Impact of Hepatic Steatosis on Resting Metabolic Rate and Metabolic Adaptation in Response to Intentional Weight Loss

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Weight loss is the primary intervention for nonalcoholic fatty liver disease (NAFLD). A decrease in resting metabolic rate (RMR) out of proportion to the degree of weight loss may promote weight regain. We aimed to determine the impact of hepatic steatosis on weight loss-associated changes in RMR and metabolic adaptation, defined as the difference between predicted and measured RMR after weight loss. We retrospectively analyzed prospectively collected data from 114 subjects without diabetes (52 with NAFLD), with body mass index (BMI) >35, and who enrolled in a 6-month weight loss intervention. Hepatic steatosis was determined by unenhanced computed tomography scans by liver:spleen attenuation ratio <1.1. RMR was measured by indirect calorimetry. At baseline, patients with hepatic steatosis had higher BMI, fat mass (FM), fat-free mass (FFM), and RMR (RMR, 1,933 kcal/day; 95% confidence interval [CI], 841-2,025 kcal/day; versus 1,696; 95% CI, 1,641-1,751; P < 0.0001). After 6 months, the NAFLD group experienced larger absolute declines in weight, FM, and FFM, but percentage changes in weight, FFM, and FM were similar between groups. A greater decline in RMR was observed in patients with NAFLD (−179 kcal/day; 95% CI, −233 to −126 kcal/day; versus −100; 95% CI, −51 to −150; P = 0.0154) for the time × group interaction, and patients with NAFLD experienced greater metabolic adaptation to weight loss (−97 kcal/day; 95% CI, −143 to −50 kcal/day; versus −31.7; 95% CI, −74 to 11; P = 0.0218) for the prediction × group interaction. The change (Δ) in RMR was significantly associated with ΔFM, ΔFFM, and baseline RMR, while metabolic adaptation was significantly associated with female sex and ΔFM only. Conclusion: Hepatic steatosis is associated with a greater reduction in FM, which predicts RMR decline and a higher metabolic adaptation after weight loss, potentially increasing the risk of long-term weight regain. (Hepatology Communications 2019;3:1347-1355).

Multiple studies have proven the efficacy of weight loss for treating nonalcoholic fatty liver disease (NAFLD). There appears to be a dose-response relationship between weight loss and histologic improvements as 10% or greater weight loss is associated with marked reductions in inflammation and fibrosis.1 Despite the clinical benefit, sufficient weight loss in ambulatory patients with NAFLD remains challenging. In an analysis of a large tertiary hepatology practice, we

Abbreviations: AEE, energy expenditure in physical activity; BMI, body mass index; CI, confidence interval; CT, computed tomography; DO, diet alone; FFM, fat-free mass; FM, fat mass; L/S ratio, liver:spleen ratio; NAFLD, nonalcoholic fatty liver disease; PA, physical activity; RMR, resting metabolic rate; TDEE, total daily energy expenditure.

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reported that only 19.8% of patients achieve 5% weight loss. Furthermore, successful maintenance of weight loss outside of clinical research trials is elusive; follow-up studies of clinical weight loss trials demonstrated that 77% of patients regain weight within 3 years of initial weight loss. Therefore, there is an unmet need to understand barriers to successful weight loss in patients with NAFLD.

Metabolic adaptation may represent one explanation for poor weight loss rates in NAFLD. Metabolic adaptation refers to physiologic declines in energy expenditure and resting metabolic rate (RMR) in response to weight loss that exceed changes predicted by body composition. Reduced RMR after initial weight loss is an independent predictor of further weight loss, and low RMR is a strong predictor of future weight regain across all overweight classifications. It is unclear, however, if metabolic adaptation also negatively impacts weight loss attempts in patients with NAFLD.

The aim of our study was to examine the effect of hepatic steatosis on RMR responses to weight loss interventions. Using body composition and energy expenditure data acquired from patients with severe obesity who were undergoing structured weight loss treatment, we examined the relationship between weight loss interventions, RMR, and NAFLD. We hypothesized that NAFLD is associated with a greater metabolic adaptation to weight loss.

