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Therapeutic Approaches to Nonalcoholic Fatty Liver Disease: Exercise Intervention and Related Mechanisms

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Exercise training ameliorates nonalcoholic fatty liver disease (NAFLD) as well as obesity and metabolic syndrome. Although it is difficult to eliminate the effects of body weight reduction and increased energy expenditure—some pleiotropic effects of exercise training—a number of studies involving either aerobic exercise training or resistance training programs showed ameliorations in NAFLD that are independent of the improvements in obesity and insulin resistance. *In vivo* studies have identified effects of exercise training on the liver, which may help to explain the "direct" or "independent" effect of exercise training on NAFLD. Exercise training increases peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) expression, improves mitochondrial function and leads to reduced hepatic steatosis, inflammation, fibrosis, and tumor genesis. Crosstalk between the liver and adipose tissue, skeletal muscle and the microbiome is also a possible mechanism for the effect of exercise training on NAFLD. Although numerous studies have reported benefits of exercise training on NAFLD, the optimal duration and intensity of exercise for the prevention or treatment of NAFLD have not been established. Maintaining adherence of patients with NAFLD to exercise training regimes is another issue to be resolved. The use of comprehensive analytical approaches to identify biomarkers such as hepatokines that specifically reflect the effect of exercise training on liver functions might help to monitor the effect of exercise on NAFLD, and thereby improve adherence of these patients to exercise training. Exercise training is a robust approach for alleviating the pathogenesis of NAFLD, although further clinical and experimental studies are required.

Keywords: lifestyle modification, exercise protocol, training protocol, organ crosstalk, hepatokines, biomarkers

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease related to obesity and one of the manifestations of metabolic syndrome. In accordance with the worldwide pandemic of obesity, NAFLD is considered to be increasing and the global prevalence is estimated as 25.24% (1). A recent systematic review indicated that physical activity and inactivity are associated

with all-cause mortality, and high levels of moderate intensity physical activity eliminate the increased risk of death associated with prolonged sitting times (2). Moreover, a number of epidemiological studies have demonstrated a strong correlation between physical activity and non-communicable diseases including diabetes, metabolic syndrome, cardiovascular diseases and cancer (3–6). The prevalence of NAFLD is also related to physical activity. Sitting time was positively correlated with NAFLD prevalence as diagnosed by ultrasonography, independent of body mass index (BMI), in a large cross-sectional study (7). A recent longitudinal epidemiological study involving 169,347 men and women showed a strong negative correlation between habitual exercise and the development of a fatty liver diagnosed by ultrasonography (8). Therefore, exercise is thought to be a safe and economic choice as a therapeutic or preventative strategy against NAFLD. Indeed, numerous clinical trials have demonstrated the efficacy of exercise. However, the independence of any exercise effect on weight loss remains to be determined, and the molecular mechanism for the effect of exercise on ameliorating the pathogenesis of NAFLD is also not wholly understood. In this review, clinical evidence is analyzed in a systematic review manner and experimental evidence is summarized narratively to evaluate the therapeutic effects and mechanisms of exercise training on NAFLD. Note that the definition of "training" in this review is similar to "endurance exercise" and refers to "the number of exercise sessions" over weeks or months. "Exercise" refers to a single bout of exercise. "Exercise training" is used to generalize both exercise and training.

EXERCISE TRAINING EFFECT ON NAFLD IN CLINICAL TRIALS: A SYSTEMATIC REVIEW

Method

A published literature search was conducted in the PubMed, Web of Science, and Scopas databases to December 31, 2017. The following search terms were used to identify the relevant articles: non-alcoholic steatohepatitis OR non-alcoholic fatty liver OR fatty liver OR liver steatosis OR NAFLD OR NASH; exercise OR training. Two readers independently (H.T and K.T) reviewed the titles and abstracts of selected articles for the determination of inclusion as well as the full texts of selected studies. All relevant abstracts and full-text peer reviewed articles published in English were collected for analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for the conduct of meta-analyses of observational studies (http://www.prisma-statement.org/). Articles were selected if they met the following inclusion criteria. (i) Study design: randomized controlled trial, non-randomized controlled clinical trial, before and after clinical trial, or observational cohort study. (ii) Study issue: the effects of therapeutic exercise on hepatic steatosis in patients with NAFLD. (iii) Study subjects: patients with NAFLD diagnosed by liver biopsy or abdominal imaging including ultrasonography, computed tomography, and magnetic resonance (MR) imaging. Studies were excluded if they: (i) were not original research reports (systematic reviews, narrative reviews, commentaries, or editorials); (ii) were case reports or conference abstracts; (iii) did not provide sufficient data for this study; (iv) were animal studies; or (v) were in the non-English literature. Finally, 34 clinical studies were selected, and 39 exercise protocols were tested for their efficacy in ameliorating liver steatosis in cases of NAFLD [(9–36), **Supplementary Material 1**]. Spearman's rank correlation coefficient was used to test any correlations between changes in liver steatosis evaluated with ^{1}H magnetic resonance (^{1}HMR) and changes in BMI or training related-parameters. Wilcoxon's rank sum test was used to compare protocols with and without dietary consultation.

RESULTS AND DISCUSSION

Clinical Question 1. Is the Exercise Training Effect on NAFLD Independent of Body Weight Reduction?

Exercise training is routinely recommended for the treatment and management of NAFLD (37, 38). Following the development of imaging modalities to evaluate liver steatosis such as ^{1}HMR, conventional B-mode ultrasonography, and controlled attenuation parameters based on transient elastography, liver steatosis has been used as an endpoint of exercise training in many clinical studies. On the basis of findings from the studies of exercise training and other lifestyle modifications, Hannah et al. concluded that a 3% or more body weight reduction with lifestyle modifications ameliorates liver steatosis (39). Indeed, of the 39 exercise training protocols we reviewed, four ineffective ones were found, of which three were without significant body weight reduction and all were without dietary consultation (**Supplementary Material 2**). In this context, the question is raised of whether the effect of exercise on liver steatosis is independent of nutritional control and body weight reduction in NAFLD. In their systematic review, Hashida et al. suggested that reduction of liver steatosis by aerobic training was observed without a clinically significant weight loss, suggesting that exercise alone might independently reduce hepatic steatosis (40). Of the 39 protocols we reviewed, 22 evaluated changes in liver steatosis (%) using ^{1}HMR and assessed their correlations with changes in BMI (**Figure 1A**). Although our results showed a significant positive correlation between changes in liver fat and changes in BMI ($\rho = 0.63$, $p = 0.004$), several studies reported an improvement in hepatic steatosis without BMI reduction. Moreover, there was no significant difference in changes in hepatic steatosis between protocols with and without diet consultation (**Figure 1B**). These findings suggest that exercise *per se* might independently ameliorate hepatic steatosis.

