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Physical Activity and Liver Diseases

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Regular physical activity beneficially impacts the risk of onset and progression of several chronic diseases. However, research regarding the effects of exercising on chronic liver diseases is relatively recent. Most researchers focused on nonalcoholic fatty liver disease (NAFLD), in which increasing clinical and experimental data indicate that skeletal muscle crosstalking to the adipose tissue and the liver regulates intrahepatic fat storage. In this setting, physical activity is considered to be required in combination with calories restriction to allow an effective decrease of intrahepatic lipid component, and despite that evidence is not conclusive, some studies suggest that vigorous activity might be more beneficial than moderate activity to improve NAFLD/nonalcoholic steatohepatitis. Evidence regarding the effects of exercise on the risk of hepatocellular carcinoma is scarce; some epidemiological studies indicate a lower risk in patients regularly and vigorously exercising. In compensated cirrhosis, exercise acutely increases portal pressure, but in the longer term it has been proved safe and probably beneficial. Decreased aerobic capacity (VO_2) correlates with mortality in patients with decompensated cirrhosis, who are almost invariably sarcopenic. In these patients, VO_2 is improved by physical activity, which might also reduce the risk of hepatic encephalopathy through an increase in skeletal muscle mass. In solid organ transplantation recipients, exercise is able to improve lean mass, muscle strength, and, as a consequence, aerobic capacity. Few data exist in liver transplant recipients, in whom exercise should be an object of future studies given its high potential of providing long-term beneficial effects. *Conclusions:* Despite that evidence is far from complete, physical activity should be seen as an important part of the management of patients with liver disease in order to improve their clinical outcome. (HEPATOLOGY 2016;63:1026-1040)

Strong and growing epidemiological evidence indicates that lifestyle factors modulate the risk of developing several chronic diseases. Independent of dietary habits, the risk of developing chronic diseases is increased by sedentariness and is decreased in individuals performing regular physical activity. This clinical association is clear for obesity, diabetes mellitus (DM), arterial hypertension, coronary heart disease, osteoarthritis, and some solid neoplasias (breast and colon) and has been initially attributed to improved glucose uptake and insulin sensitivity. Subsequently, it became clear that the beneficial effects of physical activity exceeded those explained by the above-mentioned mechanisms. Skeletal muscle is now recognized as an endocrine organ that secretes cytokines and other peptides, defined as "myokines," with autocrine, paracrine and endocrine actions[(1)] (Fig. 1).

Interestingly, myokines are involved in inflammatory response, and physical activity plays a key role in the maintenance of an anti-inflammatory phenotype homeostasis. On the contrary, a sedentary lifestyle promotes a proinflammatory shift in myokines, and

Abbreviations: 6MWD, 6 minutes walking distance; 6MWT, the 6-minute walk test; ACC, acetyl-CoA carboxylase; ALT, alanine aminotransferase; AMP, adenosine monophosphate; AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; BDL, bile duct ligation; BMI, body mass index; CHC, chronic hepatitis C; ChREBP, carbohydrate response element-binding protein; CI, confidence interval; CLD, chronic liver disease; CoA, coenzyme A; CPT1, carnitine palmitoyltransferase 1; DM, diabetes mellitus; ER, endoplasmic reticulum; FAS, fatty acid synthase; FMD, flow-mediated dilatation; HBF, hepatic blood flow; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HOMA-IR, homeostatic model assessment of insulin resistance; HVPG, hepatic venous pressure gradient; IL, interleukin; IRS, insulin receptor substrate; JNK, c-Jun N-terminal kinase; LPO, lipid peroxidation; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; MRS, magnetic resonance spectroscopy; mTORC1, mammalian target of rapamycin complex 1; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NEFA, nonesterified fatty acid; NO, nitric oxide; PBC, primary biliary cholangiopathy; PFK2, phosphofructokinase 2; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator 1 alpha; PPAR, peroxisome proliferator-activated receptor; RCTs, randomized, controlled trials; ROS, reactive oxygen species; SCD-1, stearoyl-Coa desaturase 1; SREBP-1c, sterol regulatory element-binding protein 1c; TAG, triacylglycerol; TG, triglyceride; VLDL, very-low-density lipoprotein; VO_2, maximal oxygen uptake.

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inflammation, in turn, decreases muscle strength and mass.

Despite that chronic liver disease (CLD) is a major cause of morbidity and mortality worldwide, research regarding the effects of physical activity in this population is recent. A pandemic of nonalcoholic fatty liver disease (NAFLD), an obesity-related disorder, fostered studies in this clinical scenario. In addition, the effects of physical activity have been the object of investigation in patients with cirrhosis, those with hepatocellular carcinoma (HCC), and those undergoing liver transplantation (LT).

Physical Activity on Liver Steatosis, Inflammation, and Fibrosis

NAFLD/NONALCOHOLIC STEATOHEPATITIS

NAFLD is the most prevalent cause of liver disease in many parts of the world, and its incidence continues to rise as a consequence of obesity epidemics and sedentary lifestyle. The pathogenesis of NAFLD, and particularly the causes that lead to the aggressive form of presentation, nonalcoholic steatohepatitis (NASH) characterized by inflammation and fibrosis accompanying steatosis, have not been fully elucidated as yet. A multiple-hit hypothesis has been formulated.[2]

The available evidence regarding the initial development of fatty liver in subjects with positive energy balance (excess of intake vs. consumption) depicts a complex interplay among three major actors: adipose tissue, the liver, and skeletal muscle. Insulin resistance in the three organs is a central pathogenic event preceding most of the remaining mechanisms.

Concisely, the accumulation of triacylglycerols (TAGs) in hepatocytes (steatosis) is owing to different factors, including: (1) increased circulating nonesterified fatty acids (NEFAs), exceeding the individual fat-oxidation capacity. This is thought to be the trigger in the majority of patients with NAFLD/NASH who are overweight or obese, as a result of the modern diet. An additional factor for increased circulating NEFAs in this population is increased lipolysis in an insulin-resistant adipose (mainly visceral adipose) tissue. NEFAs are delivered to the liver, the taken up and accumulated as diacylglycerol and TAGs. (2) Increased *de novo* lipogenesis; (3) insufficient elimination of TAGs in excess owing to insufficient mitochondrial lipid oxidation; and (4) inhibition/dysregulation of very-low-density lipoprotein (VLDL) assembly and secretion.

As a result of lipid accumulation, hepatic insulin resistance (through phosphorylation of insulin receptor substrate [IRS] 2 mediated by protein kinase C), insulin signaling defects, and leptin resistance arise.

Energy balance is further regulated within the liver by two main transcription factors: factor sterol regulatory element-binding protein 1 (SREBP-1), induced by insulin and high-fat diet, and carbohydrate response element-binding protein (ChREBP), which is induced by hyperglycemia linked to skeletal muscle insulin resistance. Activation of these factors results in *de novo* lipogenesis and decreased free fatty acid beta-oxidation.

Proinflammatory adipokines (leptin, resistin, interleukin [IL]-6; tumor necrosis factor alpha) lipid peroxidation (LPO), mitochondrial dysfunction, and oxidative damage induced by reactive oxygen species (ROS) seem necessary to develop NASH; in this step, lipid accumulation and altered composition of phospholipids within endoplasmic reticulum (ER) membranes further promote ER stress and insulin resistance.[3] These events are associated with activation of different proinflammatory pathways, including Toll-like receptors, which, in turn, activates two main

