



Is exercise an effective treatment for NASH? Knowns and unknowns

Stephen Caldwell;¹ Mariana Lazo²

Abstract

Non-alcoholic steatohepatitis has emerged as one of the most common causes of chronic liver disease in many regions of the world. Exercise and dietary changes constitute cornerstones of overall therapy aimed at achieving weight loss in hopes of ameliorating lipid-induced hepatocellular injury by mobilizing fat out of the liver. Indeed weight loss is known to be effective as evident in several controlled trials and, in the extreme, with bariatric surgery. However, less is known about exercise in the absence of weight loss especially in terms of altering hepatic fat metabolism. As with steatosis, adipose tissue function and other targets of insulin activity, skeletal muscle physiology is closely integrated with overall energy homeostasis and calorie disposal. Although much remains to be learned, increased physical conditioning appears to be closely linked to improved hepatic metabolism independent of changes in body weight. This is of practical importance to patients attempting lifestyle changes who may become unnecessarily discouraged if there is not evidence of associated weight loss as a result of increased activity.

Moreover, the degree of physical conditioning represents an unmeasured and potentially confounding variable in most clinical trials of pharmacological intervention in NASH. Clinical investigation is needed to better understand the effects of exercise on liver fat metabolism and on how best to measure the degree of physical conditioning both as a baseline indicator of overall energy homeostasis and an end-point of treatment.

Key words: Epidemiology, NAFL, NASH, exercise, muscle function.

Nonalcoholic steatohepatitis (NASH) is the increasingly common and more aggressive form of nonalcoholic fatty liver (NAFL) which itself represents the hepatic manifestation of systemic lipotoxicity evident in the metabolic or insulin resistant syndrome. As a systemic disorder, it is not surprising that changes outside of the liver will likely have an impact either beneficially or detrimentally on liver fat metabolism and health. Indeed, the liver serves as an integrated part of the system governing energy homeostasis which includes adipose tissue, pancreatic islets and most relevant to this paper, the skeletal muscle. One needs look no further than to some of the literature regarding hepatic physiology in one the world's greatest marathon athletes, the migratory *Palmipedes*.¹

The migratory palmipedes – fatty liver and exercise: While the *Palmipedes* (migratory geese and ducks) don't develop histological NASH, seasonal or pre-migratory steatosis is well-known for thousands of years and its accentuation through carbohydrate loading serves as basis for foie gras farming.^{2,3} Similar seasonal variation in liver fat content has also been documented in a number of other non-hibernating animals.⁴ However, variation exists in the degree of steatosis in different strains of ducks and geese.¹ Interestingly, the factors governing the variable transition to fat storage include changes in thyroid metabolism, altered lipoprotein metabolism and skeletal muscle energy utilization including changes in fatty acid binding protein expression which likely reflects muscle energy substrate utilization.^{5,6} Thus, the accumulation of fat in the liver in this animal appears to represent an integrated and adaptive process preceding conditions of increased activity.⁷ While fatty liver in humans is clearly influenced by other factors such as lipid composition and

¹ The University of Virginia, Division of GI/Hepatology, Charlottesville, Virginia.

² Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland.

Abbreviations:

VO₂ max or VO₂ peak; the maximum capacity of oxygen utilization expressed as liters/minute or milliliters of oxygen per kilogram of body weight per minute in graded exercise. 'max' usually refers to a true limit while 'peak' refers to the results of a specific test although the terms are often used interchangeably in the literature. Met (metabolic unit); A met is the estimated value of VO₂ at rest (usually 3.5 mL O₂/kg/min). Thus, a VO₂ measurement of 35 mL O₂/kg/min is equal to 10 mets.

Address for correspondence:

Stephen H Caldwell, MD,
Division of Gastroenterology and Hepatology, University of Virginia Health System, P.O. Box 800708, Charlottesville, VA 22908-0708. Phone: 434-924-2626, Fax 434-924-0491, E-mail: shc5c@virginia.edu

health of the anti-oxidant system,^{8,9} a key variable seems also to be the degree of physical conditioning which influences disposal of stored calories.

