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REVIEW

Aerobic Exercise in the Management of Metabolic Dysfunction Associated Fatty Liver Disease

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Abstract: Sedentarism is the pandemic of modern times. It is associated with several medical conditions including obesity, type 2 diabetes mellitus, cardiovascular diseases and also liver disease, particularly metabolic dysfunction associated fatty liver disease (MAFLD). In an era when MAFLD is the most prevalent chronic liver disease worldwide, whilst no pharmacological therapy has been approved for it, exercise has proved to be effective in improving liver steatosis. Interestingly, exercise decreases liver fat even in the absence of weight loss. The challenge for the clinician is to motivate the obese patient with MAFLD, and associated co-morbidities, who has crystallized a sedentary behavior, at times when every need is at the distance of a click on the Internet, and the entire world can be visited behind a screen. In this review, the aggregate evidence on the mechanisms and effects of exercise in the management of MAFLD is summarized, with simple recommendations for everyday clinical practice.

Keywords: metabolic dysfunction-associated fatty liver disease, physical activity, aerobic exercise

Introduction

Sedentarism and unhealthy dieting are the pandemic behaviors of the XXI century.[1] Around 85% of the US population achieve less than what is preconized by the World Health Organization for daily physical activity for health.[2] Up to one third of the world's population is physically inactive, which is strongly associated with obesity, type 2 diabetes mellitus, cardiovascular diseases and overall mortality.[3–5] Physical inactivity is also associated with metabolic dysfunction-associated fatty liver disease (MAFLD), independently of body weight.[6]

MAFLD refers to the ectopic accumulation of fat in the hepatocytes, which can be explained by metabolic dysfunction associated with adiposopathy. Adiposopathy is the consequence of an energy overload in the adipose tissue, usually in overweight/obese patients. An overwhelmed adipose tissue can also arise in subjects with normal body mass index, in which the personal fat threshold, that is the amount of fat the individual adipose tissue can handle, is surpassed.[7] The sick adipose tissue releases fat that accumulates ectopically in the liver, but also in the cardiovascular system, and promotes systemic inflammation, insulin resistance, and the metabolic syndrome. The fatty liver further enhances insulin resistance and derangements in lipid metabolism, ensuing in a loop of metabolic dysfunction.[8] Recently, an international panel of experts proposed the following diagnostic criteria for MAFLD:[9] presence of hepatic steatosis in patients with type 2 diabetes

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mellitus and/or who are overweight/obese. In lean non-diabetic patients, it requires evidence of hepatic steatosis and the presence of at least 2 of the following metabolic abnormalities: (1) Waist circumference (WC) ≥ 102 and 88 cm in Caucasian men and women, respectively (or ≥ 90 and 80 cm in Asian men and women, respectively); (2) Blood pressure ≥ 130/85 mmHg or specific drug treatment; (3) Plasma triglycerides ≥ 150 mg/dL or specific drug treatment; (4) Plasma high-density lipoprotein (HDL)-cholesterol < 40 mg/dL for men and < 50 mg/dL for women or specific drug treatment; (5) Prediabetes (ie, fasting glucose levels 100–125 mg/dL, or 2-h post-load glucose levels 140–199 mg/dL or HbA1c 5.7–6.4%); (6) Homeostasis model assessment (HOMA) of insulin resistance score ≥ 2.5; (7) Plasma high-sensitivity C-reactive protein level > 2 mg/L.

MAFLD,[9] is the liver pandemic of our times. It afflicts up to one fourth of the global population.[10] It is also the most rapidly increasing etiology for end-stage liver disease,[11] being the second leading cause of chronic liver disease in patients on waitlist for liver transplantation overall, but already the leading cause in women.[12] Importantly, MAFLD is not only associated with an increased liver-related mortality but also associated with increased all-cause mortality.[13] Indeed, even though a recent meta-analysis could not demonstrate an association between MAFLD and cardiovascular mortality,[13] the presence of MAFLD increases over 60% the risk of having cardiovascular events, which cannot be solely explained by the association between MAFLD, obesity and the metabolic syndrome.[14]

Up to now, there is no approved treatment for MAFLD, and the management of these patients relies on the promotion of a healthy lifestyle, with diet and exercise, aiming for weight loss.[15]

The definition of sedentarism is not consensual and is often rendered as sitting time. Conversely, physical activity refers to any energy-requiring movement. Physical fitness is a set of attributes that reflect tolerance to physical activity and can be measured by specific tests. Exercise refers to planned physical activity that is structured and repetitive, with a specific intensity, frequency and duration.[16] The intensity of exercise can be graded according to the metabolic equivalent tasks (METs) spent. One MET refers to the amount of oxygen consumed while sitting at rest, and corresponds to 3.5 mL of oxygen per kg of body weight per minute. One MET is equivalent to 1 kcal per kg of body weight per hour.[17] For example, walking at a speed of 4.8 kms per hour is equivalent to 3 METs, while jogging at a speed of 6.4 to 8 kms per hour is equivalent to 7 METs. Exercise is considered light when it spends 1.1–3.9 METs; moderate 4–6 METs and vigorous/intense to more than 6 METs. Another way to represent it is according to the VO_2 max, that is, the maximum capacity of oxygen utilization expressed as L/min.[18] Exercise is considered moderate when requires 40–60% of VO_2, and vigorous when it requires at least 60%.

There are 3 different types of exercise: aerobic, resistance and flexibility. Aerobic or endurance exercise is rhythmic, can be maintained continuously and relies on large muscle groups. Resistance or strengthening exercise exerts muscle overload requiring anaerobic metabolism. Lastly, flexibility or stretching exercise aims to increase the joint range of motion and muscle extensibility.[19]

In this review, we will critically summarize the evidence of the effect of exercise on the management of MAFLD, with particular emphasis on aerobic exercise.

What is the Role of Physical Activity in the Development and Progression of MAFLD?

Epidemiological studies displayed an inverse correlation between physical activity and the prevalence of MAFLD, independently of the way physical activity was assessed: recalls, diaries, questionnaires or motion sensors/accelerometers, as shown in Table 1.

