REVIEW

Have guidelines addressing physical activity been established in nonalcoholic fatty liver disease?

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Abstract
The purpose of this review was to highlight, in relation to the currently accepted pathophysiology of non-alcoholic fatty liver disease (NAFLD), the known exercise habits of patients with NAFLD and to detail the benefits of lifestyle modification with exercise (and/or physical activity) on parameters of metabolic syndrome. More rigorous, controlled studies of longer duration and defined histopathological end-points comparing exercise alone and other treatment are needed before better, evidence-based physical activity modification guidelines can be established, since several questions remain unanswered.

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Key words: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Physical activity; Diet

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INTRODUCTION

Compared with our ancestors, Western societies today lead a lifestyle that is much more sedentary, probably as a result of cultural changes stemming from disregarded traditional customs and modern usages. Taking into account differences in body size, our energy expenditure per kilogram of body weight has been estimated to be 40% less than that of our prehistoric ancestors. Current estimates suggest that 7 out of 10 adults are inactive or lack adequate conditioning, and this lack of adequate exercise, combined with dietary indiscretion, has contributed to the worldwide epidemic of obesity and non-alcoholic fatty liver disease (NAFLD). Within the United States, data suggest that 64.5% of the adult population is now overweight or obese, with a worldwide prevalence of 40%-60%. Obesity, combined with host factors such as diet, sedentary lifestyle and genetic predisposition, has been directly associated with increases in the prevalence of insulin resistance, type 2 diabetes (T2D) and the metabolic syndrome. The hepatic manifestation of the metabolic syndrome, NAFLD, has also increased in prevalence, and is now considered to be around 20%-30% in Western countries. Among
Energy metabolism within the liver is tightly regulated. Hepatic lipid synthesis and oxidation in both skeletal muscle and adipose tissue hormone-sensitive lipase activity is not fully suppressed by insulin, resulting in enhanced lipolysis within insulin-resistant adipose tissue; (2) increased hepatic de novo lipogenesis (DNL); (3) decreased FFA oxidation; and (4) decreased triacylglycerol export from the liver in the form of very low-density lipoprotein. The largest contributor to hepatic steatosis in patients with NAFLD is increased FFA influx to the liver (60%), followed by DNL (26%) [16].

Increased hepatic lipid supply
In insulin-resistant states, principally obesity and T2D, adipose tissue hormone-sensitive lipase activity is not fully suppressed by insulin, resulting in enhanced lipolysis and non-esterified fatty acid flux into the systemic circulation (Figure 1). The precise mechanism of adipocyte insulin resistance in obesity remains a subject of controversy, but an emerging body of data suggest that an altered adipocytokine milieu in visceral fat resulting from macrophage infiltration is important [11]. This milieu is characterised by increased expression of pro-inflammatory cytokines, such as tumour necrosis factor-\(\alpha\) and interleukin-6 (IL-6), that can directly inhibit insulin, signalling, and decreased expression of adiponectin, an anti-steatosis and insulin-sensitising adipocyte-derived cytokine (adipocytokine) in both skeletal muscle and liver [12].

Hepatic lipid synthesis and oxidation
Energy metabolism within the liver is tightly regulated. Two transcription factors, sterol regulatory element-binding protein (SREBP-1) and carbohydrate response element-binding protein (ChREBP), are intimately involved in hepatic glucose and lipid metabolism, and their activity is increased in animal models of NAFLD [13,14]. The former is induced by insulin and high-fat diets, and regulates glycolytic and lipogenic gene expression resulting in increased DNL and a concomitant decrease in FFA oxidation resulting from malonyl-CoA-induced inhibition of carnitine palmitoyl transferase-1 reducing mitochondrial FFA uptake [15]. ChREBP exerts similar effects on glycolytic and lipogenic gene expression and also increases the expression of genes involved in triglyceride synthesis. In contrast to SREBP-1, ChREBP is up-regulated by glucose, which increases its nuclear translocation and its DNA binding/transcriptional activity [16].

