HIGHLIGHTED TOPIC | Physiology and Pathophysiology of Physical Inactivity

Does physical inactivity cause nonalcoholic fatty liver disease?

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TWO-THIRDS OF THE US ADULT population is classified as overweight, and one-third is now considered obese. In addition, it is reported that one in every three children (31.7%) in the US is overweight or obese (62). There is no denying that a significant contributing factor to this epidemic is the ease of access to unhealthy, calorically dense food choices. However, while our genes were selected in an environment of high physical activity, due to technological advances, there currently is little need for physical activity in our daily living. Distressingly, the negative by-product of our modern civilization is an increased risk of chronic disease. The relationship between being more physically active or having higher physical fitness and an associated reduction in mortality (cardiovascular and all-cause) has been well known for several decades (5, 6, 46, 63, 66). Moreover, we and others also believe that physical inactivity is a primary cause of obesity and associated metabolic disorders. Unfortunately, accumulating evidence suggests that we have engineered physical activity out of our normal daily living activity. One such consequence of our sedentary and excessive lifestyle is nonalcoholic fatty liver disease (NAFLD), which is now considered the most common cause of chronic liver disease in Westernized societies. In this review, we will present evidence that physical inactivity, low aerobic fitness, and overnutrition, either separately or in combination, are an underlying cause of NAFLD.

insulin resistance; aerobic fitness; overnutrition

Two-thirds of the US adult population is classified as overweight, and one-third is now considered obese. In addition, it is reported that one in every three children (31.7%) in the US is overweight or obese (62). There is no denying that a significant contributing factor to this epidemic is the ease of access to unhealthy, calorically dense food choices. However, while our genes were selected in an environment of high physical activity, due to technological advances, there currently is little need for physical activity in our daily living. Distressingly, the negative by-product of our modern civilization is an increased risk of chronic disease. The relationship between being more physically active or having higher physical fitness and an associated reduction in mortality (cardiovascular and all-cause) has been well known for several decades (5, 6, 46, 63, 66). Moreover, we and others also believe that physical inactivity is a primary cause of obesity and associated metabolic disorders (10, 72, 84). The Centers for Disease Control and Prevention estimate that 25% of US adults are completely inactive in their leisure time, and findings from the Behavior Risk Factors Surveillance Survey indicate that >75% of US adults do not get the recommended amount of physical activity per week (74). Even more shocking is that the lack of regular exercise or physical inactivity is an “actual cause of death” (50).

One consequence of being sedentary and in a state of overnutrition is nonalcoholic fatty liver disease (NAFLD), a chronic, progressive liver disease that affects >90 million Americans. In this review, we will briefly describe the clinical implications of NAFLD and what cross-sectional observations have taught us about links between physical inactivity, low cardiorespiratory fitness, and NAFLD. Further, we will discuss the impact of increasing physical activity on NAFLD outcomes and discuss the limited studies that have taken a mechanistic approach to examine the negative consequences of physical inactivity on NAFLD outcomes.

WHAT IS NAFLD AND WHY IS IT A PUBLIC HEALTH CONCERN?

NAFLD is characterized by increased hepatic triglyceride (TG) accumulation (≥5% by weight for diagnosis) that occurs in the absence of excess alcohol consumption (>20 g/day) (14). NAFLD is now considered the most common cause of chronic liver disease, affecting ~30% of the adult US population (16–20% of nonobese and 75–100% in obese and morbidly obese individuals) (3, 14). In addition, as the number of overweight and obese children has doubled in the past two to three decades in the US, there also is an increasing propensity of NAFLD and nonalcoholic steatohepatitis (NASH) development in younger individuals (18). In fact, it is estimated that 10% of lean and between 38% and 74% of obese children have fatty livers (60, 76).