In a cross-section Korean study with 3718 participants, physical activity evaluated through structured questionnaires showed an inverse association with the risk of having MAFLD, which was independent of visceral adipose tissue. Indeed, being on the highest quartile of physical activity decreased by almost one third the risk of having MAFLD[20] and to half the risk of developing de novo MAFLD.[21] A large cohort of 42,661 participants from the Netherlands showed similar associations.[22] Even lower levels of physical activity than the recommended (that is at least 150 minutes per week) conferred benefit over being entirely inactive.[22] Furthermore, patients with insulin resistance/type 2 diabetes mellitus and elderly benefited the most.[22]

The association between physical activity, assessed by questionnaires, and MAFLD was corroborated by several studies in different populations: European,[23] Israeli,[24] Asian Indians,[25] Chinese,[26] and Korean.[27] The aggregate studies suggested a dose–response association.[26] Furthermore, the

Table 1 Observational Studies Evaluating the Effect of Physical Activity on MAFLD

Reference	Country	Study Design	N	Evaluation of Physical Activity	Diagnosis of MAFLD	Main Results
Perseghin G, 2007[23]	Italy	Cross-sectional, Cohort	191	Questionnaire	^{1}H-MRS	• Inverse correlation between hepatic fat content and PA. • ↓ prevalence of MAFLD according to quartile of PA: 25 > 11 < 25 >2%
Zelber-Sagi S, 2008[24]	Israel	Cross-sectional, Cohort	349	Self-reported PA in the last year	Abdominal US	• The MAFLD group engaged in less aerobic or resistance PA
Kistler KD, 2011[42]	USA	Cross-sectional, Cohort	813 MAFLD patients	Self-reported PA questionnaire from the NHANES	Liver biopsy	• Moderate-intensity PA did not associate with steatohepatitis or fibrosis stage • Vigorous PA ↓ risk of steatohepatitis: OR 0.65 [0.43–0.98] • Doubling recommended time spent in vigorous PA ↓ risk of advanced fibrosis: OR 0.53 [0.29–0.97]
Gerber L, 2012[32]	USA	Cross-sectional, Cohort	3056	Activity counts from accelerometer readings for 7 days	FLI >60	• Patients with MAFLD spent less time participating in activity at any level • Average PA was 28.7 counts/minute/day lower in MAFLD patients than controls
Bae JC, 2012[37]	Korea	Cross-sectional, Cohort	72359	Self-reported questionnaires	Abdominal US	• Subjects who exercised >3x/week, ≥30 min/session, for 3 consecutive months presented lower risk of MAFLD: OR 0.53–0.72
Miyake T, 2015[38]	Japan	Cross-sectional, Cohort	6370	Questionnaire	Abdominal US	• Periodical exercise ↓ risk of having MAFLD: OR 0.707 [0.546–0.914]
Kwak MS, 2015[20]	Korea	Cross-sectional, Cohort	3718	PA questionnaire from the NHANES	Abdominal US	• PA was inversely associated with MAFLD: • 4th vs 1st quartile: OR 0.68 [0.54–0.85] • 3rd vs 1st quartile: OR 0.74 [0.59–0.93]
Ryu S, 2015[6]	Korea	Cross-sectional, Cohort	139056	International PA Questionnaire Short Form (Korean version)	Abdominal US	• Prevalence of MAFLD ↓ in physically active vs inactive: • Minimally active group: OR 0.94 [0.02–0.95] • HEPA group: OR 0.8 [0.78–0.82] • Prevalence of MAFLD ↑ with increasing sitting time: • 5–9 hours/day: OR 1.04 [1.02–1.07] • ≥ 10 hours/day: OR 1.09 [1.06–1.11]
Hallsworth K, 2015[33]	UK	Cross-sectional, Case-control	37 MAFLD, 37 controls	Sedentary behaviour, PA and E expenditure were assessed by a multisensor array over 7 days	^{1}H-MRS	• MAFLD patients compared to controls: • Spent an hour extra per day being sedentary • Walked 18% fewer steps • ↓ active E expenditure by 40% • ↓ total E expenditure by 8%
Tsunoda K, 2016[43]	Japan	Prospective cohort, FU 4.2 years	1149	Questionnaire	MAFLD: by US; steatohepatitis by ↑ ALT or AST	• Vigorous PA prevented progression to steatohepatitis: OR 0.55 [0.32–0.94] • Moderate or low intensity PA presented no association with progression to steatohepatitis

(*Continued*)

Table 1 (Continued).

Reference	Country	Study Design	N	Evaluation of Physical Activity	Diagnosis of MAFLD	Main Results
Sung KC, 2016[40]	Korea	Prospective cohort, FU 4.95 years	169347	International PA Questionnaire Short Form (Korean version)	Abdominal US	• ≥5x/week exercise vs no exercise: • ↓ risk of incident steatosis: OR 0.86 [0.80–0.92] • ↑ likelihood of steatosis resolution: OR 1.40 [1.25–1.55]
Wei H, 2016[28]	China	Cross-sectional, Cohort	2054 male	Self-reported questionnaire	FLI ≥60	• Dose-dependent ↑ prevalence of MAFLD across the tertiles of sitting time. • Sitting time >7.1 hours/day associated with ↑ prevalence of MAFLD (OR 1.09 [1.04–1.67])
Keating SE, 2016[34]	Australia	Cross-sectional, Cohort	82	Activity counts from accelerometer readings for 4 days	^{1}H-MRS	• No associations between PA and sedentary behavior and the prevalence of MAFLD
Kwak MS, 2017[21]	Korea	Prospective cohort, FU 4.2 years	1373	PA questionnaire from the NHANES	Incident MAFLD by US	• Total and leisure PA was inversely associated with incident MAFLD • ↓ PA at FU associated with ↑ incident MAFLD: 4th quartile vs 1st quartile of ↓ PA OR 1.45 [1.04–2.02]
Byambasukh O, 2019[22]	Netherlands	Cross-sectional, Cohort	42661	Self reported questionnaire to evaluate HEPA	FLI ≥60	• Higher moderate/vigorous PA was dose-dependently associated with ↓ risk of MAFLD: OR for PA quintiles: 0.78 [0.71–0.86] > 0.64 [0.58–0.70] > 0.53 [0.48–0.59] > 0.51 [0.46–0.56] • Even PA lower than recommendations was better than inactivity • Occupational PA offers no clear health benefits
Li YF, 2019[26]	China	Cross-sectional, Case-control	543 MAFLD, 543 controls	International PA Questionnaire Short Form (Chinese version)	Abdominal US	• Both moderate (OR 0.62 [0.41–0.92]) or vigorous (OR 0.60 [0.40–0.91]) intensity PA associated with ↓ risk of MAFLD in men, independently of sedentary time or E expenditure
Jang DK, 2019[27]	Korea	Cross-sectional, Case-control	32391	Self reported questionnaire to evaluate HEPA	Hepatic steatosis index	• PA negatively associated with MAFLD (most vs least active: OR 0.7 [0.6–0.8]) and lean MAFLD (OR 0.5 [0.4–0.7])
Gerage AM, 2019[41]	Brazil	Prospective cohort, FU 2.5 years	5860	International PA Questionnaire	Abdominal US	• Lower likelihood of improving steatosis in subjects who remained inactive (OR 0.64) or became inactive (OR 0.66) • Lower risk of acquiring MAFLD in subjects who remained active (OR 0.75) or became active (OR 0.75)
Bhatt SP, 2019[25]	India	Cross-sectional, Case-control	342	Questionnaire	Abdominal US	• Mean PA was lower in cases than controls (33.3 ±3.6 vs 36.2±0.5 MET/min) • Total E expenditure was lower in cases than controls (2707.6±505.6 vs 2904.3±690.3 kcal)
Croci I, 2019[29]	Australia	Cross-sectional, Cohort	15781	Self-reported questionnaire	FLI ≥60	• For each additional 1 hour/day of sedentary behavior, the risk of having MAFLD ↑ 4% [3–6] • High cardiorespiratory fitness attenuated the negative role of sedentary behavior up to 7 hours/day on MAFLD.

