2 billion in nursing homes.[12]

Many pathologies can be at play in those with urinary incontinence, and a careful clinical examination is required, particularly if the condition is of recent onset. Issues to be reviewed are summarized in Table 6.1.

### Urinary incontinence in athletes

Stress incontinence can affect not only the elderly, but also much younger individuals, particularly those involved in vigorous athletic pursuits.[16] The prevalence of urinary leakage is influenced by the type and level of competition.[17] One review published in 2011 found 22 articles on stress incontinence in athletes,[18] and a second review from 2010 located 49 papers;[19] in 2014, a further PubMed search increased this total to 61 articles linking stress incontinence and sport participation[20] (Table 11.2). A review by Goldstick and Constantin[21] suggested that 28–80% of athletes had such complaints, with the highest prevalence among those who engaged in high-impact activities (trampolinists, gymnasts, hockey players and ballet dancers), and the lowest prevalence among those engaged in physically less demanding sports such as golf.[22] Jumping activities such as basketball and volleyball predispose to leakage, imposing ground reaction forces as much as four times body mass.[23]

Many investigators have relied on questionnaires or postal surveys to assess urinary incontinence. It has not always been clear from the responses to such instruments how frequent or serious the problem was, and whether the issue was stress incontinence or some other form of urinary leakage. A few observers have assessed incontinence more directly, measuring urinary leakage in a weighed sanitary pad[24–27] or recording the escape of fluid as a telemetrically recorded change in the electrical resistance of the pad.[28] The correlation between questionnaire responses and objective data is only moderate (a kappa coefficient of 0.45[25]). Hermieu et al.[26] commented that many women where urinary leakage
was indicated by an increase in the weight of a sanitary pad had not admitted to any incontinence when completing a questionnaire. In the study of Eliasson et al., there was an average leakage of 28 g of urine during 15 minutes of activity on the trampoline,\(^{24}\) and Stach-Lachinen et al.\(^{27}\) reported an average loss of 26 g over 24 hours in women with active leisure pursuits. Bourcier\(^{29}\) classed the problem as severe if there was continuous leakage when exercising, moderate if leakage occurred with heavy lifting or running, and mild if it only occurred with jumping.

Only 6 of some 30 studies have made direct comparisons of the prevalence of stress incontinence between athletes and sedentary individuals from the same population,\(^{5, 25, 32, 37, 42, 44}\) and even then the data have not always been controlled for important covariates (Table 6.2). Nevertheless, the uncontrolled values cited for various classes of athlete remain convincing because the prevalence of stress incontinence in such individuals far exceeds the expected prevalence of leakage in young sedentary nulliparous women.

The pattern of exercise causing problems typically involves a high impact activity such as jumping or running, often with sudden and repeated increases of intra-abdominal pressure.\(^{17}\) Interestingly, problems seem more prevalent during training than during competition, possibly because the catecholamine secretion of competition acts on urethral α-adrenergic receptors, facilitating closure of the

Table 6.1  Issues to be considered when examining a person who reports the onset of urinary incontinence

<table>
<thead>
<tr>
<th>History:</th>
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<tbody>
<tr>
<td>• Onset of incontinence</td>
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<tr>
<td>• Associated urinary symptoms</td>
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<tr>
<td>• Frequency, volume and timing of leakage</td>
</tr>
<tr>
<td>• Precipitating factors</td>
</tr>
<tr>
<td>• Normality of bowel function</td>
</tr>
<tr>
<td>• Normality of sexual function</td>
</tr>
<tr>
<td>• Risk factors (parity, obesity, diabetes, stroke, smoking, depression, functional impairment, oestrogen deficiency, genitourinary surgery)</td>
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<tr>
<td>• Use of medications (psychotropic agents, angiotensin-converting enzyme inhibitors and diuretics)</td>
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<table>
<thead>
<tr>
<th>Physical examination:</th>
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<tbody>
<tr>
<td>• Abdomen</td>
</tr>
<tr>
<td>• Cardiovascular system (signs of volume overload?)</td>
</tr>
<tr>
<td>• Physical mobility</td>
</tr>
<tr>
<td>• Neurological examination</td>
</tr>
<tr>
<td>• Genital examination (atrophy, inflammation, presence of a pelvic mass, pelvic floor weakness, urethral hypermobility, sphincter tone and adequacy of pelvic floor muscle function)</td>
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<table>
<thead>
<tr>
<th>Additional measures:</th>
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<tbody>
<tr>
<td>• Urinalysis</td>
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<tr>
<td>• Diary of urinary voiding</td>
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<tr>
<td>• Determination of post-voiding bladder volume</td>
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</table>
Table 6.2 Reports of urinary incontinence among athletes, former athletes and other active individuals

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Survey type</th>
<th>Incidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abitaleboul et al.[30]</td>
<td>517 female amateur marathon runners aged 41 years</td>
<td>Cross-sectional questionnaire</td>
<td>30.7% had urinary incontinence, 16% during run</td>
<td>Usually seen towards end of the event, 7.5% at least 1/week</td>
</tr>
<tr>
<td>Alance et al.[31]</td>
<td>Equestrians (31 M, 173 F) and swimmers (79 M, 102 F)</td>
<td>Mail and hand-distributed questionnaires</td>
<td>Multivariate analysis showed no association of horseback riding with urinary symptoms</td>
<td>No impact upon sexual dysfunction</td>
</tr>
<tr>
<td>Almeida et al.[32]</td>
<td>67 female athletes vs. 96 non-athletes</td>
<td>Questionnaire</td>
<td>Odds ratio of incontinence 2.9 for athletes</td>
<td>Mainly in artistic gymnasts and trampoline</td>
</tr>
<tr>
<td>Barreto et al.[33]</td>
<td>47 active women, age 32 yr, average 2.2 children attending 2 gyms</td>
<td>Questionnaire</td>
<td>72% reported urinary incontinence</td>
<td>Jumping 52.9%, squatting with weight 52.9%, leg press 29.4%, running 23.5%, walking 11.8%</td>
</tr>
<tr>
<td>Benjamin &amp; Hearon[34]</td>
<td>25 women aviators</td>
<td>Questionnaire</td>
<td>High g force does not cause incontinence even in women with predisposition to incontinence</td>
<td></td>
</tr>
<tr>
<td>Bø &amp; Sundgot-Borden[5]</td>
<td>660 elite female athletes, 766 controls, aged 15–39 years</td>
<td>Cross-sectional case-control postal survey</td>
<td>Similar prevalence in athletes and in controls (41%, 39%; social problem in 15%, 16%)</td>
<td>Parity less frequent in athletes than in controls</td>
</tr>
<tr>
<td>Bø et al.[35]</td>
<td>Fitness instructors (yoga and Pilates); 152 men, 685 women</td>
<td>Online survey</td>
<td>Incontinence in 3/152 men; in women 21.4% &gt;1/week, 3.2% 2/week, 1.7% &gt;1/day</td>
<td>Bother score 4.6</td>
</tr>
<tr>
<td>Bourcier[29]</td>
<td>30 female athletes age 22 years</td>
<td>Observation during feedback sessions</td>
<td>7% severe, 24% moderate, 33% mild urinary incontinence</td>
<td>Severe = continuous drip when exercising, moderate = with heavy lift or run, mild = with jumping</td>
</tr>
<tr>
<td>Author</td>
<td>Sample</td>
<td>Survey type</td>
<td>Incidence</td>
<td>Comments</td>
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<tr>
<td>Carls[36]</td>
<td>85 female athletes aged 14–21 yr</td>
<td>Cross-sectional questionnaire</td>
<td>&gt;25% had slight incontinence, 2–4 times/wk to 2–4 times/month. 16% negative effect on social life, 8% avoided exercise</td>
<td>Low response (86/550); 90% had never reported problem or heard of Kegel exercises</td>
</tr>
<tr>
<td>Caylet et al.[37]</td>
<td>157 elite female athletes, 426 controls aged 18–35 yr</td>
<td>Cross-sectional questionnaire</td>
<td>Stress incontinence in 28% of athletes, 9.8% of controls</td>
<td>Even a small loss of urine regarded as embarrassing</td>
</tr>
<tr>
<td>David[38]</td>
<td>132 nulliparous female athletes, age 19.5 years</td>
<td>Cross-sectional questionnaire</td>
<td>30% reported incontinence in daily life</td>
<td>Risk of incontinence related to training volume</td>
</tr>
<tr>
<td>Da Roza et al.[39]</td>
<td>22 national-level female nulliparous trampolinists</td>
<td>Cross-sectional questionnaire</td>
<td>Urinary incontinence in 72.7% during practices</td>
<td></td>
</tr>
<tr>
<td>Davis &amp; Goodman[40]</td>
<td>9 nulliparous female airborne trainees with stress incontinence</td>
<td>Self-administered questionnaire</td>
<td>6 weeks of rigorous airborne infantry training induced severe incontinence</td>
<td>Minimal incontinence before training</td>
</tr>
<tr>
<td>dos Santos et al.[41]</td>
<td>58 of 95 female physical education students aged 21.4 yr</td>
<td>Cross-sectional questionnaire</td>
<td>12/58 (20.7%) reported involuntary urine loss, mainly during sports activities</td>
<td>Seriousness of problem on 0–10 scale 2.3 (range 0–6)</td>
</tr>
<tr>
<td>Eliasson et al.[24]</td>
<td>35 female national level trampolinists, aged 15 yr</td>
<td>Cross-sectional postal survey, pad test on trampoline, measures of pelvic floor strength</td>
<td>100% on survey, 51.2% on pad test, 28.6% on pelvic floor strength</td>
<td>Leak averaged 28 g (9–56 g); no leak with laughs, coughs or sneezes</td>
</tr>
<tr>
<td>Eliasson et al.[17]</td>
<td>305 female trampolinists, aged 21 years, 85 competitive, 220 recreational level</td>
<td>Questionnaire</td>
<td>Prevalence of stress incontinence greater in ex-competitive (76%) than in recreational trampolinists (48%)</td>
<td>Other risk factors: inability to interrupt urine flow and constipation</td>
</tr>
<tr>
<td>Author</td>
<td>Sample</td>
<td>Survey type</td>
<td>Incidence</td>
<td>Comments</td>
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<tr>
<td>Elleuch et al.</td>
<td>105 female athletes, 105 non-athletes, aged 21.5 yr</td>
<td>Cross-sectional questionnaire</td>
<td>Stress incontinence in 62.8% of athletes, 34% in non-athletes</td>
<td>60% of athletes affected on daily basis</td>
</tr>
<tr>
<td>Fernandes et al.</td>
<td>39 female adolescent soccer players, age 15.6 yr, 24 controls</td>
<td>Pad test and questionnaire</td>
<td>Incontinence in 62.8% of athletes, vs. 25% in controls</td>
<td>Moderate reliability between pad test and questionnaire (kappa = 0.45)</td>
</tr>
<tr>
<td>Fischer &amp; Berg</td>
<td>274 female US aircrew, sometimes exposed to 9 g while flying</td>
<td>Anonymous questionnaire</td>
<td>Prevalence 26.3%, much as in general population</td>
<td>Only 13 of 72 incidents occurred while flying</td>
</tr>
<tr>
<td>Fozzatti et al.</td>
<td>244 nulliparous women attending gyms and performing high-impact exercise vs. 244 controls</td>
<td>International incontinence questionnaire</td>
<td>Questionnaire scores 1.68 vs. 1.02 in controls</td>
<td></td>
</tr>
<tr>
<td>Hermieu et al.</td>
<td>188 female runners</td>
<td>Pad test</td>
<td>Incontinence: 28.1% during 15 km walk, 51% for 10 km run, 60% for half-marathon, 75% for marathon</td>
<td>Many of women had not admitted to urinary incontinence on questionnaire</td>
</tr>
<tr>
<td>Jacome et al.</td>
<td>105 female athletes (athletics, basketball and football)</td>
<td>Questionnaire and focus group</td>
<td>Urinary incontinence in 41.5%, no difference between sports</td>
<td>Associated with lower body mass and BMI, avoided by preventive urination</td>
</tr>
<tr>
<td>Larsen &amp; Yavorek</td>
<td>116 women, 37 involved in paratroop training</td>
<td>Questionnaire and pelvic examination</td>
<td>24/116 had incontinence, unrelated to paratroop training</td>
<td>Paratroop training increased likelihood of pelvic prolapse</td>
</tr>
<tr>
<td>Nygaard et al.</td>
<td>Female nulliparous university athletes (156, aged 19.9 yr)</td>
<td>Cross-sectional postal survey</td>
<td>28% experienced at least one episode while practising sport</td>
<td>Gymnastics 67%; tennis 50%; basketball 44%; field hockey 32%; track 26%; other sports &lt;10%</td>
</tr>
<tr>
<td>Author</td>
<td>Sample</td>
<td>Survey type</td>
<td>Incidence</td>
<td>Comments</td>
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</tr>
<tr>
<td>Nygaard et al.</td>
<td>Former US female Olympic athletes (age 44 yr)</td>
<td>Retrospective postal survey</td>
<td>35.8% experienced incontinence; while competing: (swimmers 4.5%, gym/track 35%); now (swimmers 0%, gym/track 41%)</td>
<td>Significant differences while competing, p &lt;0.005</td>
</tr>
<tr>
<td>Poswiata et al.</td>
<td>International or national female runners (55) and cross-country skiers (57)</td>
<td>Anonymous questionnaire</td>
<td>45.5% leakage with sneezing or coughing</td>
<td>No difference between runners and skiers; 42.9% slightly bothered, 18.8% moderately bothered, 8% significantly bothered, 0.9% heavily bothered</td>
</tr>
<tr>
<td>Salvatore et al.</td>
<td>Non-competitive Italian sportswomen</td>
<td>Cross-sectional questionnaire</td>
<td>Urinary incontinence in 101 (14.9%), 32/101 during sport, 48/101 in daily life, 21/101 in both</td>
<td>Highest for basketball, athletics and tennis or squash. BMI and parity also risk factors</td>
</tr>
<tr>
<td>Schettino et al.</td>
<td>105 female volleyball players</td>
<td>Questionnaire</td>
<td>29.5% reported stress incontinence</td>
<td>65.7% had at least one symptom of stress incontinence</td>
</tr>
<tr>
<td>Simeone et al.</td>
<td>623 casual female athletes 18–56 yr, 12 sports</td>
<td>Anonymous questionnaire</td>
<td>30% had urinary incontinence</td>
<td>Most frequent in football. Risk factors long training, competitive practices, high impact</td>
</tr>
<tr>
<td>Stach-Lempinen et al.</td>
<td>82 women with urinary incompetence</td>
<td>Urodynamics, pad test and diary</td>
<td>Leakage greatest in women with greatest leisure activity</td>
<td>Questionnaire and Caltrac accelerometer</td>
</tr>
<tr>
<td>Thyssen et al.</td>
<td>8 national-level Danish sport clubs; 397 women, aged 23 yr, 8.6% of group parous</td>
<td>Cross-sectional postal survey</td>
<td>Gymnastics, 56%, ballet 43%, aerobics 40%, badminton 31%, volleyball 30%, athletics 25%, handball 21%, basketball 17%</td>
<td>51.9% had incontinence in sport or daily life</td>
</tr>
</tbody>
</table>
The level of competition is also a significant variable; the prevalence of stress incontinence was low in a survey of non-competitive athletes, and no effects were seen from horseback riding at an equestrian club, among walkers or in aviators with occasional exposure to high g forces.

The problem of stress incontinence can be sufficiently embarrassing as to preclude participation in sport or physical activity. A survey of 41,000 Australian women found a negative cross-sectional association between urinary leakage and habitual physical activity. About 15% of younger individuals reported such leakage when they engaged in sport or exercise, and 7% of younger women, a third of middle-aged women and a quarter of older women claimed to be avoiding sporting activities because of problems of urinary leakage.

Likewise, questionnaire responses from 3364 women in the US found incontinence was perceived as a moderate or substantial barrier to exercise in 9.8% of the sample; one in seven women experienced leakage during physical activity, and this was more likely in highly active than in less active individuals (15.9% vs. 11.8%). Among 101 non-competitive Italian sportswomen with urinary incontinence, 10.4% abandoned their favourite sport and a further 20% were obliged to alter their manner of play. One survey of 82 women with urinary incontinence found that their physical activity was less than that of the general population, but exercise habits were not increased by successful treatment of their problem.

Habitual physical activity and incontinence

There have as yet been no randomized controlled trials examining the impact of habitual physical activity upon urinary incontinence. In cross-sectional studies, it has been somewhat unclear whether urinary incontinence limited subsequent physical activity or whether sedentary behaviour increased the risk of incontinence (Table 6.3).

Bø et al. found a much higher incidence of stress incontinence in physical education than in nutrition students, and Hygaard et al. also found that very strenuous activity as a teenager increased the risk of future incontinence. However, among older individuals, incontinence was seen less frequently in the more active members of the group, unless high-impact activities were practiced. A large prospective study of middle-aged nurses showed that in those who were initially free of urinary leakage, the subsequent incidence of incontinence was less in the more active members of the sample; the benefit associated with regular physical activity was reduced by co-varying for body mass index, suggesting that exercise may have reduced the risk in part by helping the active individuals to regulate their body mass. Certainly, there is a strong association between obesity and urinary incontinence. However, eating disorders in some categories of very active individuals such as gymnasts are also associated with an increased risk of urinary incontinence.

The strength and functional capacity of the pelvic floor can be assessed by a variety of methods, including vaginal palpation, electromyography, manometry,
dynamic ultrasound and magnetic resonance imaging. However, the influence of regular physical activity upon pelvic floor function remains unclear. Several reports have suggested that the pelvic floor muscles can be strengthened by appropriate training exercises (see section on treatment, below), but others maintain that excessive high-impact exercise, heavy lifting or a persistent cough can overload, stretch and weaken the ligaments and muscles of the pelvic floor, with a permanent increase in the risk of incontinence. The situation is further complicated by the observation that incontinence in a group of physical education students was unrelated to the strength of their pelvic floor muscles. Borin et al. compared the pressure developed by the pelvic floor when lying supine in 30 athletes and 10 controls. Volleyball and basketball players both developed significantly lower pressures than the non-athletes. Moreover, urinary leakage was negatively correlated with the extent of athletic involvement, suggesting that repeated exposure to high-impact stress may have had an adverse effect on the pelvic floor muscles. Another small-scale study compared seven former high-impact athletes with seven controls, finding a lesser pubo-visceral muscle thickness and a lesser ability to develop maximal voluntary pelvic muscle contractions in former athletes than in controls. Eliasson et al. noted that a high incidence of incontinence persisted in competitive trampolists for five to ten years after ceasing competition, although Nygaard and associates found no difference of urinary leakage between high- and low-impact athletes 20 years subsequent to their involvement in competition. Certainly, if there is continued leakage, this implies that the pelvic floor muscles are not contracting appropriately to prevent unwanted urinary flow.

An occupational comparison between Danish nurses, who engaged in frequent bouts of heavy lifting, and the general population of Denmark found that the odds ratio of requiring an operation for genital prolapse was 1.6 in the nurses. Unfortunately, no data on the extent of urinary incontinence were provided, and it is possible that the nurses may have had more frequent complaints because they had a greater knowledge of problems and/or greater access to genito-urinary surgery than the general public. Further, the study was not controlled for possible differences of parity between the nurses and the controls.

Patho-physiology and the treatment of urinary incontinence

Patho-physiology

The pelvic floor muscles normally maintain some tone, except when a person is voiding. This group of muscles can contract simultaneously, causing an inward lift and squeeze around the urethra, vagina and anus, countering a sudden rise of intra-abdominal pressure. The pelvic floor muscles are “stiffer,” and have a more cranial position in nulliparous women and in the continent than in those who present with urinary incontinence. The preventive value of habitual physical activity remains unclear, with some investigators arguing that regular exercise strengthens the pelvic floor muscles,
### Table 6.3 Influence of habitual physical activity upon urinary incontinence

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Survey type</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bø et al. [14]</td>
<td>Physical education students vs. nutrition students</td>
<td>Questionnaire</td>
<td>Urinary leakage in 26% of phys. ed. and 19% of nutrition students</td>
<td>Most active phys. ed. students vs. sedentary nutrition students: 31% vs. 10%</td>
</tr>
<tr>
<td>Bradley et al.</td>
<td>297 women aged 68 yr</td>
<td>Questionnaire</td>
<td>Urinary urgency less prevalent in women exercising at least 1/week (23.8% vs. 35.2%)</td>
<td>High body mass index a risk factor</td>
</tr>
<tr>
<td>Danforth et al.</td>
<td>Nurses/health study, initial age 66 yr</td>
<td>Biennial reporting of physical activity, self-reports of incident leakage of urine (2355 cases)</td>
<td>Odds ratio of leaking urine 0.81 (highest vs. lowest physical activity quintile)</td>
<td>Greater benefit for stress than for urge incontinence; most activity undertaken was moderate, e.g. walking</td>
</tr>
<tr>
<td>Eliasson et al.</td>
<td>665 women before and after birth of first child</td>
<td>Questionnaire at 36th week, 1 year post-partum</td>
<td>High impact exercise before pregnancy risk factor for urinary leakage, low-impact exercise protective</td>
<td>Urinary leakage before pregnancy usually persisted 1 year post-partum</td>
</tr>
<tr>
<td>Hannestad et al.</td>
<td>27,936 Norwegian women</td>
<td>Questionnaire</td>
<td>Low-impact physical activity reduces risk, but not high-impact activity</td>
<td>Strong association with BMI, weak association with smoking</td>
</tr>
<tr>
<td>Kikuchi et al.</td>
<td>Elderly aged &gt; 70 yr (507 not incontinent, 169 incontinent)</td>
<td>Questionnaire</td>
<td>Odds ratio of incontinence 0.71 (middle), 0.58 (high) physical activity</td>
<td>Prevalence 34% in women, 16% in men</td>
</tr>
<tr>
<td>Nygaard et al.</td>
<td>Case/control moderate or severe incontinence vs. mild or none, women aged 39–65 yr</td>
<td>Incontinence severity index scores relative to physical activity questionnaire</td>
<td>Incontinence increased slightly with lifetime activity (odds ratio 1.20), but not with lifetime strenuous activity</td>
<td>Strenuous activity as a teen increased incontinence</td>
</tr>
<tr>
<td>Townsend et al.</td>
<td>116,671 female nurses, 4081 incident cases of urinary incontinence</td>
<td>Questionnaire, prospective study</td>
<td>Stress and urge incontinence relative risk 0.75 top vs. bottom physical activity quintile</td>
<td>Relative risk attenuated by adjustment for BMI-benefit partly due to weight maintenance?</td>
</tr>
</tbody>
</table>
and others maintaining that excessive physical activity has a weakening effect.\footnote{66} Even the importance of the thickness of the pelvic muscle floor is debated. One small study found that at the level of the mid-vagina, the pubo-visceral muscles were actually thicker in female football players who showed incontinence than in those who did not.\footnote{75} Leakage typically occurs in the latter part of competition or training sessions,\footnote{37, 62} suggesting that cumulative fatigue may be a factor, and it seems likely that the onset of such fatigue could be delayed by a strengthening of the pelvic musculature.

Ree et al.\footnote{76} examined the effects of strenuous physical activity (90 minutes of interval training relative to 90 minutes of rest) in 12 nulliparous young women with mild stress incontinence. An intra-vaginal balloon catheter demonstrated a 20% reduction in mean contraction pressures immediately after exercise, suggesting a short-term fatigue of the pelvic floor muscles. Nevertheless, it remains uncertain if chronic participation in high-impact competitive athletics has an adverse effect upon pelvic floor function. Kruger et al.\footnote{77} used two- and three-dimensional trans-labial ultrasound to underline that there was a larger hiatal area and a greater bladder neck descent during the Valsalva manoeuvre in 24 competitors than in 22 controls; however, these same studies demonstrated a progressive increase in the average cross-sectional area and thickness of the levator ani and pubo-rectalis muscles among participants in high-impact sports.\footnote{77, 78} This could reflect a local adaptation to repeated high impacts, but other possibilities include a selective retention in the study of individuals with an initially strong pelvic musculature or a training-induced development of the foot arches that reduced the effect of impacts upon the pelvis.\footnote{79} Bø and Sundgot-Borgen\footnote{5} found no difference in the prevalence of urinary incontinence among high- and low-impact former Olympians from the period 1970–1976 when they were examined 20–30 years after competition, but some investigators still suggest that the very high physical demands of current Olympic participation may have long-term adverse effects on genito-urinary function.

\textit{Treatment of urinary incontinence}

Possible treatments of stress incontinence include bladder training, pelvic floor exercises with or without resistance, the insertion of intra-vaginal cones, biofeedback, electrical stimulation of the pelvic muscles, drug treatment and surgery (Table 6.4). It remains difficult to choose among this wide range of possible options because none has as yet been evaluated in double-blind fashion, and none has received unanimous clinical endorsement.

Stress incontinence can apparently be reduced if the affected individual develops the ability to make a quick and strong contraction of the pelvic floor muscles when a rise of intra-abdominal pressure is anticipated.\footnote{87, 88} This technique is not always included specifically in rehabilitation programmes, but it may be that many athletes make such a contraction instinctively when they are exercising.\footnote{89} Specific exercises to increase the strength of the pelvic floor muscles were first advocated by Kegel,\footnote{90} who claimed that 84% of cases of
incontinence could be cured by such a programme. Details of the approaches adopted by various authors have been reviewed by Bø.\[91\] Pelvic muscle exercises are certainly the simplest approach and are probably the most appropriate initial recommendation for athletes with small amounts of urinary leakage.\[92\] However, it takes a few weeks to learn the correct technique, and adherence to the training programme is important to the success of treatment. Moreover, because the intra-abdominal pressure levels of the athlete can be higher than in sedentary individuals, there is probably a need for greater rigour in the training programme for those who engage in high-impact sports.\[66\] A typical routine involves sustaining maximal efforts for 6–8 seconds,\[91\] possibly with 3–4 sets of 8–12 slow-velocity supervised contractions practiced three times per week, for as long as six months. There have been many demonstrations of benefit from pelvic muscle exercises in the general population,\[91\] with self-assessed cure rates of 32–84%, and several uncontrolled studies have also found this approach to be helpful in elite athletes. Bø et al.\[93\] found that after pelvic floor muscle training, 17 of 23 women reported improvements during jumping and running, and 15 noted improvements during lifting; this was confirmed by a decrease of pad leakage from an average of 28 g to 7.1 g. Mørkved et al.\[94\] reported a 67% cure rate with biofeedback assisted pelvic muscle training. Da Roza et al.\[95\] also arranged pelvic muscle training for 16 young sports students who had complained of sporadic urinary incontinence. Unfortunately, perhaps because of the time demanded by this training (60 minutes per session), only seven of the group completed the eight-week programme; in these seven individuals, the pelvic floor muscle strength was increased, and the frequency and amount of incontinence was reduced. Rivalta et al.\[96\] treated three nulliparous female athletes with a programme that combined pelvic floor muscle training with biofeedback, electrical stimulation and intra-vaginal cones; the three-month rehabilitation programme abolished the previous incontinence in all of this small sample.

Yoga and Pilates classes also have their advocates as a means of treating urinary incontinence,\[97\] but they do not seem to have any specific effect in activating the pelvic floor muscles;\[98\] nor do they offer any advantage relative to more specific forms of pelvic floor muscle training.\[83\] Many of the treatments using biofeedback have been made in the supine position, but Boursier\[29\] carried out training with the athletes standing in positions typical of their sport. Other investigators have used electrical or mechanical stimulation of the perineal muscles.\[99\]

Another simple treatment option is the insertion of an intra-vaginal tampon. One investigation found total dryness throughout 30 minutes of aerobic exercise when such a device was used by six women who had complained of stress incontinence.\[100\]

Medications such as the anti-depressant imipramine and the serotonin and norepinephrine uptake inhibitor duoxetine have improved the quality of life for some people with incontinence\[101\] but these drugs have not been tested in athletes,\[102\] and one recent Cochrane review found that their effect on urinary incontinence was only slightly greater than that of a placebo.\[103\] Anticholinergic
<table>
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<th>Findings</th>
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<tbody>
<tr>
<td>Bø et al.[80]</td>
<td>52 women aged 45.9 years with stress incontinence</td>
<td>8–12 pelvic floor max contractions, 3/day for 6 months, half of group also made sustained contractions 1/week</td>
<td>60% of intensive exercise, 17% of home exercise group almost continent after 6 months of treatment</td>
<td>Exercises much more effective if supervised. Associated gains of pelvic floor strength</td>
</tr>
<tr>
<td>Bø et al.[81]</td>
<td>107 women with stress incontinence, aged 49.5 years</td>
<td>Pelvic floor exercises (25), electrical stimulation (25), vaginal cone (27), control (30)</td>
<td>Pelvic floor exercises superior to alternatives in terms of both strength and leakage</td>
<td>Exercises decreased average urinary leakage from 30 g to 17 g</td>
</tr>
<tr>
<td>Bourcier[29]</td>
<td>68 young nulliparous women: 30 athletes, 38 active women, aged 22 years</td>
<td>Applied biofeedback while in athletic posture, 2/week for 3 weeks, 1/week for 4 weeks</td>
<td>Both groups improved, but athletes not completely cured by treatment</td>
<td>Focus on ability to control pelvic diaphragm</td>
</tr>
<tr>
<td>Castro et al.[82]</td>
<td>108 women with stress incontinence</td>
<td>Comparison of pelvic floor exercises (31), electrical stimulation (30), vaginal cones (27) vs. controls</td>
<td>Patients reporting satisfaction: 58, 55, 54 and 21% respectively</td>
<td>3 treatment options seem equally effective</td>
</tr>
<tr>
<td>Culligan et al.[83]</td>
<td>62 women with little pelvic floor dysfunction</td>
<td>Pilates vs. pelvic floor muscle exercises</td>
<td>Equal increase of pelvic floor strength by perineotomy</td>
<td>No discussion of incontinence</td>
</tr>
<tr>
<td>Fitz et al.[84]</td>
<td>Stress incontinence, 16 women given biofeedback, 16 comparison group, aged 58 years</td>
<td>3 sets of slow contractions, 3–4 fast pelvic floor contractions 2/week for 6 weeks</td>
<td>Adding biofeedback improved function, reduced urinary symptoms and improved quality of life</td>
<td></td>
</tr>
<tr>
<td>Mørkved et al.[85]</td>
<td>94 women with stress incontinence</td>
<td>Pelvic floor muscle training, half of group with biofeedback</td>
<td>Cure (2g leakage or less) in 60% of group with biofeedback, 50% in comparison group</td>
<td>Effect of biofeedback not statistically significant</td>
</tr>
</tbody>
</table>
drugs may also offer some benefit, but they are not recommended for athletes because of the concomitant reduction of sweating. Surgical interventions such as pubo-vaginal sling procedures, retropubic suspension and periurethral injections can be offered to older patients, but they are inappropriate for young athletes who only experience incontinence when they are engaged in high-intensity sport.\[104\]

Physical activity and haematuria

The issue of micro-haematuria was discussed in Chapter 4. An overt red colouration of the urine in an athlete can reflect the presence of more substantial quantities of either haemoglobin or myoglobin. A strenuous bout of exercise may occasionally lead to gross haematuria. Runners are the most vulnerable, although almost any athlete can develop visible urinary bleeding after a period of intensive physical activity. Overt haematuria may be precipitated by trauma to the bladder, dehydration or the breakdown of red blood cells that occurs with sustained aerobic exercise. Resolution is usually rapid, but a detailed clinical examination for more serious causes of bleeding is required if the haematuria does not stop within 72 hours. Other potential causes of haematuria that the clinician should consider are summarized in Table 6.5.

Physical activity and bladder cancer

Bladder cancer is the sixth most common type of neoplasm in Canada, with a ten-year survival rate of about 76%.\[105\] There is at present no evidence that the risk of developing bladder cancer is directly related to physical inactivity, although there may be a weak indirect association because one potent cause of such tumours (cigarette smoking) is linked to various facets of a poor overall lifestyle, including physical inactivity. Physical activity could also boost antioxidant mechanisms, thus countering the free radical production that is associated with exposure to arsenic compounds, another recognized cause of bladder cancer.\[106\]

The treatment of bladder cancer may include surgery or local irradiation, and local or general chemotherapy. Commonly, survivors of such treatment face sexual and/or urinary dysfunction. Following successful suppression of the
tumour, the physical activity of many patients falls below the minimum recommended for health. Encouragement of physical activity can help to correct the resulting limitations of aerobic power, muscular strength and range of motion, enhancing functional capacity and decreasing co-morbidity. Partly for this reason, Karvinen et al.[105] noted that the quality of life among survivors (particularly in the physical and functional domains) was positively related to their level of physical activity. The more active individuals showed less fatigue, had a better self-image and better erectile function. Exercisers also have a better long-term survival rate than those who remain sedentary.[106]

It might be asked whether those with a poor quality of life were the least active members of the sample because they were older, more severely affected by the tumour or had more complications during subsequent treatment, although Karvinen et al.[105] did not observe any relationship between the quality of life and age, body mass index, the invasiveness of the tumour or the type of treatment that had been implemented. Further studies are warranted to test the causal nature of this relationship. However, the information that is currently available already points to a need to encourage greater physical activity following the treatment of a bladder cancer.

**Table 6.5 Potential causes of haematuria**

- **Urinary tract infections.** Urinary tract infections usually cause a persistent urge to urinate, a burning pain with urination and strong-smelling urine, but occasionally the only sign of illness may be a persistent haematuria.
- **Renal infections.** Renal infections (pyelonephritis) can occur via the blood stream or the urethra. The signs and symptoms are often similar to those seen with infection of the bladder and lower urinary tract, but there may also be fever and pain in the loin.
- **Bladder or renal calculi.** Bladder and renal calculi often remain dormant for long periods, but can cause various degrees of urinary bleeding, intense pain and even urinary blockage as they are being passed.
- **Prostate enlargement.** The prostate enlargement of middle and old age compresses the urethra, partially blocking urine flow, and causing an urgent need to urinate, often with associated urinary bleeding. Infection of the prostate gland can cause similar signs and symptoms.
- **Renal disease.** Renal disease (glomerulonephritis) affecting the small glomerular capillaries can cause microscopic haematuria.
- **Cancers of the urinary tract.** Urinary bleeding can be a harbinger of advanced kidney, bladder or prostate cancer.
- **Sickle cell anaemia.** Sickle cell anemia can cause episodic haematuria.
- **Renal trauma.** A physical injury to the kidneys can cause a substantial haematuria.
- **Adverse drug reactions.** Urinary bleeding can result from adverse reactions to drugs, particularly anticoagulants such as heparin, ibuprofen and other non-steroidal anti-inflammatory drugs.
- **Menstrual contamination.** In women, urine samples may be contaminated by menstrual bleeding.
Areas for further research

Perhaps the most fundamental requirement in future research is an objective evaluation of the extent of urinary leakage. The correlation between questionnaire responses and objective weighed pad data (kappa value 0.45) is disturbingly low. Reasons for the discrepancy between subjective and objective data such as embarrassment when responding to questionnaires should be clarified. At present, we do not know the minimum frequency and volume of urinary leakage that is likely to cause a person to seek treatment. Whereas some have argued that regular physical activity strengthens the pelvic floor muscles, others have maintained that excessive exercise has a weakening effect. Further observations are thus required to decide whether habitual physical activity increases or reduces the risk of urinary leakage, and whether there is a useful ceiling of training, beyond which more strenuous effort impairs pelvic floor function.

It remains difficult to choose among possible options for the management of stress incontinence because none has as yet been evaluated in double-blind fashion. More controlled and blinded trials are needed to evaluate the various treatment possibilities, and to examine the impact of successful treatment upon subsequent exercise participation. There is also a need to clarify the reasons predisposing to severe haematuria following heavy endurance exercise.

Practical implications and conclusions

Stress incontinence has a high prevalence in young nulliparous female athletes involved in high-impact sports. Although leakage during competition is typically small (around 25 g), social embarrassment can cause under-reporting of the problem, impaired physical performance and unwillingness to engage in active pursuits. Physicians and coaches should monitor athletes closely for this problem. Problems can be eased by changing from a high- to a low-impact sport, but this is obviously not a practical solution for elite competitors. Some have argued that high-intensity sport and heavy lifting can cause chronic strain of the pelvic floor, but urinary leakage can probably be reduced through a combination of pelvic floor muscle exercises and development of the arches of the feet to reduce impact forces. If leakage is small, the competitor should be advised that this is a common phenomenon with no serious health consequence. It can usually be managed by using absorbent pads.

Gross haematuria can sometimes follow endurance activity; usually there are no serious consequences to such a manifestation, but a thorough genito-urinary investigation is required if bleeding persist for more than 72 hours.

Physical activity apparently has no direct influence on the risk of bladder cancer. However, following successful treatment, habitual physical activity is often less than the minimum recommended for good health. Counselling may be needed to suggest methods of continuing regular exercise in the face of urinary or faecal incontinence. Greater physical activity can enhance the quality of life, and by reducing the risk of various chronic diseases, it also increases overall survival.
References


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89. Constantinou CE, Govan DE. Contribution and timing of transmitted and generated pressure components in the female urethra. *Prog Clin Biol Res* 78; 113–120.


7 Physiology of the spleen at rest and during exercise

Introduction

In this chapter, we will explore the anatomy and physiology of the spleen in both humans and animals, looking at reactions to physical activity and other stressors. We will consider also mechanisms underlying changes in dimensions of the spleen and their practical significance in terms of changes in oxygen transport, blood clotting and the immune response. The clinical issues of athlete management in infectious mononucleosis and Sickling disease are considered in subsequent chapters (Chapters 8 and 9).

The spleen was well known to the ancient Greeks. Erasistratus maintained that it served only to maintain the symmetry of the abdomen, but Plato suggested that its responsibility was to keep the liver “bright and shining”, and Hippocrates argued that its primary function was to produce black bile, one of the four basic humours in his understanding of human physiology.[1] Galen called the spleen “mysterii organon”, claiming that humours unsuitable for its nutriment were discharged by a canal that emptied from the spleen into the stomach.