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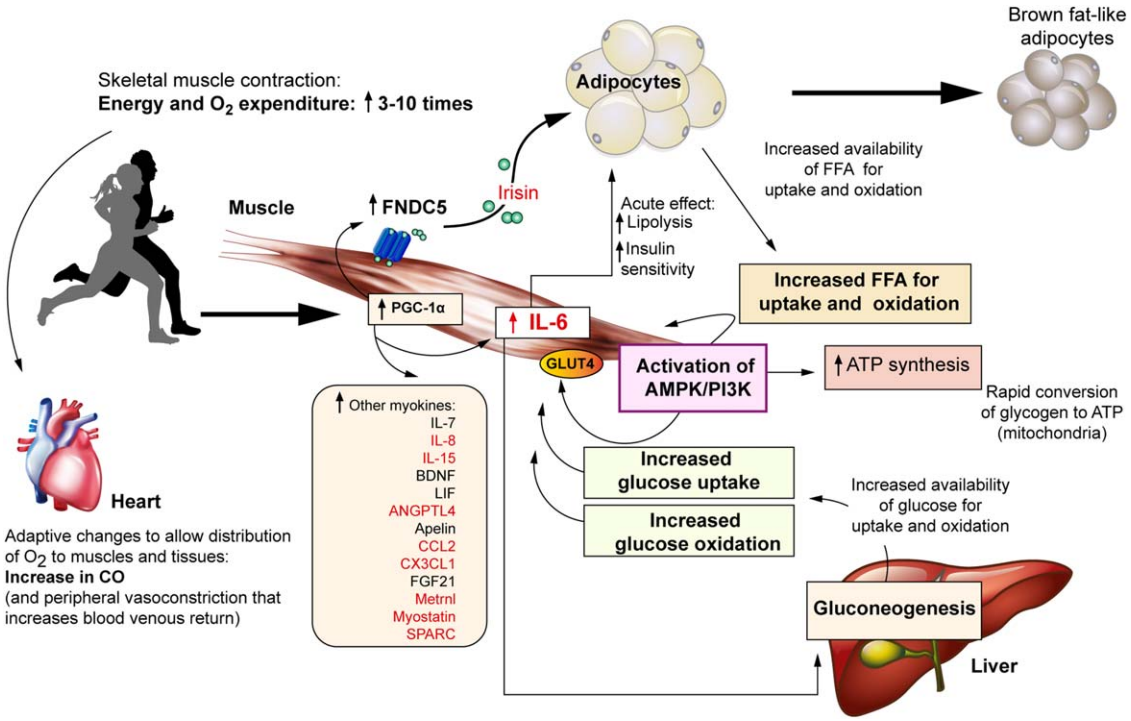

FIG. 1. Skeletal muscle as an endocrine organ and main acute cardiovascular and metabolic consequences of exercise. The figure shows the main myokines known to date (in red those considered true "exercise factors," namely, factors produced by skeletal muscle in response to exercise and secreted into the circulation). Exercise also leads to a 3- to 10-fold increase in whole-body oxygen consumption; energy required to distribute oxygen to the muscle is obtained by rapid oxidation of glucose (circulating glucose availability is regulated through the liver) and fatty acids first from the skeletal muscle, and then from hepatic and adipose depots. In parallel, oxygen needs to be distributed by the cardiovascular system, which adapts through increase in cardiac output and peripheral vasoconstriction. Abbreviations: ANGPTL4, angiopoietin-like 4; BDNF, brain derived neerotropic factor; CCL2, chemokine (C-C motif) ligand 2; CX3CL1, chemokine (C-X3-C motif) ligand 1; CO, cardiac output; FGF21, fibroblast growth factor 21; GLUT4, glucose transporter type 4; LIF, leukemia inhibitory factor; SPARC, secreted protein acidic and rich in cysteine.

intracellular signaling pathways: nuclear factor kappa B and c-Jun N-terminal kinase (JNK). The first leads to an increased transcription of several proinflammatory genes, whereas JNK induces insulin resistance through phosphorylation and degradation of IRS1, eventually reducing intracellular signaling downstream of the insulin receptor. LPO can also directly induce activation of hepatic stellate cells, the major effectors in fibrogenesis. These mechanisms finally lead to hepatocyte damage and development of liver fibrosis.[2]

EFFECTS OF EXERCISE IN PATIENTS WITH NAFLD/NASH

A large amount of evidence in patients and in murine models of NAFLD/NASH shows that weight loss is crucial to improve the histological features of the disease[4] and to avoid progression of fibrosis. Weight loss is able to improve lipid and glucose metabolism through increase in insulin sensitivity,[5] improve endothelial function, reduce blood pressure, and decrease proinflammatory markers.

Currently, to improve intrahepatic fat content, a minimum 3%-5% weight loss (and ideally ≥7%) is recommended[6]; this should be achieved not only through calorie restriction, but also with regular exercise.[4] This recommendation arises from a pilot observation showing that adding regular unstructured exercise to caloric restriction led to normalization of alanine aminotransferase (ALT) in patients with NAFLD.[7] Hence, the strict interaction between nutrition and physical activity in this scenario should be emphasized.

Many studies have reported that elevated physical activity or cardiorespiratory fitness are inversely associated with the onset of NAFLD and NASH.

Exercise influences hepatic metabolism. In sedentary subjects, adoption of either aerobic- and resistance-

based exercise regimes result in significant reduction of hepatic and visceral fat accumulation, increased fat oxidation, and increased insulin sensitivity.[8,9] Studies in monozygotic twins suggest that the effects of exercise are independent of genetic background.[10] Exercise also improves adipocytic insulin sensitivity, reducing the flow of fatty acids to the liver irrespective of body mass index (BMI).[11]

A systematic review and meta-analysis assessed the effects of exercise in patients with NAFLD/NASH[12] with the hypothesis that when compared with non-exercise control conditions, interventions involving exercise would lead to reduction in liver fat and ALT. Twelve studies, mostly performed in a small number of subjects, were included in the final pooled analysis. Regarding studies employing exercise alone versus control (without concurrent diet intervention in both groups), exercise was shown to be effective in improving liver fat (effect size = 0.37; 95% confidence interval [CI]: 0.06-0.69; $P = 0.020$), despite a minimal or absent weight loss. Importantly, increased cardiorespiratory fitness directly correlated to reductions in intrahepatic TAGs and liver enzymes in two studies. This was not observed in interventions comparing combined exercise and diet versus diet alone; furthermore, no overall effect of exercise versus control on ALT was observed.[12] Table 1 summarizes the interventional studies included in the published meta-analysis[12] as well as three more-recent randomized, controlled trials (RCTs).[13-15] In one of them, exercise was able to reverse endothelial dysfunction, evaluated by flow-mediated dilatation (FMD) of the brachial artery, in patients with NAFLD.[13] This confirms that exercise is able to improve microvascular endothelial function through nitric oxide (NO) also in patients with NAFLD. Given that intrahepatic circulation shows features of sinusoidal endothelial dysfunction early in the development of experimental NAFLD, studies evaluating whether exercise is able to revert not only systemic, but also intrahepatic endothelial dysfunction are needed.

The optimal type, duration, and intensity of exercise training for patients with NAFLD has not been established.[16] Both aerobic and anaerobic resistance training for 4 months are able to decrease hepatic fat content on magnetic resonance spectroscopy (MRS), as well as BMI, adipose tissue, and insulin resistance, to a similar extent.[17] No data regarding a potential differential effect of aerobic versus anaerobic training on other histological aspects (inflammation and fibrosis) are available so far. As for the intensity of exercise, the odds of developing advanced NASH-related fibrosis is reduced in patients that perform more-intense exercise.[16] However, in an RCT performed in 48 sedentary obese subjects, Keating et al. showed no significant differences on liver fat reduction by three regimens of aerobic exercise with different dose and/or intensity.[18] All reduced liver fat by a small amount without clinically significant weight loss as compared to placebo.

Hybrid training, a training that involves both voluntary and electrical muscle contractions, has been object of a small study in patients resistant to lifestyle counseling with encouraging results.[15]

Text Box 1 summarizes the beneficial effects of exercise on liver disease in NAFLD/NASH.