Participants and Methods

STUDY DESIGN AND PARTICIPANTS

This was a retrospective analysis of a 6-month clinical trial comparing dietary weight loss intervention to multimodal treatment with diet and physical activity (RENEW; ClinicalTrials.gov trial registration identifier, NCT00712127). The Institutional Review Board at the University of Pittsburgh approved the study, and all participants provided written informed consent before enrollment. From February 2007 to March 2009, men and women between 30 and 55 years of age were enrolled in a prospective, single-blind, randomized control trial. Inclusion criteria included World Health Organization (WHO) class II or III obesity (defined as body mass index [BMI] ≥35 kg/m²) and the ability to 1) walk without assistance, 2) obtain medical clearance for interventions, and 3) commit to scheduling assessment and intervention visits. Exclusion criteria included recent cancer within 5 years of enrollment, coronary artery disease, diabetes mellitus, uncontrolled hypertension, and pregnancy within 6 months of participation. Subjects were excluded if they had undergone prior bariatric surgery, had lost >5% of current weight in the prior 6 months, or had previously enrolled in a weight loss reduction program within the prior year. Individuals with liver enzyme elevations over 30% above the upper limit of normal were also excluded.
Details of the dietary and physical activity interventions have been described in detail. Dietary therapy included scheduled meetings with a prescribed diet shown to achieve sustained 8%-10% weight loss and portions of the diet were provided in liquid supplements. Adherence was assessed through self-recording. Physical activity intervention consisted of brisk walking for up to 60 minutes/day 5 days/week, and activity was monitored with pedometers and self-reporting in a diary. All clinical, radiographic, laboratory, and metabolic data described below were obtained at baseline and after 6 months in a cohort of 114 subjects.

DETERMINATION OF NAFLD

Hepatic steatosis was determined using hepatic and splenic attenuation measurements from nonenhanced abdominal computed tomography (CT) scans. Liver:spleen attenuation ratio (L/S ratio) strongly correlates with hepatic steatosis, and an L/S ratio <1.1 is over 80% accurate for identification of individuals at 30% steatosis. Therefore, NAFLD in the current study was defined as an L/S ratio <1.1.

DEMOGRAPHIC, CLINICAL, AND ANTHROPOMETRIC ASSESSMENT

Race was self-reported, and all subjects completed the Cut down/Annoyed/Guilty/Eye-opener (CAGE) questionnaire to screen for alcohol-use disorder and were asked to quantify the average frequency of drinking and number of drinks per episode. There was no difference in alcohol intake between the group with or without CT-determined NAFLD in the 12-month period before study enrollment. Body weight and height were measured to calculate BMI. Fat-free mass (FFM) and fat mass (FM) were quantified using either dual X-ray absorptiometry (DXA) or air-displacement plethysmography in subjects exceeding weight capacity limits for DXA.

ENERGY EXPENDITURE AND RESTING METABOLIC RATE MEASUREMENT

Total daily energy expenditure (TDEE) was measured using doubly labeled water, as described. The measured CO₂ production rate was then multiplied by the energy equivalent of CO₂ at an assumed respiratory quotient (RQ) of 0.86 to determine TDEE. RMR was determined using indirect calorimetry. The thermic effect of food was assumed to be 10% of TDEE, and energy expended in physical activity (AEE) was calculated as follows:

\[
AEE = TDEE - 0.1 \times TDEE - RMR
\]

Physical activity monitors (Sensewear Pro3; BodyMedia, Pittsburgh, PA) were worn during assessments of TDEE at baseline and at 6 months, and these were used to measure steps per day.

SERUM LEPTIN MEASUREMENT

Fasting whole-blood samples collected with the RENEW trial and serum leptin levels were measured by enzyme-linked immunosorbent assay.

STATISTICAL ANALYSIS

Statistical analysis was performed using GraphPad Prism version 6.0 (GraphPad Software, Inc., La Jolla, CA) and Stata version 13.0 (StataCorp, Boston, MA). Continuous variables were reported as means and 95% confidence intervals (CIs), and categorical variables were reported as absolute frequencies and percentages. Continuous variables were compared between groups using Welch’s t test, and categorical variables were compared using Fisher’s exact test. Two-way repeated measures analysis of variance (ANOVA) was used to compare posttreatment changes between groups. Post-hoc paired t tests were performed to determine significance of within-group (time) differences, and unpaired t tests were used to determine between-group differences. Holm-Sidak methods were used to correct for multiple comparisons. P < 0.05 was considered statistically significant.

Results

BASELINE CLINICAL AND DEMOGRAPHIC FEATURES

Among 114 participants, 52 (45.6%) met imaging criteria for NAFLD. Twelve subjects (10.5%) were men, and 11 of these men had NAFLD. There were no differences in age and ethnic distribution between groups (Table 1). The mean BMI of the
study cohort was 43.6 (95% CI, 42.6-44.6), and subjects with NAFLD had higher BMI, FM, and FFM than those without NAFLD; percentage FM and percentage FFM were similar between groups. Mean TDEE was higher in the NAFLD cohort, but there were no differences in RQ, AEE, or physical activity (as measured by steps per day) between groups. Instead, higher baseline RMR in subjects with NAFLD was responsible for increased TDEE, and RMR remained significantly elevated in NAFLD even after adjustment for age, sex, FM, and FFM. Despite higher FM in subjects with NAFLD, leptin levels were similar in subjects with and without NAFLD.