Clinical Question 2. What Is the Optimal Type and Dose of Exercise for NAFLD Therapy?

Aerobic training protocols, resistance training protocols and combined protocols are all effective on ameliorating hepatic steatosis in patients with NAFLD. For aerobic training, walking,

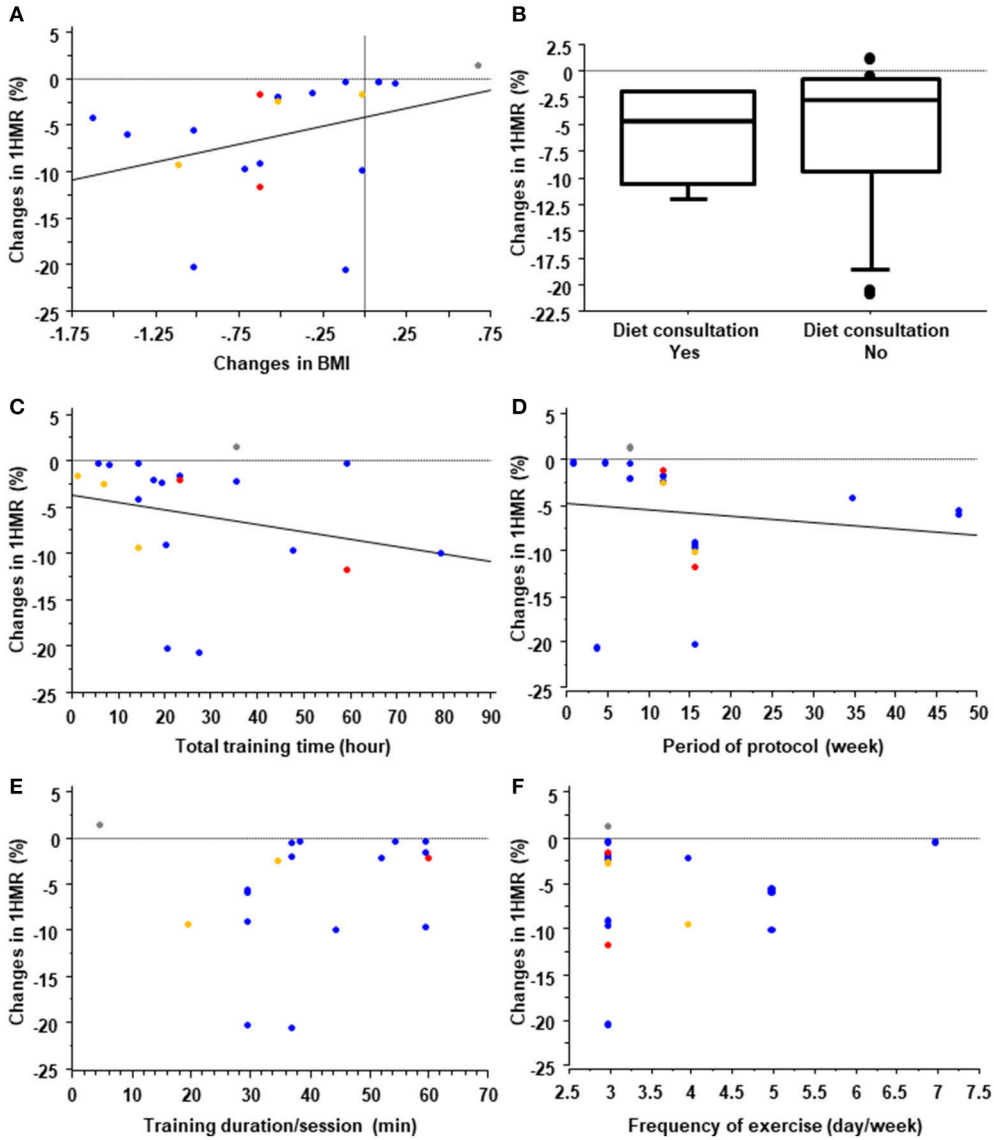

FIGURE 1 | Systematic review of training protocols. Effect of changes in body mass index (BMI) **(A)** and diet consultation **(B)** on liver steatosis measured by ^{1}H magnetic resonance (^{1}HMR) imaging in exercise training programs for treating patients with nonalcoholic fatty liver disease (NAFLD). In **(A)**, the blue, red, yellow, and gray dots represent training protocols with aerobic, resistance, aerobic plus resistance, and stretching exercises, respectively. Effects of the total training time **(C)**, protocol period **(D)**, training duration/session **(E)**, and frequency of training **(F)** on liver steatosis measured by 1HMR imaging in exercise training programs for subjects with NAFLD. Blue, red and yellow dots represent protocols with aerobic, resistance and combined exercise training, respectively.