NAFLD encompasses a histological spectrum ranging from simple hepatic steatosis to NASH, advanced fibrosis, and cirrhosis [see Tiniakos et al. (87) for recent in-depth review]. The majority of individuals with NAFLD have no symptoms with a normal physical examination; however, about 2–6% of adult Americans and 20% of those who are obese may develop steatosis with inflammation (NASH), fibrosis, and cirrhosis (92). The diagnosis usually is first suspected in an overweight or obese person who is found to have mild elevations in

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specific liver enzymes measured in circulation, including elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST), with ALT levels being greater than AST levels. Morphologically, hepatic steatosis manifests as accumulation of macrovesicular and/or microvesicular intracytoplasmic fat droplets in hepatocytes. In macrovesicular steatosis, a large single fat vacuole fills the cytoplasm of hepatocytes and displaces the nucleus to the periphery, causing a characteristic signet ring appearance. In microvesicular steatosis, numerous small lipid droplets occupy the cytoplasm of hepatocytes. Hepatic steatosis can be reversible or progress to NASH depending on the cessation or persistence of the underlying causes. NASH represents steatosis, inflammatory cell (usually lymphocytes and polymorphonuclear leukocytes) infiltration, hepatocellular injury (usually ballooning hepatocytes), apoptotic cells, and Mallory-Denk bodies. The inflammatory extent varies considerably and does not always correlate with the degree of steatosis. Hepatocyte apoptosis and inflammation activate stellate cells leading to the development of hepatic fibrosis that often commences in zone 3 and manifests as perisinusoidal, perivenular (around terminal hepatic veins), and pericellular fibrosis. Hepatic steatosis, inflammation, and aggressive fibrogenesis as well as sustained hepatocellular proliferation contribute to the development of liver cirrhosis. If the insults are great enough and the liver injury progresses to cirrhosis, ~33% of these patients will die or develop morbidity conditions (31).

While typically thought to take three or more decades to progress in the adult population, NAFLD appears to be much more progressive in children, occurring in as little as 10–20 years (58). NAFLD is strongly associated with cardiovascular disease (CVD) (83), all-cause and liver-related mortality (23, 65), and decreased quality of life in adults and children (20, 38). NAFLD also is considered the hepatic manifestation of the metabolic syndrome and strongly associated with obesity and insulin resistance (reviewed by Ref. 72). In addition, 80% of type 2 diabetics display NAFLD (82), making NAFLD both an outcome and major contributing factor in diabetes development and progression (2). A number of factors are known to contribute to NAFLD, including excess free fatty acid (FFAs) delivery from visceral adipose tissue, which drain directly into the portal vein where they circulate through the liver and overload hepatocytes with lipids (15). Other factors known to contribute to hepatic steatosis include excess dietary fat packaged as triglycerides (TG) in chylomicrons, increased de novo lipogenesis, diminished exportation of TG into very-low-density lipoproteins, and reduced hepatic fatty acid oxidation (reviewed in Ref. 72).

The liver serves as a main source for endogenous glucose production and is a major site for fatty acid disposal (both oxidation and esterification), glucose uptake and storage, and insulin clearance. While clinicians have primarily focused on progression to NASH and cirrhosis, hepatic steatosis without advanced disease also results in negative metabolic outcomes. Under normal insulin-sensitive conditions, insulin inhibits hepatic glycogenolysis and gluconeogenesis, suppressing hepatic glucose production. However, hepatic steatosis is strongly linked to hepatic insulin resistance, and disrupted insulin action in the liver appears to be pathway selective (12, 47). In the insulin-resistant state, insulin-stimulated suppression of hepatic gluconeogenesis is impaired, contributing to systemic hyperglycemia. At the same time, insulin signaling to de novo lipogenesis remains intact or enhanced, further contributing to hypertriglyceridemia. It should be noted that similar to findings in skeletal muscle, it is now becoming recognized that lipid intermediates, such as diacylglycerol (DAG), ceramides, and long-chain acyl-CoAs, etc., rather than inert TGs, may be the cause of impaired insulin signaling and metabolic dysregulation (56). These hepatic alterations have led some to postulate that hepatic insulin resistance could be the primary event that subsequently leads to development of peripheral tissue (muscle and adipose) insulin resistance (67) and altered pancreatic β-cell insulin secretion, increasing the risk for CVD and type 2 diabetes. However, others consider peripheral insulin resistance to be an essential requirement for accumulation of hepatic fat (13), due to both the insulin resistance-induced dysregulation in adipose tissue lipolysis, which chronically increases FFAs during postprandial conditions, and also because of the direct impact of hyperinsulinemia on liver metabolism. Although there is no doubt that insulin resistance and NAFLD are strongly linked, the precise mechanistic relationships remain unknown and controversial.