(*Continued*)

Table 1 (Continued).

Reference	Country	Study Design	N	Evaluation of Physical Activity	Diagnosis of MAFLD	Main Results
Joo JH, 2020[30]	Korea	Cross-sectional, Cohort	13518	International PA Questionnaire (Korean version)	Hepatic steatosis index	• The offs of having MAFLD increased across quartiles of sitting hours: 1.07 [0.88–1.31] < 1.16 [1.06–1.41] < 1.34 [1.11–1.61]
Kim D, 2021[52]	USA	Prospective cohort, FU 10.6 years	5207 MAFLD patients	PA questionnaire	Abdominal US	• ↑ duration of PA inversely associated with all-cause mortality (higher vs lower quartile: OR 0.46 [0.28–0.75]) and cardiovascular mortality (OR 0.28 [0.008–0.98]) in patients with MAFLD

Abbreviations: E, energy; FLI, Fatty Liver Index; HEPA, health-enhancing physically active; NHANES, National Health and Nutrition Examination Survey; PA, physical activity; US, ultrasound.

protective effect of physical activity was equally strong in patients with lean MAFLD.[27]

A cross-sectional study on 139,056 Korean, who underwent a comprehensive annual or biennial health examination, showed that spending more than 5 hours sitting per day increased the risk of having ultrasonography-diagnosed MAFLD.[6] Other studies in Asian and Australian populations confirmed a dose–response association between sitting time and the prevalence of MAFLD.[28–30] Indeed, spending more than 7 hours sitting per day increased by 10% the risk of MAFLD, independently of body mass index (BMI), insulin resistance and dyslipidemia.[28] The detrimental effect of spending more than 10 hours sitting per day persisted even in those who were otherwise physically active.[6] These results point out to the difference between inactivity and absence of exercise. Indeed, a small study on 19 overweight or obese adults showed that decreasing sitting time through 2 minutes bouts of light to moderate intensity walking was effective in decreasing insulin resistance.[31]

Other studies used a more objective way to quantify physical activity, such as accelerometers. Indeed, a study with 3056 participants from the National Health and Nutrition Examination Survey (NHANES) evaluated the physical activity during 7 consecutive days through accelerometer readings. When the accelerometer recorded less than 100 counts per minute per day, the patient was considered sedentary. MAFLD was diagnosed when fatty liver index (FLI) was higher than 60 and in the absence of other chronic liver diseases. In this study, patients with MAFLD spent less time participating in any activity, and presented an average of around less than 30 counts/min/day as compared to controls.[32] Similarly, a small study from Newcastle, UK, evaluated 7-days physical activity and energy expenditure using a multisensory array on 37 patients with MAFLD and 1000 healthy controls. MAFLD patients spent an extra hour being sedentary, walked up to one-fifth fewer steps and expended 40% less energy being active.[33] A small study from Australia failed to corroborate this association,[34] when hepatic steatosis was measured by magnetic resonance spectrometry (MRS).

Importantly, not all physical activities seem to equally promote health. Indeed, it is leisure or recreational, and not occupational, physical activity that seems to induce the most benefits in health. Recreational physical activity usually induces the contraction of large muscle groups while increasing whole-body metabolism and cardiac output. During recreational physical activity one can rest when fatigued. Occupational physical activity more frequently involves heavy lifting, prolonged standing, and highly repetitive movements.[35] Epidemiologic studies suggest an inverse, dose–response association between the risk of hypertension and recreational, but not occupational, physical activity.[35] Furthermore, recreational physical activity is associated negatively, whereas occupational positively, with BMI, central obesity and insulin resistance.[36] Similarly, large-population studies have shown that recreational, but not occupational, physical activity seems to be protective against having MAFLD.[22]

Regarding the practice of exercise, a large population Korean study also showed that subjects that practiced exercise at least 3 times per week, for at least 30 minutes each time for more than 3 months, decreased up to half the risk of having MAFLD.[37] A cross-sectional study from a subsample of 375 participants in the Israeli National Health And Nutrition Survey showed that engaging in any kind of sports decreased one-third the risk of having

MAFLD, per each standard deviation increase in the physical activity score. These associations were stronger for resistance exercise as compared to aerobic exercise, which was explained by probable misclassification of self-reported physical activity.[24] Similar results were shown on a large Japanese cohort.[38] Furthermore, engagement in regular exercise also seems to be associated with protection from incident MAFLD, improvement and remission of MAFLD.[39–41] Those effects presented a dose–response pattern and occurred for any amount of exercise.[40]

Engaging in physical activity not only seems to confer protection from having MAFLD, but it is also associated with less severe disease, in a dose-dependent manner. Two large-population studies from the US and Japan showed that engaging in vigorous, but not moderate, physical activity decreased the chances of progression to steatohepatitis and liver fibrosis.[42,43] The authors hypothesized that vigorous physical activity consumes large amounts of ATP, which activates AMP kinase, eliciting increased ATP production through fatty acids oxidation and glucose transport.[44] Furthermore, vigorous physical activity can lead to depletion of hepatic glycogen, triggering fat consumption.[43]