jogging with or without a treadmill and ergometer exercise were generally performed. In the protocols of resistance training, major muscles were generally trained using the biceps curl, calf raise, triceps press, chest press, seated hamstrings curl, shoulder press, leg extension, and other exercises. A recent systematic review confirmed that there are no significant differences between aerobic training and resistance training in the extent to which they decrease liver steatosis, as measured by ^{1}HMR (40). That review also indicated that the median effective aerobic exercise protocol was 4.8 metabolic equivalents for 40 min/session, 3 times/week for 12 weeks, and the median effective resistance training protocol was 3.5 metabolic equivalents for 45 min/session, 3 times/week for 12 weeks. However, the optimal doses and intensity of exercise training remain unclear. In this context, the EASL-EASD-EASO Clinical Practice Guidelines recommend "moderate exercise" for "150–200 minutes/week" that includes aerobic and resistance exercise (38). In our systematic review, we found no significant differences in the duration of sessions, frequency, protocol period, or total training time between effective and ineffective protocols for liver steatosis (**Supplementary Material 3**); however, there was a significant negative correlation between changes in liver steatosis measured

with ^{1}HMR and total training time (**Figure 1C**; $\rho = -0.38$, $p = 0.049$) and duration of the exercise protocol (**Figure 1D**; $\rho = -0.59$, $p = 0.007$), and no significant correlation between changes in liver steatosis and the duration of each session (**Figure 1E**; $\rho = 0.24$, $p = 0.351$) or frequency/week (**Figure 1F**; $\rho = 0.06$, $p = 0.80$). This suggests that at least total exercise duration and amount might be important for ameliorating liver steatosis. It is well known that adherence to lifestyle modifications including exercise decreases over time (41). Therefore, keeping the patients motivated for as long as possible and maintaining adherence to protocols is key to the success of exercise therapy for those with NAFLD.

MECHANISMS BY WHICH EXERCISE IMPROVES NAFLD; A NARRATIVE REVIEW

Increasing energy expenditure in exercise sessions promotes glucose and lipid metabolism and ameliorates obesity and NAFLD. Based on clinical studies, experimental research has focused on the effect of exercise and training on liver functions, independent of body weight reduction. Numerous studies have demonstrated that exercise and training have a beneficial effect on liver function. In this section, classical and novel exercise training effects on liver function and NAFLD are summarized.

Classical Effects of Training on Liver Metabolism

A number of studies have analyzed the effect of exercise training on liver functions (**Figure 2**). These began with an analysis of lipid metabolism in the 1970s (42). Thus, training reduced plasma and liver triglycerides in obese Zucker rats and high fat diet-fed rats (42, 43). The Otsuka Long-Evans Tokushima Fatty rat model was well analyzed in terms of its response to exercise training. Decreases in the lipogenic proteins fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC) with relative increases in the deactivation of ACC by phosphorylation were observed (44–47). Training also increased mitochondrial content markers and oxidation in the liver (44–48), which activates adenosine monophosphate-activated protein kinase (AMPK) and decreases lipogenic processes with a complementary increase in lipid oxidation.

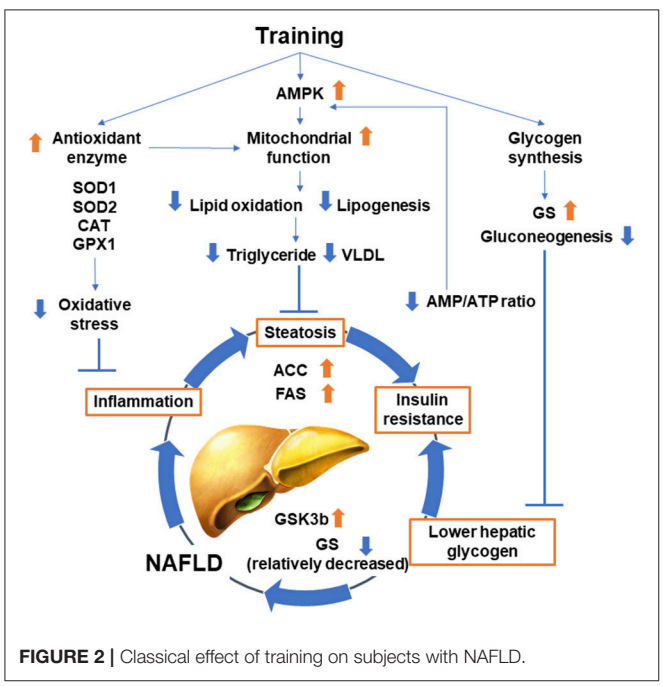

FIGURE 2 | Classical effect of training on subjects with NAFLD.

The liver supplies energy substrates to peripheral tissues by glycogen catabolism; therefore, the effect of training on glycogen metabolism has also been studied. Training reduces gluconeogenesis and has a glycogen-sparing effect on the liver to maintain glucose homeostasis during exercise (49, 50). Hepatic glycogen is reduced in subjects with obesity and diabetes by activating hepatic glycogen synthase kinase 3β, which suppresses glycogen synthase (51). Moreover, the increased synthesis of liver glycogen improved the metabolic phenotype of high fat diet-fed mice (52). Taken together, increasing hepatic glycogen might be one of the mechanisms by which training ameliorates hepatic insulin resistance and NAFLD. Increased glycogen contributes to a decrease in the AMP/ATP ratio, which activates AMPK (53, 54). Correlation between glycogen synthesis in skeletal muscle and hepatic *de novo* lipogenesis was also reported. It is well established that exercise increases glycogen synthesis in skeletal muscle, and insulin resistance in skeletal muscle reduces glycogen synthesis because of defects in insulin-stimulated glucose transport activity in skeletal muscle (55, 56). Rabøl et al. demonstrated that a single bout of exercise improved postprandial skeletal muscle glycogen synthesis concomitant with decreased postprandial *de novo* lipogenesis and hepatic triglyceride synthesis in young, lean, insulin-resistant individuals (56). Their finding suggests that improvements in insulin resistance and increased glycogen synthesis in skeletal muscle induced by exercise training or pharmacological therapy can be a therapeutic strategy for patients with NAFLD.

While training decreases hepatic gluconeogenesis, it is well known that the hepatic capacity for gluconeogenesis, as well as the lactate transport capacity and oxidative capacity, are increased by training (57). Training also increases antioxidant enzymes including superoxide dismutase-1 (SOD1) and SOD2, catalase (CAT) and glutathione peroxidase in the liver, and oxidative damage is reduced (58–60). This antioxidant effect is a possible mechanism for the effect of training on NAFLD, which is characterized by hepatic steatosis, inflammation, and oxidative damage (61). In the metabolism of amino acids, training reduced the hepatic catabolism of branched-chain amino acids in rats with streptozotocin-induced diabetes (62).