PHYSICAL INACTIVITY AND NAFLD: CROSS-SECTIONAL OBSERVATIONS

Physical inactivity and NAFLD are intimately linked, but unfortunately, the majority of this evidence is only associative, gathered from cross-sectional observations. Hsieh et al. (30) was one of the first studies to report that decreased levels of daily physical activity (≤1 day/wk vs. ≥3 days/wk) were associated with increased incidence of NAFLD. Perseghin et al. (68) reported similar findings of higher intrahepatic fat content in nonalcoholic men and women who reported reduced habitual physical activity (68), and Lawlor et al. (44) found significantly elevated liver enzymes in women who reported reduced frequency of physical activity. In addition, it has been reported that women with previously diagnosed gestational diabetes and NAFLD exercised fewer days per week compared with women with normal liver fat (86).

Observational data also suggest that individuals who do not engage in the upper end of moderate or vigorous physical activities have increased incidence and severity of NAFLD. Zelber-Sagi et al. (93) reported that individuals with NAFLD had both reduced aerobic as well as resistance type physical activity, but only the association with resistance physical activity and NAFLD remained significant after statistical adjustment for body mass index (BMI). In addition, recently published cross-sectional data from the Nonalcoholic Steatohepatitis Clinical Research Network (NASH-CRN) suggests that those individuals with biopsy-proven NAFLD not meeting vigorous physical activity recommendations (≥75 min/wk) had greater odds of having NASH, and those that did not meet the criteria for vigorous physical activity to induce health improvements (≥150 min/wk) had increased odds of having advanced fibrosis (37).

Recent retrospective data in children also support a potential role for reduced physical activity causing an increased incidence of NAFLD. Time spent in moderate-to-vigorous physical activity declined sharply in children between the ages of 9 years (where most children met or exceeded the 60 min of activity per day) and 15 years (where only 31% met the...
Physical inactivity is associated with increased insulin resistance, metabolic risk, and adiposity in youth (24, 79), and it would stand to reason that inactive children would also have a higher incidence of NAFLD; however, these studies have not been conducted to our knowledge, whereas increasing physical activity and implementing a low-fat and low-glycemic index diet significantly improved liver enzymes and insulin resistance in children without changing body weight or BMI. In addition, it recently has been shown that 12 wk of aerobic exercise training [85% of peak oxygen consumption (\( \dot{V}O_2 \text{peak} \)], 4 days/wk, 30 min/day] reduced hepatic triglyceride (TG) content [determined by magnetic resonance spectroscopy (MRS)] by \( \sim 40\% \) in sedentary, postpubertal, obese adolescents (89) in the absence of weight loss. Collectively, reduced physical activity, and dietary excess, are likely significant contributing factors to the increased incidence of NAFLD in the children and adolescent population.

In summary, there is strong support for a role of habitual physical inactivity as a primary contributor to the development and progression of NAFLD. The majority of cross-sectional studies suggest that reduced habitual physical activity is associated with hepatic fat independent of age, sex, and BMI. However, it should be noted that this relationship between inactivity and elevated liver fat is weakened to a certain extent if statistically controlling for visceral fat or abdominal obesity.

