Short-term aerobic exercise training improves gut peptide regulation in nonalcoholic fatty liver disease


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Kullman EL, Kelly KR, Haus JM, Fealy CE, Scelsi AR, Pagadala MR, Flask CA, McCullough AJ, Kirwan JP. Short-term aerobic exercise training improves gut peptide regulation in nonalcoholic fatty liver disease. J Appl Physiol 120: 1159–1164, 2016. First published March 31, 2016; doi:10.1152/japplphysiol.00693.2015.—Obesity-related nonalcoholic fatty liver disease (NAFLD) is now the most common chronic liver disease. Exercise and diet are uniformly prescribed treatments for NAFLD; however, there are limited empirical data on the effects of exercise training on metabolic function in these patients. The purpose of this study was to investigate the fasting and glucose-stimulated adaptation of gut peptides to short-term aerobic exercise training in patients with NAFLD. Twenty-two obese subjects, 16 with NAFLD (body mass index [BMI], 33.2 ± 1.1 [SE] kg/m²) and 6 obese controls (BMI, 31.3 ± 1.2 kg/m²), were enrolled in a supervised aerobic exercise program (60 min/day, 85% of their heart rate maximum, for 7 days). Fasting and glucose-stimulated glucagon-like peptide-1 (GLP-1[7–36]) and peptide tyrosine tyrosine (PYYTotal) concentrations in plasma were assessed before and after the exercise program. Initially, the NAFLD group had higher fasting PYY (NAFLD 10.7 ± 2.0 pg/ml, control 6.4 ± 1.6 pg/ml, P < 0.05) and GLP-1 (NAFLD 12.4 ± 2.2 pg/ml, control 8.2 ± 1.0 pg/ml, P < 0.05) and did not significantly increase GLP-1 or PYY in response to glucose ingestion. After the exercise program, fasting GLP-1 was reduced in the NAFLD group (10.7 ± 2.0 pg/ml, P < 0.05). Furthermore, exercise training led to significant increase in the acute (0–30 min) PYY and GLP-1 responses to glucose in the NAFLD group, while the total area under the glucose-stimulated GLP-1 response curve was reduced in both NAFLD and controls (P < 0.05). In summary, 7 days of vigorous aerobic exercise normalized the dynamic PYY and GLP-1 responses to nutrient stimulation and reduced the GLP-1 response in NAFLD, suggesting that exercise positively modulates gut hormone regulation in obese adults with NAFLD.

fatty liver disease; obesity; insulin resistance; nonalcoholic steatohepatitis; physical activity

NEW & NOTEWORTHY

Nonalcoholic fatty liver disease (NAFLD) is the most common liver-related disease. Exercise is widely prescribed as treatment, but the mechanism is unknown. We examined the effects of exercise on gut peptides [peptide tyrosine tyrosine (PYY) and glucagon-like peptide-1 (GLP-1)] in patients with clinically diagnosed NAFLD. Prior to training, those with NAFLD exhibited elevated fasting plasma PYY and GLP-1, and the response to glucose ingestion was abnormal. Exercise reduced fasting GLP-1 and normalized the glucose-stimulated response of both hormones.

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Nonalcoholic fatty liver disease (NAFLD) is a major contributor to the progression of a multitude of lifestyle-related diseases, including metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease (35). It is estimated that ~30% of the U.S. adult population have NAFLD (33), and this is closely linked to obesity, physical inactivity, and poor diet (42). Recently, in an attempt to develop targeted strategies to address obesity and related disease, much attention has been directed toward two gut-derived hormones that are known to modulate nutrient intake and metabolism. Peptide tyrosine tyrosine (PYY) and glucagon-like peptide-1 (GLP-1) are primarily secreted from the intestinal L cells of the distal gut in response to glucose or meal ingestion. It is well established that PYY targets higher brain centers to induce satiety (16) and also plays a role in the regulation of glucose metabolism (23). Likewise, GLP-1 regulates satiety, but it is also an insulin secretagogue and a potential regulator of lipid metabolism (2).

