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Exercising the hepatobiliary-gut axis. The impact of physical activity performance

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Abstract

Background: Physical inactivity puts the populations at risk of several health problems, while regular physical activity brings beneficial effects on cardiovascular disease, mortality and other health outcomes, including obesity, glycaemic control and insulin resistance. The hepatobiliary tract is greatly involved in several metabolic aspects which include digestion and absorption of nutrients in concert with intestinal motility, bile acid secretion and flow across the enterohepatic circulation and intestinal microbiota. Several metabolic abnormalities, including nonalcoholic fatty liver as well as cholesterol cholelithiasis, represent two conditions explained by changes of the aforementioned pathways.

Materials and Methods: This review defines different training modalities and discusses the effects of physical activity in two metabolic disorders, that is nonalcoholic fatty liver disease (NAFLD) and cholelithiasis. Emphasis is given to pathogenic mechanisms involving intestinal bile acids, microbiota and inflammatory status.

Results: A full definition of physical activity includes the knowledge of aerobic and endurance exercise, metabolic equivalent tasks, duration, frequency and intensity, beneficial and harmful effects. Physical activity influences the hepatobiliary-gut axis at different levels and brings benefits to fat distribution, liver fat and gallbladder disease while interacting with bile acids as signalling molecules, intestinal microbiota and inflammatory changes in the body.

Conclusions: Several beneficial effects of physical activity are anticipated on metabolic disorders linking liver steatosis, gallstone disease, gut motility, enterohepatic circulation of signalling bile acids in relation to intestinal microbiota and inflammatory changes.

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CONFLICT OF INTEREST

We declare that we have no conflict of interests.

Keywords

bile acids; farnesoid X receptor; G protein–coupled bile acid receptor-1; gallstone disease; gut microbiota; nonalcoholic fatty liver disease

1 | INTRODUCTION

The beneficial effects of physical activity are shown on several health outcomes, such as cardiovascular disease (CVD) and mortality for all causes.[1] Sedentary behaviour, in contrast, affects negatively cardiovascular risk factors[2] and represents 23% of the deaths related to chronic diseases.[3] Being inactive for several years may lead to increased risks for type 2 diabetes (T2D), CVD and premature mortality.[4] The health benefits of physical activity extend to the hepatobiliary and the gastrointestinal tract and involve nonalcoholic fatty liver disease (NAFLD) and cholesterol gallstone disease.

Nonalcoholic fatty liver disease is the most frequent chronic liver disease in developed countries[5] with no medication approved as a standard care treatment.[6] NAFLD refers to the excess accumulation of hepatic fat (triglycerides) in the liver due to metabolic, rather than alcoholic or viral reasons, and encompasses a wide range of chronic liver abnormalities ranging from simple steatosis (NAFL) to steatohepatitis (NASH), to significant liver fibrosis and cirrhosis, and even hepatocellular carcinoma.[7] The estimated prevalence of NAFLD is 20%−30% in Western adults and is strongly associated with other metabolic disorders such as obesity and T2D.[8] NAFLD is also linked to a lack of physical activity and improper dietary regimens,[9] and patients with NAFLD are more sedentary than their healthy counterparts.[10] There are evidences that physical inactivity, low aerobic fitness and overnutrition contribute to NAFLD either separately or in combination.[11,12]

Cholesterol gallstone disease also shares many metabolic risk factors with NAFLD, such as hyperlipidaemia, obesity and T2D.[13] Physical activity has been associated with a decreased progression of gallstone disease at ultrasonography.[14] Gallbladder function has also been linked to physical activity.[15]

The role of physical activity should also be considered with respect to intestinal bile acid (BA) metabolism and intestinal microbiota. BAs are soluble amphiphiles and major lipid components of bile; intestinal BAs contribute to the digestion and absorption of lipids and fat-soluble vitamins as either primary BAs (ie, synthetized in the liver) and secondary/tertiary BAs (ie, biotransformed by the resident colonic microbiota), while re-entering the enterohepatic circulation. Of note, BAs are also signalling molecules which modulate epithelial cell proliferation, gene expression and energy, glucose, lipid and lipoprotein metabolism via activation of intestinal farnesoid X receptor (FXR) and G protein–coupled bile acid receptor-1 (GPBAR-1) found in the intestine, liver Kupffer cells, striated muscle and brown adipose tissue.[16]

This review discusses current views on the mechanisms relating physical activity to NAFLD, gallbladder disease, bile acids, gut microbiota and metabolic inflammatory changes (Figure 1).

2 | CLASSIFICATION OF PHYSICAL ACTIVITY

Physical activity is defined as any body movement which uses energy to activate the skeletal muscles, whereas “exercise” defines a subgroup of planned physical activity over time with the main aim of becoming healthier.[17] Appropriate understanding of these two terms is needed to avoid misclassification of terminology.[18] Sedentary behaviour, in contrast, is defined as sitting, lying down or spending very low energy, reporting a value of 1–1.5 units of metabolic equivalent tasks (MET).[19] A MET refers to the resting metabolic rate or its equivalent in oxygen (O_2) consumed while resting (3.5 mL/kg/min, which at the same time would equal to burning 1.2 kcal/min for a 70 kg individual in sitting condition).[20] A compendium of several physical activities (structured or not) has already been developed in terms of METs equivalent by activity, for example, bathing (1.5), driving a car (2.5) or static cycling (7.0).[21] However, the resting metabolic rate of men differs from that of women, as well as within ages, given the changes in body weight and height.[22] One classification of physical activity is based on duration, frequency and intensity. The duration refers to the amount of exercise which is performed over time. The normal measurement for physical activity duration is in minutes. Additionally, the term “volume” refers to any indicator of exercising, for example, load, energy expenditure or calories burned,[23] or to the product of all duration, frequency, intensity and length of a training programme.[24] Frequency is associated with the total number of physical activity sessions during a certain week[23] or the number of bouts (times) of physical activity per day[25]; that is, how often we are exercising for a certain period of time (whereas sessions or bouts per week). Intensity refers to the level of effort perceived in order to perform an activity.[24] Intensity can be measured either absolutely (MET) or relatively (maximum heart rate and aerobic capacity).[26] Another classification of physical activity is based on aerobic exercise and resistance exercise. Aerobic exercise refers to the use of large amounts of energy, which ultimately leads to a significant increase in heart rate and improvements seen in the cardiovascular system (increase in aerobic capacity, translated into endurance performance). Resistance exercise responds to the adaptations seen in the skeletal muscle after the force generated during muscular contractions, resulting in augmented force production, power and overall strength.[27]