NASH and physical activity: A number of experimental models of both NAFL and NASH exist but surprisingly little experimental work has examined the influence of activity on hepatic steatosis. Moreover, in both experimental models and in the available human data on lifestyle intervention, it is often difficult to dissociate activity or exercise per se from the effects of weight loss as part of a lifestyle intervention combining both dietary changes and exercise. However, emerging data from several groups including work from Rector et al indicate that the simple addition of an exercise wheel to an animal model of insulin resistance (Otsuka Long-Evans Tokushima rats) has profound effects on the development of fatty liver and multiple related parameters of hepatic fat metabolism.¹⁰ Furthermore, in humans the recognition of a more benign form of obesity associated with both less hepatic fat and skeletal muscle fat suggests that different levels of activity and physical conditioning may be among the factors that strongly influence hepatic fat metabolism even among obese individuals.¹¹ Conversely, the recognition of metabolic risk among normal weight individuals and similarly the occurrence of NAFL among normal weight individuals might also reflect the presence of physical deconditioning in the absence of obesity.¹²

The physically conditioned Sumo wrestler of Japan are sometimes cited as an example of a relatively more benign form of obesity and perhaps offers a model of more sustained activity in the setting of persistent obesity. Prior studies have shown that conventional measures of obesity such as BMI don't accurately reflect the percentage of body fat in these individuals which is thought to be due to increased muscle mass. Yamauchi et al reported a prevalence of obesity measured by total body fat as only 40% in spite of a mean BMI of 40 among entry level Sumo.¹³ None the less, diabetes and other metabolic disorders are reported to be increased in this group suggesting that any salutary benefits of rigorous exercise training without weight loss have significant limitations.¹⁴

Exercise without weight loss in humans: Does exercise ameliorate fatty liver in humans in the absence of associated weight loss? This constitutes a simple but practical question because weight loss is often perceived as a natural consequence of increased activity. Its absence in a motivated patient who increases their activity (as usually prescribed by health care providers) may become a source of non-compliance if there is not objective evidence of a significant consequence of increased activity i.e. weight loss. Thus the question of a potential benefit of activity with *or* without weight loss is of practical importance in patient management. It may also be a hidden factor in interpreting pharmacological trials which usually measure weight but seldom assess levels of conditioning in either actively treated patients or placebo controls.

Epidemiological associations (Table I): In a cross-sectional prevalence study, Perseghin et al reported on the relationship between estimated activity level and liver fat by ¹H magnetic resonance spectroscopy in 191 Italian volunteers. 13 of 52 subjects reporting the lowest level of activity had > 5% liver triglyceride compared to only 1 of 46 subjects reporting the highest level of activity. Additionally, the authors noted a highly significant inverse correlation between a physical activity index and hepatic fat content ($p < 0.0001$), adjusting for age, sex, BMI, HOMA, and adiponectin.¹⁵ Similar associations were noted more recently by McMillan et al.¹ In another study, Church et al found an inverse association between fitness categories with the prevalence of NAFL independent of BMI, but not so for waist circumference.¹⁷ The prevalence of NAFL in the lowest (MET < 10.2), middle (MET 10.2 to 11.7) and highest tertiles (MET \geq 11.8) were 22, 9 and 2.2% respectively. Moreover, Krasnoff et al showed a significant relationship between the severity of histological injury and diminished oxygen utilization at peak exercise (VO_2 peak) - an index of physical conditioning - among overweight and obese patients with NAFL.¹⁸

Although a lower level of physical activity appears to correlate to higher liver fat and histological injury in both experimental animals and humans (Table I), does a prescription for exercise change steatosis in the absence of concomitant weight loss once after a patient has developed NAFL? Current data offers a mixed answer on this issue.