Organ Crosstalk and Novel Mechanisms of the Effect of Training on Liver Functions

Training affects multiple organs in addition to skeletal muscle. Many studies have identified organ crosstalk involving the liver, which is a possible mechanism for NAFLD amelioration. In terms of the direction of organ crosstalk involving the liver, the training effect can be categorized as liver to other organs or other organs

to liver. Recently, the term "hepatokine" has been proposed to describe the proteins secreted from hepatocytes (63, 64). Because the liver is one of the major endocrine organs, hormonal crosstalk involving growth factors from the liver to other organs has already been studied in the context of the training effect (**Table 1**, **Figure 3**). Proteins secreted from adipose tissue known as adipokines and those from skeletal muscle known as myokines are also putative factors in the effect of exercise training on ameliorating NAFLD. Secreted proteins induced by exercise training can be used as a "training biomarker" of NAFLD.

Exercise Training-Induced Protein Secretion From Liver: Hepatokines

Insulin-like growth factor (IGF)-1 is released from the liver in response to hypothalamic hormones. In humans, the serum IGF-1 concentration is lower in patients with diabetes and NAFLD than in healthy subjects (65, 66). Moreover, serum IGF-1 concentrations correlated negatively with the severity of liver fibrosis in patients with NAFLD (67). Zanconato identified that *Igf-1* mRNA expression was enhanced by resistance training in rats (68). In alloxan-induced diabetic rats, serum and hepatic IGF-1 concentrations were reduced compared with those of control rats but recovered to control levels after 8 weeks-of swimming training (69). Training also increased serum IGF-1 concentrations in humans (70). IGF-I stimulates insulin-like actions *in vitro*, including glucose transport, glucose oxidation and translocation of the glucose transporter GLUT-4 to the plasma membrane (71). Skeletal muscle is particularly sensitive to IGF-1 reactions that decrease blood glucose concentrations (65). In addition, a deficiency of IGF-1 *in vivo* results in increased concentrations of growth hormone (GH). These high GH concentrations lead to anti-insulin effects in both liver and adipose tissues, which increase insulin resistance (72). IGF-1 plays an important role in exercise training and increasing IGF-1 levels mediate a lowering of the GH concentration in terms of skeletal muscle growth and repair (73). It mediates protein kinase B activation and concomitantly promotes protein synthesis and inhibits protein degradation (74). It also modulates muscle growth, promoting muscle cell activation, differentiation and hypertrophy (75–77). Moreover, skeletal muscle mass has been linked to the pathogenesis of NAFLD; thus, sarcopenia was an independent risk factor for nonalcoholic steatohepatitis (NASH; nonalcoholic steatohepatitis) and NAFLD with severe fibrosis (78, 79). Taken together, increased or sustained IGF-1 concentrations in the blood and liver are putative factors in the effect of exercise training on ameliorating NAFLD.

Adropin consists of 76 amino acids and has been linked to metabolic homeostasis, cardiovascular function and endothelial cell function (80, 81). It is expressed in multiple tissues, including the brain, heart, kidney, liver, pancreas, skeletal muscle, and small intestine (82, 83). Kumar et al. suggested that adropin is an hepatokine that is decreased in diet-induced obese mice and showed that transgenic overexpression or systemic adropin treatment attenuated steatosis by suppressing the expression of *Fas* and the gene for Stearoyl-CoA desaturase-1 (*Scd1*) (80). Aerobic training increased serum adropin levels in humans, and this was associated with reduced arterial stiffness (84) and improvements in endothelial function (85).

Angiopoietin-like protein 4 (ANGPTL4) is secreted from multiple tissues including the liver (86) and is considered to be an exercise-induced hepatokine (87). ANGPTL4 has been associated with lipid homeostasis (86, 88), but its effect on glucose metabolism remains equivocal (89, 90). ANGPTL4 was found to stimulate lipolysis (91) and to inhibit the clearance of triglycerides from plasma by inhibiting lipoprotein lipase (92, 93). ANGPTL4 overexpression in either normal chow diet-fed mice or high fat diet-fed mice reduced the weight of adipose tissue but increased liver steatosis and elevated plasma triglycerides, free fatty acids, glycerol, total cholesterol and high-density lipoprotein cholesterol (89, 90). Therefore, the effect of ANGPTL4 on NAFLD can be explained as being both positive and negative: increasing liver steatosis and decreasing adiposity. Plasma ANGPTL4 concentration was increased by a single bout of acute exercise but not by chronic exercise or training in humans (87, 88, 94). Increased *Angptl4* mRNA expression in liver was also recognized in mice after treadmill exercise (95). During exercise, ANGPTL4 levels are positively regulated by free fatty acids, glucagon and cAMP, and negatively regulated by AMPK (87, 88). ANGPTL4 is also related to the microbiome; thus, conventionalization of germ-free mice suppressed ANGPTL4 expression in gut epithelial cells (96). Further research is required to elucidate the link between ANGPTL4 and the microbiome in cases of NAFLD.

Circulating sex hormone-binding globulin (SHBG) secreted from the liver regulates the biological action and signaling of sex hormones (97). The relationship between these hormones and glucose homeostasis is complicated. For example, testosterone levels correlate positively with insulin resistance, glucose intolerance and an increased risk of type 2 diabetes in women, whereas the opposite appears to be true in men. Conversely, high estradiol levels are associated with elevated insulin resistance and increased risk of type 2 diabetes in both genders (98, 99). The relationship between SHBG and glucose metabolism is more consistent than that between the sex hormones and glucose metabolism across the genders. Circulating SHBG concentrations correlate positively with insulin sensitivity in humans, suggesting that circulating SHBG might prevent the development of type 2 diabetes (100). In a cross-sectional study that measured plasma SHBG in 233 dysmetabolic men, there was a significant correlation between plasma SHBG concentration and intrahepatic fat measured by ultrasonography (101). In addition, circulating SHBG increased with lifestyle modifications including diet control and aerobic exercise, and the response to increasing SHBG correlated more strongly with decreasing liver steatosis than with visceral adiposity (100). According to *in vitro* experiments, adiponectin positively regulates SHBG production in hepatocytes through the transcription factor hepatocyte nuclear factor 4α (102). SHBG also suppresses proinflammatory cytokines including interleukin (IL)-1β (103) and tumor necrosis factor-alpha (TNF-α) (104), reactions that are mediated by hepatocyte nuclear factor 4α. Changes in SHBG after training have been analyzed, with some reporting an increase in circulating SHBG concentrations (105, 106). Daily walking for 3

TABLE 1 | Hepatokines and exercise training.