The biological importance of the spleen seems to vary substantially from one species to another. The English cardiovascular physiologist Sir Joseph Barcroft and his colleagues first drew attention to the contribution of the spleen to running ability in the dog and cat.[2, 3] In these animals the haemoglobin concentration and haematocrit were about 50% higher for the splenic pulp than for the general circulation. Moreover, vigorous treadmill exercise caused the volume of the spleen to shrink to a half or even a third of its resting value, thus increasing the animal’s blood volume and potential oxygen carrying capacity by 6–15%. Furthermore, this seemed to be an active, neurally regulated response to exercise which was lost if the nerve supply to the spleen was sectioned. In the same era, Scheunert and Krywanek[4] demonstrated that the increased haematocrit and haemoglobin that developed in experimental animals during vigorous exercise was abolished if the spleen was removed surgically. Granaat[5] pointed out that the spleen contained relatively large amounts of the hormone norepinephrine, and that the release of this substance or some other pressor hormone into the circulation could influence performance, contributing to the rise of blood pressure observed at the onset of exercise.
The practical importance of the spleen to the human exercise response for long remained open to debate. Certainly, people have lived for many years following splenectomy, with no apparent difficulty in exercising, although with an increased risk increase of death from some medical conditions. A 28-year follow-up of 740 American World War II veterans who had undergone splenectomy found that relative to control subjects who had been treated for an acute inflammation of the nose and throat, there was a 4.6-fold increase in deaths from pneumonia and a 1.35-fold increase in deaths from ischaemic heart disease, but apparently no other adverse effects.\[6\] The pneumonia was attributed to some reduction of immune function, and the increased incidence of ischaemic heart disease was thought to reflect either a loss of the normal splenic function of sequestering and eliminating aging and injured red cells, or to an increase in platelet counts (which often persists for a long time after splenectomy).

Ebert and Stead\[7\] argued strongly against a reservoir function for the spleen in humans. Their research appeared to confirm earlier observations that exercise-\[8\] and epinephrine-induced\[9\] changes of haematocrit were identical in normal and splenectomized subjects, and they attributed the contrary results of some investigators to technical errors. Despite a careful marshalling of evidence by Stewart and McKenzie,\[10\] the view thus persisted that in humans, the main functions of the spleen were the breakdown of senescent erythrocytes, the synthesis of antibodies and the storage of monocytes, iron and viable red cells.\[11\] As recently as 2012, a highly respected respiratory physiologist (John West) affirmed that stress did not lead to any expulsion of red cells from the human spleen.\[12\]

The present chapter makes a critical examination of the contribution of the spleen to the human exercise response. After summarizing the classical findings in experimental animals, it looks at the anatomy of the spleen and methods of determining its volume. It then considers findings during exercise and other forms of stress, and evaluates the practical role of this organ in oxygen transport, blood clotting and immune function both at rest and during physical activity. Finally, it examines likely mechanisms causing any changes in splenic dimensions.

Physical activity and the spleen in experimental animals

In some species, the spleen is a large organ, containing a substantial fraction of the body’s red blood cells. For example, in a 350 kg Weddell seal, the spleen contains some 20 L of red cells\[13, 14\] or as much as 50% of the animal’s total red cell volume. Comparable figures are 54% of the total blood volume for the horse, 26% for the sheep and 20% for the dog, compared with less than 10% of the total blood volume in humans.\[15\]

Dating from the classical observations of Sir Joseph Barcroft,\[2, 3\] there has been strong evidence that the splenic store of red cells has an important reservoir function in many animals, and that this store is called upon during vigorous physical activity and other forms of stress (Table 7.1). The extent of the splenic contribution has been demonstrated by direct observation of changes in
dimensions of an exteriorized spleen, by data showing an increased red blood cell count and haematocrit during vigorous exercise, by finding an increased proportion of large (spleen-derived) red cells in the circulation, and by ultrasonic measurements showing decreases in spleen area or volume. The practical contribution of the infused blood to endurance performance has been reflected by temporary increases in maximal oxygen intake, a response analogous to that obtained through the banned practice of athletic “blood doping”. Changes are abolished by splenectomy, both in horses[22] and in dogs.[16, 28, 30]

The reservoir function of the spleen has been demonstrated for a substantial range of experimental animals (Table 7.1), including thoroughbred- and race-horses,[26, 29, 31–34] greyhounds, foxhounds and other types of dog,[18, 19, 21, 23–25, 28] sheep,[20] guinea pigs[17] and diving seals.[13, 27, 35, 36] Horses show a 65–75% increase of haematocrit during exercise,[31, 37] and in the diving seal a reduction of splenic volume from 24 to 4 L augments the red cell volume by 20 L, increasing oxygen stores by enough to allow the animal to sustain an underwater dive for an additional eight minutes.[14]

Anatomy of the human spleen

If the human spleen can contract in response to the circulatory needs of vigorous physical activity, one would anticipate finding smooth muscle in its capsule and/or trabeculae. Early investigators failed to demonstrate any smooth muscle in the human spleen.[11] However, tests using antigens that react to smooth muscle myosin have now shown significant if small amounts of smooth muscle in both the collagenous walls of the splenic capsule and its trabeculae.[38] Contraction of the smooth muscle appears to be mediated by α-adrenoreceptors, since α-adrenergic stimulation increases blood reticulocyte counts, with an associated decrease in size of the spleen. In contrast, the stimulation of β-adrenoreceptors has the opposite effect, leading to a drop in reticulocyte count, apparently with an increase in the dimensions of the spleen.[39]

The precise volume of the human spleen has yet to be clearly established. Rushmer[40] suggested that under resting conditions it contained 200–250 mL of blood. Ayers et al.[41] found that the average mass of 30 isolated spleens was 212 g, and autopsy records for 539 spleens found an average mass of 168 g.[42] However, these figures probably underestimated the normal volume, since blood tends to leak from the spleen during autopsy. In vivo estimates[43–46] range from 130 to 360 mL,[45, 46] depending in part on methodology. Scintigraphic data tend to yield high values, and these figures may have been biased upwards by failure to allow for counts coming from radiographically tagged red cells in overlapping organs such as the heart and kidney rather than from the spleen itself.

The practical implication of current estimates is that even if vigorous physical activity were to cause a 50% emptying of the human spleen, it could contribute no more than 100–120 mL to a total blood volume of 5 L (at most, an increase of 2.0–2.4%).
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<tr>
<td>Barcroft &amp; Florey</td>
<td>2 dogs with exteriorized spleens</td>
<td>17 seconds of running in laboratory and to and fro on laboratory roof</td>
<td>Volume of spleen decreased to 40% of resting size</td>
<td>Effects persisted 20 min after ceasing exercise</td>
</tr>
<tr>
<td>Florey et al.</td>
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<tr>
<td>Barcroft &amp; Stephens</td>
<td>2 dogs with exteriorized spleens. Some observations also on cats</td>
<td>Running and swimming; even larger response with severe haemorrhage</td>
<td>Spleen reduced to a half or a third of initial volume, increasing blood volume by up to 20%</td>
<td>Response depends on integrity of splenic nerve supply</td>
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<td>Dane et al.</td>
<td>6 adult foxhounds</td>
<td>Treadmill running at 60–80% of maximal oxygen intake</td>
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<td>Splenectomy caused a 30% reduction in maximal oxygen intake</td>
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<td>Digges et al.</td>
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<td>Alpha-type adrenoreceptors demonstrated in splenic capsule</td>
<td>Alpha-type adrenoreceptors demonstrated in splenic capsule</td>
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<tr>
<td>Gunteroth et al.</td>
<td>30 dogs</td>
<td>Epinephrine injection</td>
<td>Within 15 seconds of injection, 45–50% increase of haematocrit</td>
<td>Similar response to fright</td>
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<tr>
<td>Gunteroth &amp; Mullins</td>
<td>37 dogs with barium titanate crystals sewn to spleen, ultrasound and impedance data</td>
<td>Treadmill exercise 6.4 km/h, 5% grade</td>
<td>Half of dogs initially showed splenic contraction</td>
<td>Effect lessened with habituation to exercise</td>
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<td>Hodgetts et al.</td>
<td>13 Merino sheep</td>
<td>Injection of epinephrine</td>
<td>Increase in haematocrit from 31% to 40%</td>
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<td>Horvath et al.</td>
<td>50 greyhounds</td>
<td>Racing on track</td>
<td>Increase in reticulocyte count immediately after the race, normalized after 1–2 hours</td>
<td>Probably due to catecholamine-mediated splenic contraction</td>
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<td>Hurford et al.</td>
<td>5 Wedell seals</td>
<td>Diving or injection of epinephrine</td>
<td>Ultrasonography shows 30% change in spleen size with dive; haematocrit increased from 44% to 55%</td>
<td>Equivalent to infusion of 20 L blood</td>
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*Table 7.1* Response of the spleen to physical activity and other stimuli, as seen in experimental animals
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<tr>
<td>Kunugiyama et al. [22]</td>
<td>6 thoroughbred horses</td>
<td>Treadmill running</td>
<td>Total erythrocyte volume, measured by $^{51}$Cr, increased by exercise</td>
<td>Effect of running abolished by splenectomy</td>
</tr>
<tr>
<td>Longhurst et al. [23]</td>
<td>Dogs</td>
<td>Treadmill running</td>
<td>Alpha-adrenergic blockade (by phentolamine) reduced maximal oxygen intake 16.7%, splenectomy reduced 12.6%</td>
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<tr>
<td>Neuhaus et al. [24]</td>
<td>6 greyhounds</td>
<td>704 m race</td>
<td>Haematocrit increased from 48% to 67%</td>
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<tr>
<td>Rovira et al. [25]</td>
<td>15 dogs</td>
<td>100 second agility exercise</td>
<td>12% increase of blood volume, 21% increase of red cell volume, 4% increase of packed cell volume</td>
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<tr>
<td>Thomas &amp; Fregin [26]</td>
<td>5 sedentary horses</td>
<td>Treadmill exercise to 90% of maximal heart rate</td>
<td>Haematocrit increased from 33% to 47% (50% increase in circulating red cells)</td>
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<td>Thornton et al. [27]</td>
<td>Seal pups</td>
<td>Magnetic resonance imaging of spleen</td>
<td>Rapid contraction of spleen to 16% of original volume during forced dives</td>
<td>Blood transferred to hepatic sinus with splenic contraction</td>
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<td>Vatner et al. [28]</td>
<td>6 unrestrained dogs</td>
<td>Running 3.2 km behind recording van at up to 40 km/h</td>
<td>Haematocrit increased from 40% to 49%</td>
<td>Effect of running abolished by splenectomy</td>
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<tr>
<td>Wagner et al. [29]</td>
<td>6 thoroughbred horses (3 with splenectomy)</td>
<td>Treadmill running</td>
<td>Splenectomy reduced maximal oxygen intake by 31%</td>
<td>Decrease in maximal oxygen intake restored by transfusion</td>
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Physical activity and changes in volume of the human spleen

Issues of methodology

Except in rare circumstances,\(^4\) the human spleen cannot be exteriorized in the manner adopted in some animal experiments. Methods to determine changes in volume of the human spleen include haemoglobin and haematocrit determinations, ultrasonography, magnetic resonance imaging and most frequently recording of changes in the emissions of previously injected \(^{99}\)Technetium-labelled red cells and \(^{11}\)Indium labelled granulocytes and platelets from the region of the spleen (Table 7.2).

Each of these approaches has its limitations. Haemoglobin and haematocrit-based estimates of changes in splenic volume depend on a knowledge of associated exercise-related changes in plasma volume. Ultrasound or radio-nuclide measurements commonly assume that the changes of splenic dimensions are uniform and can be visualized in a single plane, and some radionuclide data have been compromised by failure to exclude emissions from the presence of radioisotopes in adjacent organs such as the kidneys and the lungs.

Experimental findings

Two early studies\(^7, 8\) based on changes in haemoglobin and serum protein concentrations found no evidence that physical activity affected the splenic volume of human subjects. Although vigorous physical activity increased haemoglobin and haematocrit levels, similar responses were observed after splenectomy, suggesting that the spleen was not responsible (Table 7.2).

Wolski\(^4\) scanned both anterior and posterior views of the spleen following the radionuclide labelling of red cells. She found that exercising for 30 minutes at a load increasing from 25 to 50 and then 75% of maximal oxygen intake led to a 7–9% increase in the total circulating red cell volume under both normoxic and hypoxic conditions; she suggested that filtration of fluid through the walls of the blood vessels explained 68–78% of the changes in haematocrit that were seen during exercise.

Twelve more recent cycle ergometer or treadmill studies\(^4\) have found the splenic contents making a significant contribution to the red cell count during physical activity, with recovery of pre-exercise values over a recovery period of 10–20 minutes (Table 7.2).

One study was based on 21 patients with thalassaemia, 10 of whom had undergone splenectomy. Changes in haematocrit and plasma protein concentrations were measured.\(^4\) Maximal voluntary cycle ergometer exercise induced small increases of both haemoglobin (1.0 g/dL in those with intact spleens, 0.4 g/dL in splenectomized patients) and haematocrit (3.3%, 1.4%), with larger increases in the concentration of serum proteins (4–5 g/L) due to extravasation of fluid from the circulation.

Other observers, using the more precise technologies of technetium scintigraphy or ultrasound, found that physical activity induced decreases in splenic


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<td>Changes in haemoglobin and serum protein concentrations</td>
<td>10 healthy men, 2 splenectomized individuals</td>
<td>20 minute treadmill run at 9.3 km/h</td>
<td>Changes in haemoglobin parallel changes in serum protein concentrations; similar response seen in splenectomized individuals</td>
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<td>Ebert &amp; Stead [7]</td>
<td>Changes in haemoglobin, haematocrit and serum protein, dye estimate of plasma volume</td>
<td>6 healthy men, 2 with splenectomy</td>
<td>Cycle ergometer test to exhaustion in 3–5 min; splenectomized subjects did not exercise to exhaustion</td>
<td>Increase of haemoglobin and haematocrit with exercise similar in normal and splenectomized individuals</td>
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<td><strong>Positive findings</strong></td>
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<td>Haemoglobin-based estimates</td>
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<td>Allsop et al. [43]</td>
<td>Technetium labelling of erythrocytes, Indium labelling of platelets and granulocytes</td>
<td>10 normal healthy individuals (5 for technetium, 5 for Indium studies)</td>
<td>4 minutes of supra-maximal exercise on cycle ergometer (110–120% of steady-state maximal value)</td>
<td>Rapid 54% drop of splenic volume (technetium) radioactivity, with rapid recovery post-exercise. Much slower changes in platelets and granulocytes</td>
</tr>
<tr>
<td>Flamm et al. [46]</td>
<td>Technetium labelling of erythrocytes</td>
<td>10 men, 4 women</td>
<td>Cycle ergometry at 0%, 50%, 75% and 100% of maximal oxygen intake</td>
<td>46% decrease of blood volume in spleen, 4.3% increase of haematocrit</td>
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<tr>
<td>Froelich et al.</td>
<td>$^{99}$Technetium labelling of erythrocytes</td>
<td>7 women, 3 men</td>
<td>Graded cycle ergometer exercise to voluntary exhaustion</td>
<td>39% decrease of splenic volume (compared with 14% decrease in liver)</td>
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<tr>
<td>Laub et al.</td>
<td>$^{99}$Technetium labelling of erythrocytes and changes in haematocrit</td>
<td>4 men, 1 woman</td>
<td>Graded cycle ergometry to maximal effort</td>
<td>Progressive decrease of spleen volume to 34% initial value, 3.4% increase of haematocrit</td>
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<tr>
<td>Otto et al.</td>
<td>$^{99}$Technetium labelling of erythrocytes</td>
<td>20 healthy men, 10 controls</td>
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<td>Sandler et al.</td>
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<td>10 patients undergoing radionuclide ventriculography</td>
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<tr>
<td>Stewart et al.</td>
<td>$^{99}$Technetium labelling of erythrocytes</td>
<td>9 healthy men</td>
<td>Cycle ergometer exercise at 60% of maximal oxygen intake for 5, 10 or 15 min, followed by ride to exhaustion</td>
<td>Submaximal exercise reduced splenic volume 28, 30 and 36%, ride to exhaustion gave 56% decrease in splenic volume, recovery over 20 min</td>
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**Ultra-sound based estimates**

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<td>Engan et al.</td>
<td>Ultrasound and capillary haemoglobin concentration</td>
<td>1 woman, 7 men</td>
<td>Cycling at 100 W at altitudes of 0, 1370 metres</td>
<td>Decreases of spleen volumes: 213 to 186, 186 to 112 mL with exercise</td>
</tr>
<tr>
<td>Frances et al.</td>
<td>Ultrasound data</td>
<td>7 women, 1 man</td>
<td>1 min isometric and grip at 40% max. voluntary contraction</td>
<td>13% decrease of spleen volume</td>
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volumes of 11–66% (average 34%), with a corresponding increase in circulating red blood cell volumes. In most studies, the activity undertaken was aerobic, but one investigation looked at the effects of a maximal isometric hand grip exercise;[54] this form of activity produced a smaller splenic response than that seen in most of the aerobic exercise tests.

Four studies compared healthy individuals and small numbers of patients who had undergone splenectomy.[7, 8, 46, 47] In two of these four investigations, the anticipated effects of physical activity were absent in those who had undergone splenectomy.

Two studies examined the effects of adding hypoxia to the stress of vigorous physical activity.[53, 55] The effects seemed additive, with a larger decrease of splenic volume in response to the combined stimuli.

Circulatory impact of changes in splenic dimensions during physical activity

Any expulsion of red cells from the spleen increases the oxygen carrying capacity of the blood. The process is analogous to the banned practice of blood doping, detected in some endurance athletes such as the long-distance cyclist Lance Armstrong.[1] Although unit volume of a person’s blood has a greater oxygen-carrying capacity after splenic emptying, this advantage must be set against the negative effects of an associated increase in blood viscosity, and thus a potential

### Table 7.2 continued

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<td>Lodin-Sundström et al.[55]</td>
<td>Ultrasound</td>
<td>11 healthy lowlanders (5 women, 6 men)</td>
<td>Modified Harvard step test at altitudes of 1370, 3700 and 4200 m</td>
<td>Decreases of spleen volumes: 250 to 207, 230 to 173 and 221 to 158 mL, respectively</td>
</tr>
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<td>Multiple techniques</td>
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<tr>
<td>Wolski[46]</td>
<td>$^{51}$Cr red cell volume, $^{125}$I plasma volume, $^{99}$technetium, haematocrit</td>
<td>6 trained, 6 untrained subjects, 4 splenectomized</td>
<td>Maximal exercise and 30 min exercise at 25 rising to 50 and 75% of maximal oxygen intake in normoxia and 16% oxygen</td>
<td>142–187 mL of red cells released by spleen (7–9% of total red cell volume). Increase of haematocrit not seen in splenectomized subjects. Response similar in normoxia and hypoxia</td>
</tr>
</tbody>
</table>
reduction in maximal cardiac output. The adverse effect of greater viscosity is compounded by any decrease of plasma volume, particularly when an athlete is exercising in a hot environment.

Observations on rats\textsuperscript{[56, 57]} compared the treadmill running endurance of splenectomized and sham-operated animals after 120 days of recovery from surgery. Somewhat surprisingly, although the two groups of female animals showed no substantial differences in physical endurance, the splenectomized males were able to maintain exhausting exercise at a speed of 24 m/min on a 12% slope for a longer period than the control animals with normal spleens (10.2 vs. 6.7 min). However, in other animal studies splenectomy has adversely affected the exercise response. Studies in horses have suggested that blood viscosity may rise by as much as 50% during exercise, whether running at speeds of 6–9 or 13–16 m/s.\textsuperscript{[37]} Splenectomy decreased the rise of mean arterial pressure normally seen during treadmill running, and this was attributed to a reduced preloading of the ventricle.\textsuperscript{[14, 58]} In the seal, a sphincter on the hepatic sinus appears to buffer the release of red cells into the blood stream during diving or vigorous physical activity, thus reducing immediate adverse changes in blood viscosity.\textsuperscript{[27]} A second important function of the spleen, particularly in animals such as the horse, may be to reduce the resting red cell count and thus the viscosity of the blood when the cardiac output is low.\textsuperscript{[59, 60]}

What are the implications of a 40% decrease in splenic volume for the human circulation? Assuming a resting splenic volume of 200 mL, the total blood volume would increase by some 80 mL or 1.6%. In addition to increased ventricular loading, there would be a small increase of haematocrit, supplementing the effects of exercise-induced dehydration on the oxygen-carrying capacity of the blood. Various observers have suggested that exercise and other stressors can increase the oxygen carrying capacity of unit volume of blood by 3.4%\textsuperscript{[44]}, 6.5%\textsuperscript{[61]} or 7–9\textsuperscript{[66]} but that emptying of the spleen accounts for only a part of this response. Nevertheless, contraction of the spleen could influence the outcome of a closely competed endurance event, even if the circulatory functions of the human spleen are of much less practical importance than in animals such as the horse and the seal.

**Response of the spleen to stressors other than physical activity**

When a person faces actual or simulated stressors, including injection of epinephrine, splenic nerve stimulation, exposure to hypoxia, performance of the Valsalva manoeuvre, breath-holding and breath-hold diving, the responses of the spleen seem rather similar to those seen during vigorous to maximal exercise (Table 7.3). Decreases of splenic volume are accompanied by increases of haemoglobin and haematocrit values, and these responses are generally absent in individuals who have undergone splenectomy.\textsuperscript{[61, 62]}

The common mediating factor for physical activity and other stressors is probably a contraction of the splenic capsule in response to epinephrine and/or adrenergic nerve stimulation. A combination of hypoxia with physical activity
**Table 7.3 Response of human spleen to stressors other than physical activity**

<table>
<thead>
<tr>
<th>Author</th>
<th>Methodology</th>
<th>Participants</th>
<th>Stressor</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nerve stimulation, catecholamines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ayers et al.[41]</td>
<td>Volume recorded directly on dynograph</td>
<td>13 isolated perfused spleens obtained at operation</td>
<td>Splanchnic nerve stimulation and infusion of catecholamines</td>
<td>Decreases in volume of 0.3 mL 6 mL and 8 mL at stimulation frequencies of 3, 7 and 10 Hz, respectively; changes of 11–13 mL with catecholamines</td>
</tr>
<tr>
<td>Bakovic et al.[65]</td>
<td>Ultrasound</td>
<td>13 healthy men</td>
<td>Intravenous epinephrine (slow infusion of low doses)</td>
<td>Early 30% decrease of splenic volume; associated decrease of blood pressure and activation of sympathetic nerves to muscles</td>
</tr>
<tr>
<td>Knecht et al.[66]</td>
<td>Ultrasound</td>
<td>10 healthy, 5 splenectomized men</td>
<td>Subcutaneous epinephrine, 0.5 mg/m²</td>
<td>Splenic contraction 34.8%, 36.4% increase of granulocyte and 13.2% increase of platelet counts. Changes not seen after splenectomy</td>
</tr>
<tr>
<td><strong>Valsalva manoeuvre</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frances et al.[54]</td>
<td>Ultrasound data</td>
<td>7 women, 1 man</td>
<td>Lower body negative pressure, Valsalva manoeuvre</td>
<td>Respective decreases of spleen volume of 9%, 8%</td>
</tr>
<tr>
<td>Inoue et al.[67]</td>
<td>Magnetic resonance imaging</td>
<td>6 men, 6 women</td>
<td>Valsalva manoeuvre</td>
<td>13.3% decrease of splenic volume on volume of 173 mL</td>
</tr>
<tr>
<td><strong>Hypoxia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engan et al.[53]</td>
<td>Ultrasound and capillary haemoglobin concentration</td>
<td>1 woman, 7 men</td>
<td>5 min cycling at 100 W at altitudes of 0, 1370 m</td>
<td>Decreases of spleen volumes: 213 to 186 and 186 to 112 mL respectively</td>
</tr>
<tr>
<td>Haffner et al.[68]</td>
<td>Ratio of spleen weight to body weight</td>
<td>42 cases of drowning vs. 42 cases of hanging or strangulation</td>
<td>Spleen weight 18% lower in drowning, possibly related to stresses of hypoxia and cooling</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Methodology</td>
<td>Participants</td>
<td>Stressor</td>
<td>Findings</td>
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</tr>
<tr>
<td>Lodin-Sundström and Schagatay</td>
<td>Ultrasound (splenic diameter)</td>
<td>5 women, 4 men</td>
<td>20 min breathing 14.2% oxygen</td>
<td>Arterial oxygen saturation 87%, Spleen volume decreased 16%</td>
</tr>
<tr>
<td>Lodin-Sundström et al.</td>
<td>Ultrasound</td>
<td>11 healthy lowlanders (5 women, 6 men)</td>
<td>Modified Harvard step test at altitudes of 1370, 3700 and 4200 m</td>
<td>Greater decrease of spleen volumes with hypoxia 250 to 207, 230 to 173 and 221 to 158 mL, respectively</td>
</tr>
<tr>
<td>Richardson et al.</td>
<td>Ultrasound, haemoglobin, haematocrit</td>
<td>4 men, 1 woman</td>
<td>20 min breathing 12.8% oxygen</td>
<td>18% reduction of spleen volume, 2.1% increase of haemoglobin and haematocrit</td>
</tr>
<tr>
<td>Wolski</td>
<td>51Cr red cell volume, 125I plasma volume, 99technetium, haematocrit</td>
<td>6 trained, 6 untrained subjects, 4 splenectomized</td>
<td>Maximal exercise and 30 min exercise at 25 rising to 50 and 75% of maximal oxygen intake in normoxia and 16% oxygen</td>
<td>142–187 mL of red cells released by spleen (7–9% of total red cell volume). Increase of haematocrit not seen in splenectomized subjects. Response similar in normoxia and hypoxia</td>
</tr>
<tr>
<td>Bakovic et al.</td>
<td>Ultrasound</td>
<td>10 breath-hold divers, 17 others (7 post-splenectomy)</td>
<td>5 maximal breath-holds with face immersed in cold water</td>
<td>20% decrease in spleen volume after first dive, partial recovery 60 min after final dive</td>
</tr>
<tr>
<td>Bakovic et al.</td>
<td>Changes of red and white cell counts, plasma protein concentrations</td>
<td>18 breath-hold divers, 21 others, 6 post-splenectomy</td>
<td>5 maximal breath-holds with face immersed in cold water</td>
<td>Total red cell volume increased 4.9% in divers, 1.7% in nondivers, no change after splenectomy. Plasma protein. 5.8, 2.2, 9%. White cells +14.9%, +7.2%, no change</td>
</tr>
<tr>
<td>Engan et al.</td>
<td>Ultrasound and capillary haemoglobin concentration</td>
<td>1 woman, 7 men</td>
<td>Maximum breath-holds, before and after Mt Everest climb</td>
<td>Decreases of spleen volumes: 213 to 184, 206 to 132 mL</td>
</tr>
<tr>
<td>Author</td>
<td>Methodology</td>
<td>Participants</td>
<td>Stressor</td>
<td>Findings</td>
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</tr>
<tr>
<td>Espersen et al.</td>
<td>Technetium and ultrasound</td>
<td>10 divers, 12 non-divers</td>
<td>30 s and maximum breath-holds</td>
<td>Splenic contractions of 10, 30–40%</td>
</tr>
<tr>
<td>Hurford et al.</td>
<td>Ultrasound, hamatocrit and haemoglobin</td>
<td>Pearl divers (10 women, 3 men)</td>
<td>Repeated breath-hold dives to 6 m</td>
<td>Splenic volume decreased 19.5%. 9.5% increase of haemoglobin, 10.5% increase of haematocrit</td>
</tr>
<tr>
<td>Inoue et al.</td>
<td>Magnetic resonance imaging</td>
<td>6 men, 6 women</td>
<td>30 s expiratory or inspiratory breath-hold</td>
<td>10.2% decrease of splenic volume on volume of 173 mL</td>
</tr>
<tr>
<td>Lodin-Sundström and Schagatay</td>
<td>Ultrasound (splenic diameter)</td>
<td>5 women, 4 men</td>
<td>2 min breath-holds</td>
<td>Arterial oxygen saturation 89%. Spleen volume decreased 34%</td>
</tr>
<tr>
<td>Palada et al.</td>
<td>Ultrasound</td>
<td>7 trained divers</td>
<td>15–20 s breath-holds</td>
<td>Decrease of splenic volume within 3 s, 20% at full inspiration, 10% at small lung volume, accentuated by cold forehead</td>
</tr>
<tr>
<td>Prommer et al.</td>
<td>Ultrasound, blood volumes by CO rebreathing</td>
<td>10 breath-hold divers (3 men, 7 male scuba divers)</td>
<td>5 dives to 3 m depth</td>
<td>25% reduction of spleen size in breath-hold divers, no significant change in scuba group</td>
</tr>
<tr>
<td>Richardson et al.</td>
<td>Haemoglobin levels</td>
<td>78 volunteers, divers, skiers and untrained</td>
<td>3 maximal breath-holds, separated by 2 min rest</td>
<td>Increase of haemoglobin in all groups, especially divers (2.7%)</td>
</tr>
<tr>
<td>Schagatay et al.</td>
<td>Haemoglobin, haematocrit, plasma protein</td>
<td>20 subjects (10 splenectomized)</td>
<td>5 maximal breath-holds, separated by 2 min intervals</td>
<td>Haemoglobin +3.3%, haematocrit + 6.4%, no change in splenectomized</td>
</tr>
<tr>
<td>Schagatay et al.</td>
<td>Haemoglobin, haematocrit, ultrasound</td>
<td>5 men, 5 women with varied diving experience</td>
<td>3 maximal breath-holds, separated by 2 min intervals</td>
<td>All subjects showed splenic contraction, average 18%, haemoglobin + 2.4%, haematocrit + 2.2%</td>
</tr>
</tbody>
</table>
augments the extent of such contraction. Hurford et al. found a different response in trained breath-hold divers, suggesting that training can increase the splenic response to breath-holding, and possibly to other stressors. However, Espersen et al. did not find any difference in the resting size of the spleen or its contractility between divers and control subjects.

**Impact of physical activity upon splenic functions other than red cell storage**

The spleen provides a reservoir, not only of red cells, but also of white cells and thrombocytes. Thus, this organ is important to immune responses and mechanisms of blood clotting, and physical activity-induced emptying or partial emptying of the spleen has an impact upon both of these processes.

The importance of the spleen to the immune response became apparent in the early part of the 20th century. Morris and Bullock noted the role of the spleen in offering an adequate resistance to infections. In 1926, O’Donnell had reported a case of acute septicaemia in a six-year-old boy, apparently a sequel to a splenectomy that had been performed two years earlier. His father had also undergone splenectomy, and had died of a septic pneumonia. Perla and Marmoston and King and Shumacker also presented case reports showing a reduced resistance to infection following splenectomy.

It is now thought that the white pulp of the spleen provides a reservoir of lymphocytes, initiates the humoral (antibody) response to infections and synthesizes antibodies. The red pulp of the spleen acts as a filter that removes aging red cells while conserving their iron content, and it provides a reservoir of thrombocytes and immature red cells.

The spleen contains around 40% of the body’s white blood cells and as many as a third of the body’s platelets. In stressful situations, including vigorous physical activity, these elements are liberated into the general circulation as a part of the general “fight or flight” reaction. However, the timing of their release differs from that of the red cells. Most of the red cells have left the spleen within 60 seconds of commencing a bout of physical activity, whereas the release of granulocytes and platelets occurs over a period of about ten minutes of sustained exercise. This suggests that the movement of the leucocytes is mediated by the progressive, exercise-related decrease in visceral blood flow rather than an active contraction of the splenic capsule. The release of leucocytes is exacerbated by the administration of adrenergic agonists; adrenergic mechanisms modify the expression of adhesion molecules that normally attach leucocytes to the vessel walls in reservoir sites such as the spleen, the lungs and Peyer’s patches.

The administration of either epinephrine or norepinephrine increases circulating lymphocyte and granulocyte counts. There is a biphasic response, with a lymphocytosis predominating in the first 30 minutes, followed later by a granulocytosis and a decrease in lymphocyte numbers. The largest response is an α-adrenergic effect upon the release of natural killer cell and granulocytes, with lesser β-adrenergic effects upon T and B lymphocyte numbers. A blockage of
both alpha and beta-adrenergic nerve pathways is needed to prevent all leucocytic responses to either physical activity\cite{85} or the infusion of catecholamines\cite{86}. However, the blockade of β-adrenergic receptors suppresses much of the exercise-induced leucocytosis\cite{87}, particularly the natural killer cell component\cite{88}. In contrast, increased granulocyte count are α-adrenergic receptor dependent\cite{84} and selective α-adrenergic agonists such as salbutamol augment overall lymphocyte counts\cite{89}.

The possible contribution of splenic contraction to these changes remains a matter of dispute. Frey\cite{90} demonstrated that the catecholamine-induced lymphocytosis was absent in rabbits following splenectomy and Nielsen et al. had similar findings in human subjects.\cite{91} Schaffner et al.\cite{92} measured splenic size sonographically. In their study of 13 human subjects, the increase of granulocyte count with epinephrine injection was closely correlated with splenic contraction. Ojiri et al.\cite{93} further noted that in dogs, the lymphocytic effect of epinephrine was abolished by isolating the spleen from the rest of the circulation. However, several authors have found a persistence of exercise-and catecholamine-induced leucocytosis, even in recently splenectomized individuals.\cite{94-97} Schedlowski et al.\cite{98} further reported that epinephrine infusion induced equal increases of natural killer cell counts in both normal and splenectomized individuals, and the response to norepinephrine was actually increased after splenectomy. Early human studies indicated that although catecholamines did not induce a lymphocytosis immediately after splenectomy, other mechanisms apparently restored this function over the following weeks.\cite{90, 99}

The spleen contains about a third of the body’s platelets, including a high proportion of the large platelets that are active in coagulation. The expulsion of these large platelets into the general circulation in response to physical activity or stress is presumably an attempt to protect against haemorrhage during a fight, but it could also predispose to thrombosis, particularly if arteries that are narrowed by arteriosclerosis.\cite{80, 100}

**Influence of splenic contraction upon calculations of changes in plasma volume**

The traditional method for examining changes of plasma volume during exercise relies upon haematocrit readings. How far is this widely used calculation threatened by the effects of splenic contraction?

Some authors have attributed the increases of red cell count during physical activity entirely to the changes in plasma volume that result from increases in blood pressure, changes of osmotic pressure within the muscles, changes in permeability of the blood vessel walls and fluid losses in sweating.\cite{12, 101} Certainly, substantial amounts of fluid can be lost from the blood through such mechanisms.

Stewart used radio-isotope labelled serum albumin to assess plasma volume changes during a bout of exhausting exercise.\cite{15} There was no change in total red cell volume, but the splenic component of the plasma volume decreased from 3.8% to 1.6%. It was thus argued that there had been splenic infusion of blood with
a high concentration of red cells, and that this could account for 25% of the increase in haematocrit observed during physical activity. Such a response would be enough to introduce a substantial error into the traditional Dill and Costill calculation of changes in plasma volume[102]. These authors had assumed that a constant circulating red cell volume would serve as a marker to detect changes of plasma volume. Plainly, their assumption would become invalid if splenic contraction boosted the circulating red cell concentration by up to 10%.[44, 46] However, Agostoni et al.[47] found similar changes of plasma protein and red cell volume during exercise, arguing that most of the increase in red cell count was due to extravasation of fluid from the circulation. Accepting these findings, a splenic boosting of haematocrit would not be large enough to cause a major error in the time-honoured method of evaluating exercise-induced changes in plasma volumes.

**Mechanism of changes in splenic volume**

The splenic nerve comprises 98% sympathetic fibres, and there are α-adrenergic receptors in the wall of the spleen.[103] Moreover, the capsule of the spleen contains at least some myosin. Further, both sympathetic nerve activity and venous catecholamine concentrations have been shown to increase in parallel with splenic constriction.[52, 62, 104] The volume of the isolated human spleen also decreases in response to stimulation of the splanchnic nerves[41] or the infusion of small doses of epinephrine.[65, 66] It is thus tempting to attribute the decrease of splenic volume during exercise or environmental stress as a response to an increase in sympathetic nerve activity, although one objection to this explanation is that the time course of the exercise response is not closely related to the increase in catecholamine concentrations.[44]

It remains important to underline that even if sympathetic nerves are involved in the process, the decrease of splenic volume could still reflect either an active contraction of the splenic capsule or an effect of the sympathetic nerves in restricting the local arterial in-flow.[43] One argument against a circulatory explanation is that the changes of splenic volume follow a differing time course to changes in heart rate or mean systemic arterial blood pressure. Specifically, the onset of splenic contraction is more rapid than the exercise-induced increase in sympathetic nerve activity observed in the leg vessels. Nevertheless, the sympathetic innervation of the visceral blood vessels could proceed more rapidly than that of the leg vasculature, since a differential activation of lumbar and renal sympathetic nerves has been demonstrated, at least in rabbits.[105] The recovery of resting splenic dimensions also occurs more slower than restoration of the resting heart rate, taking as long as 2 minutes following a single maximal breath-hold,[64] 8–9 minutes following serial breath-holds,[75] around 10 minutes after the cessation of breathing low oxygen mixtures[70] and as much as 20 minutes following a bout of maximal exercise.[52]

By relating changes in splenic volume to the duration of exercise, it may be possible to determine whether changes in splenic volume are a passive response to a reduction of the local arterial blood supply or a consequence of active
contraction of the splenic capsule. A reduction of the local blood supply would likely induce a progressive change, proportional to the duration of exercise, whereas an active contraction would probably be relatively rapid and independent of the duration of activity. Stewart\(^\text{[15]}\) compared changes of spleen volume in response to constant intensity exercise of varying duration. The decrements of spleen volume were similar (28–36%) with 5, 10 and 15 minute bouts of activity at 60% of maximal oxygen intake, supporting the hypothesis of an intensity-dependent contraction.\(^\text{[52]}\) After exercise to exhaustion, there was a 59% decrease of splenic volume, with recovery over the following 20 minutes. The decrease in splenic volume bore a semi-logarithmic relationship to catecholamine concentrations, although the correlation coefficients of 0.67 and 0.46 for epinephrine and norepinephrine respectively suggest that factors other than catecholamines also contributed to the change in splenic dimensions.

