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CE Energy Expenditure and Liver Transplantation: What We Know and Where We Are

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Abstract

Patients with end-stage liver disease (ESLD) and undergoing liver transplantation (LTx) commonly present with malnutrition attributed to various etiologies. One of the causes is potential hypermetabolism resulting from increased resting energy expenditure (REE). After the surgery, it is hypothesized that these patients show a reduction in REE, which may contribute to the weight gain observed in this population. However, there have been controversial results regarding the metabolic status of ESLD patients and liver recipients, which has led us to critically review the pertinent literature. We enrolled studies with the following goals: assessment of REE of these patients either before or after surgery by using indirect calorimetry (measured REE [mREE]) and comparison of these mREE values with those of healthy controls or with REE values obtained using predictive equations (predicted REE [pREE]). For most patients, mREE and pREE values were comparable. However, ≥5.3% of patients exhibited hypermetabolism when the mREE was compared with the pREE using the Harris-Benedict formula. Three follow-up studies that were conducted postsurgery showed a progressive reduction in the mREE for ≤1 year. However, conflicting data have been published, and cross-sectional studies have not reported hypometabolic patients. In conclusion, there is no consensus regarding the metabolic status of pre-LTx and post-LTx patients, which may be due to differences in the methods used for comparison. Therefore, we highlight this aspect of LTx patient management, which impacts the quality of nutrition therapy required by these patients. (*JPEN J Parenter Enteral Nutr.* 2021;45:456–464)

Keywords

energy expenditure; energy metabolism; indirect calorimetry; liver transplantation

Introduction

Transplantation is the standard treatment for patients with advanced liver disease. Before liver transplantation (LTx), malnutrition is a common condition and is associated with worse prognosis.[1] After surgery, patients often exhibit excessive weight gain with an increased prevalence of the metabolic syndrome, indicating that alterations in their metabolism may predominate after transplantation.[2]

Malnutrition is prevalent in patients with end-stage liver disease (ESLD), observed in ≤74.7% of patients on the waiting list for LTx.[3] In a study of 268 patients with ESLD, the authors assessed the patients' nutrition status using several methods, such as in vivo neutron activation analysis and dual-energy x-ray absorptiometry. The prevalence of significant protein depletion was 51%, and the patients with a higher degree of protein depletion also presented with lower muscle functionality, as assessed by dynamometry, indicating impairment in muscle strength.[4] Other authors assessed 73 patients with reference to energy balance. Energy intake was evaluated with a 3-day food record, and the energy requirements were derived from the resting energy expenditure (REE) measured by indirect calorimetry and further corrected by using daily physical-activity factors. The majority of patients (78.1%) exhibited a negative energy balance, secondary to insufficient energy intake.[5]

After the transplant, alterations in the REE were investigated as part of the etiology of weight gain.[6-8] The exact mechanisms behind the metabolic changes that occur in liver recipients, including in the long-term postsurgery, are

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yet unclear. However, one of the plausible causes may be related to the loss of hepatic innervations, which may impair the ability to control energy metabolism.[9]

Total energy expenditure is equal to the heat energy required to maintain daily functions. It includes 3 main components: REE, diet-induced thermogenesis, and energy needed to carry out physical activity.[10] REE is the major component of the total energy expenditure and is the energy expended by an individual at rest and in the postabsorptive state.[11] The gold-standard tool to assess the REE is indirect calorimetry, and the REE value obtained by using this method is commonly referred to as the measured REE (mREE).[12] Oxygen consumption and carbon dioxide production are measured, using either a canopy or a mask.[13] The mean oxygen consumption and carbon dioxide production per minute are used in indirect formulas, such as the one developed by Weir (REE = [3.9 (VO_2) +1.1 (VCO_2)]).[14] This value is multiplied by 1440 to obtain the 24-hour mREE. It is necessary to take some precautions while performing the test to assure that the energy measurement is accurate. Therefore, indirect calorimetry should be carried out in a temperature-controlled room, after an overnight fast, and after a period of rest.[10] The calorimeter should be calibrated before each test, and the 2 gases should be collected for a period between 12 and 30 minutes.[15]