Hepatokine	Effect on metabolism and NAFLD	Secretion in NAFLD and obesity	Changes of secretion or blood concentration by exercise training			
			Experimental model		Clinical study	
			Significance	Protocol (ref)	Significance	Protocols (ref)
Adropin	Positive	Decreased	–	–	Increase (plasma)	**Ergometer** 55 min, 3 days/weeks , 8 weeks (D42). **Aerobic training** 90 min, 3-5 days/weeks. 12 weeks (D43)
ANGPTL4	Negative/ positive	Decreased	Increase (liver mRNA)	**Treadmill** 60 min, single bout (D55)	Increase (plasma)	**One-legged cycling** 60-180 min, single bout (D 45) **Endurance exercise** 120 min, single bout (D54) **Knee-extensor exercise** 120 min, single bout (D44)
SHBG	Positive	Decreased	–	–	Mostly Increase (serum)	**Walking** 30-45 min, daily, 3 weeks s with diet therapy (D64) **Line dance** 60 min, 3 days/weeks, 16 weeks (D65)
Fetuin A	Negative	Increased	Increase up to normal level (serum)	**Treadmill** 60 min, 5 days/weeks, 16 (D80)	Decrease (serum, plasma)	**Ergometer** 60 min, 5 days/weeks, 12 weeks (D75, D76) **Walking** 60 min, daily, 1 weeks (D77)
FGF21	Positive	Increased	Increase in acute exercise (serum and liver mRNA)	**Treadmill** 30 min, single bout (E12) ***Running wheel** 8 weeks (E13)	Increase (plasma)	**Treadmill running** 60 min, single bout (D79) **Treadmill running** 30 min, single bout (E12)
Hepassocin	Negative	Increased	–	–	–	–
LECT2	Negative	Increased	–	–	No change (plasma)	**Treadmill running** 60 min, single bout (D79)
RBP4	Negative	Increased	Probably decrease	**Treadmill** 60 min, 5 days/weeks, 10 weeks (D99)	Decrease (serum, plasma)	**Resistance training** 5 days/weeks, 12 weeks (D98) **Stepping training** 60 min, 3 days/weeks, 10 weeks (D100)
Selenoprotein P	Negative	Increased	No change (plasma and liver mRNA)	**Treadmill** 30 min, 6 days/weeks, 1 weeks (F3) **Treadmill** 30 min, 5 days/weeks, 4 weeks (F3)	No change (plasma)	**Treadmill running** 60 min, single bout (D79) **Military training** 360 min, 5 days/weeks, 12 weeks (F2) **Cycling and walking** 30-45 min, 3 days/weeks, 8 weeks (F3)

**non-significant protocol.*

weeks combined with dietary therapy increased serum SHBG by 38% in obese men (105). Aerobic exercise training for 16 weeks increased serum SHBG by 6% in obese postmenopausal women (106). However, a single bout of running exercise for 45 min in healthy, physically active men showed only a nonsignificant tendency for increased serum SHBG (107).

Alpha-2-HS-glycoprotein, also known as fetuin-A, shows diverse functions including osteogenesis and bone resorption, and regulation of the insulin and hepatocyte growth factor receptors and responses to systemic inflammation (64, 108). Fetuin-A is predominantly secreted by the liver (109) and inhibits the insulin receptor tyrosine kinase in liver and skeletal muscle (110, 111). Mice with deletion of the *Ahsg* gene, encoding fetuin-A, showed improved insulin signaling (112). Fetuin-A is also an adaptor protein for saturated fatty acids, allowing them to activate Toll-like receptor 4 and increase insulin resistance (113). A clinical study confirmed a positive correlation between circulating fetuin-A concentrations and insulin resistance (114). Exercise training including aerobic exercise using an ergometer or walking generally reduces (115–117) or tends to reduce (118, 119) circulating fetuin-A in subjects with type 2 diabetes and NAFLD. Improvements in hepatic insulin resistance correlated with decreasing levels of blood fetuin-A (116). Sedentary and cholesterol diet-fed mice with low-density lipoprotein receptor deficiency showed a lower serum fetuin-A concentration than sedentary control mice fed a normal chow diet, but treadmill

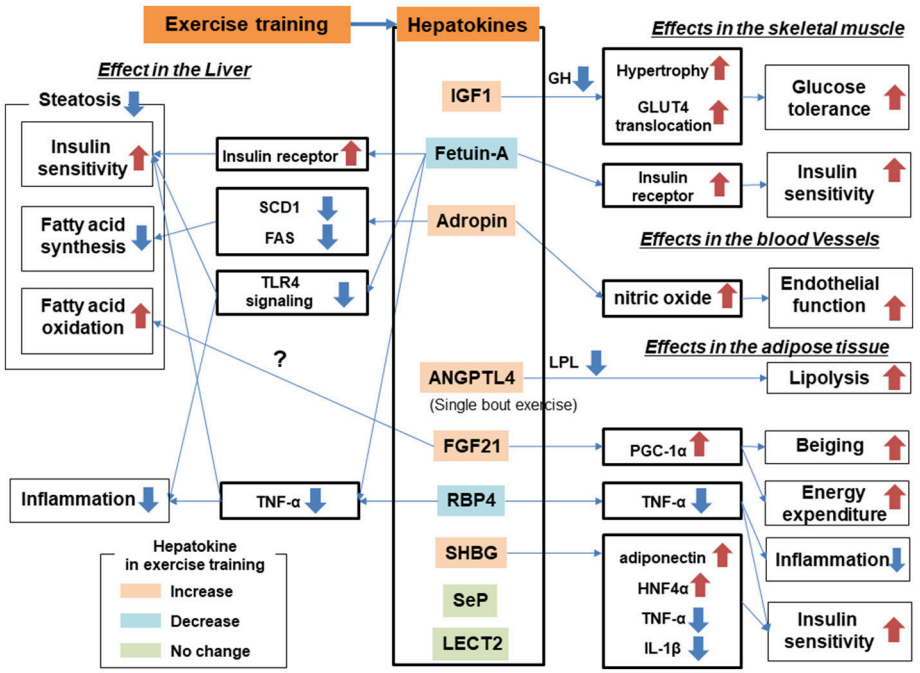

FIGURE 3 | Hepatokines and organ crosstalk in exercise training for subjects with nonalcoholic fatty liver disease (NAFLD).

running (60 min/day, 5 days/week) for 16 weeks negated the dietary effect of cholesterol by increasing the serum fetuin-A concentration to the level of control mice (120). According to those findings, training generally reduces the increased circulating fetuin-A in obesity but increases fetuin-A in the case of low-density lipoprotein receptor deficiency. Fetuin-B, also considered to be a hepatokine, has been shown to impair glucose tolerance and is associated with hepatic steatosis in mice (121). Further research is required to elucidate the effect of exercise training on the regulation of fetuin-B.

