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Hypometabolism as a potential risk factor for overweight and obesity in liver recipients

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Objective: The aim of the present study was to identify whether overweight liver recipients are hypometabolic.
Methods: Liver transplantation (LT) recipients (n = 20), who were 18 to 65 y of age, had a body mass index (BMI) $\geq$25 kg/m^2, and were 1 to 3 y post-transplant. They were matched with healthy controls in terms of sex, age, BMI, and body composition. Dietary intake data were collected using a 3-d food record. The individuals' daily activities were converted into metabolic equivalents. Resting energy expenditure (REE) was assessed in the morning after an overnight fast (12 h), by indirect calorimetry, using an open-circuit calorimeter.
Results: Total energy and macronutrient intakes were similar among liver recipients and controls. The majority of the individuals from both groups were sedentary (75%; n = 15/group). Patients who underwent LT showed lower REE (1449.15 $\pm$ 101.25 kcal) compared with the control group (1768.45 $\pm$ 86.94 kcal). Likewise, the ratio of REE to fat-free mass (FFM) was lower in the LT group (28.9 $\pm$ 1.7 kcal/ kg) than in the control group (32.9 $\pm$ 0.9 kcal/ kg; $P < 0.05$). The correlation between the FFM and the REE was strong in control participants ($r = 0.73$; $P < 0.01$), whereas it was moderate in the LT group ($r = 0.45$).
Conclusion: The REE of overweight liver recipients is reduced and it might be a risk factor for excessive body weight gain in this population.

Introduction

Recent advances in the treatment of patients who have undergone liver transplantation (LT) have resulted in a substantial increase in survival rates. Consequently, long-term complications such as obesity [1], hypertension [2,3], diabetes [4], dyslipidemia [5], cardiovascular disease [2,6], and other metabolic disorders have become prevalent. In addition, excessive body weight gain after the transplant is an important risk factor for graft failure and death [7], which highlights the utmost importance of adopting effective strategies to control exacerbated adiposity.

Multiple factors have been implicated in weight gain after LT, including positive energy balance [8,9], etiology of liver disease [10], and the immunosuppressive regimen [11,12]. Physical inactivity and inadequate dietary habits also are factors that might affect body weight, particularly in the first year after surgery [13,14]. On the other hand, there is a hypothesis that these patients might be hypometabolic [15], but this has not been elucidated yet and it is sometimes excluded [8].

The liver is an immunologically and metabolically privileged organ. It acts as a hub to connect various tissues, including skeletal muscles, adipose tissue, the gut, and the brain [16]. Multiple nutrients, hormones, and neuronal signals regulate liver metabolism. Furthermore, immunosuppressive drugs are used to downregulate the immune system activity after LT to reduce the risk for organ rejection. Taking into account the notorious integration of metabolism and the immune system [17,18], it is important to consider that the immunosuppressed state might play a role in weight gain after LT. It is our hypothesis that liver recipients develop a

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state of hypometabolism, which plays a key role in weight gain in the long term after surgery.

To our knowledge data in the literature about resting energy expenditure (REE) in patients who underwent LT is limited. Only a few studies regarding health conditions and the new lifestyle after LT were carried out in the long run when most of the patients were more stable. Moreover, the metabolic status of LT recipients is frequently evaluated based on predictive equations [8], which may lead to limited interpretations.

The aim of the present study was to identify whether overweight liver recipients are hypometabolic, which can be a possible factor associated with body weight gain after LT. A better understanding about the metabolic status of liver recipients could help individualize dietary treatments after LT.

Material and methods

Study design and participants

This was a cross-sectional study conducted as part of a baseline evaluation on studies of immunosuppression and obesity in transplanted patients. The study was carried out at Hospital das Clínicas/ Universidade Federal de Minas Gerais, Brazil, and was approved by the ethics committee of that university. Between August 2014 and May 2016, data from LT recipients were screened and those who were 18 to 65 y of age, had a BMI $\geq$25 kg/m^2, and were 1 to 3 y post-transplantation were selected. This post-transplantation period was chosen because it when many liver recipients become overweight and have adapted themselves to the new routine [14]. The exclusion criteria were regraft, pregnancy, breastfeeding, external nutritional counseling in progress, and use of hormonal therapy or weight loss medication. Patients were then invited to participate in the study.