In clinical practice, when calorimeters are not available because of high cost, or because of a lack of time to perform the test, REE can also be predicted by using specific equations. The main equations used to obtain predicted REE (pREE) are those published by Harris and Benedict,[16] Mifflin et al,[17] Schofield,[18] Owen et al,[19] Muller et al,[20] and Cunningham.[21] Although useful, there are some concerns about the accuracy of these equations in nonhealthy individuals.[22,23] According to the authors of a recent systematic review on the accuracy of predictive equations for ESLD patients, the abovementioned formulas underestimate the REE. The authors evaluated studies that compared pREE obtained by using different formulas with mREE and observed that the difference between the pREE and mREE was lowest when the pREE was obtained by using the Harris-Benedict (HB) equation.[12]

These equations are normally used to classify the metabolic status as hypometabolic, normometabolic, or hypermetabolic. Most authors perform this classification by comparing the pREE with the mREE.[24–30] When the mREE is <80%[27] of the pREE, the metabolic status is designated as hypometabolic, and when the mREE is >120% of the pREE, it is designated as hypermetabolic. However, as highlighted by the latest European Association for the Study of the Liver (EASL) guidelines, the formulas usually underestimate the REE of patients with ESLD, which is a cause for concern.[31] Some authors also assessed the metabolic status by comparing the mREE of ESLD patients with the mREE of healthy controls, matched by age, sex, and body mass index ([BMI] calculated as weight in kilograms divided by height in meters squared)[9,32]; this method is a more accurate way to assess the metabolic status of patients with ESLD.

In patients who underwent LTx, assessment of alterations in the REE may help in adjusting nutrition therapy. Therefore, the aim of this review is to critically assess data regarding the mREE both before and after LTx and to verify the prevalence of hypermetabolism in patients with ESLD and hypometabolism in patients who underwent LTx. In this study, we have reviewed articles comparing the mREE with that of healthy controls or with that obtained by predictive equations.

REE of Patients With ESLD Undergoing Transplantation

In patients with ESLD, the liver is marked by tissue fibrosis and nodule formation, leading to severe morphologic alterations.[33] These alterations cause substantial changes in metabolism, such as liver glycogen depletion, impaired glucose metabolism, increased protein catabolism, and accumulation of total body water.[1]

The metabolism in these patients is characterized by a rapid reduction in the respiratory quotient in the postabsorptive state, indicating the use of fatty acids as the primary fuel instead of glucose.[32] Furthermore, decreased protein synthesis and increased gluconeogenesis is observed, which may lead to an increase in REE. Ascites, commonly seen in these patients, may also impact the REE.[31] Dolz et al[29] assessed the influence of ascites in the energy metabolism of 10 ascitic patients. They measured the REE of 10 patients with moderate or severe ascites before and after paracentesis. The authors observed that, after the procedure, mREE was significantly decreased by 9.1%. On the other hand, more recently, Knudsen et al investigated changes in the mREE of 19 patients with ascites, measuring REE both preparacentesis and postparacentesis and after 4 weeks of paracentesis, and did not find significant changes in the values when compared to baseline values.[30] Thus, important possible causes of increased mREE in ESLD patients include alterations in substrate oxidation, with an increase in energy-expensive metabolic pathways, such as gluconeogenesis.[34] Also, hypermetabolism was associated with a higher Model for ELD (MELD) score, higher body weight, and higher body-water content in a study including 256 patients with ESLD.[35] Other independent factors potentially related to hypermetabolism are insulin resistance, leptin adjusted for fat-free mass (FFM), percentage of FFM,[36] and increased fasting glucose.[28] Furthermore, catecholamine levels are often increased in patients with

Table 1. Resting Energy Expenditure (REE) in Patients With End-Stage Liver Disease (ESLD).