Inhibition of ChREBP in ob/ob leptin-deficient mice reduces hepatic steatosis by decreasing lipogenesis and enhancing FFA \(\beta\)-oxidation, with a concomitant decrease in circulating plasma triglycerides and FFA resulting in the restoration of hepatic, skeletal muscle and adipose tissue insulin sensitivity [17]. This study provides further evidence linking fat accumulation to insulin resistance in both hepatic and non-hepatic tissues, principally skeletal muscle [17].

Insulin resistance
Skeletal muscle is the primary site for glucose disposal via insulin-dependent pathways, accounting for about 75% of whole-body insulin-stimulated glucose uptake [19]. Insulin binding to the insulin receptor on the myocyte plasma membrane results in autophosphorylation of the receptor, allowing insulin receptor substrate (IRS)-1 adaptor protein to bind and undergo tyrosine phosphorylation (Figure 2A). IRS-1-associated phosphatidylinositol 3-kinase (PI3K) activity is increased, which results in downstream activation of protein kinase B, leading to enhanced glucose uptake into the cell, via increased glucose transporter (GLUT)-4 translocation from the cytosol to the cell membrane, and up-regulation of glycogen synthesis and glucose oxidation [18]. In obese individuals, there is reduced insulin-stimulated glucose disposal in skeletal muscle, most probably due to increased intramyocellular lipid content (Figure 2B) [18]. The increased concentration of FFA (or more probably their esterification product, diacylglycerol (DAG), activates the serine/threonine kinase PKCh, which phosphorylates IRS-1 on critical serine sites, thereby inhibiting its tyrosine phosphorylation and subsequently the activation of PI3K and the resulting glucose uptake, glycogen synthesis and glycolysis. Other cytokine-regulated serine/threonine kinases including IKK\(\beta\) and JNK-1 may also be involved since the inhibition of IKK\(\beta\) via exercise [23] or salicylates results in improved insulin sensitivity [21]. As discussed above, hyperglycaemia resulting from skeletal muscle insulin resistance in obesity leads to increased hepatic fat synthesis, reduced fat oxidation and steatosis via activation of ChREBP. Moreover, the accumulation of FFA/DAG in the liver results in hepatic steatosis...
insulin resistance, via PKCe-induced IRS-2 serine phosphorylation, which reduces insulin’s inhibitory effect on gluconeogenesis, contributing further to hyperglycaemia.\(^{18,22}\)

**Leptin resistance**

Lack of response to the adipocytokine leptin (leptin resistance) rather than insulin resistance may be an important factor in the pathogenesis of hepatic steatosis. The evidence for leptin resistance in NAFLD, though indirect, is compelling. Leptin exerts a number of anti-steatosis effects on the liver, including inhibition of lipid synthesis via reduced expression of stearoyl CoA desaturase (SCD)-1\(^{19}\) and enhanced FFA oxidation, via up-regulation of peroxisome proliferator-activated receptor-\(\alpha\) (PPAR-\(\alpha\))\(^{6}\), and yet patients with NAFLD...
AMP-activated protein kinase

Of particular relevance to modify NAFLD natural history, AMP-activated protein kinase (AMPK) has recently emerged as a key orchestrator of both hormonal and non-hormonal regulators of energy metabolism in liver, skeletal muscle and adipose tissue. Activated by an increase in the AMP/ATP ratio, AMPK activity is enhanced by physiological processes that induce metabolic stress and either decrease ATP production (ischaemia, hypoxia) or increase its consumption (exercise)\(^\text{[29]}\). Once activated, AMPK acts to increase ATP-generating cellular events while turning off energy-consuming processes to restore energy balance. In the liver, the activation of AMPK by exercise\(^\text{[30]}\), starvation, adiponectin\(^\text{[11]}\), leptin \((\text{via} \ \text{inhibition of} \ \text{SCD-1})\), the biguanide metformin\(^\text{[12]}\) or the thiazolidinedione class of insulin sensitizers\(^\text{[13]}\) suppresses expression of SREBP-1\(^\text{[14]}\), ChREBP\(^\text{[37]}\) and acetyl-CoA carboxylase\(^\text{[38]}\) resulting in decreased DNL and increased FFA oxidation. Hepatic gluconeogenesis is also inhibited. Within skeletal muscle, exercise, leptin or drug related AMPK activation enhances glucose uptake \((\text{via} \ \text{direct non-insulin-dependent GLUT-4 translocation})\), and increases pyruvate oxidation\(^\text{[15]}\). In adipose tissue, hormone-sensitive lipase activation is suppressed, resulting in decreased lipolysis\(^\text{[32]}\).