Compliance to exercise is an issue; dropout rate was high in the published trials regarding physical activity in NAFLD/NASH, and in the only large cross-sectional analysis of subjective concerns related to exercise published so far, patients with NAFLD (and patients with other CLDs) showed a low confidence to perform physical activity.[19]

EFFECTS OF EXERCISE IN EXPERIMENTAL MODELS OF NAFLD AND MOLECULAR PATHWAYS INVOLVED

Experimental data shed light on some of the mechanisms by which exercise exerts a beneficial effect on liver disease in NAFLD/NASH[20] (Fig. 2). In animal models, exercise programs improved adipose mass, steatosis, insulin resistance, and inflammation. These beneficial effects are also observed when exercise is introduced midway through a high-fat diet regimen (e.g., a previous work[21]). Physical activity improved insulin sensitivity by reducing ER stress.[22] When comparing exercise with calorie restriction, Rector et al.[23] noted elevated mitochondrial β-oxidation, oxidative enzyme function, improved glucose tolerance, and suppression of hepatic *de novo* lipogenesis in the exercise-only group, providing support to the claim that exercise has effects superior to those of dietary modification. Halting exercise for short periods (7 days) does not appear to hamper its benefits, although longer interruptions (4 weeks) caused deterioration of overall metabolic health and liver phenotype in hyperphagic rats.[24]

A central role in exercise-mediated metabolic changes is played by adenosine monophosphate (AMP)-activated protein kinase (AMPK), a protein

TABLE 1. RCTs and Pilot Interventional Studies Assessing the Effect of Exercise in Patients With NAFLD

Author	N Controls	N Exercise	Kind of Exercise	Duration	Endpoint and Main Results
Tamura et al.*	7 CR	7 CR+Ex	Aerobic exercise; 30 min exercise 2-3 sessions+walking 5-6 days/wk. Exercise intensity was targeted at 50%-60% of VO_2.	2 weeks	IHL by ^{1}H-MRS showed a significant and similar decrease in both groups (by 25%-27%).
Shojaee-Moradie et al.*	7 NR	10 Ex	Aerobic exercise; a minimum of 20 min training up at 60%-85% of VO_{2max} for at least 3 days/wk.	6 weeks	IHL by ^{1}H-MRS; no change after exercise and no significant differences between the two groups
Chen et al.*	16 CR+Ex 25 NL	23 Ex	Aerobic exercise; high-intensity stationary bicycle exercise program at a frequency of 1hour twice a week.	10 weeks	Total cholesterol, ALT, and GGT decreased significantly only in the CR+Ex group.
Johnson et al.*	7 NL+stretching	12 Ex	Aerobic exercise; supervised 3 cycleergometer sessions/wk; progressive VO_2 peak increase: 50%-70%; 15 min efforts × 3+5 min rest.	4 weeks	IHL by ^{1}H-MRS, ALT, HOMA. Intraheptic TAG decreased by 21% with intervention; no change in ALT and HOMA.
Larson-Meyer et al.*	12 CR	11 CR+Ex	Aerobic exercise; individualized structured exercise (walking, running, or stationary cycling) 5 days/wk to increase energy expenditure by 12.5%.	6 months	10% decrease in body weight in both groups; IHL by ^{1}H-MRS and CT significantly and similarly decreased in both groups.
Levinger et al.*	15 with low met. risk+15 with high met. risk NL	15 with low met. risk + 15 with high met. risk Ex	Resistance training (7 exercises); 2-3 sets of 15-20 repetitions at 40%-50% of 1RM for 3 days/wk until week 3; then at 50%-75% of 1RM until week 6; then 8-12 repetitions at 75%-85% of 1RM.	10 weeks	Ex did not significantly change inflammatory markers or hepatic enzymes.
Shah et al.*	9 CR	9 CR+Ex	Aerobic + progressive resistance training; 90 minutes/session 3 times/wk, supervised; initially: moderate intensity (~70% of peak heart rate); then intensity was gradually increased to ~85% of peak heart rate.	6 months	IHL by MRS. IHL (-45%), body weight, fat mass, and insulin resistance decreased significantly and similarly in both groups. CR+Ex group only showed improvements in VO_2 peak, strength, plasma TGs, LDL-C, and diastolic blood pressure.
Thompson et al.*	21 NL	20 Ex	Not specified;exercise was progressively increased in time (from 30 min 3 days/wk to 70 min 4 days/wk) and intensity (from 50% to 70% of VO_{2max}).	6 months	Markers of inflammation and ALT. IL-6 decreased in Ex by wk 12. ALT decreased in Ex only at 24 wk, suggesting the need for a more vigorous-intensity activity and/or amore prolonged intervention.
Goodpaster et al.*	63 CR	66 CR+Ex	Aerobic exercise; 60 min moderate-intensity physical activity (brisk walking) up to 5 days/wk.	6 months	Body weight; IHL by CT. Weight loss and IHL decrease were significanltly higher in the CR+Ex group.
Lazo et al.*	50 NC	46 CR+Ex	Aerobic+progressive resistance training; increased physical activity with a goal of 175 min of moderate intensity/wk; 4 sessions per month supervised.	12 months	IHL by ^{1}H-MRS; ALT; body weight. CR+Ex group showed a significant decrease in body weight (−8.5%); IHL decrease was greater in the CR+Ex group: −51 vs. −23%. ALT did not change.
Hallsworth et al.*	8 NL	11 Ex	Progressive resistance training (8 exercises); 45-60 min/session 3 times/wk. Sessions began and ended with 10 min warmup at approximately 60% maximum heart rate on a cycle ergometer. For the first 6 weeks: 50% of 1RM; then 70% of 1RM.	8 weeks	IHL by ^{1}H-MRS; body weight and fat mass, lipid oxidation, HOMA. Ex reduced IHL by 13%; lipid oxidation and HOMA also significantly improved. Body weight and fat mass did not change.
Sullivan et al.*	6	12	Aerobic exercise;	16 weeks	

TABLE 1. *Continued*

Author	N Controls	N Exercise	Kind of Exercise	Duration	Endpoint and Main Results
	NL	Ex	30 (initially) to 60 min, 5 times per week (1/wk supervised) at 45%-55% of their VO_2 peak.		IHTG content by MRS; VLDL kinetics. Ex decreased IHTG by 10% without modifying body weight. No change in hepatic VLDL-TG and VLDL apoB^{-}. 100 secretion rate.
Kawaguchi et al.[15]	12	23	Hybrid exercise training	12 weeks	ALT, hepatic steatosis, HOMA-IR, and IL-6 decreased in hybrid-
	DC	Ex	(19 minutes twice a week).		training group and did not change in control group.
Yoshimura et al.[14]	18	15	Aerobic exercise:supervised bicycle ergometry, and walking	12 weeks	IHL by CT decreased significantly and similarly in both
	CR alone	CR+Ex	or running (60 min/session), 3 times/week+120 min/wk (nonsupervised).		groups. Only the exercise group showed improvement in VO_2 peak.
Pugh et al.[13]	8	13	Aerobic exercise: supervised 30 min/3 times/wk at 30% of	16 weeks	IHL by ^{1}H-MRS decreased similarly in the two groups. Only the
	CR	Ex	HRR for the initial 4 wk; then intensity increased to 45% HRR for 4 wk, then duration increased to 45 min for 4 wk. From week 12, participants were exercising 5 times/wk for 45 min at 60% of their individual HRR.		exercise group showed improvement in VO_2 peak and FMD.

1RM = one repetition maximum; this indicates the largest load that an individual can lift/move in a single maximal effort.
*These papers are the object of a systematic review and meta-analysis.[12]
Abbreviations: apoB, apolipoprotein B; CR, calories restriction; CT, computed tomography; Ex, exercise training; DC, dietary counseling; GGT, gamma-glutamyl transpeptidase; HRR, heart rate reserve; IHL, intrahepatic lipid content; met., metabolic; min, minutes; NL, normal life; NR, not reported; wk, week.

that acts as the energy gauge in the body sensing AMP levels. Exercise mediates a drop in adenosine triphosphate (ATP) and a consequent increased AMP cytosolic concentration, which is an indicator of reduced intracellular energy level.

Activation of AMPK tends to restore energy by reducing expenditure on one side and by activating the transcription of genes improving the efficiency of ATP synthesis and utilization on the other (Fig. 3).

