Eur J Appl Physiol (2015) 115:1–46
DOI 10.1007/s00421-014-3031-6

INVITED REVIEW

Effects of physical activity upon the liver

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Received: 5 March 2014 / Accepted: 14 October 2014 / Published online: 4 November 2014

Abstract
Purpose To review the responses of the liver to acute and chronic physical activity and to summarize relationships between physical activity and liver health.
Methods A systematic search of HealthStar/Ovid from 1975 through June of 2013, supplemented by articles from other sources.
Results 351 of 8,010 articles identified by HealthStar/Ovid were supplemented by 92 other papers; after focussing, the review was reduced to 435 citations. Prolonged acute exercise reduces hepatic blood flow, stimulating hepatic glycogenolysis, gluconeogenesis and synthesis of some proteins; however, lipid metabolism shows little change. Glutathione depletion suggests oxidative stress. Enzymes affecting carbohydrate metabolism are up-regulated, and lipogenic enzymes are down-regulated. The main triggers are humoral, but hepatic afferent nerves, cytokines, reactive oxygen species, and changes in hepatic blood flow may all play some role. Regular aerobic exercise training improves blood glucose control during exercise by increasing glycogen stores and up-regulating enzymes involved in gluconeogenesis and carbohydrate metabolism. Resistance to oxidant stress is generally increased by training. Lipogenic enzymes are down-regulated, and lipid metabolism is augmented. Modulations of insulin, insulin-like growth factor, glucagon and interleukin-6 may trigger the adaptive responses to training. Cross-sectional and longitudinal studies show that regular exercise can reduce hepatic fat, but the effect on circulating aminotransferases is unclear and the modality and dose of physical activity optimizing health benefits need clarification.
Conclusions Regular moderate physical activity enhances liver health. Adverse functional changes can develop if habitual activity is inadequate, and extremely prolonged competitive exercise may also be harmful, particularly under harsh environmental conditions.

Keywords Diabetes mellitus · Fatty liver · Hepatic blood flow · Hepatic clearance · Metabolic syndrome · Obesity · Oxidative stress · Steatosis · Steato-hepatitis · Ultra-marathons

Abbreviations

ACC	Acetyl-coa carboxylase
ADP	Adenosine diphosphate
AKT	Protein kinase B
ALT	Alanine transaminase
AMP	Adenosine monophosphate
AMPK	Adenosine monophosphate kinase
ARFRP1	ADP-ribosylation factor-related protein 1
AST	Aspartate transaminase
ATP	Adenosine triphosphate
BCKDH	Branched-chain alpha-ketoacid dehydrogenase

Communicated by Nigel A.S. Taylor.

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cAMP	Cyclic adenosine monophosphate
CK	Cytokeratin
CoA	Coenzyme A
CT	Computerized tomography
DNA	Desoxyribonucleic acid
eIF2	Eukaryotic initiation factor 2
ERK	Extracellular signal-regulated kinase
FFA	Free fatty acid
GGT	Gamma glutamyl transferase
GLUT-2	Glucose-transporter-2
G protein	Guanine-nucleotide binding protein
GTP	Guanosine triphosphate
HAD	*B*-hydroxyacyl-dehydrogenase
HDL-c	High-density lipoprotein cholesterol
HISS	Hepatic insulin sensitizing substance
HMG-CoA	Hydroxymethylglutaryl-CoA
HSP	Heat shock protein
IGF-1	Insulin-like growth factor-1
IGFBP	Insulin-like growth factor binding protein
IL	Interleukin
IMTG	Intramyocellular triglyceride
JAK	Janus kinase
JNK	c-jun N-terminal kinase
LDH	Lactate dehydrogenase
MAPK	Mitogen-activated protein kinase
MDA	Malondialdehyde
mRNA	Messenger ribonucleic acid
NAFLD	Non-alcoholic fatty liver disease
NF-κB	Nuclear factor kappa-B
NOx	Mononitrogen oxides
PECPK	Phosphoenolpyruvate carboxykinase
PERK	Protein-kinase like endoplasmic reticular kinase
SCD-1	Stearoyl-CoA desaturase-1
sFasL	Soluble Fas ligand
SREBP-1c	Regulatory element-binding protein-1c
STAT	Signal transducer and activator of transcription
TRB3	Tribbles-related protein 3
VLDL	Very low density lipoprotein triglycerides
$\dot{V}O_{2max}$	Maximal oxygen intake

Introduction

The liver is a major body organ that plays a central role in the regulation of carbohydrate and lipid stores, and ensures an adequate supply of metabolites for both vigorous physical activity and the synthesis of muscle and brain tissue (Wasserman and Cherrington 1991; Kjaer 1998; Wahren and Ekberg 2007; Fritsche et al. 2008). It also plays a vital role in metabolizing and/or excreting many unwanted substances from the circulation. However, until recently there has been a relative dearth of literature describing the effects of physical activity upon the liver.

Interest in this question has arisen from the understanding that hepatic fatty infiltration (fatty liver) is independently associated with the metabolic syndrome, cardiovascular disease and type 2 diabetes mellitus, and from emerging evidence of an inverse association between physical activity and the risk of developing fatty liver. The latter topic has been the subject of other reviews, although with five exceptions (Eslami et al. 2009; Socha et al. 2009; Thoma et al. 2012; Keating et al. 2012; Musso et al. 2012), these have been unstructured. The contribution of physical inactivity to the development of fatty liver has been commonly acknowledged, and many authors have recommended exercise programmes or an increase of habitual activity as one element in therapy for this pathology (Table 1). Historically, this reflected a widespread view that lifestyle therapy, including regular exercise, could moderate fatty liver by assisting in weight loss, but more recently there has been a growing perception that regular physical activity in itself can exert beneficial effects upon the liver.

Much less is known about the homeostatic role of the liver during acute and chronic physical activity, even in healthy individuals. Available human studies have generally documented positive effects of acute and chronic exercise on liver glucose homeostasis and overall benefits of exercise training upon lipids and lipoprotein metabolism, including a reduction in hepatic fat infiltration (steatosis). These tissue-level observations have been amplified by rodent investigations showing an association between inadequate habitual physical activity and a down-regulation of the key hepatic enzymes associated with glucose and fat metabolism.

The present review examines gross and cellular responses of the liver to both acute and chronic physical activity, spanning the spectrum from physical inactivity to large volumes of vigorous exercise. The primary intention is to compile the collective research (from rodent to human, and tissue-level to molecular) concerning the acute and chronic effects of physical activity upon the healthy liver, in order to characterize the typical physiological responses of the liver to exercise. The review includes exercise-induced effects on hepatic blood flow and lipid and protein metabolism, with particular emphasis upon the interactions between exercise and glucose homeostasis, the molecular changes underlying these interactions, and their potential triggers. Secondary goals are to examine the patterns of regular physical activity associated with maintenance of normal hepatic function, and to document relationships between inadequate habitual physical activity and abnormalities of hepatic function.

Table 1 Reviews considering the potential of exercise in the treatment of steatosis

Author	Number of references	Type of review	Comments	Conclusions
Alisi et al. (2010)	54	Unstructured review	Drugs might enhance response	Combination of diet and exercise can modify course of simple steatosis
Bacchi and Moghetti (2013)	18	Unstructured review		Exercise may reduce hepatic fat and hepatic enzymes, independent of dietary modifications
Caldwell and Lazo (2009)	48	Unstructured review		More exercise seems better, but optimal intensity not known
Cheung and Sanyal (2009)	101	Unstructured review	Some discussion of possible cellular mechanisms	Weight loss and increased exercise consistently associated with improved liver histology
Centis et al. (2010)	65	Unstructured review	Drugs should remain a second line of treatment	Weight loss and physical activity have specific therapeutic role
Conjeevaram and Tiniakos (2011)	26	Editorial review		Physical activity recommended, but lack of criteria for intensity, volume and duration of exercise
Della Corte et al. (2011)	96	Unstructured review	Drugs may serve as adjuvants	Weight loss diet and exercise are first line therapeutic measures
Dowman et al. (2011)	167	Unstructured review	No highly effective drug treatment	Need for multifaceted treatment: diet, exercise and behavioural counselling
Duvnjak et al. (2009)	151	Unstructured review	Value of pharmacological adjuvants unproven	Diet and exercise first line interventions, but problems of poor compliance. Lack of specific exercise guidelines
Eslami et al. (2009)	70	Systematic review		No effective treatment for steatosis- but weight loss and increased physical activity can improve enzymes and hepatic histology
Johnson and George (2010)	57	Unstructured review	Weight loss needs to be 3–10 % of body mass to reduce steatosis	Enzyme levels reduced and steatosis improved with exercise independent of weight loss
Keating et al. (2012)	47	Systematic review and meta-analysis to August 2011	12 studies included in meta-analysis	Beneficial effect of exercise on liver fat with little or no weight loss. No effect on ALT
Mencin and Lavine (2011)	95	Unstructured review	Vitamin E may be a helpful adjunct	Treatment remains diet and exercise
Musso et al. (2012)	140	Systematic review and meta-analysis	Statins and polyunsaturated fats also improved steatosis, but effects on liver histology unclear	Lifestyle weight loss >7 % safe, improved hepatic risk profile, but achieved by <50 % of patients
Nobili et al. (2011)	40	Unstructured review		Improved physical activity and nutrition needed to manage and treat condition
Nobili and Sanyal (2012)	72	Unstructured review	No drugs yet of proven value	Best approach is diet + exercise, but motivation is difficult
Rector and Thyfault (2011)	93	Unstructured review		Due to physical inactivity, low aerobic fitness and overnutrition singly or in combination
Reynoso and Lavine (2012)	10	Editorial	Conclusions based on guidelines of American Association for the Study of Liver Diseases, the American Gastroenterological Association, and the American College of Gastroenterology	Exercise (unspecified) might reduce steatosis but effect on other aspects of histology unknown
Rodriguez et al. (2012)	25	Semi-structured review		Optimal exercise regimen in terms of effectiveness and compliance has yet to be determined; reduction in sedentary time might also help

Table 1 continued

Author	Number of references	Type of review	Comments	Conclusions
Socha et al. (2009)	57	Structured review	Main focus on patients unable or unwilling to change lifestyle	Data insufficient to determine value of alternatives to lifestyle change
Spassiani and Kuk (2008)	28	Unstructured review	Most studies to date have included multiple therapies	Independent effect of exercise upon liver fat content unclear
Targher et al. (2010)	125	Unstructured review	Pharmacotherapy a questionable option	Team of experts needed to correct "unhealthy" habits, including exercise specialist
Thoma et al. (2012)	49	Structured review		23 studies identified; seven had control groups, six randomized. Consistent reductions in liver fat and ALT, correlated most strongly with decrease in body mass. Usually reduced insulin resistance, but changes of fibrosis less consistent
Yoneda et al. (2006)	Not stated in abstract	6-page review in Japanese		Since central obesity and insulin resistance are likely causes, exercise and nutritional counselling warranted. Lack of specific exercise guidelines
Zelber-Sagi et al. (2011)	151	Unstructured review	2-year compliance with physical activity as low as 20 %	Lifestyle modification with increased physical activity first line, aim of 5–10 % weight reduction

Search techniques and classification of physical activity

The data base of HealthStar/Ovid was scanned from 1975 through June of 2013, using the terms exercise, exercise therapy, exercise training, activity, motor activity and physical activity vs. liver, liver cirrhosis, liver disease, fatty liver, liver failure, liver neoplasms, liver regeneration and liver transplants. This search yielded 8,010 hits. All articles that included a full abstract were examined, and 351 items that were specifically designed to examine the effects of acute or chronic physical activity upon the liver were included. This initial database was supplemented with 92 articles gleaned from reference lists and the authors' own extensive personal files; 8 reports were eliminated with a subsequent focusing of the review to exclude studies of the gall bladder and biliary tract, thus yielding a total of 435 citations.

For the purpose of this review, we have adopted the international consensus definitions (Bouchard and Shephard 1994) of physical activity (any bodily movement produced by the skeletal muscles and resulting in significant energy expenditure) and exercise (physical activity undertaken purposefully, with the intent of developing physical or physiological condition (e.g. cycling, treadmill running or athletic competition in humans and wheel/treadmill running in rodents)). Semantic descriptions have arbitrarily classed the intensity of effort as: low (30–50 % of $\dot{V}O_{2max}$), moderate (50–65 % of $\dot{V}O_{2max}$), vigorous or strenuous (>65 % of $\dot{V}O_{2max}$), and exhausting (exercise pursued to exhaustion), based on the ranges previously described (Thompson 2010). Prolonged exercise is arbitrarily defined as bouts of 30 min or longer.

Acute effects of moderate endurance exercise

Hepatic blood flow

An acute bout of exercise transiently reduces blood flow to the liver. Estimates of hepatic blood flow in humans are commonly based upon indocyanine clearance. Studies using this technique have shown that blood flow to the liver and viscera decreases by up to 20 % during a brief period of vigorous effort, and even more if exercise is prolonged or is undertaken in a hot environment (Lundbergh and Strandell 1974; Rowell et al. 1964; Rowell 1974; Rowell 1986; van Wijck et al. 2011). There appears to be a dose–response relationship, with hepatic blood flow decreasing progressively as exercise intensity increases towards $\dot{V}O_{2max}$.

Elimination of indocyanine depends upon both hepatic blood flow and cellular function (Daemen et al. 1989). Thus, it has been argued that this method of measuring hepatic blood flow may be confounded by altered hepatic

metabolism during heavy exercise. Nevertheless, the trends indicated by the indocyanine method have been corroborated by studies based on sorbitol clearance; the latter technique has shown blood flow reductions of ~40 % at 40 % of $\dot{V}O_{2max}$ (Busse et al. 2004), of 60–70 % at 60–70 % of $\dot{V}O_{2max}$ (Kemme et al. 2000), and of 83 % during near-maximal exercise (Schoemaker et al. 1998). Although the magnitude of the immediate decrease in hepatic blood flow remains contentious (Froelich et al. 1988; Flamm et al. 1990), observations on human subjects have been confirmed by animal studies, where para-aminohippuric acid and sulfobromthalein were injected into a mesenteric vein, and samples drawn from both portal and hepatic veins (Katz and Bergman 1969; Yano et al. 1996).

On cessation of acute exercise, recovery of the resting hepatic blood flow appears to be rapid and indeed there is some evidence from ultrasound studies of human hepatic portal blood flow that hepatic blood flow exceeds normal resting levels for a few hours following physical activity (Hurren et al. 2011). This may reflect inflammation; arguably, it also serves to replenish glycogen reserves and speed the clearance of triacylglycerol from the circulation (Hurren et al. 2011).

We may thus conclude that although vigorous exercise induces a substantial immediate reduction of hepatic blood flow, this is rapidly reversed during recovery, and there is no evidence of subsequent harm to the liver.

Carbohydrate metabolism

Human experimental studies using the stable isotope technique have demonstrated that liver glucose output is increased during exercise (Ahlborg et al. 1974). This serves to maintain blood glucose levels and contributes to the overall increase in the rate of glucose oxidation that is observed using indirect calorimetry. The rate of glucose oxidation is closely matched to work rate, (Bergstrom et al. 1967; Romijn et al. 1993), although even when exercising at ~50–85 % of $\dot{V}O_{2max}$, liver-derived glucose contributes considerably less to the total energy requirement than the oxidation of skeletal muscle glycogen (Romijn et al. 1993).