Authors	N (patients + controls)	mREE ESLD patients	pREE ESLD patients	mREE to pREE value	Prediction equation	mREE healthy controls
Dolz et al (1991)[29]	10	1523.40 ± 240.0	1429.0 ± 205.0	94.4	HB	NA
Vermeij et al (1991)[37]	60	1530.0 ± 235.0	1419.0 ± 303.0	111.0	HB	1645.0 ± 315.0
Waluga et al (1996)[45]	35	1693.0 ± 400.0	1571.0 ± 291.0	122.0	HB	1756.0 ± 344.0
Selberg et al (1997)[40]	75	1707.0 ± 268.0	NG	NA	HB	NA
Madden et al (1999)[48]	141	1660.0 ± 337.0[a,b]	1532.0 ± 252.0	128.0	HB	1590.0 ± 306.0
Muller et al (1999)[27]	473	1700.5 ± 320.0	1648.0 ± 212.5	52.5	HB	NA
Scolapio et al (2000)[38]	15	1637.0	1572.0	65.0	HB	NA
Plank et al (2001)[24]	14	1943.0 ± 53.0[a]	1476.0[c]	467.0	16.85 x FFMc + 725	NA
Richardson et al (2001)[9]	41	1462.0 ± 59.0	NG	NA	Schofield's age-specific equation	1468.0 ± 59.0
Perseghin et al (2002)[25]	26	1692.1 ± 50.1	1596[c]	96.1	HB	1684.9 ± 35.8
Kalaitzakis et al (2007)[49]	41	1500.0 (1400.0–1790.0)	NA	NA	NA	1430.0 (1320.0–1477.5)
Shiraki et al (2010)[39]	24	1188.0 (892–1830)	1170.0 (1077–1760)	18.0	HB	NA
Meng et al (2011)[44]	100	1274.2 ± 316.3[a]	1493.8 ± 246.8	−219.6	HB	NA
Schutz et al (2012)[26]	42	1566.0 (959–2017)[a]	1234.0 (1059–1777)	332.0	28.765 x BCM + 727.074 (males); 25.822 x BCM + 784.956 (females)	NG
Glass et al (2013)[32]	50	1525.6 ± 305.3	1711.6 ± 293.9	−186	HB	1571.2 ± 278.3
Ferreira et al (2014)[28]	81	1587.5 ± 426.6	1511.9 ± 239.9	75.6	HB	NA
Teramoto et al (2014)[42]	488	1256.0	1279.0	−23	HB	NA
Knudsen et al (2016)[30]	19	1587.7(1363.7–1716.0)	NA	NA	HB	NA
Prieto-Frías (2016)[36]	57	1987.0 ± 229.0[a,b]	1676.0 ± 209.0	311	HB	1791.0 ± 83.0

BCM, body cell mass; FFMc, fat-free mass (kg) corrected for abnormal hydration; HB, Harris-Benedict; mREE, measured REE; NG, not given; NA, not analyzed
[a] Statistically different from pREE
[b] Statistically different from mREE of healthy controls
[c] Estimated from the percentage of mREE to pREE

ESLD, which may also increase the REE. Muller et al[27] assessed the mREE and catecholamine levels of 59 patients with ESLD and reported elevated concentrations in hypermetabolic patients. The infusion of a β-blocker on a subgroup of 19 patients caused a significant reduction in the mREE. Thus, in studies regarding the mREE of patients with ESLD, authors often consider the use of β-blockers as exclusion criteria[30] or verify whether it significantly affected the mREE.[28,36]

Hypermetabolism is reported to have an influence on prognosis. Mathur et al[35] assessed the role of REE on survival and found that, after 5 years of LTx, hypermetabolic patients had lower transplant-free survival rates when compared with patients with a normal metabolic status (29% vs 45%, respectively). Hypermetabolism was predictive of prognosis independently of the Child-Pugh score and the MELD score.