Another way to evaluate the role of physical activity on the development of MAFLD is through physical fitness, translating the ability of the subject to engage physical activity. Physically fit subjects, assessed using maximal treadmill exercise test or cycle ergometer data, seem less susceptible to having MAFLD, steatohepatitis, and severe liver fibrosis, independently of BMI.[45–50]

A recent study followed 125,264 participants from the Nurses' Health Study and the Health Professionals Follow up Study, for up to 25 years. It showed that higher physical activity also predicted a lower risk of liver-related mortality, across all the range of BMI. Physical activity could even abrogate the excessive liver-related mortality observed with obesity. Indeed, walking at least 3 hours per week could have prevented 25% of liver-related deaths.[51] Furthermore, engaging in physical activity seems to have a profound impact on the survival of patients with MAFLD. A study that evaluated 5207 participants from the NHANES followed them for 10 years, assessing physical activity by accelerometer readings. The duration spent on physical activity was inversely associated with all-cause mortality. Subjects with the highest quartile of physical activity presented a more than half decreased risk of all-cause mortality compared to the lowest quartile of physical activity. The effect was even stronger for cardiovascular mortality.[52] A different Australian cohort that also followed MAFLD patients over a 10-year period and showed that low cardiorespiratory fitness was associated with a 50% increase in all-cause mortality.[29]

Physiopathology of Exercise and MAFLD

MAFLD occurs when there is an imbalance between fat uptake and triglycerides production in the liver, and hepatic fat oxidation. Most of the fat uptake into the liver derives from the adipose tissue, particularly visceral adipose tissue. Insulin resistance promotes the release of fat from the adipose tissue that can reach the liver, and also, increases hepatic lipogenesis. In the liver, lipotoxicity can induce cell stress, through different mechanisms, such as oxidative stress, ER stress, impaired autophagy and cell death.[8] Metabolic systemic inflammation and gut dysbiota also seem to play a role in the development and progression of MAFLD.[53] Physical activity and exercise can protect against MAFLD through several mechanisms, acting on different players, such as the adipose tissue, the muscle, directly on the liver and on the gut microbiota[54] (Figure 1).

Exercise can decrease visceral adiposity, particularly aerobic exercise.[55] The decrease in visceral adipose tissue decreases the influx of free fatty acids into the liver.[56] It also decreases the metabolic-associated systemic inflammation while improving the adipokine profile (inducing an increase in adiponectin and a decrease in leptin).[57,58] Exercise not only decreases the quantity of the adipose tissue but also changes the structure and function of the adipocyte. The importance of the qualitative changes in the adipose tissue induced by exercise can be illustrated by an interesting experiment in which recipient sedentary mice were transplanted with adipose tissue from trained donor mice (voluntary wheel running for 11 days). The recipient mice experienced a dramatic improvement in glucose tolerance.[59]

Exercise decreases adiposity by decreasing the size of the adipocytes and its lipid content.[60] This is of extreme relevance since the enlargement of adipocytes induces cellular stress (for example, oxidative and ER stress),[61,62] leading to a distinct adipokine profile, to insulin resistance[63] (which increases its lipolytic capacity by spilling out of free fatty acids into the circulation),[64] and to

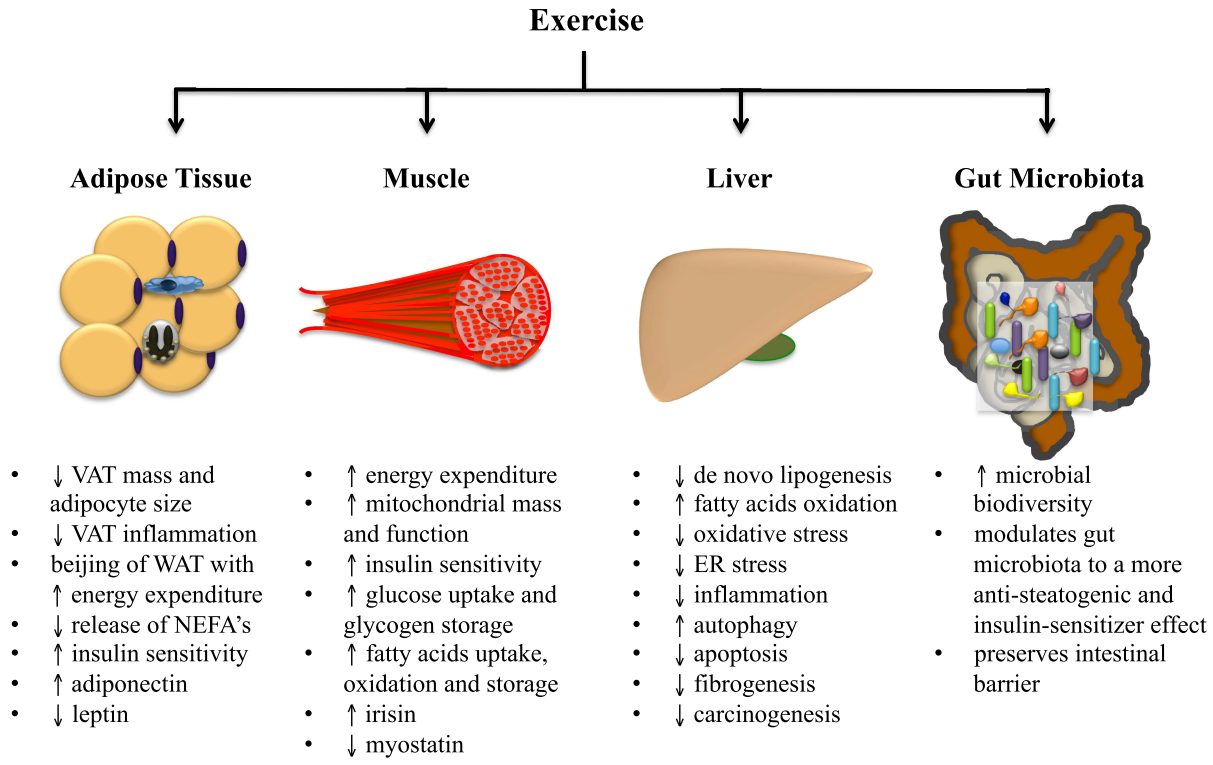

Figure 1 The anti-steatogenic mechanisms of exercise.
Abbreviations: VAT, visceral adipose tissue; WAT, white adipose tissue; NEFA's, non-esterified fatty acids; ER, endoplasmic reticulum.