The increased liver glucose output is partly a result of glycogenolysis, particularly during the first hour or more of sustained exercise (Kjaer 1998). However, the relative contribution of hepatic gluconeogenesis to total glucose output increases progressively as work duration is increased, and it accounts for some 50 % of glucose production during physical activity that is prolonged for more than one hour (Suh et al. 2007). Lactate (Shephard 1982; Wasserman and Cherrington 1991; Nielsen et al. 2007), amino acids (released from skeletal muscle through the action of cortisol), and glycerol all contribute to gluconeogenesis during exercise (Rowell 1971). As hepatic glycogen reserves become depleted, the rate of gluconeogenesis is usually insufficient to sustain vigorous exercise, and a decline in the blood glucose concentration can therefore occur unless the work rate is reduced (Ahlborg et al. 1974). Depending upon an individual's training status and diet, both liver and muscle glycogen reserves can be almost completely exhausted over 90–180 min of vigorous aerobic exercise (Terjung et al. 1971).

In conclusion, exercise significantly increases liver glucose output by way of hepatic glycolysis and gluconeogenesis, making an important contribution to blood glucose control and oxidation during sustained endurance activity. These mechanisms can become exhausted during exercise such as a marathon run that continues for more than 90 min.

Lipid metabolism

Under resting, fasted conditions, the liver accounts for a significant proportion (~40 %) of circulating fatty acid uptake, substantially exceeding the uptake of skeletal muscle (~15 %) (Jensen 1995; Meek et al. 1999). A portion of these fatty acids are converted to ketones or oxidized by the liver and other tissues in the splanchnic vascular bed (Havel et al. 1970; Wolfe et al. 1976). There is also a significant re-esterification of fatty acids to triglycerides in the liver (Klein et al. 1989); the triglycerides can then be secreted as very low density lipoprotein triglycerides (VLDLs).

The liver's dominant role in disposing of circulating (included ingested) fatty acids is suspended during exercise. Hormonal responses to exercise increase the net availability of circulating FFA during physical activity (Wolfe et al. 1990), but with the ensuing changes in blood flow distribution, the majority of these FFAs are directed to the contracting muscle; their oxidation accounts for most of the whole-body fat that is metabolized during exercise, although there is also a small contribution from intramyocellular triglyceride (IMTG)-derived fatty acids (Romijn et al. 1993). The splanchnic vascular bed accounts for less than 20 % of whole-body FFA uptake during exercise (Wolfe et al. 1990), but the relative partitioning of this uptake between hepatic oxidation and triglyceride synthesis remains unknown. Whilst it is believed that hepatic VLDL-derived fatty acids can be oxidized by skeletal muscle (Kiens 1993), the hepatic release of triglyceride in the form of VLDL remains unchanged during exercise (BØrsheim et al. 1999). The current consensus is thus that VLDL makes a trivial contribution to whole-body fat metabolism during exercise (Helge et al. 2001).

Even a sustained bout of physical activity appears to have little immediate effect upon hepatic lipid metabolism. For instance, endurance-trained men showed no change in proton magnetic resonance spectroscopy estimates of hepatic triglycerides following 90 min of cycle ergometry at

65 % of $\dot{V}O_{2peak}$ (Johnson et al. 2012). Likewise, a 60-min bout of cycle ergometry at 60 % of $\dot{V}O_{2max}$ had no influence upon hepatic lipid metabolism in sedentary women (Magkos et al. 2009). One review also concluded that exercise had no effect upon the hepatic concentrations of total lipids, phospholipids and cholesterol in normally fed rats (Gorski et al. 1990). However, the high levels of circulating fatty acids induced by 60–90 min bouts of exercise led to an increase of hepatic triglycerides 3–4 h post-exercise in both mice (Hu et al. 2010) and human (Johnson et al. 2012) studies. A single 4-h bout of swimming also up-regulated hepatic stearyl CoA desaturase in rats and increased hepatic triglyceride content (Ochiai and Matsuo 2012). Further, exercise to exhaustion increased the hepatic content of the bound form of alpha-lipoic acid (lipoyl–lysine), an important co-factor for many mitochondrial proteins that are active in metabolism (Khanna et al. 1998). On the other hand, a single 3-h bout of exercise to exhaustion decreased the hepatic fatty acid synthase mRNA and enzyme activity induced by a high carbohydrate diet in both normal and diabetic (streptozotocin-treated) rats (Fiebig et al. 2001).

In conclusion, in contrast to its effects on glucose and protein metabolism, an acute bout of exercise has little immediate effect upon hepatic lipid metabolism and it may actually slightly increase hepatic triglyceride content. However, evidence (detailed later) showing up-regulation of hepatic enzymes and an overall reduction in hepatic fat levels with chronic exercise suggests that this is a transient response, with no detrimental effect upon the liver, and that a positive adaptation leading to a reduction of hepatic triglycerides occurs post-exercise and/or with chronic exercise.

Protein metabolism

Sustained exercise can augment the hepatic synthesis of a number of proteins, including albumin and insulin-like growth factor binding protein (IGFBP). The latter binds IGF-1, allowing the growth hormone to act continuously upon the liver in paracrine fashion, producing more IGF-1.

Isotope infusion studies in humans have demonstrated increases in both the fractional (6 %) and the absolute synthesis (16 %) of albumin 6 h after completing a session of vigorous interval exercise (Yang et al. 1998). In rats, an increase in hepatic IGFBP-1 mRNA expression was also observed for up to 12 h following vigorous treadmill running; this response may serve to curtail an excessive muscle glucose uptake immediately post-exercise, thus preventing hypoglycemia (Anthony et al. 2001).

There is also evidence from the determination of arterial–hepatic venous differences in human subjects that the splanchnic uptake of alanine, synthesized and released by the peripheral muscles, is increased 15–20 % during mild and moderate exercise (Felig and Wahren 1971). Presumably, this then serves for gluconeogenesis, a view that is supported by an increase of sweat nitrogen during exercise (Lemon and Nagle 1981).

In conclusion, a sustained acute bout of exercise can increase hepatic protein synthesis, but during prolonged activity, the liver also plays an important role in forming glucose from amino acids that are released from skeletal muscle.

Triggers of changes in hepatic glucose metabolism during exercise

The classical view has been that changes in hepatic glucose metabolism with exercise are largely a consequence of the altered hormonal milieu. Thus, the exercise-induced increase in gluconeogensis is stimulated by an attenuated secretion of insulin (Kjaer et al. 1993) and rising glucagon concentrations (Wasserman et al. 1989). If exercise is prolonged for more than one hour, these changes can be accentuated by declining plasma glucose concentrations (Trimmer et al. 2002) and depletion of hepatic glycogen reserves (Wahren et al. 1971; Peterson et al. 2004). Rising glucagon levels boost the extraction of glucose precursors from the blood, accelerating their conversion to glucose (Wasserman et al. 1989) and also stimulating glycogenolysis (Wasserman et al. 1995). The stimulation of glucagon receptors increases concentrations of cyclic adenosine monophosphate (cAMP), with activation of protein kinase A and extracellular signal-regulated kinase (ERK) (Jiang et al. 2001), and it also amplifies adenosine monophosphate kinase (AMPK) signaling (Berglund et al. 2009).

Somewhat surprisingly, moderate exercise does not cause much change in peripheral glucagon levels; however, this may be because plasma concentrations do not necessarily reflect glucagon levels in the portal vein (Wasserman et al. 1993). During vigorous exercise, catecholamine secretion may also play a regulatory role, either by providing the liver with additional substrate from adipose lipolysis and increased peripheral lactate formation (Wasserman et al. 1991), or by activating hepatic catecholamine receptors and thus mitogen-activated protein kinase (MAPK) (Christensen and Galbo 1983). Against this last hypothesis, hepatic glucose output does not seem to be affected greatly by adrenoreceptor blockade (Coker et al. 1997).

Some correlate of glycogen depletion, albeit changes in concentration of a substrate, a derivative of substrate oxidation, an energy-related compound such as ATP, or an alteration in cell volume, might also trigger metabolic alterations more directly via the hepatic afferent nerves (Lavoie 2002). In support of this view, if glucagon secretion is suppressed,

an increased activity of the hepatic sympathetic nerves can be detected (van Dijk et al. 1994). On the other hand, glucose release is unaffected by hepatic nerve blockade (Kjaer et al. 1993; van Dijk et al. 1994), and hepatic denervation did not alter the glycemic response of rats to a brief bout of exercise (Lindfeldt et al. 1993).

Some of the changes seen during exercise may occur independently of both hormones and the autonomic nerves, with muscle-derived interleukin-6, for instance, playing a triggering role (Banzet et al. 2009). There are a number of pointers to an action of IL-6 upon the liver. For example, IL-6 stimulation of hepatoma cells increased their glucose production, and the injection of IL-6 into mice induced a small increase of hepatic phosphoenolpyruvate carboxykinase (PECPK) (Fritsche et al. 2010). Exercised mice also showed an increase of the hepatic chemokine CXCL-1 that attracts neutrophils and is involved in inflammation and wound healing, and muscle-derived IL-6 seems the trigger for this response (Pedersen et al. 2011). Finally, IL-6 may mediate the very large increase of hepcidin, a hormone that inhibits iron uptake, as seen in some athletes following prolonged and strenuous exercise such as a marathon run (Roecker et al. 2005; Peeling 2010).

Exercise might also modify liver function through an increased generation of reactive oxygen species, much as in skeletal muscle (Davies et al. 1982; Koyama et al. 1999; Liu et al. 2000). Certainly vigorous prolonged exercise (particularly if performed under hot and humid conditions) significantly restricts visceral blood flow (Wade and Bishop 1962; Rowell 1971), temporarily depriving the internal organs of an adequate oxygen supply (Shephard 2013), and this could favour the formation of reactive oxygen species. The exercise-induced up-regulation of heat shock proteins in rat studies seems to support this hypothesis (Salo et al. 1991; Kregel and Mosely 1996; Gonzalez and Manso 2004), On the other hand, some researchers have found little evidence of oxidative stress in the rat liver following acute exhausting exercise (Bejma et al. 2000; Ogonovszky et al. 2005), with no changes in the activity of anti-oxidant enzymes (Hoene and Weigert 2010).

There seems no fundamental reason why triggers should differ between humans and laboratory animals, but one issue to remember in interpreting these various findings is that much of the available research has been conducted on rodents, where hepatic glycogen reserves are relatively much larger than in humans (Baldwin et al. 1973; Terjung et al. 1974).

In conclusion, there remain several competing hypotheses concerning triggers to the hepatic adaptations of carbohydrate metabolism during acute exercise. It is unclear whether changes in hormonal milieu, substrate/metabolite concentration, cytokines, reactive oxygen species or associated changes in hepatic blood flow initiate these metabolic changes; further research is needed to decide among these possibilities.

Molecular changes

Information on the molecular changes induced in the liver induced by acute exercise is based almost exclusively on studies of normally inactive rodents (Table 2). An analysis of the hepatocyte transcriptome in mice following 60 min of moderate intensity exercise showed that 352 transcripts were up-regulated, and 184 were down-regulated. Many of these changes affected genes that are important for glycolysis, gluconeogenesis and fatty acid metabolism (Hoene and Weigert 2010). Some of these same genes were activated in skeletal muscle, but the response was generally more marked in the liver. The effect was also transient, disappearing within a few hours of ceasing exercise (Hoene and Weigert 2010; Hoene et al. 2010).

Exercise has consistently led to an up-regulation of gluconeogenic and metabolic enzymes such as glucose-6-phosphatase, pyruvate dehydrogenase, and phosphoenolpyruvate carboxykinase (PEPCK) (Banzet et al. 2009; Hoene et al. 2009), reduced expression of lipogenic enzymes (Griffiths et al. 1996; Fiebig et al. 2001), the induction of metabolic regulators such as insulin receptor substrate (Hoene et al. 2009), and an up-regulation of the genes induced by energy depletion. Cortisol is normally implicated in the activation of hepatic PEPCK transcription. Such an involvement is supported by the greatly attenuated exercise responses in adrenalectomized animals, and by the absence of an exercise effect in transgenic mice with deletion of the glucocorticoid regulatory unit (Friedman 1994).

Another exercise-related change is activation of interleukin-6 type cytokine/cytokine receptor signaling, particularly the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, which can transmit information from outside of the cell to gene promoters on intracellular DNA (Hoene and Weigert 2010). Exercise was shown to increase the activity of hepatic AMP-activated protein kinase activity several fold in rats and this response was diminished in IL-6 knock-out animals (Kelly et al. 2004); however, it is not yet quite clear how this particular cytokine is involved, since IL-6 deficiency did not impair the induction of metabolic genes by moderate exercise (Fritsche et al. 2010). An acute exercise bout also induced a marked activation of the mitogen-activated protein kinase (MAPK) signaling pathway, which transmits information from receptors on the cell surface to nuclear DNA (Hoene et al. 2010).

There is an up-regulation of the hepatic p53 tumour-suppressing pathway that guards against genome mutation (Hoene and Weigert 2010; Hoene et al. 2010), much as seen in skeletal muscle, particularly following eccentric exercise (Chen et al. 2002; Hoene and Weigert 2010). Exercise also stimulates an increased synthesis of heat shock

Table 2 Molecular changes in the liver induced by acute exercise

Author	Change	Biological significance
Anthony et al. (2001)	Increased IGFBP-1 mRNA expression	May help to limit hypoglycaemia post-exercise
Dohm et al. (1985); Nizielski et al. (1996); Banzet et al. (2009); Hoene et al. (2009)	Up-regulation of glucose-6-phosphatase, pyruvate dehydrogenase, phosphoenol pyruvate carboxylase	Increase of gluconeogenesis
Griffiths et al. (1996); Fiebig et al. (2001)	Reduced expression of lipogenic enzymes	Less fat synthesis
Hoene et al. (2009)	Induction of insulin-receptor substrate	Increases insulin binding, facilitates gluconeogenesis
Hoene and Weigert (2010)	Changes in 352 gene transcripts	Many of genes active in glycolysis, gluconeogenesis and fatty acid metabolism
Friedman (1994); Ropelle et al. (2009)	Increase of PECPK gene and PECPK mRNA in mice, decrease of PECPK and glucose phosphatase in obese rats	Regulation of gluconeogenesis
Huang et al. (2007)	Increase of adiponectin receptor 1, decrease of adiponectin receptor 2, increase of the transcription factor forkhead box O1	Regulation of gluconeogenesis
Heinrich et al. (2003); Banzet et al. (2009); Hoene et al. (2009)	Increase of peroxisome proliferator-activated receptor coactivator PGC-1	Increased levels of protein that regulates mitochondrial biogenesis
Gonzalez and Manso (2004)	Increased synthesis of heat shock protein molecular chaperones	Protection of proteins against environmental stressors
Hoene and Weigert (2010); Hoene et al. (2010)	Activation of the mitogen-activated protein kinase (MAPK) signaling pathway and p53 tumour suppressing pathway	Regulation of proliferation, gene expression, differentiation and cell survival
Kelly et al. (2004)	Increased hepatic AMP-activated protein kinase activity	Regulation of carbohydrate and lipid metabolism; effect less in IL-6 knock-out mice
Haase et al. (2011)	Increased mRNA and cytochrome *c* protein	Improves oxidative capacity
Hansen et al. (2011)	Increased production of follistatin	Inhibits myostatin, facilitates muscle hypertrophy
Khanna et al. (1998)	Increased hepatic content of bound form of alpha-lipoic acid	Co-factor for many mitochondrial proteins active in metabolism
Lavoie et al. (2002); Leu and George (2007)	Increased blood levels of insulin binding growth factor binding protein	Helps glucose regulation by neutralizing insulin-like effects of insulin-like growth factor-1; also counters apoptotic effect of p53
Ochiai and Matsuo (2012)	Up-regulation of hepatic stearyl CoA desaturase	May protect against insulin resistance
Roecker et al. (2005); Peeling (2010)	Increase of hepicidin	Inhibition of iron uptake; could contribute to athlete's anaemia

protein (HSP-72, HSP-73 and of the glucose-regulated proteins 75 and 78) in rat liver (Gonzalez and Manso 2004) with a marked up-regulation of genes associated with a stress response, such as transcription factors of the Fos/Jun-family (Hoene et al. 2010). The only human study available to date confirmed that HSP72 from the hepato-splanchnic viscera increased in the first 2 h following prolonged moderate intensity exercise (Febbraio et al. 2002).