Data on studies regarding REE of patients with ESLD are depicted in Table 1.[9,24–30,32]

REE of Patients With ESLD: Measured Values vs Values Predicted By Equations Before LTx

In a study including 10 inpatients with ESLD, Vermeij et al did not observe significant differences between mREE and pREE values.[37] In the study published by Scolapio et al, when mREE and pREE values of 15 patients diagnosed with cirrhosis were assessed, the mean mREE was 1637.0 kcal/d, and the pREE (as per the HB formula) was 1572.0 kcal/d, with a good correlation between both methods.[38] Dolz et al,[29] as well as Knudsen et al,[30] also found a good correlation between mREE and pREE (HB formula) in patients with ESLD, with no significant difference between the values.

On the other hand, some of the studies in the current literature report hypermetabolism in patients with ESLD. Shiraki et al assessed 24 patients with viral cirrhosis, and mREE was significantly higher than the pREE obtained by the HB formula.[39] Selberg et al assessed the mREE of

75 patients with ESLD, and pREE was calculated with the HB formula. The authors identified 31% of the participants as hypermetabolic.[40] Muller et al measured the REE of 473 patients with ESLD and also used the HB formula to calculate pREE,[27] identifying 160 patients (33.8% of the population) as hypermetabolic. Plank et al[24] measured the REE of 14 patients with ESLD and compared the results with the pREE using an equation previously developed by the authors. The equation was developed with data from 80 healthy volunteers by using FFM. Before the surgery, there was a significant difference between the pREE and mREE values, and the latter was 24% higher. Using the same predictive equation, as well as the HB formula, Mathur et al[35] found similar results among 256 patients with ESLD. The average mREE of the patients was 1571.0 ± 316.0 kcal/d. It was reported that 15% were hypermetabolic according to the FFM formula and 8% as per the HB formula. In a group of 26 patients with ESLD, Perseghin et al found that 18% were hypermetabolic, with 91% of the population presenting with an mREE higher than the pREE (HB formula).[25] Schutz et al assessed 39 patients with ESLD[26] and reported that the mREE was higher than the pREE obtained by using an equation developed by the authors with data derived from 310 healthy controls.[41] Ferreira et al assessed 81 patients with indications for LTx, and 24.7% of them were classified as hypermetabolic when the mREE and pREE by HB formula were compared.[28] Hypermetabolism was also found by Teramoto and colleagues in 5.3% of a group of 488 patients with ESLD[42] and by Brito-Costa et al in 21.4% within a group of 56 patients.[43] Prieto-Frías et al evaluated 48 inpatients with ESLD[36] and observed a higher mREE when compared with pREE (HB formula), with 58.3% of the participants classified as hypermetabolic. However, this study only included male patients who had no ascites or edema, and the authors defined hypermetabolism as an mREE >115% of the pREE instead of the 120% threshold, which is commonly used.[27]

Unlike the other authors, Meng et al found that the mREE of 100 patients with ESLD was significantly lower than the pREE obtained by the HB formula.[44]

REE of Patients With ESLD vs REE of Healthy Controls

Studies comparing the mREE of ESLD patients with that of healthy controls have also yielded controversial results. Waluga et al assessed 15 patients and 20 controls[45] and reported no significant differences between the study groups. In another study, Richardson et al compared the mREE values of 23 patients with ESLD and 18 healthy controls, and no significant differences were reported.[9] In agreement with these results, no differences were found between the mREE of patients with viral cirrhosis and healthy controls in the study published by Tajika et al.[46] Sugihara et al compared the mREE data (1 week before surgery) of 14 patients undergoing living-donor LTx to those of 10 healthy donors and reported no differences between the values.[47] Similarly, Perseghin et al assessed 26 patients with ESLD, and the mREE was not significantly different between patients and healthy controls.[25]

On the other hand, some authors present contradictory results. Prieto-Frías et al assessed male inpatients with ESLD (n = 48) and reported increased mREE as compared with that of 9 healthy controls.[36] Madden et al[48] also found that patients had higher mREE when compared with controls. Nonetheless, in this study, malnourished patients presented with significantly lower mREE values when compared with nourished patients, and the presence of ascites did not influence the mREE.