cell death[65] promoting adipose tissue inflammation.[66] Furthermore, exercise induces beijing of the white adipose tissue, conferring a brown-like phenotype, with increased mitochondrial activity,[59] increased uncoupling proteins leading to increased thermogenesis and increased energy expenditure.[67,68]

Exercise also protects against MAFLD through its effects on the muscle. Regular exercise increases the muscle capacity for oxygen consumption and oxidative function, by increasing capillary density and increasing muscle mitochondrial content and function,[69] for example through upregulation of proteins involved in mitochondrial biogenesis, such as peroxisome proliferator-activated receptor gamma (PPAR-γ) co-activator 1-alpha (PGC1α).[18]

The muscle is the main tissue for glucose uptake and storage.[70] Exercise and muscle contraction promote muscle glucose uptake by the translocation of the glucose receptor GLUT-4 into the cellular membrane, independently of insulin action, and by increasing muscle insulin sensitivity.[71,72] Also, exercise increases the muscle glucose storage as glycogen.[73,74] On the other hand, during exercise, the redistribution of blood flow from the splanchnic circulation to the working muscles, redirects circulating free fatty acids from the liver into the muscle.[75] Indeed, regular exercise increases the uptake and oxidation of fatty acids by the muscle, as well as the ability to store fatty acids such as intramyocellular triglycerides.[76] The relative contribution of glucose as fuel, compared to fat, increases with work rate, but declines with exercise duration.[77] Furthermore, in the post-exercise period, glucose oxidation decreases at the expense of fat oxidation, in order to replenish glycogen storage.[78]

Lastly, exercise modulates myokines production.[7] Exercise induces the release of irisin that promotes beijing of white adipose tissue, increasing energy expenditure.[68] Irisin also has direct anti-steatogenic effects on the liver, through activation of PPAR-γ and upregulation of fibroblast growth factor (FGF)-21.[79] On the other hand, exercise downregulates myostatin,[80] a myokine that promotes adipose tissue expansion through direct effects on the adipose tissue and through downregulation of irisin.[81,82] Myostatin can also promote hepatic fibrogenesis through direct action on hepatic stellate cells.[83] Moreover, exercise increases transiently the synthesis of interleukin(IL)-6,[84]

which induces subsequent increase in IL-10, IL-1 receptor antagonist and cortisol, with a net anti-inflammatory effect.[85]

Exercise has independent anti-steatogenic effects on the liver. Studies on animal models showed that exercise decreases de novo lipogenesis by downregulating the lipogenic transcription factor sterol regulatory-element binding protein-1c (SREBP-1c)[86,87] and decreasing the levels and activity of key enzymes in lipid synthesis such as acetyl CoA carboxylase (ACC) and fatty acids synthase (FAS).[88] Simultaneously, exercise increases hepatic mitochondrial fatty acids oxidation, by upregulating the lipolytic transcription factor PPAR-γ[89] and increasing the activity of key enzymes in beta-oxidation such as beta-hydroxyacyl-CoA-dehydrogenase (β-HAD), citrate synthase and cytochrome c oxidase.[90–92]

Exercise has an anti-oxidant effect on the liver, which translates into a decrease in lipid peroxidation, an increase in reduced glutathione content, and an increase in the activity of anti-oxidant enzymes, such as catalase, superoxide dismutase and glutathione peroxidase.[93–98] It also has an anti-inflammatory effect, through a decrease in systemic inflammation mediated by the adipose tissue[99] and the muscle,[85] and through direct effects on the liver. Exercise decreases the hepatic tumor necrosis factor-alpha (TNF-α) and hepatic resident macrophages infiltration.[100,101] Furthermore, it inhibits the expression of toll-like receptors (TLR) on monocytes and macrophages,[102] and increases the pool of T regulatory cells.[103] Physical activity/exercise modulates other important cellular pathways: it promotes hepatoprotective autophagy,[104] and it improves mitochondrial function, protecting the mitochondria from structural damage.[105–107] Moreover, exercise attenuates mitochondrial-dependent hepatocyte apoptosis.[108–110] All those actions are hepatoprotective, with the potential to decrease the progression from isolated steatosis to steatohepatitis and hepatic fibrosis. Animal studies also suggested exercise to decrease the risk of hepatocellular carcinoma in steatotic livers.[111–113]

Finally, exercise can modulate the gut microbiota towards a less steatogenic and insulin sensitizer phenotype. Indeed, in humans, exercise is associated with an increase in microbial richness/diversity,[114,115] an increase in the relative proportion of Bacteroidetes and Euryarchaeota, whereas a decrease in Actinobacteria, at the phylum level.[116,117] Obesity and MAFLD are known to be associated with a decrease in the Bacteroidetes/Firmicutes ratio, which is associated with higher efficiency in harvesting energy from the diet.[53] Furthermore, exercise helps preserve the intestinal barrier, and improves bile acids homeostasis.[118]

Aerobic Exercise and MAFLD

Several studies, mostly randomized controlled studies, and 7 meta-analyses evaluated the effect of structured interventions on aerobic exercise in MAFLD[119–125] as shown in Table 2. Studies used different exercise regimens, with different intensities, and with durations ranging[121] from 1 week[109] to 1 year.[126] Most of them showed improvements in hepatic steatosis.[54,127,128] A small percentage of published studies with negative results more often used less discriminative tools to quantify liver fat, such as CT scan.[129]

The effect on liver fat of exercise-only interventions ranged from a decrease of 2% up to 50%.[121] Exercise also had a modest effect, decreasing aminotransferases levels.[120]

Globally, the published studies found a significant positive correlation between changes in BMI and changes in liver fat content.[54,130] For each 1% decrease in body weight, studies reported 1% decrease in liver fat content.[123] The effect was also more profound when baseline BMI was higher.[120] However, improvements in liver steatosis were also reported in the absence of weight loss,[56,131–133] suggesting that exercise exerts beneficial effects on liver steatosis that are independent of weight loss.[54] This may be, in part, explained by a more consistent improvement in visceral/abdominal fat with preservation of muscle mass,[56,127,130,132,134–137] in insulin resistance and lipid profile,[135,136,138–140] and modification of inter-organ cross-talk with a favorable cytokine expression (for example, adiponectin and myostatin) and reduction of inflammation and oxidative stress,[141] after an exercise intervention.