Finally, increased production of the transforming growth factor follistatin has been demonstrated in mouse liver during exercise (Hansen et al. 2011). Follistatin inhibits myostatin, thus encouraging muscle hypertrophy, and it also acts as a growth promoter for hepatocytes (Fuwii et al. 2005). Observations on human subjects during cycling have confirmed that liver is the source of the follistatin during exercise; active muscles do not liberate this substance into the circulation (Hansen et al. 2011).

In conclusion, information on the molecular changes during acute exercise generally conforms with expectations based on the gross biochemical changes, including the up-regulation of metabolic enzymes and a decreased expression of lipogenic enzymes. There is also an up-regulation of systems protecting against gene mutation and heat shock, and an increased formation of transforming growth factors such as follistatin.

Adverse responses to acute exercise

Whilst moderate exercise appears to have little effect upon either the morphological characteristics of hepatic tissue (Latour et al. 1999) or liver function and oxidative stress, histological changes, impaired pharmokinetics, markers of oxidative stress and altered blood levels of hepatic enzymes have been observed after heavy and prolonged exercise (Table 3, particularly if there is associated heat stress (Berg and Keul 1982; Hassanein et al. 1992; Giercksky et al. 1999; Eran et al. 2004; Miura et al. 2010). Such findings all point to adverse changes of hepatic function, which could have negative implications for those participating in prolonged endurance events such as marathon running, distance cycling, and long-distance triathlons. However, information to date suggests that normal liver function is regained, at most within a few days of ceasing exercise.

Histological changes

The histological changes associated with vigorous and/or exhausting exercise have been examined mainly in animals. A very heavy bout of exercise has been shown to cause an inflammatory response, with an increase in peripheral leucocyte count (Kayashima et al. 1995). Exercise that results in hepatic hypoxia can also predispose to central lobular necrosis (Rowell 1971; Praphatsorn et al. 2010). Prolonged exercise to exhaustion has further been shown to induce mitochondrial swelling in hepatocytes surrounding hepatic venules, and oncotic and/or apoptotic necrosis of the hepatocytes in rodents (Yano et al. 1997; Huang et al. 2013).

Impaired pharmacokinetics

The study of pharmacokinetic changes induced by exercise provides further insight into possible disturbances of liver function and health. Most pharmacokinetic investigations have been conducted in human subjects. The elimination of "low clearance" drugs such as acetaminophen, antipyrine, diazepam, amylobarbitone and verapamil is affected primarily by changes in hepatic enzyme activity and biliary excretion (Khazaeinia et al. 2000). Their clearance is largely unaffected by either moderate exercise (Balasubramian et al. 1970; Swartz et al. 1974; Klotz and Lucke 1978; Mooy et al. 1986; Loniewski et al. 2001) or very prolonged low to moderate intensity activity such as 6–9 h of marching (Theilade et al. 1979; Fabbri et al. 1991). In contrast, bouts of vigorous and/or prolonged exercise reduce the elimination of such substances as indocyanine, bromsulphthalein, sorbitol and lidocaine (Mooy et al. 1986; van Griensven et al. 1995), whose clearance rate mainly reflects hepatic blood flow (Rowell et al. 1964; Døssing 1985). There remains a need to examine the effects of vigorous and very prolonged events such as ultra-marathon runs or long course triathlon on hepatic clearance function, particular with respect to low clearance drugs.

Oxidant stress

As with the gross changes observed in lipid and lipoprotein concentrations, significant changes in oxidant status may develop after, rather than during an exercise bout (Koyama et al. 1999). It is therefore important that research studies continue observations sufficiently far into the recovery period to detect such changes. Importantly, as in skeletal muscle, these changes are not necessarily 'adverse' per se, as they may be important factors in inducing adaptations to regular exercise (Hoene and Weigert 2010).

Some (Neubauer et al. 2008; Pinho et al. 2010; Turner et al. 2011) but not all studies (Margaritis et al. 1997) in humans have demonstrated a transient increase of oxidant stress following prolonged and/or vigorous exercise. However, none of these studies have examined changes within the liver itself.

Animal studies (Table 4) provide more direct evidence that exhausting exercise causes oxidative stress in the liver. For instance, the hepatic glutathione levels have been shown to fall in rats following exhausting exercise, reflecting a large increase in oxidative metabolism, and a reduced ability to buffer reactive oxygen species (Sen

Table 3 Reports of adverse changes in the liver following prolonged endurance exercise

Author	Subjects	Exercise	Findings	Comment
Apple and McGue (1983)	Two male runners	6 weeks of training for a marathon	ALT increased in ½ subjects; large increases of LDH and CK	
Beard et al. (1979)	Two joggers with heat stroke		Reduced level of clotting factors produced by liver	
Bunch (1980)	Six runners		Clinically "abnormal" levels of hepatic enzymes	
Bűrger-Mendonça et al. (2008)	Six male athletes	Half-triathlon	Comparison of blood samples before and after race; significant change in AST and ALP but not ALT	Moderate temperatures. All enzyme values remained within normal limits
De Paz et al. (1995)	13 male runners, mean age 36 years	100-km race	Post-race increases in ALT +42 %, AST +193 %, GGT +56 %, CK +2,000 %	Cool conditions; serum bilirubin +106 %. Also decrease of serum haptoglobins
Fallon et al. (1999)	Seven male, two female runners	1,600-km ultramarathon	Increases of ALT, AST, GGT, LDFH, CK; ALT remains high when AST and CK falling	Temperatures 11–32 °C
Foigt et al. (1976)	Six male volunteers	Cycle ergometer exercise at 70–85 % maximal oxygen intake to exhaustion (26–60 min)	Hepatic vein shows increased content of ALT	
Hammouda et al. (2012)	18 male football players	Wingate test	Small increases of CK 11 %; AST 10 %; ALT 16 %; LDH 13 %	
Holly et al. (1986)	Six male, three female triathlon competitors	Hawaiian Ironman competition	SGOT +700 %, SGPT +262 %, LDH +222 % immediately after competition	Initial resting values high normal; enzymes marginally increased 5–6 days later
Kayashima et al. (1995)	14 soldiers aged 24–36 years	80-km trek on limited diet over 4 days	Enzymes sampled immediately and after 8 days. Increases: AST 177, 152 %; ALT 39, 234 %; LDH 66, 8 %; CK 208, −68 %	Associated leucocytosis and bilirubinaemia immediately after exercise
Kratz et al. (2002)	32 male, five female runners, average age 49 years	Boston marathon	AST +265 %, ALT +37 %, CK +2,343 % increased after race, 24 h > 4 h	Cool environment; bilirubin increased 60 %, serum urea nitrogen 29 %
Lippi et al. (2011)	15 healthy males	21-km half-marathon	AST, LDH, CK increased 0–24 h following run	ALT not measured
Litvinova and Viru (1995)	Male Wistar rats aged 10–12 weeks	10-h swimming with loading 10 % body mass	103 % increase in hepatic ^{14}C urea content	Effect decreased by adrenalectomy
Long et al. (1990)	Ten athletes	Short triathlon (10-km run, 20–40 km cycle, 1.0–1.5 km swim)	Modest increases of AST (30 %) and LDH (53 %)	Moderate temperatures; ALT not measured
Malinoski (1992)	Three soldiers	Several days of strenuous training	Increases of ALT, AST and CK	
Mena et al. (1996)	Professional cyclists	800 km/6 days and 2,700 km/20 days with overnight rests	Increases of ALT, AST, ALP, and (in longer race) LDH; partial return to normal with overnight rest	Cumulative increase over race
Nagel et al. (1990)	55 runners	1,000 km in 20 days	AST increased 500 %, ALT 300 %, GGT 600 %, CK 2,000 %; ALT remains high when AST and CK falling	Decreases in serum albumin and choline esterase (could reflect decreased synthesis or increase of IL-1)
Nathwani et al. (2005)	Four prison inmates	Three, vigorous squatting; one, long-distance run	Increases of AST, ALT, CPK and LDH	Liver damage unlikely since normal serum bilirubin and prothrombin times

Table 3 continued

Author	Subjects	Exercise	Findings	Comment
Noakes and Carter (1976)	13 athletes	160-km run	Increases of LDH 241 %; AST 821 %; CPK 1,732 % in those completing event	Temperatures not stated; total bilirubin also increased twofold; ALT and GGT not determined
Noakes and Carter (1982)	18 experienced, five novice competitors	56-km ultramarathon	Greater rise of AST and CPK in novices, despite slower running speed	
Ohno et al. (1988)	Seven sedentary male students	Running 5 km, 6 times/week for 10 weeks	50 % decrease of resting GGT	
Pettersson et al. (2008)	15 healthy men not used to weight-lifting	1 h of weight-lifting	AST, ALT, LDH, CK all remained elevated for 7 days post-exercise	Laboratory conditions
Rama et al. (1994)	7 well-trained male distance runners, mean age 37 years	100-km road race	GGT +19 %, CK +3,121 %	Cool conditions; ALT not measured
Richards et al. (1979)	43 successful runners (28 M, 16 F) vs. ten who collapsed (9 M, 1 F)	14 km Sydney city to surf run	Casualties showed higher values for blood urea nitrogen, serum creatinine, uric acid and bilirubin	
Shapiro et al. (1973)	26 untrained men	110 km march in 2 days	Increases in CK, GOT and aldolase	Midday temperatures 30 °C; ALT not measured. Increased enzyme levels only seen in those marching at 6 km/h
Smith et al. (2004)	27 male, seven female runners, aged 18–65 years	Marathon run	Significant increases in CK, AST, LDH immediately following event	ALT not determined; climate not specified
Suzuki et al. (2006)	Nine well-trained male triathletes	Ironman triathlon	Significant increases immediately and especially 24 h after race: ALT 185 %; AST 759 %; CK 2,680 %; GGT −20 %	Moderately warm conditions
Takahashi et al. (2007)	Seven male rugby players, average age 21 years	Two successive Rugby sevens matches of 10 min duration, with 4-h inter-game interval	Increases of CK 42 %; LDH 25 %; AST 13 %; but not ALT	Cool conditions
Van Rensburg et al. (1986)	23 male athletes, average age 33 years	Triathlon competition	Significant increases of AST, CK and LDH immediately post-race	ALT not measured; 4.5 % decrease of body mass over event
Waskiewicz et al. (2012)	14 male runners mean age 43 years	24-h ultra-marathon	Increased enzymes 24 h after run; ALT 350 %, AST 1,354 %, CK 1,204 %, no change of GGT	Cool conditions
Wu et al. (2004)	Ten males, one female	24-h marathon	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	Moderately warm conditions; bilirubin increased immediately post-race

et al. 1992). Increased blood levels of malondialdehyde (MDA, a marker of lipid peroxidation), NOx, and xanthine oxidase have also been shown in mice, accompanied by large increases in serum aminotransferases and lactate dehydrogenase (LDH) (Kayatekin et al. 2002). Relative to control animals, liver samples showed increased neutrophil infiltration and reductions in levels of superoxide dismutase, catalase and glutathione peroxidase (Huang et al. 2008). Other studies of rats have found significant increases in measures of hepatic lipid peroxidation following exhaustive exercise (Turgut et al. 2003; Aydin et al. 2005). 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 and 72 kDa HSPs (Salo et al. 1991; Gonzalez and Manso 2004).

Thus, animal studies support the human inference of increased oxidant stress and increased hepatic concentrations of HSP following heavy exercise, but further research is needed to determine how far such changes are an inherent part of the adaptive response to physical activity.

Serum hepatic enzyme levels

Clinicians frequently evaluate human hepatic function in terms of serum levels of hepatic enzymes. Short periods of acute exercise usually have little or no effect upon such indices (Takahashi et al. 2007; Hammouda et al. 2012). However, in the hours following vigorous and very prolonged exercise such as marathon or triathlon competition, many investigators have found increased concentrations of serum aminotransferases, often accompanied by increased bilirubin concentrations and markers of inflammation such as IL-6 and C-reactive protein, similar to the findings in laboratory animals after prolonged vigorous exercise (Moses 1990; Praphatsorn et al. 2010) (Table 3). The cause of these changes (recent physical activity, hepatic injury, haemolysis, or muscle injury) remains unclear (Kindermann et al. 1983; Koutedakis et al. 1993; Rosales et al. 2008). Confirmation of sustained hepatic malfunction has been sought in decreased plasma levels of albumin, globulin and cholinesterase (Nagel et al. 1990; Wu et al. 2004), although reduced concentrations of these substances could also reflect the influence of increased serum concentrations of interleukin-1 (Nagel et al. 1990). Further information is thus required before we can interpret exercise-induced changes in clinical liver function tests as evidence of hepatic damage.

Summary of responses to acute exercise

Hepatic responses to acute exercise include a decrease in regional blood flow, and an increase of glucose output by way of glycogenolysis and glucogeneogenesis. These changes are exacerbated as the intensity and duration of exercise is increased, and they contribute to maintenance of a stable blood glucose concentration. At rest, the liver is a major site for fatty acid uptake, much of which is re-packaged and secreted as VLDLs. However, during an acute bout of physical activity, possibly as a consequence of reduced hepatic blood flow and increased fatty acid uptake by muscle, the liver adopts a more 'passive' role, with no measurable change in liver triglyceride concentrations. Albumin and IGF-1 levels are increased after an acute bout of exercise; they likely have growth-promoting effects and contribute to euglycaemia. Although glucagon and insulin have some regulatory influence, the precise stimuli triggering the changes in hepatic function that maintain blood glucose during exercise remain unclear, as do the underlying molecular adaptations. Changes in catecholamines, intracellular high-energy phosphate concentrations related to substrate availability, reactive oxygen species, cytokines and tissue hypoxia have all been suggested as playing a regulatory role. Understanding these stimuli and the molecular effects of acute exercise is made difficult by a lack of direct human evidence, and potential difficulties in translating rodent findings to an interpretation of human responses. Whilst moderate exercise appears well tolerated by the liver, vigorous and/or prolonged or exhaustive activity may result in inflammation, altered pharmacokinetics, oxidative stress and increases in concentrations of HSPs and serum amino-transferases. Vigorous and/or prolonged exercise can cause a slowing in the elimination of markers dependent upon hepatic blood flow, signs of oxidative stress in both humans and animals, and a transient appearance of hepatic enzymes in the serum. However, there is little evidence of permanent hepatic damage; such disturbances seem transient and possibly contribute to exercise adaptations.

Chronic effects of moderate endurance exercise

As with the acute effects of exercise, we will consider changes in the metabolism of carbohydrates, lipids and protein, and triggers for these changes. We will focus particularly upon the role of oxidant stress, and implications for hepatic function.