### Areas for further research

The most convincing demonstration of the importance of the spleen to exercise performance is to compare responses between healthy individuals and those who have undergone splenectomy. Human research of this type has been limited to date, and there is scope for further observations, including data on maximal oxygen intake and endurance at known fractions of peak effort. There is also a need for more studies of additive responses, examining how typical responses to physical activity are modified by combination with such stimuli as hypoxia or competitive stress. Finally, there is a need for clarification of the contribution of splenic contraction to the changes of leucocyte numbers seen during physical activity and other forms of stress.

### Practical implications and conclusions

In some animals, an active contraction of the spleen can make a substantial contribution to red cell count and total blood volume, boosting performance during vigorous physical activity. Because the human spleen is relatively small (~200 mL volume), a 30–40% emptying early during vigorous activity has only a small effect on blood volume (<5%) and haematocrit (<10%). Nevertheless, the infusion of red cells from the spleen may cause some errors in the traditional method for calculating changes of plasma volume during exercise and could affect the outcome of a closely competed race. Similar responses are seen with the injection of epinephrine or the presentation of other stressful stimuli such as a maximal breath-hold or the breathing of a hypoxic gas mixture. Emptying seems an active response, mediated by alpha-adrenergic fibres in the splenic nerve, although it remains to be clarified how far this reflects a contraction of smooth muscle in the splenic capsule and how far it is attributable to a reduction of local arterial blood flow.

The spleen is also an important component of the body’s immune system, contributing leukocytes and platelets to the general circulation as part of the
“fight or flight” reaction. The mobilization of leukocytes proceeds more slowly than that of the red cells; it depends not only upon an active contraction of the spleen, but also upon a catecholamine-mediated modulation of leucocyte adhesion molecules.

Splenectomy impairs exercise performance in horses. However, data on the responses of humans following splenectomy are sparse. Patients can live many years after removal of their spleens, although there may be some impairment of immune responses and a loss of blood boosting during vigorous exercise.

References


8 Physical activity and infectious mononucleosis

Introduction

The previous chapter examined normal responses of animal and human spleens to various intensities of exercise. This chapter turns to the clinical problem of how the spleen is affected by infectious mononucleosis and the extent to which physical activity should be restricted during such infections.

Infectious mononucleosis is an infection that affects the function of the spleen and other body organs, with adverse effects upon the health of both athletes and other physically active individuals. A clinical syndrome of fever, a sore throat and swollen glands was first described in 1889 by the German physician Emil Pfeiffer (1846–1921). He termed the condition “Drüsenfieber” or glandular fever.[1, 2] The term infectious mononucleosis was coined by Sprunt and Evans in 1920.[3] They wrote an article entitled Mononuclear leukocytosis in reaction to acute infection (infectious mononucleosis). A new virus was discovered by Epstein and Barr in 1968, and this was quickly linked to the development of infectious mononucleosis.[4] Estimates of the prevalence of infectious mononucleosis show substantial variation, depending upon the thoroughness of population testing and the rigour of diagnostic criteria. The annual infection rate for 253,000 US university entrants, based upon observation of a typical clinical picture, the appearance of atypical lymphocytes in blood samples and a positive heterophile antibody test was estimated at 1–3%.[5–7] There have been suggestions that the condition is more prevalent in athletes than in sedentary subjects, due to such factors as the sharing of drinking bottles, although this supposition lacks clear documentation and no differences were seen in one comparison between 202 endurance athletes and 200 controls.[8] Concerns of the sports physician include a possible rupture of the enlarged spleen during infection and a possible progression of the disease from infectious mononucleosis to the chronic fatigue syndrome if normal activity is resumed too rapidly.

Infectious mononucleosis is often transmitted in saliva and has thus been called the “kissing disease”. It is particularly prevalent in young adults, and its clinical manifestations can seriously compromise both a student’s athletic performance and his or her ability to study for several weeks.[10] Physical activity is normally restricted during the acute phase because of fears of rupture of the
enlarged spleen and a possible subsequent progression of the disease to the chronic fatigue syndrome (CFS).\textsuperscript{[11, 12]} We will here consider issues of diagnosis, methods of determining the extent of splenic enlargement and other measures of disease status, and the potential relationship of infectious mononucleosis to CFS, assessing the practical risks associated with engaging in vigorous physical activity at various points in the disease process.

**Diagnosis of infectious mononucleosis**

Infectious mononucleosis has a long incubation period (30–50 days). This hampers detection of disease onset and a description of its subsequent course.

**Clinical signs**

Clinical manifestations during the acute phase of the disease include a painful swelling of the lymph glands, particularly at the back of the neck, a general feeling of malaise and fatigue, fever, sweating, a sore throat, inflammation of the pharynx and a loss of appetite.\textsuperscript{[9, 19, 21]} These complaints are relatively consistent (Table 8.1) but unfortunately they are seen also with a number of other common infectious diseases.

**Laboratory tests**

Laboratory tests provide more certain proof of infection. Common manifestations (Table 8.2) includes a lymphocytosis (with more than 10% of the total white cells being atypical lymphocytes) and a positive heterophile IgM antibody test.\textsuperscript{[22–24]} These basic laboratory indices are relatively specific, and a positive finding can be accepted with reasonable confidence, but unfortunately they lack sensitivity, missing a substantial proportion of those who are in fact infected. Additional options include a search for Epstein-Barr nuclear antigen and IgG and IgM viral capsid antigens (VCA).\textsuperscript{[17, 24, 25]} Although such tests are several times more expensive than the basic measures, they are more sensitive, particularly in the early phases of the disease. False positive results can arise from the persistence of antibodies formed during a past infection, a problem that can be addressed by

\begin{table}[h]
\centering
\begin{tabular}{|l|}
\hline
• 80–100\% of cases: painful swelling of lymph gland in the neck, malaise, fatigue, sweats and a sore throat \\
• 50–80\% of cases: inflammation of the pharynx, a loss of appetite, nausea, enlargement of the spleen, headache and chills \\
• 30–50\% of cases: cough, a swelling around the eyes (periorbital oedema) and red spots on the palate (palatine petechiae) \\
• <30\% of cases: enlargement of the liver, jaundice and a rash \\
\hline
\end{tabular}
\caption{Acute clinical manifestations of infectious mononucleosis, based in part on the analysis of Kinderknecht\textsuperscript{[9]} }
\end{table}
Table 8.2: Sensitivity and specificity of common laboratory evidence of infectious mononucleosis relative to an accepted reference standard (the presence of a heterophile antibody or specific markers of Epstein Barr virus in the serum)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sample</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Reference standard</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50% lymphocytes, &gt;10% atypical lymphocytes</td>
<td>709 patients aged 16–73 yr with clinical mononucleosis</td>
<td>27%</td>
<td>100%</td>
<td>Heterophile antibody*</td>
<td>Aronson et al. [13]</td>
</tr>
<tr>
<td>&gt;50% lymphocytes, &gt;10% atypical lymphocytes</td>
<td>181 patients with clinical mononucleosis, 181 controls</td>
<td>27%</td>
<td>100%</td>
<td>Heterophile antibody*</td>
<td>Brigden et al. [14]</td>
</tr>
<tr>
<td>Heterophile antibody (latex agglutination)*</td>
<td>140 recent EBV infections, 40 controls</td>
<td>87–95%</td>
<td>98–100%</td>
<td>Heterophile antibodies* and recent EBV antibodies</td>
<td>Bruu et al. [15]</td>
</tr>
<tr>
<td>Heterophile antibody (latex agglutination or solid-phase based kits)*</td>
<td>53 serum samples from EBV infection, 47 EBV immune or healthy individuals</td>
<td>70–92%</td>
<td>96–100%</td>
<td>EBV specific serology</td>
<td>Elgh &amp; Linderholm [16]</td>
</tr>
<tr>
<td>Heterophile antibody (latex agglutination or solid-phase based kits)*</td>
<td>103 patients with suspected infectious mononucleosis, aged 2–60 yr</td>
<td>63–84%</td>
<td>84–100%</td>
<td>EBV specific serology (VCA Ig G, IgM, EBV NA)</td>
<td>Linderholm et al. [17]</td>
</tr>
<tr>
<td>Polymerase chain reaction</td>
<td>Children, average age 9 yr; 28 with mononucleosis, 26 sero-positive, 25 sero-negative</td>
<td>75% at 1 week</td>
<td>98% at 1 week</td>
<td>Serology (anti VCA IgM and anti EBV nuclear antibodies)</td>
<td>Pitetti et al. [18]</td>
</tr>
<tr>
<td>Epstein Barr specific antibodies (EDV VCA, EBV NA)</td>
<td>139 patients with recent mononucleosis infection, 40 healthy controls</td>
<td>95–99%</td>
<td>84–100%</td>
<td>Positive heterophile antibody test and EBV antibodies typical of recent infection</td>
<td>Bruu et al. [15]</td>
</tr>
</tbody>
</table>

Notes: * Sensitivity measures the percentage of true cases detected by the test procedure; specificity measures the proportion of abnormal test results that are true indicators of infection. False negative results are found with 25% of cases in week 1, 5–10% in week 2 and 5% in week 3. EBV = Epstein Barr virus; VCA = viral capsid antigens; EBV NSA = Epstein Barr virus nuclear antibodies.
determining the avidity of VCA IgG for its target, or making an immunoassay with a late marker antigen such as Epstein Barr virus nuclear antibodies.\textsuperscript{[8, 26, 27]} Other ancillary and less reliable laboratory evidence of infection includes abnormal liver function tests, particularly increased circulating concentrations of the hepatic enzyme alkaline phosphatase,\textsuperscript{[22]} and increased concentrations of circulating pro-inflammatory cytokines.\textsuperscript{[28]}

**Measuring splenic enlargement**

The spleen is usually enlarged during the first few weeks of infection.\textsuperscript{[29]} Unfortunately, this is not a very helpful diagnostic marker. Clinical attempts to detect an enlarged spleen are highly fallible, and even when using more sophisticated laboratory techniques, differences of methodology and the spread of normal values is such that serial measurements of spleen dimensions are needed to avoid missing pathological enlargement of what may have initially been a small spleen. Moreover, differential diagnosis must consider a multiplicity of other causes of splenic enlargement. However, laboratory evidence of a progressive decrease in splenic size is often used as an indicator of resolution of the disease.

**Clinical determinations**

Clinical attempts to detect an enlarged spleen by palpation and/or percussion are relatively ineffective (Table 8.3). The results of clinical examination vary widely from one observer to another. The coefficient of inter-observer agreement for abdominal palpation as measured by Cohen’s kappa is 0.56–0.70\textsuperscript{[30]}, and for abdominal percussion, kappa is only 0.19–0.41.\textsuperscript{[31]} The reported reproducibility of the clinical information also depends on whether the study is part of a routine examination or is a deliberate and careful experimental assessment\textsuperscript{[32]} on the method of palpation or percussion that is used, on the obesity of the individuals that are assessed and on the proportion of enlarged spleens present in the sample. Tamayo et al.\textsuperscript{[38]} compared three differing techniques of palpation and three techniques of percussion. The figures cited (Table 8.3) are for the most effective of each of these approaches: ballottement (palpation of the abdominal wall while applying pressure over the spleen from the back) and Castell percussion (noting the difference of tone when percussioning over the seventh inter-ternal space during inspiration and expiration). One final but important objection to attempts at clinical estimates of splenomegaly is the risk that over-vigorous palpation of the abdomen could cause the rupture of an infected spleen.\textsuperscript{[40]}

**Laboratory determinations**

Splenic dimensions are commonly determined by two- or three-dimensional ultrasonography.\textsuperscript{[41]} This has an important advantage over scintigraphy in that it avoids repeated exposure to radiation. Other laboratory approaches include computed tomography (CT),\textsuperscript{[42–45]} scintigraphy (detecting radiation from $^{99m}$Technetium}
Table 8.3  Sensitivity and specificity of clinical attempts to detect an enlarged spleen by palpation or percussion of the abdomen, using ultrasound, scintigraphy or autopsy as the gold standard of spleen size

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Reference standard</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barkun et al. [30, 31]</td>
<td>118 patients, average spleen length = 15.4 cm</td>
<td>Ultrasound</td>
<td>62%, 46%</td>
<td>72%, 97%</td>
<td>1–3 examiners, Traube’s space percussion and palpation + percussion</td>
</tr>
<tr>
<td>Dommerby et al. [33]</td>
<td>29 patients with infectious mononucleosis</td>
<td>Ultrasound</td>
<td>17%</td>
<td>Not stated</td>
<td>Method of clinical examination not stated</td>
</tr>
<tr>
<td>Halpern et al. [34]</td>
<td>214 patients, 92 with enlarged spleens at scintigraphy</td>
<td>Scintigraphy</td>
<td>28%</td>
<td>69%</td>
<td>3 clinical examiners for most patients</td>
</tr>
<tr>
<td>Ingeberg et al. [35]</td>
<td>32 patients prior to splenectomy for various disorders</td>
<td>Scintigraphy and operation</td>
<td>59% (16/27)</td>
<td>100% (5/5)</td>
<td>Palpability</td>
</tr>
<tr>
<td>Rea et al. [29]</td>
<td>150 patients with infectious mononucleosis</td>
<td>None</td>
<td>8% have palpable spleen</td>
<td></td>
<td>Routine clinical examinations</td>
</tr>
<tr>
<td>Riemen-schneider et al. [36]</td>
<td>47 patients</td>
<td>Autopsy</td>
<td>20%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Sullivan et al. [37]</td>
<td>65 patients, 17 with enlarged spleens</td>
<td>Scintigraphy</td>
<td>70.6% (palpation), 82.4% (Castell percussion)</td>
<td>89.6% (palpation), 83.3% (Castell percussion)</td>
<td></td>
</tr>
<tr>
<td>Tamayo [38]</td>
<td>27 men with suspected HIV infection, 9 with splenomegaly; values reported for most effective of 3 techniques</td>
<td>Ultrasound</td>
<td>Ballottement 0–58.3% (37.2%), Castell percussion 23.1–75.0% (39.4%)</td>
<td>Ballottement 50–100% (84.1%), Castell percussion 60–100% (81.0%)</td>
<td>Individual values and average for 8 examiners</td>
</tr>
<tr>
<td>Westin et al. [39]</td>
<td>99 patients</td>
<td>Scintigraphy</td>
<td>57%</td>
<td>100%</td>
<td>Palpation</td>
</tr>
</tbody>
</table>
sulphur colloid\footnote{46, 47} or $^{113}$Indium-labelled granulocytes or platelets\footnote{48} and simple radiography.\footnote{49} Measurements of splenic volume have also been made at autopsy.\footnote{50}

The volumes reported depend substantially on methodology, and it is thus inappropriate to make comparisons of dimensions between studies that have used different measuring techniques. De Odorico et al.\footnote{41} compared the results for two- or three-dimensional ultrasonography. They concluded that the 3D method was the more reliable, and gave systematically lower estimates, but in normal clinical practice where multiple determinations were needed, 2D data provided simpler and more practicable indices. Radionuclide data generally indicate larger volumes than ultrasonography, but in some instances the accuracy of scintigraphy has been compromised by a failure to exclude emissions from adjacent organs such as the kidneys and lungs. However, autopsy values tend to be smaller than ultrasonography data, perhaps because of postmortem changes in the shape of the spleen.

The spleen is irregularly shaped, and the translation of linear measurements into an estimate of volume is another source of controversy. Many formulae have been proposed to calculate splenic volumes\footnote{45, 46, 48, 51–55} (Table 8.4). Some formulae show a close correlation with the weights of resected spleens, and can thus be used to judge changes in the size of a given individual’s spleen. However, it is difficult to compare absolute values between authors who have used differing formulae. Because of these problems, some investigators have simply reported percentage changes relative to their initial estimate of splenic volume.\footnote{56–58} Others have gauged splenomegaly in terms of the length rather than the volume of the organ, or have calculated an arbitrary volumetric “index”.\footnote{59–61}

**Dimensions of the normal, healthy spleen**

Ultrasonography probably provides the best estimate of normal splenic dimensions. The length of the normal adult spleen is in the range 12–14 cm.\footnote{63–65} However, such estimates are based on small and rather heterogeneous population samples, and have not considered the likely dimensions in some classes of athlete such as basketball players with extreme body builds.

Reported values are summarized in Table 8.5. Rosenberg et al.\footnote{66} proposed age-related upper limits of length increasing from 7 cm at an age of 12 months to 12 cm in girls and 13 cm in boys aged >15 years. Using 3D ultrasonography, De Odorico et al.\footnote{41} estimated that the normal adult spleen had a length of 8.9 cm, a height of 8.6 cm and a thickness of 4.0 cm. Using an ellipsoid formula, the estimated average volume was then 164 mL. Such values were said to agree with subsequent measurements on three cadavers to within 2%. Zhang and Lewis\footnote{48} used a radionuclide technique; they set the upper limit of normal volumes at 256 mL, but they also claimed that their absolute estimates differed by only 0.2 ± 6.7% from the volumes as measured at postmortem. Other autopsy data defined 2.5–97.5% confidence limits of 61 to 364 mL in 1266 men and 63 to 310 mL in 316 women.\footnote{42} Assuming these volumes were normally distributed, they would...
imply a standard deviation of ± 68 mL about respective mean values of 213 and 187 mL for men and women.\textsuperscript{[67]} The axial CT data of Henderson et al.\textsuperscript{[42]} imply a similar SD of ± 76 mL, but the postmortem data of Myers and Segal\textsuperscript{[78]} show a much smaller SD, of ± 38 mL.

### Table 8.4 Formulae proposed by various authors for calculating splenic dimensions

<table>
<thead>
<tr>
<th>Author</th>
<th>Proposed formula</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allsop et al.\textsuperscript{[56]}</td>
<td>Percentage of initial estimate</td>
<td>Uncertainties inherent in absolute Technetium estimates</td>
</tr>
<tr>
<td>Downey\textsuperscript{[51]}</td>
<td>Volumetric index [0.43 \times (L \times B \times V)]</td>
<td>Correlation with autopsy weight of spleen in 101 patients (r = 0.78)</td>
</tr>
<tr>
<td>Ishibashi et al.\textsuperscript{[61]}</td>
<td>Splenic index [(L \times T)]</td>
<td>Index correlates well with spleen weight at surgical resection (r = 0.92)</td>
</tr>
<tr>
<td>Laub et al.\textsuperscript{[57]}</td>
<td>Percentage of initial estimate</td>
<td>Uncertainties inherent in absolute Technetium estimates</td>
</tr>
<tr>
<td>Pietri &amp; Boscaini\textsuperscript{[59]}</td>
<td>Volumetric index [(L \times B \times T)/27]</td>
<td>Recommended to use as an empirical index, able to distinguish normal from enlarged spleen</td>
</tr>
<tr>
<td>Prassopoulos et al.\textsuperscript{[53]}</td>
<td>(V = 30 + 0.58(\frac{L \times B 	imes T}{27}))</td>
<td>Chosen formula shows strong correlation with summated areas as measured by computed tomography in 140 normal individuals</td>
</tr>
<tr>
<td>Rodrigues et al.\textsuperscript{[60]}</td>
<td>Volumetric index [V = (L \times B \times T)]</td>
<td>Yields much larger volume than found at post-mortem (284 vs. 148 mL), but index shows linear relationship to post-mortem values (r(^2) = 0.94)</td>
</tr>
<tr>
<td>Samuels\textsuperscript{[54, 62]}</td>
<td>(V = (3.14 \times B^2L)/3)</td>
<td>Arbitrary formula, giving somewhat lower absolute volumes than Spencer formula</td>
</tr>
<tr>
<td>Silverman et al.\textsuperscript{[46]}</td>
<td>(V = (L \times B)^{1/2})</td>
<td>Assumption that mass and volume are proportional; correlation with actual mass to within ± 45 mL</td>
</tr>
<tr>
<td>Spencer\textsuperscript{[55]}</td>
<td>(V = 0.257(L)\times(lateral\ area)^{1.5})</td>
<td>Formula based on theoretical relationships between lateral area and volume</td>
</tr>
<tr>
<td>Wolski\textsuperscript{[48]}</td>
<td>Radioactivity in anterior and posterior scans, relative to unit volume of blood</td>
<td>Expressed as absolute values &amp; percentage change</td>
</tr>
<tr>
<td>Yetter et al.\textsuperscript{[45]}</td>
<td>(V = 0.524(B \times T \times \frac{maximum\ L \times cranio-caudal\ L}{2}))</td>
<td>Comparison of various ellipsoid formulae with “gold standard” values obtained by helical computed tomography</td>
</tr>
<tr>
<td>Zhang &amp; Lewis\textsuperscript{[49]}</td>
<td>(V\ (mL) = 9.88A\ (cm^2) - 534,\ where\ A\ was\ the\ area\ of\ a\ posterior\ radionuclide\ scan)</td>
<td>Mean difference from volume of resected spleens as low as 0.2 ± 6.7%</td>
</tr>
</tbody>
</table>

Notes: L = length, B = breadth, T = thickness, V = volume of spleen
## Table 8.5 Estimates of absolute splenic dimensions in healthy but (in most cases) non-athletic individuals

<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>Methodology</th>
<th>Dimensions</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyd[67]</td>
<td>1266 men, 316 women</td>
<td>Autopsy, accidental death</td>
<td>V = 187 mL (women), 263 mL (men)</td>
<td>2.5–97.5% range approximates SD of ± 68 mL</td>
</tr>
<tr>
<td>DeLand[68]</td>
<td>440 adults</td>
<td>Autopsy</td>
<td>V = 163 mL</td>
<td>Correlated with height and body mass</td>
</tr>
<tr>
<td>De Odorico et al.[41]</td>
<td>52 normal subjects, aged 21–58 yr</td>
<td>2D ultrasound</td>
<td>L = 9.11 cm, B = 9.55 cm, T = 4.09 cm, V = 191.5 mL</td>
<td>2 observers</td>
</tr>
<tr>
<td>De Odorico et al.[41]</td>
<td>52 normal subjects, aged 21–58 yr</td>
<td>3D ultrasound; V = 164.2 mL</td>
<td>2 observers; values consistently smaller than 2D ellipsoid formulae.</td>
<td></td>
</tr>
<tr>
<td>Frank et al.[69]</td>
<td>793 adults, 17–82 yr</td>
<td>Ultrasound</td>
<td>95% of sample less than L = 11 cm, B = 7 cm, T = 5 cm</td>
<td></td>
</tr>
<tr>
<td>Garby et al.[70]</td>
<td>1598 subjects aged &gt;16 yr</td>
<td>Autopsy</td>
<td>V = 117 mL (F), 167 mL (M)</td>
<td>Volumes related to height and body mass</td>
</tr>
<tr>
<td>Henderson et al.[42]</td>
<td>11 normal subjects</td>
<td>Axial CT</td>
<td>V = 219 ± 76 mL</td>
<td></td>
</tr>
<tr>
<td>Hoefs et al.[71]</td>
<td>11 normal subjects</td>
<td>Scintigraphy</td>
<td>V = 201 ± 77 mL</td>
<td></td>
</tr>
<tr>
<td>Hosey et al.[72]</td>
<td>631 university athletes</td>
<td>Ultrasound</td>
<td>L = 10.7, B = 5.2</td>
<td>Men &gt; women, 7% met current criteria for splenomegaly</td>
</tr>
<tr>
<td>Hosey et al.[73]</td>
<td>Longitudinal observations on 20 patients with infectious mononucleosis</td>
<td>Ultrasound</td>
<td>Peak increase in splenic length of 33.6% with infectious mononucleosis</td>
<td>Peak change 12 days after onset of illness</td>
</tr>
<tr>
<td>Krumbhart &amp; Lippencott[74]</td>
<td>4000 adults without noteworthy disease of spleen</td>
<td>Autopsy</td>
<td>V = 151 mL</td>
<td></td>
</tr>
<tr>
<td>Loftus et al.[75]</td>
<td>30 autopsy cases</td>
<td>Post-mortem and ultrasound</td>
<td>L = 8.8 cm; postmortem L = 10.5 cm, V = 110 mL</td>
<td>? change of shape when spleen removed from body</td>
</tr>
<tr>
<td>Author</td>
<td>Subjects</td>
<td>Methodology</td>
<td>Dimensions</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------------------------------------------</td>
<td>------------------------------</td>
<td>------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Markisz et al. [47]</td>
<td>116 children with liver or spleen trauma</td>
<td>Scintigraphy (Technetium 99m sulphur colloid)</td>
<td>Volume linearly related to body mass, ( V = 260 ) mL at 60 kg</td>
<td>Measurements not made by a registered sonographer; population mean for L = 8.9 cm</td>
</tr>
<tr>
<td>McCorkle et al. [76]</td>
<td>Tall athletes (n = 66); height = 1.92 m (M), 1.77 m (F)</td>
<td>2D ultrasound</td>
<td>( L = 12.2, B = 8.9, T = 5.6 ) cm</td>
<td></td>
</tr>
<tr>
<td>Megremis et al. [77]</td>
<td>512 healthy children</td>
<td>Ultrasound</td>
<td>( L = 10.3 ) cm (F), ( 10.7 ) cm (M) at age 14–17 yr</td>
<td>Values strongly correlated with age, height and body mass</td>
</tr>
<tr>
<td>Meyers and Segal [84]</td>
<td>366 adults</td>
<td>Autopsy</td>
<td>( V = 125 ) mL (F), ( 175 ) mL (M)</td>
<td>SD approximates ( \pm 39 ) mL, based on 2.5–97.5% confidence limits</td>
</tr>
<tr>
<td>Prassopoulos and Cavouras [43]</td>
<td>87 boys, 66 girls aged 5 months to 15 yr</td>
<td>Computed tomography</td>
<td>Values peaked at 13 yr, ( V = 177 ) mL</td>
<td>No sex difference in volumes; no effect of age after 13 yr</td>
</tr>
<tr>
<td>Prassopoulos et al. [53]</td>
<td>140 patients free of splenic disease</td>
<td>Computed tomography</td>
<td>Mean ( V = 214.6 ) mL, range 107–315 mL</td>
<td>No effect of height; ( V = 30 + 0.58 ) (L ( \times ) B ( \times ) T)</td>
</tr>
<tr>
<td>Rodrigues et al. [60]</td>
<td>32 normal spleens</td>
<td>Ultrasound and postmortem</td>
<td>Post-mortem ( V = 148 ) mL, ultrasound ( V = 284 ) mL</td>
<td>Ultrasound ( V = (L \times B \times T) )</td>
</tr>
<tr>
<td>Rosenberg et al. [66]</td>
<td>89 boys and 141 girls, neonates to age 20 yr</td>
<td>2D Ultrasound</td>
<td>Length 7 cm at 12 months, rising to 12 cm (F) and 13 cm (M) at age &gt;15 yr</td>
<td>22 patients with abnormal spleens all exceeded guidelines</td>
</tr>
<tr>
<td>Spielman et al. [79]</td>
<td>82 male, 47 female university students</td>
<td>2D ultrasound (3D testing cumbersome, and issues with complex shape of spleen)</td>
<td>( L =11.4 ) cm, ( B = 10.8 ) cm, ( T = 5.0 ) cm ( V = 334 ) mL (men),( 10.3 \times 9.5 \times 4.2 ) cm, ( 220 ) mL (women)</td>
<td>Spleen length, width and volume correlated with standing height, lesser correlation between height and spleen thickness</td>
</tr>
<tr>
<td>Sprogøe-Jakobsen &amp; Sprogøe-Jakobsen [50]</td>
<td>539 normal spleens</td>
<td>Autopsy</td>
<td>Average ( V = 135 ) mL (female), ( 168 ) mL (male)</td>
<td>Related to height and body mass</td>
</tr>
</tbody>
</table>
The spleen must often be assessed in children, adolescents and athletes with unusual body builds. In children, splenic dimensions show moderately strong relationships to standing height, body mass and age, commonly with correlation coefficients of 0.7 to 0.8. The spleen appears to reach its maximal size around the age of 13 years.\textsuperscript{[43]} Some observers have also reported modest effects of height upon splenic volume in adults, particularly in tall basketball players.\textsuperscript{[50, 79]} Thus, in a sample of 129 university athletes, Spielman et al.\textsuperscript{[79]} found height correlations of 0.4 for men and 0.3 for women. However, significant correlations with height have been seen only if the sample included individuals with extreme body types, or both children and adults; in adults, the correlation coefficients are generally too weak (r < 0.03) to warrant size-specific adjustments of norms.\textsuperscript{[53, 80]}

### Splenic size in infectious mononucleosis

We have already emphasized challenges to the use of laboratory determinations of splenic size as a component in the diagnosis of infectious mononucleosis. Some authors have nevertheless claimed that the increase over normal dimensions is usually large enough to contribute to a confident clinical diagnosis. Thus, Dommerby et al.\textsuperscript{[33]} reported that at ultrasonography, infected individuals showed a splenic enlargement of at least 25%, and that three days after appearance of the first symptoms, spleen lengths and widths were 50–60% greater than in a control group with other throat infections. In their patients, dimensions progressively returned to normal over four weeks, as the mononucleosis abated. In contrast, Hosey et al.\textsuperscript{[72]} found that in healthy university athletes the lengths and breadths of the spleen as measured by ultrasound were such that 7% of these individuals would have been classed as having splenic enlargement. Although on average

<table>
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<tr>
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<th>Methodology</th>
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<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yetter et al.\textsuperscript{[45]}</td>
<td>66 M, 51 F, average age 57 yr, including various splenic pathologies</td>
<td>Ultrasound and helical computed tomography</td>
<td>Methodological difference of 61.8 mL; computed tomography V = 512.6 mL, sonography V = 450.8 to 570.8 mL, depending on formula used</td>
<td>CT volume differs from ultrasonic (ellipsoid formula)</td>
</tr>
<tr>
<td>Zhang and Lewis\textsuperscript{[48]}</td>
<td>14 patients with hematologic disorders</td>
<td>Scintigraphy (\textsuperscript{113}Indium)</td>
<td>Upper limit of normality V = 256 mL</td>
<td>Difference from actual volume at post-mortem 0.2 ± 6.7%</td>
</tr>
</tbody>
</table>

Notes: L = length, B= breadth, T = thickness, V = spherical volume

Table 8.5 continued

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The spleen must often be assessed in children, adolescents and athletes with unusual body builds. In children, splenic dimensions show moderately strong relationships to standing height, body mass and age, commonly with correlation coefficients of 0.7 to 0.8. The spleen appears to reach its maximal size around the age of 13 years.\textsuperscript{[43]} Some observers have also reported modest effects of height upon splenic volume in adults, particularly in tall basketball players.\textsuperscript{[50, 79]} Thus, in a sample of 129 university athletes, Spielman et al.\textsuperscript{[79]} found height correlations of 0.4 for men and 0.3 for women. However, significant correlations with height have been seen only if the sample included individuals with extreme body types, or both children and adults; in adults, the correlation coefficients are generally too weak (r < 0.03) to warrant size-specific adjustments of norms.\textsuperscript{[53, 80]}

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there was a 33.6% increase in size of the spleen with infection,\textsuperscript{[73]} this was no greater than the standard deviation commonly reported for healthy adults (above). Moreover, even if incontrovertible evidence of an enlarged spleen can be adduced, the many other possible causes of such enlargement have to be considered before reaching a diagnosis of infectious mononucleosis (Table 8.6).

The splenomegaly associated with infectious mononucleosis peaks around the 12th day of infection, and substantial changes in splenic dimensions over serial measurements provide a clearer indication of that the spleen has been infected. In healthy controls, weekly intra-individual changes in spleen length are less than 10%\textsuperscript{, [73]}

### Management of the athlete with an enlarged spleen

The effects of the disease process upon tissue structures increase the vulnerability of the enlarged spleen to rupture,\textsuperscript{[82]} and a normalization of splenic volume is often one consideration in clinical decisions as to when an athlete can with infectious mononucleosis can return to competitive activity. Dommerby et al.\textsuperscript{[33]} suggested that although the initial enlargements of the liver and spleen were unrelated to abnormal hepatic enzyme levels, a parallel normalization of these two indicators occurred over the course of the following month, as the disease resolved. However, there remain uncertainties about the sensitivity of either illness severity or splenic enlargement as measures of the immediate risk of splenic rupture.\textsuperscript{[22, 83, 84]}

### Likelihood of splenic rupture

Splenic rupture usually occurs during the first three to four weeks of infectious mononucleosis,\textsuperscript{[22, 85]} although one case has been reported seven weeks after onset

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Table 8.6 Possible pathologies to be considered in the differential diagnosis of splenic enlargement

- **Trauma:** splenic haematoma or contusion
- **Infections:** bacterial, viral, fungal or parasitic infections affecting spleen
- **Haematological problems:** acute or chronic anaemia, sickle cell disease
- **Chronic inflammatory conditions:** sarcoidosis, lupus erythematosis, rheumatoid arthritis, inflammatory bowel disease, systemic vasculitis
- **Liver conditions:** cirrhosis or hepatitis of the liver, congestive heart failure, portal hypertension
- **Metabolic diseases:** disorders of amino acid, lipid and carbohydrate metabolism, glycogen storage disease, glycoprotein disorders, mucopolysaccharoidoses
- **Malignancies and other infiltrative disease:** splenic tumours, leukaemia, lymphoma, multiple myeloma, polycythaemia, thrombocytopenia, myelofibrosis, metastases of tumours elsewhere in the body, amyloidosis, histocytosis

Source: Based in part on Turner and Garg\textsuperscript{[81]}
of the illness, and one recurrence of rupture was seen ten weeks after the first symptoms had developed. Most such incidents are concentrated in contact sports, but damage can also follow a Valsalva manouevre and in some instances the injury appears to be “spontaneous”. Five actual and four suspected cases of atraumatic splenic rupture were found in a series of 8116 patients with infectious mononucleosis. Given that symptoms are often vague, the risk of spontaneous rupture remains uncertain, but a prevalence of 0.1–0.5% has been suggested in athletes. Rupture should be suspected if the patient suddenly complains of acute abdominal pain. The escape of blood into the peritoneum may irritate the diaphragm, with a resulting referral of pain to the shoulder. Following rupture, radiography, ultrasonography and/or computed tomography may reveal not only an enlarged spleen, but also an accumulation of fluid in the peritoneum and a subcapsular splenic haematoma.

**Surgical vs. expectant treatment of splenic rupture**

Early splenectomy was once regarded as the safest clinical option following splenic rupture, but this reflected an overestimation of the mortality associated with expectant treatment. There are occasional fatalities following a “spontaneous” rupture of the spleen but such incidents are rare and they do not warrant a hasty splenectomy. There are indeed several arguments against such surgery. Some reports have shown an immediate operative death rate as high as 1% from an overwhelming meningeal or pneumococcal septicemia, although this risk can now be attenuated by the preoperative administration of pneumococcal and other vaccines. Moreover, removal of the spleen may compromise the individual’s subsequent immune responses.

Many authors now regard conservative treatment as a better option, provided that the condition of the patient is stable, and that transfusion can be limited to fewer than four units of blood (in order to minimize the risks of transmitting hepatitis and/or HIV infection via the infused blood). Arguments against conservative management include a slower return to competition, the risks of repeated blood transfusion and the danger that the enlarged spleen may still contain undetected haematomas that will predispose to an early second rupture.

**Overall management of infectious mononucleosis**

The general management of infectious mononucleosis is largely symptomatic. There is no evidence of benefit from routine use of corticosteroids or antiviral drugs like acyclovir. However, corticosteroids may be indicated if there is severe oedematous obstruction of the airway, and antiviral medication may prove helpful in the late treatment of individuals who have developed chronic fatigue.

Following a period of modified bed rest, recovery is usually uneventful, although serious complications can develop in some 5% of patients.
collected reports of some 100 cases with fatal outcomes, including deaths attributed to neurological complications, respiratory obstruction, inflammation of the heart muscle and liver failure. For the athlete, the most serious issues are inflammation of the pharynx, enlargement of the spleen with a potential for its rupture and possible progression to a variant of CFS in the later phases of the disease. However, the factors triggering such a progression and the nature of the relationship to CFS as yet remain controversial.

One controlled study of university students noted a slightly faster recovery from infectious mononucleosis in those individuals who were permitted ad libitum physical activity during their illness, and another study of army cadets found no complications from a return to light training as soon as the patients were afebrile. However, vigorous activity seems to be unwise while the virus is still active. In addition to issues of possible splenic rupture and progression to CFS, there is a slight risk of developing myocarditis, with chest pain, ECG abnormalities and damage to the heart muscle as shown by the release of cardiac troponin.

Clinical decisions on a return to light, non-contact physical activity and progressive reconditioning are guided by (1) regression of symptoms, (2) normalization of splenic size and (3) epidemiologic data on the likelihood of splenic rupture. Rutkow somewhat arbitrarily recommended against athletic participation for as long as six months post-infection. More recently, most authors have opted for only three to four weeks of rest if the athlete is asymptomatic and ultrasound demonstrates a recovery of normal splenic dimensions. Nevertheless, some sports physicians still advise avoiding contact sports and activities demanding the Valsalva manoeuvre for at least two months, and highly trained athletes may take as long as three months to regain their normal level of competitive performance.

Shah and Richards suggested that athletes with mononucleosis be protected by a customized spleen guard immediately after infection, and others have advocated wearing a flak jacket. However, there is as yet no objective evidence of protection against splenic rupture from either of these measures.

Potential progression to chronic fatigue syndrome

There have been suggestions that in a patient with infectious mononucleosis, premature vigorous physical activity prolongs chronic fatigue and is a risk factor for progression to CFS. If true, this could be a further argument for restricting physical activity during and immediately following infection.

