PERSPECTIVES

Higher levels of cardiorespiratory fitness keep liver mitochondria happy!

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The concept that regular physical activity (PA) and exercise training promote mitochondrial biogenesis in skeletal muscle, enhancing mitochondrial quality and quantity and in doing so increasing oxidative phosphorylation capacity, has been well established for almost 50 years. Significantly, and less well known, the stimulatory effects of PA on mitochondrial biogenesis and oxidative phosphorylation also occurs in other tissues including the liver, adipose tissue, brain and kidney, with the widespread increased metabolic demand of contractile activity requiring a co-ordinated response with inter-organ 'cross-talk'.

Regular PA and maintenance of higher levels of cardiorespiratory fitness (also termed aerobic capacity) have been shown to be not only protective against, but also therapeutic in, non-alcoholic fatty liver disease (NAFLD). In human studies, an inverse association exists between levels of cardiorespiratory fitness and the presence of NAFLD (Church *et al.* 2006). Data from monozygotic twins, discordant for physical activity, show increased liver fat in the least physically active twin highlighting the contribution of low levels of PA to NAFLD (Hannukainen *et al.* 2011). Thus, a wealth of data exist to support regular PA being considered as a first-line measure to prevent and reverse NAFLD (Fig. 1, bottom left pointing arrows). NAFLD describes a spectrum of histopathological changes in individuals with minimal or no alcohol consumption, from the earliest stage of simple steatosis (with triglyceride deposition in the hepatocytes), through to non-alcoholic steatohepatitis (NASH; characterised by an inflammatory infiltrate with evidence of hepatocyte injury, hepatocyte ballooning and cell death) and to liver fibrosis/cirrhosis with collagen deposition. Factors influencing progression across the disease spectrum remain uncertain and identifying individuals who will progress remains a challenge.

To date, the main benefits of regular PA have been demonstrated in reducing liver fat, preventing or reversing hepatic steatosis, restoring the liver to normal. While avoidance of a 'fatty liver' is important for preservation of cardiometabolic health, much less is known about the effects of high aerobic capacity in preventing or reversing hepatic inflammatory or fibrotic changes, the cause of liver-related morbidity and mortality. There are human data highlighting lifestyle intervention (incorporating dietary intervention and increased PA to effect modest weight loss of 7–10% and improve aerobic capacity, respectively) as a strategy to improve the histological features of NASH and cause regression of fibrosis (Vilar-Gomez *et al.* 2015).

