Do patients with amyotrophic lateral sclerosis (ALS) have increased energy needs?

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ABSTRACT

Background and aims: Nutritional status is a prognostic factor for survival in amyotrophic lateral sclerosis (ALS) patients. We investigated the contribution of some of the components contributing to resting energy expenditure (REE) in order to determine whether potentially higher energy needs should be considered for these patients.

Methods: Thirty three ALS patients and 33 age- and gender-matched healthy controls participated. REE was measured by an open-circuit indirect calorimeter, body composition by dual energy X-ray absorptiometry, and estimated caloric intake by 7-day food records.

Results: Patients had lower body mass indices and lower lean body mass (LBM) than healthy controls. REE was measured by an open-circuit indirect calorimeter, body composition by dual energy X-ray absorptiometry, and estimated caloric intake by 7-day food records.

Conclusions: ALS is associated with increased REE. Various factors, such as poor caloric intake and mechanical ventilation, may mask this tendency. All the above parameters need to be considered during nutritional intervention to prevent additional muscle loss.

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disorder that affects upper and lower motor neurons. Reports suggest that nutritional status is a prognostic factor for survival in ALS patients [1,2]. Nutritional status is affected by energy intake, energy expenditure and nutrient absorption. Different studies have indicated a low caloric intake in ALS patients [2] as well as increased energy expenditure [3-5], both of which theoretically contribute to poor nutritional status. Impaired nutrient absorption has not been reported in ALS patients.

In the face of unmet nutritional needs, the body uses endogenous caloric sources, such as muscle and fat tissue which, in turn, affect body composition. In ALS patients, increased muscle loss due to malnutrition may add to the decrease in lean body mass (LBM), mainly muscle mass, which characterizes the disease and, therefore, affects functionality in these patients [6]. Undernutrition is accompanied by a compensatory decrease in resting energy expenditure (REE), reflected by a decrease in the measured REE [7]. Nutritional support, on the other hand, may increase energy expenditure [8]. Since most of the expended energy takes place in LBM, comparing the results of patients to age- and sex-matched healthy controls may be misleading due to differences in body composition. It was, therefore, suggested that LBM be measured concomitantly and that the measured REE values be adjusted accordingly in order to determine whether a disease process is actually accompanied by increased energy expenditure [9]. This may also apply to the recent suggestion of an increase in energy expenditure in ALS patients which is attributed to mitochondrial dysfunction in their skeletal muscles [10,11].

We sought to understand the complexity of energy needs of ALS patients and the contribution of the different components in order to establish whether or not they have higher energy needs which should be taken into account when planning their therapeutic management.

2. Materials and methods

The study population included 33 patients with definitive or probable ALS as defined by the revised El Escorial criteria [12] and 33 age- and sex-matched healthy controls. The patients were recruited from the ALS outpatient clinic of the Tel Aviv Sourasky Medical Center. Mean age 59.0±12.6 years, 22 of them were males. One patient had a
familial history of ALS (non-SOD). Their disease duration (from time of first symptoms) ranged from 3 months to 5 years (23.4±13.9 months, mean±SD). 12/33 (36%) had a bulbar form at onset. The patients had different degrees of neurological disability, and most of them had some degree of dysphagia. Patients on feeding tubes, on ventilators or with very advanced disease were excluded due to technical difficulties. We excluded also patients with any other concomitant diseases or medications which could interfere with the metabolic evaluation. The clinical disability was evaluated by the revised ALS functional rating scale (ALSFRS-R) [13] in the ALS clinic, and all the other measurements took place in the laboratory of the medical center’s Clinical Nutrition Unit. Ten patients were reassessed 6 months later. The study was approved by the Human Subject Committee of the Tel Aviv Sourasky Medical Center.

2.1. REE and body composition

REE was measured by an open-circuit indirect calorimeter (Deltatrac, Datex, Helsinki, Finland). The patients fasted (water was unrestricted) from 20:00 the night before the test until the next morning. They lay supine for 20 min prior to commencing the study at 08:00. After calibration with standardized oxygen and carbon dioxide gas concentrations (95% O₂, 5% CO₂), a plastic canopy was placed over the patient’s head and REE was measured for one hour. There was a 10-min washout period before starting data collection. The inter-individual coefficient of variation in our laboratory is <3%. The respiratory quotient (RQ) was determined based on the above measurements (an RQ value of 1 indicated exclusive carbohydrate utilization while an RQ of 0.7 indicated exclusive lipid utilization) [14]. The average RQ of healthy controls in our laboratory is 0.83±0.04. Body fat percentage and LBM were determined by a dual energy X-ray absorptiometry (DEXA) machine [15].