A predictor of the efficacy of an exercise intervention in reducing liver fat was baseline cardiorespiratory fitness, independently of total and visceral adipose tissue loss or exercise intensity.[142] Cardiorespiratory fitness probably reflected the functional consequences of genetics and recent physical activity habits.

The beneficial effects of exercise on liver fat were transversal across the lifespan, with positive results from studies on adolescents[143] to the elderly.[144] However, the effect seemed to be more pronounced in the elderly. Exercise was also beneficial in patients with MAFLD who had normal weight at baseline.[7]

Table 2 Randomized Controlled Studies Evaluating the Effect of Aerobic Exercise on MAFLD

Reference	Country	N	Intervention			Controls	Main Findings
			Intensity	Sessions/ Week	Duration		
Sullivan S, 2012[131]	USA	19 obese MAFLD patients	45–55 VO_2 peak, 30–60 minutes	5	16	No exercise	• Exercise ↓ IHLC (10.3±4.6%) • Exercise had no effect on weight or % of body fat
Hallsworth K, 2015[33]	UK	23 MAFLD patients	H-I interval training	3	12 weeks	Standard of care	• Exercise associated with: • ↓ liver fat and whole body fat mass • ↓ ALT and AST • ↑ early diastolic filling rate • No effect on glucose or lipid metabolism
Keating SE, 2015[58]	Australia	48 inactive overweight/ obese adults	1. L/M-I (50% VO_2 peak), 60 min, 4x/week 2. H-I (70% VO_2 peak), 45 min, 3x/week 3. L/M-I (50% VO_2 peak), 45 min, 3x/week		8 weeks	No exercise	• L/M-I, 60 min, 4x/week: ↓ IHLC 2.62 ±1.00%, ↓ VAT 386.8±119.5 cm^2 • H-I, 45 min, 3x/week: ↓ IHLC 2.38 ±0.73%, ↓ VAT 258.4±87.2 cm^2 • L/M-I, 45 min, 3x/week: ↓ IHLC 0.84 ±0.45%, ↓ VAT 212.9±105.5 cm^2 • Placebo: ↑ IHLC 1.10±0.62%, ↑ VAT 92.6±83.5 cm^2
Zhang HS, 2016[126]	China	220 MAFLD patients with central obesity	1. H-I: 65–80% maximal HR 2. M-I: 45–55% maximal HR	150 minutes	6 months	No exercise	• No difference on IHLC in M-I vs H-I exercise, even though H-I exercise associated with higher decrease in body weight • No effect on aminotransferases
Shojaee-Moradie F, 2016[127]	UK	27 sedentary MAFLD patients	1 hour at 40–60% HR reserve	4–5	16 weeks	Conventional life-style advice	• Exercise versus control ↓ IHLC, visceral fat and subcutaneous abdominal fat and ↑ VLDL clearance
Cuthbertson DS, 2016[140]	UK	69 MAFLD patients	30% HR reserve 30 minutes → 60% HR reserve 45 minutes	3 → 5	16 weeks	Counseling	• Greater ↓ of IHLC in intervention group (4.7% [0.01–9.4]), improvement on insulin sensitivity and SC abdominal fat
Rezende R, 2016[132]	Brazil	40 sedentary post-menopausal women	Treadmill aerobic exercise	120 minutes	24 weeks	No exercise	• Exercise associated with ↓ waist circumference • Exercise did not associate with improvements on steatosis (by CAP-Fibroscan) or glucose metabolism
Cheng S, 2017[139]	China	115 patients with MAFLD and IR, 50–65 years	60–75% VO_2 max, 30–60 minutes ± fiber-enriched diet	2–3	8.6 months	No intervention	• Effect on IHLC: • exercise alone: ↓ 24.4% • diet alone: ↓ 23.2% • exercise + diet: ↓ 47.9% • no intervention: ↓ 20.9% • Only exercise associated with ↓ HbA1c

(*Continued*)

Table 2 (Continued).

Reference	Country	N	Intervention			Controls	Main Findings
			Intensity	Sessions/ Week	Duration		
Winn NC, 2018[133]	USA	23 obese adults	H-I interval (4 min 80%VO_2 peak/3 min, 50%VO_2 peak) or M-I continuous (55%VO_2 peak, 60 min). Duration calculated to spend 400 kcal		4 weeks	No exercise	• Both exercises similarly ↓ IHLC (H-I −37.0±12.4% and M-I 20.1±6.6%) • Exercise ↓ postprandial insulin and lipid peroxidation levels • Exercise did not ↓ BMI, visceral AT or liver enzymes
Abdelbasset WK, 2019[135]	Saudi Arabia	32 obese MAFLD patients	H-I interval training, 40 minutes	3	8 weeks	No exercise	• Exercise associated with: • ↓ IHLC (12.4±4.5% to 10.1±1.3%) • ↓ visceral AT (184.5±12.3 to 160.4±11.6 cm^2) • ↓ BMI (36.3±4.5 to 34.1±3.1 kg/m^2) • improvement in glucose and lipid metabolism
Abdelbasset WK, 2020[136]	Saudi Arabia	72 obese diabetic MAFLD patients	H-I interval vs M-I continuous	3	8 weeks	No exercise	• No differences between H-I interval or M-I continuous on IHLC, visceral AT, BMI or glucose metabolism
O'Gorman P, 2020[157]	Ireland	24 biopsy-proven MAFLD patients	Supervised and unsupervised sessions	3–5	12 weeks	Standard of care	• Exercise associated with ↓ hepatocyte ballooning and fibrosis for one stage, but showed no effect on steatosis, lobular inflammation or NAFLD activity score

Abbreviations: AT, adipose tissue; BMI, body mass index; H, high; HR, heart rate; IHLC, intra-hepatic liver content; IR, insulin resistance; L, low; M, moderate, VLDL, very-low density lipoproteins.

An interesting study from China evaluated the long-term effect of 1 year of exercise intervention in 220 obese subjects with MAFLD. At the end of the experiment, exercise was associated with a decrease in visceral abdominal fat, blood pressure and intrahepatic lipid content. Interestingly, 1 year after the active intervention, the beneficial effects on blood pressure and intrahepatic lipid content persisted, albeit the effect on visceral abdominal fat was abrogated.[126] This study suggests long-standing effects after an exercise intervention.