LT recipients were matched with non-transplanted controls regarding sex, age, BMI, and body composition. Control group individuals followed the same inclusion and exclusion criteria applied to the LT group, except they were not liver transplant patients and were not taking immunosuppressive or anti-inflammatory drugs. Bariatric surgery patients also were excluded.

The procedures regarding the study protocol were explained to the participants, who were required to give written consent.

Procedures

The participants were interviewed to assess their demographic and socioeconomic data, eating habits, physical activity levels, and clinical parameters. To assess their anthropometric data, body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, using a floor model scale and stadiometer (Filizola®). Waist circumference was obtained using an inextensible measuring tape with accuracy of 0.1 cm and it was measured at the level of the umbilicus [19]. Body composition was determined by bioelectrical impedance analysis (Quantum X - RJL Systems, Inc., Clinton Township, MI, USA). BMI was calculated and classified according to the World Health Organization [20].

Dietary intake data were collected using a 3-d food record. We also used pictures representing portion sizes and household measures to estimate food weights. All participants were instructed in how to complete the record (i.e., fill it in with 3 non-consecutive days throughout the week they entered the study, considering 1 weekend day). Food intake data were entered into the software Brasil Nutri and converted into calories, carbohydrates, proteins, and lipids, using tables of food composition [21,22].

Participants were asked about their routine to transform their daily activities into metabolic equivalents (METs) [23]. The obtained values were then multiplied by the time spent on the respective activity, summed and divided by 24 (corresponding to 1 d). From this, we were able to classify individuals into sedentary (<1.4), limited activity (1.55–1.60), and physically active ($\geq$1.75) [20].

REE was assessed in the morning after an overnight fast (12 h), by indirect calorimetry (IC), using an open-circuit calorimeter (MetaCheck metabolic rate analysis system, model 7100, Korr Medical Technologies, Salt Lake City, Utah) [24,25]. The calorimeter was autocalibrated before each measurement according to the manufacturer's instructions. Participants were placed in a quiet, temperature-controlled room (22°C–24°C) and remained seated throughout the study. After 30 min of acclimatization, measurements were made over 10 min. Participants were instructed to relax, breathe normally, and minimize movement. The REE was then divided by kilogram of fat-free mass (REE/FFM).

Statistical analysis

The sample size was estimated in 20 participants. For this, we considered an standard deviation of 226.7 kcal in the REE of liver recipients, based on a study carried out with a similar population [8]; a confidence interval of 95% with an α level of 0.05; and an acceptable error of 100 kcal.

Data were analyzed with the SPSS version 19 (IBM, Armonk, NY, USA). For descriptive purposes, categorical variables were compared using the χ^2 test. All data were analyzed for normality using the Kolmogorov–Smirnov test. Comparisons between both groups were performed using Student's t or Mann–Whitney tests, for parametric and nonparametric variables, respectively. Correlation between REE and FFM were calculated with Pearson's coefficient because these variables were parametric. Differences were considered statistically significant at the $P < 0.05$ level.

Results

Of 100 patients, 80 were excluded owing to the following reasons: insulin use (n = 7), regraft (n = 10), age <18 (n = 4) or >65 y old (n = 13), BMI <25 kg/m^2 (n = 30), external nutritional counseling in progress (n = 2), and lack of interest (n = 14). Thus, 20 patients met the inclusion criteria and agreed to be included in the study (Fig. 1).

Baseline characteristics of the patients and controls are listed in Table 1. Most of the LT patients were male (n = 14; 70%) with a mean age of 50 ± 3 y old. There were no differences between the marital status and the family income in both groups. The mean BMI of the LT patients was 30.10 ± 0.89 kg/m^2 and they had, on average, 102.11 ± 2.09 cm of waist circumference, 35.99 ± 1.68% of body fat, and 64.01 ± 1.68% of FFM. All characteristics listed match those from the control group.

The average time since LT was 26 ± 2 mo (Table 1). The most frequent indication for LT was alcohol use (40%; n = 8), followed by hepatitis C virus infection (30%; n = 6), cryptogenic cirrhosis (15%; n = 3), and autoimmune hepatitis (15%; n = 3).