Carbohydrate metabolism

It is well known that regular exercise training increases a person's ability to sustain a higher work-rate during prolonged activity, and to exercise for longer before the onset of fatigue. One component of this change is an enhanced resistance to hypoglycemia during exercise. This is partly a

consequence of an increased capacity for skeletal muscle to store glycogen and to oxidize fat at the expense of glucose. Although there is relatively little human data, further 'glucose sparing' adaptations likely include an increased resting liver glycogen concentration and a reduced rate of both glycogenolysis and gluconeogenesis at any given intensity of exercise (Coggan et al. 1995; Murakami et al. 1997). Other changes associated with exercise training include a reduced availability of gluconeogenic precursors (lactate and glycerol) at a given volume of exercise, and altered hormonal responses (a higher insulin, and lower glucagon and catecholamine concentrations).

Rodent investigations generally agree with human observations in showing that the glyconeogenic and the gluconeogenic responses to glucagon are enhanced with training (Podolin et al. 2001; Drouin et al. 2004). However, there are some differences in the responses of rats, probably related to the fact that gluconeogenesis accounts for some 20 % of glucose production when humans undertake moderate exercise, whereas in rats the figure ranges from 40 to 70 %. In particular, training increases exercise hepatic glucose clearance in humans, but not in rats (Coggan et al. 1995).

Underlying mechanisms apparently include a normalizing of the ratio of inhibitory to stimulatory guanine-nucleotide binding protein (G protein), and a resultant increase in activity of the "second messenger" adenyl cyclase (Podolin et al. 2001). The increased capacity for glucose output contributes to the ability of trained individuals to sustain higher work-rates and to maintain euglycaemia during exercise (Donovan and Sumida 1990). Moreover, the liver of a trained person has an increased absolute capacity for lactate (Donovan and Pagliassotti 1990) and alanine (Sumida and Donovan 1995) clearance, and associated gluconeogenesis (Sumida and Donovan 1993).

Most, but not all (James and Kraegen 1984), rodent studies have shown increases in activity of the enzymes and signaling molecules involved in both carbohydrate and lipid metabolism following aerobic training (Colombo et al. 2005; Aoi et al. 2011).

In conclusion, aerobic training induces metabolic adaptations in both humans and laboratory animals that help to conserve glucose homeostasis during prolonged exercise, including greater glycogen storage in both liver and muscle, and the sparing of carbohydrate through greater fat metabolism.

Lipid metabolism

The enhanced ability to utilize fat during exercise following regular training is largely a function of adaptations in skeletal muscle (and associated hormonal changes); there is little evidence that the liver contributes to this response. This is perhaps understandable, given the apparently trivial role of the liver in contributing to fat oxidation (via VLDLs) (Helge et al. 2001). Moreover, exercise training blunts the lipolytic hormone response to exercise, so that after training circulating concentrations of insulin and insulin-like growth factor binding protein-1 tend to be higher (Prior et al. 2012), and blood glycerol and FFA concentrations are lower at a given absolute exercise intensity (Martin et al. 1993). These changes further reduce the liver's role, including its exposure to FFAs. Nevertheless, regular exercise is associated with alterations in lipid/lipoprotein metabolism, and it appears to reduce the amount of triglyceride stored in the liver.

Several studies have examined the effect of regular exercise upon liver fat content (discussed later), and the associated liver mass in rats and mice (Table 8). Most investigators have observed a reduction in liver mass with regular exercise training, although such findings have not been universal (James and Kraegen 1984; Murakami et al. 1997). A limitation of many animal studies is that control animals have lived unnatural lives of physical inactivity and over-eating relative to their natural state, and in consequence differences in hepatic tissue mass between sedentary and exercised animals have varied between investigations. For example, in the study of Yiamouyiannis et al. (1992), rats that were fed ad libitum and given free access to a running wheel also ate more, thus presenting with increased values for total, mitochondrial and cytosolic protein (Yiamouyiannis et al. 1992). The total activity of several enzymes was also increased, although the activity per g of liver or per g of hepatic protein remained unchanged (Yiamouyiannis et al. 1992).

The cardio-protective benefit of regular exercise in modifying circulating lipids and lipoproteins is well documented in both human subjects and experimental animals. Cross-sectional research shows that high-density lipoprotein cholesterol (HDL-c) levels are higher in regular exercisers versus their inactive counterparts (Williams et al. 1981), and HDL-c increases with exercise training interventions (Kelley et al. 2005, 2006; Dressendorfer et al. 1982; Terao et al. 1989). Similarly, exercise training may reduce circulating triglycerides and VLDL secretion (Tsekouras et al. 2008). These benefits are associated with a decreased activity of hepatic lipase (Thompson et al. 1991) and alterations in the levels of other hepatic enzymes involved in HDL-c remodelling (including cholesteryl ester transfer protein and lecithin cholesteryl acyl transferase) (Kraus et al. 2002; Halverstadt et al. 2007).

Inter-individual human differences in lipid responses to training programmes have been traced to a polymorphism in the hepatic lipase gene LIPC -514C-T (Brinkley et al. 2011). However, the relative contribution of acute versus chronic responses to these exercise-induced improvements in lipids and lipoproteins remains unclear (Cullinane et al. 1982; Thompson et al. 2001; Magkos et al. 2007).

Table 4 Effects of chronic exercise upon oxidative stress in the liver

Author	Subjects	Training	Outcome
Burneiko et al. (2006)	60-day-old male Wistar rats	Swimming up to 60 min/day, 2 times/week for 8 weeks	Hepatic superoxide dismutase increased, catalase decreased, increase of total antioxidant substances
Chapados and Lavoie (2010)	6-week-old female Sprague–Dawley rats	Treadmill running for 6 weeks (progressing to 60 min/session at 26 m/min, 10 % slope), 5 times/week	Increased gene expression of unfolded protein response markers may protect against endoplasmic reticulum stress
da Silva et al. (2009)	3-month-old male mice	Intermittent or continuous or downhill running 45 min/day for 8 weeks increasing to speed of 16 m/min	Continuous or downhill running increased hepatic superoxide dismutase, decreased catalase, decreased lipoperoxidation and protein carbonylation
Gore et al. (1998)	4-month female Sprague–Dawley rats	10-week heavy training (2 h/day running 25 m/min up 10 % grade)	58 % increase of hepatic superoxide dismutase
Gündüz et al. (2004)	9-month-old albino Wistar rats	1 year of swimming 1 h/day	Reversed age-related decrease of hepatic catalase
Haase et al. (2011)	Mice	5 weeks of exercise (combination of 1 h/day of treadmill running, 14 m/min 10 % slope, and wheel running 5 days/week)	No change of mRNA expression for hepatic anti-oxidant enzymes
Ho et al. (2001)	2-month-old female Sprague–Dawley rats	3 months swimming (2 h/day)	Down-regulation of cytosolic aconitase, possibly counters increase production of NO and a related decrease in the iron content of the liver
Hong and Johnson (1995)	Normotensive and hypertensive male rats	10-week treadmill training, progressing to 60 min/day at 20 m/min, 5 % slope (exercise caused some weight loss)	Down-regulation of hepatic superoxide dismutase, catalase, glutathione peroxide and glutathione reductase, BUT decrease of TBARS seen 7 days post-training
Huang et al. (2010)	6-week-old Sprague–Dawley rats	12-week running up 12 % grade, 60 min/day	Increased anti-oxidant content of liver
Kiraly et al. (2010)	6-week-old male ZDF diabetic fatty rats	10-week voluntary wheel running	Decreased markers of inflammation and oxidative stress in the liver, lower circulating IL-6 and malondialdehyde levels, less hepatic protein oxidation, decreased c-Jun-terminal kinase activity (heralds apoptosis), lower PECPK levels, lower Ser (307)-phosphorylated insulin receptor substrate-1 concentrations
Navarro et al. (2003)	28-week-old mice	50-week treadmill running (5 min at 6–12 m/min, thrice weekly)	Reduced oxidative stress markers in hepatic mitochondria
Radak et al. (2004)	30-month-old rats	8-week exercise (2 h/day at 2.1 km/h)	Reversed age-related increased concentration of reactive oxygen species in the liver; attenuation of DNA binding activity of NF-κB (could decrease transcription of inflammation-related genes)
Reddy Avula and Ferandes (1999)	3-month-old mice	8-week treadmill running (45–50 min/day at 1 km/h)	Increased levels of hepatic catalase and glutathione transferase activity and lower lipid peroxide levels
Romani et al. (2009)	8-week-old male Sprague–Dawley albino rats	10-week treadmill running (1 h/day, 3 times/week at speeds increasing to 65 % of maximal oxygen intake)	Increased paraoxanase-3 (increases anti-oxidant properties of HDL-cholesterol)
Sen et al. (1992)	10-week-old Han Wistar rats	8-week treadmill training (2 h/day at 2.1 km/h)	21 % increase of hepatic glutathione levels
Sen et al. (1992)	15-week-old female beagle dogs	55 weeks of treadmill training (40 km/day at 5.5–6.8 km/h, 15 % slope)	30 % increase in activity of hepatic glutathione transferase S activity, 8 % increase of total hepatic glutathione

Table 4 continued

Author	Subjects	Training	Outcome
Venditti and di Meo (1997)	12-month-old rats	10-week swimming	Reduced lipid peroxidation and increased glutathione peroxidase, glutathione reductase and overall anti-oxidant activity
Wilson and Johnson (2000)	11–12 week male Sprague–Dawley rats	10-week treadmill running (60 min/day, 20 m/min 5 % slope)	Hepatic superoxide dismutase mRNA down-regulated, but catalase mRNA up-regulated

Rodent investigations have provided insights into the molecular changes underlying the effects of regular physical activity upon lipid/lipoprotein metabolism. Training sessions reduced hepatic acetyl-coenzyme A carboxylase and fatty acid synthase activity and mRNA (Askew et al. 1975; Fiebig et al. 1998, 2001, 2002; Lavoie and Gauthier 2006). Regular exercise also down-regulated the hepatic gene and protein content of stearoyl-CoA desaturase-1 (SCD-1), the rate limiting enzyme in the biosynthesis of saturated-derived monounsaturated fats that are a major constituent of VLDLs. Further, there was a down-regulation of the microsomal triglyceride transfer protein that plays a key role in the assembly and secretion of VLDL lipoprotein (Chapados et al. 2009), and training increased levels of hepatic mRNA for the ATP-binding cassette transporter A-1 that plays a vital role in membrane transport and plasma HDL cholesterol remodeling (Ghanbari-Niaki et al. 2007). Changes in the composition of hepatic phospholipids following training likely have implications for membrane properties, cell signalling and gene expression (Petridou et al. 2005).

In conclusion, exercise training increases muscular oxidation of fat and leads to molecular changes of hepatic function that reduce liver fat content and enhance the blood lipid profile.

Protein metabolism

An expansion of plasma volume is a well-recognized adaptation to regular exercise; expression of the hepatic albumin gene mRNA facilitates this response by increasing serum albumin concentrations, and rodent studies indicate that such an adaptation can occur within days of the initiation of training (Bexfield et al. 2009).

Endurance training also increases the hepatic production of heat shock proteins and decreases the secretion of orixogenic proteins. Thus, endurance training in mice increased hepatic 70 kDa HSP (Mikami et al. 2004) and HSP72 (Atalay et al. 2004) expression in both the liver and other tissues, and the expression of hepatic orixogenic Agouti-related protein was reduced in rats after training (Ghanbari-Niaki et al. 2009); the latter change likely reduces the animals' appetite.

Triggers of hepatic responses

Both changes in the concentrations of hormones (insulin, glucagon and oestrogen) and cytokines (IL-1-β, IL-6, IL-10 and IGF-1) and altered tissue sensitivity to these agents may contribute to the changes of hepatic metabolism observed following aerobic training.

Hepatic insulin sensitivity was increased in some animal studies. Regular exercise reduced the hepatic mRNA level and protein content of hepatic PEPCK, thus contributing to the improved insulin sensitivity (Chang et al. 2006).

However, training has not enhanced hepatic insulin sensitivity in all human studies (Hickman et al. 2004).

A week of repeated bouts of swimming reduced the liver fat content of male rats (Hu et al. 2000; Peijie et al. 2004). Regular training also increased the hepatic glucagon receptor density and glucocorticoid receptor count in exercise-trained rats (Légaré et al. 2001); an increased availability of glucagon may be important to this effect of exercise training, since liver fat was not reduced in animals that lacked glucagon receptors (Berglund et al. 2011).

Hepatic oestrogen receptors appear to influence the effects of exercise training on hepatic lipid metabolism (Paquette et al. 2007). Ovariectomy predisposes rats to hepatic steatosis, an increase of inflammatory biomarkers (e.g. inhibitor-κB kinase β and interleukin-6), an increased activity of hepatic lipogenic enzymes (e.g. sterol regulatory element-binding protein-1c, acetyl-CoA carboxylase (ACC) and stearoyl CoA desaturase), and a decreased expression of enzymes related to fat oxidation (e.g. carnitine palmitoyltransferase and hydroxyacyl-CoA-dehydrogenase). With the exception of increases in ACC, these adverse changes could be reversed, at least in rats and mice, through regular exercise (Jackson et al. 2011; Pighon et al. 2011; Domingos et al. 2012). Carnitine is an important co-factor for the oxidation of both long-chained fatty acids and carbohydrate, and may itself play an important role in the hepatic response; regular exercise attenuates the high-fat diet-induced reduction in carnitine palmitoyltransferase I activity (Cha et al. 2003), and up-regulates the genes involved in hepatic carnitine synthesis and uptake (Ringseis et al. 2011). Training also increased gene expression of microsomal triglyceride transfer protein and diacylglycerol acyltransferase-2 in ovariectomized rats, with a reduction in hepatic triglyceride content (Barsalani et al. 2010).

Some studies have observed greater serum levels of free IGF following aerobic training, either via increased hepatic IGF production (Prior et al. 2012), or because of increased hydrolysis of the corresponding binding factor (Schwarz et al. 1996). Resistance training likely has a similar effect (Bermon et al. 1999). On the other hand, a combination of regular exercise and a low fat diet increased serum concentrations of IGF-1 binding protein, thus decreasing circulating levels of free IGF-1, both in rats and in humans (Nishida et al. 2010; Wieczorek-Baranowska et al. 2011).

Rodent studies have suggested that regular aerobic exercise training may decrease tissue levels of the inflammatory cytokines IL-6 (Moon et al. 2012b) and IL-1β (de Araújo et al. 2012), and increase levels of the anti-inflammatory cytokine IL-10 (with an associated decrease in hepatic apoptosis) (de Araújo et al. 2012). Whilst there is some evidence from human investigations demonstrating a net hepato-splanchnic uptake of IL-6 during moderate intensity exercise (Febbraio et al. 2003), it remains to be determined whether the liver is merely clearing this cytokine from the circulation, or whether it has a specific role in glucose homeostasis.

In conclusion, a variety of triggers have been suggested for the adaptations of hepatic metabolism associated with exercise training, including alterations in concentrations of and sensitivity to hormones (glucagon, insulin, oestrogen and IGF) and cytokines (IL-1β, IL-6 and IL-10); further research is needed to determine which are important factors, and which are incidental consequences of the observed adaptations.

Role of oxidant stress

Oxidant stress reflects a disequilibrium between the protein load and the ability of the hepatocyte endoplasmic reticulum to fold and assemble proteins correctly. It can be caused either by aging or by severe exercise, with an increased production of superoxides, a decrease of buffering agents, and/or a decrease of peroxidases. In rats, prolonged bouts of vigorous exercise (2 h swimming/day for 3 months) led to a down-regulation of cytosolic aconitase, a key factor in cellular iron homeostasis (Ho et al. 2001), possibly because of an increased production of NO and oxidative stress.