The duration/intensity of exercise necessary to improve liver steatosis is still to be determined. Globally, studies presented a dose-dependent effect between a decrease in liver fat and total training time,[121] but not with the duration of each exercise session or the frequency of sessions per week.[54] Liver fat content decreased 0.27% for each week of exercise intervention.[123] Importantly, interventional studies taught us that even very short interventions, as short as one week, may be beneficial, resulting in an improvement in markers of hepatocyte cell death, even though hepatic lipid content did not decrease.[109]

Light intensity exercise, in opposition to moderate intensity exercise, failed to elicit a decrease in liver fat.[145] The lowest reported energy consumption to elicit a decrease in liver fat was 6349 kcal during the total period of aerobic exercise,[54] which is still less than the recommended for obesity management.[146,147]

A pivotal study evaluating the effect of exercise intensity on liver fat is the one by Keating et al[58] that randomized 48 inactive and overweight/obese adults to an 8-week intervention that consisted in: 1) low to moderate intensity, high volume aerobic exercise (50% VO_2 peak for 60 minutes, 4 days per week); 2) high intensity, low volume aerobic exercise (70% VO_2 peak for 45 minutes, 3 days per week); 3) low to moderate intensity, low volume aerobic exercise (50% VO_2 peak for 45 minutes, 3 days per week); and 4) placebo. The authors did not find

differences between the dose or intensity of the exercise regimen and reductions in liver fat or visceral adipose tissue.

Globally, studies comparing moderate to high-intensity exercise interventions did not find differences in the improvement of hepatic steatosis from 1 month up to 1 year, even though vigorous exercise would elicit higher weight loss in the short term.[126,136,148] However, a study of 169 patients submitted to a 12-week exercise intervention did find a higher decrease in liver fat content, assessed by CAP incorporated in Fibroscan®, for vigorous compared to moderate intensity exercise (32% versus 23%).[149]

Winn et al[133] randomized 23 obese subjects to a 4-week intervention with either high-intensity interval exercise training on motorized treadmill (consisting of 4 minutes of training in 80% of VO_2 peak alternating with 3 minutes of active recovery at 50% VO_2 peak) or moderate intensity continuous training (at 55% VO_2 peak, for 60 minutes), versus non-exercising controls. The 2 exercise regimens were matched for energy expenditure, with 400 kcal consumed per session. Both exercise regimens achieved similar changes in liver fat and in glucose metabolism. A similar study, by Abdelbasset et al[136] on 72 obese, diabetic patients with MAFLD, submitted to an 8-week intervention, also found no differences in the effect of high-intensity interval versus moderate intensity continuous exercise on liver fat content.

Even though it might be difficult to discriminate the effect of aerobic exercise from a global lifestyle changes intervention including diet, on liver fat, some studies did specifically evaluate an exercise intervention without dietary modifications, and did find a decrease in liver fat.[140] A recent meta-analysis confirmed that exercise alone without diet can induce reductions in liver fat content.[150] While studies were not consensual,[151–153] global evidence suggests that diet and exercise seem to have an additive effect on liver fat improvement.[121,139,154] Furthermore, the combination of diet and exercise did induce synergic effects on metabolic control, either glucose and lipid metabolism or blood pressure.[151,152]

In rodent animal models, exercise interventions improved hepatic inflammation and fibrosis.[92,155] In humans, however, there is little evidence to support it.[147] A pilot study on 27 patients, with paired liver biopsies before and after a 6-month exercise intervention, did not achieve improvements in necroinflammatory activity or fibrosis.[156] A 6 months interventional study with moderate intensity exercise in postmenopausal women did not find a decrease in liver fibrosis assessed by elastography.[132] A recent pilot study, not controlled, on 24 patients with biopsy-proven MAFLD, performed a paired biopsy after a 12-weeks intervention with moderate to vigorous intensity aerobic exercise. In this study, half of the patients had improved 1-stage liver fibrosis and two thirds improved ballooning score, even though there was no significant improvement in steatosis or lobular inflammation.[157] Also, a study on 61 sedentary obese men with NAFLD, randomized for high or moderate intensity aerobic exercise during 12 weeks, found that patients on the high-intensity arm improved liver fibrosis assessed by transient elastography.[158]

Human trials assessing the effect of exercise on the severity of liver disease, in patients with MAFLD, are underpowered. Also, the duration of the intervention might not have been enough. Indeed, two large-population epidemiological studies did show a decreased risk of having steatohepatitis and significant fibrosis in MAFLD patients who engaged vigorous (albeit not for moderate) intensity physical activity.[42,43]

Aerobic versus Resistance Exercise and MAFLD

The evidence for the effect of resistance exercise on MAFLD is less consistent, with studies presenting high heterogeneity. However, resistance exercise consistently improved muscle strength and function, as well as, insulin sensitivity.[159]

Skeletal muscle present 3 different muscle fibers: 1) type I or slow oxidative, specialized for long-duration contractile activity that resynthesizes ATP through aerobic metabolism; 2) type IIA or fast oxidative, which has moderate aerobic and anaerobic activity; and 3) IIX or fast glycolytic, which resynthesize ATP through anaerobic glycolysis.[160] Aerobic training acts mainly on type I fibers and promotes an increase in aerobic capacity. Aerobic training not only modulates the muscle fibers (increasing mitochondrial biogenesis and capillary density) but it also induces cardiorespiratory adaptations in order to facilitate the body's utilization of O_2. As such, it strengthens respiratory muscles and increases cardiac dimension and contractility, allowing greater filling of ventricles, resulting in an increase in stroke volume and decreased resting heart rate.[161] Aerobic exercise also improves microcirculation and arterial compliance, resulting in a favorable decrease in blood pressure.[162] Conversely, anaerobic training acts mainly on type II fibers, promoting muscle hypertrophy and neural adaptation resulting in improved strength. It also increases bone density.[163]

Some studies and meta-analysis found a more profound decrease in intrahepatic lipid content (SMD −0.28, p=0.006) for aerobic exercise compared to resistance exercise,[120,164] while others failed to demonstrate a difference between them.[121,122,137,165] Importantly, resistance exercise improved hepatic steatosis with less energy consumption, and might be better tolerated by patients with poor cardiorespiratory fitness.[122] Interestingly, this anti-steatogenic energy sparing property might, in part, be explained by an increase in muscle myokines, such as irisin, which occurs during resistance but not aerobic exercise.[166]

Studies suggest that aerobic exercise, as compared to resistance exercise, has a more profound effect on visceral adipose tissue and glucose or lipid metabolic control.[164,167] However, there is no compelling evidence that the differences in the metabolic effects of aerobic and resistance exercise are clinically significant.[161] Indeed, both aerobic and resistance training can improve skeletal muscle insulin sensitivity in the muscles recruited for the exercise performance.[87]

Aerobic exercise requires high cardiorespiratory fitness and causes fatigue and discomfort, which has a negative impact on long-term compliance. In its turn, resistance exercise is less accessible, since it requires specialized equipment and specific exercise methods.[122] In resistance exercise, it is recommended to use 7–8 different types of weight training exercises targeting major muscles, including pectoralis major, latissimus dorsi, gluteus maximus, quadriceps femoris, and hamstring muscles (eg chest press, shoulder press, vertical traction, leg press, leg extension, leg curl, abdominal crunch, and bicep curl).