2.2. Caloric intake

All subjects received a Food Intake Diary and were requested to register everything they ate or drank for 7 days, noting the exact time and quantity of ingestion. After discussing the technique with the subjects and or the family we felt that the reports were reliable. The Food Intake Diaries were reviewed and analyzed by M.L. according to the Food Composition Tables published by the Israel Ministry of Health. (Nutritional Tables, H. Meir, A. Reshef, Jerusalem 1996). The analysis included daily intake of Kcal, Carbohydrates (g), Fats (g), and Proteins (g).

Table 1
Comparison of amyotrophic lateral sclerosis (ALS) patients and age- and gender-matched healthy controls, mean±1SD (median)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ALS patients (n=33)</th>
<th>Healthy controls (n=33)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>59.4±12.6 (58.2)</td>
<td>57.8±12.3 (56.0)</td>
<td>0.59</td>
</tr>
<tr>
<td>Gender M/F</td>
<td>22/10</td>
<td>22/10</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>65.4±11.0 (65.4)</td>
<td>84.8±15.4 (86.2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.68±0.09 (1.70)</td>
<td>1.72±0.11 (1.74)</td>
<td>0.077</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.3±3.3 (22.0)</td>
<td>28.7±4.8 (27.6)</td>
<td></td>
</tr>
<tr>
<td>LBM, kg</td>
<td>41.9±7.2 (42.8)</td>
<td>54.6±12.3 (56.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>32.8±9.4 (32.4)</td>
<td>32.7±10.9 (30.2)</td>
<td>0.87</td>
</tr>
<tr>
<td>REEm, kcal/d</td>
<td>1467±218 (1486)</td>
<td>1744±367 (1725)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>REEEP, %</td>
<td>103.6±11.0 (102.0)</td>
<td>103.8±10.0 (104.1)</td>
<td>0.72</td>
</tr>
<tr>
<td>REE/FFM, kcal/kg</td>
<td>35.4±4.3 (35.5)</td>
<td>32.3±3.6 (32.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>RQ</td>
<td>0.81±0.06 (0.80)</td>
<td>0.83±0.05 (0.83)</td>
<td>0.24</td>
</tr>
<tr>
<td>Daily caloric intake kcal/d</td>
<td>1384±508 (1250)</td>
<td>1912±577 (1822)</td>
<td>0.001</td>
</tr>
<tr>
<td>ALSFRS-R</td>
<td>25.25±8.34</td>
<td>48.0±0.0</td>
<td>0.001</td>
</tr>
</tbody>
</table>

2.3. Statistical analysis

There was a healthy gender- and age- (~±5 years) matched control for each ALS patient. Since most parameters were not normally distributed, non-parametric tests were performed and the results are presented as medians, means and standard deviations (SDs). Comparisons between ALS patients and their matched healthy controls were done using the Wilcoxon non-parametric test. The change in clinical findings of 10 ALS patients over time was analyzed by the Wilcoxon non-parametric test. A linear regression model was constructed in order to predict the level of measured REE in ALS patients based on their demographic (gender, age) and clinical (LBM, caloric intake, ALSFRS-R score, etc) parameters. The model’s goodness of fit and the relative contribution of each parameter were assessed by the R square. The SPSS for windows software, version 14 (Chicago, IL) was used for the analysis.

3. Results

The relevant demographic features of the study and control groups are listed in Table 1. We were unable to estimate the time between the first signs of the disease and the neurological examination from patients’ history. Our 33 ALS patients had a significant lower mean weight compared to our healthy controls and a significantly lower mean body mass index (BMI). There was no significant difference in height. Body fat percentage was similar (~32%) for the two groups, but LBM was significantly lower in the ALS patients (P<0.0001) (Table 1). The measured REE and the predicted REE based on the Harris Benedict equations were significantly lower in the ALS patients, but the measured REE as a percent of the predicted was not different between the groups and was in the normal range±10% of the predicted (Table 1). When normalizing REE by LBM, REE/LBM was significantly increased in the ALS patients compared to the healthy controls (P<0.001). There were no differences between the groups in the measured respiratory quotient. Daily caloric intake was significantly lower in the ALS patients (P<0.002) (Table 1).