2.1 | Beneficial effects of physical activity

The American Heart Association’s guidelines for physical activity in 2013 recommended at least 150 minutes of moderate physical activity, 75 minutes of vigorous physical activity or a combination of both per week.[28] Similarly, the American College of Sports Medicine and the American Heart Association prescribes 5 days of moderate aerobic exercise lasting 30 minutes or 3 days of vigorous aerobic exercise for 20 minutes on a weekly basis.[29] It is also suggested to maintain or even increase the muscular strength by engaging on endurance and resistance exercise at least twice a week.

Physical activity by different interventions brings a number of health benefits (Table 1). Long-term moderate aerobic exercise, as measured by number of steps, accelerates fat oxidation in the body, improving the lipid profile.[30] In a large cohort, Rognmo et al[31] found that a unique session of short-duration aerobic exercise reduced the risk of CVD, especially

at a higher intensity. Aerobic exercise decreases arterial stiffness by increasing blood flow[32] and decreases serum triglyceride levels in obese adults.[33] Combining aerobic and resistance exercise increased aerobic capacity and fat mobilization.[34] Short-duration anaerobic exercise was effective in reducing blood pressure and heart rate, while increasing aerobic capacity; the effect was also seen in untrained individuals.[35]

Few reviews also support the beneficial effect of physical activity. Resistance exercise improves insulin sensitivity[36] and reduces muscle weakness.[37] Both aerobic and anaerobic exercise impacts CVD risks by improving the overall health markers and cardiovascular function.[38] Furthermore, in the scientific statement of the American Heart Association, resistance exercise was beneficial on muscular strength, endurance and quality of life, regardless of CVD diagnosis.[39]

2.2 | Harmful effects of physical activity

Very intense or inappropriate physical activity could lead to harmful consequences on health such as musculoskeletal injury, arrhythmia, sudden cardiac death, myocardial infarction, rhabdomyolysis or bronchoconstriction.[40] A form of intensive physical activity is the so-called overtraining syndrome, that is, a maladaptation to excessive exercise without adequate rest.[41] Overtraining syndrome may last months, including severe symptoms at the endocrine, as well as immunological, neurological and psychological levels.[42,43] Overtraining syndrome-induced impairment of the adrenal glands, for example, leads to adrenal insufficiency and damages in the hypothalamus[44] and may increase cortisol levels, resulting in muscle damage.[45] Heavy exertion produces perturbations at the immunological level, as seen in the host-pathogen defence and incremented levels of stress hormones, anti-inflammatory cytokines and reactive oxygen species.[42] Infections related to the upper respiratory tract have also been associated with overtraining syndrome, with decreased levels of secretory immunoglobulin A, responsible for the mucosal immune defence to external pathogens.[46] Similarly and as measured in T and B cell response, immune depression might follow overtraining syndrome.[45,47] The main consequence of overtraining syndrome appears to be a decrease in response of neurotransmitters, due to the fatigue deriving from overtraining.[43] Decreased reserves of glycogen within the muscle appear to be linked to both fatigue and the immune depression response.[41]

In athletes, inflammatory cytokines progressively influence the neurotransmitter function as overtraining syndrome develops under strenuous performance, as also shown in neurodegenerative diseases.[48] At the level of the central nervous system, the link between nutrition and overtraining syndrome is a matter of research.[49] Overtraining and chronic fatigue have shown to induce mood deterioration in elite athletes, causing a decrease in motivation towards training.[45] Mood changes could also depend on cardiovascular, endocrine and hormonal factors.[50] Overtraining syndrome-related psychological stressors, however, could be also dependent on the social context of the individual.[42]

3 | PHYSICAL ACTIVITY AND NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

The term “lifestyle” consists of structured physical activity and restricted caloric intake.[12] Lifestyle factors influence the onset and the natural history of chronic liver diseases[51] and unhealthy lifestyles (ie, sedentary behaviour, low physical activity and poor diet) contribute to the development and progression of NAFLD.[52] Conversely, increased physical activity was related to decreased risk of liver cancer, independently of body mass index.[53] A sedentary behaviour might act as an independent risk factor for NAFLD[54] and lower levels of physical activity are found in patients with NAFLD.[55,56] Also, reduced physical activity such as longer habitual day napping was independently associated with NAFLD.[57]

Maintenance of ideal weight or weight loss in overweight/obese patients via lifestyle interventions has become an established strategy also to prevent or treat NAFLD,[52,58,59] although the goal might be difficult to achieve in the ambulatory care setting.[60] Reducing weight by ≥10% can contribute to the nonalcoholic steatohepatitis (NASH) resolution and fibrosis improvement, while a modest weight loss >5%−7% also produces important benefits on the components of the NAFLD activity score.[9,52,61] Thus, gradual weight loss due to caloric restriction, even without increased physical activity, will lead to an improvement in serum liver enzymes, liver fat, degree of hepatic inflammation and fibrosis.[52,62] However, when comparing interventions of diet alone vs physical activity alone vs diet plus physical activity, the latter induces the greatest changes in obesity,[63,64] insulin resistance[65] and NAFLD.[62,66,67] The genetic background of patients (ie, *PNLPA3* gene polymorphism) is part of the lifestyle response in patients with NAFLD.[68,69]