In the liver, AMPK inhibits lipid synthesis through suppression of SREBPF, a key transcription factor that activates lipogenic genes, including acetyl-CoA (coenzyme A) carboxylase (ACC1) and fatty acid synthase (FAS).[23,25] AMPK activation results in the reduction of malonyl CoA, an allosteric inhibitor of carnitine palmitoyltransferase 1 (CPT1), the enzyme that controls the transfer of cytosolic long-chain fatty-acyl-CoA into the mitochondria.[26] Exercise decreases hepatic stearoyl-Coa desaturase 1 (SCD-1) activity, a rate-limiting enzyme in the biosynthesis of saturated-derived monounsaturated fat that are the major constituents of VLDL-TG (triglyceride).[23] Reduced SCD-1 activity decreases lipogenesis while enhancing hepatic fatty acid oxidation. Glucagon has also a regulatory role in the liver by increasing β-oxidation by upregulation of peroxisome proliferator-activated receptor (PPAR)α, an inducer of genes required for fatty acid catabolism, including CPT1, in either an AMPK- or a p38-dependent manner.[23,27,28] Specific myokines are released as exercise effectors and increase energy consumption by different mechanisms. Irisin is released as a consequence of the activation of peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α), which promotes the expression of its membrane precursor, FNCD5. Irisin holds the ability of inducing a brown-adipocyte phenotype in white fat adipocytes, thereby increasing energy expenditure (heat loss) independent of food intake.[29]

Exercise might act also through other pathways; it seems to influence gut microbiota diversity, with potentially relevant effects on immune interaction between microbiota and host.[30] Whether exercise might beneficially modulate gut microbiome-derived inflammation and NASH progression is open to future research.

CHRONIC VIRAL HEPATITIS

There is published evidence only for chronic hepatitis C (CHC). This is likely owing to the fact that hepatitis C virus (HCV) has metabolic effects. Insulin

Box 1 Summary of the major beneficial effects of exercise on liver disease in NAFLD/NASH.

- Improvement of peripheral and hepatic insulin sensitivity: obtained even by moderate exercise, independent of its kind (aerobic and resistance training)
- Reduction in oxidative stress in the liver and in the vascular endothelium, mainly through increase of antioxidant enzymes
- Decrease in hepatic lipid content: Owing to several different mechanisms, most of them are, at least in part, mediated by AMPK activation.
- Decrease in inflammation and fibrosis progression: Data are still scarce; exercise of higher intensity and longer duration seem to exert a positive effect
- Improvement in oxygen consumption (aerobic fitness), mainly through AMPK activation
- Improvement in systemic endothelial function, mainly through AMPK activation

resistance in CHC is partially virus-mediated. Two studies so far reported the effect of exercise training in patients with CHC. In the first study,[31] 15 patients with genotype 1 HCV infection, most of whom had normal weight (mean BMI: 25.6 kg/m^2), completed a 6-month lifestyle intervention program consisting of adequate nutritional intake and increase in light-moderate physical activity (walking, with the objective of achieving 8,000 steps per day). This exercise threshold was achieved by 47% of patients, who showed a significant improvement in several parameters: body weight; fat mass; ALT; homeostatic model assessment of insulin resistance (HOMA-IR); and leptin. Adiponectin increased only in patients who significantly decreased body weight, and other liver function tests did not change.

The second study[32] prospectively included 16 patients with CHC and obesity (10 patients without cirrhosis and 6 with cirrhosis). Patients underwent a 6-month lifestyle modification program, including individualized dietary restriction and pedometer monitor increase in physical activity up to 10,000 steps per day. Patients showed a significant decrease in BMI and HOMA-IR, and 50% of patients no longer showed insulin resistance at the end of the study. Fatigue, assessed by a specific scoring system, also improved. Adiponectin increased, whereas leptin and resistin decreased. The major drawback of these studies is that they do not allow dissecting whether these beneficial effects are mainly related to a decrease in body weight or to a direct effect of exercise training.

CLD FROM OTHER CAUSES

We lack specific evidence on the effect of physical activity on the natural history of CLD owing to nonviral, non-NAFLD causes. Only one study, conducted in mice, assessed the effect of endurance training (60 minutes on treadmill 5 times per week for 4 weeks) on acute alcohol exposure. Trained mice displayed a significantly smaller increase in transaminases. The researchers attributed this protective effect to the induction of heat shock protein 70.[33]

Osteodystrophy is a common complication of all CLDs and, in particular, of cholestatic liver diseases. In the general and elderly population, exercising is critical to prevent loss of bone mass and to increase it in depleted conditions.[34] Physical activity could be highly beneficial on bone metabolism in cholestatic liver diseases. However, excessive fatigue can limit the ability to exercising of patients with primary biliary cholangiopathy (PBC). Ninety-five percent of PBC patients have autoantibody responses against the mitochondrial antigen pyruvate dehydrogenase complex mediating mitochondrial dysfunction with consequent excess muscle acidosis; in addition, PBC patients (but not patients with primary sclerosing cholangitis) showed significant prolongation of muscle pH recovery time after exercise, which correlated with clinical fatigue.[35]

Physical Activity and Cirrhosis

Patients with cirrhosis show a reduced tolerance to exercise and usually stop exercise testing because of symptoms before reaching their predicted maximal cardiac frequency.[36] Maximal oxygen consumption at peak exercise (VO_2 peak) assesses the aerobic capacity of individuals and is directly related with tolerance to exercise, physical fitness, and physiological reserve.

The decrease in aerobic capacity, which shows an inverse correlation with liver function assessed by

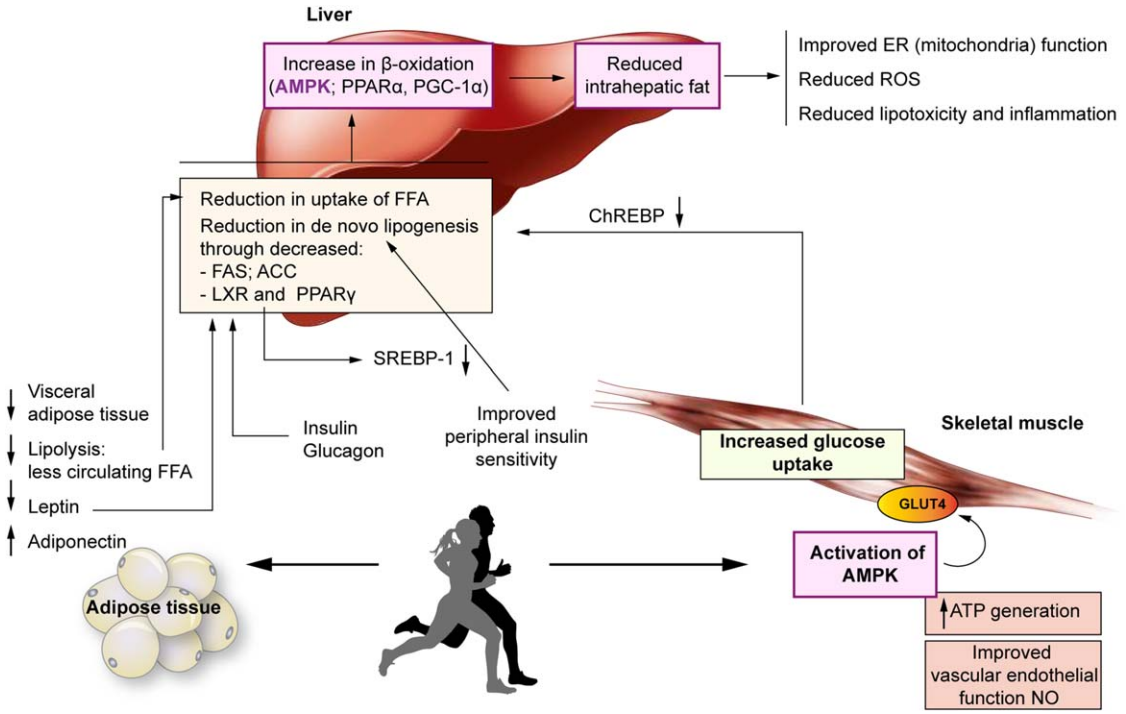

FIG. 2. Beneficial effects of exercise in NAFLD. Exercise effects occur through different mechanisms that involve three major actors, namely, skeletal muscle, adipose tissue, and the liver; the major metabolic changes induced by exercise are summarized in the figure. Abbreviation: LXR, liver X receptor.