Clinical trials (Table II): Devries et al studied hepatic lipid content by CT attenuation in 20 obese (BMI = 34 ± 2) and 21 lean (BMI = 24 ± 1) subjects undergoing 12 weeks of endurance exercise training consisting of up to three 60 minute bicycle sessions at 65-70% of peak aerobic capacity (VO_2 peak) without concomitant weight loss.¹⁹ The regimen improved VO_2 peak (+ 16%), lowered waist circumference overall (- 4% change) and serum GGT in the males but overall the intervention was not associated with decreased serum ALT, body weight or liver fat by CT attenuation. Similarly, Shojaee-Moradie et al showed that 6 weeks of exercise (20 min of physical activity, 3 times per week at 60-85% VO_2 max) significantly improved parameters of insulin metabolism including non-esterified fatty acid (NEFA) without a change in BMI, muscle or liver fat content by MR spectroscopy.²⁰ In another study, Dekker et al examined the effects of 12 weeks of exercise intervention without weight loss in 16 previously sedentary obese males on interleukin-6 (IL-6) - a cytokine which has been associated with increased histological injury among obese patients with NAFL but has also been implicated with changes in insulin resistance and glucose disposal.²¹⁻²⁴ The overall exercise intervention was weekly moderate intensity jogging or walking at 60% maximum VO_2 . Surprisingly, even this light intervention resulted in significantly reduced waist circumference and serum IL-6 without a change in body weight.

Table I. Observational studies of physical activity (PA), cardio respiratory fitness and NAFL/NASH.

Author, Year	Study population/ Design	Assessment of PA	Main outcome	Main results
Lawlor D, 2005 ⁴⁵	3,789 British women aged 60–79 years/cross-sectional	Self-reported number of hours/wk spent in moderate or vigorous activity	Levels of ALT and GGT	Adjusting for BMI, increase in exercise is associated with a reduction on GGT (> 3 hours mod/vig activity, -5.16, (95% CI-7.97, -2.34)), but not with ALT
Suzuki A, 2005 ⁴⁰	348 men with elevated ALT, mean age 42±7/longitudinal	Self-reported exercise	Levels ALT	Regular exercise was associated with significantly greater ALT improvement and normalization, even after adjusting for weight change. ALT normalization was 2.5 times more likely to occur when people kept regular exercise
Church T, 2006 ¹⁷	218 men age 33–73/cross-sectional	Cardiorespiratory fitness by a maximal treadmill test (MET)	Liver fat by CT scan, liver-spleen ratio	Inverse association between fitness categories with the prevalence of NAFL (P for trend < .001) independent of BMI, but no so of waist circumference (P value changed from < .0001 to .06) Prevalence of NAFL in the lowest (MET < 10.2), middle (MET 10.2 to 11.7) and highest tertiles (MET ≥ 11.8) were 22, 9 and 2.2% respectively
Perseghin G, 2007 ¹⁵	77 women and 114 men, age 19–62/cross-sectional	Self-reported work, sport and leisure time PA. Validated questionnaire	Hepatic Fat by 1H- MRS	Correlation between the IHF content and the total score of the physical activity index, controlling for age, sex, BMI, HOMA2-%S, and adiponectin
McMillan, 2008 ¹⁶	293 men/cross-sectional	Cardiorespiratory fitness (MET)	Liver fat by CT scan, liver-spleen ratio	Cardiorespiratory fitness correlated with liver fat (r = -0.24)
Zelber-Sagi S, 2008 ⁴⁸	375 men and women aged 20–74/cross-sectional	Self reported PA type, frequency and duration, and length of time in the last year	Abdominal Ultrasound	Only the association with resistance PA remained significant with further adjustment for BMI (OR 0.61, 95% CI 0.38-0.85). However, when adjusting for leptin or waist circumference, the association became non significant