MECHANISTIC INSIGHT INTO PHYSICAL INACTIVITY AND NAFLD

It is well known that exercise cessation (or reduced daily ambulatory activity) and induction of acute, short-term physical inactivity leads to a rapid reduction of systemic and skeletal muscle insulin sensitivity (8–10, 17, 42, 64, 80). Short-term physical inactivity also increases fat mass and reduces lean body mass in both rodents and humans (43, 45, 64). In addition, bed rest, an extreme model of physical inactivity, has been shown to reduce sympathetic activity, increase insulin resistance and lipogenesis, reduce lipid oxidation, and reduce glucose oxidation in humans (7). Furthermore, longitudinal data highlight the negative consequences of long-term physical inactivity on virtually all health outcomes including insulin resistance and type 2 diabetes. Despite the evidence that both acute and chronic physical inactivity can activate pathologies (insulin resistance and central adiposity) that are closely linked to NAFLD, studies confirming a mechanistic link are lacking. For example, the direct effects of exercise cessation or induction of physical inactivity on hepatic steatosis development in humans has not been examined. It has been reported that less physically active individuals with greater amounts of intra-abdominal adiposity exhibit higher rates of hepatic FFA uptake compared with more active individuals (28), whereas habitual endurance training is associated with a lowering of hepatic FFA uptake (32). In addition, hepatic insulin resistance is present in first-degree relatives of type 2 diabetics and is exacerbated in response to 9 days of bed rest-induced physical inactivity (1). These studies begin to shed some light on the metabolic maladaptations that occur in the liver in the absence of being physically active.

In an attempt to understand early alterations in hepatic lipid metabolism caused by physical inactivity, our research group has utilized the commonly studied animal model of obesity and type 2 diabetes, the Otsuka Long-Evans Tokushima Fatty (OLETF) rat. The OLETF rat is selectively bred for null expression of the cholecystokinin-1 receptor and, thus, exhibits hyperphagia (52), which leads to the progressive development of obesity, insulin resistance, type 2 diabetes, and NAFLD. In characterizing NAFLD development and progression in the OLETF animals, we have observed reduced hepatic mitochondrial content and function by 5 wk of age, hepatic steatosis by 8 wk, systemic insulin resistance by 13 wk, and NAFLD progression through 40 wk of age (71). They also develop frank type 2 diabetes between 30 and 40 wk of age. However, 100% of these pathological metabolic events are prevented when the OLETFs are given daily access to voluntary running wheels and allowed to be physically active, despite the animals remaining hyperphagic (69, 70). Mechanistically, our data suggest that daily physical activity in the OLETF rat prevents hepatic steatosis development and NAFLD progression in part by increasing hepatic mitochondrial content and function and suppressing hepatic de novo lipogenesis (70).

We next questioned if locking their running wheels and transitioning the OLETF animals to inactivity would negatively impact hepatic metabolism and lead to NAFLD. After chronic access to daily running, we locked the rats’ running wheels for 173 h (7 days) and compared them to rats whose wheels were only locked for 5 and 53 h (69). Despite no significant change in many peripheral factors previously associated with hepatic steatosis (body weight, fat pad mass, food intake, serum insulin), we found that the 7-day wheel lock period led to a significant reduction in hepatic complete fatty acid oxidation and activity of mitochondrial enzymes (citrate synthase, \( \beta \)-hydroxy-acyl-CoA dehydrogenase, and cytochrome c oxidase) (69). In addition, cessation of daily exercise quickly increased the hepatic protein contents of fatty acid synthase (FAS) and acetylcoenzyme A carboxylase (ACC), reduced ACC phosphorylation status, and dramatically increased hepatic malonyl-CoA concentrations, all integral steps in hepatic fatty acid synthesis and TG accumulation. However, despite these metabolic alterations, we did not see a significant increase in hepatic TG content following the 7-day wheel lock.

Physical inactivity could also be a primary cause of disruptions in hepatic insulin signaling and subsequent NAFLD. DeSouza et al. (21) recently reported that obese models of NAFLD (\( ob/ob \) and diet-induced obesity mice) have impaired hepatic insulin signaling when studied under sedentary cage conditions. However, after one acute exercise bout (swimming), the obese mice displayed marked improvements in hepatic insulin signaling (21). This suggests that perhaps obesity alone is not the primary defect causing hepatic insulin resistance, but rather the combination of sedentary conditions and obesity that are the driving force. Although not assessed in that report, there is evidence that disruption of the hepatic insulin signaling pathway can induce NAFLD. Inducing hepatic insulin resistance through deletion of the insulin receptor substrate (IRS)-2 gene causes an upregulation in SREBP-1, resulting in obesity, NAFLD, and diabetes development in these animals (88). In addition, IRS-1 and IRS-2 knockout mice develop hepatic insulin resistance and also impaired mitochondrial function and mitochondrial biogenesis (48).