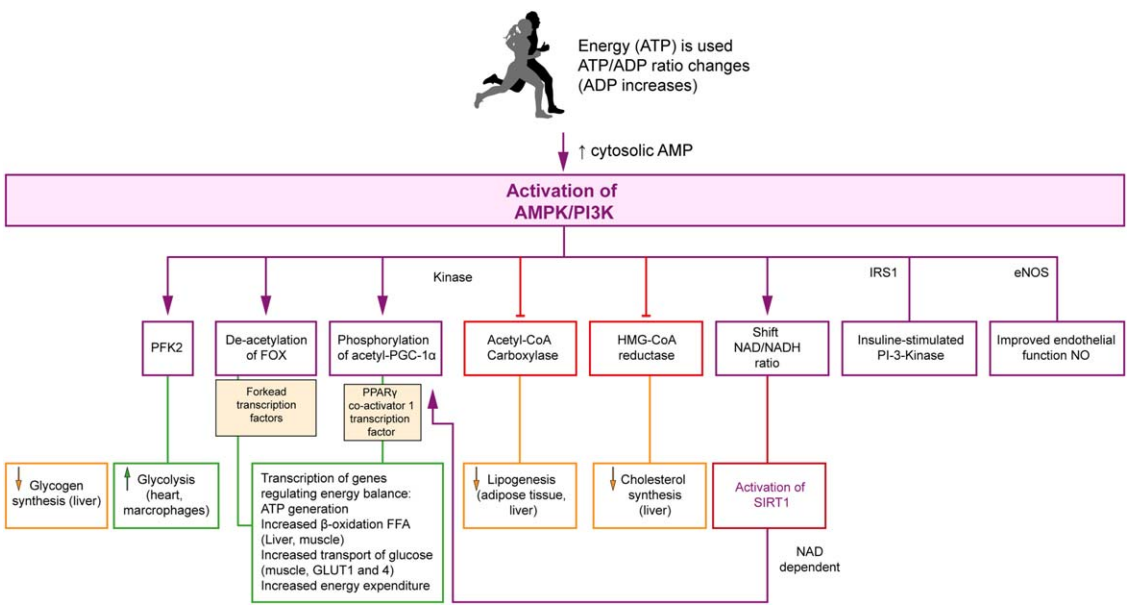

FIG. 3. Main effects of AMPK activation. AMPK activation triggers many different pathways, eventually leading to fatty acid oxidation in the liver and skeletal muscle, inhibition of cholesterol synthesis and lipogenesis in the liver, and increase in energy expenditure. ADP, adenosine diphosphate; FOX, forkhead box; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; NAD/NADH, nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide plus hydrogen; PFK2, phosphofructokinase 2; SIRT1, sirtuin 1.

Model for End-Stage Liver Disease (MELD) or Child-Pugh score,[36] and the impairment in VO_2 is particularly severe in decompensated, Child C patients. In a series of 135 patients with cirrhosis awaiting LT,[36] 88% showed decreased VO_2. The cause of aerobic capacity reduction in cirrhosis is probably multifactorial, including fatigue, deconditioning, disturbances of carbohydrate metabolism (insulin resistance) secondary to portal hypertension, and reduced hepatocellular function and protein-energy malnutrition.[37] The latter contributes to reduced muscle mass and strength in this population, particularly in the decompensated phase of the disease. In this context, it has been shown in alcoholic cirrhosis that fasting is oversensed and boosts a phenomenon of "accelerated starvation" further precipitating sarcopenia. Furthermore, patients showing pulmonary complications of portal hypertension (portopulmonary hypertension and hepatopulmonary syndrome), as well as patients with alcoholic cirrhosis and alcoholic cardiomyopathy, may have added factors decreasing their cardiopulmonary reserve.

COMPENSATED CIRRHOSIS: EFFECTS OF EXERCISE ON PORTAL HYPERTENSION

Garcia-Pagán et al.[38] studied 8 patients with preserved hepatic function (Child score: 6.9±0.7 points) and clinically significant portal hypertension before and after an acute workload consisting in 8-10 minutes of cycling up to 30% and 50% of the peak workload. It was observed that at 30% of maximal workload, portal pressure significantly increased by 16% and that hepatic blood flow (HBF) decreased by 18%; as expected, arterial blood pressure also significantly increased. These changes were further, even if not significantly, accentuated at the 50% workload (hepatic venous pressure gradient [HVPG] increase: 21% vs. baseline; HBF decrease: 29% vs. baseline). Given that, according to Ohm's law, portal pressure gradient is the product of intrahepatic resistance and portal inflow; these data suggest that a marked increase in intrahepatic resistance takes place during acute exercising in cirrhosis. These changes can be explained by the increase in endogenous neurohumoral vasoconstrictive factors, such as norepinephrine, angiotensin II, and vasopressin, which can further exaggerate the intrahepatic vasoconstriction occurring in the cirrhotic liver. The same researchers showed that pretreatment with propranolol (the most commonly used nonselective beta-blocker for portal hypertension treatment) blunts the aggravating effects of acute exercise on portal pressure.[39] In this regard, it should be noted that despite their negative chronotropic and inotropic effect, initiation of beta-blocker therapy is not associated with a worsening in aerobic capacity,[40] except when portopulmonary hypertension is present,[41] and in cirrhosis nonselective beta-blocker discontinuation post-LT did not lead to improvement in aerobic capacity.

In patients with portal hypertension not undergoing beta-blockers, therapy exercise could lead to an increased risk of variceal bleeding through an increase in portal pressure.

Data in patients undergoing exercise for a longer period of time did not confirm this hypothesis. In the 78 patients with compensated cirrhosis (Child A or B) included in the four prospective studies available so far[42-45] (Table 2), no episodes of variceal bleeding or other decompensation of cirrhosis were observed during 8-16 weeks of moderate exercise. Exercise improved VO_2 in all the studies and improved quality of life.

Two studies published in abstract form addressed the changes in HVPG after chronic exercise[42,45]; one was performed in 50 patients with cirrhosis, portal hypertension, and overweight/obesity, and intervention consisted in a combination of diet and exercise.[42] A ≥10% decrease in HVPG was observed in 42% of patients, and a weight reduction ≥5% was observed in 52% of cases. No changes in HBF were observed, and the intervention led to a significant (over 30%) decrease in serum insulin, HOMA index, and leptin. The observed decrease in portal pressure might be explained, in part, by a decrease in the dynamic component of hepatic resistance mediated by the decrease in these adypokines. It remains to be investigated whether the beneficial effect on portal pressure is related to body-weight decrease rather than exercise, and whether it is only observed in overweight/obese patients.

The second study evaluated 23 patients, of whom 11 underwent the exercise program[45]; a 2.5 mm Hg decrease in HVPG was observed in the exercise group; however, in the control arm an unexpected increase of 4 mm Hg was observed.

Regarding the practical recommendations to be given to patients with compensated cirrhosis, a recent survey performed in a Japanese population[46] suggested that walking 5,000 or more steps per day and maintaining a total energy intake of 30 kcal/kg of ideal body weight would be sufficient to prevent sarcopenia

TABLE 2. Studies Assessing the Effects of Exercise in Patients With Compensated Cirrhosis

Author and NCT No.	Design	N in Exercise Group	Child Score and Class	MELD Score	Body Mass Index (kg/m^2)	Exercise Scheme	Duration	Endpoint and Main Results
Zenith et al.[44] NCT01799785	Randomized, controlled pilot study of exercise vs. control arm	9	6.2 ± 1.4 A and B	9.7 ± 2.4	27.7 ± 3.8	Cycloergometry 30 min 3 days/week up to 60%-80% of peak VO_2	8 weeks	Peak VO_2 (main); thigh circumference; 6MWD; quality of life. All significantly improved at the end of the study. No safety issues.
Roman et al.[43] NCT01060813	Randomized open, controlled pilot study of exercise+leucine vs. control arm+leucine	8	7 Child A 1 Child B	9.5 (7-12)	26.7 (18.3-34.7)	Treadmill walking and cycloergometry 60 min, 3 days/wkup to 60%-70% of the maximum heart rate	12 weeks	Exercise capacity, muscle mass, and quality of life. All significantly improved at the end of the study. No safety issues.
Berzigotti et al.[42] NCT01409356	Pilot prospective, multicentric study; all patients underwent exercise and tailored diet.	50 (overweight or obese)	46 Child A 4 Child B	9 ± 3	33.3 ± 3.2	60 min/wk moderate exercise up to a subjective scale 4-5/10+tailored advice for increase in day-by-day physical activity+tailored hypocaloric diet	16 weeks	HVPG and body weight (main); peak VO_2; quality of life. All significantly improved at the end of the study. HVPG and BW decreased by 10%. No safety issues.
Macias-Rodriguez et al.[45] (not provided)	Randomized, open, controlled pilot study of exercise+nutrition vs. nutrition alone	11	A and B (15 A and 8 B over the two arms)	10 ± 3	NR	Stationary bicycle and kinesiotherapy sessions 2-3 days/wk up to 60%-80% of peak VO_2 (total of 40 sessions)	14 weeks	HVPG. HVPG significantly decreased after exercise. No safety issues.