Previous individual trials suggest that moderate aerobic exercises is associated with decreased serum levels of liver enzymes.[70,71] In a retrospective analysis on 813 adults with biopsy-proven NAFLD, vigorous physical exercise was more beneficial to NAFLD than physical activity in general, with reduced odds of advanced liver fibrosis, especially when exceeding minimum exercise recommendations.[72] Resistance exercise reduced insulin resistance and liver fat content,[73] with similar effects found in obese patients with NAFLD after 16 weeks of moderate aerobic exercise[74,75] and increased cardiorespiratory fitness,[76] without changing body composition. Patients with NAFLD performing aerobic or resistance exercise had a similar significant decrease in abdominal, liver and visceral fat,[77] serum liver enzymes and diastolic function.[71] Indeed, most aerobic exercise interventions reduce liver fat by a small amount, irrespective of weight loss or exercise intensity and volume.[78] In a recent randomized clinical trial (RCT) lasting 12 months, both vigorous and moderate aerobic exercise reduced intrahepatic triglyceride content in patients with NAFLD, and vigorous exercise was more effective on weight loss and blood pressure.[79]

The beneficial effects of physical activity go beyond the weight loss and involve additional pathways. There are concerns, however, regarding the low sample sizes, the insufficient power of several exercise interventions, the variable short duration and modalities of exercise interventions. Moreover, using questionnaires to recall frequency, duration and intensity of physical activity may be inaccurate.[61] This context makes the interpretation of hepatic benefits clinically difficult.

Few exhaustive reviews and meta-analyses have more precisely addressed the benefits of physical activity in NAFLD[61,80–84] (Table 2). Magkos[80] reviewed the extreme variability of results linking physical exercise and liver fat accumulation (ie, intrahepatic triglycerides). In general, habitual physical activity and cardiorespiratory fitness are inversely associated with liver fat. Although independent on age and body size, intra-abdominal obesity appears to govern the exercise-induced reduction in liver fat and visceral fat, and the effect is specific in the male sex. Both hypocaloric diet and exercise appear interchangeable and significantly reduce liver fat (≈35%−45%) acting through an even moderate (≈10%) weight loss (ie, institution of a negative energy balance). Exercise training with decreased visceral fat but without weight loss had either no effect[85,86] or decreased liver fat in obese adults,[33] obese adolescents[87] and elderly subjects.[88] Resistance (anaerobic) exercise training, at variance with evidences in few animal studies, could not affect intrahepatic fat content, at least in obese adolescents.[89]

A systematic review and meta-analysis by Keating et al[81] also pointed to the scarcity of data and poor meaningful effect in the majority of current literature. However, by focusing on 12 (out of 16 822) relevant studies (n = 439 adult participants, 11 randomized studies[33,73,85,90–97]), the authors confirm a benefit of exercise therapy (with minimal or no weight loss) on liver fat but not on serum alanine aminotransferase. The gain is achieved with exercise levels below current exercise recommendations for obesity management and, together with studies in adolescents[87] and elderly subjects,[88] suggest a lifespan effect of physical exercise per se.

Musso et al[83] in his systematic review and meta-analysis on 78 RCTs on NAFLD (n = 38 RCTs) and NASH patients (n = 40 RCTs) listed five studies assessing the effect of moderate-intensity aerobic exercise alone in NAFLD.[33,55,73,97,98] Physical exercise improved the liver steatosis assessed by magnetic resonance spectroscopy (MRS) as well as serum level of liver aspartate aminotransferase (ALT), while in the only available study liver histology was unchanged.[55]

Orci et al[84] studied 28 RCTs[33,55,74,78,85,90,91,93,94,99–111] focusing on patients with NAFLD or patients with metabolic abnormalities (with established or likely NAFLD). Interventions consisted of exercise alone vs no exercise and exercise + diet vs diet alone, looking at the effect on intrahepatic lipid content, and serum transaminases ALT and aspartate aminotransferase (AST). There was a significant exercise-induced reduction in intrahepatic lipid content assessed by MRS, computed tomography, ultrasonography, liver histology, AST and ALT, independently from dietary change. Also, individuals with increasing body mass index are more likely to benefit from the intervention, while the intensity of the intervention is less important.

Katsagoni et al[82] examined a total of 20 RCTs[71,73,74,76,77,79,103,110–122] and confirmed that aerobic and resistance exercise alone or with dietary intervention improve serum levels of liver enzymes and liver fat or histology. Again, the beneficial effects of exercise liver fat are seen even in the absence of weight loss. Continuous moderate-to-high volume moderate-intensity training is superior to continuous low-to-moderate volume moderate-intensity training or high-intensity interval training exercise protocols.

