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Resting and Exercise Energy Metabolism After Liver Transplantation for Nonalcoholic Steatohepatitis

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Background. Nonalcoholic steatohepatitis (NASH) is a leading indication for liver transplantation (LT). We hypothesized that weight gain after LT may be exacerbated by reduced metabolic rates due to the LT procedure, particularly during exercise. We aimed to compare resting and exercise energy expenditure between patients transplanted for NASH and nontransplant nonalcoholic fatty liver disease (NAFLD) subjects. **Methods.** NASH LT recipients (>1-year post, n = 14) and NAFLD controls (n = 13) underwent analysis of body composition, resting energy expenditure (REE), and exercise energy expenditure (VO_{2max}), the latter using a ramped-Bruce protocol assessed by expired gas analysis and peak heart rate. **Results.** Participants were mean 61.5 ± 7.9 years, 48.1% men, and 66.7% white. Baseline comorbidities were similar between groups. Among men, mean REE adjusted for total (17.7 vs 18.8, $P = 0.87$) and lean body mass (23.5 vs 26.9, $P = 0.26$), as well as VO_2 (20.1 vs 23.9, $P = 0.29$), was lower in NASH LT recipients compared with NAFLD controls, respectively, although not statistically significant. However, female NASH LT recipients had significantly lower mean REE than NAFLD controls when adjusted for total (14.2 vs 18.9, $P = 0.01$) and lean body mass (19.3 vs 26.5, $P = 0.002$), as well as significantly lower VO_{2max} (14.4 vs 20.6, $P = 0.017$). **Conclusions.** NASH LT recipients, particularly women, have lower REE and exercise energy expenditure compared with nontransplant NAFLD patients. More aggressive diet and exercise programs for post-LT NASH recipients to account for reduced resting and exercise metabolic rates may attenuate weight gain in this vulnerable population.

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Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease and is largely fueled by obesity and the metabolic syndrome.¹ Nonalcoholic steatohepatitis (NASH), a subset of NAFLD, is characterized by fatty change accompanied by lobular inflammation and hepatocellular injury and can result in progressive fibrosis that necessitates liver transplantation (LT).^{2,3} In fact, 2 large studies have shown that 66% of patients with diabetes or obesity older than 50 years had NASH

with advanced fibrosis.^{4,5} Studies have estimated that the development of NASH occurs over decades; however, after LT, disease may recur at an accelerated rate, as early as within 2 years of transplant.⁶⁻⁸ After LT, patients typically gain weight and metabolic syndrome features persist or worsen. The prevalence of metabolic syndrome after LT is 44% to 58%,⁹⁻¹¹ and not surprisingly, the leading cause of morbidity and mortality after LT is cardiovascular disease.^{12,13} These consequences are particularly relevant in those transplanted

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for NASH cirrhosis, a population that appears to have increased cardiovascular morbidity before and after transplant.^{14,15}

The mechanisms for accelerated weight gain and metabolic syndrome after LT are not well understood. Studies have implicated preexisting and new risk factors for post-LT metabolic syndrome, such as older age, men, pre- and post-LT weight gain and diabetes, the etiology of liver disease (eg, NASH cirrhosis), and many of the immunosuppressive agents.^{11,16} In addition, visceral adiposity developing post-LT may promote inflammation, insulin resistance, and liver fat accumulation, again perpetuating the development of metabolic syndrome.¹¹

Resting energy expenditure (REE) is a marker of metabolic status¹⁷ and has been studied in patients with acute and chronic liver disease. While REE seems to remain stable in patients with cirrhosis due to alcohol or viral hepatitis compared to healthy controls,^{18,19} resting metabolic rates are lower in patients with NASH.²⁰ However, the impact of LT on REE is debated in the literature. An evaluation of REE, body composition, and dietary intake found that the overall REE was reduced at the end of 1 year after LT with increased body weight and positive energy balance.²¹ This reduced REE could contribute to the weight gain seen in NASH LT recipients, despite imposed caloric restriction. Conversely, others have shown that posttransplant patients are not hypometabolic.²² Importantly, studies on energy expenditure during activities that increase oxygen consumption (ie, meals and exercise) have not been reported, and patients typically fail to lose weight post-LT despite seemingly appropriate diet and exercise strategies.²³ A better understanding of the relationship between exercise energy expenditure and transplant status could help individualize dietary and exercise programs in LT recipients.