ChREBP, a newly discovered transcription factor, plays an essential role in glucose-induced L-pyruvate kinase \((L-PK)\)\(^\text{[17]}\) gene transcription by binding to the carbohydrate-responsive element of \(L-PK\) promoter\(^\text{[18,19]}\). It is well known that glucose metabolism is inhibited by fatty acids, which serve as an alternative fuel source and thus conserve glucose. This phenomenon has been termed the fat sparing effect on glucose\(^\text{[20,21]}\).

Kawaguchi \textit{et al} \(^\text{[22]}\) investigated the mechanism by which feeding high fat diets results in decreased activity of ChREBP in the liver. It’s strongly suggested that the fatty acid inhibition of glucose-induced \(L-PK\) transcription resulted from AMPK phosphorylation of ChREBP at Ser\(568\), which inactivated the DNA binding activity. AMPK was activated by the increased AMP that was generated by the fatty acid activation.

AMPK is a metabolic master switch mediating adaptation of the cell to variations in nutritional environ-

ment\(^\text{[23]}\). Its activity is stimulated by increases in intracellular AMP-to-ATP ratio in response to stresses such as exercise, hypoxia, and glucose deprivation. AMPK has acute effects on energy metabolism pathways and long-term effects involving changes in gene expression.

AMPK is a major therapeutic target for the treatment of diabetes. The effect of a short-term overexpression of AMPK specifically in the liver by adenovirus-mediated transfer of a gene encoding a constitutively active form of AMPK\(\alpha2\) (AMPK\(\alpha2\)-CA) has been investigated\(^\text{[24]}\). The short-term overexpression of AMPK\(\alpha2\)-CA in the liver results in a metabolic switch from glucose to lipid metabolism. The lower plasma glucose concentrations in Ad AMPK\(\alpha2\)-CA-infected mice lead to an increase in hepatic lipid utilization, resulting in a decrease in white adipose mass. The concomitant accumulation of hepatic triglycerides leads to the generation of ketone bodies, which are required as alternative substrates to supply energy to peripheral tissues in conditions of low glucose availability.

Another study investigated the effects of fasting and refeeding on AMPK and ChREBP mRNA, protein and activity levels; as well as the expression of lipogenic genes involved in regulating lipid synthesis in broiler chicken \((\text{Gallus gallus})\) liver\(^\text{[25]}\). In general, evidence was found for coordinate transcriptional regulation of lipogenic program genes in broiler chicken liver, but specific regulatory roles for AMPK and ChREBP in that process remain to be further characterized.

Moreover, thioredoxin-interacting protein \((TXNIP)\) regulates critical biological processes including inflammation, stress and apoptosis. TXNIP is upregulated by glucose and is a critical mediator of hyperglycaemia-induced beta-cell apoptosis in diabetes. In contrast, the saturated long-chain fatty acid palmitate, although toxic to the beta-cell, inhibits TXNIP expression. The mechanisms involved in the opposing effects of glucose and fatty acids on TXNIP expression are unknown. Shaked \textit{et al} \(^\text{[26]}\) showed that AMPK is an important regulator of Txnip transcription \((\text{via} \ \text{modulation of} \ \text{ChREBP activity})\). The divergent effects of glucose and fatty acids on TXNIP expression result in part from their opposing effects on AMPK activity. In light of the important role of TXNIP in beta-cell apoptosis, its inhibition by fatty acids can be regarded as an adaptive/protective response to gluco-lipotoxicity. The finding that AMPK mediates nutrient regulation of TXNIP may have important implications for the pathophysiology and treatment of diabetes.