The lower muscle mass of patients with ESLD, resulting from metabolic alterations induced by the disease,[4] may also affect REE. In a study with 31 patients with ESLD,[49] Kalaitzakis et al did not observe differences between the mREE values of the patients and those of the healthy controls. However, when mREE was adjusted for FFM, the patients exhibited a significantly higher median mREE value (1509.0 kcal for patients and 1353.0 kcal for controls). Similarly, Glass et al evaluated 25 patients with ESLD and 25 matched, healthy controls and found that the mREE was similar between the 2 groups (mREE, mean and SD: 1525.6 ± 305.3 and 1571.2 ± 278.3 kcal in patients with ESLD and healthy individuals, respectively). No significant difference between the pREE and the mREE was observed for patients with ESLD. However, patients exhibited lower ($P < .01$) muscle mass when compared with controls, and when the mREE was normalized to muscle area, patients with liver disease showed significantly higher values.[32]

Most of the assessed studies that compared mREE with pREE reported that the patients with ESLD were hypermetabolic, as depicted in Tables 1 and 2.[24,26–28,35,40] On the other hand, when ESLD patients were compared with healthy controls, matched by sex, age, and BMI, there were no significant differences between the mREE values of the 2 groups.[9,32] Therefore, it is difficult to determine if ESLD patients are indeed hypermetabolic.

Nonetheless, because of a large variability in the methods used in the studies, it is necessary to be cautious while analyzing the results. The majority of the studies included a small sample size. Additionally, there was heterogeneity in the patient groups regarding the following: severity of disease, as shown by the differences in the Child-Pugh and MELD scores; nutrition status; etiology of the liver disease; and presence of complications, such as fluid retention. When comparing mREE with pREE, there were differences when the formulas that require body weight were used to calculate pREE, and this may have affected the results. Some authors used the dry weight of the participants,[6,28,47–51] whereas others excluded patients with clinically detectable

Table 2. Prevalence of Alterations in Resting Energy Expenditure (REE) of Patients With End-Stage Liver Disease (ESLD).

Authors	N (patients + controls)	% Measured/predicted REE[a]	% Hypermetabolism	% Hypometabolism
Dolz et al (1991)[29]	10	106.6%	NG	NG
Vermeij et al (1991)[37]	60	107.8%	NG	NG
Waluga et al (1996)[45]	35	107.7%	NG	NG
Selberg et al (1997)[40]	75	113.2%	31.0%	NG
Madden et al (1999)[48]	141	108.3%	30.0%	12.0%
Muller et al (1999)[27]	473	103.1%	33.8%	3.2%
Scolapio et al (2000)[38]	15	104.1%	NG	NG
Plank et al (2001)[24]	14	124.0%	NG	NG
Perseghin et al (2002)[25]	26	108.5%	18%	0%
Shiraki et al (2010)[39]	24	101.5%	NG	NG
Meng et al (2011)[44]	100	85.3%	NG	NG
Schutz et al (2012)[26]	42	126.9%	NG	NG
Glass et al (2013)[32]	50	89.0%	12.0%	28.0%
Ferreira et al (2014)[28]	81	105.0%	24.7%	7.4%
Teramoto et al (2014)[42]	488	98.2%	5.3%	5.1%
Knudsen et al (2016)[30]	19	106.9%	NG	NG
Prieto-Frías (2016)[36]	57	119.0%	—	—

NG, not given.
[a] A number >100 indicates increased REE.

fluid retention.[36,39,40] However, these corrections were not performed (or mentioned) in a majority of the studies. Since ascites and edema are common in patients with ESLD, the body weight should be corrected for fluid retention by recording the postparacentesis weight or the weight before any fluid retention or by deducting the percentage of fluid retention according to its severity.[31] Furthermore, there were crucial methodological differences pertaining to REE assessment, such as period of fasting and the gas-exchange measurement method.