Abbreviations: 6MWD, 6 minutes walking distance; BW, body weight; NR, not reported; wk, week.

in patients with compensated cirrhosis. These data require confirmation in prospective studies, but strongly suggest that both a correct nutrition and physical activity are needed to improve outcomes in advanced CLD.

DECOMPENSATED CIRRHOSIS: EFFECTS OF EXERCISE ON SARCOPENIA AND ENCEPHALOPATHY

Sarcopenia is extremely frequent in patients with decompensated cirrhosis and is associated with a poorer prognosis in this population.[47] In patients listed for LT, maximal exercise capacity identifies patients at high risk of 90 days post-transplant mortality[36,48] as well as 1-year mortality and/or perioperative complications and early in-hospital mortality[49]; this is relevant, given that preoperative MELD score is not appropriate to predict postoperative outcomes in this population.

Skeletal muscle mass is crucial for the removal of plasma ammonia, and, in turn, hyperammoniemia impairs skeletal muscle synthesis, contributing to worsening of sarcopenia. It is well known that further loss of muscle mass can play a role in precipitating/worsening hepatic encephalopathy. Therefore, some researchers postulated that exercise and supplementation of the branched-chain amino acid, leucine, could attenuate muscle mass loss and prevent hepatic encephalopathy. In a recent study,[50] the effects of leucine (1.35 mg/kg/day) alone or in combination with 15 minutes of exercise (10 cm/s) every other day for 5 weeks were tested in a rat model of cirrhosis (bile duct ligation; BDL). Leucine-treated BDL showed an improvement in brain edema, muscle mass, and metabolic activity, further ameliorated by exercise. In addition, BDL rats treated by leucine and exercise showed an improved cognitive and psychomotor function.

From a practical point of view, it should be underlined that exercising under insufficient nutrients and proteins intake could be dangerous in patients with decompensated cirrhosis, given that it could promote further protein catabolism and loss of muscle mass. Therefore, a proper nutritional assessment and supplementation are indicated before initiating physical activity in this population. In addition, caution should be paid in patients with ascites and marked stimulation of vasoconstrictor systems (renin-aldosterone and sympathetic nervous systems), given that impairment in renal function can take place after exercise in this population.[51] Finally, the best method to assess aerobic capacity in this setting, as well as the optimal exercise regimen to be applied, has not been yet defined. The 6-minute walk test (6MWT) is simple and applicable in most patients with cirrhosis, even in the decompensated phase, and correlates well with the results of more-complex tests.

A personalized, adapted physical activity program (cycloergometry + muscle strengthening according to ventilatory threshold) for 12 weeks seems feasible and sufficiently safe in patients awaiting LT and improves peak VO_2, maximum power, ventilator threshold power, 6 minutes walking distance (6MWD), and strength of knee extensor muscles.[52]

Given that exercise has been shown to modulate gut microbioma,[30] it might also reduce bacterial translocation in cirrhosis[53]; however, no data are available in this regard so far.

Physical Activity and HCC

Exercise is protective against some solid tumors, such as breast cancer and prostate cancer. Limited data are available so far regarding HCC; overall, in the published cohort studies, a higher degree of physical activity was associated with a progressive reduction in HCC risk. In particular, in one of the cohorts (n = 415) vigorous physical activity (≥5 days/week) was associated with a relative risk of 0.56 (95% CI: 0.41-0.78).[54]

As for the mechanisms mediating the beneficial effects of exercise on HCC risk, we recently demonstrated that regular exercise has a positive effect on HCC in a mouse model of NASH.[55] Exercise stimulated AMPK activity and decreases activity of mammalian target of rapamycin complex 1 (mTORC1), which function as key metabolic growth promoters. AMPK activation in HCC seems to induce apoptosis and decreased AMPK activity, which has been associated with poor outcome, suggesting that exercise could counteract HCC risk/progression, in part, by activating AMPK and impairing mTORC1 activity. Exercise-induced changes in AMPK/protein kinase B/mTORC1 do not require the presence of obesity/DM, indicating an independent effect of exercise to HCC inhibition. Furthermore, exercise may strengthen tumor perfusion, thus counteracting tumor hypoxia and hence avoiding an aggressive cancer phenotype.

Despite promising evidence in animal models of HCC, and despite that in patients diagnosed with

Box 2 Recommendations on physical activity for adults ages 50-64 with clinically significant chronic conditions or functional limitations that affect movement ability, fitness, or physical activity by the American College of Sports Medicine,[62] American Heart Association, and World Health Organization.

- To promote and maintain health, moderate-intensity aerobic physical activity for a minimum of 30 minutes 5 days each week or vigorous-intensity aerobic activity for a minimum of 20 minutes 3 days each week. **Evidence grade IA**.
- Combinations of moderate- and vigorous-intensity activity can be performed to meet this recommendation. **Evidence grade IIB**.
- On 2 or more nonconsecutive days per week, further physical activity should be performed to: (1) improve muscle strength and endurance: minimum of 8-10 exercises should be performed using the major muscle groups; (2) resistance (weight): 10-15 repetitions for each exercise. The level of effort should be moderate (5-6 on a scale of 10) to high (7-8 on a scale of 10). **Evidence grade IIA**.
- Flexibility exercises should be performed for at least 10 minutes each day. **Evidence grade IIB**.
- Participation in aerobic and muscle-strengthening activities above the minimum recommended amounts provides additional health benefits andresults in higher levels of physical fitness. **Evidence grade IA**.

Definitions:

- *Moderate-intensity aerobic activity*: moderate level of effort relative to an individual's aerobic fitness. On a 10-point scale, where sitting is 0 andall-out effort is 10, moderate-intensity activity is a 5 or 6 and produces noticeable increases in heart rate and breathing.
- *Vigorous-intensity activity* is a 7 or 8 on the same scale and produces large increases in heart rate and breathing. This recommended amount of aerobic activity is in addition to routine activities of daily living of light intensity (e.g., self-care, cooking, casual walking, or shopping) or moderate-intensity activities lasting less than 10 minutes in duration (e.g., walking around home or office).

HCC, preoperative exercise capacity was an independent prognostic indicator of event-free (recurrence of HCC and complications of cirrhosis including liver failure) survival posthepatectomy in one study, no data are available on the effects of exercise on long-term HCC-related outcomes.

Physical Activity Post-LT

Impairment of aerobic capacity is common and severe in liver transplanted patients[56] and is often reported as fatigue after small-load physical activity (e.g., walking). This is explained by multiple factors, including, in the early post-transplantation phase, deconditioning associated to bed rest owing to extended hospital and intensive care stay, which has itself an extremely negative effect, immunosuppressant drugs-associated myopathy (particularly steroids), and episodes of organ rejection.

In later phases, calcineurin inhibitors induced effects (e.g., reduction in mitochondrial respiration and muscle regeneration/remodeling) and metabolic syndrome and overweight-related problems are common post-LT and contribute to further worsening of aerobic capacity. Hence, liver transplanted recipients should benefit of exercise; however, only approximately 50% of patients perform regular physical activity within 2 years of LT, one of the potential reasons for this being failure to reverse muscle loss post-transplantation}.

In the post-transplantation phase, exercise is aimed at restoring a normal physical function allowing a normal life in all aspects (work, family, and leisure). As such, post-transplant physical activity should be seen as a long-term commitment.

The existing evidence in solid organ transplanted populations suggests that exercise is able to improve lean mass, muscle strength, and, as a consequence, aerobic capacity.[57,58] In the only RCT published so far, regular exercise training increased exercise capacity by 27% post-transplant.[57] However, adherence to the proposed program was only 37% over 10 months, and exercise did not restore completely peak VO_2, which remained lower as compared to the predicted values for

sedentary nontransplanted subjects. In other nonrandomized studies, an early training program increased up to 40% the VO_2 peak.[59]

As for the effects of exercising on post-transplantation metabolic syndrome, a major source of morbidity and mortality post-LT, a study performed in 204 patients, of whom 59% had metabolic syndrome,[60] showed that in patients with a time from transplantation over 1 year, metabolic syndrome was associated with a lower exercise intensity independent of age and pretransplantation diabetes. However, only 24% of patients were compliant to the recommendations regarding the amount of exercise-related physical activity to be undertaken (namely, at least 150 minutes per week; Text Box 2), and approximately 50% of them reported no physical activity at all.

