

Illness Severity by MELD-Na is not Associated with Energy Expenditure in Cirrhotic Liver Transplant Candidates

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Abstract

Purpose: Hypermetabolism contributes to malnutrition in cirrhosis and it often goes undetected. Indirect calorimetry is a high-cost, time-consuming tool which is not accessible to many health care institutions. Predictive equations often underestimate true caloric requirements in cirrhosis. The aim of this study was to assess whether illness severity, defined by MELD-Na score, is associated with increases in measured Resting Energy Expenditure (REE) in patients awaiting liver transplantation. We also sought to quantify a stress factor for improved accuracy of predicted energy requirements in this population.

Methods: Data from 40 patients awaiting liver transplantation were retrospectively assessed. MELD-Na was calculated from serum markers; measured REE was quantified using an indirect calorimetry; and predicted REE was determined by the Harris-Benedict equation.

Results: MELD-Na scores were not associated with measured REE or prevalence of Hypermetabolism. Forty-three percent of patients required a 20-50% addition to predictive estimates to cover their basal metabolic needs.

Conclusions: Our findings suggest a stress factor of 1.2 to 1.3 should be considered when predicting caloric requirements of candidates awaiting liver transplantation in the absence of indirect calorimetry. Illness severity by MELD-Na does not appear to be a useful marker in identifying patients who are hypermetabolic and at higher risk of underfeeding.

Keywords: End-stage liver disease; Resting energy expenditure; Indirect calorimetry; Nutritional needs; Liver transplantation;

Introduction

Protein-Energy Malnutrition (PEM) is a frequent complication of liver cirrhosis, affecting an estimated 65 to 100% of patients with chronic liver disease [1]. Unfortunately, accurate assessment of nutrition status in patients with decompensated cirrhosis is difficult [2]. Conventional measures of nutritional assessment are often confounded by fluid retention, metabolic disturbances and impaired hepatic protein synthesis [3]. Malnutrition is

an independent predictor of poor prognosis in liver cirrhosis, impacting survival rate, length of hospital and intensive care unit stay, and quality of life both prior to and following Liver Transplantation (LT)[1,3,4]. Therefore, identifying strategies to prevent the occurrence and further progression of malnutrition and to promote nutrient repletion are of crucial importance to optimizing outcomes in this patient population [3,5].

The causes of malnutrition in end-stage liver disease (ESLD) are multi-factorial and include reduced dietary intake, nutrient malabsorption and Hypermetabolism, amongst others [1]. In the context of ESLD, hypermetabolism has been defined as a Measured Resting Energy Expenditure (mREE) that exceeds the Predicted Resting Energy Expenditure (pREE) by 20% or more, with pREE as determined by predictive formula [4,6,7]. Hypermetabolism appears to affect at least 30% of patients with cirrhosis; however, it frequently goes undetected, thus contributing to malnutrition in the absence of a corresponding energy and nutrient supply [3,8,9]. This phenomenon has been associated with reduced survival in patients with liver cirrhosis independent of markers of disease severity, including the Model for End-Stage Liver Disease (MELD) and Child-Pugh (CP) scores [6].

No clinical or biochemical markers of liver disease have been identified that would help predict increases in resting energy expenditure (REE) in this patient population [7]. The best way to identify Hypermetabolism in patients with decompensated liver cirrhosis is with the use of indirect calorimetry (IC), which is the gold standard tool for measuring REE. With IC, a more accurate estimate of total energy requirements can be made [10]. However, IC is expensive, time-consuming and not readily available to many hospitals in Canada and the United States [11,12]. Thus, predictive equations have become necessary for estimates of energy expenditure. The Harris-Benedict Equation (HBE) is commonly used; though, this and other predictive formulas consistently underestimate REE in this patient population, often by more than 20% [9].

In the absence of IC, identifying patients at increased risk of underfeeding due to Hypermetabolism is a priority. Chronic liver disease has considerable influence on REE; hence, it is possible that the progression of disease severity and decompensation of liver function may lead to a proportional increase in REE(6,13). Past research has evaluated the relationship between REE and liver disease severity as defined by Child-Pugh and MELD scoring systems; however, inconsistent findings have been reported [6,7,14,15]. The Sodium Model for End-Stage Liver Disease (MELD-Na) scoring system has since been recognized as a better measure of disease severity and an improved predictor of mortality among cirrhotic candidates awaiting LT [8,16]. The present study seeks to evaluate the usefulness of the MELD-Na score as a marker to identify patients who are more likely to be hypermetabolic and therefore at higher risk of underfeeding. Furthermore, a secondary objective was to determine a stress factor that could be added to HBE estimates of caloric expenditure in cirrhotic patients awaiting LT in order to improve predictions of energy requirements, thus mitigating the adverse outcomes associated with malnutrition.