Romero-Gomez et al[61] pointed to the role of sedentary life, unstructured physical activity and structured physical activity (exercise) in NAFLD. Exercise, even without weight loss, is associated with a 20%−30% relative reduction in intrahepatic lipid, and the benefits are reached using different modalities of exercise, that is moderate- and high-intensity aerobic and resistance exercise.[81,123,124] No additional benefit on liver fat occurs by more vigorous aerobic exercise.[78,79]

While many studies have a short duration, that is 2–4 months of physical exercise,[71,73,78] recent data show that the favourable effects of continued exercise can last up to 1 year[79,125] but that benefits disappear upon exercise discontinuation.[126]

Despite lifestyle interventions are fully recommended in patients with NAFLD, cognitive and behavioural functioning might influence the ultimate outcome.[127] A recent exhaustive systematic review[128] suggests that NAFLD encompasses a cognitive-behavioural disease and confirms that lifestyle changes (ie, diet and exercise) are the most effective approaches. However, despite the intrinsic importance of exercise is understood, the confidence to exercise is poor because of fear of falling in older patients with NAFLD, an aspect which makes more difficult to engage in constant structured physical activity.[129] Also, ratings of perceived exertion (a measure to monitor and prescribe exercise intensity) in patients with NAFLD were related to a metabolic factor (fasting glucose level) and level of physical activity in adulthood.[130] Patients with NAFLD appear poorly motivated towards dietary and physical activity changes.[131] Patients with NAFLD also have disrupted levels of physical activity as daily activities of physical functioning.[132]

4 | PHYSICAL ACTIVITY AND GALLBLADDER DISEASE

Cholesterol gallstone disease is one of the most prevalent and costly digestive diseases in the USA. About 20 million Americans (10%−15% of adults in Europe and the USA) suffer from gallstones,[133,134] and the prevalence of gallstones is increasing because of the obesity epidemic.[135] Gallstones in Western countries are composed mainly of cholesterol in 75% −80% of cases and often associated with systemic metabolic abnormalities.[136] The pathogenesis of cholesterol gallstones is determined by interaction of five primary defects which include (i) lithogenic (*LITH)* genes and genetic factors, (ii) hepatic hypersecretion of cholesterol contributing to supersaturated gallbladder bile, (iii) rapid phase transitions of cholesterol in bile leading to precipitation of solid cholesterol crystals, (iv) impaired gallbladder motility with hypersecretion and accumulation of mucin gel in the gallbladder lumen and immune-mediated gallbladder inflammation, and (v) intestinal factors involving absorption of cholesterol, slow intestinal motility and altered gut microbiota.[137]

Physical activity acts as a protective agent against gallstones formation, as recently underscored by the European Association for the Study of the Liver (EASL) guidelines.[135] Physical activity is inversely related to gallstone occurrence, as found in an American Indian population,[4] but rapid weight loss results in increased gallstone formation in about 30% of the individuals.[138] Both physical inactivity and overnutrition lead to increased body mass index and hepatic cholesterol synthesis rate, acting as precursors of gallstones formation.[138] The chances of developing gallstones are associated with the degree of obesity at baseline as

well as weight loss.[139] Central obesity is linked to gastrointestinal morbidity and mortality, including gallstone disease, similar to the effect induced by tobacco smoking or aspirin intake.[140]

A list of benefits of physical activity in gallstone disease is anticipated (Table 3). Vigorous aerobic exercise (measured by history of running distance) and cardiorespiratory fitness (an independent predictor of liver fat[141]) are both inversely related to gallstone disease risk.[142] Indeed, the highest level of physical activity achieved after 5 years may be associated with a 70% decrease of suffering from symptomatic gallstones.[143] Recreational physical activity is inversely related to risk of asymptomatic gallstones in adult women.[144] Also in women, vigorous exercise is associated with a decreased rate of cholecystectomy,[145] an additional potential risk factor for NAFLD.[146] Of note, an increment of cardiorespiratory fitness by one MET reduces the odds of suffering from gallstone disease by 8% in men and 13% in women.[147] Performance of vigorous physical activity has been inversely associated with risk of gallstone disease in comparison with inactivity,[148] and regular aerobic exercise may potentially decrease the risk of gallstones formation and gallbladder cancer.[149] The intensity response seems however to be stronger for vigorous vs nonvigorous physical activity in gallbladder disease.[150]

The main mechanism behind physical activity effect in gallstone disease might be linked to the release of the upper gastrointestinal hormone cholecystokinin (CCK),[151] with a prokinetic effect.[152] Suppression of hunger has also been identified with increased levels of CCK after acute exercise (ranging from 30 to 120 minutes).[153] Similarly, smooth muscle activation enhances gallbladder emptying and refilling processes, which influence the pathogenesis of cholesterol gallstones.[154]

Conversely, excessive physical activity may have a gallbladder-related injury effect, as seen by liver transaminases and high-density lipoprotein cholesterol levels, measured 2 and 9 days after a 24 hours ultra-marathon performance in 11 athletes.[155] In mice, however, plasma cholesterol and triglyceride concentrations did not change after 12 weeks of endurance exercise. Changes in gene expression could explain the inhibition of gallstone formation by hepatic cholesterol clearance.[156] More objective measurements (accelerometers and physical activity questionnaires) are still required to come with a clear association between gallstone disease and physical activity levels.[14]

5 | PHYSICAL ACTIVITY, MICROBIOTA, BILE ACIDS AND INFLAMMATION

The effect of physical activity on the hepatobiliary tract should also consider additional factors, namely intestinal microbiota, the enterohepatic circulation of BAs acting as signalling molecules on metabolic function and with anti-inflammatory properties.

5.1 | Microbiota

A relationship occurs between intestinal digestion/absorption and physical activity-induced catabolic state.[157] Physical activity alters gut bacteria composition and diversity.[158] The relationship is mostly beneficial, but also relies on dietary patterns.[159] The effects of physical activity on microbiota are very wide, from increasing commensal bacteria to