Hepassocin is important for the regeneration and proliferation of hepatocytes, acting through extracellular signal-regulated kinase 1/2 (122–124). It appears to be a hepatokine (125) and is related to glucose intolerance and insulin resistance. Hepassocin levels are increased in human subjects with prediabetes, type 2 diabetes, and NAFLD (126, 127). Administration of recombinant hepassocin increased NAFLD activity including steatosis and induced insulin resistance in both liver and skeletal muscle tissues (126). To date, there have been no reports analyzing the effect of exercise training on hepassocin expression or secretion.

Leukocyte cell-derived chemotaxin 2 (LECT2) was originally identified as a neutrophil chemotactic protein (127) and is considered to be a hepatokine (128, 129). It impairs insulin signaling and increased c-jun *N*-terminal kinase signaling, suggesting that LECT2 has a pro-inflammatory role (130). Indeed, deletion of *Lect2* in mice improved high fat diet-induced insulin resistance with decreased c-jun N-terminal kinase signaling in skeletal muscle (130). In humans, serum LECT2 concentrations correlated positively with insulin resistance (130). Changes in circulating LECT2 or secretion of LECT2 from liver during exercise training have not been well-studied. A single bout of exercise on a moderate-intensity treadmill for 1 h failed to increase the serum LECT2 concentration in humans (119).

Although serum fibroblast growth factor 21 (FGF21) is predominantly secreted from the liver, it has also been found in the pancreas, testis, duodenum and adipose tissue. Administration of FGF21 improved the metabolic phenotype and reduced hepatic triglyceride levels in high fat diet-fed mice, diabetic monkeys, and humans with diabetes (131, 132). Hepatocytes are a main source of FGF21; thus, FGF21 is considered to be a hepatokine. Fletcher et al. tested the effect of FGF21 on exercise-induced hepatic mitochondrial adaptations in FGF21 knockout mice (133). FGF21 gene knockout mice showed 30–50% lower hepatic mitochondrial complete palmitate oxidation, β-hydroxyacyl-CoA dehydrogenase activity, and nuclear content of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) in the sedentary condition; however, the effect of exercise on these markers was minimal. Although the direct effect of FGF21 on liver is still controversial because of the lack of an FGF receptor 1 in hepatocytes, NAFLD might be alleviated through the effect of training on adipose tissues: namely, the development of brown fat-like cells in white adipose tissue (the "beiging" phenomenon) and increased levels of adiponectin (134, 135). A single bout of exercise increased circulating FGF21 levels in mice and humans and FGF21 mRNA expression in the liver of mice (119, 136), whereas wheel running failed to increase FGF21 mRNA and protein expression in the livers of mice (137). This suggests that acute rather than chronic

exercise or training contributes to increasing hepatic FGF21 production.

Retinol-binding protein 4 (RBP4) is secreted from hepatocytes and adipocytes and is considered to be both a hepatokine and an adipokine (138). It was originally identified as a transport protein for vitamin A (139), and its expression is linked to obesity, metabolic syndrome, and insulin resistance. Serum RBP4 concentration correlated positively with the magnitude of insulin resistance in subjects with obesity or diabetes (140). Elevated serum RBP4 levels were also associated with components of the metabolic syndrome (140). Transgenic overexpression of human RBP4 or injection of recombinant RBP4 in normal mice caused insulin resistance (138), whereas deletion of RBP4 enhanced insulin sensitivity (138, 141). Improvement of metabolic syndrome with diet therapy and bariatric surgery decreased serum RBP4 concentrations (142, 143). Exercise training also reduced circulating RBP4 levels and resistance training decreased circulating RBP4 in people with type 2 diabetes (144). Training with aerobic exercise for 10 weeks also decreased the circulating RBP4 levels in healthy women (145), whereas a single bout of resistance exercise failed to decrease the RPB4 concentration (146). In spontaneously hypertensive rats with insulin resistance, treadmill running reduced circulating RBP4 concentrations (147). Circulating RBP4 decreased in streptozotocin-induced diabetic rats (148). Interestingly, RBP4 mRNA expression decreased in visceral fat tissue but not in the liver, suggesting that adipocytes are predominant in the response of circulating RBP4 levels to training.

Selenoprotein P (SeP) is a liver-derived secretory protein, and a significant positive correlation in humans between SeP mRNA expression and insulin resistance was identified using serial analysis of gene expression and DNA chip methods (149). SeP-deficient mice showed more endurance capacity after training through upregulation of reactive oxygen species and AMPK (150); however, there was no change in SeP secretion with exercise training in rodents (150) or humans (119, 151), suggesting that inhibition of SeP is an exercise-enhancer rather than an exercise mimicker.