Previous studies have shown that obesity is associated with abnormalities in PYY and GLP-1 secretion and regulation (4, 13, 40), and this may be linked to eating behaviors, as well as the metabolic disorders that subsequently arise. Metabolic conditions such as insulin resistance and type 2 diabetes coexist with NAFLD and are tied to further dysregulation of these hormones (7, 23, 38). However, the influence of NAFLD on the regulation of GLP-1 and PYY is currently unknown. Aerobic exercise training is an effective therapy for preventing progression of NAFLD-associated disease and reversing related negative health consequences (8, 10–12, 29, 42), particularly when patients perform >250 min/wk of moderate- to high-intensity aerobic exercise (28). Mechanisms of metabolic improvement include increased insulin sensitivity (5), decreased hyperlipidemia, decreased delivery of fatty acids to the liver (11), enhanced hepatic fatty acid oxidation (32), and reduced visceral adipose tissue (VAT) (17). Additionally, aerobic exercise can have anorexigenic effects in both lean and obese individuals that are mediated through increases in GLP-1 and PYY (3, 4, 34, 36). Over time this may contribute to reduced energy intake and successive weight loss, although evidence suggests that such a response may be blunted in obese individuals (1). Thus the purpose of this study was to investigate fasting and glucagon-stimulated plasma GLP-1 and PYY responses in NAFLD and determine if a short-term aerobic exercise intervention could improve the regulation of these peptides in this high-risk patient group.

We hypothesized that individuals with NAFLD would exhibit altered gut peptide responses in both the fasting and glucose-stimulated state because of NAFLD-related hepatic
dysfunction and that short-term exercise would ameliorate these effects. We further hypothesized that obese individuals without NAFLD would show beneficial gut peptide changes after short-term exercise.

MATERIALS AND METHODS

Participants. Twenty-two obese sedentary adults [age 53 ± 3 (SE) yr; 32.7 ± 0.9 kg/m²] were recruited to participate in this study. Sixteen of the participants had NAFLD (8 male, 8 female) based on a measured intrahepatic fat content greater than 5%. Six obese participants (2 male, 4 female) without NAFLD and similar body mass index (BMI) served as obesity-matched controls. All subjects underwent a medical history and physical examination, a complete blood profile (lipid profile and hepatic/renal/hematological function tests), a resting 12-lead ECG and submaximal exercise stress test, and an oral glucose tolerance test (OGTT). Subjects were asked to keep a 24-h food diary prior to the preintervention OGTT and were asked to replicate their diet prior to the post-exercise-training OGTT. Subjects were instructed to maintain their typical diet throughout the study. Volunteers were excluded if they were taking any medications or supplements known to affect outcome variables, if they presented any contraindications to physical activity, or if they participated in 20 min or more of exercise at least two times per week. All participants provided signed informed consent in accordance with the guidelines for the protection of human subjects. This study was approved by the Cleveland Clinic Institutional Review Board.

Intrahepatic and visceral fat content. Intrahepatic fat content was determined by 1H magnetic resonance spectroscopy as previously described (10). Individuals with intrahepatic fat content higher than 5% were categorized as having NAFLD based on the diagnostic criteria for hepatic steatosis (37). Visceral fat content was quantified using cross-sectional images of 5-mm slices obtained during computed tomography scans (Somotom Sensation 16 scanner; Siemens Medical Solutions, Malvern, PA). The subjects were scanned in the supine position, images were obtained at the fourth lumen vertebra (L4), and visceral fat content was measured (ImageJ; National Institutes of Health).

Glucose metabolism. Glucose metabolism was assessed during a 75-g OGTT performed prior to and 24–48 h following the 7 days of aerobic exercise training. Participants arrived for testing at ~7:00 AM after an overnight fast. Following baseline blood samples, subjects ingested a glucose solution and blood was subsequently drawn at 30, 60, 90, and 120 min. Blood was collected in EDTA tubes containing aprotinin and dipeptidyl peptidase 4 (DPP-IV) inhibitor and was immediately placed on ice. Blood was centrifuged (15 min, 3,000 rpm) and plasma was aliquoted and stored at −80°C until analyzed for GLP-1, PYY, glucose, insulin, and C-peptide. The Matsuda index (25) was used to assess insulin sensitivity during the OGTT (ISIOGTT).

Exercise intervention. All subjects completed 7 consecutive days of supervised aerobic exercise (treadmill/cycle ergometer) for 60 min/day performed at 85% of their heart rate maximum. Each exercise session was preceded with a 5-min warm-up and followed by a 5-min cool-down. Heart rate was measured continuously during exercise using heart rate monitors (Polar Electro, Woodbury, NY).