enriching microflora diversity and to augmenting the number of microbial species.[160] The influence of physical activity on microbiota selection and richness/diversity might also be mediated by changes in expression of inter-leukin-6 and tumour necrosis factor (TNF)-α cytokines, as shown in athletes compared with control group.[161] A modality of vigorous physical activity, high-intensity interval training, improved the microbiota of obese mice, countering the changes following a high-fat diet.[162] High degree of physical conditioning, as seen in elite athletes, results in a distinctive microbiota and more metabolic and inflammatory profiles.[163] Especially in endurance athletes, mitochondrial oxidative capacity is increased as mediated by mitochondrial regulation of inflammasomes; however, the effects of overtraining on the intestinal tract results in a major production of stressors, which facilitates the entrance of pathogens.[164] In line with the previous study, the effect of long-term aerobic exercise (over 90 minutes or 60% of the individual's aerobic capacity) may disrupt the metabolic homeostasis and lead to physical stress, being more significant as exercise intensity increases. This stressful event is comparable to food deprivation or psychological stress in athletes during the precompetition periods.[165] They all lead to the triggering of the hypothalamic-pituitary-adrenal axis, and together with stress, it may change the gut microbiota composition.[166] Contrarily, moderate-to-vigorous physical activity can improve gastrointestinal symptoms (gas clearance/transit and abdominal bloating/distension), provide a feeling of relaxation as well as decrease the severity of symptoms in patients with irritable bowel syndrome.[167] Furthermore, in rugby athletes, gut microbiota was more diverse when compared to sedentary subjects.[159] This major variation on microbiota composition is positively associated with the metabolic status.[168] It has also been hypothesized that a higher training regime plus a higher intake of protein (as in many endurance athletes) may negatively influence the microbiota composition.[164] In a mouse model, an increase in the ratio of *Bacteroidetes* (Gram−)*/Firmicutes* (Gram+) phyla is proportional to an increase in running distance.[169] In mice, there is a significant relationship between myocardial infarction and gut microbiota composition after physical exercise.[170] Other studies, however, found only moderate changes to gut microbiota composition and no significant changes reported in the inflammatory profile, after a moderate aerobic exercise intervention in mice.[171] Observations, therefore, need to be translated to a more meaningful clinical setting.

5.2 | Bile acids

Primary BAs (namely cholic acid and chenodeoxycholic acid) are synthetized from cholesterol in hepatocytes, conjugated to taurine and glycine, secreted in bile and biotransformed into secondary BAs (namely deoxycholic acid and lithocholic acid), and tertiary ursodeoxycholic acid, upon contact with the resident colonic microbiota. Approximately 50% of secondary BAs are reabsorbed in the terminal ileum and colon and return to the liver via the portal vein across the enterohepatic circulation.[16] BAs contribute to digestion and absorption of fat, cholesterol and fat-soluble vitamins, but also act as signalling molecules and display antimicrobial and anti-inflammatory functions.[16]

Physical activity might ameliorate BAs circulation and their pleiotropic functions because of improved gastrointestinal motility and peristalsis, but studies show conflicting results.[172] Previous animals studies found that moderate physical activity increased bile acid excretion.

[173–175] BAs activate intestinal farnesoid X receptor (FXR) which, in turn, increases the expression of the human enterokine fibroblast growth factor 19 (FGF19) leading to activation of the hepatic FGF4 receptor/β-clotho and subsequent small heterodimer-mediated inhibition of BA synthesis.[16] Thus, one might speculate that increased intestinal motility would also increase BA flow and therefore FXR expression, with ultimate inhibition of BA synthesis. However, a recent study in mice found that physical activity indeed stimulated BA secretion and faecal output; a mechanism likely mediated by increased reverse cholesterol transport and is independent on upregulation of genes involved in BA synthesis and FXR-FGF15 (FGF19 in humans) feedback.[176] Metabolic post-transcriptional mechanisms (ie, increased fatty acid absorption) might be involved, instead. The situation might differ in humans: both faecal and serum concentrations of BAs were significantly decreased in runners,[177,178] with less mutagenic secondary BAs.[178] FXR pathways, however, were not investigated in these studies.

Bile acids also interact with the GPBAR-1 receptor in the intestine and in the liver Kupffer cells. Intestinal GPBAR-1 governs metabolically relevant hormonal pathways (ie, release of peptide YY and glucagon-like peptides GLP-1 and GLP-2) with effects on appetite, glucose and insulin metabolism via the tissue GPBAR-1 receptors located in the cells of brown adipose tissue and skeletal muscle.[16,179] Whether physical exercise will induce additional BA-mediated metabolic or anti-inflammatory effects (see below) is unclear so far, due to the poor translational value of animal studies (see above).

5.3 | Inflammation

Physical activity might also induce inflammatory effects in the body, and BAs as well as additional mechanisms might play a role. In the liver Kupffer cells, GPBAR-1 activation induced by circulating BAs might promote an anti-inflammatory effect.[180] Physical activity might partly mediate this effect.[181,182] Moreover, BA-induced activation of GPBAR-1, also expressed in other immune cells such as macrophages, monocytes and dendritic cells[183] might modulate the inflammatory changes by inhibiting the NACHT, LRR and PYD domain-containing protein 3 (NLRP3) inflammasome, with protective mechanism against lipopolysaccharide-induced inflammation and atherosclerosis.[184] Change in gut microbiota during physical exercise might also induce additional anti-inflammatory effects. Gut microbiota interacts with BAs in the enterohepatic circulation by converting primary to secondary BAs which, in turn, regulate microbiota by exerting antimicrobial effects.[185] Ursodeoxycholic acid and lithocholic acid have been recently shown to have anti-inflammatory properties by decreasing the release of proinflammatory cytokines while increasing macrophage release of anti-inflammatory cytokines.[185]

Regular physical activity also leads to increased vagal tone[186,187] and decreased expression of inflammatory markers,[187] although recent studies provide conflicting results or suggest reduction in circulatory apoptosis marker[112,188], an effect correlating with high cardiorespiratory fitness.[189] This scenario might also involve a neurohormonal mechanism with vagal-mediated gallbladder emptying before exercise.[149,190]