Therefore, we performed a study to assess metabolic composition, metabolic rates, and exercise energy expenditure in NASH LT recipients compared to NAFLD controls. We hypothesized that NASH LT recipients would have both lower resting metabolic rates and exercise energy expenditures.

MATERIALS AND METHODS

Study Design

In this single-center, cross-sectional study, participants were recruited and divided into 2 groups—participants who had undergone LT for NASH/cryptogenic cirrhosis ($n = 14$) and nontransplant NAFLD controls ($n = 13$). Participants were further subdivided into men and women to create a total of 4 groups given inherent sex-related differences in metabolic rates.^{24,25} All participants were being regularly followed in the hepatology and LT clinics at Northwestern Memorial Hospital and were recruited between March 2015 and May 2016. NASH LT recipients were greater than 18 years old, between 1 and 10 years posttransplant, and had no other indication for transplantation. We excluded participants if they had received multiorgan transplant, had been retransplanted, or were hospitalized in the past month. NAFLD control patients were recruited with comparable age, body mass index (BMI), and sex to the LT recipient group, and were confirmed to have NAFLD by biopsy ($n = 10$) or imaging ($n = 3$) with exclusion of other liver disease.

The Northwestern University Institutional Review Board approved the research protocol and all participants signed

the consent form before enrollment. The same trained investigator (H.S.S.) performed all measurements to reduce errors. Participants underwent metabolic assessment, REE, and exercise energy expenditure on the same day of testing (Figure 1). All participants were in stable condition at the time of the study and able to participate in the required study tasks.

Metabolic Assessment

A complete physical exam was performed for each participant. All participants fasted for 12 hours before the following laboratory assessments: complete blood count, comprehensive metabolic panel, lipid profile, hemoglobin A1c, and immunosuppressive drug levels (LT group). Anthropometric evaluation included body weight (seca700 Mechanical Column Scale w/eye-level beam, SECA Corp., Chino, CA), height (to nearest 1-half centimeter), and skinfold thickness (Lange skinfold caliper; Cambridge Scientific Industries, Cambridge, MA). Estimations of percent body fat were made from the average of 3 skinfold measurements at each of four sites as previously described.²⁶ Excessive weight was defined by BMI according to the World Health Organization.²⁷

REE

We determined REE via open-circuit indirect calorimetry using a computerized metabolic measurement cart (TrueOne 2400, ParvoMedics, Sandy, UT). Ventilation is measured by directing expired gases through an oronasal mask (7400 Series Oro-Nasal Mask with a 2700 Two-Way Nonbreathing Valve; Hans Rudolph, Inc., Shawnee, KS) to a heated linear pneumotachometer (3813 Heated Pneumotach, Hans Rudolph, Inc., Shawnee, KS) and a 4-L baffled mixing chamber. The mixed expired gas was continuously sampled using a Nafion tube (Permapure, Toms River, NJ) by a paramagnetic oxygen analyzer (0-25% range, with 0.1% accuracy), a single-beam infrared carbon dioxide analyzer (0-10% range, with 0.1% accuracy) to measure fractions of expired oxygen ($F_{E}O_2$) and carbon dioxide ($F_{E}CO_2$). The analyzers were calibrated before each measurement with room air and a 2-point standard gas (15.09% O_2 , 4.01% CO_2 , remainder N_2). The pneumotach was calibrated (5 strokes at graduated flow-rates from 50 to 80 $L \cdot min^{-1}$ up to 400 $L \cdot min^{-1}$) using a 3.0-L syringe (5530 Calibration Syringe, Hans Rudolph, Shawnee, KS).