Methods

Patients

We conducted a cross-sectional, retrospective evaluation of data from 40 patients listed and awaiting LT at one hospital in Southwestern Ontario, Canada, between December 2005 and July 2014. The sample size used is based on the number of eligible participants for inclusion in this study who had complete data within this time frame. Patients were eligible to participate if they were 18+ years of age at the time of listing, had a confirmed diagnosis of decompensated chronic liver disease, and were in stable clinical condition awaiting LT. Participants were excluded if they had acute liver disease, prior liver transplant, lung disease requiring ventilation, active infection, significant encephalopathy, renal impairment requiring hemodialysis therapy, and/or claustrophobia. This study was approved by the Research Ethics Board at the University of Western Ontario. Written informed consent was obtained from participating subjects.

Measurements

Indirect Calorimetry

mREE was measured via IC using a ventilated hood open-circuit metabolic cart (Vmax® metabolic cart, VIASYS Healthcare Inc., Yorba Linda, CA). Patients were asked to lay in supine position on a hospital bed while the test was conducted by an experienced dietary technician. Before the IC test was started, a two-hour fast was requested along with a 15 minute rest just prior to initiation. One trained expert conducted all the tests, thus minimizing intra- and inter-examiner error or bias. The instrument was calibrated immediately before each measurement [14]. mREE was obtained by measuring oxygen consumption and carbon dioxide production as described elsewhere [17].

Predicted Resting Energy Expenditure

pREE was calculated using HBE [18]. Estimated dry body weight was used to determine pREE and BMI. Dry body weight was estimated using body weight after the most recent paracentesis, if available. Otherwise, the usual body weight prior to ascites and fluid accumulation was used [6,9].

MELD-Na Score

MELD-Na score was calculated using the Mayo Clinic MELD-Na calculator and verified by the following formula as described by Kim, et al. [19,20]:

$$\text{MELD-Na score} = \text{MELD} - \text{Na} - [0.025 \times \text{MELD} \times (140 - \text{Na})] + 140$$

Since hyperglycemia can falsely lower serum sodium concentration, a corrected serum sodium value was also calculated for each of the 40 patients based on the Hillier formula [21]. The data analyses were conducted with both sets of MELD-Na scores (corrected and non-corrected). MELD score was also calculated using the Mayo Clinic calculator and verified using the formula previously described in other reports [19,20,22,23]. All scores were rounded to the nearest integer [20].

Calculation of Stress Factors

Stress factors were calculated by dividing mREE by pREE [24]. Hypermetabolism was defined as mREE that exceeds pREE by $\geq 20\%$ [4,6,7]. Norm metabolic patients had an mREE that was within $\pm 20\%$ of their pREE by HBE [7].

Statistical Methods

MELD-Na scores were divided into three groups: MELD-Na ≤ 18 , MELD-Na 19-24, MELD-Na ≥ 25 . These categories were based on the Reassessment and Recertification Schedule for MELD-Na score described in the 2013 OTPN/UNOS Liver and Intestinal Organ Transplantation committee proposal to add sodium to MELD score [25]. Patients were also stratified based on BMI categories (26) to assess possible differences in metabolic status based on BMI. The Shapiro-Wilk test was used to determine normality of the data distribution. Categorical variables are expressed as percentages. Continuous variables are expressed as mean values \pm standard deviation. One-way analysis of variance tests and Student t tests and were used to compare normally distributed continuous variables. Statistical significance was defined as $P < 0.05$. All statistical analysis was performed using SPSS v.21 software (IBM, Armonk, NY).

Results

Demographics and baseline characteristics for the 40 patients who participated in the study are listed in Table 1. Seventeen patients (43%) were hypermetabolic, with deficiency in energy

Table 1: Demographics and baseline characteristics (n=40)