6 | FUTURE DIRECTIONS

The benefits of physical activity extend beyond the typical effect on risk factors for cardiovascular disease. The knowledge about the interaction between physical activity and the hepatobiliary-gut axis is gaining importance but protocols employed so far show nonstandardized approaches and wide variability (Table 4). Overall, several benefits of physical activity are anticipated in the hepatobiliary tract in conditions such as liver steatosis, gallbladder disease and also gut motility, enterohepatic recirculation of signalling BAs, intestinal microbiota and metabolic inflammatory changes. More studies are urgently required in this field to dissect the role of type, duration, intensity of exercise alone and in relation to gender, diet, weight loss and starting health status. Clinicians should not underestimate the relationship between the gut and the liver when addressing physical activity recommendations to the patients: “Just do it, keep on doing it, don’t stop it!”.[58,126]

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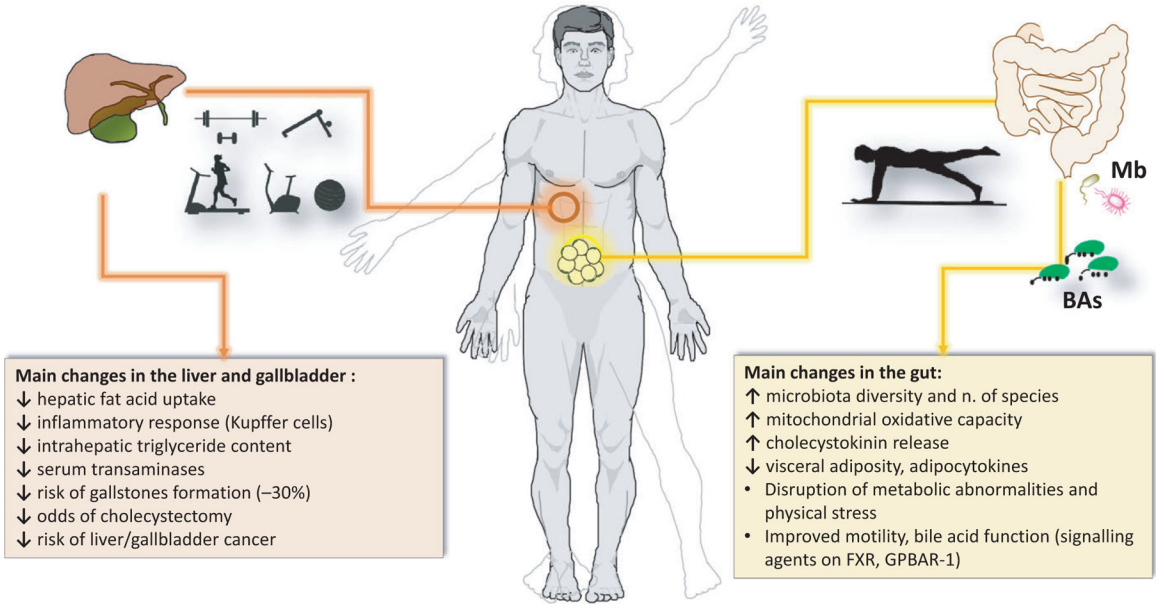

FIGURE 1.

Summary of changes observed in the liver, gallbladder and gut after physical activity. ↑, increased; ↓, decreased; BAs, bile acids; FXR, farnesoid X receptor; GPBAR-1, G protein–coupled bile acid receptor-1; Mb, microbiota

TABLE 1

Overall benefits from physical activity

Author	Study	Country	Sample size	Intervention(s)	Benefits
Sugiura et al[30]	Clinical	Japan	48F	Increasing number of steps	Reduced serum lipid levels
Rognmo et al[31]	Clinical	Norway	4846 (3392M, 1454F)	Short-duration aerobic exercise	Reduced risk of CVD
Collier et al[32]	Clinical	USA	30 (20M, 10F)	Four weeks of aerobic or resistance training	Reduced arterial stiffness
Johnson et al[33]	Clinical	Australia	23 (15M, 8F)	Four weeks of aerobic cycling exercise	Reduced serum triglyceride levels
Ho et al[34]	Clinical	Australia	97 (16M, 81F)	Combined aerobic and resistance exercise	Increased aerobic capacity and fat mobilization
Zhang et al[35]	Clinical	China	518F	Short-duration anaerobic exercise	Decreased systemic blood pressure and heart rateIncreased aerobic capacity
Braith & Stewart[36]	Review	USA	N/R	Resistance exercise	Improved insulin sensitivity
Meka et al[37]	Review	USA	N/R	Resistance exercise	Reduced muscle weakness
Patel et al[38]	Review	USA	N/R	Aerobic/anaerobic exercise	Improved health markers and cardiovascular function
Williams et al[39]	Scientific Statement (AHA)	USA	N/R	Resistance exercise	Enhanced muscular strength and endurance and quality of life

AHA, American Heart Association; CVD, cardiovascular disease; F, females; M, males; N/R, not reported.

TABLE 2

Benefits of physical activity in nonalcoholic fatty liver disease (NAFLD) according to recent reviews, systematic reviews and meta-analyses