Most studies of mice, rats and dogs (Table 4) have shown moderate aerobic training as minimizing oxidative stress. Markers of oxidative stress are decreased (Navarro et al. 2003), and the activities of hepatic antioxidant enzymes such as superoxide dismutase (Gore et al. 1998; Burneiko et al. 2006; da Silva et al. 2009) and the corresponding signaling molecules (Huang et al. 2010) are increased. Further, hepatic glutathione transferase S activity and concentrations of reduced glutathione are increased (Sen et al. 1992; Radak et al. 2004), and the gene expression of unfolded protein response markers is enhanced (Chapados and Lavoie 2010).

Nevertheless, a few investigators have found no change or even a decrease of anti-oxidant enzyme activity following heavy endurance training (Hong and Johnson 1995), with a decreased hepatic superoxide dismutase mRNA, but an increase of catalase mRNA (Wilson and Johnson 2000), and [contrary to early observations on isolated hepatocytes (Eklöw et al. 1984)], little relationship between anti-oxidant enzyme levels and local oxidant stress (Ji et al. 1990; Godin and Garnett 1992).

Thus, we may conclude that moderate exercise training reduces hepatic oxidant stress, but very heavy training may have adverse effects upon oxidant status.

Functional activity

It is unclear from human studies of serum enzyme levels and pharmacokinetics how far liver function is influenced

either by habitual physical activity or by regular low to moderate intensities of exercise training. Nevertheless, the traditional clinical markers of hepatic function (serum ALT and GGT levels) do show a negative correlation with habitual physical activity (Robinson and Whitehead 1989; Nilssen et al. 1990; Pintus and Mascia 1996), probably because a sedentary lifestyle predisposes to steatosis (Whitfield 2001). Whether there is a more direct relationship between physical activity level, fitness and serum aminotransferase levels is discussed below.

In terms of pharmacokinetics, exercise training did not alter creatinine clearance in boxers (Saengsirisuwan et al. 1998), or the pharmacodynamics of propranolol in sedentary subjects (Frank et al. 1990; Panton et al. 1995). Likewise, cross-sectional research showed no significant differences in aminopyrine metabolism, galactose elimination, or indocyanine green clearance between endurance runners and relatively sedentary medical students (Ducry et al. 1979).

However, other reports suggest that hepatic function may be enhanced by vigorous (but not exhausting) training (Døssing 1985). Thus, the clearance of antipyrine (which depends almost exclusively upon hepatic metabolism) was faster in athletes than in controls, with no difference between sprinters and endurance competitors (Orioli et al. 1990). Likewise, endurance runners had a faster clearance of antipyrine than sedentary but otherwise healthy men (Villa et al. 1998). Longitudinal evidence supports these cross-sectional inferences. Three months of exercise training increased the clearance of antipyrine and aminopyrine in previously inactive students; moreover, individual improvements in these indices correlated highly with gains in $\dot{V}O_{2max}$, which averaged 6 % (Boel et al. 1984). Three months of moderate intensity exercise (combined aerobic and resistance training) also increased antipyrine clearance in elderly women (Mauriz et al. 2000).

Animal experiments generally confirm the beneficial effects of regular exercise on liver function seen in human subjects. Five weeks of training increased antipyrine clearance in mares (Dyke et al. 1998), 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 (Yiamouyiannis et al. 1992) and halothane (Daggan et al. 2000). In the study of halothane toxicity, hepatic glutathione levels were unchanged by 10 weeks of treadmill exercise, and it remained unclear whether benefit was due to enhanced antioxidant defence mechanisms or the associated decrease in hepatic fat (Daggan et al. 2000).

A further factor increasing the liver's ability to eliminate some substances is an increased secretion of biliary transporters. Chronic exercise such as swimming or running augments the hepatic production of bile acids (Frenkl et al. 1980) and increases the availability of bile acid transporters (Yiamouyiannis et al. 1993). These changes may accelerate biliary clearance (but not necessarily blood stream clearance) of substances such as indocyanine green (Yiamouyiannis et al. 1993) acetaminophen and antipyrine (Frenkl et al. 1980).

Thus, the general impression from studies of pharmacokinetics is that regular moderate exercise enhances the functional clearance capacity of the liver.

Summary of responses to chronic exercise training

Regular exercise training increases liver glycogen storage and the hepatic capacity for glucose output. On the other hand, glycogenolysis and gluconeogensis are reduced at a given work-rate after training, with a reduced availability of gluconogenic precursors. The net effect is an improved ability to maintain euglycaemia, probably triggered by changes in hormone concentrations and sensitivity. Regular exercise training appears to reduce overall liver mass and associated fat mass, with an increase in HDL-c levels. Hepatic albumin and HSPs increase, and orixogenic proteins decrease with regular exercise training. The precise triggers for these changes of hepatic function are contentious, although hormones (insulin, glucagon and oestrogen) and a number of cytokines appear to be involved. Most (but not all) studies suggest that regular exercise training reduces markers of oxidative stress and increases antioxidant enzyme levels in the liver. Evidence for the overall effect of exercise training in terms of serum aminotransferase levels is conflicting, but most cross-sectional and longitudinal research indicates an improvement of hepatic clearance function with regular exercise.

The role of physical activity in liver disease

In the final section of this review, we will examine interactions between physical activity and certain chronic liver conditions, including non-alcoholic fatty liver disease (NAFLD), hepatic inflammation and cirrhosis, and hepatic carcinoma, considering specifically the roles of inadequate habitual physical activity and co-pathologies in the genesis of these syndromes. We will also examine the impact of exercise training upon liver fat, as seen in both cross-sectional and longitudinal studies, and will finally consider appropriate exercise dose recommendations for the treatment of these disorders.

Non-alcoholic fatty liver disease (NAFLD)

NAFLD is characterized by the accumulation of fat in hepatocytes in the absence of excessive alcohol

consumption. The liver normally contains some fat (the triglycerides stored in hepatocytes), but NAFLD is commonly diagnosed when fat stores exceed ~5 % of hepatic mass. NAFLD accounts for the majority of liver disease worldwide; the condition is thought to affect up to one-third of adults (Browning et al. 2004; Szczepaniak et al. 2005) and it is found in most individuals who are obese (Bellentani et al. 2000). Even in children, the prevalence of NAFLD ranges from 2.6 to 9.6 %, depending upon age, sex, ethnic group and habitual physical activity (Takahashi and Fukusato 2010; Tsuruta et al. 2010). Liver biopsy and histological assessment provides the gold standard for the diagnosis of NAFLD, but in human research studies the liver fat content has more commonly been inferred from proton magnetic resonance spectroscopy or CT scan, and in animal experimentation the usual approach has been tissue analysis at sacrifice.

Hepatic fat accumulation is commonly associated with obesity, cardiovascular disease and diabetes. The build-up of triglycerides in the liver could reflect an increased delivery of fatty acids 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. The first of these mechanisms is probably the most important (Katsanos 2004); it accounts for the major fraction of fatty acids incorporated into liver fat in obese individuals under fasting conditions (Donnelly et al. 2005). The increase in hepatic fat may impair the insulin sensitivity of the hepatocytes (above), and insulin resistance is also manifest in adipose tissue (Kotronen et al. 2008), so that any given secretion of insulin is less effective in reducing lipolysis (Korenblat et al. 2008).

NAFLD can progress from a simple accumulation of fat through inflammation (steato-hepatitis) to fibrosis, cirrhosis and liver failure and even hepatic carcinoma (Angulo 2002). It is not entirely clear why the condition remains a simple steatosis in some individuals, but shows a progression of pathology 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 (Angulo 2002). Progression from simple steatosis to steatohepatitis probably reflects the combined effects of hepatic fat accumulation and oxidative stress, possibly exacerbated by endoplasmic reticulum stress (Malhi and Kaufman 2011) and gut barrier dysfunction (Rao 2009); anti-oxidant therapy is not necessarily helpful in preventing disease progression (Nobili et al. 2008).

Hepatic inflammation and cirrhosis

There is relatively little research evidence concerning interactions between physical activity and the more advanced stages in the spectrum of NAFLD. From available information, it could be suggested that physical activity has some direct positive influence on hepatic pathology beyond simply modifying liver fat levels. For instance, as fibrosis develops, markers of hepatic apoptosis [plasma cytokeratin 18 (CK18) fragments, soluble Fas (sFas), and sFas ligand (sFasL)] increase (Fealy et al. 2012), and these changes have been positively associated with physical inactivity (Lee et al. 2008).

The situation can become a vicious cycle, since any form of hepatitis may discourage physical activity. Individuals affected by chronic hepatitis C infection were found to be less active than their peers, and to engage in less vigorous activity (Moon et al. 2012a). The intensity of physical activity seems important in preventing disease progression, since in a large adult cohort with biopsy-proven steatosis, neither total reported exercise per week nor the duration of moderate physical activity was associated with either the risk of steatohepatitis or the histological stage of fibrosis. On the other hand, meeting the weekly vigorous physical activity recommendation reduced the odds of steato-hepatitis to 0.65, and spending double the recommended time in vigorous activity also reduced the odds of advanced fibrosis to 0.53 (Kistler et al. 2011).

Three months of moderate intensity exercise therapy (5 days/week) lowered serum amino-transferases (ALT and AST) in patients with cirrhosis (Baba et al. 2006), and as little as a week of vigorous exercise training was sufficient to decrease ALT and CK-18 fragments (Fealy et al. 2012). Nevertheless, the primary rationale for advocating exercise therapy in patients with advanced liver disease is arguably for the multiplicity of other benefits of chronic exercise, especially those relating to physical weakness and co-morbidities. Thirteen studies of patients with hepatic cirrhosis noted substantial decreases in aerobic capacity and muscular strength relative to healthy controls (Jones et al. 2012). Low levels of aerobic fitness and exercise tolerance (Wiesinger et al. 2001; Pieber et al. 2006; Dharancy et al. 2008) have been confirmed in other studies (Ritland et al. 1982, 1983; Campillo et al. 1990a, b; DeLissio et al. 1991; Terziyski et al. 2008), particularly in individuals with associated ascites (Campillo et al. 1990b; Wong et al. 2001). There is also evidence of muscular weakness (Tarter et al. 1997; Andersen et al. 1998), proportional to the severity of disease, but independent of its etiology (Campillo et al. 1990b; Wiesinger et al. 2001; Terziyski et al. 2008).

Thus, exercise that includes an element of resistance training is arguably a useful therapy for improving fitness and functional capacity in this population, but it remains unclear whether exercise can restore liver health (and if so, the dose that is needed). One major obstacle to implementing and sustaining a programme of exercise training in advanced liver disease is initial fatigue; this has an adverse effect upon the

individual's quality of life (Stanca et al. 2005), and by discouraging physical activity, it progressively exacerbates the initial loss of muscular strength (Wu et al. 2012). Nevertheless, a programme of regular progressive exercise can counter fatigue, even in people with advanced fibrosis (Zucker 2004). Moreover, given adequate motivation, patients with cirrhosis can tolerate quite vigorous exercise, maintaining oxygenation of the brain and muscles (Bay Nielsen et al. 2005) and showing no evidence of hypoglycemia while they are active (DeLissio et al. 1991). The one major concern in this condition is the potential to develop oesophageal bleeding. The hepatic venous pressure gradient is increased even at low levels of physical activity (30 % of peak work-rate) (Garcia-Pagan et al. 1996), and in patients with oesophageal varices, portal hypertension induced by over-vigorous exercise could cause such bleeding.

There have been few investigations of the effect of aerobic training in hepatic cirrhosis. One investigation reported a 29 % gain of predicted $\dot{V}O_{2max}$ over 10–12 weeks of training (Ritland et al. 1983), and a second trial with only four subjects found an increase of $\dot{V}O_{2max}$ in two of the four individuals, with an 18–20 % improvement of muscle strength in these two individuals (Campillo et al. 1990b).

Animal studies of exercise and liver pathologies

Animal studies have underlined the potential of exercise to have direct beneficial effects upon the diseased liver. In one such study, mice were fed a high-fat diet; however, those animals that subsequently underwent a progressive 16-week aerobic exercise intervention showed an elevation of hepatic tumor necrosis factor levels, together with a reduction or abolition of macrophage infiltration and signs of fibrosis (Sirius red and -smooth muscle actin staining and tissue inhibitor of matrix metalloproteinase-1 mRNA) (Kawanishi et al. 2012). A second investigation noted signs of inflammation and steatohepatitis (macro-vesicular steatosis and lymphocytosis) in sedentary rats that were fed a high-fat diet, but such findings were greatly attenuated in their peers who exercised daily; ALT but not AST levels were also reduced in exercised animals (He et al. 2008).

We may thus conclude that exercise programmes have favourable effects in advanced hepatic disease, provided that patients can be motivated to sustain such activity.

Hepatocellular carcinoma

There has been a paucity of research into interactions between physical activity and hepato-cellular carcinoma. A 10-year follow-up of study of 507,897 retired Americans found a significantly reduced risk of hepatic carcinoma in those who were regularly active (>5 times a week) vs. those who reported exercising never or rarely (odds ratio 0.64) (Behrens et al. 2013). A moderate exercise programme may be beneficial, even if the hepatic carcinoma is quite advanced. One case report noted an increase in aerobic capacity after 6 weeks of supervised aerobic exercise therapy (Crevenna et al. 2003).

The influence of other pathologies associated with inadequate habitual physical activity

The vast majority of research concerning physical activity in the aetiology and management of liver disease has focused on simple hepatic steatosis (detailed below). However, NAFLD is commonly associated with other markers of inadequate habitual physical activity, including cardiovascular disease, metabolic syndrome and type 2 diabetes mellitus. In terms of associated insulin sensitivity, univariate correlations suggest that although body fatness is a prime determinant of whole-body insulin sensitivity, the main determinant of hepatic insulin sensitivity may be the individual's active energy expenditure (Holt et al. 2007). A follow-up of 6,003 patients with non-alcoholic fatty liver disease found 411 developed type 2 diabetes over a follow-up averaging 4.9 years; a Cox proportional hazards analysis demonstrated that a gamma glutamyl transferase (GGT) >109 IU/L and an exercise level of less than 60 min per week were significant predictors of diabetes, both with hazard ratios averaging 1.60 (Arase et al. 2009). GGT facilitates the intracellular transport of glutathione, and increases in levels of this enzyme are a possible indicator of oxidative stress, which in turn can predispose to diabetes (Nannipierri et al. 2005).

Whilst it has been thoroughly documented that low levels of habitual physical activity predispose to the obesity, dyslipidaemia, impaired glucose tolerance and high blood pressure that characterize cardiovascular disease, the metabolic syndrome and diabetes, and that a physical activity intervention is effective in their management (Winnick et al. 2008), fat reduction in the liver is also an important component of both prevention and treatment. A decrease of hepatic fat content has been thought to avert type 2 diabetes mellitus, particularly in older individuals (Tamura et al. 2005; Thamer et al. 2007). Similarly, a normalizing of liver fat content in patients with type 2 diabetes improves the insulin-induced suppression of hepatic glucose output and restores normal fasting blood glucose concentration (Petersen et al. 2005). Recent research interest has thus centred on the role of NAFLD in these pathologies, and the effect of physical activity on liver fat levels.