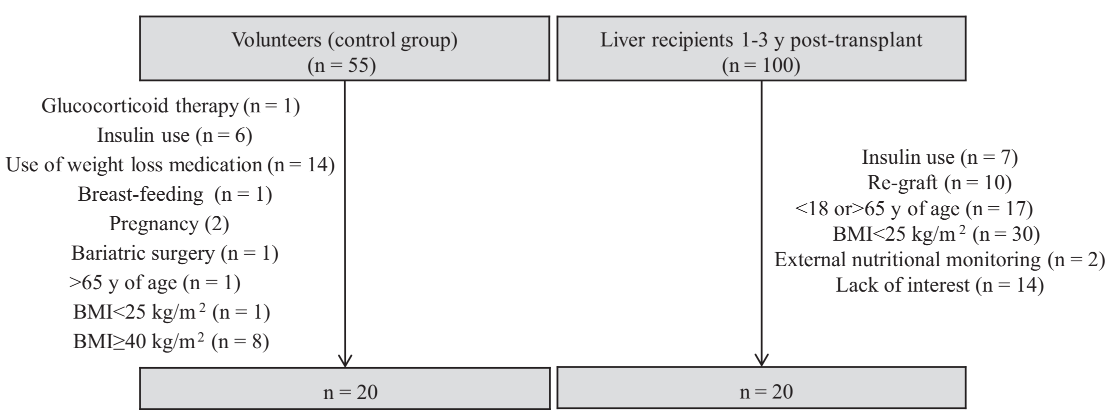

Fig. 1. Flow diagram of the study. BMI, body mass index.

Table 1
Baseline characteristics of controls and patients who underwent liver transplantation

Variables	Controls (n = 20)	Liver transplantation (n = 20)	*P*-value
Sex, n (%)			
Male	12 (60)	14 (70)	>0.05*
Female	8 (40)	6 (30)	
Age, y (mean ± SEM)	45 (± 2)	50 (± 3)	>0.05†
Marital status, n (%)			
Single	1 (5)	2 (10)	>0.05*
Married	17 (85)	14 (70)	
Divorced	2 (10)	4 (20)	
Family income, $ (min – max)	953.35 (462.62 – 3,833.87)	740.26 (231.31 – 4.464.22)	>0.05‡
BMI, kg/m^2 (mean ± SEM)	31.19 ± 0.58	30.10 ± 0.89	>0.05†
WC, cm (mean ± SEM)	104.32 ± 1.69	102.11 ± 2.09	>0.05†
Body fat, % (mean ± SEM)	35.78 ± 1.92	35.99 ± 1.68	>0.05†
Fat-free mass, % (mean ± SEM)	64.22 ± 1.92	64.01 ± 1.68	>0.05†
Time since LT, mo (mean ± SEM)	–	26 ± 2	
Indication for LT, n (%)			
Alcohol abuse	–	8 (40)	
Hepatitis C virus	–	6 (30)	
Cryptogenic cirrhosis	–	3 (15)	
Autoimmune hepatitis	–	3 (15)	
Immunosuppressive treatment, n (%)			
Tacrolimus	–	18 (90)	
Cyclosporine	–	2 (10)	
Corticosteroids	–	2 (10)	

BMI, body mass index; LT, liver transplantation; WC, waist circumference.
*χ^2.
†Student's *t* test.
‡Mann-Whitney.

Table 2
Energy and macronutrient intake of controls and patients who underwent liver transplantation

Variables	Controls (n = 20)	Liver transplantation (n = 20)	*P*-value*
Energy intake, kcal (mean ± SEM)	1799.62 ± 151.73	1601.27 ± 294.85	>0.05
Carbohydrates, g (mean ± SEM)	222.73 ± 13.17	204.62 ± 18.62	>0.05
Proteins, g (mean ± SEM)	79.18 ± 5.99	83.11 ± 16.48	>0.05
Lipids, g (mean ± SEM)	70.42 ± 5.43	66.49 ± 12.72	>0.05

*Student's *t* test.
SEM, standard error of the mean.

Most of the patients (n = 18, 90%) were treated with tacrolimus and only 2 (10%) were taking cyclosporine. Two (10%) patients were also treated with corticosteroids (Table 1).

The total energy and macronutrient intakes (Table 2) did not differ between the two groups. There were no differences between the level of physical activity of the two groups (Table 3) and the majority of the participants were classified as sedentary (75%; n = 15 in each group).