Effects of Training Through Adipokines and Myokines on the Liver and NAFLD

Regular physical activity and exercise training have long been known to cause adaptations to white adipose tissue, including decreases in cell size and lipid content and increases in mitochondrial proteins (152). Exercise training also alters adipokine secretion. According to a recent systematic review including 1774 obese subjects, exercise training significantly reduced serum leptin and increased adiponectin concentrations (153). Leptin regulates appetite through an afferent signal, and acute intravenous or intracerebroventricular administrations of leptin increased glucose turnover and glucose uptake independently of the blood insulin and glucose levels (154). Leptin treatment improved insulin resistance and diabetes in mice with congenital lipodystrophy (155). In general, serum leptin levels correlated positively with adiposity and hyperleptinemia and leptin resistance were observed in obese subjects (156, 157). In the liver, leptin directly promotes fibrogenesis. Leptin induced transforming growth factor β (TGF-β) in hepatic stellate cells through indirect effects on Küpffer cells in an animal model (158). Therefore, reducing circulating leptin levels by exercise training might contribute to ameliorating liver fibrosis in subjects with NAFLD. On the other hand, no association between circulating leptin levels and the severity of liver fibrosis has been confirmed in human (159). Adiponectin is secreted from adipose tissues and is abundant in serum (160). Adiponectin negatively correlates with serum triglyceride and with apolipoprotein B (ApoB) levels, which is a triglyceride-rich very-low-density lipoprotein (VLDL) (161, 162). In hepatocytes, adiponectin reduced triglyceride and ApoB levels and served to reduce VLDL secretion from the liver (163). Numerous studies have revealed the beneficial effect of adiponectin on the pathogenesis of NAFLD (164). Adiponectin administration suppressed the expression of sterol regulatory element-binding protein (SREBP) 1c in the liver of leptin-receptor deficient (db/db) mice as well as in cultured hepatocytes (165). Choline and L-amino acid-deficient diet fed-mice showed more severe hepatic steatosis in adiponectin-deficient mice than in wild type mice (166). In db/db mice and high fat diet-fed mice, reduced adiponectin signaling genes and protein expression including adiponectin receptor levels were linked with the severe hepatic phenotype of NASH, reduced mitochondrial biogenesis markers and reduced AMPK signaling (167). Peroxisome proliferator-activated receptor alpha (PPARα) is a key regulator of lipid metabolism and associates with fatty acid oxidation in the liver. In human subjects with NASH, hepatic expression of the gene encoding PPARα was correlated positively with serum adiponectin levels (168). Serum adiponectin levels were negatively correlated with hepatic steatosis in such subjects (169). Adiponectin has demonstrated beneficial effects against hepatic inflammation and fibrosis. In several mouse models of immune-mediated hepatitis, adiponectin reduced TNF levels and induced IL-10 release from Küpffer cells (170). Lower nuclear factor kappa B (NFκB) levels were also reported (171, 172). Adiponectin receptor 2 (AdipoR2)-deficient mice fed a methionine-choline deficient diet showed higher levels of steatosis, inflammation and fibrosis (173). Moreover, overexpression of AdipoR2 inhibited TGF-β signaling and stimulation of PPARα activity (173). Adiponectin reduced the proliferation of human stellate cells and lowered the levels of alpha smooth muscle actin induced in activated hepatic stellate cells (174). Adiponectin also inhibited leptin-induced STAT3 phosphorylation in activated hepatic stellate cells and leptin-mediated upregulation of tissue inhibitor of metalloproteinase 1 (TIMP-1) release both *in vitro* and *in vivo* (175). These studies suggest that adiponectin ameliorates hepatic steatosis, inflammation and fibrosis in NAFLD through multiple mechanisms and increased adiponectin levels by exercise training is one potential explanation for the benefit of exercise training on NAFLD.

Perilipin 5 (PLIN5) is a lipid droplet-associated protein that is highly expressed in oxidative tissue. In high fat diet-fed mice trained on a treadmill, mice with muscle-specific PLIN5 overexpression showed decreased liver fat and mRNA expression of genes encoding proinflammatory cytokines (176). In these

mice, the increase in serum FGF21 was double that of the control mice, suggesting that increased PLIN5 expression might mediate an increase in the levels of circulating FGF21 after training.

IL-6 is released from contracting muscle, and was first identified as a myokine (177, 178). In skeletal muscle, IL-6 increases glucose uptake and fatty acid oxidation through activation of AMPK and/or phosphatidylinositol-3-kinase (PI3-kinase) pathways (179). Circulating IL-6 released from skeletal muscle directly affects whole body metabolism in distant organs. In adipose tissues, IL-6 induces lipolysis and increases fatty acid oxidation through activation of AMPK (180). IL-6 also increases the proliferation of pancreatic β cells and increases glucose-stimulated insulin secretion from them (181, 182). In the liver, muscle-derived IL-6 enhances hepatic glucose production during exercise (183) and has been reported to upregulate the expressions of gluconeogenic genes directly leading to increased hepatic glucose production (183, 184). These action of IL-6 in the liver might contribute to maintain glucose homeostasis during exercise. Indeed, circulating IL-6 levels negatively correlates with those of plasma glucose during exercise in humans (185), suggesting that IL-6 might be a sensor of carbohydrate availability (186). L-6 infusion reduced hepatic steatosis and ischemia/reperfusion injury and promoted the proliferation of hepatocytes in rodent models (187–190). As well as skeletal muscle and adipose tissue, these effects in the liver were linked with an increase in mitochondrial fatty acid oxidation. IL-6 also affected PPARα levels in the liver (188), mediated the levels of fatty acid binding protein and positively regulated PPARα production in the liver (191). PPARα was shown to upregulate the expression of genes including those involved in fatty acid transport and mitochondrial fatty acid oxidation (192). These experimental studies suggest that IL-6 might be involved in the way exercise training alleviates NAFLD. In addition, findings from IL-6-deficient mice, which develop mature-onset obesity, demonstrated a suppressive effect of IL-6 on the development of obesity (191). On the other hand, it is well known that IL-6 is an inflammatory cytokine and serum IL-6 concentrations are generally increased in subjects showing obesity, diabetes and NAFLD (193, 194). TNF-α upregulates obesity-induced IL-6 production and causes hepatic inflammation through activation of extracellular signal-regulated kinase (ERK) and signal transducers and activator of transcription 3 (Stat3) signaling (195). IL-6-deficient mice gained body weight slower than wild type mice under high fat diet-fed-conditions (196). Moreover, IL-6-deficient mice showed less severe steatosis and inflammation in the liver (195). In a clinical study including subjects with NASH, IL-6 was decreased significantly in those subjects who received either aerobic exercise training or resistance exercise training (197). Taken together, there are discrepancies among studies in terms of the effects of IL-6 on obesity and NAFLD, and further research is required to clarify the effects of IL-6 on NAFLD as a myokine and as an inflammatory cytokine.