\section*{EFFECT OF EXERCISE ALONE ON OBESITY, VISCERAL FAT AND INSULIN RESISTANCE}

Exercise physiology and the salutatory effects on weight loss, fat reduction and insulin sensitivity have been described in great detail. These beneficial effects are now considered to reflect, at least in part, the effect of exer-
Exercise on the activation of AMPK. In obese non-diabetics, exercise has been shown to reduce the risk of developing T2D by up to 46%[33].

Physical training, consisting of 20 min cycling or running, 20 min swimming at submaximal heart rate, followed by 20 min of warm up/cool down three times per week for 4 wk, resulted in a significant reduction in body weight and percentage body fat, and this was associated with improved whole-body glucose uptake, decreased fasting insulin concentrations and increased circulating adiponectin and mRNA expression in muscle. Among patients with T2D, increasing exercise led to a reduction in fasting plasma glucose[34].

The intensity of exercise needed to show improvement in metabolic profiles has been studied by several investigators. O’Donovan and colleagues evaluated the effects of 24 wk of moderate intensity exercise, defined as cycling three times weekly at 60% VO$_{2\text{max}}$ to burn 400 kcal, vs high-intensity exercise, defined as cycling three times weekly at 80% VO$_{2\text{max}}$ to burn 400 kcal, versus no exercise, on insulin sensitivity, triglycerides and glucose concentration[35]. Training at 60% VO$_{2\text{max}}$ was as effective as training at 80% VO$_{2\text{max}}$ when 400 kcal were expended per session, suggesting that moderate exercise, expending 400 kcal per session, three times per week is sufficient to improve insulin sensitivity. The overall energy expenditure achieved per work-out session appears to be more important than the intensity of the exercise. This is supported by two recent studies performed in obese patients[36,40]. Daily exercise for 12 wk, performed at not greater than 70% VO$_{2\text{max}}$ (about 80% maximum heart rate) on a treadmill to achieve 700 kcal energy expenditure (about 60 min) resulted in an 8% body weight loss and was associated with significant reductions in abdominal obesity, visceral fat, waist circumference and insulin resistance[36]. Furthermore, this study showed that exercise without weight loss also reduced both abdominal and visceral fat. Ray et al[40] also demonstrated that daily aerobic exercise for 50-60 min, starting at 60%-65% maximum heart rate and increasing to 80%-85% maximum heart rate (about 70% VO$_{2\text{max}}$) over 4 wk improved visceral fat content and this correlated with improved glucose metabolism and loss of insulin resistance. These encouraging results were seen with only a 3% weight loss over this time period.

The effects of aerobic vs restrictive exercise have also been debated. A Turkish study examined the effects of aerobic exercise, defined as walking briskly for 15 min and exercising on a stationary bicycle for 12-15 min three times per week the first month, exercising 20-30 min four times per week the second week, and 30-45 min five times per week the third month, in a group of 20 obese women compared with a restrictive exercise utilizing a stationary exercise unit in a similar group of women over a 3-mo period[47]. While improvement in body mass index (BMI), fasting glucose and postprandial glucose were seen in both groups, reduced fat mass (as measured by bioelectric impedance), decreased low-density lipoprotein and insulin resistance were seen only in the aerobic exercise group. In another study in 39 older obese men, aerobic or restrictive exercise training 3 d per week for 6 mo resulted in similar improvement in whole-body glucose disposal[48].