The association between habitual physical activity/fitness and liver fat (cross-sectional studies)

A possible role for exercise therapy in the management of NAFLD is supported by many cross-sectional

investigations that show an association between low levels of habitual physical activity and/or fitness and the prevalence of NAFLD. Sixteen such studies of human subjects have made cross-sectional assessments of habitual physical activity (Table 5); 12 used physical activity questionnaires, three used objective activity monitors (Newton et al. 2008; Fintini et al. 2012; Gerber et al. 2012), and one classified subjects based upon their obesity (Viitasalo et al. 2012). Sample size ranged from small groups to populations >30,000, and one analysis was based upon twins with dissimilar activity patterns (Leskinen et al. 2009). In one instance, objective monitoring suggested an effect of physical activity, but (probably because of lesser reliability and validity) subjective questionnaires completed by the same individuals did not (Fintini et al. 2012). Collectively, these studies showed that habitual physical activity was an important correlate of hepatic fat in most comparisons, with a possible exercise volume-response relationship (Hsieh et al. 1998), although two reports found no relationship between the severity of histological abnormalities and physical activity (Kang et al. 2006; Kistler et al. 2011).

Eleven reports [including the one twin study (Leskinen et al. 2009)] related cycle ergometer or treadmill assessments of aerobic fitness to hepatic fat accumulation (Table 6). With two exceptions (Seppala-Lindroos et al. 2007; Krasnoff et al. 2008), an inverse relationship was seen. However, in some studies the negative association was relatively weak (Nguyen-Duy et al. 2003; McMillan et al. 2007), particularly if data were co-varied for inter-individual differences in obesity.

Physical activity interventions and liver fat (longitudinal trials in humans)

Forty-six longitudinal human trials were identified (Table 7). Often, sample sizes were small; 19 trials included some form of non-exercise control group, often "usual treatment" or a dietary regimen. Interventions ranged from general lifestyle recommendations to specific programmes with careful control of both exercise and diet. Programmes typically yielded consistent reductions in liver fat, and this was usually associated with decreased insulin resistance. One report noted an improvement of histopathology in response to a combined exercise and weight loss programme (Goodpaster et al. 2010), but there is little evidence in this regard. Effects on serum aminotransferase levels have also been unclear, possibly confounded by normal or near-normal levels in the studied cohorts prior to interventions (Keating et al. 2012; Thoma et al. 2012).

It seems likely that benefits such as a reduction of hepatic fat and a possible normalization of serum aminotransferases will be maximized by a combination of physical activity and dieting which results in significant weight loss, but the respective contributions of diet, physical activity and weight loss to improvements in hepatic function remain to be defined (Thoma et al. 2012). Exercise has traditionally been employed with the goal of weight loss, but some investigators have found benefits from exercise in the absence of dieting (Larson-Meyer et al. 2008) or any change in body mass (Johnson et al. 2009). Further, benefits have persisted after statistical adjustment of data for changes of body mass (Bonekamp et al. 2008). Moreover, at least one study found that dietary manipulation did not enhance the effects of exercise (Eckard et al. 2013).

Nevertheless, much of the current evidence suggests that exercise training may, at best, enhance the hepatic effects of dieting (Goodpaster et al. 2010), and may (Coker et al. 2009) or may not (Tamura et al. 2005; Shah et al. 2009) further increase the insulin sensitization induced by dieting. Significant weight loss (10 %) seems the most effective means to lower liver fat content and aminotransferase levels; lesser effects are seen in studies where the decrease in body mass was 5 % or less (Chen et al. 2008), or if exercise did not induce weight loss. Several reports have found that although exercise has other benefits, such as insulin sensitization, it does not enhance the hepatic response to dieting (Tamura et al. 2005; Shojaee-Moradie et al. 2007; Shah et al. 2009; van der Heijden et al. 2009, 2010b; Jenkins and Hagberg 2011; Straznicky et al. 2012).

Most investigations have evaluated aerobic training programmes. A few reports have also noted favourable responses to resistance exercise training, although its effectiveness in NAFLD is less clearly established. Two of three comparisons between aerobic and resistance training (Lee et al. 2012; Bacchi and Moghetti 2013) 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 enhanced by adding resistance activity (Slentz et al. 2012). Another study of a resistance exercise programme found no reduction of inflammatory markers (Levinger et al. 2009), and one 12-week trial of resistance exercise found a decrease of insulin resistance without a change of hepatic fat content (van der Heijden et al. 2010a). In contrast, a controlled 3-month trial in obese adolescent boys found that thrice weekly 60-min sessions of either aerobic exercise or resistance exercise reduced liver fat, but only resistance exercise was effective in increasing insulin sensitivity (Lee et al. 2012). It is plainly as yet unclear and important to resolve how effective resistance training is for decreasing steatosis and associated comorbidities, particularly as it has been suggested that resistance exercise is important to correct the muscular weakness and autonomic dysfunction that is often associated with this condition (Jakovljevic et al. 2013).

Table 5 Cross-sectional analysis of the inverse association between reported physical activity and steatosis

Author	Sample	Liver assessment	Activity assessment	Outcome	Comment
Bae et al. (2012)	72,359 Korean adults without diabetes	Ultrasound, liver enzymes	Self-reported physical activity	Those exercising at least 3 times per week for at least 30 min per session over a period of 3 months had reduced risk of steatosis (0.53–0.72)	Active individuals also had a decreased risk of elevated hepatic AST (0.85) and ALT (0.74)
Fintini et al. (2012)	Comparison of children with steatosis ($n = 40$) obese ($n = 30$) and lean peers ($n = 41$)		Physical activity questionnaires and sense-wear arm bands	Sense-wear data showed steatosis group devoted more time to sedentary pursuits than lean, and engaged in less physical activity	Questionnaire data did not agree with Sense-wear data
Gerber et al. (2012)	3,056 participants in the US NHANES survey of 2003–2006 aged >20 years	Fatty liver index based on BMI, waist circumference, triglycerides and GGT	Accelerometer step counts	Individuals with high fatty liver index (>60 units) had lower levels of accelerometer readings (29 counts/min per day), and spent less time than controls at all levels of activity	
Hattar et al. (2011)	57 Hispanic children, average age 12.1 years (20 steatosis, 20 obese, 17 controls)	Liver biopsy, liver enzymes	Retrospective physical activity scores, based on questionnaire	Sedentary score >2 associated with stage 2–3 hepatic fibrosis	15 % of children with steatohepatitis performed light exercise, compared with 35 % of obese and 59 % of non-obese children
Hsieh et al. (1998)	3,331 adult Japanese men	Ultrasound	Physical activity questionnaire	Fatty liver less prevalent in those regularly exercising >2 days/week than in sedentary men	Dose–response relationship (sedentary vs. those active 1, 2 and 3 days/week)
Kang et al. (2006)	39 M, 52 F with steatosis, age 48 years	Liver biopsy	Physical activity questionnaire	No difference of histological severity with reported physical activity	
Kistler et al. (2011)	302 men, 511 women with steatosis	Histology	Self-reported physical activity	Neither moderate nor total exercise associated with stage of fibrosis; however, meeting vigorous recommendations reduced odds of steatohepatitis	
Lawlor et al. (2005)	3,789 British women aged 60–79 years	Liver enzymes (ALT, GGT)	British regional heart activity questionnaire	Frequency of activity inversely related to GGT, but relationship to ALT attenuated by adjustment for body mass index and waist hip ratio	
Lee et al. (2006)	201 children >140 % of ideal body mass	Liver enzymes	Physical activity questionnaire	53/201 children show increased ALT and AST; odds ratio if low activity 2.39	Increase of ALT and AST not well correlated with body mass or body fat, but associated with insulin resistance
Leskinen et al. (2009)	16 same-sex middle-aged twin pairs discordant for activity	Proton magnetic resonance spectroscopy	Physical activity questionnaire	Inactive twins had 3 times as much liver fat	Inactive twins also had greater body mass, fat mass, visceral fat and lower fitness
Mager et al. (2010)	38 children (36 obese) aged 5–19 years	Ultrasound and transferases	3-day reported dietary intake and activity questionnaire	Physical activity low in almost all children	No clear comparison group

Table 5 continued

Author	Sample	Liver assessment	Activity assessment	Outcome	Comment
Newton et al. (2008)	36 M, 36 F (36 with steatosis, 36 controls)	Liver biopsy	Pedometer (6-day record)	Cases of steatosis took 20 % fewer steps/day	
Perseghin et al. (2007)	114 M, 77 F aged 19–62 years	Proton magnetic resonance spectroscopy, Fatty liver defined as >5 % wet weight	Physical activity questionnaire	Prevalence of steatosis (defined as hepatic fat >5 %) 25 % in least active quartile, 2 % in most active quartile	Association attenuated by adjustments for age, sex, BMI, insulin sensitivity and adiponectin
Suzuki et al. (2005)	348 men with elevated ALT, mean age 42 year	ALT levels	Self-report	Regular exercise associated with lower ALT, and 2.5-fold greater likelihood of normalizing even after adjusting for change in body weight	
Tiikkainen et al. (2002)	27 women with previous gestational diabetes	Proton magnetic spectroscopy; categorized as hepatic fat above or below 5 %	Frequency of 30 min bouts of physical activity per week	Women with low fat exercising 5 times/week, those with steatosis only 3 times/week	Steatosis associated with insulin resistance
Viitasalo et al. (2012)	492 children aged 6–8 years	Hepatic enzymes	Activity not reported	Overweight or obesity increases risk of high ALT 2.1-fold, high GGT 4.5-fold	GGT linked to c-reactive protein in obesity, suggesting low-grade inflammation
Zelber-Sagi et al. (2008)	375 Israeli men and women, mean age 51 years	Abdominal ultra-sound	Self-reported physical activity	Hepatic fat related to sports participation (odds ratio 0.66) and resistance exercise (0.61), but only related to reports of resistance exercise after adjustment for BMI; even this relationship non-significant if also adjusted for leptin or waist circumference	

Physical activity interventions and liver fat (longitudinal trials in animals)

Some 21 animal studies of exercise and hepatic steatosis generally confirm the findings of human longitudinal investigations (Table 8). They provide growing empirical evidence that fat accumulation has direct adverse effects upon hepatic function, and that these changes can be reversed by exercise; further, they add helpful information on cellular mechanisms underlying the adverse effect of hepatic fat upon glucose homeostasis (Table 9).

In mice fed a high-fat diet, regular exercise reduced the accumulation of fat in the liver, improved insulin resistance and reduced circulating cholesterol, triglycerides, and AST and ALT levels (Marques et al. 2010). Dietary restriction, voluntary wheel running and imposed swimming or treadmill running all seem effective in preventing steatosis (see Table 8 for references), and in one report hepatic benefits were elicited more readily by intermittent swim training than by continuous bouts of swimming (Sene-Fiorese et al. 2009). Yasari et al. (2006) found that after 6 weeks of detraining, rats trained on a treadmill for 4 weeks had regained a similar body fat to sedentary animals, although liver lipid infiltration was not increased with cessation of training. In contrast, Linden et al. (2013) found that 4 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.

Among mechanisms underlying the adverse effect of hepatic fat upon glucose homeostasis, lipid accumulation appears to down-regulate phosphatidylinositol 3-kinase, an enzyme that has a central role in mediating the action of insulin in hepatocytes (Katsanos 2004). Rats fed an obesity-inducing diet not only developed peripheral insulin resistance, but also demonstrated endoplasmic reticular stress in both hepatic and adipose tissues, with activation of the proinflammatory molecules c-jun N-terminal kinase (JNK) and nuclear factor kappa-B (NF-κB).

Cellular adaptations associated with the benefits of enhanced activity have included increased hepatic mitochondrial fatty acid oxidation, enhanced oxidative enzyme function and protein content, and suppression of de novo lipogenesis (Rector et al. 2011). Specific molecular mechanisms identified as contributing to attenuation of fat accumulation and/or reversal of steatosis have included increased hepatic mitochondrial activity (citrate synthase, β-hydroxyacyl-dehydrogenase [HAD] and cytochrome c oxidase) and subsequent beta-oxidation (Rector et al. 2011), a decrease of regulatory element-binding protein-1c (SREBP-1c, one of a group of transcription factors regulating the genes involved in cholesterol and fatty acid synthesis) (Cintra et al. 2012), down-regulation of the hepatic SCD-1 gene, and thus of SCD-1, a rate-limiting enzyme in the biosynthesis of monounsaturated fats (Yasari et al. 2010), and a decreased activity of the hepatic ketone synthesis pathway seen in streptozotocin-diabetic rats, with a decreased activity of the corresponding rate-limiting enzyme HMG-CoA (El Midaoui et al. 2006). Whereas streptozotocin diabetic rats showed a greatly increased activity of the branched-chain alpha-ketoacid dehydrogenase (BCKDH) complex, the rate-limiting enzyme in the catabolism of branched-chain amino acids, such activity was normalized by regular exercise (Li et al. 2001). Regular exercise also attenuated the reduction in hepatic IGF-1 seen in alloxan-diabetic rats (Leme et al. 2009).

Exercise training also reduced hepatic JNK and NF-κB, and lessened endoplasmic reticular stress as shown by decreasing phosphorylation of the two major metabolic markers of this condition (protein-kinase like endoplasmic reticular kinase, PERK and eukaryotic initiation factor 2, eIF2 phosphorylation) (da Luz et al. 2011). Moreover, the glucose stimulation of insulin secretion was decreased in rats that were given access to an exercise wheel, without any deterioration in glucose homeostasis; activity of the insulin-inducible enzyme hepatic glucose kinase (the first stage in glucose utilization) was decreased, possibly due to the lesser output of insulin (Zawalich et al. 1982). Seven days of voluntary wheel running increased the release of the hormone-like hepatic insulin sensitizing substance (HISS), thus decreasing the peripheral insulin resistance of rats (Chowdhury et al. 2013). Aging decreases the hepatic output of HISS, but again this could be countered by allowing the rat free access to a running wheel (Chowdhury et al. 2011). Exercise partially reversed attenuated insulin and leptin signalling in chlorpromazine-induced diabetes in rats by increasing concentrations of insulin-receptor substrate-2 protein (Park et al. 2007). In exercised mice, the enhanced insulin sensitivity was associated with an increased hepatic expression of endosomal adaptor protein APPL1, which blocks the association of protein kinase AKT with its endogenous inhibitor tribbles-related protein 3 (TRB3), and there was a decreased expression of TRB3 (Marinho et al. 2012).

In contrast, several metabolic precursors of steatosis were seen in hyperphagic obese rats following a sudden 1-week cessation of exercise. Changes included a decrease in hepatic mitochondrial oxidative capacity, an increased hepatic expression of lipogenetic proteins, and increased levels of hepatic malonyl CoA (Rector et al. 2008).