CT: Computed tomography, 1H-MRS: Magnetic Resonance Spectroscopy

We can conclude from these studies that short term (3 months or less) periods of exercise appears to favorably change a number of parameters related to more severe NAFL without weight loss. Whether this translates into resolution or improvement of NASH remains unproven but these studies suggest that more extended periods are necessary to achieve benefit in the liver. This is supported by a study from Bonekamp et al. who conducted a RCT among 45 men and women 40–65 years of age, with type 2 diabetes and found that after a 6-month intervention of 45 minutes of moderate-intensity aerobic exercise plus weight lifting - 3 times per week, there was a significant reduction of liver fat in the absence of significant weight loss.²⁵

These findings are consistent with prior studies showing that visceral adiposity and steatosis correlate inversely with the degree of cardiorespiratory fitness.^{26,27} In a recent report on the effects of different levels of exercise on abdominal visceral fat, Irving et al reported significant reduction of waist circumference and visceral fat measured by L4-L5 level CT in middle-aged obese females undergoing 16 weeks of minimal versus light versus high intensity exercise in spite of only slight (< 5% weight reduction).²⁸ However, the benefit was only seen

in the high intensity group defined as exercise 5 days per week with two of the exercise sessions exceeding the lactate threshold or the point at which there is a transition to anaerobic metabolism which is usually accompanied by some level of discomfort. Kraus et al studied the effects of different levels of exercise without significant weight loss on lipoprotein metabolism in 111 over-weight and obese subjects. They showed that 8 months of high intensity-high frequency had greater beneficial effects on multiple parameters of lipoprotein metabolism compared to low intensity-low frequency exercise.²⁹

These results raise the difficult questions of how long, how often and how intense must the exercise be to offer benefit. Does one need to hit the lactate threshold – a much higher and difficult target with met levels of 10-12 to obtain benefit? It also raises question of risk-benefit in a population at risk for vascular disease.

Relationships between muscle activity and hepatic steatosis: Exercise impacts muscle metabolism in a number of ways that may influence hepatic fat deposition and metabolism.³⁰ The most direct mechanism involves changes in skeletal muscle mitochondrial metabolism and resulting alteration of the partitioning of calorie disposal between target organs of insulin activity which is

Table II. Randomized clinical trials of exercise only or exercise and diet with liver fat.

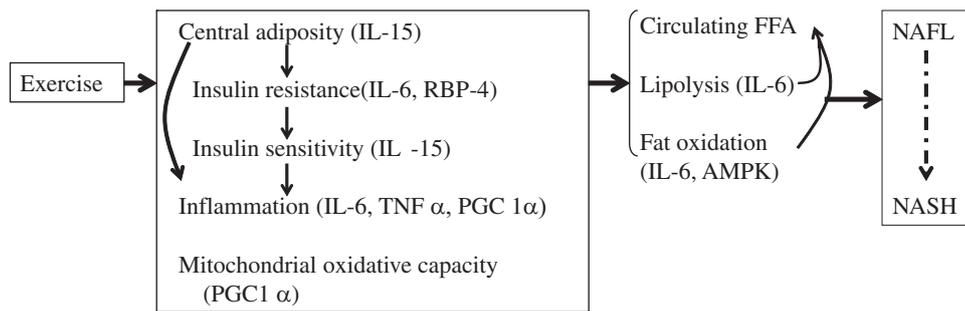
Author, year	Study population	Intervention	Duration	Main outcome (Secondary)	Main Results
Exercise only					
Shojaee-Moradie, 2007 ²⁰	17 pts. healthy male, mean age 53, BMI 25 to 30 kg/m ²	20 min, 3 times per week at 60-85% VO ² max	6 weeks	Hepatic fat by 1H-MRS, (hepatic insulin sensitivity)	No significant changes in BMI, liver fat and intramuscular lipids. However, significant decrease in peripheral and hepatic insulin resistance and in free fatty acids
Bonekamp S, 2008 ²⁵	45 pts. age 40-65 T2DM, not requiring insulin	45 minutes of moderate-intensity aerobic exercise plus weight lifting - 3 times per week	6 months	Hepatic fat by 1H-MRS	Adjusted for changes in BMI or visceral adiposity, moderate-intensity exercise training significantly reduced hepatic fat, -2.3 and -2.5 decrease respectively
Diet & exercise					
Ueno T, 1997 ⁴²	25 pts adults, with obesity	3 months restricted diet (ideal weight - 25 Cal * Kg ⁻¹ and exercise (walking or jogging) for a trial period of 3 months	3 months	Histological changes, liver enzymes	Significant reduction of liver enzymes in the treated arm from baseline. (Mean AST baseline 66, 3 mo. follow up 27, for ALT: 83 baseline, 27 3-mo follow up). Histologically: only steatosis changed significantly
Lazo M, 2008 ⁴¹	105 overweight or obese pts. with T2DM, age 45 to 76	Weekly group or individual meetings. Calorie (energy goal for persons 250 pounds of 1,200 to 1,500 kcal/d and of 1,500 to 1,800 kcal/d for those individuals > 250 pounds and physical activity goals (gradual increases in at-home exercise from 50 min/week toward a goal of 175 min of moderate intensity physical activity per week)	12 months	Hepatic Fat by 1H-MRS	In patients with T2DM, ILI was associated with a reduction in steatosis and lower incidence of NAFLD compared to DSE. Loss of 5% or more of body weight was significantly associated with hepatic steatosis reduction
Nobili V, 2008 ⁴³	53 pts. age 5.7-18.8 years	Lifestyle intervention: diet tailored to the patient's calorie needs, and increased physical activity. Patients were concomitantly randomized to alpha-tocopherol 600 IU/day plus ascorbic acid 500 mg/day or placebo	24 months	Liver histology (liver enzymes)	Significant improvement in steatosis, lobular inflammation, and ballooning, and in the NAFL activity score in both groups. Aminotransferases, triglycerides, cholesterol, fasting glucose, and insulin, sensitivity indices improved significantly