Weight loss remains fundamental to the management of NAFLD, but is mistakenly perceived as the primary rationale for promoting physical activity (PA) participation. However, obesity management is not simply a function of weight loss. Outside the context of liver disease, it is well established that exercise enhances insulin sensitivity, reduces progression to T2D, and favorably modifies serum lipids independent of weight loss[49,50]. When combined with the observation that high fitness and habitual PA are associated with improved functional capacity, quality-of-life measures, well-being, and reduced all-cause mortality[51], the importance of incorporating PA therapy, beyond assisting weight loss, becomes apparent.

At present, there is an overall paucity of evidence concerning the benefits of PA as treatment for NAFLD, even though PA is certainly useful in NAFLD-associated diseases such as obesity, T2D and cardiovascular disease.

What is available shows a conclusive benefit of PA when coupled with energy restriction when weight loss is achieved, and it is encouraging for an independent benefit in the absence of weight loss. Although weight loss remains fundamental, patients should be counseled on the spectrum of benefits conferred by regular PA. Management should include assessment of cardiorespiratory fitness and PA levels, and the setting of lifestyle goals based on adoption of regular exercise, with a focus on the attainment of sustainable PA habits.

The dose (intensity and volume) of PA required to reduce liver fat remains unclear. Furthermore, from the present evidence, it is difficult to discern the relative importance of structured exercise and fitness vs less structured PA.

Although several examples of a hepatic benefit from low-dose PA therapy have been cited[52-54], in the absence of robust data and knowledge of the long-term sustainability of such outcomes, it would seem reasonable to promote the current public health recommendations for health promotion, disease prevention, and weight management (Table 1). This recommends that individuals accumulate 20-60 min or more of moderate intensity (about 45%-70% of VO$_{2\text{max}}$) exercise on most days of the week[51]. If weight loss is the goal, exercise confers a reduction in body weight in an apparent dose-response fashion with exercise volume, even when prescribed without associated restriction of energy intake[51]. Greater amounts of exercise may be needed for most individuals to induce significant weight loss or prevent weight being regained in the long term. The consensus suggests that little weight loss is achieved with < 150 min of exercise per week, modest (2-3 kg) losses are attainable with > 150 min/wk (with an energy equivalent of 1200-2000 kcal/wk), and moderate weight loss (5-7.5 kg) often results from 225-420 min/wk (1800-3300 kcal) of aerobic
activity". These targets can be achieved using a variety of exercise modalities, with the outcome of cardiorespiratory fitness being a reliable and easily quantifiable endpoint measure of structured aerobic exercise. Although there is currently no longitudinal evidence available concerning its benefit in NAFLD, progressive resistance training may be useful for the management of obesity-related comorbidities, particularly insulin resistance. The benefits of nonstructured leisure-time PA, including reduced sedentary time, are becoming increasingly recognized and have, in some studies, shown efficacy in improving cardiometabolic risk and promoting weight loss. Clear guidelines for such “lifestyle PA” are lacking, and reliable measurement, particularly of intensity, is more difficult. PA habits and adherence can be estimated by questionnaires, pedometers, and accelerometers (reviews of which can be found elsewhere) and the latter may further promote adherence to PA.

Hybrid training of voluntary and electrical muscle contractions

“Hybrid exercise” is an exercise method that combines electrically stimulated and volitional contraction. This technique produces resistance against the motion of a volitionally contracting muscle by means of a force generated by an electrically stimulated antagonist. In particular, hybrid exercise resists utilizes electrically stimulated eccentric contractions and concentric volitional contractions with reciprocal limb movements. Both the volitionally activated agonist and the electrically stimulated antagonist contract during joint motion. The result is that both muscles are trained and that a longitudinal compressive load is placed on the bone. This technique requires minimal external stabilization as compared with conventional weight training. Matsuse et al. have shown that such hybrid exercise increased the extension torque of the elbow joint by about 30% and the cross-sectional areas (CSA) of the proximal upper extremity muscles by about 15% over a 12-wk period. In addition, Iwasaki et al. demonstrated that 6 wk of hybrid exercise effectively increased the extension of the knee joint by 19-33%. Takano et al. demonstrated that 12 wk of treatment increased extension torque by 39% and the CSA of quadriceps muscle by 9% in elderly subjects. However, the mechanism by which hybrid exercise achieves these increases in muscular strength and bulk is still unknown.