Aerobic capacity (V̇O₂ max). Aerobic capacity was measured within 1 day prior to the start of the exercise intervention and 1 day after completion of the 7-day program and the OGTT. Maximal oxygen consumption was determined using an incremental treadmill exercise test as previously described (18).Expired air was monitored throughout the protocol using an automated system (Jaeger Oxycon Pro; Viasys, Yorba Linda, CA).

Blood analysis. At each time point plasma glucose was determined using a YSI 2300 STAT Plus analyzer (Yellow Springs, OH), and plasma insulin and C-peptide were determined via radioimmunoassay (Millipore, Billerica, MA). GLP-1, PYY, and PYYtotal were also measured through the 120-min time point of the OGTT using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Millipore, St. Charles, MO). All samples were batch analyzed and measured in duplicate to reduce interassay variability, and the coefficient of variation between duplicates was 6.1 ± 0.4 and 3.3 ± 1.1% for PYY and GLP-1, respectively. Baseline preintervention aspartate transaminase (AST) and alanine transaminase (ALT) were measured to assess liver function using the Cobas Integra Aspartate Aminotransferase (ASTL) test and the Alanine Aminotransferase (ALTL) test (Roche Diagnostics, Indianapolis, IN), respectively.

Statistical analysis. Statistical analysis was carried out using StatView Version 5.0.1 (SAS Institute, Cary, NC). In general, data are expressed as means ± SE. Primary dependent variables were analyzed by repeated-measures ANOVA. The ANOVA models first tested the interaction between groups (NAFLD vs. control) and trial (pre- vs. postexercise) by including the two main effect terms and their interactions. If the interaction was not statistically significant, it was dropped from the model, and the model proceeded with two main effect terms (this was true for all variables) in combination with Bonferroni post hoc analysis. Variables with a high degree of skew (GLP-1 and PYY) were log transformed. Pearson product-moment correlations were used to explore relationships between selected outcomes. Statistical significance was set at two-sided P values <0.05.

RESULTS

Subject characteristics are presented in Table 1. There were no differences in age, weight, or BMI between NAFLD and controls. However, the NAFLD group had higher intrahepatic fat content (IHC) (22.6 ± 3.1% vs. control 3.5 ± 0.7%; P < 0.01) and elevated liver enzymes (AST, 41.1 ± 6.4 U/l vs. control 27.2 ± 4.6 U/l; ALT, 57.9 ± 10.7 U/l vs. control 33.3 ± 10.1 U/l), which confirms the presence of NAFLD. There were no significant changes in weight, BMI, or IHC in either group following 7 days of exercise. Furthermore, there were no interactions between group responses after 7 days of exercise, indicating that the NAFLD group had similar responses to exercise training compared with the obese control group.

Baseline fasting and OGTT glucose concentrations were significantly higher (P = 0.02) in NAFLD compared with controls. The NAFLD group had higher fasting C-peptide (3.5 ± 0.3 vs. 2.2 ± 0.4 ng/ml) compared with controls (P = 0.02). After exercise training, fasting glucose was significantly decreased (P = 0.03) in the NAFLD group, but still remained higher (P = 0.02) than controls. Exercise training lowered both fasting insulin (P = 0.02) and C-peptide (P = 0.04) and decreased insulin (P < 0.001) and C-peptide total area under the curve 0–120 min (AUC120; P < 0.01) in NAFLD, but not in control. Insulin sensitivity (ISIOGTT) was significantly lower (P < 0.01) in the NAFLD group compared with control both pre- and postexercise, but significantly increased within the NAFLD group in response to exercise training (P < 0.001, Fig. 1).

Fasting PYY was significantly higher in NAFLD (P = 0.04) than controls at baseline (Table 1), and this was directly correlated with VAT (r = 0.60, P = 0.049, Fig. 2A). Furthermore, subjects with NAFLD exhibited a blunted PYY response to oral glucose ingestion (Fig. 3A), while the response in the control group trended toward an increase (P = 0.06). Posttraining, the relationship between fasting PYY and VAT disappeared (r = 0.28, P = 0.421, Fig. 2B). Notably, a dynamic PYY response, as reflected in secretion 30 min following glucose ingestion, was significantly increased (P = 0.04) in the NAFLD group after exercise training, suggesting a restoration
of the acute PYY response to nutrient stimulation. The control group also significantly increased the dynamic PYY response after exercise training (P = 0.02). While the dynamic component of the PYY response is likely to contribute to satiety regulation immediately after a meal, it should be noted that the total PYY response, as assessed by the PYY tAUC120, was not significantly increased in either group after glucose ingestion, nor was it altered by this short exercise-training stimulus (Fig. 3B).