Additional effects of exercise training upon insulin sensitivity arise outside the liver, from an increase in muscle mass, an alteration in muscle quality, the greater energy demands of skeletal muscle, and the reduction of visceral fat stores (with a lesser incorporation of fatty acids into the liver). Exercise programmes may also influence

Table 6 Cross-sectional analysis of benefits of cardiorespiratory fitness in steatosis

Author	Sample	Liver assessment	Fitness assessment	Outcome	Comment
Church et al. (2006)	218 men aged 33–73 years	CT scan, ALT > 30 U/L, AST/ALT ratio <1.0	Peak treadmill endurance time	Treadmill endurance and BMI independently associated with steatosis	Associations attenuated if abdominal fatness included in model
Hannukainen et al. (2007)	Nine male monozygotic twin pairs differing in habitual activity	Proton magnetic resonance spectroscopy	Cycle ergometry (active twins had 18 % higher maximal oxygen intake)	20 % less visceral fat in more active twins	Hepatic uptake of free fatty acids lower in active twins
Haufe et al. (2010)	Overweight and obese subjects (31 M, 108 F aged 40–50 years)	Proton magnetic resonance spectroscopy	Cycle ergometry, peak oxygen intake	Negative correlation between aerobic fitness and hepatic fat, M > F	In men, correlation independent of visceral adipose tissue
Kantartzis et al. (2009)	70 M, 100 F (50 with steatosis)	Proton magnetic resonance spectroscopy	Peak oxygen intake on cycle ergometer	Initial peak oxygen intake strongest predictor of reduction in hepatic fat with diet and physical activity lifestyle programme	Authors conclude cardiorespiratory fitness determines liver fat content
Krasnoff et al. (2008)	19 M, 18 F, average age 45.9 years	Steatosis classified by biopsy	Symptom-limited peak oxygen intake on treadmill	No relationship between peak oxygen intake and steatosis, but lower aerobic power if hepatitis (34.0 vs. 25.1 ml/[kg.min]	Histological severity of liver disease influences health-related fitness
Kuk et al. (2004)	86 lean premenopausal women	CT scan	Peak treadmill endurance time	Treadmill endurance lower in those with steatosis	Liver fat not related to other metabolic risk factors
Leskinen et al. (2009)	16 same-sex middle-aged twin pairs discordant for activity	Proton magnetic resonance spectroscopy	Peak oxygen intake on cycle ergometer	Inactive twins had 3 times as much liver fat	Inactive also had greater body mass, fat mass, visceral fat and lower fitness
McMillan et al. (2007)	293 men aged 29–78 years	CT scan	Peak treadmill endurance time	Peak treadmill time weakly correlated with liver fat ($r = -0.24$)	Difference of predicted peak oxygen intake small after control for adiposity (35.3 vs. 34.1 ml/[kg.min]
Nguyen-Duy et al. (2003)	161 men aged 33–72 years	CT scan	Peak treadmill endurance time	Peak treadmill time weakly correlated with liver fat ($r = -0.26$)	Probable overlap of sample with McMillan et al. (2007)
O'Donovan et al. (2009)	50 men aged 34–56, both obese and lean	Proton magnetic resonance spectroscopy	Peak oxygen intake on cycle ergometer	Liver fat was greater in unfit	Relationship eliminated by introduction of waist circumference
Seppala-Lindroos et al. (2007)	30 middle-aged men (15 with steatosis)	Proton magnetic resonance spectroscopy	Directly measured maximal oxygen intake	No significant difference of maximal oxygen intake between high and low fat groups (35.6 vs. 33.5 ml/(kg min)	High liver fat defined as >3 %, so that some normal individuals in supposed high fat group?

Table 7 Longitudinal human studies of changes in hepatic fat content with exercise interventions

Author	Sample	Liver assessment	Intervention	Measures and comments	Outcome
Albu et al. (2010)	58 obese, average age 59 years	CT scan	175-min moderate aerobic exercise/week + moderate energy restriction	No control group	18 % decrease in hepatic fat content
Bacchi and Moghetti (2013); Bacchi et al. (2013)	31 overweight or obese	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	Diet unchanged. No non-exercise control	Hepatic fat reduced 33 % (aerobic) vs. 26 % resistance programme
Barsalani et al. (2013)	54 overweight or obese post-menopausal women	Liver enzymes and liver index	6 months of exercise (3 times/week, mixed training) + placebo, or similar exercise + flavones	No non-exercise control	Fatty index reduced 29 % in combined treatment, 18 % with exercise alone
Bonekamp et al. (2008)	45 adults with type 2 diabetes mellitus, mean age 53 years	Proton magnetic resonance spectroscopy	45 min of moderate aerobic exercise plus weight lifting, 3 times/week for 6 months, vs. control group	Dietary policy unclear	Significant reduction in hepatic fat (2.5 % absolute change), effect persisted even if adjusted for BMI or visceral fat. Abstract report only
Bozzetto et al. (2012)	45 obese diabetic subjects aged 35–70 years	Proton magnetic resonance spectroscopy	8-week aerobic exercise, 45 min at 70 % of peak oxygen intake, 2 times/week	4-way trial, with 2 diets (CHO/fibre or multiunsaturated fat)	Multi-unsaturated fat reduced liver fat 29 %; no added effect from exercise
Chen et al. (2008)	54 M and F Taiwanese with steatosis, average age 38–40 years	Ultrasound. Liver enzymes (AST, ALT, GGT)	10-week diet + exercise (high-intensity cycle ergometry, 1 h twice/week) vs. exercise alone vs. control		Diet + exercise decreased liver fat, ALT and GGT; exercise alone less effective, only decreased liver fat
de Piano et al. (2012)	58 post-pubertal obese adolescents, with or without steatosis, average age 16.5 years	Ultrasound, ALT	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	No non-exercise control group	Combined aerobic + resistance therapy more effective in improving ALT, insulin resistance and non-invasive markers of steatosis than aerobic exercise alone
Devries et al. (2008)	41 men and women, aged 38–40 years; half of sample lean, half obese	CT scan, liver enzymes	3 months of cycle ergometer training, 60 min/day, 3 times/week, progressing to 65 % of maximal oxygen intake in women and 70 % in men	Liver attenuation negatively correlated with ALT. No control group	Training did not alter liver attenuation on CT scan or ALT, but it reduced GGT in men only

Table 7 continued

Author	Sample	Liver assessment	Intervention	Measures and comments	Outcome
Eckard et al. (2013)	56 adults aged 18–70 with steatosis	Biopsy, liver enzymes	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		All intervention groups improved, with no significant inter-group differences
Fealy et al. (2012)	13 obese aged 58 years, sex not specified	Proton magnetic resonance spectroscopy	1 week of walking, 60 min/day at 85 % of maximal heart rate	Liver enzymes, CK18 markers of apoptosis. No control group	Reduced markers of apoptosis, mediated through increased oxidative capacity and greater insulin sensitivity
Finucane et al. (2010)	100 healthy older people (50 served as controls)	Proton magnetic resonance spectroscopy	12-week cycle ergometer exercise, 60 min, 3 times/week vs. control group	Increase of predicted maximal oxygen intake, no change of body mass	Significant reduction of liver fat in intervention group
Franzese et al. (1997)	41 M, 34 F obese children age 9.5 years	Ultrasound, liver enzymes	6 months of diet + exercise	No control group	Liver fat and transaminases decreased with loss of weight
Goodpaster et al. (2010)	130 severely obese adults (101 completed trial)	CT scan	6 months, diet + exercise vs. diet		Both groups lost weight, exercised group lost more liver fat
Grønbæk et al. (2012)	117 obese children, average age 12.1 years	Ultrasound	10-week period at a weight-loss camp with daily hour of varied aerobic exercise	Insulin sensitivity increased. No control group	Reduction of steatosis, decreased ALT in all participants; two-thirds of improvement in liver score retained at 12 months
Hallsworth et al. (2011)	19 sedentary adults with steatosis (average age 52 years experimental, 62 years controls)	Proton magnetic resonance spectroscopy	8-week resistance exercise ($n = 11$) vs. standard treatment ($n = 8$); physical activity monitored by sensewear arm band	Lipid oxidation, glucose control and insulin resistance all improved. Control group older	13 % reduction of liver fat with no change in body mass, total fat mass or visceral fat volume
Hickman et al. (2004)	35 men and women (21 with hepatitis C virus), average age 44 years	Liver biopsy and enzymes	15-month programme of diet plus encouraging 150 min aerobic exercise per week	Exercise monitored by activity diaries. No control group	Improvement of ALT levels correlated with development and maintenance of weight loss; 14 patients biopsied after 3–6 months of exercise showed lessening of steatosis
Jin et al. (2012)	120 potential liver donors with steatosis	Hepatic biopsy	Dietary restriction + 10 weeks of exercise (three 20-min sessions of jogging or walking per week)	Improvement of steatosis associated with weight reduction >5 % and cholesterol reduction >10 %. No control group	Histological improvement in 103 of 120 subjects

Table 7 continued

Author	Sample	Liver assessment	Intervention	Measures and comments	Outcome
Johnson et al. (2009)	19 sedentary obese men and women	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	No change of body mass. No control group	21 % reduction of hepatic triglycerides
Kawaguchi et al. (2011)	35 adults with steatosis resistant to lifestyle counselling (12 trained, 23 controls)	Ultrasound and liver enzymes	Hybrid training (voluntary and electrical contraction of quadriceps and hamstrings, 19 min. 2 times/week for 12 weeks	Associated reduction of insulin resistance and small decrease of body mass. No control group	Steatosis reduced, ALT decreased in trained group
Koot et al. (2011)	144 obese children, mean age 14.1 years	Ultrasound	6-month programme, with three 1-h sessions of unspecified exercise/week plus changes in eating behaviour	Changes related to decreased insulin resistance and 12 % decrease of body mass. No control group	Prevalence of steatosis decreased from 31 to 12 %. Prevalence of elevated ALT decreased from 26 to 11 %, elevated AST decreased from 13 to 4 %. of sample
Kugelmas et al. (2003)	16 patients with steatosis, 18–65 years	Hepatic enzymes	12-week programme of diet and encouragement to walk or jog 30 min/day; half of group also received 800 IU vitamin E daily	No non-exercise control group	Reduction of ALT and AST in first 6 weeks, benefits sustained at 12 weeks
Larson-Meyer et al. (2008)	46 overweight men and women	Proton magnetic resonance spectroscopy, CT scan, liver enzymes	6-month study: dietary restriction + exercise (structured to increase energy expenditure 12.5 %) vs. dietary restriction vs. low-calorie diet vs. control	Liver fat initially correlated with ALT	Liver fat reduced in all three experimental groups; changes not associated with ALT or inflammatory markers
Lazo et al. (2008)	96 men and women with diabetes mellitus, aged 45–76 years, divided between lifestyle intervention and education/support group	Proton magnetic resonance spectroscopy	Weekly meetings to encourage dieting and progression to 175 min of moderate exercise per week for 1 year		Decrease in steatosis 50.8 % (intervention) vs. 22.8 % (controls). No changes in AST or ALT
Lee et al. (2012)	48 obese adolescent boys divided into three groups	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	Subjects instructed to follow weight maintenance diet; only resistance exercise increased insulin sensitivity	Both types of exercise reduced hepatic lipids
Levinger et al. (2009)	28 M, 27 F aged 50.8 years (high vs. low metabolic risk factors)	Liver enzymes, inflammatory markers	10 weeks of resistance training 3 days/week, 50 % rising to 75–85 % 1RM exercise vs. controls	Risk factors associated with enzymes and inflammatory markers	Liver enzymes and inflammatory markers not reduced in those with high metabolic risk factors

Table 7 continued

Author	Sample	Liver assessment	Intervention	Measures and comments	Outcome
Nobili et al. (2008)	37 boys, 16 girls, aged 5.7–18.8 years (plus 33 drop-outs)	Liver enzymes and biopsy (lobular and portal inflammation and ballooning)	Diet plus physical activity for 24 months	Weight loss, insulin sensitivity, physical activity recall. No non-exercise control group	Improvement of enzymes and histology, not further improved by alpha tocopherol and ascorbic acid
Oza et al. (2009)	67 cases of steatosis, only 22 completed treatment	CT scan, liver enzymes	6-month home-based diet + exercise (target of 23 MET-h/week physical activity + 4 MET-h/week of exercise)	Poor compliance, no control group	19/22 showed decreases of visceral fat, liver/spleen ratio, AST, ALT, GGT
Promrat et al. (2010)	Overweight or obese subjects randomized to lifestyle (20) or education (10) groups	Histology	48-week intervention; weekly, then biweekly counselling aiming for 7–10 % weight loss, exercise and altered behaviour	Improvements in hepatic condition associated with weight loss	Histology improvement >3 points in 14/20 of intervention vs. 3/10 of control subjects
Rohrer et al. (2008)	16 boys, six girls, median age 11.9 years	Liver enzymes	1-year weight loss programme that included physical activity	Gains of physical strength and endurance. No control group	Improvement of hepatic enzymes associated with improved fitness
Santomauro et al. (2012)	36 obese children with steatosis	Ultrasound	1-year lifestyle approach, focusing on dieting and increased physical activity	Weight loss main variable accounting for reduction of steatosis. No control group	Reduction or disappearance of steatosis linked to increased physical activity and associated weight loss in 12 of 36 children
Schäfer et al. (2007)	48 impaired glucose tolerance, 133 normal subjects	Proton magnetic resonance spectroscopy	24-month diet + exercise at anaerobic threshold (Polar heart rate monitor)	Body mass decreased 3 % in both groups. No non-exercise control group	Liver fat decreased 28 %, visceral fat 8 % in those with impaired glucose tolerance
Shah et al. (2009)	18 obese >65 years	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)	Body mass decreased 9–10 % in both groups. No non-exercise control	Both treatments reduced liver fat and insulin resistance to similar extent, but added exercise improved physical function
Shojaee-Moradie et al. (2007)	17 initially sedentary men (seven of 17 served as controls)	Proton magnetic resonance spectroscopy	Exercised for 6 weeks. 60–85 % of maximal aerobic power for 20 min, 3 times/week	No control group	No change of liver fat content, but decrease in hepatic insulin resistance and increase in maximal oxygen intake
Slentz et al. (2012)	155 overweight adults aged 18–70 years	Computed tomography, ALT	8-month training 3 days/week: aerobic (running 19 km/week at 75 % aerobic power) vs. resistance vs. combined aerobic + resistance training	No non-exercise controls. ALT inversely related to hepatic fat content	Aerobic training decreased hepatic fat 5.6 %. Also 13.7 % decrease of ALT. No benefit from resistance training alone. Aerobic and combined aerobic + resistance training yielded similar reductions in liver fat

Table 7 continued

Author	Sample	Liver assessment	Intervention	Measures and comments	Outcome
Steenivasa Baba et al. (2006)	65 men and women aged 38.7 years with nonalcoholic steatohepatitis	Liver enzymes	3-month diet plus 30-min exercise, 5 days/week at 60–70 % of maximal heart rate	Compliant patients also showed a decrease of BMI. No control group	AST and ALT normalized only in patients complying with exercise programme
St George et al. (2009)	141 cases of steatosis aged 48–50 years, divided between moderate-intensity exercise, low-intensity exercise and control group	Liver enzymes	3-month trial, 6 vs. 3 lifestyle counselling sessions given over 10 weeks, with advice to walk 150 min/week vs. control group; 60 % of intervention groups reported increased physical activity	Cycle ergometer prediction of maximal oxygen intake. Gains of hepatic function seen independently of weight loss.	Greatest improvement of ALT, GGT, AST if walking 150 min/week and/or increased predicted maximal oxygen intake
Straznicky et al. (2012)	63 obese adults average age 55 years	Liver enzymes	Dietary restriction alone vs. dietary restriction plus moderate exercise (40 min at 65 % of maximal heart rate on alternate days, with only one session per week supervised)		7.6 % loss of body mass with dietary restriction alone. ALT decreased 20 % by dieting. No added advantage if exercise added to dieting
Sullivan et al. (2012)	18 obese adults with steatosis, average age 48 years	Proton magnetic resonance spectroscopy	16-week exercise (45–55 % peak oxygen intake, 30–60 min/day, 5 times/week, $n = 12$) vs. control ($n = 6$)	No change in hepatic VLDL-TG secretion or VDL-apoB-100 secretion	Exercise reduced liver fat 10 %, but no change in body mass or % body fat
Suzuki et al. (2005)	348 males with high ALT values	Liver enzymes	Lifestyle change	Weight loss, binary classification of increase in activity. No control group	Improvement in ALT associated with weight loss >5 % and increase of activity
Tamura et al. (2005)	14 patients with type 2 diabetes mellitus	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)	Diet + exercise group younger than diet alone	Hepatic lipids decreased in both groups, but no added effect of exercise
Thamer et al. (2007, 2008)	48 M, 64 F, average age 46 years	Proton magnetic resonance spectroscopy	Diet + 3 h/week aerobic exercise monitored by Polar pulse-counter, average follow-up of 264 days	Decrease of liver fat associated with improved insulin sensitivity. Subjects with high adipose and liver fat profit less from lifestyle. No control group intervention. No control group	33 % decrease of liver fat, despite little change in overall body fat; response less marked in alleles of peroxisome proliferator-activated receptor-gene
Thomas et al. (2006)	Ten obese adults, age not stated	Proton magnetic resonance spectroscopy, liver enzymes	Diet + pedometer monitored recommendation of 10,000 steps/day	Changes associated with loss of body fat. No control group	40 % decrease of liver fat, improvement of AST but not ALT