Hence, both forms of exercise seem complementary. Indeed, if aerobic exercise is not tolerated, resistance exercise is an alternative, since it also can improve liver fat content.[168,169]

Recommendations

The American College of Sports Medicine recommends cardiorespiratory, resistance, and flexibility exercise training, beyond activities of daily living, to apparently healthy adults of all ages.[170] The college recommends moderate intensity cardiorespiratory exercise training for at least 30 minutes on at least 5 days per week, for a total of at least 150 minutes per week, or vigorous intensity cardiorespiratory exercise training for at least 20 minutes on at least 3 days a week, for a total of at least 75 minutes per week. Adults are also advised to perform resistance exercise for each of the major muscle groups on 2 to 3 days per week, as well as, performing a series of flexibility exercise for each major muscle-tendon group during 60 seconds per exercise on at least 2 days per week.[170] It is equally acceptable to perform one continuous session or multiple shorter sessions of at least 10 minutes. In either case, patients should gradually increase the duration, frequency, and intensity of exercise sessions.

Most guidelines on MAFLD[171–175] support the recommendations from the American College of Sports Medicine for healthy adults (Table 3).

Table 3 International Guidelines on Exercise for Patients with MAFLD

	AGA 2021	AASLD 2018	EASL, EASD, EASO 2016	NICE 2016	WGO 2016
Type of exercise	Aerobic ± resistance	Aerobic ± resistance	Aerobic ± resistance	Aerobic	Aerobic
Intensity	Moderate or vigorous	Moderate	Moderate	Moderate	Moderate
Exercise examples			Brisk walking, stationary cycling	Brisk walking, cycling or gardening	Achieving heart rate 60–75% of the age-based maximum
Duration and frequency	150–300 min /week if moderate or 75–150 min/week if vigorous 2–3x /week	150 min/week or increase 60 min /week	150 min /week 2–3x /week	45–60 min /day	3–4x /week

Abbreviations: AGA, American Gastroenterological Association; AASLD, American Association for the Study of the Liver; EASL, European Association for the Study of the Liver; EASD, European Association for the Study of Diabetes; EASO, European Association for the Study of Obesity; NICE, National Institute for Health and Care Excellence; WGO, World Gastroenterology Organization.

One must keep in mind that patients with MAFLD often present important co-morbidities such as chronic fatigue associated with obstructive sleep apnea, cardiovascular diseases, osteoarthritis (particularly frequent in the knees) and depression with poor motivation, among others.[3] Even though exercise, including vigorous exercise, seems safe in patients with those co-morbidities, including coronary disease,[176] exercise prescription must be individualized for the patient's age and medical status. Importantly, even if the patient is unable to meet the minimum exercise recommended by international societies, any increase in physical activity can have beneficial effects on the hepatic and general health of the patient.

A critical issue in lifestyle modification strategies, and particularly exercise programs, is the patient's lack of motivation.[177] MAFLD is still perceived by the patients as a benign condition with low impact on their health. Furthermore, even when MAFLD patients are aware of the benefits of exercise, they lack confidence and have low expectations.[178] As a result, up to 75% of patients fail to achieve the recommended exercise goals.[179] To increase adherence to an exercise program, instructions must be simple, goals must be attainable and measurable.[3] Patients tend to adhere more to physical activity performed at home, surpassing the need to attend on-site, supervised exercise-sessions.[180] Also could help, to exercise by increasing daily activities (for example, using stairs and walking)[181] or by engaging in pleasant, leisure-time activities, such as dancing.[182] Finally, cognitive behavioral therapy has been shown to considerably increase adherence to lifestyle interventions.[183]

Conclusions

MAFLD is considered the liver manifestation of a sick overwhelmed adipose tissue. Recent studies showed us that MAFLD should probably be more accurately perceived as the liver expression of sedentarism, irrespective of body weight.

Currently, we still lack an approved pharmacological treatment for MAFLD, even though MAFLD is the main chronic liver disease worldwide, and it is rapidly rising towards the top causes of end-stage liver disease in the Occidental world. However, weight loss through lifestyle changes favoring healthy diet and exercise, when accomplished, is highly effective in reverting to hepatic steatosis and even steatohepatitis and fibrosis. Exercise per se, even in the absence of diet, is also effective in decreasing liver fat content. Moreover, exercise, even when it does not elicit weight loss, is still beneficial in the management of hepatic steatosis. Evidence for the role of exercise in reverting to steatohepatitis and liver fibrosis is still scarce, but probably only occurs when engaging in long-term vigorous exercise. Nevertheless, even when exercise goals are not achieved, any increase in physical activity should be encouraged, since it has beneficial effects on the liver and in the associated metabolic disturbances.

Evidence is stronger for aerobic exercise, but probably aerobic or resistance exercise is similarly effective in the management of MAFLD.

Recommendations for exercise should be proposed to all patients with MAFLD, and hepatology clinics should implement a multidisciplinary team that would assist patients in planning an individualized exercise program according to their age and health status.

Abbreviations

ACC, acetyl CoA carboxylase; β-HAD, beta-hydroxyacyl-CoA-dehydrogenase; BMI, body mass index; FAS, fatty acids synthase; FGF, fibroblast growth factor; FLI, fatty liver index; IL, interleukin; MAFLD, metabolic dysfunction associated fatty liver disease; MET, metabolic equivalent task; MRS, magnetic resonance spectrometry; NAS, NAFLD fibrosis score; NHANES, National Health and Nutrition Examination Survey; PGC-1α, peroxisome proliferator-activated receptor gamma co-activator 1-alpha; PPAR-γ, peroxisome proliferator-activated receptor gamma; SREBP-1c, sterol regulatory-element binding protein-1c; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-alpha; VO_2, maximum capacity of oxygen utilization.

Disclosure

The author reports no conflicts of interest in this work.

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