At baseline, fasting GLP-1 was significantly higher (P < 0.05) in NAFLD compared with controls (Table 1), and those with NAFLD did not show the significant GLP-1 response (P = 0.06) 30-min post-glucose ingestion that was evident in the control group (P < 0.05). However, this may have been driven by a high degree of variability in response among NAFLD patients, with 5 of 16 NAFLD subjects exhibiting a decrease in their 30-min GLP-1 response. The abnormal 30-min GLP-1 response was mitigated in the NAFLD group following exercise training with a statistically significant increase (P < 0.001) and GLP-1 tAUC120 (P = 0.01) in both NAFLD and controls (Fig. 4B).

DISCUSSION

Our data reveal important differences in gut hormones between obese individuals with and without NAFLD, most notably GLP-1 (P < 0.001) and GLP-1 tAUC120 (P = 0.01) in both NAFLD and controls (Fig. 4B).

*Table 1. Subject characteristics and responses to exercise training*

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>NAFLD</th>
<th>Posttraining</th>
<th>NAFLD</th>
<th>Control</th>
<th>NAFLD</th>
<th>Control</th>
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<tr>
<td>Age, y</td>
<td>46.8 ± 6.3</td>
<td>55.8 ± 2.9</td>
<td>46.8 ± 5.8</td>
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<td>—</td>
<td>0.009</td>
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<tr>
<td>Weight, kg</td>
<td>92.6 ± 6.0</td>
<td>94.8 ± 3.5</td>
<td>92.6 ± 6.0</td>
<td>94.8 ± 3.5</td>
<td>—</td>
<td>—</td>
<td>0.009</td>
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</tr>
<tr>
<td>BMI, kg/m²</td>
<td>31.3 ± 1.2</td>
<td>33.2 ± 1.1</td>
<td>31.3 ± 1.2</td>
<td>33.2 ± 1.1</td>
<td>—</td>
<td>—</td>
<td>0.009</td>
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<tr>
<td>HTGC, %</td>
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<td>22.6 ± 3.1</td>
<td>3.5 ± 0.7</td>
<td>22.6 ± 3.1</td>
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<td>—</td>
<td>0.009</td>
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<tr>
<td>VAT, cm²</td>
<td>51.7 ± 10.3</td>
<td>124.7 ± 16.4</td>
<td>51.7 ± 10.3</td>
<td>124.7 ± 16.4</td>
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<td>—</td>
<td>0.009</td>
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<tr>
<td>FPG, mg/dl</td>
<td>93 ± 2</td>
<td>113 ± 5.3</td>
<td>93 ± 2</td>
<td>113 ± 5.3</td>
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<td>—</td>
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<tr>
<td>FPI, μU/ml</td>
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<td>25.4 ± 2.5</td>
<td>18.1 ± 3.5</td>
<td>25.4 ± 2.5</td>
<td>—</td>
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<tr>
<td>I_AUC, μU/ml</td>
<td>11.837 ± 2.104</td>
<td>15.955 ± 1.744</td>
<td>11.837 ± 2.104</td>
<td>15.955 ± 1.744</td>
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<td>FCPEP, μg/ml</td>
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<td>—</td>
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<td>0.009</td>
<td></td>
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<td>CPEP_AUC, ng/ml</td>
<td>793 ± 66</td>
<td>1,069 ± 115</td>
<td>793 ± 66</td>
<td>1,069 ± 115</td>
<td>—</td>
<td>—</td>
<td>0.009</td>
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<tr>
<td>FGLP-1, pg/ml</td>
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<td>12.4 ± 2.2</td>
<td>6.2 ± 0.2</td>
<td>12.4 ± 2.2</td>
<td>—</td>
<td>—</td>
<td>0.009</td>
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</tr>
<tr>
<td>FPYY, pg/ml</td>
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<td>117 ± 18.6</td>
<td>47.2 ± 6.4</td>
<td>117 ± 18.6</td>
<td>—</td>
<td>—</td>
<td>0.009</td>
<td></td>
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</tbody>
</table>