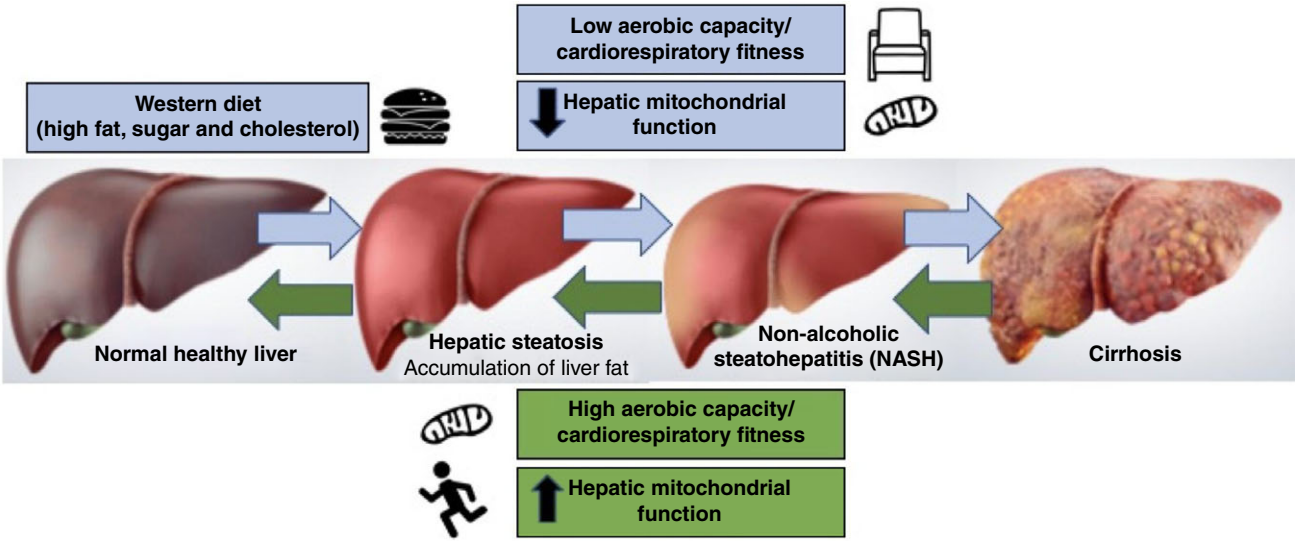

Figure 1. Bidirectional progression between a normal healthy liver, accumulation of hepatic triglyceride (hepatic steatosis), development of inflammatory changes (NASH) and liver fibrosis/cirrhosis
A background of a Western diet predisposes to hepatic steatosis. Low aerobic capacity accelerates the transition from steatosis to non-alcoholic steatohepatitis (NASH) through an effect on hepatic mitochondrial respiratory capacity, generation of oxidative stress and induction of hepatocyte injury, inflammation and programmed cell death. High aerobic capacity/cardiorespiratory fitness has the ability to prevent or reverse this transition causing regression of fibrosis with improvement in NASH and reductions in steatosis.

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The Journal of Physiology

In a recent issue of *The Journal of Physiology*, Morris *et al.* (2017) have used a well-established model to investigate the contribution of inherited differences in aerobic capacity. The model began with selective breeding of rats with high (top 10%) or low (bottom 10%) running performance through successive generations. Aerobic capacity, the whole body's ability to deliver and utilise oxygen during maximal intensity exercise, is governed by a variety of factors including behavioural patterns (particularly the frequency, duration and intensity of physical activity) and age, but significantly approximately 70% of aerobic capacity is explained by genetic factors, independent of daily activities or exercise training. Rats selectively bred for differences in intrinsic running capacity (high capacity runner (HCR) *versus* low capacity runner (LCR) rats) diverge in their susceptibility to metabolic diseases (insulin resistance and NAFLD) as well as cardiovascular disease. LCR rats have increased susceptibility to hepatic steatosis, associated with lower whole body and liver fatty acid oxidation, reduced mitochondrial respiratory capacity and greater induction of mitochondrial oxidative stress when fed a high-fat diet (HFD), compared with HCR rats, which enjoy a degree of hepatoprotection. This model effectively mimics the physiological effects of being either physically inactive (with low fitness) or being exercise trained (with high fitness) without the experimental complications of controlling for the effects of exercise itself. Thus, the model allows investigators to disentangle the acute/chronic effects of exercise from intrinsic/genetic differences in cardiorespiratory fitness.

Morris *et al.* (2017) studied the response of LCR *versus* HCR rats to a 16-week 'Western diet' (WD) *versus* a low-fat 'control diet' (LFD) (10% fat and 3.5% sucrose). The WD was high in fat, sugar and cholesterol (45% fat, 15% sucrose and 1% cholesterol), with the addition of refined sugar and cholesterol to a HFD able to induce the development of NASH (rather than simply steatosis) in rodent models. Both LCR and HCR rats developed significant body weight gain with the WD, and significant liver triacylglycerol deposition and thus hepatomegaly. However, the WD-fed LCR rats had clear evidence of hepatocyte injury with higher serum alanine aminotransferase concentrations, evidence of inflammatory cell infiltration, increased expression of pro-inflammatory markers and increased oxidative stress, compared with HCR rats (Fig. 1, top right pointing arrows). However, even the HCR rats were not completely protected from hepatocyte injury/inflammation. This greater evidence of liver inflammation/injury in LCR rats was associated with reduced hepatic fatty acid oxidation and reduced mitochondrial respiratory capacity. From these data, the authors found evidence that LCR rats, on a diet-induced background of NAFLD, exhibited greater susceptibility to progressive liver disease with NASH, clearly implicating hepatic mitochondrial dysfunction and providing an important mechanistic link between low levels of cardiorespiratory fitness and progression of the NAFLD spectrum/development of NASH. While hepatic mitochondrial dysfunction has been implicated in human NASH previously (Koliaki *et al.* 2015) this study provides mechanistic evidence to implicate liver mitochondria as the mediator by which higher aerobic capacity improves liver health (Fig. 1, bottom left pointing arrows). The cellular/molecular pathways by which these liver mitochondria respond to the increased aerobic capacity remain unclear – perhaps through alterations in mitochondrial biogenesis or autophagy, but this will be certain to be focus of further investigation.

In summary, aerobic capacity plays a key role in the progression and regression of all stages of the NAFLD spectrum: regular PA and maintenance of higher cardiorespiratory fitness appear to have a hepatoprotective effect by enhancing liver mitochondrial respiratory capacity. Move for the mitochondria and preserve liver health!

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Additional information

Competing interests

None declared.

Author contributions

Both authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.