MRS: Magnetic resonance spectroscopy, T2DM: Type 2 diabetes mellitus.

known to be abnormal in sedentary subjects. For example, it is known that intramyocellular triglyceride, measured by ¹H MRS, is a better predictor of insulin resistance in a high risk group (young relatives of type 2 diabetics) than are conventional parameters such as age, BMI, total body fat or the waist-hip ratio.³¹ Moreover, older (age 51-62) compared to younger (age 21-30) subjects have less type 2 (fast twitch) fibers and less capillary contacts in muscle biopsy samples of the vastus lateralis muscle.³² However, from the same study, endurance trained older patients had increased capillary supply and similar oxidative capacity (measured by succinate dehydrogenase activity) as the younger group and twice that of the untrained older

subjects. Does this relationship form an endorsement of the old adage 'no pain, no gain'?

In light of the association between muscle fat and insulin resistance noted above, it is somewhat paradoxical that 12 weeks of exercise training without significant weight loss increased intramyocellular lipid (determined histologically from the vastus lateralis muscle) in older, previously sedentary subjects.³³ However, the key difference was that oxidative capacity significantly increased as well. Among those with more advanced lipotoxicity evident by co-existing type 2 diabetes, skeletal muscle mitochondrial oxidative capacity is decreased although it is unclear whether this is related primarily to decreased mitochondrial mass or to intrinsic mitochondrial defects



IL: Interleukin, RBP: Retinol binding protein, TNF: Tumor necrosis factor, PGC: peroxisome-proliferator-activated receptor gamma co-activator

Figure 1. Potential mechanisms (mediators) of the therapeutic effect of exercise on NAFL/NASH.

or to both.³⁴ In contrast to the pre-migratory goose with fatty liver, this condition is also associated with diminished free fatty acid utilization and decreased muscle fatty acid binding protein.³⁵