CHANGES IN BODY COMPOSITION AFTER WEIGHT LOSS INTERVENTIONS DIFFER BETWEEN PATIENTS WITH AND WITHOUT NAFLD

Study participants underwent a 6-month supervised weight loss intervention consisting of either dietary modification alone (DO) or with physical activity (DO + PA; Table 1). There was no difference in prescribed treatment regimens between groups as similar proportions of subjects with and without NAFLD were assigned to DO (24 subjects [46.2%] versus 31 [50.0%], respectively) and DO + PA arms (28 [53.8%] versus 31 [50.0%], respectively; \( P = 0.170 \)). As we previously reported, subjects with NAFLD lost more weight, but the proportion of patients achieving 5% and 10% weight loss goals did not differ between subjects with and without NAFLD. Although patients with NAFLD experienced greater absolute declines in FM and FFM, percentage reductions in BMI, FM, and FFM were similar between groups (Supporting Table S1). Interestingly, subjects with NAFLD lost a greater proportion of their weight as FM (80.2% versus 71.3%-89.1%; versus 62.8%; 95% CI, 49.0%-76.5%; \( P = 0.0215 \)), while subjects with and without NAFLD lost a similar proportion of their weight as FFM (19.8% versus 17.3%-29.2%; versus 32.2%; 95% CI, 19.1%-45.4%, respectively; \( P = 0.1530 \)) (Fig. 1).
RMR changed by -179 kcal/day (95% CI, -232 to -125) and -100 kcal/day (95% CI, -149 to -51) in subjects with and without NAFLD, respectively ($P = 0.0154$ for time × NAFLD interaction; Table 2). To account for alterations in body mass and body composition with weight loss, we used baseline data to generate a least-squares linear regression equation to calculate predicted RMR after weight loss intervention as follows:

$$RMR_{predicted} = 232.3637 + 26.63398 \times FFM + 2.279 \times FAT + 171.711 \times \{1 \text{if African American, else 0}\} - 4.407 \times AGE - 3.313 \times \{1 \text{if FEMALE, 0 if MALE}\}$$

$$R^2 = 0.7495, P < 0.0001.$$

Using this equation, postintervention RMR was predicted to be 1,851 kcal/day (95% CI, 1,770-1,931) in subjects with NAFLD and 1,627 kcal/day (95% CI, 1,586-1,689) in subjects without NAFLD. However, RMR decreased by -98 kcal/day (95% CI, -143 to -50) more than expected in patients with NAFLD, while there was no statistically significant difference in predicted and measured RMR after weight loss intervention in participants without NAFLD ($P = 0.0218$; Table 3). Together, these findings demonstrate that only subjects with NAFLD experienced metabolic adaptation to weight loss.

Using linear regression, we examined changes in clinical variables to identify factors associated with changes in RMR and metabolic adaptation after weight loss. In univariate models of RMR change, female sex, presence of NAFLD, and changes in leptin, FM, and FFM exhibited positive linear relationships with change in RMR, while Caucasian race and baseline RMR were inversely associated with RMR change. In the multivariate (adjusted) model, only FM change, FFM change, and baseline RMR were associated with RMR change (Table 4).
In univariate models of metabolic adaptation, female sex, FM change, and presence of NAFLD were positively linearly related with metabolic adaptation, while Caucasian race was inversely associated with metabolic adaptation. In adjusted models, however, only FM change and female sex were independently associated with metabolic adaptation (Table 5). Metabolic adaptation increased linearly with FM loss, but no such relationship was observed with FFM loss (Fig. 2). Although both FM and FFM change are important determinants of RMR responses to weight loss interventions, these findings suggest that only FM change influences metabolic adaptation to weight loss. Furthermore, the univariate association between presence of NAFLD and metabolic association may be explained by greater declines in FM loss after weight loss intervention. Finally, treatment intervention (diet versus diet plus exercise) had no effect on either RMR change or metabolic adaptation (Tables 4 and 5).

We performed Spearman correlations between change in L/S ratio and change in RMR (ρ = 0.166 and P = 0.0828) and between L/S ratio and metabolic adaptation (ρ = −0.034 and P = 0.7247). Thus, we did not find a significant correlation between either of these outcomes and L/S ratio change.