Data are presented as means ± SE. BMI, body mass index; HTGC, hepatic triglyceride content; VAT, visceral adipose tissue; FPG, fasting plasma glucose; FPI, fasting plasma insulin; I_AUC, insulin tAUC120; FCPEP, fasting C-peptide; CPEP_AUC, C-peptide tAUC120; FGLP-1, fasting GLP-1; FPYY, fasting PYY. P for interaction represents statistical significance between group responses after exercise training. *P < 0.05 from pre- to posttraining, †P < 0.05 from control.

Fig. 1. Insulin sensitivity in the NAFLD and control groups as determined by the Matsuda index at baseline and after the 7-day exercise-training program. *P < 0.05, significantly different from pre-exercise training. †P < 0.05, significantly lower than the control group. AU, arbitrary units.

Fig. 2. A: significant correlation (P = 0.049, r = 0.60) between visceral adipose tissue (VAT) and fasting PYY for NAFLD subjects before exercise training. B: nonsignificant correlation (P = 0.421, r = 0.277) between visceral adipose tissue (VAT) and fasting PYY for NAFLD subjects after exercise training.
ably higher fasting PYY and GLP-1 concentrations and a blunted 30-min PYY response to glucose ingestion in patients with NAFLD. Importantly, following short-term exercise, NAFLD patients showed a marked improvement in PYY and GLP-1 responses to glucose stimulation. These data suggest that compromised liver and metabolic function in NAFLD coexists with gastrointestinal dysfunction that may perpetuate the cycle of disease. However, short-term vigorous aerobic exercise training alleviated this effect, even in the absence of weight loss.

PYY regulates satiety, and circulating levels substantially rise in healthy individuals shortly after meal ingestion (16). It was previously shown that fasting PYY is directly associated with the degree of metabolic disease and that individuals with type 2 diabetes exhibit the highest fasting PYY levels (38). Although our analysis did not reveal any correlations between PYY and ISI, glucose or insulin measurements, it is difficult to say that NAFLD independently causes elevations in fasting PYY since all of our subjects had some level of insulin resistance. However, it is noteworthy that we observed a nearly 2.5-fold higher fasting PYY concentration among NAFLD patients, which, interestingly, was directly correlated with a visceral adiposity that was also 2.5 times higher than non-NAFLD controls. This was evident despite the fact that subjects had similar anthropometric measurements, which suggests that signals specific to visceral adipose tissue, such as adipokines, may in part regulate PYY concentrations in this patient group. Exercise training did not change fasting PYY concentrations in either the NAFLD or the control groups, and others have made similar observations in non-NAFLD populations (15, 22, 24). However, after exercise training, the correlation between visceral fat and fasting PYY was no longer evident, suggesting that exercise had a beneficial effect on PYY regulation independent of visceral fat, considering the latter did not change.

In addition to altered fasting PYY, several studies have shown a blunted acute PYY response to food stimulation in subjects who are obese (7, 9), and this is now considered to be a contributing factor to the underlying pathophysiology of obesity. The rapid increase in PYY observed after food ingestion is an important satiety signal that controls the overall intake of food during a meal. In the present study, the diminished acute 0–30-min PYY response to glucose, which was most evident in the NAFLD group, may lead to excess energy consumption during a meal, perpetuating the downward spiral of obesity-related comorbidities in these patients. Exercise training can have an anorexigenic effect, which is mediated in part by increased PYY secretion (3). In the current study, exercise training resulted in an improvement in the 30-min

Fig. 3. A: dynamic plasma PYY response to glucose (0–30 min) in NAFLD and control subjects at baseline and after the 7-day exercise-training program. *P < 0.05, significant increase from fasting. +Trend (P = 0.06) for an increase from fasting. ●P < 0.05, significantly different from the control group. Trend (P < 0.06) for an increase from fasting.

B: PYY total area under the curve (tAUC, 0–120 min) after glucose ingestion in NAFLD and control subjects at baseline and after exercise training. There were no significant differences between groups, nor were there any significant changes resulting from exercise training.