Muscle atrophy occurs as a consequence of denervation, injury, joint immobilization, bed rest, glucocorticoid treatment, sepsis, cancer and aging. Unfortunately, there is no effective treatment for muscle atrophy. The maintenance of muscle mass is controlled by a balance between protein synthesis and protein degradation pathways, which is thought to shift toward protein degradation during atrophy. Recently, a signaling pathway that increases protein synthesis was shown to promote muscle hypertrophy, thereby overcoming muscle atrophy.

The “Hybrid Training” (HYBT) method utilizing combined electrical stimulation and voluntary muscle contraction has been developed as a muscle training method. It has already been shown that the method is technically sound and clinically effective in healthy young subjects. The HYBT method increases muscle strength and mass and is as effective as the weight machine training (WMT), an effective method for improving muscle strength and hypertrophy in elderly people.

However, a critical problem is that the equipment for WMT is large in size and takes space. In addition, unlike the WMT, the HYBT device, which is portable and not large in size, is so easy to handle that it can be placed at the bedside. Therefore, the HYBT may become a safe, effective method of muscle training for elderly people.

Although skeletal muscle regulates glucose metabolism, partly by releasing IL-6, the effects of hybrid training on glucose metabolism remain unclear. Kawaguchi et al. showed the effects of hybrid training on glucose metabolism and serum IL-6 levels in elderly people. This study showed the safety and good adherence of hybrid training for lower extremities in elderly people. Furthermore, hybrid training decreased fasting blood glucose and serum IL-6 levels in elderly people.

Kawaguchi et al. investigated the therapeutic efficacy of hybrid training in patients with NAFLD. Physical inactivity is a risk factor for the development of NAFLD. HYBT of voluntary and electrical muscle contractions improved hepatic steatosis and reduced insulin resistance and serum IL-6 levels in NAFLD patients who are resistant to lifestyle counseling.

Possible role of myokine in patients with NAFLD

Skeletal muscle has recently been identified as an organ that produces and releases cytokines, which have been named “myokines”. Given that skeletal muscle is the largest organ in the human body, our discovery that contracting skeletal muscle secretes proteins sets a novel paradigm: skeletal muscle is an endocrine organ producing and releasing myokines in response to contraction which can influence metabolism in other tissues and organs. With the discovery that exercise provokes an in-

Table 1 Recommendations for physical activity in non-alcoholic fatty liver disease

| Recommendations for physical activity in non-alcoholic fatty liver disease |
|---------------------------------------------------------------|
| Patients should be appropriately screened for contraindications |
| prior to initiating exercise testing or therapy               |
| Physical fitness assessment via exercise testing. Physical   |
| activity level assessment by subjective (questionnaire/diary) |
| or objective (e.g., accelerometer) means                      |
| Accumulate 20-60 min or more of moderate intensity rhythmic   |
| exercise using large muscle groups on at least 5 d/wk         |
| Moderate intensity physical activity between 150 and 250 min/ |
| wk for preventing weight gain                                  |
| Physical activity > 250 min/wk for clinically significant     |
| weight loss                                                   |
| Moderate-to-high intensity resistance training 3 d/wk for     |
| enhancing insulin sensitivity                                 |
|                                                               |

Finelli C et al. NAFLD and physical activity
crease in a number of cytokines, a possible link between skeletal muscle contractile activity and immune changes was established.

For most of the last century, researchers sought a link between muscle contraction and humoral changes in the form of an “exercise factor”, which could be released from skeletal muscle during contraction and mediate some of the exercise-induced metabolic changes in other organs such as the liver and adipose tissue. It has been suggested that cytokines or other peptides that are produced, expressed, and released by muscle fibers and exert either paracrine or endocrine effects should be classified as “myokines”[71]. The nervous, endocrine, and immune systems all contribute to the maintenance of homeostasis. Interestingly, although these individual systems operate independently to a certain degree, each with their own collection of highly specific cells and regulatory factors, they also depend on each other for normal development and function.