Complaints of persistent fatigue, daytime sleepiness and depression often follow the acute phase of infectious mononucleosis. Sometimes, the characteristics of this fatigue match the American Psychological Association criteria for the diagnosis of CFS, although reported relationships between infectious mononucleosis and CFS are inconsistent (Table 8.7). One major problem in resolving the risk is that CFS itself seems to be a heterogenous group of conditions. The Epstein-Barr virus is not universally detected in CFS,
<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Study design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buchwald et al. [131]</td>
<td>150 patients with IM</td>
<td>6-month prospective survey</td>
<td>Fatigue and poor functional status in 38% of patients with IM at 2 months, 12% at 6 months</td>
</tr>
<tr>
<td>Candy et al. [132]</td>
<td>71 primary care patients with IM</td>
<td>Postal questionnaire at 1 yr (70% response rate)</td>
<td>Fatigue in 4% of IM patients persists &gt;6 months. No clear precipitating factors</td>
</tr>
<tr>
<td>Crawford et al. [133]</td>
<td>110 university students who underwent serum conversion for EBV</td>
<td>3-year follow-up</td>
<td>EBV type I infection is associated with the 25% of students with IM who develop CFS</td>
</tr>
<tr>
<td>Feder et al. [134]</td>
<td>48 pediatric patients with chronic fatigue</td>
<td>Follow-up averaging 3.8 years</td>
<td>Acute illness preceded fatigue in 78% of cases of CFS</td>
</tr>
<tr>
<td>Hickie et al. [135]</td>
<td>253 patients with EBV or other viral infections</td>
<td>6-month prospective study</td>
<td>11% of patients with IM met APA criteria of CFS at 6 months, irrespective of infecting virus</td>
</tr>
<tr>
<td>Katz &amp; Jason; [136]</td>
<td>301 adolescents with heterophile positive IM</td>
<td>2-year prospective study</td>
<td>Criteria for CFS met in 13%, 7% and 4% of patients with IM at 6, 12 and 24 months, mainly in females</td>
</tr>
<tr>
<td>Kraus et al. [21]</td>
<td>178 students with IM (Hoagland criteria), matched controls with non EBV respiratory infections</td>
<td>1-year prospective study</td>
<td>IM causes greater fatigue in acute phase, persistent in 11% of patients for 100 days, 6% for 1 yr</td>
</tr>
<tr>
<td>Krilov et al. [138]</td>
<td>58 children aged 7–14 years with chronic fatigue</td>
<td>Retrospective evaluation of charts</td>
<td>Symptoms of CFS began with acute illness in 60% of cases</td>
</tr>
<tr>
<td>Lerner et al. [139]</td>
<td>58 patients with CFS, 68 controls</td>
<td>Testing every 6–12 weeks for 24–42 months</td>
<td>Serum EBV VCA IgM consistently positive in subset of 33/58 CFS patients</td>
</tr>
<tr>
<td>Marshall et al. [140]</td>
<td>23 children</td>
<td>Clinical examination, 17–40 month follow-up on 17/23</td>
<td>Only 3 of 23 patients had current or recent EBV infection; 6/17 had episodes of fatigue at follow-up</td>
</tr>
</tbody>
</table>
although type 1 EBV is present in a subset of cases who have previously experienced infectious mononucleosis.\[133, 139\] Moreover, retrospective questioning of patients with CFS often provides evidence of a prior illness resembling infectious mononucleosis,\[134, 138, 142\] and prospective studies of adolescents with infectious mononucleosis have found that six months later, 13% develop CFS.\[137, 148\] It remains unclear whether late complaints of fatigue indicate a lingering infection, as suggested by a continued elevation of pro-inflammatory cytokines,\[28\] or whether the initial infection is simply triggering what is essentially a psychological disorder.\[136, 141, 149\]

A retrospective comparison of 47 CFS cases with matched controls found a greater number of the affected individuals reporting exercise >3 times/week in the period before onset of the disease (67% vs. 40%).\[144\] However, the statistical significance of this observation (p <0.02) is weakened by the fact that it is but 1 of 18 post-hoc comparisons. A pedometer case-control study of 301 adolescents with infectious mononucleosis found that CFS was usually associated with a low rather than a high level of habitual physical activity\[150–152\] but, by contrast, an increase of physical activity was often associated with an immediate worsening of symptoms.\[153\] In a third study, Huang et al.\[137\] found no differences of physical activity between individuals who developed late fatigue and those who did not.

We may conclude that a small proportion of cases of infectious mononucleosis progress to CFS. More information is needed on the contribution of premature physical activity to this outcome and on exercise responses in such individuals. But as with other forms of CFS, it seems likely that excessive physical activity may worsen the patient’s condition once CFS has developed.

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Study design</th>
<th>Findings</th>
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</thead>
<tbody>
<tr>
<td>Moss-Morris et al.</td>
<td>246 cases of IM without prior</td>
<td>6-month prospective</td>
<td>9.4% of patients met APA criteria of CFS at 3 months, 7.8% at 6 months.</td>
</tr>
<tr>
<td></td>
<td>history of CFS</td>
<td>study</td>
<td>Perceived stress and limitation of physical activity during IM unrelated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>to likelihood of developing CFS</td>
</tr>
<tr>
<td>Smith et al.</td>
<td>15 adolescents with chronic</td>
<td>9-month follow-up</td>
<td>Acute illness coincided with onset of symptoms in 11 cases; monospot</td>
</tr>
<tr>
<td></td>
<td>fatigue</td>
<td>in 6 subjects</td>
<td>positive in 7 cases</td>
</tr>
<tr>
<td>White et al.</td>
<td>250 cases of IM or upper</td>
<td>6-month prospective</td>
<td>CFS at 6 months associated with positive monospot test (odds ratio 2.1)</td>
</tr>
<tr>
<td></td>
<td>respiratory infections</td>
<td>cohort study</td>
<td>and lower physical fitness (odds ratio 0.35)</td>
</tr>
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</table>

Notes: APA = American Psychological Association; CFS = chronic fatigue syndrome; EBV = Epstein-Barr virus; IM = infectious mononucleosis
Areas for further research

There remains scope to find a better method of determining splenic dimensions. It is also desirable to clarify the value of splenic size as a means of determining the current status of mononucleosis infections and the immediate risk of splenic rupture. The risk of spontaneous rupture in patients with infectious mononucleosis remains uncertain, and a clearer assessment of this risk would help to determine the amount of caution that should be adopted with respect to sport participation during the later stages of infection. Does the wearing of a customized spleen guard offer useful protection against splenic rupture? And in the event of rupture, what are the relative merits of surgery vs. conservative treatment? Finally, is physical activity during infection likely to trigger a progression of the condition to CFS? It remains unclear whether late complaints of fatigue indicate a lingering infection, as suggested by a continued elevation of pro-inflammatory cytokines, or whether the infection has simply triggered what is essentially a psychological disorder.

Practical implications and conclusions

Infectious mononucleosis is sufficiently prevalent among young adults that the condition must be suspected if an athlete presents with fever, swollen lymph glands, a sore throat and tiredness. Although most patients recover without incident, physical activity should be moderated until the acute infection has passed and spleen size has normalized because of potential dangers of splenic rupture and progression to CFS. Careful assessment is important, as symptoms are non-specific, and a positive diagnosis may entail a substantial period of withdrawal from normal competition. Physical examination must be reinforced by laboratory tests, including demonstration of a lymphocytosis with abnormal lymphocytes, a heterophil positive slide test and the appearance of specific EBV antigens. Palpation and percussion are ineffective methods of detecting any associated splenic enlargement. Even laboratory evaluations of splenic enlargement must take account of methodology, the formulae used in calculating dimensions, and the individual’s body size. Sonographic data usually demonstrate an enlarged spleen during the first few weeks of infection, but the dimensions of the spleen in any given individual may remain within what is a broad range of normality. Splenic dimensions are more useful in following the course of the disease. By three to four weeks after the onset of infection, the risks of injury from contact trauma, a Valsalva manoeuvre or spontaneous rupture of the spleen are sufficiently low to allow a graded return to physical activity. Sudden onset of abdominal pain should nevertheless arouse suspicions of splenic rupture. Debate continues on the merits of surgical vs. conservative treatment of such an incident. Surgical intervention may trigger a dangerous septicaemia and compromise subsequent immune function. Conservative treatment entails a longer absence from competition, the risk of substantial blood transfusions and the possibility of a recurrent rupture. Discussion continues on the frequency with
which infectious mononucleosis can progress to CFS and on possible factors that provoke prolonged fatigue. But for most athletes, infectious mononucleosis offers no more than the inconvenience of four weeks of restricted activity, with little risk to long-term health.

References


Physical activity and infectious mononucleosis


139. Lerner AM, Beqaj SH, Deeter RG, et al. IgM serum antibodies to Epstein-Barr virus are uniquely present in a subset of patients with the chronic fatigue syndrome. *In Vivo* 2004; 18: 101–106.


9 Physical activity and sickle cell disease

Introduction

Normal responses of the spleen to physical activity were reviewed in Chapter 7. This chapter looks at issues in the clinical management of athletes where the risk of splenic rupture is increased because of sickle cell disease. A person with sickle cell disease has abnormalities in the molecular structure of his or her haemoglobin, and this can affect the function of the spleen and other visceral organs, particularly during physical activity.

There are normally three types of haemoglobin: haemoglobin A (the most common variety, formed by two alpha and two beta chains), haemoglobin A1 (formed by two alpha and two delta chains) and haemoglobin F (formed by two alpha and two gamma chains, and characteristic of very young children). In sickle cell disease, a mutation of DNA sequencing causes valine to be substituted for glutamic acid as the sixth amino acid on the beta chain of haemoglobin, thus converting haemoglobin-A to the variant haemoglobin-S. Homozygotes who inherit the genetic abnormality from both birth parents develop sickle cell disease, with an associated anaemia, and many major health issues. Heterozygotes who inherit the abnormality from one birth parent develop the largely recessive sickle cell trait. The heterozygotes are able to transmit the condition to their offspring, and their red cells contain a varying proportion of haemoglobin-S, with a potential for adverse effects upon capillary blood flow.

A leakage of potassium ions from sickle cells confers some protection against malaria,[1] and this may explain why the prevalence of sickle cell trait is as high as 10–40% in Equatorial Africa.[2] About 100,000 people in the US also have sickle cell disease, including 1 in 500 African Americans and 1 in 36,000 Hispanic Americans.[3] The heterozygous condition is much more common, affecting 8–9% of African Americans,[4, 5] about 1.5% of the total US population and perhaps 200 million people worldwide.[6] There are substantial inter-individual differences in clinical course of the condition, reflecting the fact that several abnormal genes contribute to and moderate manifestations of the disease.[7]

The clinical prognosis for those with homozygous sickle cell disease is not good. About 1% of US children with sickle cell disease die during the first three years of life, and the survivors face 75,000 hospitalizations per year, at an annual
economic cost of $475 million.[3] Sickling-induced episodes of vascular occlusion can lead to infarction of the spleen, haematuria and a rhabdomyolytic breakdown of muscle tissue, with a potential for ischaemic damage to bone, brain, lung and gut.[9] Leakage of potassium ions from the breakdown of red cells and ischaemic muscle may also precipitate death due to an excessive accumulation of potassium in the blood.[8] Acute exacerbations of the disease (sickling crises) are frequent. Other complications include an increased risk of infections, defective development of bone marrow and bone necrosis, hypertension, chronic kidney disease, stroke and episodes of severe pain. Pulmonary involvement (the acute chest syndrome) can be fatal. Athletes with sickle cell trait also seem to face a small increase in the risk of exercise-related death, and some organizations such as the US National Football League thus make sport participation contingent upon either the demonstrated absence of sickle cell trait or the signing of a comprehensive waiver.

This chapter looks first at the physiopathology of sickling and its impact upon physical performance and other aspects of health. Risks, diagnostic procedures and potential preventive measures are then considered. Finally, attention is directed to policy implications, particularly the likely number of critical incidents, the costs and negative consequences of widespread athletic screening and the extent of benefits from prohibiting sport involvement.

**Physiology and pathology of sickle cell trait**

At rest, heterozygous sickle cell carriers show some abnormal blood characteristics, including an increase in viscosity.[9–11] The red cells are also less readily deformed than in a normal person,[9, 12] the shear force needed to separate aggregated red cells is increased[12] and there is a rise in plasma levels of the adhesion molecule-1 that binds red and white cells to the vascular endothelium.[6, 13, 14] Often, these changes are small and of no clinical importance, but the increase of blood viscosity is substantial in a third of individuals with the sickle cell trait.[10] Moreover, physical activity leads to a greater decrease in red cell deformability than that seen in normal individuals.[15]

Sickling during a brief physical effort such as a progressive maximal exercise test may affect only 1% of cells,[16, 17] and the working capacity of the typical sickle cell carrier thus remains essentially normal. Moderate physical activity is not harmful to the heterozygote;[18] it does not increase serum myoglobin levels more than would be expected in a normal person,[19] it does not increase blood viscosity[20] and it may even reduce red cell aggregation 30–60 hours after activity has ceased.[21]

Any type of oxidative stress accelerates the sickling process, and physical training is helpful to a person with sickle cell trait in that it reduces the oxidative stress associated with a given absolute intensity of effort.[22, 23] If there is a coexistence of α-thalassaemia, this blunts the problem of oxidative stress in individuals with sickle cell disease.[24] Muscle biopsy data suggest that a person with sickle cell trait has a greater number of blood vessels and a greater than
normal vascular tortuosity, but a reduced capillary density. Possibly, these changes facilitate the circulation of more viscous blood through the muscles. The vascular tortuosity persists if the affected individuals engage in an aerobic training programme.

The adverse changes seen in sickle cell trait carriers are much more pronounced in homozygotes. In one sample from Lagos, the haemoglobin concentration averaged only 7.9 g/100mL, but white cell and platelet counts were twice as high as in control subjects. Moreover, the abnormal haemoglobin had a reduced affinity for oxygen, compounding the effects of anaemia.

Those with sickle cell disease are vulnerable to sickle cell crises, which typically occur several times per year; such episodes lead to a blockage of the blood supply to vital organs and the haemolysis of red cells. The sickling process is marked by the appearance of red cells with an abnormal shape and diminished flexibility as the deoxygenated form of haemoglobin S undergoes polymerization. Exercise can provoke sickling, also causing activation of white cells and platelets and other changes that favour local coagulation. Exposure to high altitudes, the lactic acidosis of extreme exertion, muscle hyperthermia and red cell dehydration can all exacerbate sickling. The process can develop within two minutes in vitro, but it is less certain how far it can occur in vivo, except under extreme conditions; the red cells take only one to two seconds to pass through the body’s capillary system, and deoxygenation is usually only partial by the time that the blood has reached the veins.

Impact of sickling upon physical performance and health

Functional capacity in sickle cell disease

Sickle cell disease is often associated with poor physical and mental health, a low level of habitual physical activity, cardiac enlargement, non-specific ECG changes and an impaired physical performance (Table 9.1).

One study looking at the effects of transfusion concluded that any small loss of aerobic performance in sickle cell disease reflected repeated haemolytic crises and a resulting anaemia, rather than the immediate circulatory effects of changes in blood viscosity. However, maximal oxygen intake is reduced by a greater amount than would be anticipated from anaemia alone, implying other derangements of oxygen uptake. Muscular pain may limit habitual physical activity, giving rise to a pessimistic mood and a substantial use of pain-killing medications such as opioids. Increased sympathetic nerve activity may also trigger vaso-occlusive crises. However, when lying supine or following a tilt test the autonomic response of patients with sickle cell disease was less than that of normal individuals, and brief periods of moderate exercise did not augment autonomic activity in a manner that could trigger a vaso-occlusive crisis.

Homozygotes show a substantial retardation of normal growth, and thus rarely seek permission to participate in high-performance athletics.
### Table 9.1 Effects of sickle cell disease upon health and physical performance

<table>
<thead>
<tr>
<th>Author</th>
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<th>Findings</th>
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<tbody>
<tr>
<td><strong>Overall health</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Henderson et al.[29]</td>
<td>63 children with sickle cell disease</td>
<td>Height and body mass</td>
<td>25% of children below 5th percentile for growth norms</td>
<td></td>
</tr>
<tr>
<td>Connes et al.[30]</td>
<td>Review article</td>
<td></td>
<td>Exercise limitations from anemia, pulmonary vascular or parenchymal disease or congestive heart failure</td>
<td></td>
</tr>
<tr>
<td>Anie et al.[31]</td>
<td>21 adults with sickle cell disease</td>
<td>Self-monitoring</td>
<td>Patients needing to use opioids are less active, more pessimistic and face greater disruption of normal living</td>
<td></td>
</tr>
<tr>
<td>Artz et al.[32]</td>
<td>145 adults with sickle cell disease</td>
<td>SF-12 physical and mental health questionnaire</td>
<td>Length of hospital stay related to poor physical rather than poor mental health</td>
<td>Mental health corresponded to national norms</td>
</tr>
<tr>
<td>Adebayo et al.[33]</td>
<td>41 adults with sickle cell anaemia,</td>
<td>Percussion, ECG, self-paced walking test</td>
<td>Cardiac enlargement, non-specific electrocardiographic changes, slow walking speed</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Habitual physical activity</strong></th>
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<tr>
<td>Barden et al.[34]</td>
<td>20 girls, 16 boys aged 11 years with sickle cell disease</td>
<td>Doubly labelled water</td>
<td>Active energy expenditure decreased</td>
<td>Increased resting energy expenditure</td>
</tr>
<tr>
<td>Buchowski et al.[35]</td>
<td>28 adolescents with sickle cell anaemia</td>
<td>Tri-axial accelerometry</td>
<td>Active energy expenditure decreased</td>
<td>Increased resting energy expenditure</td>
</tr>
<tr>
<td>Charlot et al.[36]</td>
<td>22 cases of sickle cell anaemia,</td>
<td>Questionnaire</td>
<td>Active energy expenditure less than a half of normal</td>
<td>Reduced activity of autonomic nervous system</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Physical performance</strong></th>
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<tbody>
<tr>
<td>Millis et al.[37]</td>
<td>15 girls with sickle cell disease, 15 controls</td>
<td>Times for 20, 40 yd swims and 100 yd potato race</td>
<td>All times impaired relative to size matched controls</td>
<td>Suggested as due to left ventricular dysfunction</td>
</tr>
<tr>
<td>Dedeken et al.[38]</td>
<td>46 children with sickle cell disease</td>
<td>Self-paced walking test</td>
<td>14/46 had slow walking speed</td>
<td>Poor performance correlated with silent infarction</td>
</tr>
</tbody>
</table>
Functional capacity in sickle cell trait

Most heterozygotes have an aerobic power, anaerobic power and exercise tolerance matching that of healthy controls (Table 9.2). In general, there is no compromise of aerobic or anaerobic performance, although one report noted that sickle cell trait limited the achievements of top competitors in a semi-marathon event. [53]
### Table 9.2 Effects of sickle cell trait upon physical performance

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Test</th>
<th>Findings</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td><strong>Athletic performance</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Marlin et al. [50]</td>
<td>3 of 16 West Indian sprinters had sickle cell trait</td>
<td>Analysis of sprint records</td>
<td>Those with sickle cell trait achieved best performances</td>
<td></td>
</tr>
<tr>
<td>Bilé et al. [51]</td>
<td>34 of 122 national champions with sickle cell trait</td>
<td>Analysis of records for throwing and jumping champions</td>
<td>Sickle cell trait appeared to contribute to outstanding performance</td>
<td></td>
</tr>
<tr>
<td>Le Gallais et al. [52]</td>
<td>13 of 129 Ivory Coast athletic champions with sickle cell trait</td>
<td>Analysis of athletic records</td>
<td>Those with sickle cell trait performed well in sprint events, but achieved fewer endurance records</td>
<td></td>
</tr>
<tr>
<td>Le Gallais et al. [53]</td>
<td>123 runners with sickle cell trait of 1506 semi-marathon participants</td>
<td>Competitive involvement of cases and race results</td>
<td>Proportion of cases similar to general population; race performance of cases also matched population</td>
<td>But only 1 case with thalassaemia reached international level</td>
</tr>
<tr>
<td><strong>Aerobic performance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpert et al. [16]</td>
<td>48 cases of sickle cell trait aged 4–21 yr, 184 controls</td>
<td>Progressive cycle ergometer test</td>
<td>Lower peak working capacity in cases than in controls</td>
<td>4 cases showed equivocal ischaemia on ECG</td>
</tr>
<tr>
<td>Robinson et al. [54]</td>
<td>16 sickle cell males, 16 controls</td>
<td>Progressive treadmill test</td>
<td>No significant differences of maximal oxygen intake or heart rates</td>
<td></td>
</tr>
<tr>
<td>Weisman et al. [55]</td>
<td>22 sickle cell trait males, 15 controls</td>
<td>7 weeks basic army training at 1270 m</td>
<td>Slightly lower initial maximal oxygen intake in cases; difference disappeared over training, no medical complications</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Population</td>
<td>Test</td>
<td>Findings</td>
<td>Comments</td>
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<tr>
<td>Connes et al. [56]</td>
<td>6 athletes with sickle cell trait, 9 cases with associated α-thalassaemia and 10 controls</td>
<td>Cycle ergometer test</td>
<td>Larger slow component to oxygen on-transient in cases with and without α-thalassaemia</td>
<td>Possible cause lower muscle flow, added fibre recruitment or increased cardiac loading</td>
</tr>
<tr>
<td>Shasky et al. [57]</td>
<td>Review</td>
<td>Exercise capacity near normal</td>
<td>Sudden death in sickle cell trait rare, associated with rhabdomyolysis in heat or at altitude</td>
<td></td>
</tr>
<tr>
<td>Marlin et al. [58]</td>
<td>7 subjects with sickle cell trait, 8 controls</td>
<td>Incremental cycle ergometer test</td>
<td>Normal ventilatory and lactate thresholds</td>
<td></td>
</tr>
<tr>
<td>Sara et al. [59, 60]</td>
<td>8 male sickle cell trait cases, 8 controls</td>
<td>Lactate levels in whole blood, plasma and red cells</td>
<td>Maximal oxygen intake and ventilatory thresholds unchanged, lactate distribution normal; maximal lactate across red cell membrane fast in sickle cell anaemia</td>
<td></td>
</tr>
<tr>
<td>Oyono-Enguèll et al. [61]</td>
<td>11 double heterozygous cases, 7 controls</td>
<td>20 minute cycle ergometer test</td>
<td>Lower exercise tolerance in cases</td>
<td></td>
</tr>
<tr>
<td>Hedreville et al. [62]</td>
<td>Seven patients with sickle cell anaemia</td>
<td>Temporal and spatial analyses of heart rate variability</td>
<td>Moderate exercise does not increase sympathetic activation</td>
<td></td>
</tr>
</tbody>
</table>

**Anaerobic performance**

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Test</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connes et al. [63]</td>
<td>7 male athletes with sickle cell trait, 7 controls</td>
<td>Five 6 sec cycling sprints</td>
<td>Peak work unchanged but earlier decrement of performance in repeated sprints</td>
<td></td>
</tr>
<tr>
<td>Hue et al. [64]</td>
<td>16 cases of sickle cell trait, 180 normal subjects</td>
<td>Field tests of explosive muscular performance</td>
<td>Performance similar for sprint, long jump and shuttle-run, but cases excelled for jump and reach test</td>
<td></td>
</tr>
<tr>
<td>Bilé et al. [65]</td>
<td>9 males with sickle cell trait, 9 controls</td>
<td>Cycle ergometer force/velocity test</td>
<td>No inter-group difference</td>
<td></td>
</tr>
</tbody>
</table>
Given that inheritance influences many aspects of athletic performance, it is not surprising that sickle cell trait is associated with success in some types of competition. In particular, it is associated with a high proportion of type II muscle fibres, thus boosting achievements demanding explosive force, anaerobic activity\cite{50, 51} and anaerobic power.\cite{64} However, runners with sickle cell trait rarely win in events of 800 m or longer,\cite{65} and performance is poorer than controls in 30 minute laboratory endurance tests.\cite{61}

Few individuals with sickle cell trait are discouraged from athletic competition.\cite{52} Proportions of affected individuals on athletic teams usually match numbers in the general population,\cite{68} and indeed 11 athletes with sickle cell trait competed in the 1968 Olympics at an altitude of around 2249 m without incident.\cite{69} A 31-year review of 2462 athletic deaths in the US found that only 23 (about 1%) occurred in individuals with the sickle cell trait,\cite{70} as expected from the current prevalence of the condition in the US population (1.5%). However, one NFL competitor with sickle cell trait (Ryan Clark) suffered a splenic infarction when playing American football in the Denver stadium (at an altitude of 1610 m) in 2007, and sickle cell trait has been reported as a leading cause of death among African Americans during military training and sports participation.\cite{71}

One study of heterozygotes aged 4–21 years found a low maximal heart rate and peak cycle ergometer work capacity relative to controls, although there was no electrocardiographic evidence that exercise had induced cardiac ischaemia.\cite{16} Other investigators have noted a normal peak aerobic power and ventilatory threshold,\cite{54, 72} although with a lesser build-up of lactate\cite{51} and a larger slow component to the oxygen on-transient.\cite{56} The performance of heterozygotes on repeated force/velocity tests also shows no difference from that of controls,\cite{65} and single sprint ability matches that of their peers, although there is an earlier onset of fatigue with repeated sprints.\cite{63} Lactate distribution and clearance are in general normal,\cite{59} although lactate transport across the red cell membrane occurs faster than normal.\cite{60} Finally, the response to basic military training seems normal.\cite{55}

**Specific risks of physical activity with sickle cell trait**

Vascular auto-regulation can compensate for some degree of intravascular red cell sickling and coagulation,\cite{73} and despite the possible hazards of altered blood flow dynamics during sleep,\cite{74} sickle cell carriers can lead normal lives, with a normal life span\cite{75} and morbidity.\cite{76–78} Moderate physical activity (15 minutes of cycle ergometry at the first ventilatory threshold) had little effect on blood coagulation relative to a control group,\cite{18} and the usual markers of coagulation were unchanged by three progressive exercise tests undertaken with short (10-min) rest intervals.\cite{79} But if heterozygotes are faced by adverse circumstances such as a hot environment, dehydration and/or hypoxia, there is a risk of more extensive sickling, with activation of neutrophils and increased circulating levels of adhesion molecules.\cite{79, 80} Resulting complications (Table 9.3) remain rare,\cite{75} but
include splenic infarction, exertional rhabdomyolysis, cardiac dysfunction, renal problems (exercise haematuria, loss of renal concentrating power and medullary carcinoma) and vascular occlusions (haemorrhagic stroke, venous thrombosis and pulmonary embolism),[81] about a quarter of sickling episodes have a fatal outcome.[82]

**Splenic infarction**

Sustained and vigorous activity at high altitude can occasionally provoke a splenic infarction in patients with the sickle cell trait.[1, 83, 84] Polymerization of the haemoglobin S and formation of sickle cell-shaped red cells is liable to occur at altitudes above 3500 m.[85–87] In one study, sickling in arm-vein blood increased from a resting value of 1.5% to 8.5% after two to five minutes of vigorous arm cranking at a simulated altitude of 4000 m,[86] however, infarction can only occur if the spleen is still functional. Often, previous infarctions have led to what is in effect an auto-splenectomy.[67] Many people with sickle cell trait have enlarged spleens, with multiple small infarctions.[88]

Splenic infarction can occur without altitude exposure.[89] Polymerization of the haemoglobin S is also induced by hyperthermia,[90–92] acidosis and dehydration,[82, 93] particularly if the individual is in poor physical condition relative to the effort that is being undertaken.[94] Other factors that encourage sickling are an increase of oxidative stress and the release of inflammatory mediators. However, the risk is reduced if hydration is well maintained,[93] and Goldsmith and associates[69] have queried whether the 10% sickling commonly observed when exercising under adverse conditions is in itself enough to explain the clinical findings.

Splenic infarction typically presents as a severe mid-line or upper quadrant abdominal pain, followed by nausea, vomiting, respiratory splinting and collapse.[1, 6, 95] Infarction has sometimes occurred after only a few minutes of sprinting drills. Debate continues on the merits of splenectomy versus conservative treatment.[87, 96]

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Table 9.3 Potential hazards faced by individuals with sickle cell trait during prolonged physical activity under challenging conditions

- splenic infarction
- muscle damage and exertional rhabdomyolysis
- muscle compartment syndrome
- cardiac dysfunction
- haematuria and impaired kidney function
- renal medullary carcinoma
- haemorrhagic stroke
- venous thrombosis
- pulmonary embolism
- sudden death
The infarct is usually self-limiting and often responds well to hydration, analgesics, oxygen and antibacterial vaccines. However, splenectomy may be needed if there is evidence of extensive necrosis.

One early report documented 15 splenic infarcts that were apparently precipitated by flying in aircraft with unpressurized cabins. More recently, several individuals have undertaken short commercial flights in aircraft pressurized to an altitude of about 2500 m within 48 hours of splenic infarction, apparently without any worsening of their condition.

**Exertional rhabdomyolysis**

Exertional rhabdomyolysis can develop in anyone who exercises at a high intensity relative to their physical condition. The release of myoglobin during the breakdown of muscle tissue causes an associated myoglobinuria. In 5–7% of cases, the ferrihaemate that is released from myoglobin in an acidic environment reaches a sufficient concentration to damage the renal tubules, leading to progressive renal failure. Manifestations of renal damage include an increase in serum potassium that causes muscle weakness, abnormalities of cardiac rhythm and a possibility of cardiac arrest, and decreases of calcium ion concentrations that induce muscular tremors and weakness of cardiac contraction. Even if a fatal outcome can be avoided, prolonged dialysis is often needed until renal function recovers.

Individuals with sickle cell trait seem at particular risk of developing exertional rhabdomyolysis. One estimate suggested it was 200 times more likely in individuals with sickle cell trait, although it is often difficult to be certain whether the cause was sickling disease or simply the performance of severe exercise under arduous conditions. The rhabdomyolysis reflects ischaemic blockage of the muscle microcirculation by an agglutination of sickling cells. One reviewer suggested that those with sickle trait have difficulty in conserving water, and that this increases their vulnerability to dehydration, thus predisposing to sickling. The blockage of the local blood supply causes extensive muscle necrosis and multiple muscle compartment syndromes as well as exertional rhabdomyolysis. Tissue pressures in the affected compartments rise to 30–80 mm Hg, rather than the normal 0–15 mm Hg, compounding tissue necrosis.

Four cases of fatal exertional rhabdomyolysis were encountered among US military trainees between 1970 and 1974; all were in individuals with sickle cell trait. Genetic variants other than sickle cell trait are sometimes responsible for exertional rhabdomyolysis. In fatal cases, autopsy has generally revealed an accumulation of sickle cells in the spleen, liver and kidneys, but it is less clear how much of the sickling occurred before death. The main arguments for ante-mortem sickling are a patchy rather than a generalized distribution around the body and that postmortem treatment with either formaldehyde or glutaraldehyde does not induce sickling if the tissues are fixed rapidly. Hypotension during circulatory collapse could contribute to muscle ischaemia and thus tissue breakdown.
A rapid exertional rhabdomyolysis has been said to account for some 5% of sudden deaths in sports.\textsuperscript{[104]} Seven fatal incidents of exertional rhabdomyolysis were seen in 136 non-traumatic deaths; all occurred in African Americans athletes with sickle cell trait, although a causal relationship to the anomaly remained unproven. More recently, 15 deaths in football players and some sudden deaths in other sports have again been attributed to exertional rhabdomyolysis.\textsuperscript{[48]}

**Cardiac dysfunction**

Cardiac dysfunction is seen mainly in sickle cell homozygotes. It is probably associated with intravascular haemolysis and progressive obstruction of the coronary blood vessels. The tricuspid regurgitation velocity is increased, as is mortality.\textsuperscript{[114]} Pulmonary hypertension and tricuspid regurgitation point to a high risk of sudden death.\textsuperscript{[115]}

**Renal problems**

Microinfarctions can cause ischaemic damage to the kidneys, with acute tubular necrosis, a loss of renal concentrating ability, defects in urinary acidification and decreased potassium excretion.\textsuperscript{[116]} Exercise haematuria and bacteriuria can be followed by renal papillary necrosis and even medullary carcinoma.\textsuperscript{[69, 77, 117, 118]} The tendency to sickling is exacerbated in the renal capillaries, where there is a low pH, a low oxygen tension and an osmotic pressure gradient that progressively dehydrates the red cells.

Gross haematuria may persist for two weeks after a sickling episode.\textsuperscript{[119]} The left kidney is most commonly implicated because it is larger and has a higher venous pressure than the right kidney. Occasionally, the immediate renal blood loss can cause a significant anaemia.\textsuperscript{[116]} While bleeding persists, hydration must be maintained to avoid clotting of the red cells in the urethra. Bed rest and a blood transfusion may be needed. Occasionally, it may become necessary to administer a synthetic vasopressin (desmopressin) to increase clotting factors, or the anti-fibrinolytic agent ε-aminocaproic acid or to consider ureteroscopic intervention to apply a balloon or cauterize the site of bleeding.\textsuperscript{[120]}

Metaplasia is provoked by repeated ischaemic damage and regeneration of the renal medullary cells, and the risk of renal medullary carcinoma is thus increased in sickle cell carriers.\textsuperscript{[75, 116]}

**Vascular problems**

Sickling gives a ten-fold increase in the risk of a haemorrhagic stroke.\textsuperscript{[121]} Minor strokes often pass undetected, but if repeated, they can lead to a cumulative decline of cognitive function.\textsuperscript{[122]} One report described severe cognitive dysfunction with disorientation and amnesia following the collapse of a sickle cell trait participant in a 5000 m ski race.\textsuperscript{[123]} One year earlier this same individual had collapsed with severe abdominal pain during another cross-country event.
A case control study found a four-fold increase in the incidence of sickle cell trait among athletes with venous thrombo-embolism, and a two-fold increase among those developing a pulmonary embolism.\textsuperscript{124} In one instance, a retinal vein thrombosis precipitated sudden and painful blindness in an athlete with sickle cell trait who had just completed a 138 km cycle race across mountainous terrain in a tropical environment (35°C, 60% relative humidity).\textsuperscript{125}

Some authors have described autonomic disturbances, abnormal capillary blood flow and sudden death\textsuperscript{126} in individuals with sickle cell trait even during sleep, but others argue that the evidence supporting sickling episodes while sleeping is not convincing.\textsuperscript{127}

**Overall risk**

Homozygotes with overt sickle cell disease must expect painful sickling episodes, a reduced quality of life, pulmonary hypertension and orthopaedic or neurologic complications\textsuperscript{128}. If pulmonary hypertension has developed, the 2-year mortality is as high as 50\%.\textsuperscript{129} However, the risk of vigorous physical activity for those with sickle cell trait is more controversial (Table 9.4). There are concerns about

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**Table 9.4 Evidence of association between sickle cell trait and sudden death during rigorous military exercises and athletic competition**

<table>
<thead>
<tr>
<th>Author</th>
<th>Population sample</th>
<th>Activity</th>
<th>Risk in those with sickle cell trait</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Military recruits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jones et al.\textsuperscript{108}</td>
<td>4000 military recruits</td>
<td>Basic military training</td>
<td>4 deaths – all had sickle cell trait</td>
</tr>
<tr>
<td>Kark et al.\textsuperscript{92}</td>
<td>2 million military recruits</td>
<td>Basic military training</td>
<td>39.8-fold increase in sudden unexplained deaths</td>
</tr>
<tr>
<td>Drehner et al.\textsuperscript{118}</td>
<td>3 million US Air Force recruits</td>
<td>Basic training</td>
<td>23.5-fold increase in risk of non-traumatic deaths</td>
</tr>
<tr>
<td>Eckhart et al.\textsuperscript{134}</td>
<td>Military autopsies in US over 25 years</td>
<td>Heat-related deaths</td>
<td>12 of 38 idiopathic deaths associated with sickle cell trait</td>
</tr>
<tr>
<td>Scoville et al.\textsuperscript{135}</td>
<td>US recruits over 25 years</td>
<td></td>
<td>14 of 31 associated with sickle cell trait</td>
</tr>
<tr>
<td><strong>Athletes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harmon et al.\textsuperscript{136}</td>
<td>NCAA football competitors</td>
<td>Exercise-related deaths</td>
<td>37-fold increase in risk</td>
</tr>
<tr>
<td>Eichner\textsuperscript{82}</td>
<td>NCAA Division I players</td>
<td>10-year review</td>
<td>10 of 16 deaths attributed to sickle cell trait (16–21-fold excess)</td>
</tr>
<tr>
<td>Harris\textsuperscript{70}</td>
<td>US athletes</td>
<td>Sudden death registry</td>
<td>0.9% attributed to sickle cell trait</td>
</tr>
</tbody>
</table>

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venous thrombo-embolism and renal complications\cite{130} but the overall danger to health seems low. People with sickle cell trait apparently show no increases in hospital admissions, morbidity or mortality.\cite{77, 78} Reports have been criticized for a small sample size and thus a lack of statistical power to detect risks, but in some studies the person-years experience of sickle cell trait has been substantial (for example, 2396 person-years\cite{131} and 4018 person-years\cite{132}). A more important weakness is that most of the individuals concerned have led a sedentary life, and such data do not establish the safety of athletic competition for those with sickle cell trait, particularly under demanding environmental conditions.