	All (n = 40)	Hypermetabolic (n = 17)	Non-hypermetabolic (n = 23)	P
Male:Female	27(68):13(32)	10(25):7(18)	17(42):6(15)	0.199
Age (y)	52 ± 11	50 ± 13	53 ± 8	0.161
Primary etiology of cirrhosis				
Viral	10 (25)	3 (17)	7 (31)	
Alcohol	5 (12)	4 (24)	1 (4)	
Cholestatic	10 (25)	5 (29)	5 (22)	
NASH	9 (23)	3 (18)	6 (26)	
Other	6 (15)	2 (12)	4 (17)	
BMI (estimated dry weight)(kg/m²)	24.0 ± 6.2	22.3 ± 6.0	25.2 ± 6.1	0.143
mREE (kcal/d) (Joules/d)	1702 ± 308 7121168±1288672	1851 ± 322 7744584±1347248	1591 ± 249 6656744±1041816	0.01
mREE (kcal/kg/d) (Joules/kg/d)	25 ± 5 104600±20920	29 ± 4.6 121336±19246	22 ± 3.2 92048±13389	0.001
pREE (kcal/d) (Joules/d)	1497 ± 231 6263448±966504	1417 ± 207 5928728±866088	1556 ± 233 6510304±974872	0.054
pREE (kcal/kg/d) (Joules/kg/d)	22 ± 3 92048±12552	23 ±3.6 96232±15062	21 ± 2.1 87864±8786	0.188
MELD-Na score	24 ± 7	25 ± 7.0	23 ± 6.1	0.447
MELD score	21 ± 7	22 ± 8.5	20 ± 6.4	0.518
Bilirubin (umol/L)	229 ± 250	293 ± 278	182 ± 222	0.184
Creatinine (umol/L)	95 ± 44	80 ± 34.5	105 ± 47.7	0.063
INR	1.8 ± 0.6	1.9 ± 0.8	1.6 ± 0.4	0.289
Sodium (mmol/L)	133 ± 6	132 ± 6.2	132 ± 5.7	0.785
NASH, nonalcoholic steatohepatitis; BMI, body mass index; mREE, measured resting energy expenditure; pREE, predicted resting energy expenditure; MELD-Na, sodium model for end-stage liver disease; MELD, model for end-stage liver disease; INR, international normalized ratio. Data are presented as number of patients (%), or mean ± SD.				

predictions ranging between 20 and 51%. Six additional patients (15%) had an mREE that exceeded their pREE by 10 to 19 percent, but were not considered hypermetabolic by our definition. Overall, pREE was found to routinely underestimate mREE (Table 2). Hypermetabolism and mREE were not significantly associated with sex, age, bilirubin, creatinine, international normalized ratio (INR), sodium, MELD score or MELD-Na score (Table 1). An association between BMI and mREE (P=0.04) and between BMI and pREE (P=0.002) was found, and was still evident when mREE and pREE were defined per kg of body weight (P=0.001 for both mREE/kg and pREE/kg).

Table 2 shows the metabolic state of patients as stratified per BMI categories. Of the seven (18%) patients that were classified as underweight based on their BMI, four (57%) were hypermetabolic and three (42%) were normometabolic. Of the 21 (52%) patients within the normal weight category, nine (43%) were hypermetabolic and 12 (57%) were normometabolic. Lastly, of the 12 (30%) patients with a BMI ≥25 kg/m², four (33%) were hypermetabolic and eight (67%) were normometabolic. Table 2 also demonstrates that, on average, pREE underestimated mREE by 14 percent. However, certain subgroups of patients experienced greater deviations in actual energy expenditure from that which was predicted by HBE. Specifically, hypermetabolic patients demonstrated the highest deviation from HBE (26%) at 29 kcal/kg or 121,336 J/kg, closely followed by those with a BMI <18.5 kg/m²(20%) at 30 kcal/kg or 125,520 J/kg. The underestimates/stress factors calculated for each subgroup of patients are also recorded in Table 2.

Table 2: mREE vs. pREE (HBE) in subgroups of ESLD patients

	All patients	Hypermetabolic (>120% HBE)	Normometabolic (80-120% HBE)	BMI <18.5	BMI 18.5-24.9	BMI ≥25
n (%)	40	17 (43)	23 (57)	7 (18)	21 (52)	12 (30)
Mean mREE (kcal/kg/d)	25 ± 5.4	29 ± 4.6	22 ± 3.2	30 ± 4.1	26 ± 5.1	21 ± 3.8
Mean pREE (kcal/kg/d)	22 ± 2.9	23 ± 3.6	21 ± 2.1	25 ± 1.4	23 ± 2.1	19 ± 1.9
Underestimate (stress factor) (%)	14	26	5	20	13	11

HBE, Harris-Benedict Equation; BMI, body mass index; mREE, measured resting energy expenditure; pREE, predicted resting energy expenditure
Data are presented as number of patients (%), or mean ± SD.