It appears that skeletal muscle has the capacity to express several myokines. To date the list includes IL-6, IL-8 and IL-15[71]. Contractile activity plays a role in regulating the expression of many of these cytokines in skeletal muscle[78]. The discovery that IL-6 is released from contracting skeletal muscle has generated much interest among the scientific community because this finding is somewhat paradoxical. On one hand, IL-6 is markedly produced and released in the postexercise period when insulin action is enhanced, but on the other hand, IL-6 has been associated with obesity and reduced insulin action. Given the controversy, this review focuses on the metabolic roles of IL-6.

Despite the fact that acute IL-6 treatment may enhance glucose uptake and fat oxidation in skeletal muscle, there are, nonetheless, a number of studies both in vitro[72-75] and in rodents in vivo[76-78] that demonstrate that IL-6 is capable of inducing insulin resistance. It appears that most, if not all, in vitro studies seem to suggest that IL-6 induces insulin resistance via adverse effects on the liver. Subjecting lean mice to chronically elevated IL-6 for 5 days causes hepatic insulin resistance[75], while treating either ob/ob (leptin-deficient) mice[77] or liver-inducible kappa kinase transgenic mice that display hepatic insulin resistance[79] with IL-6 neutralizing antibodies improves hepatic insulin resistance. The IL-6-induced insulin resistance appears due to increased SOCS proteins (SOCS-3) expression[80], since it is thought that SOCS-3 may directly inhibit the insulin receptor[81]. However, even the negative effect of SOCS-3 on insulin action has recently been brought into question. Liver specific activator of transcription 3 (STAT3) knockout mice that express low levels of hepatic SOCS-3 protein, paradoxically are unable to suppress hepatic glucose production after intracerebral ventricular insulin infusion[82]. Moreover, the prevention of IL-6 signaling either by neutralizing antibodies or by genetic deletion of IL-6 markedly reduces insulin-induced phosphorylation of hepatic STAT3[81]. These results suggest that the local production of IL-6 is important for the phosphorylation of hepatic STAT3 induced by the brain insulin action. In a separate study, liver specific SOCS-3 knockout mice exhibited obesity and systemic insulin resistance with age[82]. Furthermore, in this recent study, insulin signaling was reduced in skeletal muscle[82], suggesting that deletion of the SOCS-3 gene in the liver modulates insulin sensitivity in other organs. Possibly, the most convincing data to suggest that IL-6 may be antiobesogenic is the observation that IL-6 knockout mice develop mature onset obesity and glucose intolerance[83]; however, even this observation is unclear[84]. Whether IL-6 has positive effects on obesity and insulin action is clearly unresolved and requires further work. However, IL-6 unquestionably has a poor prognosis for certain inflammatory diseases[85], and due to the immunoreactive nature of IL-6, it is clear that rhIL-6 treatment may not be a wise therapeutic treatment strategy in human disease. This is most likely due to the previously described trans-signaling of IL-6. The soluble IL-6 receptor controls the transition from the acute to the chronic phase in many proinflammatory diseases such as peritonitis[86], a transition that can be inhibited by treatment with a soluble gp130 receptor fragment that neutralizes the trans-signaling process[86]. Therefore, other cytokines that signal through the gp130 receptor, but which do not activate trans-signaling of IL-6, such as ciliary neutrotrophic factor, show some therapeutic promise as an antiobesity therapy[87].