The issue is not easy to resolve, since sudden death during exercise is rare and its cause is often obscure. Possibly, some of the fatalities traditionally attributed to hypertrophic cardiomyopathy could in fact have been due to sickling.\cite{104, 133} The diagnosis of a sickling-related death is based largely on its reported pattern.\cite{70} This includes severe rhabdomyolysis, metabolic acidosis, acute renal failure and disseminated intravascular coagulation occurring over a period of 8–24 hours.\cite{57}

Jones et al.\cite{108} were the first to suggest that sickle cell trait posed a risk during vigorous physical activity. They noted that among 4000 recruits engaged in basic military training, the four who sustained exercise-related deaths all had the sickle cell trait. Their observations stimulated much larger studies of military personnel. A retrospective study of 2 million US army recruits found that between 1977 and 1981 the risk of sudden unexplained death was 27.6 times greater in black recruits and 39.8 times greater in all recruits with haemoglobin AS,\cite{62} but that the risk was similar for black and white recruits if the sickle cell trait was absent. Again, in some 3 million US Air Force recruits, the average death rate of 2.8/100,000 rose 23.5 fold to a total of 7 deaths in individuals with sickle cell trait.\cite{118} Further, a 25-year review of US military autopsies found that a disproportionate 12 of 38 cases of idiopathic deaths during exercise were linked to presence of the sickle cell trait.\cite{134} Another study of non-traumatic deaths in US recruits from 1977–2001 noted that 14 of 31 heat-related deaths were in individuals with sickle cell trait, and all 26 deaths in African Americans with sickle cell trait were exercise related.\cite{135} Based on these findings, it was concluded that sickle cell trait accounted for around 0.3% of exercise-related deaths.\cite{2, 69} Despite recent attempts to increase the safety of basic training, a substantial number of recruits with sickle cell trait are still dying after performing activities such as the Cooper 2.4 km running test.\cite{137}

Athletic organizations have had a similar experience to the US military. A four-year study of NCAA football competitors found five cases of exertional death in athletes with sickle cell trait, a risk 37 times higher than that for athletes without the sickle cell anomaly,\cite{136} and a ten-year review attributed 10 of 16 deaths in NCAA Division I to sickle cell trait, a 16–21-fold excess.\cite{82} Finally, 23 of 2462 entries in the athletes’ sudden death registry\cite{70} were attributed to sickle cell trait (0.9%), although 7 of the fatalities were drawn from the 271 African Americans in the register. Prospective trials are still needed. Although the current findings suggest that the sickle cell trait poses some risk to athletes, they could also be explained by linked abnormality or co-existent disease.\cite{130} Small case series have suggested associations between malignant hyperthermia, variants in the
ryamodine receptors that regulate calcium release and coexistent haemoglobin AS.\cite{138} Abnormalities in the gene controlling the cardiac sodium-pumping channel may also predispose to sudden death.\cite{139} The high proportion of type II muscle fibres found in many black athletes further modifies exercise responses.\cite{69} Finally, black recruits may initially be less fit than their white counterparts, or they may exercise harder when they are evaluated in their attempts to gain a military commission.\cite{140}

Ajayi\cite{121} argued that sickle cell trait should be considered a disease state rather than a benign condition. To date, policy decisions on the need for athletic screening have been based largely rather alarming risk ratios suggesting a substantial disadvantage to those with sickle cell trait, but they obscure the fact that even under very adverse circumstances (untrained individuals performing very demanding exercise in hot and humid conditions), the absolute number of deaths among those with sickle cell trait remains small. The risks, already quite low, could be greatly attenuated by better control of heat stress and exercise intensity in those who are initially untrained, with benefit to all recruits.\cite{6}

**Diagnostic approaches to sickle cell trait**

Given the concern that sickle cell trait can precipitate major illnesses and even sudden death, there has been interest in developing simple and reliable tests to identify the sickle cell anomaly. Athletes are usually classified simply as positive or negative. However, the risk is not as simple as this binary classification might suggest; ancillary factors can modify expression of sickle cell-related disorders.\cite{7} The blood leucocyte concentration affects coagulation and thus the incidence of acute chest syndrome and cerebral infarction, a higher concentration of foetal haemoglobin attenuates sickling, and nitric oxide bioavailability influences the vascular adhesion of red cells during sickling.\cite{141}

**Table 9.5 Sensitivity and specificity of tests for the diagnosis of sickle cell trait**

<table>
<thead>
<tr>
<th>Author</th>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluoch et al.\cite{143}</td>
<td>Microscopy of peripheral blood smear</td>
<td>76%</td>
<td>99.7%</td>
<td>Patients with sickle cell anaemia; gold standard cellulose-acetate paper electrophoresis</td>
</tr>
<tr>
<td>Hicks et al.\cite{144}</td>
<td>Solubility test</td>
<td>99%</td>
<td>100%</td>
<td>487/493 sickle cell trait, compared relative to electrophoresis</td>
</tr>
<tr>
<td>Hicks et al.\cite{144}</td>
<td>Metabisulphite</td>
<td>97%</td>
<td>99.9%</td>
<td>487/493 sickle cell trait, compared relative to electrophoresis</td>
</tr>
<tr>
<td>Hicks et al.\cite{144}</td>
<td>Sickledex</td>
<td>98.9%</td>
<td>100%</td>
<td>487/493 sickle cell trait, compared relative to electrophoresis</td>
</tr>
</tbody>
</table>
Available tests vary in their cost, sensitivity and specificity (Table 9.5). The “solubility test”, based on the relative insolubility of deoxyhaemoglobin-S in an aqueous solution[6] can cost as little as $10, but the fee for a haemoglobin electrophoresis test[142] ranges from $30–150.[136] The simplest diagnostic option is to examine a peripheral blood film; this has a sensitivity of 76% and a specificity of 99.7%.[143] Hicks and associates[144] evaluated the success of other screening methods in a sample of 4243 people, 487 of whom had the sickle cell trait and 6 of whom had sickle cell disease. All of the procedures evaluated were relatively satisfactory. The standard meta-bisulphite test gave 3% of false negative and 0.07% false positive results. The solubility test fared somewhat better, with 1% false negative and 0% false positive results, and cellulose-acetate electrophoresis gave 100% sensitivity and specificity. The methods currently recommended are electrophoresis (thin-layer isoelectric focusing) or high-performance liquid chromatography, both of which are reported as having an “extremely high” sensitivity and specificity.[145] High-performance liquid chromatography can detect as little as 0.5% of a haemoglobin variant in a blood sample.[146, 147]

Potential for preventive measures

Given the high sensitivity and specificity of current tests, some physicians have proposed that universal sickle cell screening should be carried out at birth. However, at least 50 heterozygotes with sickle cell trait are identified for every homozygote, and the negative personal consequences of being diagnosed with the sickle cell trait as yet remain unclear.[145] Further, even if universal birth screening were to be adopted, occasional cases of sickle cell trait would probably remain undetected because of clerical errors such as mislabeled specimens, blood transfusion prior to screening or the inability to locate affected infants after their discharge from hospital.

The possibility of an exercise-related death in an athlete with sickle cell trait depends upon the intensity of training and competition relative to the individual’s initial status. Because competition was more intense in older age groups, one report estimated that the risk of sickle cell deaths was 66 times higher in university than in high school football athletes, although at 0.57 per 100,000 deaths the incidence of sickling deaths in the university group still remained relatively low.[148]

Habitual physical activity such as eight hours of soccer training per week[94] apparently offers some protection against sickling, in part by reducing an individual’s relative intensity of effort when performing any given task. Oxidative stress plays a major role in sickling, and the accumulation of reactive species may lead to endothelial activation, with an increased adherence of red cells to the vascular linings.[149] Physical training reduces the oxidative stress associated with a given bout of physical activity, and this also attenuates the risk of sickling.[22] Fluid ingestion sufficient to maintain body mass is another important precaution;[150, 151] well-hydrated subjects showed no evidence of sickling during 45 minutes of brisk treadmill walking at a temperature of 33 °C,
whereas their peers showed at least 5% sickling if they performed the same exercise but no fluid was provided.\[93\] Dehydration apparently has particularly adverse effects in those with the sickle cell trait.\[90\] Control subjects showed only small increments of blood viscosity over the course of a soccer game, even if no fluids were provided. However, in players with sickle cell trait, a game without fluids increased what was initially a high blood viscosity, although this could be normalized quite easily by the \textit{ad libitum} provision of fluids.\[151\] Further, playing a match without water increased red cell rigidity in players with sickle cell trait, whereas the provision of \textit{ad libitum} fluids decreased rigidity.\[150\] Blood viscosity also increased during 40 minutes of exercise at 55% of peak aerobic power in those with sickle cell trait if they were deprived of water,\[11\] and even a brief bout of exercise at 110% of maximal oxygen intake increased blood viscosity.\[47\]

Paradoxically, the sickle cell trait does not seem to increase the risk of exertional heat stroke.\[67\] However, the risks of heat-related death for all athletes can be mitigated by the sensible precautions of adequate heat acclimatization\[67\] and maintenance of hydration.\[99\] In known sickle cell trait exercisers, intensities of training should be reduced, and longer periods of rest and recovery intervals allowed. Supplemental oxygen should also be readily available, particularly if athletes are exercising at altitude.\[152\] Above all, athletes should be encouraged to set their own pace during training and to cease exercising if symptoms develop.

The complications of sickling have been said to increase eight-fold from the late teens to the late 20s.\[92, 135, 153\] This could reflect an age-related loss of physical condition, or the cumulative influence of such factors as repeated incidents of renal papillary necrosis and poorer regulation of fluid balance; in any event, greater caution should be shown when planning exercise programmes for older athletes with the sickle cell trait.

Nutritional deficiencies, particularly an inadequate intake of zinc, may contribute to occlusive crises in sickle cell trait.\[154\] Vitamin D supplements may also reduce pain and thus contribute to greater physical activity and quality of life in such individuals.\[155\]

Administration of hydrourea appears to improve physical functioning and the health-related quality of life in children with sickle cell disease;\[156, 157\] this drug appears to stimulate production of foetal-type haemoglobin and reduce the production of haemoglobin S.

Finally, those who are providing medical care at an athletic event should become familiar with the warning signs of sickling, keeping a careful watch kept for lower extremity or low back pain, cramp or spasm, muscle weakness and fatigue, difficulty in recovering from exercise, shortness of breath and/or a slow collapse.\[152\]

\textbf{Areas for further research}

There is a need to identify unidentified risk factors, whether genetic or non-genetic, that increase the risk of complications in athletes with the sickle cell trait.\[158, 159\] It would be helpful to explore further why certain sports and certain
forms of physical conditioning are particularly risky. One useful line of enquiry would be to examine how far small but cumulative renal infarcts limit the regulation of hydration in those with the sickle cell trait. Further studies are also needed to determine whether increased levels of adhesion molecules such as the L and P selectins pose a particular risk for sickle cell carriers. Establishment of a national or international registry of athletes with sickle cell trait would help to answer many of these questions.

**Practical implications and conclusions**

The recessive sickle cell trait is much more commonly encountered than the homozygous condition of sickle cell disease. Sickle cell trait has little influence upon morbidity and mortality in normal daily life, but there is some risk of sickling when undertaking very vigorous exercise at high altitude or in the heat with fluid deprivation. In many jurisdictions, infants are now screened for sickle cell trait at birth. This allows the early prescription of antibiotics to curtail the potential risk of bacterial infections. However, information on sickle cell status is not always available when a young adult wishes to engage in sport, and even if such information is available, it remains debatable how far it should influence habitual physical activity. Vigorous controversy continues on the ethics of sickle cell trait screening among adolescents and adults. The US National Athletic Trainers Association concluded that there was a strong case for screening if data had not been collected at birth. In the absence of testing as an infant or the signing of a comprehensive written waiver, the NCAA also began required testing of sickle cell status for Division I competitors in 2010, and this requirement was extended to Division III competitors as of 2014–2015. This was largely a defensive response to litigation from the relatives of an athlete with sickle cell trait who died of exertional rhabdomyolysis during a football practice.

Despite NCAA policy statements, a 2011 survey found that because of costs, few colleges and universities were undertaking comprehensive sickle cell screening. Given the relatively low risk that heterozygotes would develop complications, it was argued that decisions should be based not on the seemingly alarming risk ratios found when contrasting the experience of black and white athletes but upon a careful cost–benefit analysis, looking at the likely number of lives that would be saved by a given policy. Further, it was recommended that the analysis should consider not only the immediate diagnostic costs, but also the likelihood that testing would extend the individual’s life and any negative economic consequences such as denial of participation in a major sports team.

Health economists commonly argue that a procedure can be considered as cost effective if one person-year of life can be saved for less than $50,000. Harmon et al. made such an analysis for collegiate athletes who were participating in NCAA football over the period 2004–2008. The sample was large (2 million athlete-years), and most of the 72 deaths (52/72) were due to trauma; only 5 deaths were associated with sickle cell trait. All of the sickle cell related incidents
were in black players, and all occurred during conditioning rather than competition. One weakness in their calculation was the assumption of a simple but effective $5 test; in fact, a reliable analysis, based on electrophoresis, would more likely cost $150 per athlete. It was further assumed that the chosen test had 100% sensitivity and specificity in preventing death, and that the prevention of sudden exercise-related death would extend an athlete’s life by 50 years. On this basis, the cost of preventing one death over five years among NCAA athletes would range from $40,580 for black footballers to $23,907,984 for competitors in all sports, irrespective of race, and with 50 years of survival, the costs per life-year saved would range from an acceptable $812 for black footballers to an excessive $478,160 for all athletes. If the sensitivity and specificity of the test were to be assured by use of a more sophisticated electrophoretic test, the cost per life-year would range from $24,360 for the black footballer to an astronomic $1,444,800 for all athletes. Another criticism, even with electrophoretic testing, is that the diagnosis is limited to identification of the sickle cell trait, and it fails to detect other genetic characteristics that could modify the risk of sickling.

It has yet to be demonstrated that a targeted diagnosis can indeed reduce the risk of death relative to the adoption of more general precautions regarding exposure to heat, hypoxia and dehydration that would protect all athletes. Currently, diagnosis does not seem to confer great survival benefit, as athletes with known sickle cell trait continue to die during exercise. Further, the negative personal effects of screening must be considered. Potential consequences include a weakened self-image, parental over-protection, a loss of athletic scholarships, limitations upon employment and increased health insurance premiums. Military recruits with sickle cell trait are denied employment as pilots, co-pilots or divers because of potential exposure to hypoxia that could provoke sickling, and many insurance companies have raised premiums for patients with sickle cell trait, despite the demonstration that such individuals have normal morbidity and mortality statistics.

Even enthusiastic proponents have estimated that the universal screening of NCAA Division I student athletes would at most save about seven lives over ten years. A survey conducted by the American Medical Society for Sports Medicine found a preference for a review of medical records and targeted solubility testing focused upon those black athletes who were involved in American football and basketball. Moreover, most respondents indicated that they would still allow sport participation if an athlete or the parents opted out of screening. A case for targeted screening can certainly be made, based on current cost–benefit analyses, but further study is needed to establish that such an approach reduces mortality relative to the alternative option of a more careful management of all athletes, regardless of their genetic background.

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10 Physical activity, benign prostate hyperplasia and prostatitis

Introduction

Physical activity is associated with a clinically useful reduction in the risk of benign prostatic hyperplasia. It is also of interest as a potential palliative treatment in chronic prostatitis.

Benign prostatic hyperplasia is a non-cancerous enlargement of the prostate gland. There is an increased growth of both glandular epithelial cells and stromal cells, with the formation of distinct nodules. As the nodules become larger, they impinge on the urethra, increasing resistance to emptying of the bladder, and the condition is no longer benign due to an augmented risk of urinary and prostate infections. Hyperplasia of the prostate can begin at an age as early as 30 years; 50% of men show some prostatic enlargement by the age of 50 years, and 75% by the age of 80 years. About a half of those affected note significant urinary problems and a quarter require surgical treatment. Because of inflammation and/or an increase in size of the prostate, serum levels of prostate specific antigen may rise, but not to the levels considered diagnostic of prostatic cancer.

The influence of habitual physical activity upon benign prostatic hyperplasia has attracted less attention than its possible role in the prevention of prostate carcinoma (Chapter 11). Nevertheless, a growing number of studies of suggest a reduction of risk with either occupational or leisure activity, possibly because of associated changes in growth hormone levels (Table 10.1). In studying the effects of physical activity, evidence of prostate hypertrophy has been sought in the onset of lower urinary tract symptoms, a need for prostatic surgery, a combination of increased prostate weight, symptoms and a reduced urinary flow rate or the reaching of specific scores on standardized prostate symptom questionnaires.

Occupational activity and prostate hyperplasia

Three investigations have examined the risk of benign prostatic hyperplasia in relation to occupational activity; one found an advantageous trend and the other two a significant reduction of risk for those engaged in heavy, physically demanding employment.
Lacey et al.\(^2\) compared 206 men with prostatic hyperplasia requiring surgery and 471 age-matched controls. All were classified by occupational titles. After co-varying for age, marital status, education, body mass index, energy intake and waist/hip ratio, there was a trend to reduced risk favouring those who were involved in heavy work at age 40–49 years (odds ratio 0.6 \([0.4–0.87]\)), but no benefit was seen with heavy work at 20–29 years of age (odds ratio 1.1, not statistically significant).

Dal Maso et al.\(^3\) studied 1369 histologically confirmed cases of benign prostatic hyperplasia and 1451 hospital controls. After controlling data for age, study centre and the subject’s level of education, a multivariate analysis compared risks between individuals with heavy/strenuous and light occupations. At ages 15–19 and 30–39 years, the odds ratios of 0.6 \((0.4–0.8)\) significantly favoured physically active workers, and at age 50–59 years the odds were still 0.7 \((0.5–0.9)\). Lagiou et al.\(^4\) compared 184 surgically treated cases of benign prostatic hyperplasia with 246 hospital controls. A blinded assessment of the physical demands of occupation was made for each participant. After allowing for the effects of age and educational attainment, the odds ratio for those engaged in heavy work was 0.59, with a significant inverse trend of risk \((p = 0.04)\).

Recreational activity and prostate hyperplasia

Thirteen investigations have related recreational activity to the risk of benign prostatic hyperplasia. One report found an adverse effect of physical activity, and two gave inconsistent results, but the remaining ten reports pointed to a beneficial outcome, statistically significant in seven of the ten trials.

Lacey et al.\(^2\) compared 206 men requiring surgery for benign prostatic hyperplasia with 471 age-matched controls. After allowing for age, marital status, educational attainment, body mass index, energy intake and waist/hip ratio, the two groups were compared in terms of the volume of moderate, vigorous and all physical activity (MET-h/wk). This analysis may have been compromised by co-varying the data for reported energy intake. The results pointed to a significant adverse effect of physical activity at age 20–29 years (odds ratios 1.6 and 1.9 \([p = 0.01]\)), but physical activity at age 40–49 years had no significant effect upon risk (odds ratios 1.4, 1.3).

Hong et al.\(^5\) completed a cross-sectional study of men aged 50–79 years. Three frequencies of physical activity were identified (less than twice per week, three to five times per week and nearly every day). After co-varying the data for age, chronic bronchitis, prostate serum antigen and alcohol consumption, physical activity showed no consistent association with benign prostatic hyperplasia, as defined by the International Prostate Symptom Score (IPSS), prostate volume or urinary flow rate (odds ratios of 1.0, 0.48 and 1.73, respectively). Kristal et al.\(^6\) followed 5667 men for 7 years, to end-points of either surgical treatment or an IPSS score >14 on at least two items. After co-varying for age, ethnicity, smoking, diabetes mellitus and the initial IPSS score, physical
activity was not associated with either the total IPPS score or with the incidence of severe cases requiring surgical attention.

Gann et al.[7] completed a case-control study on participants in the physicians’ health study; 320 individuals who developed benign prostatic hyperplasia over 9 years were compared with 320 who did not. After co-varying data for diastolic blood pressure and alcohol consumption, there was a non-significant trend to a lower odds ratio in individuals active >5 times per week versus those who exercised rarely or never (odds ratio of 0.7 [0.32–1.51]). In this study, hyperplasia was unrelated to blood levels of testosterone, dihydrotestosterone or androstenedione, but there was a trend for increasing risk with oestradiol levels and a weak inverse trend linking risk to oestrone levels. Rohrman et al.[8] studied 1723 twin pairs, collecting information on those who developed moderate or severe urinary tract symptoms; after adjusting for age, smoking, alcohol consumption and zygosity, the odds ratio of moderate or severe urinary tract symptoms showed a suggestive but non-significant odds ratio favouring the more physically active of the twin pairs (0.60 [0.34–1.08]). Rohrman et al.[9] also compared 279 men with lower urinary tract symptoms versus 599 controls. After co-varying for age, ethnicity, waist circumference, smoking and alcohol consumption, the odds ratio of finding at least three components of the metabolic syndrome in those with symptoms of benign prostatic hyperplasia was 1.80 (1.11–2.94); by implication, this group also tended to a low level of habitual physical activity.

Dal Maso et al.[3] compared those who took less than two hours of active recreation per week with those taking more than five hours per week. The odds ratios significantly favoured the more active individuals, with odds ratios of 0.5 (0.4–0.7) at age 15–19 years, 0.6 (0.5–0.8) at 30–39 years and 0.7 (0.5–0.8) at 50–59 years. Joseph et al.[10] used the IPSS to evaluate 708 African-American men. Introducing age, income, smoking, alcohol consumption, heart disease, hypertension and diabetes mellitus as co-variates, the odds ratio favoured those who engaged in sufficient vigorous physical activity to work up a sweat (0.61 [0.44–0.85]). Meigs et al.[11] followed 1709 men initially aged 40–70 years for 9 years, looking for the onset of symptoms or a need for lower urinary tract surgery. After controlling for age, marital status, waist/hip ratio, alcohol consumption, hypertension, heart disease and medication use, a comparison of the most active quartile (energy expenditure >3.6 MJ/day) with the least active (<0.5 MJ/day) yielded an odds ratio of 0.5 (0.3–0.9) for the more active individuals. Platz et al.[12] followed 30,364 health professionals for 8 years; during this time, 1890 underwent surgery for benign prostatic hyperplasia and 1853 developed severe urinary tract symptoms. Comparing the highest versus the lowest quintile of physical activity (>33.8 vs. <3.0 MET-h/wk), after co-varying for age, ethnicity, smoking and alcohol consumption, the odds ratio for those requiring surgery was 0.76 (0.64–0.90), and for those with severe lower urinary tract symptoms it was 0.79 (0.62–1.00). Prezioso et al.[13] questioned 1033 men; after allowing for age, body mass index, smoking and alcohol consumption, a high level of reported physical activity was associated with lower prostate volumes (p = 0.04) and a lower IPSS score (p = 0.008), with a diminished frequency of incomplete bladder
### Table 10.1 Habitual physical activity and a reduced risk of benign prostatic hyperplasia

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Activity</th>
<th>Findings</th>
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<tr>
<td><strong>Occupational activity</strong></td>
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<tr>
<td>Dal Maso et al.[3]</td>
<td>1369 histologically confirmed BPH, 1451 hospital controls</td>
<td>Occupation (heavy vs. light activity)</td>
<td>OR 0.6 (0.4–0.8) age 15–19 and 30–39, 0.7 (0.5–0.9) age 50–59 year</td>
<td>Data controlled for age, study centre and educational level</td>
</tr>
<tr>
<td>Lacey et al.[2]</td>
<td>206 men with BPH requiring surgery, 471 age-matched controls</td>
<td>Occupational titles, heavy vs. sedentary work</td>
<td>OR 1.1 age 20–29 (ns), 0.6 (0.4–0.87) age 40–49 yr</td>
<td>Age, marital status, education, BMI, energy intake, waist/hip ratio</td>
</tr>
<tr>
<td>Lagiou et al.[4]</td>
<td>184 surgically treated cases, 246 hospital controls</td>
<td>Blinded classification of occupations (high vs. low activity)</td>
<td>OR 0.59, p = 0.04 for trend</td>
<td>Age and educational level</td>
</tr>
<tr>
<td><strong>Recreational activity</strong></td>
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</tr>
<tr>
<td>Dal Maso et al.[3]</td>
<td>1369 histologically confirmed BPH cases, 1451 hospital controls</td>
<td>&gt;5h/wk vs. &lt;2 h/wk recreational activity</td>
<td>OR 0.5 (0.4–0.7) age 15–19, 0.6 (0.5–0.8) age 30–39, 0.7 (0.5–0.8) age 50–59</td>
<td>Data controlled for age, study centre and educational level</td>
</tr>
<tr>
<td>Gann et al.[7]</td>
<td>Participants in physicians’ health study; 320 developing BPH over 9-yr follow-up, 320 controls</td>
<td>Exercise (&gt;5 times/wk vs. rarely/never)</td>
<td>OR 0.7 (0.32–1.51)</td>
<td>Co-variates diastolic blood pressure and alcohol consumption</td>
</tr>
<tr>
<td>Hong et al.[5]</td>
<td>Cross-sectional study of 641 men aged 50–79. BPH defined by IPSS, prostate volume and bladder outflow rate</td>
<td>Exercise &lt;2/wk, 3–5/wk, nearly every day</td>
<td>Inconsistent effect of exercise (OR 1.0, 0.48, 1.73 for 3 categories)</td>
<td>Co-variates age, chronic bronchitis, PSA, alcohol consumption</td>
</tr>
<tr>
<td>Joseph et al.[10]</td>
<td>708 African-American men, IPSS</td>
<td>Engaging in vigorous physical activity sufficient to work up a sweat</td>
<td>OR 0.61 (0.44–0.85)</td>
<td>Co-variates age, income, smoking, alcohol consumption, heart disease, hypertension and diabetes mellitus</td>
</tr>
<tr>
<td>Author</td>
<td>Sample</td>
<td>Activity</td>
<td>Findings</td>
<td>Comments</td>
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<tr>
<td>Kristal et al.</td>
<td>5667 men followed for 7 yr, to treatment or IPSS score &gt;14 on 2 items</td>
<td>Sedentary vs. highly active</td>
<td>No effect of physical activity on risk of total or severe BPH symptoms</td>
<td>Co-variied for age, ethnicity, smoking, diabetes mellitus, initial IPSS score</td>
</tr>
<tr>
<td>Lacey et al.</td>
<td>206 men with BPH requiring surgery, 471 age-matched controls</td>
<td>Moderate or vigorous energy expenditure (MET-h/wk). All activity, high vs. sedentary</td>
<td>OR 1.6 age 20–29 (p = 0.01), 1.4 (ns) age 40–49; OR 1.9 age 20–29 (p = 0.01), 1.3 (ns) age 40–49</td>
<td>Age, marital status, educational level, BMI, energy intake, waist/hip ratio</td>
</tr>
<tr>
<td>Meigs et al.</td>
<td>1709 men aged 40–70 followed for 9 yrs, to symptoms or surgery</td>
<td>Top vs. bottom quartile of physical activity, kJ/day</td>
<td>&gt;3.6 vs. &lt;0.6 kJ/day, OR 0.5 (0.3–0.9)</td>
<td>Age, marital status, waist/hip ratio, alcohol consumption, hypertension, heart disease, medication use</td>
</tr>
<tr>
<td>Platz et al.</td>
<td>1890 men who underwent surgery, 1853 with symptoms (8-yr follow-up of 30,364 health professionals)</td>
<td>Highest vs. lowest quintile of physical activity (&gt;33.8 vs. &lt;3.0 MET-h/wk)</td>
<td>OR surgery 0.76 (0.64–0.90), severe symptoms 0.79 (0.62–1.00)</td>
<td>Age, ethnicity, smoking, alcohol consumption</td>
</tr>
<tr>
<td>Prezioso et al.</td>
<td>Lower urinary tract symptoms in 1033 men</td>
<td>Reported physical activity</td>
<td>Physical activity associated with lower frequency of incomplete bladder emptying, repeated urination, intermittence and urgency</td>
<td>Age, BMI, smoking, alcohol consumption</td>
</tr>
<tr>
<td>Rohrman et al.</td>
<td>279 men aged &gt;60 with lower urinary tract symptoms vs. 599 controls</td>
<td>Men with at least 3 components of metabolic syndrome</td>
<td>OR 1.80 (1.11–2.94)</td>
<td>Age, ethnicity, waist circumference, smoking, alcohol consumption</td>
</tr>
<tr>
<td>Rohrman et al.</td>
<td>1723 twin pairs with information on moderate/severe urinary tract symptoms</td>
<td>High vs. low physical activity score</td>
<td>OR 0.60 (0.34–1.08)</td>
<td>Age, smoking, alcohol consumption, zygosity</td>
</tr>
</tbody>
</table>
emptying, repeated urination, intermittence and urgency. Safarinejad\cite{14} completed a cross-sectional survey of 8466 Iranian men over the age of 40 years. Prostate size, urine flow and prostatic symptom score were inversely related to reported physical activity, with a multivariate adjusted odds ratio of 0.4 (p = 0.01). Williams\cite{15} followed 28,612 non-smoking runners for an average of 7.7 years, accumulating 1899 physician-reported cases of benign prostatic hyperplasia. Physical activity levels were categorized in terms of distance run per week and the fastest 10 km times, and by both criteria, after adjusting for age, diet, alcohol consumption and body mass index, a significant odds ratio of ~0.64 favoured those who were the most deeply involved in distance running.

Conclusions regarding benign prostate hyperplasia

The data generally support the idea of benefit from habitual physical activity, with a significant decrease in the risk of benign prostatic hyperplasia in seven studies of recreational activity and two of occupational activity, and positive trends in three recreational and one occupational investigations, against only one study showing an adverse effect and two reports with inconsistent findings. Possibly, beneficial effects arise through a modulation of growth hormones, although such changes would require a substantial volume of endurance activity. Further research on possible mechanisms of benefit is needed as a guide to those planning exercise programmes. Although many authors have included a substantial number of co-variates in their analyses, there remains some possibility that the reported associations between physical activity and a low risk of benign prostatic hyperplasia could have been produced by associated unmeasured variables rather than by physical activity itself.

Table 10.1 continued

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Activity</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safarinejad\cite{14}</td>
<td>Cross-sectional survey of 8466 men aged &gt;40, noting prostate size, urine flow and IPSS</td>
<td>Reported physical activity</td>
<td>OR 0.4 (p = 0.01)</td>
<td>Multivariate adjusted</td>
</tr>
<tr>
<td>Williams\cite{15}</td>
<td>28,612 runners followed for 7.7 yrs, with 1899 physician-reported cases</td>
<td>Distance run/week, fastest 10 km time</td>
<td>OR ~0.64 in terms of distance and times</td>
<td>Age, diet, alcohol consumption, BMI (all non-smokers)</td>
</tr>
</tbody>
</table>

Notes: ns = non-significant; BMI = body mass index; BPH = benign prostate hyperplasia; IPSS = International Prostate Symptom Score; MET = metabolic equivalent; OR = odds ratio; PSA = prostate serum antigen.
Physical activity and chronic prostatitis

Prostatitis is an inflammation of the prostate gland that occurs in a substantial proportion of older men. One review based on 10,617 subjects found a prevalence of 8.2%,\(^1\) and others have set prevalence at 9 to 17%\(^2\). In 90–95% of cases, the prostatitis occurs without obvious bacterial cause. However, chronic prostatitis may result from urinary tract infections that have spread to the prostate gland. If a bacterial infection has developed, early treatment with intravenous antibiotics is required. There is often an enlarged prostate, a back-up of urine into the prostatic tissue, chemical irritation and/or problems with the nerve supply to the lower urinary tract.

Although chronic prostatitis is often treated by a prolonged course of antibiotics, before embarking upon such an intervention it is important to determine the sensitivity of the micro-organisms involved, as they are often resistant to most antibiotics. Treatment may have only limited long-term success, leaving the patient with chronic pelvic pain, depression and a poor quality of life. Given the well-recognized ability of exercise to elevate mood state, there is interest in the symptomatic benefits that affected individuals can derive from increased habitual physical activity, even if the chronic prostatitis is not entirely remedied.

Giubilei et al.\(^3\) recruited 231 men aged 20–50 years who had chronic prostatitis and associated complaints of pelvic pain. A half of the group was assigned to an aerobic training programme (40 minutes of walking at 70–80% of maximal heart rate 3 times/week) and a half to a placebo stretching and motion programme. At 16 weeks, those assigned to the aerobics programme had a more favourable score than the controls in terms of the National Institutes of Health prostatitis symptom index, quality of life and pain scores as assessed by a visual analogue. However, there are large placebo effects associated with most methods of treating prostatitis\(^4\) and the intensity and duration of effort used in this study seems rather low to have induced any substantial secretion of mood-elevating endorphins. Further studies are thus needed before the symptomatic benefits of aerobic activity can be asserted with confidence.

Areas for further research

Evidence suggesting a reduced risk of benign prostatic hyperplasia in physically active individuals is fairly consistent, but further research on mechanisms is needed. Many authors have included a substantial number of co-variates in their analyses, and there remains some possibility that the apparent benefits of an active lifestyle could have been produced by associated but unmeasured variables.

Given the lack of effective long-term treatments for chronic prostatitis, there is a need to repeat and expand the observations of Giubilei et al.\(^3\) suggesting that aerobic exercise may offer an effective method of alleviating symptoms and to ascertain mechanisms. Is aerobic activity simply inducing a general elevation of mood state or is there some more fundamental basis for the enhanced quality of life among exercisers?
Practical implications and conclusions

There is growing evidence that regular physical activity is helpful in reducing the risk of benign prostatic hyperplasia, with its attendant complications. The mechanisms of benefit remain to be elucidated. However, there is little epidemiological evidence suggesting that moderate physical activity has any adverse effect upon the health of the prostate. Thus, the probable favourable impact of exercise upon the course of prostate hyperplasia seems yet one more reason to recommend regular physical activity to sedentary populations. The pelvic pain of chronic prostatitis can be a major cause of poor health, but the mood-elevating effects of prolonged endurance exercise could offer a helpful symptomatic treatment for this problem.

References


11 Physical activity and prostate cancer

Introduction

This final chapter looks at the value of physical activity in the prevention and management of prostate cancer. Prostate cancer is second only to lung cancer as a cause of cancer morbidity and mortality in male patients. Known modifiable risk factors include the level of male hormones, diet, obesity, smoking, alcohol consumption, sexually transmitted diseases, vasectomy and occupational exposures to toxins such as cadmium and agricultural pesticides.[1] There is also growing evidence of a reduced risk of prostate cancer in physically active individuals. Potential beneficial actions of exercise could include the prevention of obesity, an increased natural killer cell count, a greater ability to counter oxidant stress and the reduction in testosterone levels that is frequently seen in endurance competitors.[2] Exercise programmes also play an important role in management following the successful treatment of prostate cancers by androgen deprivation therapy and/or surgery.

Role of physical activity in preventing prostate cancer

A systematic review[3] noted that early studies were retrospective; two reports found an association between heavy occupational work and the risk of prostate cancer, and a third report found an increased risk among those who had once been enrolled in university athletic teams. Between 1989 and 2001, 13 cohort studies used incident prostate cancer as the end-point. Of these, nine showed an association between exercise and a decreased risk of prostate cancer. Generally, these studies allowed for several important co-variates. Five of 11 case-control studies conducted between 1988 and 2002 also reported an association between high levels of physical activity and a decreased risk of prostatic cancer. In all, 16 of 27 studies through the year 2002 reported a 10–30% reduction of risk in the most active men, with a statistically significant benefit in 9 of the 16 analyses favouring the most active individuals. It was suggested that the inconsistency of trial outcomes reflected in part the weakness in physical activity assessments and in part issues in the diagnosis of prostatic cancer (such as reliance on increased levels of prostate-specific antigens rather than on a histological confirmation of
clinically important disease). A further potential difficulty complicating occupational analyses is the association between heavy work and a lower socio-economic status, with less frequent medical examinations and thus a lesser likelihood of an early diagnosis of prostate cancer.\(^4\)

Given the practical importance of containing prostate cancer, many further investigations have now looked at the preventive value of regular physical activity. Despite some duplication of reports, there have now been around 80 investigations. As with cancer in other parts of the body, associations have been sought with the physical demands of occupation, reported leisure activity (sometimes in the same population sample as in an occupational study), sport involvement and attained levels of physical fitness. This considerable volume of research encourages belief in the value of exercise, but we still lack incontrovertible proof of protection from a physically active lifestyle.

### Occupational activity and risk of prostate cancer

In occupational analyses, a worker has typically maintained a relatively known level of physical activity at work for many years, including the period 10–30 years prior to diagnosis, when carcinogenesis is likely to have begun. The intensity of occupational effort has generally been moderate, but this activity has usually been maintained for four to five hours per day, thus accumulating a substantial total energy expenditure over the course of a working week. However, heavy physical employment has sometimes involved also exposure to industrial carcinogens. Moreover, there have often been large socio-economic differences between heavy and sedentary workers, influencing the employee’s area of residence and issues of lifestyle such as diet, smoking habits and alcohol consumption. Some (but not all) investigations have attempted to allow for such confounding influences by covariance analysis. In recent years, mechanization and automation have reduced the energy costs of what were once physically demanding occupations, and this limits the possibility of future studies based upon the individual’s job classification.

### Retrospective and prospective cohort studies

There have been at least 19 cohort studies relating occupation to the risk of prostate cancer (Table 11.1). The findings are sometimes nuanced, with differing responses in sub-groups identified post hoc, but the conclusions from seven investigations have been essentially negative, six have identified a possible favourable trend, and six have demonstrated a significant reduction of risk of prostate cancer in the most active workers.