In summary, it appears that the relevant molecular and biochemical adaptations to exercise in the liver are readily
reversed with acute exercise cessation; however, changes in hepatic fat content appear to manifest later in time and perhaps only when additional insults are present. This has been demonstrated in our work and others, where 7–14 days of inactivity did not result in significant hepatic TG accumulation (69, 91). We have since followed up our previous work in the OLETF rat and found that 4 wk of physical inactivity following 12 wk of voluntary wheel running does result in significant hepatic TG accumulation and hepatic steatosis, concurrent with increases in body weight and body fat (R. S. Rector, unpublished observations). Nonetheless, these findings collectively support our contention that physical inactivity increases susceptibility or in fact may be necessary for the development of NAFLD.

**BENEFICIAL IMPACT OF INCREASING PHYSICAL ACTIVITY ON NAFLD**

Endurance training or increasing physical activity is considered to be protective against the development of multiple metabolic disorders. Likewise, increasing physical activity and reducing energy intake are the most common prescribed therapies for NAFLD. A recent review by Johnson and George (33) summarized the majority of studies that have incorporated exercise and weight loss in the treatment of NAFLD and conclude that therapies which include dietary energy restriction and increases in physical activity positively influence reductions in hepatic steatosis when weight loss of 3–10% of body weight is achieved. In addition, others have suggested that maintaining or increasing physical activity provides health benefits for patients with fatty liver, independent of changes in weight (16, 78). However, while there are hundreds of studies showing the benefits of increasing physical activity levels (without inducing weight loss) on insulin sensitivity, blood lipids, CVD risk, blood pressure, etc., long-term randomized clinical trials examining the effects of exercise/physical activity on NAFLD, in the absence of weight loss, are lacking.

To date, there are only four studies that have examined the effects of short-term, moderate-intensity, aerobic exercise interventions (ranging from 4 to 12 wk in duration) on NAFLD outcomes without a dietary and weight loss component. Unfortunately, these studies have yielded mixed results, with two studies reporting no significant reductions (22, 77) and two studies reporting a beneficial impact in reducing (34, 89) hepatic lipid content. Six weeks of moderate-intensity aerobic exercise failed to reduce hepatic lipid content in healthy, sedentary, overweight nondiabetic men, most likely due to lack of clinical fatty liver disease in participants at baseline (77). A second study reported similar findings where 12 wk of moderate intensity (70% of VO2peak) aerobic exercise in healthy, sedentary obese men and women was ineffective in reducing hepatic fat content assessed by CT (22). However, Johnson et al. (34) recently found that 4 wk of moderate-intensity (70% of VO2peak) exercise (30–45 min/day, 3 days/wk) in sedentary, obese men and women reduced serum FFAs and visceral adiposity and lowered hepatic TG content (assessed by MRS) by 21% in participants with clinical hepatic steatosis at baseline. In addition, as mentioned previously, 12 wk of moderate-intensity aerobic exercise reduced hepatic TG content in sedentary, postpubertal obese adolescents (89).

These findings shed some light on the role of physical activity on NAFLD and although a couple of the short-term interventions were unsuccessful in reducing hepatic lipid content, they may have prevented the future development of clinically relevant hepatic steatosis in these participants if they were carried out longer. This would have important clinical implications, due to the lack of success in long-term weight maintenance approaches utilizing dietary therapies in human studies. However, to date, a direct comparison between increases in physical activity vs. reducing energy intake to prevent obesity and NAFLD in humans has not been completed. To address this question, we recently conducted studies in the OLETF rat where either daily wheel running or daily caloric restriction was utilized to prevent obesity and NAFLD (73). We found that both daily exercise and daily caloric restriction were equally effective in preventing NAFLD in the OLETF rat (73) but through different mechanism(s). Daily exercise prevented hepatic steatosis and DAG accumulation in part through an upregulation in hepatic mitochondrial function/content and suppression of de novo lipogenesis, whereas caloric restriction prevented hepatic lipid accumulation through elimination of the hyperphagic environment with no upregulation of hepatic mitochondrial content or function. Furthermore, hepatic de novo lipogenesis markers were upregulated in the calorically restricted animals, suggesting that if the calorically restricted animals returned to ad libitum feeding their livers would be primed to store excess fat rapidly.