Changes in REE After LTx

Patients often exhibit excessive weight gain after LTx, with an increased prevalence of obesity and metabolic syndrome.[2] The exact explanation for these disorders has not been fully elucidated, but it has been hypothesized that hypometabolism, with concomitant appetite recovery and increased food intake, may lead to a positive energy balance and weight gain.[6] Immunosuppressive therapy is prescribed to avoid graft rejection after LTx, mainly with the use of calcineurin inhibitors, corticosteroids, and antimetabolites. Some authors[6,25] assessed the potential impact of immunosuppressive drugs on the REE, with controversial results. Perseghin et al[25] compared the mREE of patients with chronic uveitis and healthy controls. The patients with chronic uveitis were on an immunosuppressive regimen similar to that of LTx patients, with the use of cyclosporine and prednisone. There were no significant differences in the mREE between the study groups. However, in the study by Ferreira et al,[6] the cumulative dose of prednisone was inversely associated with the mREE of LTx patients assessed ≤1 year postsurgery.

Independent factors associated with the REE measured 6 days after LTx were reported to be the MELD score before the surgery, the surgical time, and the time of cold ischemia.[52] Ferreira et al also identified presurgery mREE values ($\beta = 0.56$) and the triceps skinfold thickness ($\beta = 10.84$) as predictors of mREE after LTx. The occurrence of hypometabolism after LTx has also been associated with fat mass and percentage of fat intake before the surgery.[6]

Longitudinal Assessment of REE in Patients Who Underwent LTx

Several authors have performed longitudinal follow-up assessments of mREE in LTx patients[8,9,24–26,50,53] for ≤50 months postsurgery (Table 3).

Richardson et al[9] evaluated the mREE of 23 patients before and ≤9 months after LTx. They observed a progressive reduction in the mREE and additionally identified that the mREE by body weight was inversely related to fat mass. The mREE was revealed to be the strongest predictor of increased fat mass 9 months after transplantation. In agreement with the above, Plank et al and Ferreira et al,[6,24] who assessed 14 and 17 patients, respectively, from the preoperative phase until 1 year postsurgery, reported a progressive reduction in the mean mREE, with a decrease of 19.5%[24] and 6.2%,[6] respectively.

Table 3. Differences Between Resting Energy Expenditure (REE) Before and After Liver Transplantation (LTx).

Author	N	Period post-LTx	mREE pre-LTx (kcal ± SD)	mREE post-LTx (kcal ± SD)
Muller et al (1994)[8]	26	432 days	1638.0 (1220.0–2190.0)	1612.0 (1010.0–2490.0)
Richardson et al (2001)[9]	23	9 months	1462.0 ± 59.0	1410.0 ± 58.0
Plank et al (2001)[24]	14	360 days	1943.0 ± 53.0	1564.0 ± 60.0[a]
Perseghin et al (2002)[25]	11	9 months	1692.1 ± 50.1	1701.7 ± 69.3
Schutz et al (2012)[26]	42	50 months	1566.0 (959.0–2017.0)	1579.0 (1016.0–2564.0)
Ferreira et al (2013)[6]	17	379 days	1706.3 ± 607.0	1601.0 ± 509.3
Brito-Costa et al (2016)[50]	56	36 days	1469.6 ± 472.2	1638.2 ± 446.2
Ribeiro et al (2019)[53]	29	8 days	1570.0 (1307.8–1870.5)	1630.5 (1455.0–1773.0)

mREE, measured REE.
[a] mREE post-LTx significantly different from mREE pre-LTx.

On the other hand, other authors have not observed a reduction in the mREE after LTx. Muller et al[8] reported no differences in mREE of 26 patients assessed before and ≤432 days after LTx. Perseghin et al enrolled 11 patients, including 5 patients with a diagnosis of diabetes who were evaluated before and 9 months after surgery. The mREE did not show significant alterations. Other authors who followed 42 patients for a longer time (≤50 months after the surgery) reported no significant changes in median mREE.[26] In Figure 1, we summarize the changes in REE reported in longitudinal studies with a follow-up of >6 months.