Among the seven negative reports, Paffenbarger et al.\(^5\) followed 2665 longshoremen for 12 years, during which time 30 of the group developed a prostate cancer. Despite the small number of neoplasms, relative risks of carcinogenesis were classified in relation to four levels of work (heavy, moderate, light-to-moderate and light). Age-adjusted risk ratios showed no significant inter-
Table 11.1  Physical demands of occupation and the risk of developing prostate cancer

<table>
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<td><strong>Cohort studies</strong></td>
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<tr>
<td>Albanes et al. [11]</td>
<td>95 cases of PC in 5141 men over 10-yr follow-up</td>
<td>Very active vs. quite inactive</td>
<td>RR 1.3 if quite inactive (ns)</td>
<td>Age adjusted</td>
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<tr>
<td>Clarke &amp; Whittemore [12]</td>
<td>5377 men followed for 17–21 yr, 201 cases of PC</td>
<td>Very active vs. inactive</td>
<td>RR for inactive 1.75 (1.12–2.67), p = 0.05 for trend (effect greater in African-Americans)</td>
<td>Adjusted for age, education, ethnicity and family history</td>
</tr>
<tr>
<td>Grotta et al. [13]</td>
<td>13,109 Swedish men followed for 13 yr, 904 cases of PC</td>
<td>Low vs. high level of occupational activity</td>
<td>HR 0.81 (0.61–1.07, ns)</td>
<td>Adjusted for age, education, smoking, BMI, alcohol consumption, diabetes mellitus</td>
</tr>
<tr>
<td>Hartman et al. [6]</td>
<td>29,133 men followed for up to 9 yr, 317 cases of PC</td>
<td>Sedentary vs. walkers/ lifters vs. heavy labourers</td>
<td>RR 1.0, 0.6, 0.8, 1.2 (ns)</td>
<td>Adjusted for age, urban living, smoking, benign hyperplasia</td>
</tr>
<tr>
<td>Hrafnkelsdóttir et al. [14]</td>
<td>24-year follow-up of 8221 Icelandic men</td>
<td>Occupation involves mostly sitting vs. standing vs. on the move</td>
<td>HR 1.0, 0.97, 0.91 (0.79–1.06, ns)</td>
<td>Adjusted for age, height, BMI, diabetes, family history, education, medical check-ups</td>
</tr>
<tr>
<td>Hsing et al. [15]</td>
<td>264 cases of PC, occupational title</td>
<td>Sitting time &lt;2h/d vs. &gt;6h/d, intensity of physical activity (&lt;8, &gt;12 kJ/min)</td>
<td>SIR 0.94 vs. 1.23, p = 0.14; SIR 1.23 vs. 0.92, p = 0.06</td>
<td>No co- variates</td>
</tr>
<tr>
<td>Johnsen et al. [7]</td>
<td>127,923 men followed for 8.5 yr; 2458 cases of PC</td>
<td>Sitting, standing or manual work; inactive, moderately inactive, moderately active, active</td>
<td>Occupational activity unrelated to PC</td>
<td>Adjusted for leisure activity, height, weight, marital status and education</td>
</tr>
<tr>
<td>Author</td>
<td>Sample</td>
<td>Activity measure</td>
<td>Findings</td>
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<tr>
<td>Lund-Nielsen et al.</td>
<td>22,895 Norwegian men followed for 9.3 yr, with 644 cases of PC</td>
<td>High vs. low level of occupational activity</td>
<td>No effect on PC</td>
<td>Multivariate adjusted</td>
</tr>
<tr>
<td>Norman et al.</td>
<td>3 cohorts of 43,836, 28,702 and 19,670 prostate cancers</td>
<td>Occupational titles (sedentary to very high level of activity)</td>
<td>RR for sedentary groups 1.11, 1.10 and 1.11 (p = 0.0001)</td>
<td>Adjusted for age, year of follow-up and area of residence</td>
</tr>
<tr>
<td>Orsini et al.</td>
<td>45,887 men followed for 8 yr, 2735 incident cases of PC</td>
<td>4 categories of occupation (mostly sitting vs. heavy manual)</td>
<td>RR = 0.72 (0.57–0.90) p for trend 0.007; effects smaller for advanced and fatal cancers</td>
<td>Adjusted for leisure activity, age, smoking, alcohol consumption, education, diet, energy intake, waist/hip ratio, diabetes mellitus</td>
</tr>
<tr>
<td>Paffenbarger et al.</td>
<td>2665 longshoremen followed for 12 yr, 30 cases of PC</td>
<td>Heavy, moderate, light-to-moderate, light work</td>
<td>Inconsistent RR (1.0, 0.14, 1.41, 1.54, ns)</td>
<td>Age adjusted, small number of cases</td>
</tr>
<tr>
<td>Parent et al.</td>
<td>449 incident cases of PC</td>
<td>High vs. low lifetime occupational activity (METs)</td>
<td>OR 0.54 (0.31–0.95) favours active work</td>
<td></td>
</tr>
<tr>
<td>Putnam et al.</td>
<td>101 cases of PC in 1572 initially cancer-free men followed for 4 yr</td>
<td>Very active, moderately active or inactive at work</td>
<td>Risk of PC unrelated to occupational activity</td>
<td>Adjusted for age</td>
</tr>
<tr>
<td>Severson et al.</td>
<td>8006 Japanese men on Oahu; 205 cases of PC</td>
<td>Self-estimate of job energy demands</td>
<td>Risk of PC unrelated to job activity</td>
<td></td>
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<tr>
<td>Thune &amp; Lund</td>
<td>220 cases of PC in 53,242 Norwegians followed for 16.3 yr</td>
<td>4-level classification of work, sedentary to heavy manual</td>
<td>RR for heavy manual work 0.81 (0.50–1.30)</td>
<td>Age, BMI, geographic region of residence</td>
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<tr>
<td>Vena et al.</td>
<td>430,000 men in Washington State, 8116 deaths from PC</td>
<td>4-level classification of occupational activity</td>
<td>PMR low = 109, high = 93 (p = 0.05)</td>
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### Table 11.1 continued

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<td>Zeegers et al. [21]</td>
<td>58,279 men aged 55–69 yr, 1386 cases of PC over 9.3 yr</td>
<td>Occupational activity (energy expenditure, sitting time)</td>
<td>Unrelated to PC</td>
<td>Adjusted for age, alcohol consumption, BMI, energy intake, family history, education</td>
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<tr>
<td>Case-control studies</td>
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<tr>
<td>Bairati et al. [22]</td>
<td>64 cases of PC, 5456 cases of benign prostate hyperplasia aged &gt;45 yr</td>
<td>Ever had sedentary job or light work; 0, 1–49%, &gt;50% of career spent in sedentary or light work</td>
<td>OR 2.0 (1.1–3.6); 1.0, 1.7, 2.8 (trend, p = 0.007)</td>
<td>Adjusted for age, education, total energy intake, smoking, use of vitamin supplements</td>
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<tr>
<td>Brownson et al. [23]</td>
<td>Missouri cancer registry, 2878 cases of PC, controls are cancers at other body sites</td>
<td>High vs. moderate vs. low occupational activity</td>
<td>OR 1.0, 1.1, 1.5 (1.2–1.8), p &lt;0.01</td>
<td>Adjusted for age, smoking</td>
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<td>Doolan et al. [24]</td>
<td>1436 cases of PC, 1349 matched controls</td>
<td>Finnish job matrix, physical workload tertiles</td>
<td>OR highest tertile 1.15 (0.95–1.40, ns)</td>
<td>Adjusted for age, family history, economic resources</td>
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<tr>
<td>Dosemeci et al. [25]</td>
<td>27 cases PC, 2127 hospital controls</td>
<td>&lt;8 kJ/min vs. &gt;12 kJ/min; active at work &lt;2h/day vs. &gt; 6h/day</td>
<td>OR 5.0 (1.1–31.7); OR 3.4 (1.1–10.6)</td>
<td>Adjusted for age and smoking; very small sample</td>
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<tr>
<td>Friedenreich et al. [26]</td>
<td>988 incident cases of PC, 1063 population controls</td>
<td>Energy expenditure &lt;74.2 vs. &gt;161.9 MET-h/ wk</td>
<td>OR 0.90, 0.60–1.22 (ns)</td>
<td>Adjusted for age, region, education, BMI, waist/hip ratio, energy intake, alcohol consumption, family and medical history</td>
</tr>
<tr>
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<tr>
<td>Hosseini et al. [27]</td>
<td>137 cases of PC, 137 neighbourhood controls</td>
<td>Walking to work (&lt;10 vs. &gt;10 h/wk), intensity of work (inactive/moderately active vs. highly active)</td>
<td>OR 0.7 (0.4–1.2) for longer walk (ns); OR = 6.7 (1.3–35.1) for highly active work (p = 0.02)</td>
<td>Multivariate adjusted</td>
</tr>
<tr>
<td>Krishnadasan et al. [28]</td>
<td>362 cases of PC, 1805 matched controls</td>
<td>Low vs. moderate vs. high occupational energy expenditure</td>
<td>OR 0.63 (0.40–1.00, p = 0.06 for trend)</td>
<td>Adjusted for matching variables, pay, trichloroethylene exposure</td>
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<tr>
<td>Lacey et al. [29]</td>
<td>258 cases of PC, 471 age-matched controls</td>
<td>Sedentary, moderate or high occupational energy expenditures at 20–29 yr, 40–49 yr or 12 yrs ago</td>
<td>RR 1.1 (0.7–1.7), 1.3 (0.8–1.9), 0.9 (0.5–1.8) favouring sedentary group</td>
<td>Adjusted for age, marital status, education, BMI, energy intake, waist/hip ratio</td>
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<tr>
<td>Lagiou et al. [30]</td>
<td>320 histologically confirmed PC, 246 hospital controls</td>
<td>Low, medium, high level of occupational activity</td>
<td>OR 0.69 (0.40–1.22, ns) for physically demanding occupation</td>
<td>Adjusted for age and education</td>
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<tr>
<td>Le Marchand et al. [31]</td>
<td>452 cases from Hawaii tumour registry, 899 population controls</td>
<td>Time spent in sedentary jobs (0–&gt;54%)</td>
<td>No effect if &lt;70 yrs; if &gt;70 yrs, OR 0.6 (0.4–1.0, p for trend = 0.07)</td>
<td>Adjusted for age and ethnicity</td>
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<tr>
<td>Sass-Kortak et al. [32]</td>
<td>760 PC cases, 1632 telephone controls</td>
<td>Quartiles of lifetime occupational activity</td>
<td>OR 1.33 for active workers (1.02–1.74) p for trend = 0.18</td>
<td>Adjusted for age, family history, sunlight exposure</td>
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<tr>
<td>Strom et al. [33]</td>
<td>176 cases of PC in Mexican-Americans, 176 controls</td>
<td>None/low vs. moderate/high energy demands of work</td>
<td>Reduced risk in active (OR 0.46, 0.28–0.77, p = 0.003)</td>
<td>Adjusted for age, education, screening, exposure to agricultural chemicals</td>
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category trend (1.0, 0.14, 1.41, 1.54, ns). Hartman et al.\[6\] observed 29,133 men for up to 9 years. There were 317 incident cases of prostate cancer in their study. Risk was contrasted between those who were employed in sedentary occupations and those whose jobs required walking, combinations of walking and lifting, or heavy labour. After adjusting data for age, urban living, smoking and a history of benign prostatic hyperplasia, the relative risk of prostate cancer showed no association with the physical demands of work (respective risk ratios of 1.0, 0.6, 0.8 and 1.2). Johnsen et al.[7] followed 127,923 men for an average of 8.5 years, accumulating 2458 cases of prostate cancer. Data were controlled for leisure activity, height, body mass, marital status and educational attainment. The individual's occupational activity (whether classed as sitting, standing or manual work, or as inactive, moderately inactive, moderately active and active) bore no relationship to the risk of prostate cancer, although advanced prostate cancer was seen less frequently in those with a high level of occupational activity (p = 0.024). Lund-Nielsen et al.[8] observed 22,895 Norwegian men for 9.3 years, finding 644 incident cases of prostate cancer. Occupational activity was classed as high or low, and after adjustment for co-variates, there was no association between energy expenditures at work and prostate cancer. Putnam et al.[9] found 101 cases of prostate cancer in a sample of 1572 initially cancer-free men who were followed for 4 years. In this study, employment was classified as very active, moderately active or inactive, but after controlling for age, the incidence of

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<tr>
<td>Villeneuve et al.[34]</td>
<td>1623 histologically confirmed cases of PC, 1623 controls</td>
<td>4-level classification of work (sitting to strenuous)</td>
<td>Significant benefit from activity in teens or early 20s (OR 0.6, 0.4–0.9), ns 30s, 50s or 2 yr before interview</td>
<td>Adjusted for age, area of residence, smoking, alcohol consumption, BMI, diet, income, family history</td>
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<tr>
<td>Wiklund et al.[35]</td>
<td>1449 incident cases of PC, 1118 population controls</td>
<td>MET-h/day of lifetime occupational activity, &lt;11.8 to &gt;19.8</td>
<td>OR 0.84 (0.61–1.15), ns; trend to benefit from active employment</td>
<td>Adjusted for age, region, education, BMI, alcohol consumption, family history, diabetes mellitus, energy intake</td>
</tr>
</tbody>
</table>

Notes: ns = not significant; HR = hazard ratio; PC = prostate cancer; OR = odds ratio; PMR = proportionate mortality ratio; RR = relative risk or rate ratio; SIR = standardized incidence ratio
prostate cancer was unrelated to the energy demands of work. Severson et al.\cite{10} questioned 8006 Japanese men living on the island of Oahu, Hawaii; 205 had developed prostate cancer. A self-estimate of the physical demands of employment was unrelated to their risk of this condition. Zeegers et al.\cite{21} followed 58,279 Dutch men initially aged 55–69 years over a period of 9.3 years, encountering 1386 cases of prostate cancer. Occupational activity was classed in terms of energy expenditure and sitting time, and after allowance for age, alcohol consumption, body mass index, total energy intake, family history and education, no association was found between the physical demands of occupation and the risk of prostate cancer.

Of the 6 investigations pointing to a possible trend, Albanes et al.\cite{11} observed 95 cases of prostate cancer in 5141 men who had been followed for an average of 10 years. Comparing those who very active with those who were quite inactive at work, the age-adjusted relative risk for the sedentary employees was 1.3, but given the relatively small total number of cases, the trend to a 30% disadvantage was not statistically significant. Grotta et al.\cite{13} followed 13,109 Swedish men for a total of 13 years, finding 904 cases of prostate cancer. There was a weak and non-significant trend to benefit from a high level of occupational activity after adjusting data for age, education, smoking, body mass index, alcohol consumption and diabetes mellitus (a hazard ratio for the physical workers of 0.81 [0.61–1.07]). Hrafnkelsdóttir et al.\cite{14} carried out a 24-year follow-up of 822 Icelandic men. Occupational activity was classed as mostly sitting, standing or “on the move”. The hazard ratios, adjusted for age, height, body mass index, diabetes mellitus, family history, education and medical check-ups showed a weak trend favouring those who were engaged in more demanding work (respective values of 1.0, 0.97 and [for the most active group] 0.91 [0.79–1.06, ns]). Hsing et al.\cite{15} obtained occupational titles on 264 cases of prostate cancer, calculating standardized incidence ratios (SIR) for prostate cancer in relation to both the anticipated sitting time and energy expenditures at work, apparently without using any co-variates. The SIR was 0.94 for those who were seated less than 2 hours per day, compared with 1.23 for those sitting longer than 6 hours per day (p = 0.14), and in terms of estimated energy costs the SIR was 1.23 for those with work-place expenditures averaging <8 kJ/min, compared with 0.92 for those expending >12 kJ/min (p = 0.06). Thune and Lund\cite{19} examined 220 cases of prostate cancer in 53,242 Norwegians who had been followed for an average of 16.3 years. A four-level classification of the physical demands of occupation (ranging from sedentary to heavy manual) found a trend to an advantageous risk ratio (0.81 [0.50–1.30]) in those who were engaged in heavy physical work, after adjusting data for age, body mass index and geographic region of residence.

Among the 6 investigations observing statistically significant evidence of benefit, Clarke and Whittemore\cite{12} followed 5377 men for 17–21 years, accumulating 201 incident cases of prostate cancer. Controlling data for age, educational attainment, ethnicity and family history, the relative risk of inactive vs. active employment was 1.75 (1.12–2.67, p = 0.05 for a trend), apparently with an even greater benefit to heavy workers in the African-American subset of the sample.
Norman et al. [16] examined data for 3 cohorts of 43,836, 28,702 and 19,670 patients with prostate cancer. Occupational titles were categorized from sedentary to a very high level of physical activity, and with adjustment of data for age, year of follow-up and area of residence, a small but highly significant increase of relative risk was seen in sedentary individuals (respective risks for the 3 cohorts of sedentary individuals, 1.11, 1.10 and 1.11 [p = 0.0001]). Orsini et al. [17] followed 45,887 men for 8 years, accumulating 2735 incident cases of prostate cancer. Four categories of employment were recognized (ranging from mostly sitting to heavy manual work). After allowing for leisure activity, age, smoking, alcohol consumption, educational attainment, diet, energy intake, waist/hip ratio and diabetes mellitus, the risk ratio favoured active workers (0.72 [0.57–0.90], p for trend = 0.007). However, the advantage was smaller for individuals with advanced or fatal cancers. Parent et al. [18] questioned 449 incident cases of prostate cancer on their lifetime occupational energy expenditures (high vs. low, estimated in METs); the odds ratio for this sample strongly favoured those in active employment (0.54 [0.31–0.95]). Vena et al. [20] obtained data on 430,000 men in Washington State, including 8116 men who died from prostate cancer. A four-level classification of occupational activity was made, and although the findings were not altogether consistent from decade to decade and did not show clear trends, a comparison of the overall proportional mortality between those with low (109) and high (93) occupational demands showed a clear advantage to the heavy workers (p <0.05).

**Case-control studies**

Of 15 case-control studies, 5 found either no effect or a trend to a higher risk of prostate cancer in individuals with heavy employment. Doolan et al. [24] compared 1436 cases of prostate cancer with 1349 matched controls, using the Finnish job matrix to classify occupational workload into tertiles of physical demand. After adjusting for age, family history and economic resources, the odds ratio for developing prostate cancer tended to be higher in those individuals with the highest energy expenditures (odds ratio 1.15 [0.95–1.40]). Hosseini et al. [27] related 137 cases of prostate cancer to 137 neighbourhood controls. Although a binary classification of the time study participants spent walking to work (<10 vs. >10 h/wk) trended to a reduce risk for those with a longer active commute (odds ratio 0.7 [0.4–1.2] ns), a comparison between those with inactive or moderately active employment and those with highly active work yielded a large multivariate-adjusted odds ratio favouring those with the physically less demanding work (6.7 [1.3–35.1] [p = 0.02]). Lacey et al. [29] compared 258 cases of prostate cancer with 471 age-matched controls. Occupational energy expenditures (classed as sedentary, moderate or high) yielded similar findings whether activity data were examined for the subjects at ages 20–29, 40–49 or 12 years prior to preparation of their report; after adjusting findings for age, marital status, educational attainment, body mass index, energy intake and waist/hip ratio, risk ratios 1.1 (0.7–1.7), 1.3 (0.8–1.9) and 0.9 (0.5–1.8) tended to favour the
sedentary vs. the highly active group. Sass-Kortak et al.\[32\] compared 760 prostate cancer cases with 1632 controls gleaned from telephone listings. Quartiles of lifetime occupational activity adjusted for age, family history and sunlight exposure showed an adverse experience in the most active workers (odds ratio of prostate cancer 1.33 [1.02–1.74], \(p\) for trend 0.18). Friedenreich et al.\[26\] compared data for 988 incident cases of prostate cancer with 1063 population controls in terms of the energy expended at work (less than 74.2 vs. more than 161.9 MET-h/wk). After controlling for age, region, educational attainment, body mass index, waist/hip ratio, energy intake, alcohol consumption, family and medical history, there was no association between prostate cancer and the physical demands of work.

Of the 3 reports with trends suggestive of benefit, Lagiou et al.\[30\] assigned 320 histologically confirmed cases of prostate cancer and 246 hospital controls between 3 categories of occupational activity (low, medium or high). Following data adjustment for age and educational attainment, there was a non-significant trend (odds ratio 0.69 [0.40–1.22]) suggesting protection from physically demanding work. Le Marchand et al.\[31\] found 452 cases of prostate cancer in the Hawaii tumour registry. The portion of the lifespan spent in sedentary jobs (from 0% to more than 54%) was compared with that seen in 899 population controls. After adjustment of data for age and ethnicity, the risk of prostate cancer was unaffected by the duration of sedentary employment in those under the age of 70 years, but among those older than 70 years there was a trend for a decreased risk in those with more active jobs (an odds ratio of 0.6 [0.4–1.0, \(p = 0.07\) for trend]). Wiklund et al.\[35\] compared 1449 incident cases of prostate cancer with 1118 population controls; the average intensity of lifetime occupational activity was classified over a range from less than 11.8 to more than 19.8 MET-h/day, and there was a weak trend to benefit among those with physically demanding occupations (odds ratio 0.84 [0.61–1.15], ns) after controlling data for age, region, educational attainment, body mass index, alcohol consumption, family history, diabetes mellitus and total energy intake.

Seven case-control studies found a significant association of benefit with physically active employment. Bairati et al.\[22\] compared 64 cases of prostate cancer with 5456 cases of benign prostate hyperplasia. After adjusting data for age, educational attainment, total energy intake, smoking and the use of vitamin supplements, the odds ratio associated with ever having had a sedentary job or light work was 2.0 (1.1–3.6). Classifying subjects on the basis of spending 0%, 1–49% or >50% of one’s career in sedentary or light work, the respective odds of developing prostate cancer were 1.0, 1.7 and 2.8 (trend, \(p = 0.007\)). The benefit was even greater for those whose longest-held job had involved high or very high rates of energy expenditure (an odds ratio of 0.2 [0.1–0.7] for a highly active vs. a sedentary job). Brownson et al.\[23\] drew 2878 cases of prostate cancer from the Missouri cancer registry, comparing the reported level of occupational activity (a high vs. a moderate vs. a low physical demand) with that of controls having other types of cancer. Respective odds ratios for the 3 categories of work, after controlling for age and smoking, were 1.0, 1.1 and 1.5 (1.2–1.8), with a
statistically significant trend favouring the more active employees (p < 0.01). Darlington et al. [50] drew a comparison between the experience of 752 cases of prostate cancer aged 50–84 years who had been selected from the Ontario cancer registry, and that of telephone listing controls. Subjects were asked about undertaking strenuous occupational activity in their mid-teens, early 30s and early 50s. After adjusting data for age, educational attainment, body mass index, family history and occupation, strenuous physical activity by men in their 50s was associated with a reduced risk of prostate cancer (an odds ratio of 0.8 [0.6–0.9]), but benefit was not statistically significant if the heavy work had been performed during the other age periods. Dosemeci et al. [25] contrasted occupations between a small sample of 27 cases of prostate cancer and 2127 hospital controls; after adjusting for age and smoking habits, significant adverse odds were found for men having a low energy expenditure at work (less than 8 kJ/min vs. more than 12 kJ/min) and for those spending a low proportion of their working day in physical activity (less than two hours vs. more than six hours) with respective odds ratios of 5.0 (1.1–31.7) and 3.4 (1.1–10.6). In a nested case-control study, Krishnadasan et al. [28] rated occupational energy expenditures as low, moderate or high in 362 cases of prostate cancer and 1805 matched controls. Adjusting data for matching variables, pay and trichlorethylene exposure, there was a strong trend for reduced risk in the more active workers (an odds ratio of 0.63 [0.40–1.00, p = 0.06 for trend]). The benefit was statistically significant for aerospace workers, but not for radiation workers, although the reason for the discordance of outcome between the two types of employment was not explained. Strom et al. [33] compared 176 cases of prostate cancer in Mexican-Americans, with data for 176 matched controls. Occupational activity was rated as none/low vs. moderate/high, and after allowing for the effects of age, educational attainment, cancer screening and exposure to agricultural chemicals, a reduced risk was seen in those with active occupations (an odds ratio of 0.46 [0.28–0.77], p = 0.003). Villeneuve et al. [34] compared 1623 histologically confirmed cases of prostate cancer with 1623 controls. After adjusting data for age, area of residence, smoking, alcohol consumption, body mass index, diet, income and family history, a four-level classification of occupational demand (ranging from sitting to strenuous work) found significant benefit was associated with heavy physical activity in the teens or early 20s (an odds ratio of 0.6, [0.4–0.9]), with parallel but non-significant trends in the 30s, 50s and two years before being interviewed.

Leisure activities and risk of prostate cancer

Patterns of recent leisure activity could theoretically be ascertained by interview or by the use of a personal monitor such as an accelerometer, but because large number of subjects have been involved in many studies of prostate cancer, recourse has usually been to physical activity questionnaires. These instruments have limited accuracy and usually examine current or recent activity, rather than an individual’s behaviour 10–30 years previously, when carcinogenesis began.
**Retrospective and prospective cohort studies**

Of 28 retrospective and prospective cohort studies (Table 11.2), 1 found a strong adverse (but not statistically significant) trend, and in a further 11 there was no association between physical activity and the risk of prostate cancer; 12 reports found trends suggesting some benefit, and 4 found statistically significant evidence of a favorable outcome for active individuals.

Cerhan et al.\[54\] found a strong trend to an adverse effect in rural Iowa, with a relative risk of 2.7 (0.87–9.9) in those members of a small sample of 71 cases of prostate cancer who reported engaging in vigorous physical activity. The measure of physical activity used in this study was relatively crude, and although data were adjusted for age, body mass index and smoking, no information was obtained on occupational activity or exposure to agricultural toxins. Among the 11 investigations with neutral findings, Crespo et al.\[36\] followed a group of 9824 men initially aged 35–79 years until their death. Data were adjusted for age, educational attainment, urban residence, smoking and body mass index, and no relationship was found between the likelihood of death from prostate cancer and physical activity as assessed by the Framingham index. Giovannucci et al.\[37\] observed 47,452 health professionals for 8 years, finding 1362 incident cases of prostate cancer. Leisure activity, graded from 1 to 46.8 MET-h per week, was adjusted for age, vasectomy, diabetes mellitus, smoking, energy intake and diet. No significant relationship to prostate cancer was seen, except for a suggestion of less metastatic activity in the more active individuals. Grotta et al.\[13\] followed 13,109 Swedish men for 13 years, during which time 904 developed prostate cancer. After co-varying data for age, educational attainment, smoking, body mass index, alcohol consumption and diabetes mellitus, the hazard ratio (0.93 [0.76–1.14, ns]) showed little tendency to a lower risk in those with greater leisure activity. Johnsen et al.\[7\] followed 127,923 men for 8.5 years, accumulating 2458 cases of prostate cancer. With adjustment of data for occupational activity, height, body mass, marital status and education, no association was seen between quartiles of leisure activity (ranging from less than 25 to more than 71 MET-h/wk) and the risk of prostate cancer. Moreover, unlike the occupational data, no significance was seen when the analysis focused simply on the risk of advanced tumours. Lee et al.\[40\] made one of several examinations of their data on the leisure activity of Harvard alumni, using a questionnaire to estimate quartiles of weekly habitual physical activity (ranging from less than 4.2 to more than 12.6 MJ) at entry to the study. After allowing for age, body mass index, smoking, alcohol consumption and family history, prostate cancer was found to be unrelated to either the total weekly energy expenditure or the volume of vigorous physical activity. Littman et al.\[41\] studied 34,757 men who were initially aged 50–76 years, finding 583 incident cases of prostate cancer. An exhaustive study of leisure behaviour looked at MET-h/wk of physical activity, typical walking pace, stair climbing, the amount of high intensity activity and activity performed at earlier ages. Controlling for family history, body mass index and income, none of these analyses found any association with prostate cancer, except in a sub-group over
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<tbody>
<tr>
<td>Albanes et al.</td>
<td>95 cases of PC in 5141 men over 10 yr follow-up</td>
<td>Much vs. little or no recreational exercise</td>
<td>RR for inactive 1.8 (1.1–3.3), p = 0.02 for trend</td>
<td>Age-adjusted</td>
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<tr>
<td>Cerhan et al.</td>
<td>20-yr follow-up of 1050 men initially aged 73.5 yr and cancer free,</td>
<td>5-question assessment of physical activity (vigorous, moderately active or inactive)</td>
<td>Risk relative to non-cases: Inactive RR = 1.0, Moderate = 1.9 (0.5–6.5), Vigorous = 2.7 (0.7–9.9)</td>
<td>Adjusted for age, BMI, smoking; no information on occupational activity or agricultural chemicals</td>
</tr>
<tr>
<td>Clarke &amp; Whittemore</td>
<td>5377 men followed for 17–21 yr, 201 cases of PC</td>
<td>Much vs. little or none</td>
<td>RR for inactive 1.17 (ns)</td>
<td>Adjusted for age, education, ethnicity and family history</td>
</tr>
<tr>
<td>Crespo et al.</td>
<td>9824 men initially aged 35–79 yr followed for mortality</td>
<td>Framingham index (quartiles)</td>
<td>No relationship between physical activity and prostate deaths</td>
<td>Adjusted for age, education, urban residence, smoking, BMI</td>
</tr>
<tr>
<td>Giovannucci et al.</td>
<td>47,452 health professionals followed for 8 yr, 1362 incident cases of PC</td>
<td>Leisure activity, 1 vs. 46.8 MET-h/wk</td>
<td>No significant relationship except suggestion of less metastatic activity with vigorous intensity exercise</td>
<td>Adjusted for age, vasectomy, diabetes mellitus, smoking, energy intake, diet</td>
</tr>
<tr>
<td>Giovannucci et al.</td>
<td>47,620 health professionals, 14 yr follow-up, 2892 incident cases of PC</td>
<td>Vigorous physical activity, 0 vs &gt;29 MET-h/wk</td>
<td>No relationship for all subjects; if &gt;65yr, OR for advanced cancer 0.33 (0.17–0.62)</td>
<td>Age, BMI, smoking, height, family history, diabetes mellitus, ethnicity, non-vigorous activity, energy intake and diet</td>
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<tr>
<td>Grotta et al.</td>
<td>13,109 Swedish men followed for 13 yr, 904 cases of PC</td>
<td>Low vs. high leisure activity</td>
<td>HR 0.93 (0.76–1.14, ns)</td>
<td>Adjusted for age, education, smoking, BMI, alcohol consumption, diabetes mellitus</td>
</tr>
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<tr>
<td>Hartman et al.⁶⁰</td>
<td>29,133 men followed for up to 9 yr, 317 cases of PC</td>
<td>Sedentary versus moderate/heavy leisure activity in working men</td>
<td>RR 0.7 (0.46–0.94) favouring active leisure</td>
<td>Adjusted for age, urban living, smoking, benign hyperplasia</td>
</tr>
<tr>
<td>Hrafnkelsdóttir et al.¹⁴</td>
<td>24-year follow-up of 822 Icelandic men</td>
<td>Regular physical activity from age of 20 yrs vs. sedentary</td>
<td>HR 0.93 (0.83–1.07) for active individuals</td>
<td>Adjusted for age, height, BMI, diabetes, family history, education, medical check-ups</td>
</tr>
<tr>
<td>Johnsen et al.⁷⁰</td>
<td>127,923 men followed for 8.5 yr, 2458 cases of PC</td>
<td>Quartiles of leisure activity (&lt;25 to &gt;71 MET-h/wk)</td>
<td>Leisure activity unrelated to PC</td>
<td>Adjusted for occup. activity, height, weight, marital status and education</td>
</tr>
<tr>
<td>Lee et al.³⁹</td>
<td>17, 719 Harvard alumni, 419 cases of PC</td>
<td>Activity questionnaire completed on 2 occasions</td>
<td>OR if weekly expenditure &gt;16 MJ 0.12 (0.02–0.89) (only 1 case of PG)</td>
<td>Adjusted for age</td>
</tr>
<tr>
<td>Lee et al.⁴⁰</td>
<td>8922 Harvard alumni, 439 developed PC</td>
<td>Physical activity questionnaire completed twice, weekly energy expenditure quartiles (&lt;4.2 MJ–&gt;12.6 MJ)</td>
<td>PC unrelated to total activity or weekly volume of vigorous physical activity</td>
<td>Adjusted for age, BMI, smoking, alcohol consumption, family history</td>
</tr>
<tr>
<td>Paffenbarger et al.⁵⁰</td>
<td>16,936 male Harvard graduates followed 12–16 yr, with 36 deaths from PC</td>
<td>Questionnaire-based physical activity index (&lt;2 MJ/wk vs &gt;8 MJ/wk)</td>
<td>Mortality rate 2.7 vs. 1.5/10,000 man-yr (ns)</td>
<td>Adjusted for age, smoking, BMI</td>
</tr>
<tr>
<td>Littman et al.⁴¹</td>
<td>34,757 men initially aged 50–76 yr, 583 cases of PC</td>
<td>MET-h/wk, walking pace, stair climbing, high intensity activity, activity at earlier ages</td>
<td>No association with PC except in sub-group aged &gt;65 yr with normal body mass</td>
<td>Adjusted for family history, BMI, income</td>
</tr>
<tr>
<td>Author</td>
<td>Sample</td>
<td>Activity measure</td>
<td>Findings</td>
<td>Comments</td>
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<tr>
<td>Liu et al.[42]</td>
<td>982 cases of PC in 22,071 physicians over 11 yr</td>
<td>Exercise sufficient to cause a sweat &amp; alcohol consumption, height, diabetes mellitus, hypertension, use of multivitamins</td>
<td>No relationship to PC</td>
<td>Adjusted for smoking, alcohol consumption, height, diabetes mellitus, hypertension, use of multivitamins</td>
</tr>
<tr>
<td>Lund-Nielsen et al.[8]</td>
<td>22,895 Norwegian men followed for 9.3 yr, with 644 cases of PC</td>
<td>High vs. low leisure activity</td>
<td>RR 0.80 (0.62–1.03)</td>
<td>Multivariate adjusted</td>
</tr>
<tr>
<td>Moore et al.[43]</td>
<td>293,902 men initially aged 50–71 yr followed for up to 8.2 yr, 17,872 cases PC</td>
<td>Exercise at baseline and in adolescence (never/rarely to &gt;5 times/wk)</td>
<td>RR 0.97 (0.91–1.03) p for trend favouring activity during adolescence = 0.03. But no relationships to exercise habits at baseline</td>
<td>Adjusted for age, marital status, education, smoking, medical history, BMI, waist circumference, family history, diet and supplements</td>
</tr>
<tr>
<td>Nilsen et al.[44]</td>
<td>29,110 Norwegian men followed for 7 yr, 957 incident cases PC</td>
<td>Score based on frequency, intensity and duration of activity (low vs. high)</td>
<td>Relationship for total cancer ns (RR = 0.86), but for advanced cancer RR = 0.64 (0.43–0.95), inverse trend p = 0.02</td>
<td>Adjusted for age, marital status, education, BMI, smoking, alcohol consumption</td>
</tr>
<tr>
<td>Orsini et al.[17]</td>
<td>45,887 men followed for 8 yr, 2735 incident PC</td>
<td>Walking or cycling, 5 categories (hardly ever to &gt;60 min/day)</td>
<td>RR = 0.86 (0.76–0.98) p for trend 0.028; effects greater for advanced (RR = 0.74) and fatal (RR = 0.72) cancers</td>
<td>Adjusted for occupational activity, age, smoking, alcohol consumption, education, diet, energy intake, waist/hip ratio, diabetes mellitus</td>
</tr>
<tr>
<td>Parent et al.[18]</td>
<td>449 incident cases of PC</td>
<td>Involvement in sports and outdoor activities</td>
<td>No significant effect on PC</td>
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</tr>
<tr>
<td>Author</td>
<td>Sample</td>
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<td>Findings</td>
<td>Comments</td>
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<tr>
<td>Patel et al.</td>
<td>72,174 men, 5503 incident cases of PC over 9 yr</td>
<td>MET-h/wk (&lt;0.7–35) at age 40 and in 1992</td>
<td>No significant effect (but active have fewer aggressive tumours, RR 0.69, 0.52–0.92, p for trend = 0.06)</td>
<td>Adjusted for age, ethnicity, BMI, weight change, energy intake, diet and vitamin use, diabetes mellitus, family and medical history</td>
</tr>
<tr>
<td>Platz et al.</td>
<td>46,786 health professionals, 2896 incident cases PC over 14 yr</td>
<td>Vigorous leisure activity &lt;3, &gt;3 MET-h/wk</td>
<td>No relationship to PC</td>
<td>Adjusted for age, family history, BMI, diabetes mellitus, smoking, diet</td>
</tr>
<tr>
<td>Putnam et al.</td>
<td>101 cases of PC in 1572 initially cancer free men followed for 4 yr</td>
<td>Very active, moderately active, inactive</td>
<td>Risk of PC unrelated to leisure activity</td>
<td>Adjusted for total energy intake</td>
</tr>
<tr>
<td>Severson et al.</td>
<td>8006 Japanese men on Oahu; 205 cases of PC</td>
<td>Framingham index, resting heart rate, self-estimate of moderate or heavy leisure activity</td>
<td>Risk of PC unrelated to Framingham index or resting heart rate; suggestion of benefit from self-assessment (OR 0.77, 0.58–1.01)</td>
<td>Adjusted for age, BMI</td>
</tr>
<tr>
<td>Steenland et al.</td>
<td>156 cases of PC in NHANES I survey follow-up</td>
<td>Physical activity: little vs. lots</td>
<td>Suggestion of benefit from activity, OR 1.31 (0.76–2.26, ns)</td>
<td>Adjusted for age, BMI, smoking, alcohol consumption, income</td>
</tr>
<tr>
<td>Thune &amp; Lund</td>
<td>220 cases of PC in 53,242 Norwegians followed for 16.3 yr</td>
<td>3-level classification, sedentary to regular training</td>
<td>No effect of leisure activity</td>
<td>Adjusted for age, BMI, geographic region</td>
</tr>
<tr>
<td>Wannamethee et al.</td>
<td>Prospective study of 7588 men with 120 incident cases of PC</td>
<td>6-level classification of leisure activity from none to vigorous</td>
<td>Benefit from vigorous activity, OR 0.25 (0.06–0.99, p for trend = 0.06)</td>
<td>Adjusted for age, smoking, alcohol consumption, BMI, social class</td>
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<tr>
<td>Author</td>
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<tr>
<td>Zeegers et al.</td>
<td>58,279 men aged 55–69 yr, 1386 cases of PC over 9.3 yr</td>
<td>Biking/walking (min/day), gardening (h/week)</td>
<td>Gardening unrelated to PC; biking/walking &lt;10 vs. &gt;60 min/d, RR 0.85 (0.69–1.05, ns)</td>
<td>Adjusted for age, alcohol consumption, BMI, energy intake, family history, gardening, sport involvement</td>
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<tr>
<td>Andersson et al.</td>
<td>252 cases of PC, 243 controls</td>
<td>Pubertal activity relative to peers, lower, same or higher</td>
<td>OR = 1.3, 1.0, 0.7 (p for trend 0.13)</td>
<td>Adjusted for age, urbanization, adult farming</td>
</tr>
<tr>
<td>Darlington et al.</td>
<td>752 cases from Ontario cancer registry aged 50–84 yr, telephone listing controls</td>
<td>Strenuous activity mid-teens, early 30s, early 50s</td>
<td>Strenuous activity by men in 50s reduced risk (OR 0.8, 0.6–0.9). Other age groups ns</td>
<td>Adjusted for age, education, BMI, family history, occupation</td>
</tr>
<tr>
<td>Friedenreich et al.</td>
<td>988 incident cases of PC, 1063 population controls</td>
<td>&lt;78.5 vs. &gt;25.1 MET-h/wk</td>
<td>OR 1.00, 0.80 (0.61–1.04) (p = 0.06 for trend)</td>
<td>Adjusted for age, region, education, BMI, waist/hip ratio, energy intake, alcohol consumption, family and medical history</td>
</tr>
<tr>
<td>Jian et al.</td>
<td>130 histologically confirmed PC, 274 controls</td>
<td>Reported MET-h of moderate and total activity (&lt;40 vs &gt;120; &lt;44 vs. &gt;135)</td>
<td>OR 0.20 (0.07–0.62, p = 0.015), 0.39 (0.15–0.99, p = 0.50 for trend)</td>
<td>Adjusted for age, area of residence, education, income, marital status, number of children, years in work force, family history, BMI, energy intake</td>
</tr>
<tr>
<td>Lacey et al.</td>
<td>258 cases of PC, 471 age-matched controls</td>
<td>Tertiles of moderate/vigorous or all physical activity at 20–29, 40–49 and 12 yrs ago</td>
<td>No relationship to PC</td>
<td>Adjusted for age, marital status, education, BMI, energy intake, waist/hip ratio</td>
</tr>
<tr>
<td>Author</td>
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<tr>
<td>Strom et al.</td>
<td>176 cases of PC in Mexican-Americans, 176 controls</td>
<td>Leisure activity &lt;1/wk vs. &gt;1/wk</td>
<td>No effect on risk of PC</td>
<td></td>
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<tr>
<td>Sung et al.</td>
<td>90 cases of PC, 180 controls</td>
<td>Exercise (yes vs. no) 5–10 yr before diagnosis</td>
<td><em>Adverse</em> effect of exercise (OR 2.16, 1.18–3.96, p = 0.01)</td>
<td>Multivariate adjusted</td>
</tr>
<tr>
<td>Villeneuve et al.</td>
<td>1623 histologically confirmed cases of PC, 1623 controls</td>
<td>5-level classification &lt;1/month to &gt;5/week</td>
<td>No clear relationship to PC</td>
<td>Adjusted for age, area of residence, smoking, alcohol consumption, BMI, diet, income, family history</td>
</tr>
<tr>
<td>West et al.</td>
<td>358 cases of PC, 679 controls</td>
<td>Activity questionnaire</td>
<td>No relationship between activity and PC</td>
<td></td>
</tr>
<tr>
<td>Whittemore et al.</td>
<td>1655 cases of PC, 1645 population controls</td>
<td>Activity questionnaire</td>
<td>No relationship between activity and PC</td>
<td></td>
</tr>
<tr>
<td>Wiklund et al.</td>
<td>1449 incident cases of PC, 1118 population controls</td>
<td>MET-h/day lifetime recreational activity, &lt;7.4 to &gt;13.5</td>
<td>OR 1.56 (1.16–2.10), p = 0.006, adverse effect of active leisure</td>
<td>Adjusted for age, region, education, BMI, alcohol consumption, family history, diabetes mellitus, energy intake</td>
</tr>
<tr>
<td>Yu et al.</td>
<td>1162 cases of PC, 3124 matched hospital controls</td>
<td>Leisure activity (active, moderate or seldom)</td>
<td>Risk higher in sedentary (OR 1.3, 1.0–1.6 p = 0.03)</td>
<td>Adjusted for age</td>
</tr>
</tbody>
</table>

Notes: ns = non-significant; BMI = body mass index; HR = hazard ratio; MET = metabolic equivalent; OR = odds ratio; PC = prostate cancer; RR = relative risk
the age of 65 years who had maintained a normal body mass. In contrast, active older subjects who were overweight had an increased risk of prostate cancer. Liu et al.\cite{42} found 982 cases of prostate cancer when following 22,071 physicians over a period of 11 years. The frequency of taking sufficient physical activity to work up a sweat was categorized from “less than once a week” to “more than five times per week”. With adjustment of data for smoking, alcohol consumption, height, diabetes mellitus, high cholesterol, hypertension and the use of multi-vitamins, their findings indicated no effect of physical activity upon the risk of prostate cancer. Parent et al.\cite{18} questioned 449 incident cases of prostate cancer on their involvement in sports and outdoor activities; no significant association with the risk of prostate tumours was seen. Parent et al.\cite{49} found 449 incident cases of prostate cancer among a total of 3730 individuals with various types of cancer. Involvement in sports and outdoor activities was classed as “never”, “not often” and “often”. Age, socio-economic status, educational attainment, ethnicity, smoking and body mass index were included as co-variates in an analysis that found no significant effect of activity upon the risk of prostate cancer. Platz et al.\cite{46} examined 46,786 health professionals; over 14 years, there were 2896 incident cases of prostate cancer. Noting all periods when leisure activity exceeded 6 METs, a binary classification of the volume of vigorous leisure activity was made (less than vs. more than 3 MET-h/wk). Adjusting data for age, family history, body mass index, diabetes mellitus, smoking and diet, there was no difference in the incidence of prostate cancer between the two halves of the sample. However, an increase of risk was seen in individuals with a high energy intake, suggesting the possibility that some people use any excess of ingested energy for growth of tumour tissue rather than for fat formation. Putnam et al.\cite{9} found 101 cases of prostate cancer in 1572 initially cancer-free men who were followed for 4 years. A three-level classification of leisure activity (very active, moderately active and inactive) was unrelated to the risk of developing prostate cancer after adjusting data for the total energy intake. Thune and Lund\cite{19} observed 220 cases of prostate cancer in 53,242 Norwegians who were followed for 16.3 years. A three-level classification of leisure activity (ranging from sedentary to regular training) found no association with the risk of developing prostate cancer after adjustments of data for age, body mass index and geographic region of residence.