**PHYSICAL INACTIVITY AND LOW AEROBIC FITNESS**

It is largely underappreciated that low aerobic fitness, independent of physical activity levels, BMI, or other risk factors, is the best overall predictor of early mortality (6, 53) and is also tightly linked to the development of CVD (53) and type 2 diabetes (51). However, it is difficult to assess the direct impact of regular physical activity from the direct effects of improved cardiorespiratory fitness on health outcomes. Physical inactivity leads to low aerobic fitness; conversely, regular exercise/physical activity will improve or maintain aerobic fitness, although the responses can be grossly heterogeneous (11, 39). In addition, while studies have shown a strong inverse association between physical activity and metabolic syndrome, this association is stronger in unfit individuals, emphasizing the importance of being both physically active and having a higher cardiorespiratory fitness level (26).

Several recent reports have highlighted an inverse association between aerobic fitness and the prevalence of NAFLD (19, 35, 41, 49, 57). Furthermore, higher cardiorespiratory fitness predicts a greater effectiveness for lifestyle modifications to reduce hepatic steatosis in patients with NAFLD (35), and hepatic fat content is higher in healthy monozygotic twins who have a lower fitness (27), although this may be attributed to differences in physical activity. These studies collectively suggest that low aerobic fitness may have a direct negative impact on hepatic metabolism or have an indirect impact through peripheral factors (insulin sensitivity or visceral adiposity) linked to fatty liver; however, there is little mechanistic information detailing these connections.

Our research group has utilized the high- and low-capacity rats (HCR/LCR) created by Drs. Steve Britton and Lauren Koch to begin to mechanistically address the association between low fitness and NAFLD. The HCR/LCR rats were selectively bred over several generations for high- and low-
endurance running, resulting in two divergent strains with grossly different intrinsic endurance exercise capacities and aerobic fitness in a sedentary condition (90). The LCR rats have a higher incidence of both CVD and metabolic syndrome risk factors compared with HCR rats (90), while in contrast the HCR rats show protection against high-fat diet-induced obesity and insulin resistance (55, 61). We also found that hepatic mitochondrial content, function, and fatty acid oxidation were significantly reduced in the LCR compared with the HCR rats (85). These reductions in the LCR rats were associated with hepatic steatosis and lipid peroxidation at an early age and elevated markers of liver injury at the time of natural death, findings not observed in the HCR rats (85). These findings suggest that low hepatic mitochondrial content and function may increase susceptibility to NAFLD particularly in conditions of nutrient excess, while in contrast, elevated hepatic mitochondrial content and fatty acid oxidation may provide protection. Studies are under way to test this hypothesis. Therefore, we speculate that lower aerobic fitness increases susceptibility to NAFLD due to specific hepatic molecular/cellular events and not just secondary to systemic modifications.

IS IT PHYSICAL INACTIVITY, LOWER AEROBIC FITNESS, OR OVERNUTRITION DRIVING NAFLD?

Westernized societies are facing an NAFLD epidemic, and undoubtedly, physical inactivity, overnutrition, and low cardiopulmonary fitness are all significant contributing factors. However, does one of these factors trump the others and it is possible to delineate the individual impact of each? As mentioned above, it is well known that short-term inactivity results in a host of metabolic maladaptations, which suggests that physical activity rather than cardiovascular fitness may be the critical factor. In fact, physical activity (energy expenditure), but not fitness, explains a large portion of the variance in hepatic insulin sensitivity in relatively healthy men with varying degrees of adiposity (29). Thus it is possible that the lower levels of ambulatory physical activity (measured in cages) witnessed in the LCR rats and not the lower aerobic fitness per se (85) may have led to reductions in hepatic mitochondrial content and steatosis development. On the other hand, the daily physical activity in the OLETF rats likely increased aerobic fitness and may have been the reason for protection against hyperphagia-induced steatosis development (70), and perhaps the sustained increase in aerobic fitness and resulting hepatic adaptations is the reason that hepatic steatosis did not return with 7 days of inactivity (69). At present, these are just speculations, but they highlight the need for more careful consideration of each factor’s contribution to NAFLD development and also therapeutic approaches.