Table 7 continued

Author	Sample	Liver assessment	Intervention	Measures and comments	Outcome
Thompson et al. (2010)	41 men aged 45–64 years	ILK-6, ALT	24-week exercise (30 min rising to 60 min at 50 % increasing to 70 % maximal oxygen intake 3 rising to 4 days/week) + 2 weeks detraining vs. control	No comment on nutrition.	IL-6 fell with 12-week moderate exercise; lost with 2-week detraining; ALT reduced at 24 weeks but not at 12 weeks, benefit retained with 2-week detraining
Ueno et al. (1997)	25 obese (ten served as controls)	Liver enzymes and histology	Restricted diet and walking or jogging for 3 months	No control group	Improvement in AST, ALT and steatosis
van der Heijden et al. (2010b)	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)	No control group. Exercise increased hepatic and peripheral insulin sensitivity	Hepatic fat reduced in obese but not in lean subjects, without weight loss
van Der Heijden et al. (2010a)	Obese adolescents (6 M, 6 F)	Proton magnetic resonance spectroscopy	12-week resistance exercise (twice/week, all major muscle groups)	No control group. Body mass increased 2.6 kg	Hepatic fat content unchanged, but insulin sensitivity increased 24 %

hepatic function by modulating myostatin output. Myostatin inhibits muscle growth, thus predisposing to obesity, hepatic insulin resistance and diabetes; it may also have more direct effects upon hepatocytes (Allen et al. 2011). Inactivation of the myostatin gene in mice caused hepatic steatosis in the absence of any change in muscle mass (Mukherjee et al. 2007), and injection of recombinant myostatin slowed overall growth through a decrease in IGF-1 induced AKT phosphorylation, again without change of muscle mass (Hittel et al. 2010). Finally, both mouse and human liver cell cultures developed apoptosis when incubated with recombinant activin, which binds to the same receptors as myostatin (Woodruff et al. 1993; Chen et al. 2000).

Exercise dose recommendations in hepatic disease

From the investigations discussed above, we may conclude that regular aerobic exercise can reduce liver fat levels and this benefit can occur, albeit probably to a lesser extent, without weight loss. In humans, the majority of therapeutic programmes have prescribed exercise at moderate to vigorous intensities for 3–5 days per week (Table 7). However, clearer information is needed on the efficacy of resistance versus aerobic exercise, the minimum dose of physical activity required for benefit, the exercise tolerance of individuals with NAFLD, and doses of exercise that may lead to hepatic injury.

Whilst it appears that regular aerobic exercise of moderate or vigorous intensity is effective in decreasing hepatic fat content, vigorous exercise may not always be practical. Fatigue (probably centrally mediated) is a frequent concomitant of hepatic steatosis (Bergasa et al. 2004), and this may reduce a patient's motivation, or even preclude participation in sustained aerobic activity, especially if this is vigorous. Moreover, co-morbid obesity can in itself reduce functional capacity and discourage involvement in exercise programmes, especially if vigorous activity is required. In this context, the only study to date that has examined predictors of physical activity adoption and adherence in a NAFLD cohort concluded that initial confidence in the ability to exercise was often low, in part because of a fear of falling (Frith et al. 2010). Whilst participation in a supervised exercise programme with individuals similar to oneself is well known to improve self-efficacy and reduce fears of falling, in patients where such an approach is found to be ineffective, more unconventional tactics may be needed to increase daily energy expenditures. One investigation demonstrated that a significant reduction of ALT could be achieved by regular voluntary and electrical stimulation of the quadriceps and hamstring muscles in individuals who were resistant to lifestyle intervention (Kawaguchi et al. 2011).

Table 8 Animal studies of metabolic syndrome and hepatic fat content with exercise interventions

Author	Animals tested	Intervention	Comments	Outcome
Botezelli et al. (2010)	Male Wistar rats initially aged 28 weeks fed on 60 % fructose diet	Swimming 1 h/day at anaerobic threshold, starting at 28 or 90 days	Swimming improved insulin sensitivity	Liver lipids and AST corrected by early or late training, but ALT unchanged
Cameron et al. (2012)	Male Wistar rats fed high-fat/high-carbohydrate diet or corn starch	8 weeks of treadmill running, 20 min/day rising to 30 min/day, 5 days/week; 0 % incline, speed 1 km/h	Exercise decreased body fat, abdominal fat and blood glucose, improved blood lipid profile	Liver mass and hepatic fat decreased in experimental group
Charbonneau et al. (2005)	Female Sprague–Dawley rats initially 10 weeks old, fed high-fat diet	Treadmill exercise progressing to 60 min/day at 26 m/min, 10 % slope	Glucagon resistance of obese rats also prevented by exercise	28 % gain of hepatic fat with high-fat diet was completely reversed by exercise
Cintra et al. (2012)	Obese mice fed high-fat diet	8 weeks of running (50 min/day 5 days/week at 1 km/h)	Associated reduction of regulatory element-binding protein-1c	1.7-fold reduction of liver fat
Colombo et al. (2005)	Male diabetic fatty Zucker rats	5 weeks of treadmill running (1 h/day, 6 days/week, 20 m/min)	Modification of many hepatic genes associated with lipogenesis and detoxification	Liver fat decreased
Corriveau et al. (2008)	Three groups of ovariectomized vs. one group sham-operated rats	25 % dietary restriction vs. dietary restriction + resistance exercise (weighted stair climbing 5 times/week)	Abdominal fat also reduced by resistance exercise	Liver lipid accumulation not stopped by dietary restriction, but reversed by resistance exercise
Gauthier et al. (2003)	Female Sprague–Dawley rats initially 6 weeks old, fed high-fat diet	Treadmill exercise progressing to 60 min/day at 26 m/min, 10 % slope		Liver triacylglycerol content substantially reduced by concomitant exercise relative to sedentary controls
Gauthier et al. (2004); Yasari et al. (2009)	Female Sprague–Dawley rats initially 6 weeks old fed high-fat diet	Treadmill exercise progressing to 60 min/day at 26 m/min, 10 % slope introduced from 8th to 16th week of high-fat diet	Leptin concentrations also reduced by exercise	Exercise decreased visceral fat 30 %
Hao et al. (2010)	12-week ovariectomized female rats	Treadmill running (10–18 min/day at 0 % grade for 15–60 days)	Associated increase in HDL/total cholesterol ratio	Exercise reduced hepatic fat relative to controls
Haram et al. (2009)	Rats bred for low intrinsic running capacity	60 min/day exercise for 8 weeks, either high-intensity interval work (4 min bouts at 85–90 % maximal oxygen intake) or running same distance at continuous 70 % maximal oxygen intake	Both programmes equally effective in reducing body mass and fat mass, and in increasing insulin receptor phosphorylation in the liver	Interval training more effective in reversing metabolic syndrome
Leite et al. (2009)	Adult F Wistar rats, half of sample ovariectomized	Sedentary vs. resistance training (weighted ladder climbing), 4–9 climbs every 3 days	Other fat depots also reduced	Exercise reduced liver fat content, less in ovariectomized than in intact animals
Marques et al. (2010)	C57/BL6 mice fed standard chow or very high-fat diet	Sedentary vs. 8 weeks treadmill running (60 min/day, 5 days/week at 1 km/h)	Exercise reduced insulin resistance, cholesterol and triglycerides	Video-microscopy estimate of hepatic fat content, AST and ALT reduced in exercised animals
Moura et al. (2011)	60-day alloxan-treated diabetic Wistar rats	Swimming 1 h/day, 5 days/week for 44 days with load 3.5 % body mass (below anaerobic threshold)		Hepatic fat content lower in swimmers than in sedentary peers
Pighon et al. 2009a, b)	Ovariectomized rats following 8 weeks of food restriction + resistance exercise	Normal feeding vs. food restriction vs. resistance training (weighted ladder climbing)		Dietary restriction prevents regain of liver fat; resistance exercise also avoids regain

Table 8 continued

Author	Animals tested	Intervention	Comments	Outcome
Rector et al. (2011)	Hyperphagic, Otsuka Long–Evans Tokushima Fatty rats initially aged 4 weeks	36-week voluntary wheel running vs. sedentary controls	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	Exercise prevented hepatic fat accumulation (also prevented by dietary restriction)
Schultz et al. (2012)	Male C57BL/6 mice fed high-fat diet	Unweighted swimming progressing to 60 min/day		15 % reduction of steatosis relative to high-fat controls
Sene-Fiorese et al. (2009)	Male Wistar rats aged 90–120 days fed high-fat diet	90 min/day swimming vs. 330-min/day swimming sessions		Intermittent exercise more effective than continuous in preventing hepatic fat accumulation
Takeshita et al. (2012)	Mice initially aged 6 weeks	Access to running wheel (covering 4.9 km/day) vs. sedentary control	Associated lower plasma leptin and insulin-like growth factor-1 levels	Exercisers had lower liver weights and liver triglyceride content
Thyfault et al. (2009)	Rats selected for high (1,514 m) and low (200 m) running capacity		Histology and biochemistry examined	Unfit rats had reduced mitochondrial content, reduced oxidative capacity, increased peroxisomal activity, steatosis and fibrosis and apoptosis
Yasari et al. (2010)	Female rats given high-fat diet from 6 to 8th week	Treadmill running progressing to 60 min/day at 26 m/min, 10 % slope	Decrease in hepatic SCD-1 mRNA levels and protein content	Liver triglyceride content not affected by exercise
Yasari et al. (2006)	Female Sprague–Dawley rats fed high-fat diet	Treadmill running progressing to 60 min/day at 26 m/min, 10 % slope		If training stopped, trained protected rats for 2 weeks, but no protection 6 weeks post-exercise

Table 9 Cellular and molecular markers of hepatic dysfunction in steatosis and insulin resistance and effects of exercise training

Manifestation	Exercise	Exercise training response	Comment	Author
	2 h of treadmill running (26 m/min, 1.5 % grade)	Increased expression of insulin-like growth factor binding protein-1 mRNA	Acute bout of exercise	Anthony et al. (2001)
	7 days of voluntary wheel running	Increased release of hepatic insulin-sensitizing substance (HISS), effective in countering age-related decrease of HISS	Leads to increased peripheral uptake of glucose	Chowdhury et al. (2011, 2013)
Activation of c-jun N-terminal kinase (JNK) and nuclear factor kappa-B (NF-κB)	8 weeks, 1 h/day, with a tail weight 5 % of body mass	Reduced hepatic JNK and NF-κB. Decreased phosphorylation of the two major metabolic markers of reticular stress (protein-kinase like endoplasmic reticular kinase, PERK and eukaryotic initiation factor 2, eIF2 phosphorylation)	Proinflammatory molecules	da Luz et al. (2011)
Increased activity of the hepatic ketone synthesis pathway	10 weeks of treadmill running, progressing to two 60-min bouts/day at 31 m/min	Ketone synthesis normalized, decrease in HMG-CoA (rate-limiting enzyme for cholesterol synthesis)		El Midaoui et al. (2006)
Depressed activity of phosphatidyl-inositol 3-kinase			Central mediating role in action of insulin on hepatocytes	Katsanos (2004)
Reduction of hepatic IGF-1	8 weeks of treadmill running progressing to 60 min/day at a speed of 31 m/min and a slope of 8 %)	Reduction of hepatic IGF-1 attenuated		Leme et al. (2009)
Increased activity of alpha-ketoacid dehydrogenase (BCKDH) complex	4 weeks of treadmill running, progressing to 45 min/day at 25 m/min, 6 % slope	Activity of alpha-ketoacid dehydrogenase (BCKDH) complex normalized	Rate-limiting enzyme in the catabolism of branched-chain amino acids	Li et al. (2001)
	8 weeks of swimming, 60 min/day, 5 days/week (mouse study)	Increased hepatic expression of endosomal adaptor protein APPL1, decreased expression of TRB3, increasing hepatic response to insulin	APPL1 blocks the association of protein kinase AKT with its endogenous inhibitor tribbles-related protein 3 (TRB3)	Marinho et al. (2012)
	70–80 days of voluntary wheel running	Glucose clearance of livers less than half of sedentary controls, whether in fed or fasting state	Hindlimb glucose clearance increased by training	Mondon et al. (1980)
Increased levels of alanine amino-transferase (ALT) and especially γ-glutamyl transferase, (GGT) in humans			Increased levels of hepatic enzymes associated with poor glucose tolerance; increased GGT facilitates intracellular transport of glutathione, increasing oxidative stress	Nannipierri et al. (2005)
Hyperinsulinaemia and hyperleptinaemia	30-min uphill treadmill running at 20 m/min 4 times/week	Up-regulation of hepatic insulin-receptor substrate-2 protein		Park et al. (2007)
	36 days of voluntary wheel running (6.4–9.7 km/day)	Down-regulation of hepatic glucose kinase	Possibly caused by hypoinsulinaemia	Zawalich et al. (1982)

All studies in rats unless otherwise indicated

Conclusions

Like many body systems, the liver seems well adapted to meet the demands of regular moderate physical activity. However, function becomes impaired with prolonged periods of inadequate physical activity, and extremely prolonged vigorous exercise can also have adverse consequences, particularly under harsh environmental conditions.

Acute exercise stimulates hepatic glycogenolysis and gluconeogenesis, increases the synthesis of some proteins, and may cause oxidative stress. Enzymes involved in carbohydrate metabolism are up-regulated, and lipogenic enzymes are down-regulated. Humoral changes seem the primary triggers for these changes, but the possible roles of hepatic afferent nerves, cytokines, reactive oxygen species, and reduced hepatic blood flow remain to be clarified.

Regular moderate exercise appears to build upon the changes induced by a single session of vigorous physical activity, although further studies are needed in individuals who began training with a low hepatic fat content. In obese subjects, hepatic fat content is reduced, hypertrophy of hepatic tissue is stimulated, and clearance functions are enhanced by exercise training. Blood glucose homeostasis is also improved because of increased glycogen storage and an up-regulation of enzymes involved in carbohydrate metabolism. Fat storage is decreased by a down-regulation of lipogenic enzymes and increased lipid metabolism. Production of heat shock proteins is increased and the secretion of orixogenic proteins is decreased. Increases of antioxidant enzymes and stores of reduced glutathione enhance resistance to oxidant stress. Triggers of metabolic responses to chronic exercise seem modulations of insulin, insulin-like growth factor, glucagon and interleukin-6.

Inadequate physical activity predisposes to steatosis and associated disorders, including the metabolic syndrome, cardiovascular disease and diabetes mellitus. Simple steatosis can progress to hepatitis, cirrhosis and even hepatic carcinoma. Therapeutic exercise programmes restore insulin sensitivity, counteract diabetes and steatosis, and may facilitate recovery from hepatitis. However, the optimal exercise prescription remains to be defined in terms of efficacy and patient acceptance.

In summary, regular moderate physical activity makes an important contribution to the maintenance of optimal liver function, and this seems one more good reason to commend daily exercise as an important part of a healthy lifestyle.

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