Twelve investigations found suggestive but non-significant trends of benefit in more active individuals. Clarke and Whittemore\cite{12} followed 5377 men for 17 to 21 years, accumulating 201 cases of prostate cancer. Data were adjusted for age, educational attainment, ethnicity and family history, and a cross-sectional comparison was made between those taking much vs. those engaging in little or no recreational activity. The relative risk for the inactive group was 1.17 (not statistically significant), but a much higher risk was found in the relatively small African-American segment of the total sample (RR 3.17 [0.96–10.46, p = 0.08]). Giovannucci et al.\cite{38} analysed findings for US health professionals over a 14-year follow-up. Data were analysed in terms of the amount of vigorous physical activity undertaken. No relationship was found for younger adults, but in those...
over the age of 65 years, vigorous physical activity was associated with a decreased risk of advanced prostate cancer and a lower Gleason tumour aggressivity score (odds ratio 0.33 [0.17–0.62]). Hrafnkelsdóttir et al.[14] completed a 24-year follow-up of 822 Icelandic men. They tested the benefit associated with engaging in regular physical activity from the age of 20 years, finding a hazard ratio of 0.93 (0.83–1.07) for the active group after adjusting their data for age, height, body mass index diabetes, family history, educational attainment and regular medical check-ups. Paffenbarger et al.[5] followed 16,936 male Harvard graduates for 12 to 16 years; there were only 36 deaths from prostate cancer during this period. Nevertheless, they attempted to relate the mortality rate to a questionnaire-based physical activity index; respective values, adjusted for age, smoking and body mass index, were 2.7 vs. 1.5/10,000 person-years (not statistically significant) in those with weekly energy expenditures of less than 2 MJ vs. more than 8 MJ. Lee et al.[39] made a further examination of data for this same Harvard alumni, including 419 men who had developed prostate cancer. The age-adjusted odds ratio for those who maintained a very high energy expenditure (more than 16 MJ) at both assessments had a value of 0.12 (0.02–0.89), but this figure must be regarded with some scepticism, since it is based on only a single case of prostate cancer in the most active group. Benefit was no longer seen when the cut-point for a high energy expenditure was reduced from 16 to 10 MJ/week.[86] Lund-Nielsen et al.[8] followed 22,895 Norwegian men for 9.3 years, encountering 644 incident cases of prostate cancer. Multi-variate adjustment of a simple binary classification of leisure activity found a trend to benefit from a high level of physical activity (relative risk of prostate cancer 0.80 [0.62–1.03]). Moore et al.[43] examined a very large sample of 293,902 men who were initially aged 50–71 years. During an 8.2-year follow-up, there were 17,872 cases of prostate cancer, 1942 of which were advanced and 513 of which were fatal. After adjusting findings for age, marital status, educational attainment, smoking, medical history, body mass index, waist circumference, family history, diet and use of nutritional supplements, vigorous exercise during adolescence was associated with a small reduction in the relative risk of developing prostate cancer (odds ratio 0.97 [0.91–1.03], p for trend favouring activity during adolescence = 0.03), but exercise at entry to the study was unrelated to the total number of tumours, to advanced lesions or to the number of fatal cases. Nilsen et al.[44] studied 29,110 Norwegian men for 7 years, finding 957 incident cases of prostate cancer. Physical activity was scored based on the frequency, intensity and duration of physical activity (low, medium or high). With statistical allowance for effects of age, marital status, educational attainment, body mass index, smoking and alcohol consumption, physical activity bore no significant relationship to the risk of all prostate cancers (risk ratio = 0.86), but there was a significant inverse trend to a decreased risk of advanced tumours (relative risk = 0.64 [0.43–0.95], trend p = 0.02). Patel et al.[45] followed a sample of 72,174 men, accruing 5503 incident cases of prostate cancer over 9 years. Leisure activity was classified in MET-h/wk (from <0.7 to >35). Following adjustment of data for age, ethnicity,
body mass index, changes in body mass, energy intake, diet and vitamin use, diabetes mellitus and family and medical history, no significant association was seen between the volume of leisure activity and the incidence of prostate cancer, but a sub-category of tumours with a high Gleason score for aggressiveness tended to be less prevalent among the more active individuals (risk ratio 0.69 [0.52–0.92], p for trend = 0.06). Severson et al.[10] found 205 cases of prostate cancer among 8006 Japanese men living on the island of Oahu, Hawaii. Leisure activity was assessed by the Framingham index, resting heart rate and a self-estimate of involvement in moderate or heavy leisure activity, all of these indices being adjusted for age and body mass index; the first two measures were unrelated to the risk of prostate cancer, although there was a suggestion of benefit associated with a subjective assessment of engagement in moderate or heavy leisure activity (an odds ratio of 0.77 [0.58–1.01]). Steenland et al.[47] found 156 cases of prostate cancer in a follow-up of participants in the NHANES I survey. Contrasting those taking little physical activity with those taking “lots”, there was a weak trend to a lower risk in the more active individuals (an odds ratio of 1.31 [0.76–2.26, ns]) after adjustment of data for age, body mass index, smoking, alcohol consumption and income. Zeegers et al.[21] followed 58,279 men who were initially aged 55–69 years for an average of 9.3 years, accumulating 1386 cases of prostate cancer. Leisure activity was assessed in terms of the time individuals allocated to bicycling or walking, and to gardening. Gardening was unrelated to the risk of prostate cancer, but after controlling for age, alcohol consumption, body mass index, energy intake, family history, gardening and sport involvement, there was a weak trend to benefit from walking and cycling; compared with those who were active for less than 10 min/day, the odds ratio for those making a time allocation of >60 minutes per day to walking and cycling was 0.85 (0.69–1.05, ns).

Among the 4 investigators with statistically significant findings, Albanes et al.[11] found 95 cases of prostate cancer in a sample of 5141 men during a 10-year follow-up of individuals who had been recruited to the NHANES I survey. Comparing those who took much vs. those who engaged in little or no recreational exercise, the age adjusted relative risk was 1.8 (1.1–3.3), with a statistically significant trend favouring those who were more active (p = 0.02). Hartman et al.[9] followed 29,133 men for up to 9 years, finding 317 incident cases of prostate cancer. After adjusting data for age, urban living, smoking and benign prostatic hyperplasia, a comparison of those who were sedentary vs. those who undertook moderate or heavy leisure activity found a relative risk of 0.7 (0.46–0.94) favouring those who engaged in active leisure. Orsini et al.[17] followed 45,887 men for 8 years, accumulating 2735 cases of prostate cancer. Walking and cycling habits were placed into five categories, ranging from “hardly ever” to “more than 60 minutes per day”. After adjusting data for a substantial range of co-variates (age, smoking, alcohol consumption, educational attainment, diet, energy intake, waist/hip ratio and diabetes mellitus), the relative risk of prostate cancer in the most active category of subjects was 0.86 (0.76–0.98), with risk decreasing by some 8% for each 30 minutes allocated to daily walking or cycling over the
range 30–120 minutes/day. Effects of an active lifestyle were greatest for advanced (RR = 0.74) and fatal (RR = 0.72) tumours. Wannamethee et al.\cite{48} carried out a prospective study of 7588 men, with 120 incident cases of prostate cancer. A six-level classification of leisure activity ranged from “none” to “vigorous”. After adjusting data for age, smoking, alcohol consumption, body mass index and social class, there was a substantial benefit associated with participation in vigorous activity (an odds ratio of 0.25 [0.06–0.99], p for trend = 0.06).

**Case-control studies**

Of 12 case-control studies, 2 found an adverse effect of physical activity, 5 no effect, 2 a positive trend and 3 provided statistically significant evidence of benefit. Sung et al.\cite{52} related 90 cases of prostate cancer to 180 controls, noting exercise participation (“yes” vs. “no”) 5 to 10 years prior to the tumour diagnosis. In a multivariate analysis, they observed that exercise was associated with a significant increase in the risk of prostate cancer (an odds ratio of 2.16 [1.18–3.96], p = 0.01). Wiklund et al.\cite{35} compared 1449 incident cases of prostate cancer with 1118 population controls. After adjusting data for age, region, educational attainment, body mass index, alcohol consumption, family history, diabetes mellitus and energy intake, a classification of lifetime recreational activity (from less than 7.4 to more than 13.5 MET-h/day) showed a significant increase of risk in those with the more active leisure (odds ratio 1.56 [1.16–2.10], p= 0.006).

Five investigations found little effect from leisure activity. Lacey et al.\cite{29} asked for information about moderate/vigorous and all physical activity at 3 time points (ages 20–29 and 40–49 years and 12 years prior to the study) in a sample of 258 cases of prostate cancer and 471 age-matched controls. Adjusting data for age, marital status, educational attainment, body mass index, energy intake and waist/hip ratio, the extent of leisure activity was unrelated to the risk of prostate cancer. Strom et al.\cite{33} compared leisure activity (a frequency of less than vs. more than once per week) between 176 cases of prostate cancer and 176 matched controls; the risk of developing prostate cancer was not associated with differences in the frequency of leisure-time physical activity. Villeneuve et al.\cite{34} related data on 1623 histologically confirmed cases of prostate cancer to findings in 1623 controls. A five-level classification of the frequency of leisure-time physical activity (from less than once per month to more than five times per week) showed no clear relationship to the risk of developing prostate cancer, after control of the data for age, area of residence, smoking, alcohol consumption, body mass index, diet, income and family history. West et al.\cite{53} compared 358 cases of prostate cancer with 679 controls; in a survey that focused primarily on diet, subjects were questioned about their physical activity and no relationship was seen between leisure activity and tumour development. In another study where physical activity was not the main emphasis, Whittemore et al.\cite{54} studied 1655 cases of prostate cancer and 1645 population controls; they, also, found no relationship between leisure activity and the development of prostate cancer.
Two studies showed trends suggesting benefit from leisure activity. Andersson et al.\cite{49} compared 252 cases of prostate cancer with 243 controls. The pubertal physical activity of these subjects was rated relative to that of their peers, as lower, the same or higher, and the respective odds ratios for subsequently developing a prostate tumour (adjusted for age, urbanization and adult farming) were 1.3, 1.0 and 0.7 (p for a trend = 0.13), favouring those who were active as adolescents. An association of carcinogenesis with living in a densely populated area was also seen; this may have reflected differences of social class, but there may also have been an adverse effect of inner-city living upon the individual’s ability to engage in physical activity as a youth. Friedenreich et al.\cite{26} examined 988 incident cases of prostate cancer and 1063 population controls. Multiple co-variates included age, region, educational attainment, body mass index, waist/hip ratio, energy intake, alcohol consumption and the family and medical history. There was a trend towards a favourable odds ratio (0.80 [0.61–1.04] p = 0.06 for trend) when those with the greatest leisure activity (more than 25.1 MET-h/week) were compared with the least active individuals (less than 8.5 MET-h/wk).

Only three case-control studies showed a significant effect favouring active individuals. Darlington et al.\cite{50} related findings on 752 cases drawn from the Ontario cancer registry to telephone-listing controls, enquiring regarding strenuous physical activity in the mid-teens, early 30s and early 50s. After adjusting data for age, educational attainment, body mass index, family history and occupation, the risk of prostate cancer was lower in those who had undertaken strenuous physical activity in their 50s, but benefit was not significantly associated with physical activity at earlier ages. Jian et al.\cite{51} compared 130 histologically confirmed cases of prostate cancer with 274 controls. After adjusting data for age, area of residence, educational attainment, income, marital status, number of children, years in the work force, family history, body mass index and energy intake, the risk of prostate tumours was more closely related to reports of a low volume of moderate physical activity (less than 40 vs. more than 120 MET-h of moderate activity per week) than to a low total volume of physical activity (less than 44 vs. more than 135 MET-h/week, with respective odds ratios for the more active individuals of 0.20 [0.07–0.62, p for trend = 0.015] and 0.39 [0.15–0.99, p for trend = 0.50]). Yu et al.\cite{55} compared 1162 cases of prostate cancer with 3124 matched hospital controls. They classed the frequency of leisure activity, adjusted for age, as active, moderate or seldom, finding a higher odds ratio (1.3 [1.0–1.6], p = 0.03) in the most sedentary group.

**Sport involvement and attained fitness**

Studies based on an individual’s involvement in organized sport are often based on the behaviour reported during youth or when attending university. This may be a relevant period in terms of carcinogenesis, but there is also the difficulty that by middle age, former university athletes are often less active and more obese than those who were not recognized as athletes while attending university. Comparisons with non-athletes are further complicated in that selection for many
sports is based upon body build, which can itself modify the risk of carcino-
genesis. A final issue is that athletes may have abused androgenic steroids, and thus increased their risk of prostate cancer.\textsuperscript{57, 58} Another option is to compare attained levels of aerobic fitness among those who have been involved in aerobic fitness programmes for substantial periods. Some have considered the attained level of aerobic fitness as a better index of habitual physical activity than responses to questionnaires, although if reliance is placed upon the individual’s attained level of maximal oxygen intake, expressed in mL/[kg.min], this measure is heavily influenced not only by the extent of recent aerobic activity, but also by the individual’s accumulation of body fat.

\textbf{Retrospective and prospective cohort studies}

Four cross-sectional and cohort studies of sport and fitness have been published (Table 11.3). Two of these reports found no advantage from sport involvement, but the third saw a reduced risk among individuals with a high attained level of aerobic fitness, and the fourth a dose-related effect from the frequency of sport participation.

Merrill et al.\textsuperscript{59} evaluated a somewhat fallible index of carcinogenic change (the prostate serum antigen levels) of 536 participants in a seniors’ games who were older than 50 years. The age-adjusted PSA was unrelated to the number of years that subjects had been physically active more than three times per week. Zeegers et al.\textsuperscript{21} also found no benefit from community sport involvement (a simple binary classification of participation, “never” vs. “ever”) when 58,279 men initially aged 55–69 years were followed for 9.3 years, with the accumulation of 1386 cases of prostate cancer. Wannamethee et al.\textsuperscript{67} included a question on sports involvement (“none,” “more than once per month”, “more than once per week” or “more than twice per week” in their prospective study of 7588 men aged 40–59 years; 120 of the group developed prostate cancer, and after adjusting data for age, smoking, alcohol consumption, body mass index and socio-economic status, the relative risks for the 4 categories of involvement were 1.0, 0.98, 0.63 and 0.53 (p for trend = 0.05).

Oliveira et al.\textsuperscript{60} obtained data on 12,975 men who had been attending the Cooper Fitness Clinic in Dallas, Texas. Quartile scores on a maximal exercise treadmill test of aerobic fitness were inversely related to the risk of prostate cancer (incidence rates for the 3 higher quartiles of fitness of 1.1; 0.73, ns; and 0.26 [0.10–0.63] relative to the least fit group), after allowing for the effects of age, body mass index and smoking.

\textbf{Case-control studies}

Three case-control studies of involvement in sport all reported substantial adverse effects. Hållmarker et al.\textsuperscript{61} completed a case-control study of 185,412 participants in the Swedish Vasaloppet long-distance cross-country ski contest and 184,617 non-participants who were matched for age, sex and county of residence. The 2 groups included 1827 and 1435 cases of prostate cancer, respectively, and
### Table 11.3 Sports involvement, attained aerobic fitness and risk of prostate cancer

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<tr>
<td>Merrill et al.</td>
<td>PSA levels of 536 participants in seniors’ games aged &gt;50 yr</td>
<td>Years active &gt;3 times/wk</td>
<td>Physical activity unrelated to PSA levels</td>
<td>Adjusted for age</td>
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<td>et al. [59]</td>
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<tr>
<td>Oliveira et al.</td>
<td>12,975 men attending Cooper Fitness Clinic</td>
<td>Quartile scores</td>
<td>Incidence rate inversely related to aerobic fitness [1.1, 0.73, ns; 0.26 (0.10–0.63)]</td>
<td>Adjusted for age, BMI, smoking</td>
</tr>
<tr>
<td>et al. [60]</td>
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<td>on maximal exercise treadmill test</td>
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<tr>
<td>Wannamethee et al.</td>
<td>Prospective study of 7588 men aged 40–59 yr, with 120 incident cases of PC</td>
<td>Sporting activity (none, &gt;1/month; &gt;1/week; &gt;2/week)</td>
<td>RR 1.00, 0.98, 0.63, 0.53 (p = 0.05)</td>
<td>Age, smoking, alcohol, BMI, SES</td>
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<tr>
<td>et al. [67]</td>
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<tr>
<td>Zeegers et al.</td>
<td>58,279 men aged 55–69 yr, 1386 cases of PC over 9.3 yr</td>
<td>Sport participation (never/ever; frequency; duration, yr)</td>
<td>Sport participation unrelated to PC</td>
<td>Adjusted for age, alcohol consumption, BMI, energy intake, family history, education</td>
</tr>
<tr>
<td>et al. [21]</td>
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<td><strong>Case/control studies</strong></td>
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<tr>
<td>Hållmarker et al.</td>
<td>185,412 participants in Vasaloppet ski contest and 184,617 non-participants</td>
<td>1827 vs. 1435 cases PC</td>
<td>HR 1.22 (1.13–1.30) favouring non-participants</td>
<td>Non-participants matched for age, sex, and county of residence</td>
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<tr>
<td>et al. [61]</td>
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<tr>
<td>Paffenbarger et al.</td>
<td>56,683 university alumni followed &gt;28 years, 104 PC cases vs. controls</td>
<td>Playing university sport &gt;5h/wk</td>
<td>RR 1.20 favouring non-athletes (p = 0.028)</td>
<td>Data adjusted for age, sex and birth year of classmate controls</td>
</tr>
<tr>
<td>et al. [5]</td>
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<tr>
<td>Polednak [62]</td>
<td>8393 university graduates, 124 PC deaths</td>
<td>Athletes vs. minor athletes vs. non-athletes</td>
<td>Age of PC death 70.9, 74.2, 74.8 (p &lt;0.05)</td>
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<tr>
<td>et al.</td>
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</table>

Notes: ns = non-significant; BMI = body mass index; PC = prostate cancer; PSA = prostate serum antigen; RR = relative risk; SES = socio-economic status
a hazard ratio of 1.22 (1.13–1.30) favoured the non-participants. Paffenbarger et al.[5] followed 56,683 university alumni for 28 or more years, accumulating 104 cases of prostate cancer. These individuals were compared with classmate controls matched for age, sex and birth year. Involvement in university sport for longer than five hours per week was associated with a significant adverse effect (relative risk 1.20 [p = 0.028]). Polednak[62] explored data for 8393 university graduates, comparing the experience of major athletes, minor athletes and non-athletes. In his study, there was a statistically significant trend for the major athletes to die of prostate cancer at a younger age than the other two categories of alumni (70.9, 74.2 and 74.8 years, p <0.05).

Possible mechanisms

The demonstration of likely mechanisms whereby exercise modifies prostate carcinogenesis could reinforce the tentative epidemiological evidence of benefit from regular physical activity and provide useful guidance for those designing preventive programmes. In addition to such general benefits of physical activity as a reduction of obesity and oxidant stress and a modulation of immune responses, prolonged endurance exercise may reduce circulating levels of testosterone and insulin-like growth factors[57, 63] thus reducing the tendency to growth of small prostate neoplasms. Barnard et al.[64] collected serum from men who were undertaking aerobic exercise five times per week and from sedentary controls; when applied to lymph nodes that were infiltrated with prostate cancer cells, the serum from the exercisers decreased levels of insulin-like growth factor, increased insulin-like growth factor binding protein and increased the extent of apoptosis among the tumour cells. However, it is less certain that the average exerciser reaches the intensity and duration of physical activity where such a humoral response might be anticipated.

Conclusions regarding prostate cancer

Despite a large volume of research and some suggestions of benefit, it is difficult to draw strong conclusions about physical activity and the risk of prostate cancer, particularly as many investigators have drawn conflicting inferences from post-hoc analyses on small sub-groups within their overall populations. In terms of occupational activity, relatively few investigators have co-varied their findings for exposure to toxic chemicals, and often there has been an incomplete allowance for socio-economic and dietary differences between those engaged in sedentary and physically demanding work.

There have been around 81 analyses, 34 based on differences of occupational activity, 40 on leisure behaviour, 6 on involvement in sport and 1 on levels of attained aerobic fitness. However, 16 of these reports have examined both occupational and leisure activity, 1 has covered both sport participation and other forms of active leisure, and in 3 instances there have been repeated analyses of the same data set. Summarizing across the various measures of physical activity,
20 reports found significant benefit in one or more of their analyses and a further 23 found a non-significant trend favouring the more active individuals, but against this must be set 31 analyses finding either no effect or an adverse response with an active lifestyle. The evidence to date is far from conclusive, although it tends to support earlier contentions of that regular physical activity may reduce the risk of prostate cancer by 10–30%. Given the other general health benefits of an active lifestyle, and the small number of analyses that have demonstrated an adverse effect, regular physical activity can thus be recommended as a potentially useful tool in reducing the risk of prostate tumours.

Side-effects of androgen deprivation therapy

In about a half of patients, the immediate treatment of prostate cancer by irradiation or surgery is followed by a two to three year course of androgen deprivation therapy (ADT). The latter has major physical side-effects (Table 11.4), including a persistent decrease in maximal aerobic power\cite{65} and muscle strength\cite{66–75}, a 3–5% loss of bone mineral density, an increased risk of fractures,\cite{66, 67, 76–91} and a decrease in the overall quality of life.\cite{65, 66, 70, 74, 92–96} There may also be an increased risk of cardiovascular disease and acute renal injury, possibly due to the breakdown of atherosclerotic plaques.\cite{97} However, most of these side effects are of the type that could be reduced by an increase in physical activity following successful initial treatment of the tumour.

Aerobic performance

Alibhai et al.\cite{65} compared 87 cases who had been receiving ADT for 36 months with 86 cases who were not receiving ADT and 86 matched controls, finding a poorer performance on a simple measure of aerobic function (the six minute walking distance) in those who were receiving ADT.

Muscle strength

Typical responses to ADT have been a decrease in lean body mass and an increase in body fat.\cite{67, 70} Thus, a comparison between 30 cases of prostate cancer who were receiving ADT for 6 months with 25 healthy men found a decrease of skeletal muscle mass and lean tissue in the limbs of the affected individuals, with an associated increase of body fat.\cite{68} Galvao et al.\cite{71} demonstrated that after 36 weeks of ADT, the decrease of lean tissue in 72 cases of prostate cancer was distributed across all body sites (decreases of 5.6, 3.7, 1.4 and 2.4% in the upper and lower limbs, trunk and total body, respectively). Van Londen et al.\cite{75} reported data for 43 men who had been receiving ADT for less than 6 months, 67 cases on chronic ADT, 81 who were not receiving ADT and 53 age-matched controls. The acute ADT group showed lean mass losses of 0.93 kg at 12 months and 1.79 kg after 24 months, although losses at 24 months were smaller in the chronic ADT group. As in the other studies, there were associated increases of fat mass.
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<td><strong>Aerobic performance</strong></td>
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<tr>
<td>Alibhai et al.</td>
<td>87 cases of non-metastatic PC receiving ADT for 36 months, 86 matched cases not receiving ADT</td>
<td>6 min walk distance poorer if receiving ADT</td>
<td>Side-effects seen at 12 months persisted at 36 months. No specific rehabilitation programme adopted</td>
</tr>
<tr>
<td><strong>Muscular performance</strong></td>
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<tr>
<td>Alibhai et al.</td>
<td>87 cases of non-metastatic PC receiving ADT, 86 matched cases not receiving ADT for 36 months</td>
<td>Grip strength and timed get-up and go poorer if receiving ADT</td>
<td>Side-effects seen at 12 months persisted at 36 months. No specific rehabilitation programme adopted</td>
</tr>
<tr>
<td>Basaria et al.</td>
<td>20 cases of PC treated by ADT, 18 treated cases of PC awaiting ADT, 20 age-matched healthy controls</td>
<td>Reduced upper body strength with ADT</td>
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<tr>
<td>Berruti et al.</td>
<td>36 cases of PC with 12 months ADT</td>
<td>Decrease of LBM</td>
<td>Increase of body fat</td>
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<tr>
<td>Boxer et al.</td>
<td>30 cases of PC with 6 months ADT vs. 25 healthy controls</td>
<td>Decrease of muscle mass and lean tissue in limbs with ADT</td>
<td>Associated increase of body fat</td>
</tr>
<tr>
<td>Bylow et al.</td>
<td>50 men aged &gt;70 yr treated with ADT</td>
<td>24% had impaired ADL, deterioration of balance, walking and chair stand times</td>
<td>22% had falls within 3 months</td>
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<tr>
<td>Galvao et al.</td>
<td>72 cases of PC, 36 weeks of ADT</td>
<td>Decrease of LBM in upper and lower limb, trunk, total 5.6, 3.7, 1.4, 2.4% respectively</td>
<td>Associated increase of body fat</td>
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<td>Levy et al.</td>
<td>23 men &lt;6 months ADT, 12 men &gt;6 months ADT, 13 not receiving ADT</td>
<td>Lean mass decreased with duration of ADT, 4 metre walk velocities slower if on ADT</td>
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<tr>
<td>Stone et al.</td>
<td>62 men receiving ADT as primary treatment of PC</td>
<td>Loss of muscle bulk and reduction in voluntary muscle function (grip, grip fatigue)</td>
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<tr>
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<tr>
<td>van Londen et al. [75]</td>
<td>43 men on ADT &lt;6 months, 67 cases on chronic ADT, 81 not on ADT, 53 age-matched controls</td>
<td>Losses of lean mass 0.93 kg at 12 months, fat mass 1.79 kg after 24 months in acute ADT, smaller loss in chronic ADT group at 24 months</td>
<td>Associated increases of bone strength</td>
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<tr>
<td>Bone strength</td>
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<tr>
<td>Basaria et al. [66]</td>
<td>20 cases of PC treated by ADT, 18 treated cases of PC awaiting ADT, 20 age-matched healthy controls</td>
<td>BMD lower, increased urinary N-telopeptide with ADT</td>
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<tr>
<td>Berrutti et al. [67]</td>
<td>36 cases of PC with 12 months ADT</td>
<td>Decreased BMD at hip and lumbar spine relative to baseline</td>
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<td>Chen et al. [76]</td>
<td>62 cases of PC, 1–5 yr of ADT, 47 healthy controls</td>
<td>Low BMD (total, trochanter, intertrochanter and hip sites)</td>
<td>Associated higher percent body fat</td>
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<td>Daniell et al. [77]</td>
<td>26 cases of PC with ADT or orchidectomy followed 6–42 months</td>
<td>2.4% and 7.6% decrease of BMD in femoral neck after 1 and 2 yr respectively</td>
<td>Further 1.4–2.6%/yr loss of BMD over yrs 3–8</td>
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<tr>
<td>Galvao et al. [71]</td>
<td>72 men treated by ADT for 36 wks</td>
<td>Decreases of BMD at hip, spine, upper limb, whole body 1.5, 3.9, 1.3, 2.4% respectively, but no change in lower limbs</td>
<td>Associated decrease of lean mass</td>
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<tr>
<td>Greenspan et al. [79]</td>
<td>30 with acute ADT &lt;6 months, 50 with chronic ADT &gt;6 months, 72 no ADT, 43 healthy controls</td>
<td>5- to 10-fold increase in loss of bone mineral relative to no ADT or healthy controls</td>
<td>Bone loss maximal in first year of ADT</td>
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<td>Hatano et al. [80]</td>
<td>218 cases of PC treated with ADT for &gt;6 months</td>
<td>6% of cases had bone fractures unrelated to metastasis</td>
<td>Low bone density and increased N-telopeptides in those developing fractures</td>
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<td>Kiratli et al. [81]</td>
<td>36 patients with PC, age matched controls; ADT or surgical castration for up to 10 yr</td>
<td>Bone mineral loss continues relative to controls for 10 yr</td>
<td>Effect greater with surgical than with chemical castration</td>
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<td>Maillefert et al. [82]</td>
<td>12 cases of PC receiving ADT for 6, 12 and 18 months</td>
<td>BMD decreased 2.7, 3.9 and 6.6% over 18 months</td>
<td>Increased serum osteocalcin</td>
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<td>Malcolm et al. [83]</td>
<td>395 cases of PC receiving ADT followed for average of 66 months</td>
<td>23% developed osteoporosis, 7% developed non-pathological fractures</td>
<td>Osteoporosis related to duration of treatment</td>
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<td>Morote et al. [84]</td>
<td>31 cases on ADT, 31 controls not on ADT</td>
<td>Bone mass loss of 2.3–5.6% at 12 months, less severe further loss at 24 months</td>
<td>Major bone loss in Ward’s triangle</td>
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<td>Oefelein et al. [85]</td>
<td>181 cases of PC on ADT</td>
<td>4% fracture at 5 yr, 20% fracture at 10 yr</td>
<td>Fractures less likely if BMI maintained</td>
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<tr>
<td>Preston et al. [86]</td>
<td>23 men receiving ADT for 24 months, 30 controls</td>
<td>Greatest bone loss in distal arm bones (−9.4% vs. −4.4% in controls)</td>
<td>Less loss in controls at all sites except lumbar spine</td>
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<td>Shahinian et al. [88]</td>
<td>50,613 cases of prostate cancer</td>
<td>If case survived &gt;5yr, risk of fracture 19.4% with ADT, 12.6% without ADT</td>
<td>Risk of fracture related to dosage of ADT</td>
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<td>Smith et al. [89]</td>
<td>Medical claims from 5% of welfare beneficiaries (3887 non-metastatic cases of PC)</td>
<td>Clinical fracture rate 7.88 per 100 person-years with ADT, 6.51 in matched controls</td>
<td>Confirmed by data for hip and vertebral fractures</td>
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<td>Stoch et al. [90]</td>
<td>60 men with PC, 19 of whom were receiving ADT</td>
<td>ADT associated with decreased BMD at various sites, increased N-telopeptides and bone-specific alkaline phosphatases</td>
<td>No bone changes in cases of PC not receiving ADT</td>
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<tr>
<td>Townsend et al. [91]</td>
<td>224 cases of PC treated with ADT</td>
<td>9% of ADT group had 1 or more fractures, mean time to fracture 22 months</td>
<td>Osteoporotic fractures 5%</td>
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**Quality of life**

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<td>Alibhai et al. [65]</td>
<td>87 cases of non-metastatic PC receiving ADT, 86 matched cases</td>
<td>36 SF QOL scores poorer if receiving ADT</td>
<td>Side-effects seen at 12 months persist at 36 months. No specific rehabilitation programme adopted</td>
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<tr>
<td>Basaria et al. [66]</td>
<td>20 cases of PC treated by ADT, 18 treated PC cases awaiting ADT, 20 age-matched healthy controls</td>
<td>Decrease in desire, arousal and erections with ADT, lower QOL (physical function, physical health)</td>
<td>Associated lower levels of testosterone and free testosterone with ADT</td>
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<tr>
<td>Dacal et al. [70]</td>
<td>96 men, including short and long term ADT, no ADT and healthy controls</td>
<td>SF-36 questionnaire shows poor physical function, general health and physical health with ADT, unrelated to duration of ADT treatment</td>
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<tr>
<td>Fowler et al. [92]</td>
<td>298 men who received ADT following radical prostatectomy compared with 2240 who did not receive ADT</td>
<td>ADT associated with lower scores on all 7 measures of health-related quality of life</td>
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<tr>
<td>Green et al. [93]</td>
<td>65 patients with PC on ADT for 6 months, 16 community controls</td>
<td>Main impact of ADT is decreased sexual function, with decreased social and role function scores</td>
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<tr>
<td>Potosky et al. [94]</td>
<td>431 cases of PC treated only by ADT or orchidectomy</td>
<td>Fewer orchidectomy patients rated their health as fair or poor than those receiving androgen suppressant drugs</td>
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<tr>
<td>Sadetsky et al. [95]</td>
<td>2922 cases of prostate cancer</td>
<td>24-month self-reported quality of life poorer in those receiving ADT</td>
<td>Adverse effects even more marked if ADT is primary therapy</td>
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<tr>
<td>Spry et al. [96]</td>
<td>250 men receiving ADT for 9 months or more</td>
<td>Decrease of global health related quality of life and most function and symptom scales</td>
<td>Recovery in 3 months when ADT halted, slower recovery in older men</td>
</tr>
<tr>
<td>Stone et al. [94]</td>
<td>62 men receiving ADT as primary treatment of PC</td>
<td>Significant increase of fatigue severity over 3 months of treatment</td>
<td>28% of fatigue explained by psychological distress; also loss of virility and potency</td>
</tr>
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</table>

Notes: ADL = activities of daily living; ADT = androgen deprivation therapy; BMD = bone mineral density; LBM = lean body mass; PC = prostate cancer; QOL = quality of life
Stone et al.\cite{74} followed 62 men who were receiving ADT as a primary treatment of prostate cancer. They observed not only a progressive loss of muscle bulk, but also a decrease of grip strength and a faster fatigue of handgrip. Basaria et al.\cite{66} also found a reduction of upper body strength when 20 cases of prostate cancer who had been treated with ADT were compared with 18 cases who were awaiting such treatment.