### Discussion

In this study, we performed a post-hoc analysis to compare RMR changes in subjects with and without NAFLD who had severe obesity without diabetes mellitus and who were enrolled in an interventional weight loss trial. We report several important findings with respect to the association between hepatic steatosis and systemic energy balance. First, RMR reductions after weight loss were greater in subjects with NAFLD, while TDEE changes were similar between groups. Second, we demonstrated that metabolic adaptation to weight loss is greater in patients with NAFLD. Finally, we found that only FM change was associated with metabolic adaptation in this cohort even though both changes in FFM and FM affect RMR responses to weight loss.
Weight loss remains the most effective treatment of NAFLD, and with increased weight loss, greater clinical benefit is conferred. While as little as 5% weight reductions are associated with improvement in aminotransferases, (16,17) weight loss of up to 7% is associated with reduced intra-hepatic triglyceride content, (18,19) and 10% or greater weight loss is associated with marked reductions in inflammation and fibrosis. (1)

A

B

FIG. 2. Scatter plots with fitted linear regression curves between metabolic adaptation. (A) FFM change and (B) FM change. Gray bands represent 95% CIs.

Table 5. Linear Regression Analysis of Factors Associated with Metabolic Adaptation to Weight Loss

| Feature          | Beta (UV)     | 95% CI (UV)       | P (UV) | Beta (MV)     | 95% CI (MV)       | P (MV) |
|------------------|---------------|-------------------|--------|---------------|-------------------|--------|
| Age              | 1.188         | −3.323 to 5.701   | 0.603  | −110.919      | −197.075 to −24.763 | 0.012  |
| Female sex       | −142.222      | −229.589 to −54.857 | 0.002  | −110.919      | −197.075 to −24.763 | 0.012  |
| Diet + exercise  | −1.592        | −57.686 to 54.500 | 0.955  |               |                   |        |
| White race       | 78.726        | 21.122 to 136.330 | 0.008  | 48.840        | −6.183 to 103.863  | 0.081  |
| FM change        | −9.443        | −14.006 to −4.881 | 0.000  | −7.467        | −12.034 to −2.901  | 0.002  |
| FFM change       | 0.816         | −9.796 to 11.428  | 0.879  |               |                   |        |
| Leptin change    | −0.625        | −2.167 to 0.916   | 0.423  |               |                   |        |
| No NAFLD         | −65.068       | −120.010 to −10.127 | 0.021  | −22.917       | −76.654 to 30.821  | 0.400  |
| Baseline RMR     | 0.064         | −0.030 to 0.158   | 0.178  |               |                   |        |

Abbreviations: MV, multivariate; UV, univariate.

Weight loss attempts in NAFLD are largely unsuccessful. (2) Furthermore, weight maintenance is challenging as approximately 80% of patients will regain within 6–12 months after initial weight loss. (20,21)

Alterations in physical activity, hunger, and metabolic efficiency have been described after weight loss, (22) with a central feature being metabolic adaptation to weight loss characterized by an RMR that exceeds changes predicted by body composition alone. (23) Responses of RMR to weight loss have important implications for future weight maintenance as multiple studies have demonstrated that both low RMR (24) and increased metabolic adaptation (23,25) are associated with decreased future weight loss and increased weight regain. Metabolic adaptation appears with even small amounts of weight loss, (25) and the metabolic impact of weight loss can persist for years after an initial weight loss intervention. (23,25) Although physiologic regulation of metabolic adaptation remains incompletely understood, previous work...
suggests that hepatic glycogen depletion and reduced insulin secretion contribute to early declines in RMR with weight loss.\(^{4,26}\) In contrast, long-term control of metabolic adaptation may be under the influence of leptin, and administration of leptin after initial weight loss prevented weight regain during maintenance of weight loss.\(^{26-28}\)

Given the critical importance of weight loss in the management of NAFLD, we sought to determine physiologic responses to weight loss in subjects with NAFLD. We found that individuals with hepatic steatosis exhibited a metabolic adaptation to weight loss that was not observed in subjects without NAFLD. One potential explanation for this finding may be higher baseline RMR in subjects with NAFLD as prior studies have shown positive associations between baseline RMR and declines in both RMR and metabolic adaptation after starvation-induced weight loss.\(^{4}\) In the current study, baseline RMR was associated with a greater reduction in RMR with weight loss. However, there was no statistically significant relationship between baseline RMR and metabolic adaptation after starvation-induced weight loss.\(^{4}\) In the current study, baseline RMR was associated with a greater reduction in RMR with weight loss. However, there was no statistically significant relationship between baseline RMR and metabolic adaptation after starvation-induced weight loss.\(^{4}\) In the current study, baseline RMR was associated with a greater reduction in RMR with weight loss. However, there was no statistically significant relationship between baseline RMR and metabolic adaptation after starvation-induced weight loss.\(^{4}\)

In conclusion, individuals with hepatic steatosis compared to those without have a greater RMR decline and higher metabolic adaptation after weight loss, potentially increasing the risk of long-term weight regain.

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Supporting Information

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