Irisin is a 112 amino acid proteolytically cleaved form of fibronectin type III domain-containing protein 5 that has been identified as a training-induced secretion factor (135). Irisin is secreted from muscles during or after exercise and induces beiging of white adipose tissue by activating PGC1α, resulting in an improvement in glucose and lipid metabolism in multiple organs (133, 198). The effect of irisin on liver has also been investigated. Recombinant irisin protein significantly inhibited the increase in the palmitic acid-induced lipogenic markers ACC and FAS and prevented palmitic acid-induced lipid accumulation in primary hepatocytes (199). The researchers also identified an anti-inflammatory effect of irisin with reductions in inflammatory mediators including TNF-α, IL-6 and NF-κB, which might be mediated by protein arginine methyltransferase 3, an enzyme actively participating in the hepatic lipogenesis pathway. Serum irisin concentrations were increased in human subjects with NAFLD (200), and this was considered to be a protective compensatory response. Irisin also acts against oxidative stress and serum irisin concentration correlates with hepatic and muscle malondialdehyde levels (201, 202). As for its anti-inflammatory effect, the antioxidative effect of irisin mediates the inhibition of protein arginine methyltransferase 3 (199).

Other Mechanisms of the Effects of Exercise Training on the Liver

MicroRNAs (miRNAs) are small untranslated RNA transcripts frequently expressed under the control of nuclear receptors. They are involved in multiple cellular pathways including metabolism. The association between exercise training and miRNAs has been studied. Thus, a comparative analysis of livers from mice subjected to exercise training showed significant changes in miRNAs (203). It was reported that miR-33 positively regulated hepatic fatty acid oxidation and insulin signaling and reduces lipogenesis (204). In high fat diet-fed mice, the expression of hepatic miR-33 was decreased significantly, whereas aerobic exercise on a treadmill for 10 weeks increased miR-33 expression to the level of the normal chow-fed control mice (205). Another miRNA array study on mice showed that increased levels of miR-212 in high fat diet-fed mice was reduced by treadmill running for 16 weeks (203). In that study, a negative correlation between miR-212 and FGF21 levels was also demonstrated in HepG2 cells, suggesting that decreased miR-212 might underlie the effect of exercise training on reducing lipogenesis through increasing FGF21 production (206).

Numerous clinical and experimental studies have indicated a strong correlation between the microbiome and the pathogenesis of NAFLD (207, 208). Lifestyle disturbances including excess "Western-style" diet consumption and diet-induced obesity cause severe microbial dysbiosis and have a direct impact on hepatic metabolism (209). Lipopolysaccharides produced by the Negativicute and Halanaerobiale bacteria, which belong to the Phylum Firmicutes, are associated with the progression of NASH, including liver inflammation and fibrosis (210). Intestinal permeability is involved in the pathogenesis of NAFLD and affects the microbiome (211). Increased intestinal permeability results in increased inflammation-based and bacterial metabolite-driven pathways (212, 213). Lifestyle modifications can affect the microbiome. Indeed, numerous studies have demonstrated that training and physical activity

changes the microbiome (214, 215). Both treadmill running and voluntary wheel running increased microbiome diversity in mice, and this effect was also observed in high fat diet-fed mice (216, 217). However, the effect of exercise training on the ratio of Firmicutes to Bacteroidetes, which is generally considered to increase in cases of obesity and diabetes (209, 218), is inconsistent in the literature because of differences in training protocols and sampling locations between studies (214–217). *Bifidobacterium* is a known regulator of intestinal permeability (219, 220) and several studies have reported an increase in *Bifidobacterium* with exercise training (218, 221), suggesting that exercise improves gut barrier function. This suggests that alteration of the microbiome is involved in the effect of exercise training on ameliorating NAFLD, and further research is warranted.

FUTURE DIRECTION OF EXERCISE TRAINING TREATMENT FOR ALLEVIATING NAFLD

According to recent studies and consensus, liver fibrosis is the most significant factor for determining the prognosis of NAFLD, independent of age and concomitant disease including diabetes (222, 223). Therefore, it is important to identify whether exercise training ameliorates or prevents liver fibrosis and improves the prognosis of subjects with NAFLD. Moreover, it is necessary to investigate the molecular pathways involved in the exercise training effect on the pathogenesis of liver fibrosis. To date, few studies have evaluated liver fibrosis in liver specimens (9, 224). In this context, the development of a noninvasive method to evaluate liver fibrosis in subjects with NASH including magnetic resonance imaging and transient elastography will contribute to further clinical trials targeting liver fibrosis with exercise training (225, 226). In experimental research, comprehensive analyses including gene microarrays, next generation sequencing and metabolomics, developed in the 2000s, have indicated possible molecular mechanisms by which NAFLD might be ameliorated in rodent models and humans (227–230). These technologies are expected to reveal the molecular mechanisms and contribute to translational research on exercise training in subjects with NAFLD. Another aspect of investigation into the effect of exercise training on NAFLD is the potential development of a therapeutic agent as a "training mimicker." It is well known that maintaining adherence to lifestyle modifications including exercise training and dietary therapy is difficult (41). Moreover, concomitant disease and complications of obesity including diabetes, cardiovascular disease and inactivity linked with orthopedic diseases and aging frequently disrupt exercise training for subjects with NAFLD. Training mimickers would provide these patients with the benefits of exercise training.

CONCLUSION

To conclude, exercise training is a robust treatment for subjects with NAFLD. There are multiple mechanisms by which this acts on the liver, including organ crosstalk. Although further clinical research is needed to evaluate the effect of exercise training on liver fibrosis and prognosis for patients with NAFLD, it is important to increase physical activity and promote lifestyle modification for the management of this disorder.

AUTHOR CONTRIBUTIONS

HT generated the manuscript including the main document, tables and figures. KK initially designed the contents of the sections and supervised writing of the manuscript. KT and HT reviewed and analyzed the literature for this systematic review. YE edited the manuscript and supervised the figure design. KA organized the data and wrote the manuscript as a corresponding author.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2018.00588/full#supplementary-material

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