Several authors have found functional consequences from the loss of muscle tissue. Alibhai et al.\cite{65} saw not only a reduction of grip strength in those receiving ADT, but also a deterioration in their times for a “get up and go” test, with the poor performance persisting throughout the 36 months of treatment. Bylow et al.\cite{69} found an adverse effect upon performance of the activities of daily living in a quarter of 50 men over the age of 70 years who were treated by ADT, with a deterioration in balance, walking and chair-stand times. Levy et al.\cite{73} reviewed data for 23 men who had received ADT for <6 months, and 12 men who had received ADT for >6 months relative to 13 who were not receiving ADT. The lean tissue mass decreased in proportion to the duration of ADT and 4-metre walk velocities were also slower in those receiving ADT.

**Bone mineral density**

Many investigations have associated androgen deprivation therapy with a progressive decrease in bone mineral density. Berruti et al.\cite{67} followed 36 cases of prostate cancer over the course of 12 months ADT; lumbar spine and hip bone mineral density were decreased relative to baseline over the 12 months of observation. Chen et al.\cite{76} compared 62 cases of prostate cancer treated with ADT for 1–5 years; relative to 47 healthy controls; a lower bone mineral density was seen in the trochanter, inter-trochanter, hip and total scores. Daniell et al.\cite{77} noted that in 26 cases treated by ADT or orchidectomy, the decrease of bone mineral density in the femoral neck continued unremittingly, with 2.4% and 7.6% decreases in years 1 and 2, and a further 1.4–2.6%/year loss over years 3–8.

The extent of bone loss seems to vary from one site to another. Preston et al.\cite{86} compared 23 men who had been receiving ADT for 24 months with 30 controls. There was less bone loss in controls at all sites except the lumbar spine. The site of greatest loss was the distal forearm, where respective losses over 2 years were −9.4% and −4.4%. Galvao et al.\cite{71} found decreases of bone mineral density of 1.5, 3.9, 1.3 and 2.4% respectively for the hip, spine, upper limb and whole body in a group of 72 men who were treated by ADT for 36 weeks. Possibly because of some protection from ambulation, this series showed no changes of bone density in the lower limbs. Greenspan et al.\cite{79} measured changes of bone mineral density in 30 men receiving ADT for <6 months, 50 men receiving ADT >6 months, 72 not receiving ADT and 43 healthy controls. The rate of loss of bone mineral with ADT was increased five- to ten-fold relative to those not receiving ADT, with the maximal bone loss occurring during the first year of such treatment. Morote et al.\cite{84} compared 31 cases of prostate cancer on ADT with 31 patients who were not
receiving ADT. Those receiving androgen suppression experienced a 2.3–5.6% loss of bone mass at 12 months, and as in the previous study, a less severe loss continued to 24 months. Kiratli et al.\cite{81} studied 36 patients with prostate cancer who received ADT or surgical castration and age matched controls. Bone mineral loss continued relative to controls for ten years, and the effect was greater following surgical treatment than after chemical castration.

Some investigations have demonstrated an increase in markers of bone turnover. Maillefert et al.\cite{82} evaluated 12 cases of prostate cancer who were receiving ADT at 6, 12 and 18 months. There was a progressive decrease of bone mineral density (2.7, 3.9 and 6.6%) and increased serum osteocalcin levels. Basaria et al.\cite{66} found a lower bone mineral density when 20 cases of prostate cancer treated with ADT were compared with 18 men who were awaiting such treatment; moreover, the ADT group showed an increase of urinary N-telopeptide, another marker of bone turnover. Stoch et al.\cite{90} examined 60 men with prostate cancer, including 19 who were receiving ADT. The ADT group showed a decreased bone mineral density at various sites, and also increased markers of bone turnover (N-telopeptides and bone-specific alkaline phosphatases). Likewise, Hatano et al.\cite{80} reported that 6% of 218 cases of prostate cancer who were treated with ADT for >6 months developed fractures that were unrelated to tumour metastasis. A low bone mineral density and increased N-telopeptide concentrations were found in those developing fractures.

A greater propensity to fracture seems an inevitable consequence of the bone mineral loss. Malcolm et al.\cite{83} followed 395 cases of prostate cancer who received ADT for an average of 66 months; 23% developed osteoporosis and 7% developed non-pathological fractures, with the risk of osteoporosis related to the duration of ADT. The primary end-point for Oefelein et al.\cite{85} was the development of a fracture. In 181 cases of prostate cancer on ADT, 4% had sustained a fracture at 5 years and 20% at 10 years, the risk being lower in those who had conserved their body mass. Shahinian et al.\cite{88} examined data for 50,613 cases of prostate cancer. In those who survived for 5 years or more, the risk of fracture with ADT was 19.6%, compared with 12.6% in those who did not receive such treatment. Moreover, in this series the risk of fracture was correlated with the dose of ADT administered. Smith et al.\cite{89} evaluated medical claims from 5% of welfare beneficiaries (providing 3887 non-metastatic cases of prostate cancer). The overall clinical fracture rate was 7.88 per 100 person-years in those receiving ADT, compared with 6.51 per 100 person-years in matched controls, and this difference was confirmed by specific data for hip and vertebral fractures. Townsend et al.\cite{91} studied 224 cases of prostate cancer who were treated with ADT; 9% of this group had 1 or more fractures within an average of 22 months of beginning treatment. Some of the fractures were due to severe trauma, but 5% were due to osteoporosis.

Although drugs such as alendronate can be given as a preventive measure, their effectiveness is limited and they have undesirable side-effects, so that it is a better tactic to counter the bone loss by a programme of weight-bearing exercise.
Quality of life

Not surprisingly, the loss of aerobic function, muscle strength and bone density are usually accompanied by a deterioration in the quality of life, particularly as reported on the scales for “physical health” and “physical function” on the short form medical health outcomes questionnaire (SF-36). Dacal et al.\cite{70} used the SF-36 to demonstrate a significant deterioration in physical function, general and physical health in men receiving ADT relative to those who did not, although changes did not seem related to the duration of ADT; there were associated lower levels of testosterone and free testosterone. Fowler et al.\cite{92} conducted a large-scale survey of men following radical prostatectomy; 298 individuals who received ADT were compared with 2240 who did not, and ADT was shown to be associated with lower scores on all 7 measures of the health-related quality of life. Potosky et al.\cite{94} evaluated 431 cases of prostate cancer treated only by ADT or orchidectomy. In this study, fewer of the orchidectomy patients rated their health as only fair or poor as compared with those who were receiving a chemical suppressants of androgens. Sadetsky et al.\cite{95} examined 2922 cases of prostate cancer; the 24-month self-reported quality of life was poorer in those receiving androgen suppressants, and they noted that the adverse effect was most marked if androgen deprivation was the primary form of therapy.

At least a part of the low scores on the SF-36 questionnaire seems related to reduced sexual function. Thus, Basaria et al.\cite{66} reported not only a low score for the physical function and physical health scales of the SF-36, but also specific decreases in sexual function that included decreases in desire, arousal and erections, and a reduced score on Watt’s scale of sexual function. Green et al.\cite{93} compared 65 cases of prostate cancer receiving ADT for 6 months and 16 community controls. In this study, the main adverse effects of ADT were a decreased sexual function and a decrease in scores for social and role functioning. Spry et al.\cite{96} followed 250 men receiving ADT for 9 months or longer. There was a decrease of global health-related quality of life and reduced scores on most function and symptom scales. Recovery commonly occurred within three months of halting ADT, but was slower in older men. Stone et al.\cite{74} followed 62 men who were receiving ADT as the primary treatment of prostate cancer. A significant increase of fatigue severity was seen over three months of treatment; 28% of this was explained by psychological distress, but there was also a loss of virility and potency. Again, mood-elevating drugs can be prescribed, but an increase of physical activity is a healthier way of countering anxiety and elevating mood state.

Countering the side-effects of androgen deprivation and prostate surgery

Urinary incontinence is a frequent early sequel to either radical prostate surgery or irradiation. Many of the side-effects of subsequent androgen deprivation mirror what might be anticipated from an excessively sedentary lifestyle, and an
early countering of the resulting loss of physical function is particularly important in what is typically an elderly population. A restoration of physical condition is likely to contribute not only to general well-being and independence, but also to long-term survival. Reviewers have found at least 25 controlled trials of various exercise programmes during the period of medical treatment (radiation or prostatectomy, androgen deprivation), and several have looked at exercise responses during after-care. These analyses have generally pointed to improvements of aerobic and muscular fitness, a reduction of fatigue, less bone demineralization, an enhanced quality of life and a lower risk of urinary incontinence.

We will look at issues of spontaneously chosen habitual physical activity and specific programmes of aerobic and resistance exercise, emphasizing the need to adapt programmes in the light of specific complications of surgery and/or irradiation such as urinary incontinence and exercise-induced diarrhoea.

**Habitual physical activity**

The spontaneously chosen level of physical activity in patients undergoing treatment for prostate cancer often falls below recommended levels (Table 11.5). Chipperfield et al. evaluated habitual physical activity in 356 men with prostate cancer; activity levels were lower in those receiving ADT than in those treated only by irradiation. Only 42% of the group met national physical activity guidelines, a low level of physical activity being associated with depression, anxiety and the presence of co-morbid conditions. Keogh et al. studied 84 cases of prostate cancer that were receiving ADT. Less than a half of the men reported that they were physically active, although those who were indeed active had a higher quality of life than their sedentary peers. The attitude towards physical activity was the dominant predictor of the intention to be active, and perceived behavioural control was the dominant predictor of actual behaviour.

Livingston et al. assigned 54 cases of prostate cancer receiving ADT to an exercise programme (2 supervised sessions/week for 12 weeks), and 93 men served as usual care controls. The 12-week programme increased the volume of self-reported vigorous activity, with gains in cognitive function and reduced levels of depression; the main unresolved issue was how long the stimulation of physical activity persisted after the patients had completed the immediate intervention.

Several reports have underlined an association between adequate physical activity and health outcomes, although given the cross-sectional nature of the observations, this could imply either benefit from the greater level of physical activity or less severe disease in those who were able to sustain an active lifestyle. Mennen-Winchell et al. used Canada Fitness Survey data to estimate the endurance activity of 96 men who had been treated with ADT for longer than 9 months. The reported absolute level of physical activity averaged 4.6 MET-h/week, and the bone mineral density of the hip and spine was significantly correlated with the volume of reported endurance activity, whether expressed in minutes per week of physical activity or MET-h per week. Self-reported
Table 11.5 Habitual physical activity and response to rehabilitation during and following the treatment of prostate cancer

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<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Type of physical activity</th>
<th>Findings</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Boisen et al. [103]</td>
<td>137 cases of PC</td>
<td>Self-selected</td>
<td>Active individuals had better quality of life on WHO scale and lower PSA levels</td>
<td>Cross-sectional comparison</td>
</tr>
<tr>
<td>Bonn et al. [104]</td>
<td>4623 men with localized PC followed for 10–15 yr</td>
<td>MET-h/day of walking/cycling, household work and exercise</td>
<td>194 deaths from PC, risk lower if walking/cycling &gt;20 min/d or exercising &gt;1 h/wk</td>
<td>Cross-sectional comparison</td>
</tr>
<tr>
<td>Chipperfield et al. [101]</td>
<td>356 men with PC</td>
<td>Adherence to national physical activity guidelines</td>
<td>42% of sample met guidelines; low activity was associated with depression, anxiety and co-morbid conditions</td>
<td>ADT patients less active than those given only irradiation</td>
</tr>
<tr>
<td>Kenfield et al. [105]</td>
<td>548 deaths in 2705 cases of PC followed 18 years</td>
<td>Vigorous activity &gt;3 hr/wk vs. &lt;1 hr/wk</td>
<td>61% lower risk of PC death (HR 0.39, 0.18–0.84) in active</td>
<td></td>
</tr>
<tr>
<td>Keogh et al. [102]</td>
<td>84 cases of PC on ADT</td>
<td>“Active” on questionnaire response</td>
<td>Less than half reported they were active; active individuals had higher QOL</td>
<td>Attitude and perceived behavioural control main determinants of physical activity</td>
</tr>
<tr>
<td>Livingston et al. [106]</td>
<td>147 cases of PC on ADT, 54 exercised, 93 usual care</td>
<td>Self-reported activity, QOL, anxiety and depression</td>
<td>Exercise programme increased vigorous exercise, cognitive functioning, reduced depression</td>
<td>Duration of study only 12 weeks</td>
</tr>
<tr>
<td>Mennen-Winchell et al. [107]</td>
<td>96 men treated with ADT &gt;9 months</td>
<td>Canadian Fitness Survey measure of habitual physical activity</td>
<td>BMD of hip and spine correlated with reported endurance activity (min/wk or MET-h/wk)</td>
<td>Self-reported exercise 4.6 MET-h/wk, Resistance exercise 0.7 MET-h/wk</td>
</tr>
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<td>Author</td>
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<tr>
<td>Richman et al.</td>
<td>1455 cases of localized PC followed ~2 years</td>
<td>Activity, walking duration and pace</td>
<td>117 events (local recurrence, secondary treatments, metastases, deaths)</td>
<td>Few engaged in vigorous physical activity</td>
</tr>
<tr>
<td>Wolin et al.</td>
<td>589 men undergoing radical prostatectomy for PC</td>
<td>Activity, obesity</td>
<td>Men active &gt;1 h/wk and not obese less likely to be urinary incontinent (RR 0.74, 0.52–1.06)</td>
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**Aerobic and/or resistance exercise**

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<th>Author</th>
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<tbody>
<tr>
<td>Buffart et al.</td>
<td>100 cases of PC aged 71.7 yr</td>
<td>6 months supervised aerobic and resistance exercise (2 times/wk), pedometer, exercise prescription, 6 months home programme vs. printed advice</td>
<td>Exercise programme had significant benefits for global QOL, physical function and social function at 6 months</td>
<td>Gains of physical function sustained at 12 months</td>
</tr>
<tr>
<td>Cormie et al.</td>
<td>63 cases of PC within 10 days of commencing ADT</td>
<td>3 months supervised aerobic and resistance exercise (32) vs. usual treatment (31)</td>
<td>Exercise preserved lean mass, avoided fat accumulation, greater aerobic power and muscle strength, lower body function, sexual function, less fatigue and psychological distress</td>
<td></td>
</tr>
<tr>
<td>Culos-Reid et al.</td>
<td>100 cases of PC receiving ADT &gt;6 months; 53 in intervention group vs. 47 controls</td>
<td>16 week programme (supervised once/wk, 4 home sessions/wk)</td>
<td>Significant increases in physical activity, changes in girth and blood pressure, trends to less depression and fatigue in exercise group</td>
<td>Conclusions limited by drop-outs (11/53 in intervention, 23/47 in controls)</td>
</tr>
</tbody>
</table>
Table 11.5 continued

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<tr>
<th>Author</th>
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</thead>
<tbody>
<tr>
<td>Galvao et al.[113]</td>
<td>10 men with localized PC on ADT</td>
<td>20 wk resistance training at 6–12 RM</td>
<td>Muscle strength and endurance increased, gains of forward and backward walking, chair rise time, stair climbing, 400 m walk and balance</td>
<td></td>
</tr>
<tr>
<td>Galvao et al.[72]</td>
<td>57 cases of PC with ADT</td>
<td>12 weeks resistance and aerobic exercise vs. usual care</td>
<td>Increase of lean mass and muscle strength, faster forward and backward walk, less reactive protein, less fatigue and enhanced QOL in exercised group</td>
<td>No adverse events among exercisers</td>
</tr>
<tr>
<td>Galvao et al.[114]</td>
<td>100 cases of PC with ADT</td>
<td>6 months supervised exercise and 6 month home programme vs. educational material</td>
<td>Intervention gave increased aerobic performance, muscle mass and strength, self-reported physical functioning</td>
<td>Benefits seen at 6 months, maintained at 12 months with home programme</td>
</tr>
<tr>
<td>Hansen et al.[115]</td>
<td>10 cases of PC, 5 receiving ADT</td>
<td>Recumbent, high force eccentric cycle ergometer exercise 3 times/wk for 12–15 min</td>
<td>Both groups showed enhanced strength and functional mobility (6 min walk distance)</td>
<td>Strength training response not impaired by ADT</td>
</tr>
<tr>
<td>Hanson et al.[116]</td>
<td>17 African Americans with PC, on ADT</td>
<td>12 weeks of strength training</td>
<td>Increase of muscle mass (2.7%), strength (28%), QOL (7%), decreased perceived fatigue (38%)</td>
<td>Muscle hypertrophy occurs in absence of testosterone. No control group</td>
</tr>
<tr>
<td>Jones et al.[117]</td>
<td>50 cases of PC treated by radical prostatectomy</td>
<td>5 walking sessions/week at 55–100% of peak oxygen intake vs. usual care</td>
<td>Similar reduction of erectile dysfunction in intervention and control group (20, 24%)</td>
<td></td>
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<tr>
<td>Kvorning et al.</td>
<td>22 healthy but untrained men, 11 treated with ADT for 12 wk</td>
<td>8 wk strength training at 6–10 RM</td>
<td>No change of isometric knee extension in ADT group, untreated men show 10% increase</td>
<td>ADT reduced testosterone level 22.6 to 2.0 nmol/L</td>
</tr>
<tr>
<td>Monga et al.</td>
<td>21 cases of PC treated by radiation alone; 11 aerobic exercise, 10 controls</td>
<td>Aerobic exercise 3 times/wk for 8 weeks</td>
<td>Exercised group showed gains in aerobic fitness, strength, flexibility, QOL, physical and social well-being, less fatigue</td>
<td></td>
</tr>
<tr>
<td>Nilsen et al.</td>
<td>58 cases of PC on ADT</td>
<td>28 followed 16 wk high-load strength training, 30 usual care controls</td>
<td>Gains of LBM in upper and lower limbs, but not total LBM; gains of 1-RM strength, sit-to-stand, stair climbing and shuttle walk in exercisers</td>
<td>No change in fat mass in exercisers</td>
</tr>
<tr>
<td>Norris et al.</td>
<td>30 cases of PC not receiving ADT</td>
<td>12 weeks of resistance exercise 3 or 2 times/wk</td>
<td>Gains of lower body strength, chair stand time, sit-and-reach and 6 min walk, distance greater for 3/wk than for 2/wk group</td>
<td>2/wk more favourable for mental component of QOL</td>
</tr>
<tr>
<td>Park et al.</td>
<td>49 cases of PC</td>
<td>Resistance, flexibility and Kegel exercises 2/wk for 12 weeks vs. Kegel exercises alone</td>
<td>Exercise group fared better on strength (except grip), continence (71% vs. 44%) and QOL</td>
<td></td>
</tr>
<tr>
<td>Segal et al.</td>
<td>155 cases of PC on ADT</td>
<td>Resistance exercise 3/wk for 12 wks (n = 82) vs. wait-list controls (n = 73)</td>
<td>Increased levels of upper and lower body fitness, less fatigue, increased QOL in exercisers</td>
<td>No changes in BMI or body fat in exercisers</td>
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<tr>
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<tr>
<td>Segal et al.</td>
<td>121 cases of PC, some receiving ADT</td>
<td>Aerobic exercise vs. resistance exercise vs. usual care</td>
<td>Both aerobic and resistance exercise reduced fatigue; resistance exercise also yielded gains of strength and QOL</td>
<td>Resistance exercise reduced triglycerides and body fat</td>
</tr>
<tr>
<td>Windsor et al.</td>
<td>66 cases of localized PC</td>
<td>Aerobic exercise (home-based walking 30 min 3/wk) vs. controls</td>
<td>Improvement of shuttle-run score with no significant increase in fatigue in exercisers</td>
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</tr>
<tr>
<td>Winters-Stone et al.</td>
<td>51 cases of PC on ADT</td>
<td>1 yr of impact + resistance exercise (2 supervised sessions, 1 home/wk) vs. placebo stretching exercises</td>
<td>Loss of BMD: 0.4% in exercisers vs. –3.1% in controls</td>
<td>84% 1 yr adherence to exercise, no injuries</td>
</tr>
<tr>
<td>Bourke et al.</td>
<td>25 patients with advanced PC on ADT, vs. 25 standard treatment</td>
<td>12-week lifestyle programme (aerobic and resistance exercise, dietary advice)</td>
<td>Improved exercise behaviour, diet, energy intake, aerobic tolerance, muscle strength, less fatigue in exercisers</td>
<td>Attrition of exercisers 44% at 6 months, no effect on clinical</td>
</tr>
<tr>
<td>Bruun et al.</td>
<td>Men receiving ADT &gt;6 months, 21 soccer group, 20 controls, 32-wk follow-up</td>
<td>Community-based recreational football (45–60 min, 2–3/wk) vs. standard care</td>
<td>Soccer gave significant advantages in bone density, jump height and stair climbing</td>
<td>2 fibula fractures and 3 muscle or tendon injuries in soccer group</td>
</tr>
<tr>
<td>Craike et al.</td>
<td>52 men treated for PC</td>
<td>3 month supervised exercise programme</td>
<td>Adherence 80%; role functioning and hormonal symptoms predicted adherence</td>
<td>Positive perceptions of ability increased adherence</td>
</tr>
<tr>
<td>Demark-Wahnefried et al.</td>
<td>543 prostate and breast cancer survivors</td>
<td>Tailored diet and exercise print intervention vs. non-tailored materials</td>
<td>Tailored programme increased exercise (59 vs. 39 min/wk), BMI –0.3 vs. +0.1 kg/m²</td>
<td>95.6% completed 1-yr intervention</td>
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</table>

**Special programmes**

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<tr>
<td>Demark-Wahnefried et al.</td>
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<td>95.6% completed 1-yr intervention</td>
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</table>
participation in endurance exercise was also associated with greater density of the hip bones as assessed by dual energy x-ray absorptiometry. Others have commented on an association of habitual physical activity with muscular fitness, physical functioning and quality of life in prostate cancer survivors. Thus, a survey of questionnaire respondents (137 of 348 men treated for prostate cancer) made a cross-sectional comparison between those who maintained an adequate level of habitual physical activity and those who did not. It found greater social participation, a better quality of life on the WHO scale and lower prostate serum antigen levels in the more active individuals.

Both a lower overall and a lower prostate-specific mortality have been seen in more active individuals. Bonn et al. followed 4623 men with localized prostate cancer for 10–15 years. A questionnaire assessed activity (MET-h/day

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<tbody>
<tr>
<td>Sajid et al.</td>
<td>19 cases of PC on ADT</td>
<td>Home-based walking/resistance exercise 5 days/wk vs. technology-mediated home programme vs. usual care for 6 wks</td>
<td>Best response is to home-based programme (increase of 2720 steps/day)</td>
<td></td>
</tr>
<tr>
<td>Santa Mina et al.</td>
<td>10 cases of PC on ADT</td>
<td>60 min group exercise or personal trainer, 3/wk for 8 wk</td>
<td>Suggestion of better response with personal trainer</td>
<td></td>
</tr>
<tr>
<td>Skinner et al.</td>
<td>51 cases of PC</td>
<td>4 sessions of supervised exercise over 4 wk</td>
<td>Gains of strength, 400 m walk, chair stands, walking speed, sit-and-reach, well-being</td>
<td>Uncontrolled study</td>
</tr>
<tr>
<td>Uth et al.</td>
<td>57 men receiving ADT &gt;6 months</td>
<td>32 weeks of recreational football 2–3 times/wk vs. standard care</td>
<td>Football gave significant gains in BMD, LBM, muscle strength, maximal oxygen intake, jump height and stair climbing</td>
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Notes: ADT = androgen deprivation therapy; BMD = bone mineral density; HR = hazard ratio; LBM = lean body mass; MET = metabolic equivalent; PC = prostate cancer; PSA = prostate serum antigen; QOL = quality of life; RM = repetition maximum; RR = relative risk
invested in walking/cycling, household work and exercise). There were 194 deaths from prostate cancer during the follow-up, with a lower risk lower among those walking/cycling >20 min/day or exercising >1 hour per week. A similar study by Kenfield et al.[105] looked at 548 deaths in 2705 cases of prostate cancer who were followed for 18 years. Survival was compared between those taking more than three hours vigorous activity per week and those spending less than one hour per week. Those taking more vigorous activity had a 61% lower risk of dying from prostate cancer (hazard ratio 0.39 [0.18–0.84]). The same group of investigators (Richman et al.[108]) followed 1455 cases of localized prostate cancer for an average of ~2 years. Over the follow-up, there were a total of 117 events (a local recurrence, a need for secondary treatment, metastases or death). Few of the sample engaged in vigorous physical activity. Nevertheless, disease progression was less likely in men who walked briskly for three or more hours per week, or who engaged in vigorous physical activity more than three hours per week than in those who did not take such exercise (HR = 0.63 [0.32–1.23], p for trend = 0.17).

Urinary incontinence is often a major handicap following radical prostatectomy. Wolin et al.[109] demonstrated that in 589 men who had undergone such treatment there was a trend to a lower risk of incontinence in men who were active for more than one hour per week (relative risk 0.74 [0.52–1.06]). However, incontinence can limit exercise participation, so it is difficult to be sure whether this is cause or effect!

Aerobic and resistance exercise programmes

Many investigators have followed the programmes recommended by consensus groups (a combination of aerobic, resistance, impact and flexibility exercises). However, some have focused uniquely on aerobic or resistance training. Some interventions have continued for as long as a year. In 100 cases of prostate cancer who were receiving ADT, Galvao et al.[114] compared responses in those individuals who received six months of supervised exercise followed by a six-month home programme with the findings in a group who were simply given educational material. The direct exercise intervention enhanced aerobic performance, muscle mass, strength and self-reported physical functioning compared to the comparison group. Benefits were apparent at six months, and were maintained after six further months of home exercises. In another report from the same laboratory, Buffart et al.[110] followed 100 cases of prostate cancer aged an average of 71.7 years for 12 months. A half of the group received six months of supervised aerobic and resistance exercise twice per week, followed by a six-month home programme with a pedometer and a detailed exercise prescription, and the remaining subjects received standard treatment plus some printed advice. At six months, the exercise group showed significant benefit relative to the comparison group in terms of the global quality of life, physical function and social function, and these gains of physical function were sustained at 12 months.
Culos-Reid et al. [112] assigned 53 of 100 cases of prostate cancer who had been receiving ADT for longer than 6 months to a 16 week programme of once-weekly supervised exercise, supplemented by up to 4 home sessions per week. Relative to 47 controls, they showed significant increases in physical activity and reductions of abdominal girth and blood pressure, with trends to less depression and fatigue; however, conclusions were limited by the small sample and a substantial number of drop-outs (11 in the intervention group and 23 among the controls).

The benefits of increased exercise can be realized quite quickly. Thus, Galvao et al. [72] examined 57 cases of prostate cancer who were receiving ADT after 12 weeks of assignment to either a bi-weekly aerobic and resistance exercise programme or usual care. The three-month intervention was sufficient to induce increases of lean mass and muscle strength, faster forward and backward walking speeds, a decrease of one marker of chronic inflammation (c-reactive protein concentrations), less fatigue and an enhanced quality of life. Moreover, there were no adverse events among the exercisers. Cormie et al. [111] examined the benefits of the early initiation of an aerobic and resistance exercise programme. Cases were contacted within 10 days of beginning ADT, with 32 following a 3-month aerobic and resistance exercise programme (twice weekly, supplemented by home exercise), and 31 subjects serving as controls. The exercise programme conserved lean mass and reduced the accumulation of body fat relative to the controls. The exercisers also showed a greater aerobic power and muscular strength, with better lower body function and sexual function, less fatigue and less psychological distress.

Segal et al. [124] compared aerobic exercise with resistance exercise or usual treatment in 121 cases of prostate cancer, some of whom were receiving ADT. Both aerobic and resistance exercise increased aerobic fitness and reduced fatigue relative to usual treatment, but the resistance exercise group also demonstrated gains of strength and quality of life, with a reduction of triglycerides and body fat.

Among studies using only aerobic training, some have found a good response, but in others gains have been disappointing. Monga et al. [119] investigated 21 patients with localized prostate cancer, treated by irradiation alone. Eleven of the group undertook eight weeks of aerobic exercise (three times/week), and despite the short duration of their programme, they showed substantial advantages relative to the ten controls (gains in aerobic fitness, strength, flexibility, quality of life, physical and social well-being, and less fatigue). Windsor et al. [125] examined 66 cases of localized prostate cancer. A half of the group were assigned to a home-based aerobic walking programme (30 minutes of walking, 3 times/week). All of the exercisers maintained at least this minimum activity over the four weeks of radiotherapy. Despite the very brief duration of the intervention, the exercised group showed an improved score on the shuttle run test, with no significant increase of fatigue.

In contrast, Jones et al. [117] studied 50 cases of prostate cancer who had undergone radical prostatectomy, but apparently were not receiving ADT. A six-months aerobic programme (5 walking sessions/week at 55–100% of peak oxygen intake)
led to no greater reduction of erectile dysfunction among the exercisers than that seen in the usual care group.

Among programmes that have focused specifically on resistance training, substantial gains of muscle strength have been observed, despite the low levels of circulating androgens caused by the ADT. Galvao et al.\cite{113} enrolled 10 men with localized prostate cancer who were receiving ADT in a 20 week resistance training at a 6–12 repetition maximum intensity. This induced gains in muscle strength and endurance, forward and backward walking times, chair-stand speed, stair climbing, 400 m walk and balance. Hansen et al.\cite{115} looked at the effects of eccentric training in ten cases of prostate cancer, five of whom were receiving ADT. The programme involved recumbent, high force eccentric cycle ergometer exercise performed for 12–15 minutes, 3 times per week. This regimen enhanced isometric strength and functional mobility, the latter shown by a greater six minute walking distance, whether or not the subject was receiving ADT. Hanson et al.\cite{116} made similar observations on 17 African Americans with prostate cancer who were receiving ADT; 12 weeks of strength training led to an increase of muscle mass (2.7%), strength (28%) and quality of life (7%) and a decreased perception of fatigue (38%), despite the demonstrated suppression of testosterone levels. Nilsen et al.\cite{120} studied 58 cases of prostate cancer on ADT; 28 of the group followed a 16-week high-load strength training programme, and the other 30 men served as usual care controls. Relative to the controls, the strength-training group showed gains of lean body mass in the upper and lower limbs (although not in the total lean mass), gains of 1-RM strength, sit-to-stand times, stair-climbing performance and shuttle-walk scores. Segal et al.\cite{123} evaluated 155 cases of prostate cancer on ADT; 82 were assigned to resistance exercise 3 times per week for 12 weeks, and 73 remained in a wait-list control group. Despite the ADT, the exercised group again showed increased levels of upper and lower body fitness, less fatigue and an increased quality of life.

In contrast to the responses observed in those with prostate cancer, Kvorning et al.\cite{118} carried out a study on 22 healthy but untrained men, administering ADT to 11 of the group for 12 weeks. In this population, strength training (8 weeks at 6–10 RM) increased the isometric knee extension of the controls by 10%, but there was no change of strength in those receiving ADT (where circulating testosterone levels had dropped from 22.6 to 2.0 nmol/L).

Possibly, the gains of muscle strength realized despite ADT in those with prostate cancer may reflect better neuromuscular coordination rather than muscle hypertrophy, since in general there have been no changes of body mass index or body fat in response to the resistance training.

How often should resistance exercise be performed? Unfortunately, the answer is not very clear. Norris et al.\cite{121} assigned 30 cases of prostate cancer who were not receiving ADT to 12 weeks of resistance exercise, performed 2 or 3 times per week. The thrice-weekly group fared better than the twice-weekly group on the physical components of response, including gains of lower body strength, chair-stand times, sit-and-reach distances and the six minute walk distance, but the twice per week group fared better on the mental component of quality of life,
including scores for mental health, vitality, emotional role, anxiety, happiness and perceived stress.

The loss of bone mineral density is a major concern with ADT. Winters-Stone et al.\cite{126} thus compared one year of high impact plus resistance exercise (two one-hour supervised and one home session/week) with a placebo programme of light stretching in 51 cases of prostate cancer on ADT. The resistance exercise group showed a one-year adherence of 84%, without injuries, and a substantially smaller decrease in bone mineral density relative to those on the stretching programme (an average loss of only $-0.4\%$ vs. $-3.1\%$).

Park et al.\cite{122} evaluated a combination of resistance, flexibility and Kegel exercises vs. Kegel exercises alone in a 12 week biweekly trial. The exercise group fared better on measures of strength (except grip strength), urinary continence ($71\%$ vs. $44\%$, with 24-hour pad weights of $12$ vs. $46$ g), quality of life and depression scales.

**Special considerations in programme design**

Unfortunately, vigorous physical activity seems necessary for enhanced outcomes during ADT.\cite{106} Relatively few prostate cancer survivors spontaneously engage in adequate volumes of physical activity.\cite{101} This may be in part because of the symptoms associated with androgen-suppression\cite{130} but another issue is the need to adapt programmes in the light of specific complications such as urinary incontinence and exercise-induced diarrhoea. Some investigators have found good sustained compliance with what seem fairly standard exercise programmes, albeit with some individual tailoring, but others have suggested that motivation can be boosted by novel approaches such as a recreational soccer programme\cite{129} or the use of a personal trainer.

Craike et al.\cite{130} examined factors influencing adherence to a 3-month exercise programme (2 supervised sessions, 1 unsupervised session/week) in 52 men who were undergoing treatment for prostate cancer. Adherence averaged $80\%$ and was influenced by role functioning and hormone-related symptoms, with effects from perceptions of ability increasing adherence.

Bourke et al.\cite{127} compared the response to a 12-week lifestyle programme with standard treatment in 2 groups of 25 men with advanced prostate cancer who were receiving ADT. The 12-week lifestyle programme comprised aerobic and resistance exercise (twice weekly for six weeks, once weekly for a further six weeks, plus self-directed exercise and dietary advice). This regimen improved exercise behaviour, diet, energy intake, aerobic tolerance, muscle strength and reduced fatigue in participants, but it had no effect on clinical disease, and the attrition rate was $44\%$ by six months.

Demark-Wahnefried et al.\cite{131} explored the value of personally tailored mailed recommendations for diet and exercise vs. non-tailored recommendations in a mixed sample of 543 breast and prostate cancer survivors. The personally tailored information led to a larger increase in weekly exercise ($59$ vs. $39$ min) relative to the non-tailored recommendations, and there was also a favourable change in the
body mass index of participants (−0.3 vs. +0.1 kg/m²). Moreover, the compliance for the one-year intervention was high (95.6%). Another comparison of a supervised programme of aerobic and resistance exercise with general printed physical activity recommendations found that the former gave greater improvements in global quality of life as well as physical and social functioning, all mediated by improved lower body functioning. Sajid et al. divided 19 cases of prostate cancer on ADT between a home-based walking and resistance exercise programme, a technology mediated programme and usual care. The sample was rather small for clear conclusions, but the home programme appeared to yield the best results, with an increase in step count of 2720 steps/day over the course of the trial.

Skinner et al. examined the effects of a minimal exercise intervention (four sessions of supervised exercise over four weeks) in an uncontrolled study of 51 cases of prostate cancer. They reported gains of muscle strength, 400 m walk times, chair-stand times, walking speed, sit-and-reach and well-being with this very limited intervention.

Bruun et al. and Uth et al. argued for the motivational value of participating in community-based recreational soccer. Men receiving ADT for longer than six months were divided into a soccer group (n = 21) and a usual treatment group (n = 20). Over a 32-week follow-up, the soccer participants gained significant advantages in bone density, jump height and stair climbing relative to standard care, but they sustained two fractures of the fibula and three muscle or tendon injuries. Uth et al. further evaluated the motivational and therapeutic value of recreational soccer (2–3 games/week for 32 weeks) in 57 men who were receiving ADT. Relative to usual-care controls, they showed substantial gains in bone mineral density, along with increases of lean body mass, muscle strength, maximal oxygen intake, jump height and stair-climbing ability.

Santa Mina et al. compared the response to 60 minutes of group exercise, 3 times per week for 8 weeks to the benefits seen with the services of a personal trainer. In ten cases, there was a trend suggesting that the personal trainer was somewhat more effective than group exercise.

Areas for further research

The value of regular physical activity as a means of reducing the risk of prostate cancer is still not proven conclusively. One obstacle to resolving this issue is that even when a large population is followed for a long period, the number of cases of cancer remains quite small. Given the number of studies that have already been carried out, meta-analysis may provide some resolution to this question, but challenges include differences between samples, differing criteria used to identify active individuals and variations in the age at which activity has been evaluated. One alternative may be to study a high-risk group, looking at the effectiveness of increased physical activity in preventing a recurrence of the tumour in those who have completed treatment. Possibly, as mechanisms of carcinogenesis are clarified, it may also become possible to determine which types of physical
activity are best suited to modulating the causal agents. It also seems worth following up suggestions from *post-hoc* analyses that susceptibility to exercise is modified by the subject’s age or by the aggressivity of the tumour.

The spontaneously chosen level of physical activity amongst those undergoing treatment for prostate cancer is typically below recommended levels for good health, and there is a need for research on tactics to increase habitual physical activity in this population. The gains of strength observed with resistance training in patients who are receiving ADT are intriguing, and studies are needed to examine how far these represent true muscle hypertrophy and how far they simply reflect test learning and greater neuromuscular coordination.

**Practical implications and conclusions**

Despite many cohort and case control studies, the suggestion that physical activity reduces the risk of prostate cancer has yet to be proven conclusively. About a half of studies show a favourable trend or a statistically significant benefit, commonly with a reduction in risk of 10–30%. Moreover, there is little evidence that moderate exercise has an adverse effect upon prostate health, so that it is good practice to advocate regular exercise while conclusive proof is awaited. The use of ADT following the immediate treatment of prostate cancer unfortunately carries many side-effects, including a reduction of aerobic and muscle power, a demineralization of bone and an impaired quality of life. However, an exercise rehabilitation programme is helpful in countering these adverse effects.

**References**


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