NAFLD and its subsequent complications create a significant health burden, and currently there is no effective treatment strategy. The biochemical mechanisms that underlie NAFLD are unclear at this time, but there is evidence that insulin resistance is a major contributing factor. In addition, circulating concentrations of inflammatory cytokines - myokines (e.g., IL-6) as well as decreased antinfammatory factors (e.g., adiponectin, IL-10) are not only implicated in the development of insulin resistance and T2D, but are also related to NAFLD. Such inflammatory mechanisms are fundamental in the progression of NAFLD toward higher risk cirrhotic states. Regular exercise can reverse insulin resistance, suppress low-grade systemic inflammation, and attenuate inflammatory markers associated with NAFLD. Thus, exercise has the potential to become an effective treatment and prevention modality for NAFLD and NASH.

CONCLUSION

Our knowledge of the pathological consequences of lack of adequate exercise on adipose tissue, skeletal muscle and the liver is improving, and this will help establish more specific guidelines for the proper exercise regimens that will improve underlying metabolic pathways and ultimately decrease the incidence and severity of NAFLD. Moderate exercise, preferably a combination of aerobic and restrictive, performed 3-4 times per week, expending about 400 calories each time seems adequate to augment improvement in the metabolic profiles of patients with
NAFLD. PA has long been considered a cornerstone of a healthy lifestyle. Although its protective role in cardiovascular and metabolic diseases is well established\(^9\), its place and importance in NAFLD still requires scientific support and clarification. In a study, an inverse association was found between cardio-respiratory fitness categories and the prevalence of NAFLD. Whereas fitness and BMI were independent of each other in their associations with the prevalence of NAFLD, the addition of waist circumference to the regression model attenuated the association\(^9\). This is in line with the fact that abdominal obesity has been shown to be a major risk factor for NAFLD, greater than BMI\(^9,10\), and is consistent with previous studies demonstrating that exercise-induced weight loss is associated with a preferential reduction in abdominal fat\(^11\),\(^12\),\(^13\) and that, at any given weight, individuals who exercise more have less visceral fat than those who are sedentary\(^14\). The suggested effect of PA on NAFLD may stem from other mechanisms as well. Exercise alone, in the absence of any change in body weight or composition, may enhance insulin sensitivity and glucose homeostasis\(^15\),\(^16\). PA appears to result in insulin-receptor up-regulation in muscle tissue and hence increased delivery of glucose and insulin to the muscles\(^17\). Exercise also has a beneficial effect on FFA metabolism by enhancing whole-body lipid oxidation\(^18\). Hepatic triglyceride accumulation was shown to decrease with exercise intervention\(^19\) and hepatic FFA uptake was lower in trained compared with untrained subjects\(^20\). From the perspective of NAFLD patients, weekly or daily performance of walking, swimming, or cycling might seem as simple as jumping of the cliff. Thus, it seems that among NAFLD patients, even small increments in regular PA can improve liver enzymes; encouraging information that can be provided to patients. Time spent sedentary, measured objectively by individually calibrated heart rate monitoring, predicted higher levels of fasting insulin, independent of the amount of time spent at moderate- and vigorous-intensity activity levels. This highlights the importance of reducing sedentary time in order to improve metabolic status, in addition to the benefits associated with a physically active lifestyle\(^21\). Environmental factors that discourage PA include an environment that encourages automobile use rather than walking (like lack of sidewalks), and that has few cues to promote activity and numerous cues that discourage activity (television, computers, etc.)\(^22\),\(^23\). It should be emphasized that associations between air pollution and a multitude of health effects are now well established. Given ubiquitous exposure to some level of air pollution, the attributable health burden can be high, particularly for susceptible populations affected by cardio-respiratory problems when walking, running at a slow or leisurely pace, or cycling\(^24\). More rigorous, controlled studies, of longer duration and defined histopathological end-points comparing exercise alone and other treatment are needed before better, evidence-based PA modification guidelines can be established, since several questions remain unanswered. Does PA modification work equally well in men vs. women? Do younger patients respond better than older patients to PA modification? Is there a diversity of response among various ethnic groups or in patients with fatty liver alone compared with patients with more progressive disease? Finally, are there different lifestyle modification approaches, i.e., diet alone vs. diet and aerobic exercise, that work better for different patient populations?

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