As mentioned, both the cases and non-cases included in this study showed the same body composition to avoid bias when comparing the REE of both groups. Patients who underwent LT showed lower REE (1449.15 ± 101.25 kcal) than the controls (1768.45 ± 86.94 kcal) at the $P = 0.02$ level (Fig. 2). The REE-to-FFM ratio was also lower in the LT group (LT: 28.9 ± 1.7 kcal/ kg versus control: 32.9 ± 0.9 kcal/ kg of FFM; $P < 0.05$).

Table 3
Physical activity level of controls and patients who underwent liver transplantation

Physical activity level	Controls (n = 20)	Liver transplantation (n = 20)	*P*-value*
Sedentary, n (%)	15 (75)	15 (75)	
Limited activity, n (%)	4 (20)	1 (5)	>0.05
Active, n (%)	1 (5)	4 (20)	

*χ^2.

The FFM was not strongly correlated with the REE in the LT group. Although this correlation was strong in the control group ($r = 0.73$; $P < 0.01$), it was moderate in the LT group ($r = 0.45$) at the $P = 0.05$ level.

Discussion

Obesity is considered a multifactorial disease and often is a consequence of multiple factors, including sex, age, genetics, sedentary

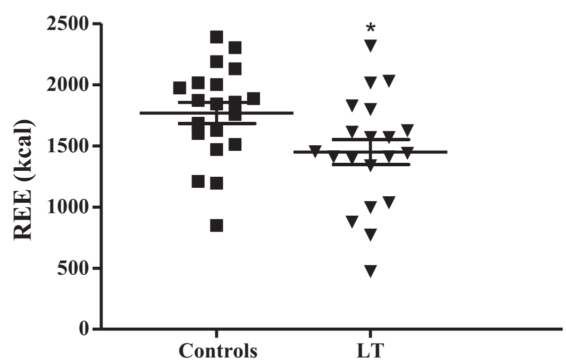

Fig. 2. REE (kcal) of controls and patients who have undergone LT. The values were measured by indirect calorimetry. LT, liver transplantation; REE, resting energy expenditure. Data are expressed as the means ± SEM. *$P < 0.05$.

lifestyle, decline in REE, high energy intake, and social and cultural aspects [26–28]. Among these numerous factors, we raised the hypothesis that the low REE could be a potential risk factor for overweight after LT. Because the liver plays a central role in energy metabolism, it is reasonable to speculate that liver recipients have altered physiological responses that lead to an excessive body weight. Herein, we have showed that overweight liver recipients have low metabolic rates that may be related to an obese phenotype 1 to 3 y after the transplant.

Some authors have measured the REE of patients after LT, but conflicting results have been the rule. Richardson et al. [15] measured the REE of liver recipients using IC and observed a reduction in the energy expenditure 9 mo after hospital discharge. Similarly, Ferreira et al. [9] followed patients throughout the first year after LT. The REE of these patients increased after 30 d and reduced in an average of 226 kcal at the end of the study period (1 y after the transplant). These studies are important to reinforce the premise that LT downregulates the energy expenditure of the recipients. However, both studies addressed the individuals' metabolic rate comparing patients' data before and after transplant. We, in turn, provided a comparison between overweight liver recipients with non-transplanted paired controls, allowing for a better understanding of the metabolic changes and the development of obesity after LT.

A recent study evaluated changes in the metabolic rate of liver recipients during resting and exercise [29]. The authors studied patients transplanted for nonalcoholic steatohepatitis and compared them with nonalcoholic fatty liver disease controls. In accordance with our data, the study demonstrated that liver recipients, particularly women, have both lower REE and exercise energy expenditure than controls. Although this study reinforces the present hypothesis, it was limited to patients transplanted for nonalcoholic steatohepatitis. In the present study, we evaluated liver recipients transplanted for different reasons, allowing a general conclusion and a broader application in the clinical practice.