Author	Study	Country	Sample size	Intervention	Benefits
Magkos[80]	Review	USA	-	• Habitual physical activity • Exercise training with weight loss • Exercise training without weight loss • Detraining • Resistance exercise	Variability in results. Increased cardiorespiratory fitness or reduced intra-abdominal obesity after training not necessarily accompanied by intrahepatic fat depletion[33,85–89]
Keating et al[81]	Systematic review and meta-analysis on 12 studies[33,73,85,90,97]	Australia	439 (241M, 177F, 21 N/R) Mean age 36–68 y	• Variability in recruitment: obese, overweight, NAFLD, T2D and metabolic syndrome • Aerobic exercise and/or progressive resistance straining • Comparisons: exercise vs control or exercise + diet vs dietary interventions only • 2–24 wk in duration and prescribed exercise on 2–6 d per wk. Intensities 45%−85% of VO2 peak or even less	• Reduced liver fat by MRS or ultrasound or CT with minimal (1.4–2.2 Kg) or no weight loss. • No effect of physical exercise on serum transaminase
Musso et al[83]	Systematic review and meta-analysis on 78 RCTs	Italy	38 RCTs NASH 40 RCTs NAFLD	• Post-treatment histology 41% • Glucose metabolism 71% • Assessed cardiovascular risk factors 88% • Lifestyle intervention, thiazolidinediones, metformin and antioxidants evaluated • Five RCTs assessed moderate-intensity aerobic exercise alone in NAFLD[33,55,73,97,98]	• Improved MRS-assessed steatosis and ALT levels • Histology unchanged in 1 RCT[55] • Patients with NAFLD understand the benefits of exercise but lack confidence to perform it and are afraid of falling[129]
Orci et al[84]	Meta-analysis and Metaregression on 28 RCTs[33,55,74,78,85,90,91,93,94–111]	Switzerland	Patients with NAFLD or patients with obesity, T2D or metabolic syndrome (with established or likely NAFLD)	• Exercise alone vs no exercise • Exercise + diet vs diet • Effect on intrahepatic lipid content, serum ALT and AST	• Significant reduction in intrahepatic lipid content (MRS, CT, ultrasonography and histology), AST and ALT independently from dietary change • Metaregression shows that individuals with increasing body mass index are more likely to benefit from the intervention

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Author	Study	Country	Sample size	Intervention	Benefits
					• No effect modification by variables related to the intensity of the intervention
Katsagoni et al[82]	Meta-analysis on 20 RCTs[71,73,74,76,77,79,103,110–122]	Greece	1073 exactly characterized NAFLD patients	• Aerobic and resistance exercise (volume/intensity) and/or diet (moderate-carbohydrate vs low/moderate-fat diet) vs standard care • Evaluation of liver enzymes, intrahepatic fat and liver histology, anthropometric and glucose metabolism parameters	• Decreased liver fat (MRS or ultrasound) irrespectively of weight change • Improved serum levels of liver enzymes (AST and ALT) • Improved liver histology (estimated by NAFLD activity score) • Continuous moderate-to-high volume MIT superior to continuous low-to-moderate-volume MIT or HIIT exercise protocols
Romero-Gomez et al[61]	Review	Spain	-	Discussion on role of physical activity in NAFLD • Sedentary behaviour • Physical activity • Exercise	• Exercise, without weight loss associated with a 20%−30% relative reduction in intrahepatic lipid • Different forms of exercise (aerobic and resistance) equally effective • Observed benefits upon exercising up to 12 mo but vanishing upon discontinuation • Decreased de novo lipogenesis, increased VLDL mobilization, and improved peripheral insulin sensitivity • Decreased visceral adipose tissue and lipid supply to the liver • Improved cardiovascular function

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; F, females; HIIT, high-intensity interval training; M, males; MIT, medium-intensity interval training; MRS, magnetic resonance spectroscopy; NAFLD, nonalcoholic fatty liver; NASH, nonalcoholic steatohepatitis; N/R not reported; RCT, randomized clinical trial; T2D, type 2 diabetes; VLDL, very low-density lipoprotein.

TABLE 3

Benefits of physical activity in gallbladder disease

Author	Study	Country	Sample Size	Intervention	Benefits
Williams[142]	Clinical	USA	278 (166M; 112F), mean age 39–50 y	Vigorous aerobic exercise reported by baseline cardiorespiratory fitness (see Table 4)	Decreased gallbladder risk in relation to higher cardiorespiratory fitness and speed: • Men running faster than 4.75 m/s had 83% lower risk • Women running faster than 4 m/s had 93% lower risk • Fittest men were at significantly less risk than men who ran between 3.25 and 3.75 m/s • Fittest women were at significantly less risk than women who ran between 2.8 and 4.0 m/s • Risk for GBD was significantly related to weekly running distance
Banim et al[143]	Clinical	UK	24 201 (11 133M; 13 068F), mean age 40–74 y	• Five-year register of physical activity (see Table 4) • Later classified into four categories: inactive, moderately inactive, moderately active and active	• Risk of gallstones after 5 y of follow-up was significantly lower in the most active group compared with the inactive • Decreased risk of symptomatic gallstones by 70% at the highest level of physical activity
Henao-Moran et al[144]	Clinical	Mexico	4953F, age 17–94 y	• Recreational physical activity classified by frequency, intensity and time and converted into METs • 16 items (see Table 4)	• ≥30 min/d of physical activity protects against asymptomatic gallstones development • Duration of physical activity correlates to level of protection
Talseth et al[145]	Clinical	Norway	63 249 (29 982M; 33 267F), age ≥20 y	Hard physical activity (h/wk)	≥1 h/wk of physical activity reduced risk of cholecystectomy
Li et al[147]	Clinical	USA	54 734 (41 528M; 13 206F), age 20–90 y	Cardiorespiratory fitness (see Table 4)	• Higher levels of cardiorespiratory fitness translated into progressively lower prevalence of gallbladder disease • Each MET increment associated aOR was 0.9 for all participants
Figuereido et al[148]	Clinical	USA	144 409 (64 901M; 79 508F), age 45–75 y	Vigorous physical activity (h/d)	• Vigorous physical activity was inversely associated with GBD risk compared to no activity • The highest level of vigorous activity was associated with a reduced risk of GBD
Shephard[149]	Review	Canada	N/R	General physical activity (questionnaires)	Likely decrease in gallstones formation and gallbladder cancer
Aune et al[150]	Review	UK	218 204	General physical activity	Higher levels of physical activity inversely relates to gallbladder disease

aOR, adjusted odd ratio; F, females; GBD, gallbladder disease; h/d, hours per day; M, males; MET, metabolic equivalent task; N/R, not reported.