An additional complication is that most people who dramatically reduce activity levels are unlikely to reduce food intake during that same time period, highlighting that energy excess and inactivity often coexist and both contribute to NAFLD (81). Furthermore, it is a common misnomer that hepatic TG content is static. In fact, hepatic TG content is greatly influenced by short-term changes in whole body energy balance. Hepatic steatosis and hepatic insulin resistance can be induced with as little as 3 days of high-fat feeding in rodents (40, 75), and fasting has been shown to increase hepatic TG content in rodents (25), whereas only 2 days of calorie restriction (~1,000 kcal/day leading to ~2% weight loss) in obese patients with NAFLD significantly reduced intrahepatic lipid content by 10–30% (36). Furthermore, a single bout of exhaustive exercise has been shown to have a dramatic effect on the energy state of the liver in mice (4). These studies highlight the plasticity in hepatic lipid content and also the role of several important factors that contribute to systemic and hepatic energy balance.

Physical inactivity and/or low aerobic fitness combined with dietary overconsumption leads to excess hepatic lipid accumulation, but the precise mechanisms remain unknown. Figure 1 displays our current hypothesis for the development of NAFLD. Physical inactivity increases the risk for a positive energy balance and inactivity/low fitness/overnutrition contribute to peripheral insulin resistance, which collectively promote increased adiposity and hyperinsulinemia, resulting in ectopic lipid storage in the liver in part through increased FFA uptake, activation of de novo lipogenesis, and suppressed TG export. However, aside from the peripheral factors altered by inactivity and lower aerobic fitness, we postulate that physical activity and/or physical fitness also has a direct impact on the intrinsic phenotype of the liver, which also impacts susceptibility for NAFLD (Fig. 1) (69, 85). Under conditions of physical inactivity and low aerobic fitness, the liver exhibits reductions in hepatic mitochondrial content and/or function, reducing the oxidative capacity and making the liver more susceptible to dietary insults and excess lipid accumulation. The steatotic liver also becomes insulin resistant and unable to suppress hepatic glucose production, which leads to increased gluconeogenesis and a feed-forward worsening of systemic insulin resistance and diabetes risk. In addition, chronic hepatic lipid accumulation coupled with elevated oxidative stress and inflammation are linked to development of advanced stages of liver disease, including fibrosis and cirrhosis, and the need for liver transplantation (56, 72). Furthermore, it also is important
to note that we do not know the full implications of excess fat storage in the liver. Much like the “athletes paradoxi” in skeletal muscle, there are likely conditions in which elevated TG storage in the liver is not pathological and does not lead to insulin resistance, particularly if it is paired with increased mitochondrial content and function, but again, future studies are needed in this area.

SUMMARY AND CONCLUSIONS

We conclude that while in-depth mechanistic examination of the effects of physical inactivity on NAFLD is minimal, physical inactivity is an actual cause of NAFLD, and most cases of NAFLD can be primarily prevented by sufficient physical activity. Recent cross-sectional and prospective studies indicate a link between physical inactivity and NAFLD and have provided some mechanistic insight into factors involved to NAFLD development. However, much more work is needed in this area. Hepatic changes that ensue following the cessation of daily exercise and transition to a sedentary lifestyle or to a less aerobically fit state still remain largely unknown. Future mechanistic studies are needed to separate the peripheral adaptations from the direct molecular and biochemical alterations occurring in the liver in response to physical inactivity. This includes in vitro primary hepatocyte work and complementary in vivo studies designed to investigate the muscle-liver-adipose tissue axis in response to physical inactivity. Because exercise training and/or increased physical activity is the proven method to increase aerobic capacity, it should remain the cornerstone therapy for fatty liver disease, although the question of the proper intensity, duration, frequency, and type of physical activity is still in its infancy. Furthermore, carefully designed studies are needed to examine the individual contributions of physical inactivity, overnutrition, and low cardiorespiratory fitness to the escalating prevalence of NAFLD being observed in Westernized societies.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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