Conversely, other studies have shown that post-transplant patients are not hypometabolic [8,30]. A previous study from our group [8] was unable to show the hypometabolism in LT patients 6.5 y after the transplant. Similarly, another study measured the REE of patients 6, 14, and 32 mo after LT (30). The authors did not find any difference in the REE after LT. The discrepancies between these studies and the present study are mainly owing to the different methodological approaches. First, in the previous studies, the authors applied the Harris–Benedict (HB) formula [31] to classify patients as hypo-, normo-, or hypermetabolic. Indeed, metabolic status is frequently studied by comparing REE with predictive equations [8,32]. The use of these formulas is more convenient because they are practical, inexpensive, and may spare the use of controls. However, the present data demonstrated that these formulas may be not fully adequate when applied to liver recipients. This might be a consequence of the methods used to develop the HB equation, which was developed based on data collected from healthy volunteers [31]. It has been shown that the HB equation is imprecise in a diversity of clinical settings [33,34]. Second, the studies just discussed did not establish a BMI inclusion criterion. The degree of overweight has been shown to be a significant factor influencing the accuracy of the predictive equations [35]. Furthermore, this aspect might be of particular importance to detect the hypometabolism in liver recipients. We believe that the comparison between the paired groups made it possible to show the hypometabolism in the liver recipients, which went undetected in other studies.

Dietary composition is a factor that can influence energy expenditure [36]. It is known that dietary factor can affect energy expenditure directly by differences in macronutrient composition, or indirectly through hormonal responses to diet [36]. Likewise, physical activity is known to effect the energy expenditure in a dose-dependent manner [37]. The present study found that both control and LT groups had the same energy and macronutrient intakes, as well as a similar level of physical activity, which may imply that both were not major determinants of the REE in these individuals. Other features can influence energy expenditure, such as sex [38], age [39], BMI [40], and FFM [41]. In the present study, the groups were carefully controlled regarding these variables to avoid bias.

Another important determinant of the REE in healthy individuals is FFM, which accounts for ~70% of the variance in REE [41,42]. Surprisingly, results of the present study did not find a strong correlation between REE and FFM in liver recipients as was seen in controls. When energy expenditure was adjusted to the FFM, liver recipients demonstrated lower values. Although not evaluated in the present study, this can be explained, at least in part, by a decrease in mitochondrial function. A previous study indirectly assessed the mitochondrial function of short-term liver recipients and controls using the ^{13}C-labeled ketoisocaproic acid breath test as well as by measuring the REE through IC [43]. For some liver recipients, the median REE was 17% to 18% higher than controls, as reported by other studies evaluating short-term liver recipients [9,44]. On the other hand, the tacrolimus exposure was correlated with the lower REE and respiratory quotient. Other studies also showed that tacrolimus impairs mitochondrial function [45,46], but this topic needs to be better studied.

Other hypotheses can be postulated to explain why LT downregulates metabolism. First, we believe that immunosuppression plays a key role in this phenomenon by the lack of inflammatory response. It was previously shown that inflammatory cytokines induce energy expenditure [17,47], which led us to suppose that a low immunologic competence may influence the energy expenditure. Second, it is possible that the transection of the hepatic nerves after LT [48] has led to a metabolic disintegration. In fact, vagal sensory neurons innervate the liver, such as other visceral organs, providing a link between the central nervous system (CNS) and the metabolic response to control feeding [49]. Vijgen et al. [50] studied the relationship between vagus nerve stimulation and energy expenditure in patients with epilepsy and found a positive relationship. Furthermore, vagal nerve stimulation can prompt the CNS to decrease eating and increase expression of neurotrophic factors able to stimulate energy expenditure [49]. On the other hand, other studies have demonstrated hepatic reinnervation at certain time points after LT [51,52]. Thus, the metabolic implications of this denervation in transplanted livers remains to be determined.

The present study had some limitations. First, the patients were recruited from the same care center. However, based on the limited data about the topic, the restricted number of liver-transplanted volunteers, and the satisfactory sample size, we believe that the present data will help the development of adequate care strategies applied to liver recipients. Another limitation is that the 3-d food record, a tool applied to estimate energy and macronutrient consumption, is frequently a questionable method [53], mainly because the underreporting of dietary intake is common, notably in overweight individuals [54]. On the other hand, it is currently the available tool and it has been extensively applied in different studies [8,9] showing high validity [55] and providing a trustworthy estimation about the individual's intake.

Overall, we believe that many factors contribute to body weight gain after LT. Nevertheless, the present findings demonstrate that a reduced rate of energy expenditure is present in overweight liver recipients and, thus, it might be a risk factor for body weight gain. It is unclear, however, what causes the hypometabolic status, and studies are needed to clarify this.

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