Prevalence of hypermetabolism and mREE were not significantly different between MELD-Na categories (Table 3). MELD-Na score was also not associated with age, sex, BMI, pREE

or stress factor. Similar results were derived when the analysis was conducted by categorizing MELD-Na scores into only two groups: MELD-Na<25 and MELD-Na≥25.

Table 3: Mean mREE and prevalence of hypermetabolism per MELD-Na category

		MELD-Na ≤18	MELD-Na 19-24	MELD-Na≥25	P
mREE	(kcal/d)	1728 ± 358	1638 ± 219	1716 ± 325	0.787
	(Joules/d)	7229952 ± 1497872	6853392 ± 916296	7179744 ± 1359800	
mREE	(kcal/kg/d)	25 ± 6	24 ± 4	25 ± 6	0.843
	(Joules/kg/d)	104600±25104	100416 ± 16736	104600±25104	
No. of hypermetabolic patients (%)		4 (23)	3 (18)	10 (59)	0.698

Data are presented as number of patients (%), or mean ± SD.



Figure 1: MELD-Na score is not associated with mREE

After correcting MELD-Na scores for hyperglycemia, nine (23%) patients had a corrected MELD-Na score that differed from the original MELD-Na score; however, most scores differed by only one unit (e.g., original MELD-Na=23; corrected MELD-Na=22). Statistical analysis using MELD-Na scores corrected for hyperglycemia yielded similar results (P=0.446 for corrected MELD-Na vs. mREE). Since MELD-Na scores are not typically corrected for hyperglycemia at this study centre, we opted to demonstrate our results (Table 1, Table 3, Figure1) using original MELD-Na scores.

Discussion

As shown in previous studies, our results support the premise that REE is highly variable in patients with cirrhosis and is generally underestimated by HBE. Furthermore, with REE underestimates as high as 50 percent for some patients, insufficient energy provision to ESLD patients is potentially detrimental to both nutritional status and consequent prognosis, both prior to and following LT [2,6,12,13]. If hypermetabolism goes unrecognized in the absence of IC, malnutrition may worsen due to underfeeding. To our knowledge, this is the first study to examine energy requirements in relation to MELD-Na score. This is of importance as MELD-Na score is currently considered the most accurate marker of illness severity and predictor of mortality in ESLD. Our findings do not demonstrate an association between mREE and MELD-Na score. Similarly, the prevalence of hypermetabolism was not found to significantly increase with rising MELD-Na scores (P=0.698). This suggests that differences in energy expenditure in ESLD likely occur independent of disease severity by MELD-Na.

Past studies evaluating the relationship between REE and liver disease severity as defined by CP and MELD scoring systems have yielded conflicting results [6,7,14,15]. Our own findings failed to find an association between hypermetabolism and MELD score (Table 1). though these contrasting results are not well understood, differences in illness severity index markers (MELD

vs. CP) and a possible extrahepatic cause of hypermetabolism are thought to play a role [2,6]. Furthermore, when using MELD-Na as a marker of illness severity, a low number of participating patients with low serum sodium levels may skew and confound results. Hence, future research in this area will add benefit by ensuring a sufficient numbers of patients with low serum sodium concentration to derive greater understanding relating to the usefulness of MELD-Na score for identifying patients at higher risk for hypermetabolism when IC is not available.

Although REE predictions underestimated true energy needs in all BMI categories, greater deviations occurred in patients with a BMI <18.5 kg/m². This finding raises an important question: Is it more appropriate to assign a specific stress factor to be added to HBE based on BMI, rather than utilize a blanket recommendation for all ESLD patients awaiting liver transplantation? It may be that underweight patients would benefit more from a higher stress factor in comparison to cirrhotic patients in the normal to obese BMI categories. The need for a higher stress factor found in this study may be related to the fact that there were proportionally more hypermetabolic than normometabolic patients in the underweight BMI category, whereas this was not the case in the normal and overweight/obese BMI categories. However, no statistically significant association was found between BMI and hypermetabolism in this study. Similarly, although an association between BMI and mREE was found, a similar relationship was noted between BMI and pREE. The association was even stronger when mREE and pREE were defined per kg of body weight. This likely points to the relationship between BMI and REE which is to be expected given that REE is strongly affected by the weight and height of the patient, from which BMI is derived [27]. One study with 473 patients by Muller et al. found body weight to be lower in patients who were hypermetabolic versus those who were not [7]. In contrast, another study with 256 cirrhosis patients found that hypermetabolism was associated with increased body weight [6]. The authors of the latter study attributed this finding to a higher body fat and body water [6]. Unfortunately, neither study appears to have assessed hypermetabolism in relation to BMI. Ferreira et al. reported no differences in body weight based on metabolic status [28]. Moreover, only four of 81 patients (4.9%) had a BMI <18.5 kg/m² in their study, and two of those patients were hypermetabolic [28]. Further studies are warranted to assess the usefulness of stress factors specific to BMI in order to more accurately predict energy requirements in the ESLD population.