Skeletal muscle mitochondrial oxidative capacity and mitochondrial biogenesis appears to be influenced especially by PPAR- γ (peroxisome-proliferator-activated receptor gamma) co-activator-1 α or PGC-1 α .³⁶ Experimentally, the expression of PGC-1 α offers a link between activity levels and muscle oxidative capacity.³⁷ In addition, other mechanisms may be implicated in the therapeutic effects of exercise in fatty liver. As shown in *Figure 1*, several pathways have been studied and demonstrated *in vitro* but deserve further validation in humans. Emerging from these studies are data to support the intuitive concept that there is extensive cross-talk between the primary targets of energy homeostasis and insulin activity including hepatic fat metabolism. Although for several years it had been hypothesized that muscle cells produced some «humoral» factor in response to the increase demand of glucose during exercise, it was not until late 90's that the first myokine (IL-6) was discovered and led to numerous studies elucidating the molecular effects of exercise, and its role in tissue-tissue communication in health and disease.³⁸ The influence of exercise on this cytokine may form a key link between muscle activity, insulin sensitivity and liver fat content.

Measuring physical conditioning (Table III): Given the foregoing discussion, is testing the degree of physical conditioning ready for clinical 'prime-time' in the evaluation of patients with NAFL or NASH? In daily practice, the answer is probably 'yes' especially for those perplexing non-obese patients with NASH where the demonstration of severe deconditioning may be especially instructive. In the research arena, the answer also seems affirmative. The presence of an unmeasured and confounding variable such as changes in activity levels, not evident in changes in weight or BMI, could have implications on the interpretation of outcomes of long-term placebo controlled trials of pharmacological intervention.

However, many questions remain unresolved and the best means of testing the degree of physical conditioning and the targets for improvement are not clear. Both the V02 max (the maximum capacity of oxygen utilization expressed as liters/minute or milliliters of oxygen per kilogram of body weight per minute in graded exercise) and the lactate threshold (perhaps simplistically, the level of exercise at which aerobic or mitochondrial capacity is overwhelmed and anaerobic or glycolytic metabolism becomes dominant) are conventional parameters for measuring the degree physical conditioning. However, target levels of an exercise intervention are not yet clear regarding the potential effects and predictability of changes in hepatocellular metabolism. In addition, the relative use of simpler surrogate measures such as waist-hip circumference or visceral fat by cross-sectional imaging awaits further clinical investigation. For now however, it would seem very prudent for any pharmacological study of NAFL/NASH to at least include these surrogates in addition to conventional measures of muscle conditioning (i.e. degree of physical conditioning).

Summary: In conclusion, on-going and prior studies have established the role of broad life-style intervention including both diet and exercise induced weight loss in NASH.³⁹⁻⁴³ While increased levels of physical activity and fitness have been associated with decreased risk for diabetes and improved glycemic control, the recent evidence highlighting cross-talk between muscle and fat metabolism in insulin-target organs such as liver supports the role of exercise, independent of weight loss, as treatment for human NAFL/NASH but many questions await further clinical investigation. The mechanism and potential interactions for such effect are only partially understood. Although there are very few well conducted human studies to date, it seems that a longer duration of physical activity is required to produce significant changes in hepatic fat. However, the optimal intensity and amount necessary for such beneficial effects are unknown. Furthermore, questions regarding the best method to measure of degree of physical conditioning/ exercise remain to be explored and validated. Moreover, the

Table III. Methods used to assess physical activity and physical conditioning.

Method	Measure			Disadvantages
	Physical activity	Physical conditioning		
Direct				
Cardiorespiratory fitness	VO ₂ max		X	Influenced by other factors ie. genetic make up
Lactate threshold/anaerobic threshold		X		Influenced by other factors i.e. heart disease with compromised blood supply
Motion sensors		X		High intra- inter- variability. May be biased
Heart rate		X		Influenced by other factors i.e. temperature, type of exercise, needs individual calibration
Indirect				
Recalls, logs/diaries, questionnaires		X		Subject to bias

effects of other variables on muscle and liver metabolism such as dietary lipid composition and ethanol consumption remain to be fully explored.^{44,45} Because the antecedent development of liver disease alters these relationships, such studies need to carefully take into account the basal health of the liver at the initiation of an intervention.⁴⁶ Clearly, while more exercise appears to be better, this field is one in need of active and well conceived investigation.

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