Fig. 4. A: dynamic plasma GLP-1 response to glucose (0–30 min) in NAFLD and control subjects at baseline and after the 7-day exercise-training program. *P < 0.05, significant increase from fasting. ●P < 0.05, significantly lower than pre-exercise training.

B: GLP-1 total area under the curve (tAUC, 0–120 min) after glucose ingestion in NAFLD and control subjects at baseline and after exercise training. *P < 0.05, significantly lower than pretraining.
PYY response to glucose ingestion in the NAFLD group. Previously, we observed improved glucose-induced PYY secretion after 12 wk of exercise training in older insulin-resistant obese adults (19). Our finding that 7 days of aerobic exercise can produce a similar result indicates that exercise elicits a very rapid and potent response, even in the presence of severe metabolic disease.

Striking differences between fasting and glucose-induced GLP-1 levels were also observed between the NAFLD and control groups, with fasting GLP-1 being 1.7 times higher in the NAFLD group. Multiple factors could have contributed to the elevated fasting GLP-1 levels, including a loss of GLP-1 sensitivity due to excessive ectopic fat and/or visceral fat (20, 31, 39), systemic chronic inflammation (6) that is associated with NAFLD (30) and excess visceral fat (31), and/or increased GLP-1 secretion from hepatic progenitor cells (HPC) (27). In the context of NAFLD, HPCs are of particular interest. NAFLD causes damage to hepatocytes, which leads to increased HPC activity as a compensatory mechanism to maintain liver function (14). It was recently reported that adolescents with NAFLD had activated HPCs that overexpress GLP-1 (27). Subjects with NAFLD in our study had elevated markers of liver damage and apoptosis (8), and therefore it is possible that increased HPC activity contributed to higher circulating GLP-1 levels, suggesting an independent role of NAFLD-associated liver dysfunction in altered gut hormone concentrations.

Exercise training reduced fasting GLP-1 in the subjects with NAFLD, which is supported by a recent cross-sectional study reporting lower fasting GLP-1 levels in aerobically trained healthy individuals (21). Exercise training was shown to reduce markers of hepatocyte apoptosis among NAFLD patients (8), which may decrease the number of activated HPCs and related expression of GLP-1. While this mechanism is speculative at this point, it is certainly worth further investigation, as it suggests a direct link between NAFLD-associated liver dysfunction and hyperinsulinemia via the incretin effect of GLP-1. Furthermore, this mechanism may explain how exercise lowers fasting GLP-1 while at the same time improving liver function.

Prior to exercise training, the dynamic 0–30-min GLP-1 response to glucose was insignificantly increased in NAFLD patients compared with a significant increase among obese controls. The lack of statistical significance is likely due to the high degree of variability in the GLP-1 responses among the NAFLD subjects. On the basis of the data presented herein and previously (1, 4, 24, 26, 40), we suggest that NAFLD-associated metabolic disruption, in addition to obesity, disturbs signals along the hepatic-gastroenteropancreatic pathway that affect GLP-1 secretion leading to an atypical and more variable response to glucose ingestion.

Few studies have examined GLP-1 changes after exercise training. We found that exercise training reduced the GLP-1 tAUC120 in NAFLD patients. This change mirrored improvements in insulin secretion, indicative of an improved incretin effect (26). Our results are supported by those of Chanoine et al. (4), who observed an improved GLP-1 response to a meal in obese adolescents after 5 days of exercise training. Conversely, others have reported no change in fasting GLP-1 (1, 24) or glucose-stimulated GLP-1 secretion in obese individuals after exercise training, or when comparing exercise trained vs. untrained groups (21, 41). Our results suggest that short-term exercise training improves GLP-1 sensitivity in people with NAFLD.

In conclusion, fasting GLP-1 and PYY, as well as the responses to glucose ingestion, indicate that NAFLD interferes with normal gut hormone regulation. However, short-term aerobic exercise training results in improved metabolic regulation, glucose sensitivity, and PYY and GLP-1 responses to nutrient ingestion, as well as decreased fasting PYY and GLP-1 concentrations in individuals with NAFLD. These findings support the use of aerobic exercise training as an effective intervention for normalizing gut hormone disturbances in patients with NAFLD and provide direction for future mechanistic studies that would reveal the underlying pathophysiology of this metabolic disease.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES