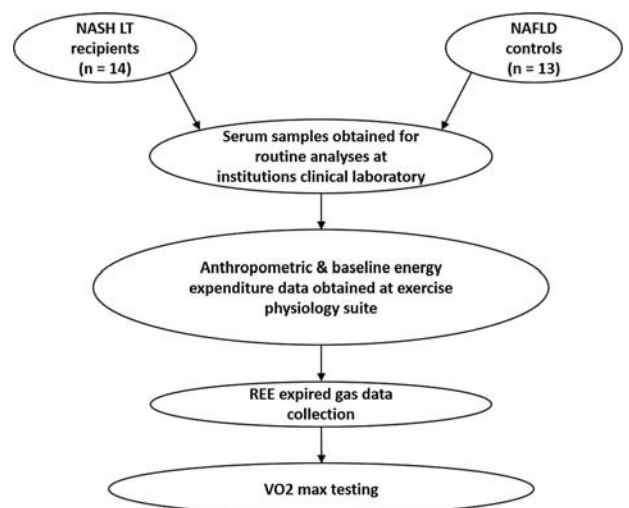


FIGURE 1. Schematic of study design.

We measured exhaled gases for 20 minutes after an initial 5 minutes for calibration and calculated the REE by mean VO_2 and VCO_2 per minute according to the Weir formula.²⁸ The REE was indexed to body mass (REE/body mass) and to fat free mass (REE/Lean Body Mass). Predicted REE was calculated using the Harris-Benedict formula (REEHB).²⁹ We then classified participants as hypermetabolic (REE/REEHB > 120%) or hypometabolic (REE/REEHB < 80%).^{30,31}

Exercise Energy Expenditure

Before aerobic fitness testing, each participant's heart rate (HR) was monitored using a 12-lead electrocardiogram. Individuals first practiced walking on the treadmill while being given instructions on proper treadmill walking technique (eg, not holding onto bars and minimizing trunk flexion). Open circuit spirometry via computerized metabolic cart (as described for REE) and treadmill (PPS Med, Woodway, Waukesha, WI) was used to measure maximal aerobic capacity ($\text{VO}_{2\text{max}}$). We used a ramped Bruce protocol to volitional fatigue.³² We monitored and recorded the ventilatory and gas exchange parameters, respiratory rate, tidal volume, VO_2 and VCO_2 every 15 seconds throughout and after exercise. Glucose levels were checked pre and postexercise.

Statistical Analyses

We stratified patients by sex (male vs female) and transplant status (NAFLD controls vs NASH LT recipients) and reported summary statistics (mean, SD, range) for the 4 groups. A χ^2 test of independence was performed to examine the association between race, sex, β -blocker usage, and transplant status. Two sample unpaired *t*-test was employed to assess the effect of sex and transplant status on selected physiological parameters. The Pearson correlation coefficient was used to assess the association between delta weight and measured $\text{VO}_{2\text{max}}$. Statistical significance was established at $P < 0.05$, and all analyses were performed using SPSS (IBM SPSS Statistics for Macintosh, Version 23.0. Armonk, NY).

RESULTS

Patient Characteristics

From our LT population, 103 NASH LT recipients met inclusion/exclusion criteria and received phone contact to gauge interest in participation. 14 agreed to participate and were consented for the study. NASH LT recipients had a mean age of 64 years (range, 53-81 years), mean time from LT is 5.2 ± 2.7 years, 42.8% were men and 78.5% were white. Comparison of race among the NAFLD controls using a χ^2 analysis was not shown to be statistically significant ($P = 0.39$). Similarly, there was no significant difference in race among NASH LT recipients ($P = 0.46$). The majority was on tacrolimus (64.2%), 35.7% mycophenolate mofetil, 14.3% cyclosporine, 7.1% on prednisone, and 35.7% on a β -blocker. 35.7% had type 2 diabetes, 50% had hypertension, and 35.7% had dyslipidemia. NAFLD control patients, identified from a list of Hepatology clinic patients, were contacted by phone and email. From these 92 patients, 13 agreed to participate in the study. Among the NAFLD controls, mean age for all NAFLD controls was 58.5 years of age (range, 48.2-71.5 years). 15.4% of patients were on a β -blocker, 46.2% had type 2 diabetes, 61.5% had hypertension,

and 38.4% had dyslipidemia. Neither a history of diabetes ($P = 0.37$) nor β -blocker usage ($P = 0.41$) were statistically significant when compared among the groups.

Metabolic Assessment and Laboratory Data

Table 1 shows patient characteristics with breakdown per sex. Age, BMI, percentage body fat, and lean body mass were not significantly different between the NASH LT recipients and NAFLD controls. Among the markers for metabolic syndrome, there were no significant differences between groups in total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, fasting blood sugar (mg/dL) and hemoglobin A1c (%).

Comparison of REEs

The mean measured REE, both adjusted for total body mass and lean body mass, as well as the ratio of measured REE to predicted REE using the HB equations are shown in Table 2. In women, NAFLD controls had significantly higher mean REE (kcal/d per kg) compared with NASH LT recipients when adjusted for total body mass (18.86 vs 14.20, $P = 0.01$) and lean body mass (26.47 vs 19.34, $P = 0.002$) (Figure 2). NAFLD females, on average had a higher ratio of measured REE to predicted REE as compared with NASH LT recipients (1.00 vs 0.81, $P = 0.09$), albeit not significant. Per definitions of hypermetabolic (REE/REEHB > 120%) or hypometabolic (REE/REEHB < 80%), this lower ratio in NASH LT recipients suggests a more hypometabolic state compared with NAFLD controls.^{30,31}

Among men, mean REE was also higher in NAFLD controls compared with NASH LT recipients, but these differences were not statistically significant when adjusted for either total body mass (18.77 vs 17.70, $P = 0.87$) or lean body mass (26.85 vs 23.45, $P = 0.26$) (Figure 2). Additionally, there was no significant difference between the ratios of measured REE to predicted REE for NAFLD controls versus NASH LT recipients (0.98 vs 0.92, $P = 0.87$).

Comparison of Exercise Energy Expenditures

Table 3 shows mean values for measured $\text{VO}_{2\text{max}}$ for total body mass, $\text{VO}_{2\text{max}}$ exercise parameters (resting and peak HRs), peak respiratory exchange ratios (RERs), and metabolic equivalents (METs). Among women, NAFLD controls had a significantly higher mean $\text{VO}_{2\text{max}}$ (mL/kg/min) compared to NASH LT recipients when adjusted for total body mass (20.59 vs 14.36, $P = 0.017$) (Figure 3). Peak HR during $\text{VO}_{2\text{max}}$ testing was also significantly higher in NAFLD women compared to NASH LT females (146.3 vs 115.2, $P = 0.013$). METs, calculated from VO_2 data, were higher in NAFLD females compared with NASH LT females (5.88 vs 4.10, $P = 0.02$).

Male exercise energy expenditure was higher in NAFLD controls compared to NASH LT recipients, though not statistically significant (23.85 vs 20.10, $P = 0.29$) (Figure 3). Parameters to assess for true $\text{VO}_{2\text{max}}$, peak HR and peak RER were not statistically distinct between the 2 groups. METs were higher in NAFLD males compared with NASH LT males (6.81 vs 5.74, $P = 0.29$).

Among the NASH LT recipients, there was an inverse correlation between delta weight (posttransplant-pretransplant) and measured $\text{VO}_{2\text{max}}$ in both males and females. Males were strongly associated with this comparison with an $r = -0.89$

TABLE 1.**Comparison of anthropometric and laboratory data between NAFLD controls and NASH LT recipients stratified by sex**

	Male			Female		
	NAFLD controls (n = 7)	NASH LT recipients (n = 6)	P	NAFLD controls (n = 6)	NASH LT recipients (n = 8)	P
Age, y	58.3 ± 7.4	60.4 ± 3.5	0.96	58.8 ± 6.8	67.1 ± 9.7	0.20
Race			0.46			0.39
White	5 (71.4%)	4 (66.7%)		2 (33.3%)	7 (87.5%)	
AA	1 (14.3%)	0 (0.0%)		2 (33.3%)	0 (0.0%)	
Hispanic	1 (14.3%)	1 (16.7%)		2 (33.3%)	1 (12.5%)	
Asian	0 (0.0%)	1 (16.7%)		0 (0.0%)	0 (0.0%)	
BMI, kg/m ²	33.9 ± 4.5	33.2 ± 5.4	0.99	30.8 ± 3.0	29.5 ± 1.8	0.93
% body fat	29.7 ± 7.3	24.7 ± 9.1	0.48	28.8 ± 1.5	26.5 ± 4.5	0.90
Lean body mass (kg)	77.6 ± 4.4	79.8 ± 10.0	0.92	56.6 ± 4.3	59.6 ± 6.1	0.82
Cholesterol (mg/dL)	142.8 ± 17.9	152.4 ± 29.8	0.98	178.0 ± 58.2	162.0 ± 38.6	0.88
TG (mg/dL)	129.2 ± 59.4	377.6 ± 598.9	0.50	175.5 ± 85.7	132.8 ± 78.5	0.99
LDL, mg/dL	79.2 ± 5.5	74.3 ± 22.5	1.00	103.5 ± 57.9	90.8 ± 30.0	0.91
HDL, mg/dL	37.6 ± 5.4	42.4 ± 15.4	0.88	39.3 ± 9.4	44.6 ± 9.2	0.78
Fasting BS, mg/dL	117.0 ± 8.2	142.7 ± 49.4	0.43	124.5 ± 20.3	107.5 ± 14.1	0.67
Hemoglobin A1c, %	6.2 ± 0.8	6.2 ± 1.7	1.00	6.4 ± 0.7	5.3 ± 0.4	0.27
History of diabetes	2 (28.6%)	3 (50.0%)	0.37	4 (66.7%)	2 (25.0%)	0.37
On a β-blocker as part of medication regimen (n)	2 (28.6%)	2 (33.3%)	0.41	0 (0.0%)	3 (37.5%)	0.41
Stage of fibrosis						
Stage 1	0 (0.0%)			4 (66.7%)		
Stage 2	3 (42.9%)			2 (33.3%)		
Stage 3	3 (42.9%)			0 (0.0%)		
Stage 4	1 (14.3%)			0 (0.0%)		
Immunosuppression						
Tacrolimus (n)		4 (66.7%)			5 (62.5%)	
MMF (n)		1 (16.7%)			4 (50.0%)	
Cyclosporine (n)		0 (0.0%)			2 (25.0%)	
Prednisone (n)		0 (0.0%)			1 (12.5%)	

Data are listed as n (%). Unless otherwise indicated, values above are listed as mean ± SD.

AA, African Americans; TG, triglycerides; LDL, low density lipoprotein; HDL, high-density lipoprotein; BS, blood sugar. Data are listed as n (%). Unless otherwise indicated, values above are listed in the form Mean ± SD.

($P = 0.04$) and females were weakly associated with this comparison with an $r = -0.28$ ($P = 0.51$) (Figure 4).

DISCUSSION

Several studies to date have described resting metabolic rates in the post-LT population,^{21,22} but little is known about the metabolic responses to exercise after transplantation. Our study aimed to evaluate changes in metabolic rates during exercise, specifically assessing for differences after LT that

might explain weight gain and poor success with weight loss programs in post LT patients. We found that LT recipients, particularly females, have both lower REE and exercise energy expenditure compared to NAFLD controls. While this post-LT change could be attributed to differences in age or BMI, our 2 groups were similar with respect to demographics and metabolic risk factors. An increased prevalence of sarcopenia after transplant has previously been linked to the development of metabolic syndrome in post-LT patients.³³ In our study, however, NASH LT recipients had

TABLE 2.**Comparison of REEs between NAFLD controls and NASH LT recipients stratified by sex**

	Male			Female		
	NAFLD controls (n = 7)	NASH LT recipients (n = 6)	P value	NAFLD controls (n = 6)	NASH LT recipients (n = 8)	P value
Relative REE for total body mass, kcal/d per kg)	18.8 ± 1.98	17.7 ± 3.44	0.87	18.9 ± 1.25	14.2 ± 2.71	0.01
Relative REE for lean body mass, kcal/d per kg	26.9 ± 3.09	23.5 ± 3.57	0.26	26.5 ± 1.71	19.3 ± 3.87	0.002
Absolute REE, kcal/d	2080 ± 241	1880 ± 409	0.58	1500 ± 181	1150 ± 252	0.13
Predicted REE (using HB equations), kcal/d	2110 ± 193	2040 ± 275	0.90	1510 ± 129	1430 ± 133	0.83
Ratio of measured REE to predicted REE	0.98 ± 0.08	0.92 ± 0.17	0.87	1.00 ± 0.16	0.81 ± 0.16	0.09

All data are presented as mean ± SD.

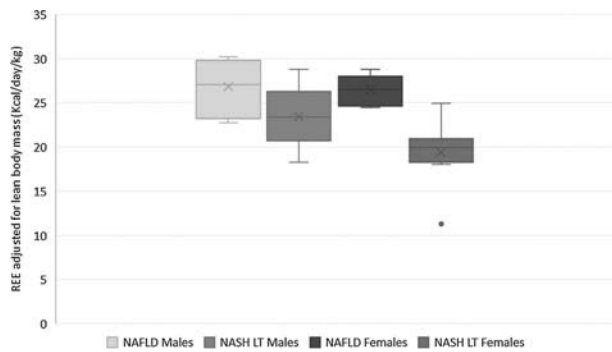


FIGURE 2. Box plot depicting REE among patient groups, adjusted for lean body mass. The middle line refers to the median, and the box represents the quartiles. The X depicts the mean of each data set. REE was significantly lower in female NASH LT recipients compared to NAFLD controls ($P = 0.002$).

similar percent body fat and lean body mass compared to NAFLD controls, suggesting that loss of skeletal muscle mass is unlikely to be a major contributor. The only observable difference was that patients in the NASH LT group received a liver transplant, suggesting that a factor inherent to the donor graft or immunosuppression led decreased metabolic function during both rest and exercise.

Overall, average VO_{2max} values in our study were lower than those of similarly aged healthy individuals based on NHANES data (mean VO_{2max} (mL/kg per min) of 31 in men and 23 in women).³⁴ Furthermore, in fitness rankings as described by Heyward,³⁵ the non-LT males in this study would be classified as “poor” and male LT recipients as “very poor.” Similarly, non-LT females would be classified as “fair” and female LT recipients as “very poor.” VO_{2max} values were lowest in patients who were NASH LT recipients, a unique finding not seen previously in the literature. In fact, most patients undergo significant improvement in muscle strength and functional status—with respect to general health, activities of daily living function, and activity level—after transplantation.^{36,37} As such, one may expect a recipient’s metabolic and functional status to eventually mirror that of the general or more likely the noncirrhotic NAFLD population. The fact that this return to “normal” was not seen in our NASH LT recipients, even in patients who were 10 years post-LT, is somewhat surprising and may be due to the LT procedure independently. Much of the literature on REE has incorporated

patients who received LT for any reason^{21,36}—not just those with NASH and NAFLD pathology—and evaluated patients serially but for no more than 1 year post-LT.

The decrease in REE and exercise energy expenditure seen in NASH LT recipients reached statistical significance only in female patients. Alterations in hepatic innervation after LT due to loss of afferent and efferent neural connections have been implicated as a potential explanation for changes in post-LT metabolic rates. The lack of efferent output, important for upregulation of metabolism, may contribute to decreases in REE in post-LT patients as demonstrated in vagotomy animal models.^{38,39} However, this mechanism would not explain the sex difference we observed. As such, we propose that a sex-specific factor contributes to the decrease in energy metabolism posttransplant. All females in our study were older than 50 years and likely postmenopausal, and it is known that this population is at increased risk of developing metabolic complications.^{40,41} Thus, a reduced estrogen state after transplantation in women may contribute to an even more profound decrease in metabolic rates and worsening of preexisting metabolic syndrome compared to males.

Decreased exercise energy expenditure after transplantation may significantly impact a patient’s ability to lose weight post-LT and contribute to weight gain. VO_{2max} values correlate directly to METs, which indicate the amount of energy a person must expend to complete a standardized task.⁴² METs, a measure of accumulated metabolic workload during an exercise session, are often helpful as a secondary measure of physical activity and reflect the sub-maximal exercise capacity of a patient. We found that peak METs in NASH LT recipients were extraordinarily low, indicating that their ability to perform tasks, even those required for daily living, may be quite limited. Thus in NASH LT recipients who have comparable BMIs to NAFLD controls but lower peak METs, losing weight will be significantly more difficult despite expending equivalent effort at rest and exercise. This finding may help explain why the post-LT population has great difficulty with weight loss. Furthermore, the inverse relationship between weight gain posttransplant and energy expenditure sheds light that too much weight gain is associated decreased levels of fitness in the posttransplant population. As such, clinicians can consider individualized diet and exercise programs for each patient, perhaps guided by baseline and serial tests utilized in our study, to meet his or her metabolic needs and overcome metabolic inefficiency.

TABLE 3.

Comparison of exercise energy expenditures between NAFLD controls and NASH LT recipients stratified by sex

	Male			Female		
	NAFLD controls (n = 7)	NASH LT recipients (n = 6)	P value	NAFLD controls (n = 6)	NASH LT recipients (n = 8)	P value
Measured relative VO_{2max} , mL/kg per min	23.9 ± 4.41	20.1 ± 4.93	0.29	20.6 ± 2.39	14.4 ± 2.10	0.017
% predicted VO_{2max}	92.0 ± 10.7	78.1 ± 10.7	0.14	99.5 ± 11.3	77.4 ± 9.71	0.004
METs	6.81 ± 1.26	5.74 ± 1.41	0.29	5.88 ± 0.68	4.10 ± 0.60	0.02
Exercise parameters						
Resting HR, beats per minute	88.3 ± 14.8	84.8 ± 13.9	0.96	85.2 ± 10.4	65.0 ± 9.97	0.028
Peak HR, beats per minute	153 ± 18.8	142 ± 12.5	0.73	146 ± 13.1	115 ± 19.2	0.013
Peak RER, mL O ₂ /kg per min	1.10 ± 0.08	1.14 ± 0.05	0.89	1.12 ± 0.08	1.09 ± 0.14	0.94

All data are presented as mean ± SD.

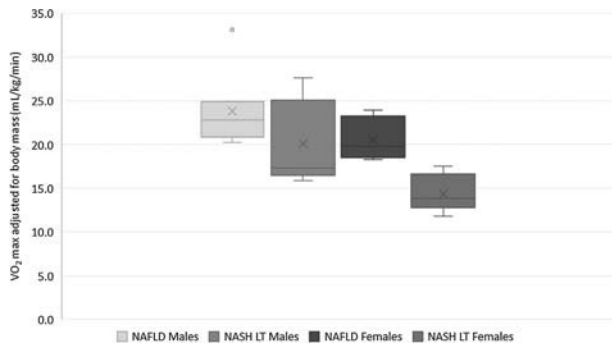


FIGURE 3. Box plot depicting VO_{2max} during exercise among patient groups, adjusted for total body mass. The middle line refers to the median, and the box represents the quartiles. The X depicts the mean of each data set. VO_{2max} was significantly lower in female NASH LT recipients compared to NAFLD controls ($P = 0.017$). NAFLD and NASH LT.

A major limitation of our study was its cross-sectional nature, which prevented comparison of an individual's metabolic rate before and after transplant. We attempted to address this by recruiting a group of non-LT NAFLD patients with a comparable age, BMI, and sex distribution. Our selection of patients who received LT only for the indication of NASH limits the study's generalizability to the universal LT population. However, the NASH population was intentionally chosen to investigate changes in metabolic factors in patients at greatest risk of developing the metabolic syndrome. Isolation of NASH and NAFLD patients in our study may have allowed us to capture the decrease in post-LT metabolic rates that other studies have not seen. Future studies should consider examining additional LT populations at risk for metabolic syndrome. Additionally, it should be noted that the variability of indirect calorimetry measurements, in general, is a limitation to any study using this measure. We attempted to minimize this variation by having only 1 observer who is trained as an exercise physiologist collect the calorimetry data.

Our study's small sample size also limits the conclusions that can be drawn from our data, especially within the male cohort. In so far as this investigation was a pilot study examining

energy metabolism in the posttransplant population, we did not account for age-related changes with respect to REE or energy expenditure. Understanding that the NASH LT females were about 8 years older than non-LT NAFLD females, our goal in this study was to present that raw data without adjusting for age related changes in energy expenditures, as a future study would be to study this phenomenon with a larger sample size. Another limitation of this study is the differences between β -blocker usage among the NASH LT recipients versus the non-LT NAFLD patients. This difference could potentially confound the findings and prevent patients from achieving true target HR max. We circumvented this issue, however, by measuring perceived- VO_{2max} with respect to patient's exhaustion, rather than aiming for a target HR for achieving VO_{2max} assessments.

Most studies investigating metabolic rates in LT patients, however, have been performed at a single time point or have followed patients serially at multiple time points for no more than up to 1-year post-LT. A study measuring REE and 6MWT before and after application of a generalized exercise program in post-LT patients did find improvements in both metrics compared to nonexercising controls, but collected data at only 2 discrete time points.⁴³ Future studies will need to follow patients longitudinally for greater than 1 year, with evaluation every few months to determine trends in REE and exercise energy expenditure over time. Future exercise studies should also incorporate metabolic carts and focus on females specifically to identify whether our findings are repeatable in larger populations.

In summary, our results demonstrate that female NASH LT recipients have lower resting and exercise energy expenditure compared to female NAFLD controls. While differences in these parameters were observed between male participants as well, the results were not statistically significant. The presence of lower metabolic rates in NASH LT recipient females, specifically, suggests that sex-specific hormonal factors may impact post-LT physiology. Our results could be quite informative in counseling NASH LT recipients on fitness and weight loss, as a standard prescription for exercise is unlikely to apply to this special population.

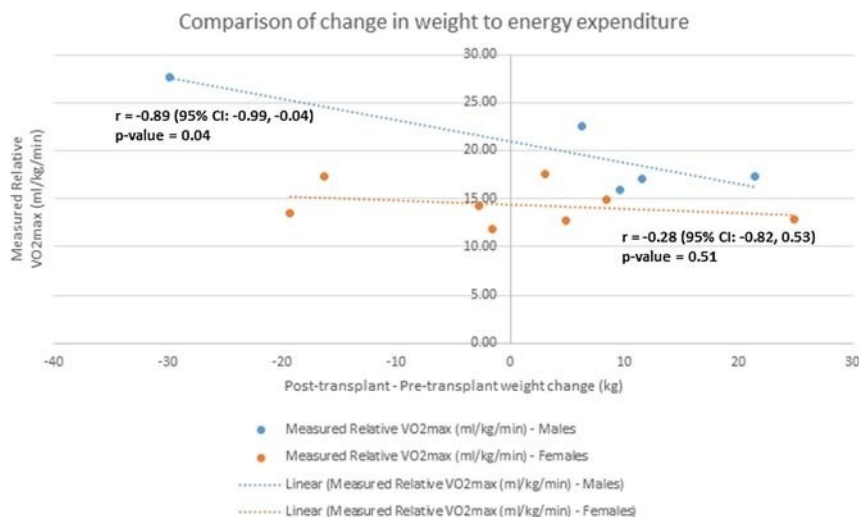


FIGURE 4. Delta weight between NASH LT recipients and pretransplant compared to exercise energy expenditure. Both male and female weights were inversely correlated with VO_{2max} measurements.

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