Studies with shorter follow-up periods post-LTx also revealed no changes in the mREE after surgery.[50,53] A survey of 25 liver recipients reported the mREE of patients, measured ≤72 hours post-LTx (baseline) and at 5, 10, and 15 days postsurgery. The mean baseline mREE was 1832.0 ± 952.0 kcal/d, decreasing to 1565.0 ± 383.0 kcal/d on the 5th day and 1578.0 ± 418.0 kcal/d on the 15th day, with no significant differences. However, a decrease of ≥250 kcal in the REE from baseline to subsequent measurements was observed.[51] The high energy expenditure at baseline observed in the first few days after transplantation may be due to the organic response to surgical stress, which causes increases in energy requirements and catabolism rates.[6,54]

Cross-Sectional Studies

Some authors evaluated mREE of LTx patients only after surgery.[55,56] The mREE of 143 patients[52] was assessed within a median time of 6 days after LTx and compared with the pREE (HB) (mean mREE: 1950 ± 461 kcal [24.5 ± 6.1 kcal/kg] and mean pREE: 1695 ± 256 kcal). Only 22% of patients had an mREE within 90%–110% of the pREE, and the mREE ranged from 61% to 195% of the pREE. The prevalence of hypometabolism and hypermetabolism was 10% and 49%, respectively. As discussed earlier, the alterations in mREE in the first few days after LTx may be due to the surgical stress. Regarding the comparison between the predictive equations, in a recent study[57] with 46 LTx recipients, pREE was calculated by using equations published by HB and Ireton-Jones,[58] as well as Penn State,[59] and using the simple, weight-based equation (25 kcal/kg/d). The pREE calculated was compared with the

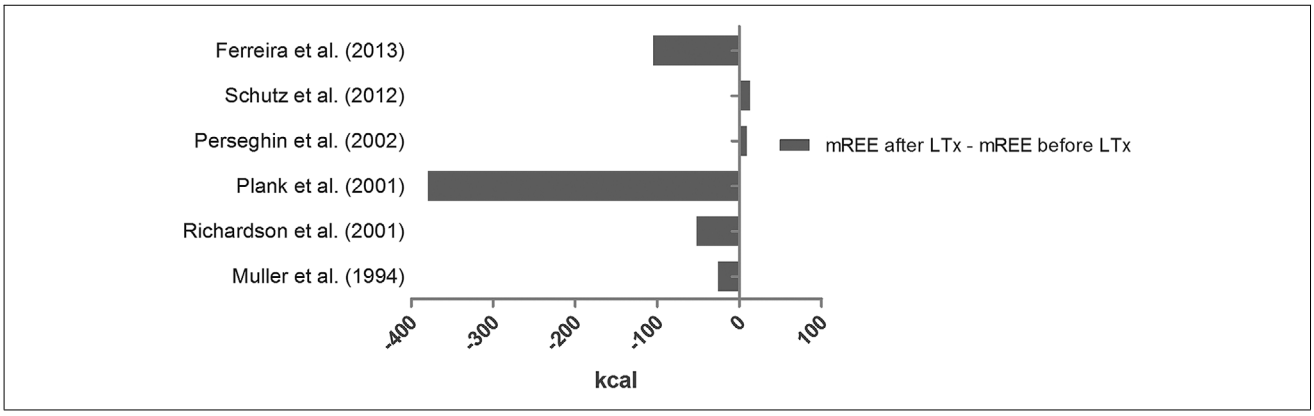

Figure 1. Changes in mREE (before and after LTx) of LTx patients in longitudinal studies with >6 months of follow-up. Bars on the left indicate a reduction in mREE. mREE, measured resting energy expenditure; LTx, liver transplantation.

mREE assessed ≤48 hours after admission into the intensive care unit. The mean mREE was 1513.8 ± 295.5 kcal (24.8 ± 4.5 kcal/kg). The HB, Ireton-Jones, Penn State, and the simple weight-based equations showed a mean difference in comparison with mREE values of 148.5 ± 247.6, −105.3 ± 284.7, −52.4 ± 249.8, and −41.4 ± 280.0 kcal, respectively. All 4 equations presented fixed bias in the Bland-Altman plot, showing inaccuracy for this group of patients. The simple, weight-based equation showed the least bias, whereas the HB formula tended to underestimate the mREE. Regarding long-term, follow-up postsurgery, the mREE of 42 patients with a follow-up of ≥1 year post-LTx (mean time of 6.5 years post-LTx) was assessed and compared with pREE obtained using the HB equation.[55] The mean mREE measured by indirect calorimetry was 1449.7 ± 226.7 kcal/d, whereas the pREE was 1404.5 ± 166.1 kcal/d; no patient was classified as hypometabolic or hypermetabolic.