These data underline the importance of a multidisciplinary approach aiming at promoting and maintaining physical activity in transplanted patients. There are no data regarding the effects of exercise on cardiovascular risk in patients undergoing LT. A recent meta-analysis of the data available in solid organ transplanted patients failed to prove beneficial effects on surrogate outcome,s such as new-onset diabetes.[58] Failure of the meta-analysis was mainly owing to the small number of patients included in the different trials, and to the availability of only one RCT in liver transplanted patients.[57] New studies in this field are needed, following the research areas pointed out by recent consensus recommendations.[61]

Conclusions

The evidence discussed in this review shows that physical activity is important in addition to calorie restriction for NAFLD/NASH patients, is safe in patients with compensated cirrhosis, might reduce the risk of HCC (particularly in NAFLD/NASH), and probably improves outcomes post-LT. Even though the scientific evidence is still limited, this topic is going to be increasingly important in the future, and a sound clinical approach to liver diseases should already involve physical activity; patient-centered care in this field should take advantage of multidisciplinary team work (Supporting Fig. 1).

The research agenda in this field remains crowded with open questions, which include addressing the molecular effects of physical activity in the diseased liver, as well as clinical studies focusing on the duration, intensity, and frequency of physical activity in all the above mentioned scenarios. Finally, a better understanding of the interactions of physical activity and nutrition and strategies aimed at achieving and maintaining an adequate compliance to lifestyle changes are urgently needed in order to improve outcomes in hepatology.

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REFERENCES

1) Catoire M, Kersten S. The search for exercise factors in humans. FASEB J 2015;29:1615-1628.
2) Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. HEPATOLOGY 2010;52:1836-1846.
3) Fu S, Yang L, Li P, Hofmann O, Dicker L, Hide W, et al. Aberrant lipid metabolism disrupts calcium homeostasis causing liver endoplasmic reticulum stress in obesity. Nature 2011;473:528-531.
4) Thoma C, Day CP, Trenell MI. Lifestyle interventions for the treatment of non-alcoholic fatty liver disease in adults: a systematic review. J Hepatol 2012;56:255-266.
5) DeFronzo RA, Sherwin RS, Kraemer N. Effect of physical training on insulin action in obesity. Diabetes 1987;36:1379-1385.
6) Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. HEPATOLOGY 2012;55:2005-2023.
7) Palmer M, Schaffner F. Effect of weight reduction on hepatic abnormalities in overweight patients. Gastroenterology 1990;99:1408-1413.
8) Johnson NA. Aerobic exercise training reduces hepatic and visceral lipids in obese individuals without weight loss. HEPATOLOGY 2009;50:1105-1112.
9) Zelber-Sagi S. Role of leisure-time activity in nonalcoholic fatty liver disease: a population-based study. HEPATOLOGY 2009;48:1791-1798.
10) Hannukainen JC, Borra R, Linderborg K, Kallio H, Kiss J, Lepomaki V, et al. Liver and pancreatic fat content and metabolism in healthy monozygotic twins with discordant physical activity. J Hepatol 2011;54:545-552.
11) DiPietro L, Dziura J, Yeckel CW, Neufer PD. Exercise and improved insulin sensitivity in older women: evidence of the enduring benefits of higher intensity training. J Appl Physiol 2006;100:142-149.
12) Keating SE, Hackett DA, George J, Johnson NA. Exercise and non-alcoholic fatty liver disease: a systematic review and meta-analysis. J Hepatol 2012;57:157-166.
13) Pugh CJ, Spring VS, Kemp GJ, Richardson P, Shojaee-Moradie F, Umpleby AM, et al. Exercise training reverses endothelial dysfunction in nonalcoholic fatty liver disease. Am J Physiol Heart Circ Physiol 2014;307:H1298-H1306.
14) Yoshimura E, Kumahara H, Tobina T, Matsuda T, Ayabe M, Kiyonaga A, et al. Lifestyle intervention involving calorie restriction with or without aerobic exercise training improves liver fat in adults with visceral adiposity. J Obes 2014;2014:197216.
15) Kawaguchi T. Hybrid training of voluntary and electrical muscle contractions reduces steatosis, insulin resistance, and IL-6 levels