It is well-known that PEM is a common complication of cirrhosis and that BMI (even when fluid overload is accounted for) alone does not sufficiently portray each patient's true nutritional status [3,29]. Often, cirrhotic patients with a normal or even high BMI will still suffer severe depletion of their muscle mass [29]. Previous studies have demonstrated that Fat Free Mass (FFM) is responsible for about 50 percent of the variability in REE in clinically stable patients with cirrhosis [7,9,14]. This suggests that FFM is a major determinant of REE in cirrhosis [30]. Hence, it may be that nutritional status affects REE and therefore, the suitability of a stress factor for energy requirement predictions

will depend on the cirrhotic patient's nutritional state. The importance of further explorations are enhanced here in light of the recent findings that muscle mass is a predictor of important clinical outcomes following LT [29].

At present, no clinical or biochemical markers of liver disease have been identified that can confidently predict increased REE in this patient population [7]. Measuring REE by IC remains the gold standard for identifying hypermetabolism in patients with ESLD [9,12]. Therefore, if available, IC remains the optimal tool for directing nutrition interventions in patients with cirrhosis [12]. With new advances in IC equipment, accessibility to these tools may improve as new calorimeter models address some of the prior concerns surrounding cost of equipment, large size, lack of portability and advanced expertise required for administering the test [11,12]. Glass and colleagues conducted a study validating the use of Handheld Respiratory Calorimeters (HHRCs) in the hospitalized cirrhotic population [12]. REE measurements with the HHRC were found to be very similar to those determined with the metabolic cart, which is the current IC reference standard. Furthermore, the HHRC is significantly more cost-effective and simple to use [12]. The use of such equipment to accurately measure REE may form the basis for nutrition interventions for cirrhotic patients in the future.

A number of studies have determined stress factors for patients with liver disease of varying severities, usually ranging from 1.08 to 1.17 [7,9,24]. However, none of these studies have determined a stress factor specifically for adult ESLD patients or for ESLD patients with hypermetabolism. The average stress factor determined for all ESLD patients in this study was 1.14; however, nearly half of patients required a more substantial stress factor for energy predictions to meet their actual needs. The average stress factor determined for hypermetabolic patients was 1.26. In light of our findings, we recommend that a stress factor of 1.2 to 1.3 be considered when assessing the energy needs of ESLD patients in the absence of IC. Clinical judgement and other nutritional assessment findings must also be factored in before determining the most appropriate stress factor for each patient. Continued monitoring of nutrition parameters and adjustments to nutritional goals and interventions will be necessary [3].

This study is limited by its retrospective nature and smaller sample size. Further research with larger numbers of eligible patients presenting with hyponatremia is necessary to confirm these results. This study did not account for nutritional status or Lean Muscle Mass (LMM) of patients, which may contribute to variability in REE. Although Mathur and colleagues did not find differences in FFM between hyper- and normometabolic cirrhotic patients, future research would be enhanced by assessment of direct and indirect measures of nutritional status and LMM in relation to hypermetabolism, mREE and MELD-Na score. Such measures could include hand-grip dynamometry, Subjective Global Assessment (SGA), and imaging techniques such as cross-sectional Computerised Tomography (CT) and Magnetic Resonance Imaging (MRI) [6,31].

Conclusion

REE predictions using HBE routinely underestimate true energy requirements in cirrhotic candidates for LT, with actual energy needs deviating from predicted values by as much as 50 percent. Reducing the barriers to measurement of REE is a priority in ensuring adequate nutrition interventions and enhancing pre- and post-transplant outcomes. Until then, tools and techniques that more accurately predict caloric requirement estimates in the absence of IC are needed. Our findings suggest that a stress factor of 1.2 to 1.3 added to HBE should be considered to more accurately meet and predict the true caloric requirements of stable ESLD patients awaiting LT. Underweight patients may require an even larger HBE stress factor compared to those patients within the normal to obese BMI categories. Illness severity by MELD-Na does not appear to be a useful marker in identifying patients who are hypermetabolic and thereby at higher risk of underfeeding. IC remains the most accurate and robust tool for evaluating energy needs in patients with ESLD.

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Conflicts of Interest: The authors declare that they have no competing interests.

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