TABLE 4

Summary of most popular physical activity protocols used in patients with hepatobiliary disease

	Duration	Frequency	Intensity	Context References
AEROBIC				
Brisk walking, jogging or rhythm aerobic	45 min/session (at least)	5x/wk (at least), minimum follow- up of 3 mo	Moderate (achieve 60%−70% of their MHR)	NAFLD[70]
Baseline cardiorespiratory fitness • Reported by baseline cardiorespiratory fitness defined as speed in metres per second (m/s) of the participant's best 10 km race	N/R	History of participants' previous 5 y	Vigorous (anaerobic event)	Gallbladder disease[142]
Brisk walking on a treadmill	30–60 min/session	5x/wk for 16 wk	45%−55% of their VO2 peak	NAFLD[74]
Psychological support to increase physical activity • Walking or cycling	3 h/wk	1x/2 wk, 3–4 mo total duration	>20 METs/wk (or 3 h/wk of moderate aerobic exercise)	NAFLD[75]
Continuous cycling on ergometer plus brisk walking at home vs stretching, self-massage and fitball programme (placebo group)	HI:LO & LO:LO: 90–135 min/wk LO:HI: 180–240 min/wk PLA: 5 min cycle	HI:LO & LO:LO: 2x/wk cycling + 1x/wk brisk walking LO:HI: 3x/wk cycling + 1x/wk brisk walking Placebo: 1x/2 wk 8 wk total duration	HI:LO: 60%−70% of their VO2 peak (from 50% to 70%) LO:HI & LO:LO: 50% of their VO2 peak PLA: 30W (cycling)	NAFLD[78]
Aerobic exercise • Treadmill, cross-trainer, bike ergometer and rower	30–45 min/session (progressively)	3–5x/wk (progressively) for 16 wk	30%−60% heart rate reserve (progressively)	NAFLD[76]
Jogging and brisk walking	V-M: 150 min/wk jogging (6 mo) + 150 min/wk brisk walking (6 mo) M: 150 min/wk brisk walking (12 mo)	5x/wk, 12 mo of duration	V-M: 65%−80% of their MHR (8–10 METs) M: 45%−55% of their MHR (120 steps/min)	NAFLD[79]
Cardiorespiratory fitness by maximal treadmill exercise (modified Balkeprotocol) • Classified by low, moderate and high based on the cut points by the Aerobics Center Longitudinal Study[191]	Minimum of 25 min	N/R	First 25 min: speed 88 m/min, with a grade of 0% (1st min), a grade of 2% 2nd min) and an increase of 1% each min thereafter. After 25 min: grade did not change, but speed increased to 5.4 m/min till the end. Participants are encouraged to do a maximal effort to reach at least 85% of their MHR.	Gallbladder disease[147]
RESISTANCE				

	Duration	Frequency	Intensity		Context References
Eight exercises • Biceps curl; calf raise; triceps press; chest press; seated hamstrings curl; shoulder press; leg extension; and lateral pull down + warm-up cycling	45–60 min/session + 10 min warm-up at the beginning and at the end		3x/wk for 8 wk	Moderate (50%−70% of their 1RM, 60% of their MHR for the warm-up)	NAFLD[73]
AEROBIC AND RESISTANCE					
Four-level physical activity index • At home, work, during recreation and flight of stairs climbed per day	N/R		Participants' previous year	N/R	Gallbladder disease[143]
19 recreational activities • Swimming, jogging, running, brisk walking, bicycling (hills/flat surfaces), hiking/climbing, aerobics, dancing, calisthenics, weightlifting, using a treadmill or step machine, golfing, singles/doubles tennis, basketball, football and soccer	Min/wk		N/R	Moderate and vigorous (METs/min/wk)	NAFLD[72]
Aerobic and resistance training combined • Treadmill, cycling or elliptical machines • Nine different exercises involving the major muscle groups on weight machines (chest press, shoulder press, vertical traction, leg press, leg extension, leg curl and abdominal crunch) and free weight (biceps and abdominal)	60 min/session and 3 series of 10 repetitions + 1 min recovery in between		3x/wk for 4 mo	60%−65% of their heart rate reserve and 70%- 80% of their 1RM	NAFLD[77]
Aerobic and resistance training combined • Cycle ergometer-based HIIT protocol • Resistance exercise-based recovery periods in between intervals	5 min warm-up + 5 intervals (2 min each) interspersed with 3 min recovery + 3 min cool-down +10s added to each interval/wk		3x/wk on nonconsecutive days for 12 wks	Warm-up: 9–13 rating of perceived exertion Intervals: 16–17 rating of perceived exertion	NAFLD[71]
16 recreational physical activity items • Walking, running, cycling, aerobics, dancing, bowling, swimming, tennis, fronton, squash, softball/baseball, soccer, volleyball, football and basketball	Hours or days/wk		Weekly time over last year	Classified by METs/h/wk	Gallbladder disease[144]
Report of hard physical activity	Less or more than 1 h/wk		Median follow-up of 0.6–16.4 y	Hard (intense)	Gallbladder disease[145]

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	Duration	Frequency	Intensity		Context References
Data on general physical activity	Hours/day using quartile distributions		Median follow-up of 10.7 y	Vigorous	Gallbladder disease[148]

1RM, one-repetition maximum; HI:LO, high-intensity low-volume aerobic exercise; LO:HI, low-to-moderate intensity high-volume aerobic exercise; LO:LO, low-to-moderate intensity low-volume aerobic exercise; M, moderate; MET, metabolic equivalent task; MHR, maximal heart rate; N/R, not reported; V-M, vigorous-moderate; VO2 peak, peak oxygen consumption.