in patients with NAFLD: a pilot study. J Gastroenterol 2011;46: 746-757.
16) Rodriguez B, Torres DM, Harrison SA. Physical activity: an essential component of lifestyle modification in NAFLD. Nat Rev Gastroenterol Hepatol 2012;9:726-731.
17) Bacchi E, Negri C, Targher G, Faccioli N, Lanza M, Zoppini G, et al. Both resistance training and aerobic training reduce hepatic fat content in type 2 diabetic subjects with nonalcoholic fatty liver disease (the RAED2 Randomized Trial). HEPATOLOGY 2013;58:1287-1295.
18) Keating SE, Hackett DA, Parker HM, O'Connor HT, Gerofi JA, Sainsbury A, et al. Effect of aerobic exercise training dose on liver fat and visceral adiposity. J Hepatol 2015;63:174-182.
19) Frith J, Day CP, Robinson L, Elliott C, Jones DE, Newton JL. Potential strategies to improve uptake of exercise interventions in non-alcoholic fatty liver disease. J Hepatol 2010;52:112-116.
20) Lavoie JM, Gauthier MS. Regulation of fat metabolism in the liver: link to non-alcoholic hepatic steatosis and impact of physical exercise. Cell Mol Life Sci 2006;63:1393-1409.
21) Gauthier MS, Couturier K, Charbonneau A, Lavoie JM. Effects of introducing physical training in the course of a 16-week high-fat diet regimen on hepatic steatosis, adipose tissue fat accumulation, and plasma lipid profile. Int J Obes Relat Metab Disord 2004;28:1064-1071.
22) da Luz G, Frederico MJ, da Silva S, Vitto MF, Cesconetto PA, de Pinho RA, et al. Endurance exercise training ameliorates insulin resistance and reticulum stress in adipose and hepatic tissue in obese rats. Eur J Appl Physiol 2011;111:2015-2023.
23) Rector RS, Uptergrove GM, Morris EM, Borengasser SJ, Laughlin MH, Booth FW, et al. Daily exercise vs. caloric restriction for prevention of nonalcoholic fatty liver disease in the OLETF rat model. Am J Physiol Gastrointest Liver Physiol 2011;300:G874-G883.
24) Linden MA, Meers GM, Ruebel ML, Jenkins NT, Booth FW, Laughlin MH, et al. Hepatic steatosis development with four weeks of physical inactivity in previously active, hyperphagic OLETF rats. Am J Physiol Regul Integr Comp Physiol 2013; 304:R763-R771.
25) Cintra DE, Ropelle ER, Vitto MF, Luciano TF, Souza DR, Engelmann J, et al. Reversion of hepatic steatosis by exercise training in obese mice: the role of sterol regulatory element-binding protein-1c. Life Sci 2012;91:395-401.
26) Neschen S, Morino K, Hammond LE, Zhang D, Liu ZX, Romanelli AJ, et al. Prevention of hepatic steatosis and hepatic insulin resistance in mitochondrial acyl-CoA:glycerol-sn-3-phosphate acyltransferase 1 knockout mice. Cell Metab 2005;2:55-65.
27) Berglund ED, Kang L, Lee-Young RS, Hasenour CM, Lustig DG, Lynes SE, et al. Glucagon and lipid interactions in the regulation of hepatic AMPK signaling and expression of PPARalpha and FGF21 transcripts in vivo. Am J Physiol Endocrinol Metab 2010;299:E607-E614.
28) Takekoshi K, Fukuhara M, Quin Z, Nissato S, Isobe K, Kawakami Y, et al. Long-term exercise stimulates adenosine monophosphate-activated protein kinase activity and subunit expression in rat visceral adipose tissue and liver. Metabolism 2006;55:1122-1128.
29) Arias-Loste MT, Ranchal I, Romero-Gomez M, Crespo J. Irisin, a link among fatty liver disease, physical inactivity and insulin resistance. Int J Mol Sci 2014;15:23163-23178.
30) Clarke SF, Murphy EF, O'Sullivan O, Lucey AJ, Humphreys M, Hogan A, et al. Exercise and associated dietary extremes impact on gut microbial diversity. Gut 2014;63:1913-1920.
31) Konishi I, Hiasa Y, Tokumoto Y, Abe M, Furukawa S, Toshimitsu K, et al. Aerobic exercise improves insulin resistance and decreases body fat and serum levels of leptin in patients with hepatitis C virus. Hepatol Res 2011;41:928-935.
32) Pattullo V, Duarte-Rojo A, Soliman W, Vargas-Vorackova F, Sockalingam S, Fantus IG, et al. A 24-week dietary and physical activity lifestyle intervention reduces hepatic insulin resistance in the obese with chronic hepatitis C. Liver Int 2013;33:410-419.
33) Mikami T, Sumida S, Ishibashi Y, Ohta S. Endurance exercise training inhibits activity of plasma GOT and liver caspase-3 of mice [correction of rats] exposed to stress by induction of heat shock protein 70. J Appl Physiol 2004;96:1776-1781.
34) Maimoun L, Sultan C. Effects of physical activity on bone remodeling. Metabolism 2011;60:373-388.
35) Hollingsworth KG, Newton JL, Robinson L, Taylor R, Blamire AM, Jones DE. Loss of capacity to recover from acidosis in repeat exercise is strongly associated with fatigue in primary biliary cirrhosis. J Hepatol 2010;53:155-161.
36) Dharancy S, Lemyze M, Boleslawski E, Neviere R, Declerck N, Canva V, et al. Impact of impaired aerobic capacity on liver transplant candidates. Transplantation 2008;86:1077-1083.
37) Peng S, Plank LD, McCall JL, Gillanders LK, McIlroy K, Gane EJ. Body composition, muscle function, and energy expenditure in patients with liver cirrhosis: a comprehensive study. Am J Clin Nutr 2007;85:1257-1266.
38) Garcia-Pagan JC, Santos C, Barbera JA, Luca A, Roca J, Rodriguez-Roisin R, et al. Physical exercise increases portal pressure in patients with cirrhosis and portal hypertension. Gastroenterology 1996;111:1300-1306.
39) Bandi JC, Garcia-Pagan JC, Escorsell A, Francois E, Moitinho E, Rodes J, et al. Effects of propranolol on the hepatic hemodynamic response to physical exercise in patients with cirrhosis. HEPATOLOGY 1998;28:677-682.
40) Maki T, Naveri H, Leinonen H, Sovijarvi A. Effect of beta-blocking agents with and without intrinsic sympathomimetic activity on work efficiency in healthy men. Clin Physiol 1996;16:543-550.
41) Provencher S, Herve P, Jais X, Lebrec D, Humbert M, Simonneau G, et al. Deleterious effects of beta-blockers on exercise capacity and hemodynamics in patients with portopulmonary hypertension. Gastroenterology 2006;130:120-126.
42) Berzigotti A, Villanueva C, Genescá J, Ardevol A, Augustín S, Calleja JL, et al. Lifestyle intervention by a 16-week programme of supervised diet and physical exercise ameliorates portal hypertension in patients with cirrhosis and obesity: the SportDiet study. HEPATOLOGY 2014;60:253A.
43) Roman E, Torrades MT, Nadal MJ, Cardenas G, Nieto JC, Vidal S, et al. Randomized pilot study: effects of an exercise programme and leucine supplementation in patients with cirrhosis. Dig Dis Sci 2014;59:1966-1975.
44) Zenith L, Meena N, Ramadi A, Yavari M, Harvey A, Carbonneau M, et al. Eight weeks of exercise training increases aerobic capacity and muscle mass and reduces fatigue in patients with cirrhosis. Clin Gastroenterol Hepatol 2014;12:1920-1926.
45) Macías-Rodríguez RT, Ilarraza-Lomelí H, Ruiz-Margáin AG, Duarte-Rojo A. Changes on hepatic venous pressure gradient induced by a physical exercise program in cirrhotic patients: a randomized open clinical trial. HEPATOLOGY 2014;60:246A.
46) Hayashi F, Matsumoto Y, Momoki C, Yuikawa M, Okada G, Hamakawa E, et al. Physical inactivity and insufficient dietary intake are associated with the frequency of sarcopenia in patients with compensated viral liver cirrhosis. Hepatol Res 2013;43: 1264-1275.
47) Montano-Loza AJ, Meza-Junco J, Prado CM, Lieffers JR, Baracos VE, Bain VG, et al. Muscle wasting is associated with mortality in patients with cirrhosis. Clin Gastroenterol Hepatol 2012;10:166-173, 173.e1.

48) Epstein SK, Freeman RB, Khayat A, Unterborn JN, Pratt DS, Kaplan MM. Aerobic capacity is associated with 100-day outcome after hepatic transplantation. Liver Transpl 2004;10:418-424.
49) Neviere R, Edme JL, Montaigne D, Boleslawski E, Pruvot FR, Dharancy S. Prognostic implications of preoperative aerobic capacity and exercise oscillatory ventilation after liver transplantation. Am J Transplant 2014;14:88-95.
50) Ghezzal SC, Bosoi CR, Beauchamp R, Tremblay M, Rose CF, Bemeur C. Optimizing muscle mass: therapeutic target to prevent experimental hepatic encephalopathy. HEPATOLOGY 2014;60:304A.
51) Salo J, Guevara M, Fernandez-Esparrach G, Bataller R, Gines A, Jimenez W, et al. Impairment of renal function during moderate physical exercise in cirrhotic patients with ascites: relationship with the activity of neurohormonal systems. HEPATOLOGY 1997;25:1338-1342.
52) Debette-Gratien M, Tabouret T, Antonini MT, Dalmay F, Carrier P, Legros R, et al. Personalized adapted physical activity before liver transplantation: acceptability and results. Transplantation 2015;99:145-150.
53) Wiest R, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. J Hepatol 2014;60:197-209.
54) Behrens G, Matthews CE, Moore SC, Freedman ND, McGlynn KA, Everhart JE, et al. The association between frequency of vigorous physical activity and hepatobiliary cancers in the NIH-AARP Diet and Health Study. Eur J Epidemiol 2013; 28:55-66.
55) Piguet AC, Saran U, Simillion C, Keller I, Terracciano L, Reeves HL, et al. Regular exercise decreases liver tumors development in hepatocyte-specific PTEN-deficient mice independently of steatosis. J Hepatol 2015;62:1296-1303.
56) Stephenson AL, Yoshida EM, Abboud RT, Fradet G, Levy RD. Impaired exercise performance after successful liver transplantation. Transplantation 2001;72:1161-1164.
57) Krasnoff JB, Vintro AQ, Ascher NL, Bass NM, Paul SM, Dodd MJ, et al. A randomized trial of exercise and dietary counseling after liver transplantation. Am J Transplant 2006;6:1896-1905.
58) Didsbury M, McGee RG, Tong A, Craig JC, Chapman JR, Chadban S, et al. Exercise training in solid organ transplant recipients: a systematic review and meta-analysis. Transplantation 2013;95:679-687.
59) Beyer N, Aadahl M, Strange B, Kirkegaard P, Hansen BA, Mohr T, et al. Improved physical performance after orthotopic liver transplantation. Liver Transpl Surg 1999;5:301-309.
60) Kallwitz ER, Loy V, Mettu P, Von Roenn N, Berkes J, Cotler SJ. Physical activity and metabolic syndrome in liver transplant recipients. Liver Transpl 2013;19:1125-1131.
61) Mathur S, Janaudis-Ferreira T, Wickerson L, Singer LG, Patcai J, Rozenberg D, et al. Meeting report: consensus recommendations for a research agenda in exercise in solid organ transplantation. Am J Transplant 2014;14:2235-2245.
62) American College of Sports Medicine, Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, Minson CT, Nigg CR, et al. American College of Sports Medicine position stand. Exercise and physical activity for older adults. Med Sci Sports Exerc 2009;41:1510-1530.

Supporting Information

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