Singhvi et al compared the mREE of 14 patients who underwent transplantion for nonalcoholic steatohepatitis (NASH) or cryptogenic cirrhosis with that of control patients with nonalcoholic fatty liver disease who did not undergo transplantation. NASH is characterized by steatosis, fibrosis, and inflammation in individuals without excessive consumption of alcohol and is usually related to obesity. However, after the development of cirrhosis, this condition is often misdiagnosed, with patients being diagnosed with cryptogenic cirrhosis instead.[60] In this group of patients, the mean mREE was significantly lower for women who underwent transplantion in comparison with controls. It was also lower in men but with no statistical significance.[57] Rodrigues et al evaluated 20 overweight (BMI ≥25) liver recipients after 1–3 years post-LTx and compared their mREE values with those of matched controls. It was observed that patients who underwent transplantion presented with significantly lower mREE (1449.1 ± 101.2 kcal/d) when compared with healthy controls (1768.4 ± 86.9 kcal/d) and exhibited a lower REE to FFM ratio. In this regard, it may be hypothesized that overweight patients with lower mREE values are at a higher risk for weight gain,[7] which is in accordance with some longitudinal studies that reported a reduction in the mREE after LTx.

The controversial results presented above may be attributable to the high variability in the study populations and the methods used. Hypometabolism cannot be disregarded as a potential contributor to weight gain in LTx patients posttransplantation. Nevertheless, other factors should be considered. For instance, the majority of patients are sedentary after LTx, as reported by several authors.[55,7,61] Therefore, physical inactivity should also be considered when assessing these individuals. More recently, our group has revealed deviation in eating behavior as another potential risk factor for weight gain and obesity.[62]

It is important to highlight that this review encompasses studies conducted at different times, and thus variability in the types of calorimeters used to determine the mREE cannot be ruled out. However, majority of the studies were performed using the Deltatrac calorimeter[35,37,39,9,40,46,24,26,27,49] and the COSMED,[6,28,50,53,52] which have previously been validated for accuracy.[63,64] Furthermore, in longitudinal studies, all the assessments were conducted using the same device.

Conclusion

Patients undergoing LTx often present with metabolic alterations, both before and after the surgery. This was clearly demonstrated by the observation that >50% of the studies included in this review showed differences in the mREE of patients who underwent LTx when compared with the pREE or with the mREE of healthy controls. However, the lack of uniformity in measurement methods, types of populations, time frames for the assessments, predictive formulas used, as well as the nutrition status and body composition of the patients, among other factors, preclude definite conclusions. To clarify the remaining questions about this topic, future research should be conducted with homogeneous populations, with reference to the nutrition status and the severity of the disease, and with an appropriate sample size, which enables accurate assessment of outcomes. Nevertheless, health professionals should be aware that because of the limitations of the predictive equations, the REE of patients undergoing LTx should be measured using indirect calorimetry whenever possible.

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Statement of Authorship

B. C. Santos, M. I. T. D. Correia, and L. R. Anastácio equally contributed to the conception and design of the research; L. R. Anastácio and M. I. T. D. Correia contributed to the design of the research; B. C. Santos, M. I. T. D. Correia, and L. R. Anastácio contributed to the acquisition and analysis of the data; B. C. Santos, M. I. T. D. Correia, and L. R. Anastácio contributed to the interpretation of the data; and B. C. Santos, M. I. T. D. Correia, and L. R. Anastácio drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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