Ten of the ALS patients had repeated measurements of body composition and REE six months after their first examination and their LBM and FRS decreased (both P<0.002), while REE/LBM values increased significantly (P=0.02). There were no significant statistical differences in their weight, BMI measured REE, body fat percentage and daily caloric intake (Table 2).

In order to formulate a prediction equation for measured REE, we tried to evaluate the contribution of the different components of the parameters which may affect it and we intentionally integrated caloric intake in these parameters. The LBM tended to increase the measured REE and contributed 59.6% to it. Caloric intake also increased the REE and accounted for 14%, gender accounted for 6.7%, increased age tended to decrease the measured REE and accounted for 2.4% of the variance.

Table 2
Changes in body composition and resting energy expenditure on follow-up after 6 months (n=10) mean±1SD (Median)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Measurement 1</th>
<th>Measurement 2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>63.5±11.8 (68.5)</td>
<td>60.7±10.2 (65.0)</td>
<td>0.098</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.5±4.3 (22.0)</td>
<td>22.4±3.4 (21.7)</td>
<td>0.074</td>
</tr>
<tr>
<td>LBM, kg</td>
<td>39.8±7.9 (39.1)</td>
<td>36.4±7.8 (35.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>34.9±10.5 (34.5)</td>
<td>37.1±10.6 (37.8)</td>
<td>0.13</td>
</tr>
<tr>
<td>REEm, kcal/d</td>
<td>1427±219 (1480)</td>
<td>1387±237 (1431)</td>
<td>0.105</td>
</tr>
<tr>
<td>REEEP, %</td>
<td>103.1±10.3 (103.4)</td>
<td>103.1±8.4 (102.8)</td>
<td>0.85</td>
</tr>
<tr>
<td>REE/LBM (kcal/kg)</td>
<td>36.0±5.3 (35.4)</td>
<td>38.9±5.0 (38.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>RQ</td>
<td>0.80±0.06 (0.81)</td>
<td>0.79±0.05 (0.81)</td>
<td>0.53</td>
</tr>
<tr>
<td>ALSFRS-R</td>
<td>34.10±6.82 (32.0)</td>
<td>29.1±7.52 (28.5)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

BMI = body mass index; LBM = lean body mass; REEm = resting energy expenditure measured; REEEP = resting energy expenditure as % of predicted by the Harris and Benedict equations; RQ = respiratory quotient ALSFRS-R = ALS functional rating scale.
value, and a higher ALSFRS-R tended to decrease the REE and accounted for 3.1% of the measured value. All the parameters, taken together, accounted for a total of 85.8% of the measured REE (Table 3).

4. Discussion

Our results indicate that ALS patients expend more energy at rest when their REE values are normalized for their impaired body composition (i.e., decreased muscle mass) compared to age- and gender-matched healthy controls. The increase tends to continue along the course of the disease, as indicated by the results of the 10 patients who underwent repeat studies 6 months after initial testing. Previous studies which suggested that patients with ALS may have increased REE are the studies of Desport et al. [3,4] and Sherman et al. [16]. While the first 2 studies measured REE in the commonly accepted way in order to compare the results to the Harris and Benedict equations, some of the patients in the study of Sherman et al. did not fast prior to the REE measurement and some were under mechanical ventilation, excluding the possibility to draw conclusions regarding changes in REE compared to healthy controls.

When expressed as a percentage of the predicted, only 13 out of the 33 patients had increased REE values based on the Harris Benedict equations. 3 had a lower REE result than predicted and the other 17 subjects were in the normal predicted range (±10% of the predicted) [17]. How, then, can we explain this discrepancy? and are really “the standard equations not accurate in assessing REE in patients with ALS”? [16]. We suggest that the explanation lies in the different components of the clinical status which can modulate energy expenditure. The first and most important component is LBM, in which most of the body metabolism takes place. LBM consists of two main components: the viscera and muscle mass. ALS is characterized by a decrease in muscle mass with no prominent change in the viscera (i.e., liver, heart, brain, kidneys, etc.). Insofar as visceral organs account for 70–80% of the daily REE compared to 22% by the muscle mass, prominent progression of the disease, i.e., loss of muscle mass, with no change in the viscera should cause a decrease in measured REE and a mild increase in REE adjusted to LBM. This tendency was seen in the 10 patients who had repeated measurements. We demonstrated the same effect in another neurological disease which involves loss of muscle mass, Emery-Dreifuss muscular dystrophy, in which we also believe that the decrease in muscle mass increases REE/LBM [18].

Another reason for increased REE is the increased effort of breathing which tend to intensify throughout the disease course [19]. This can be best illustrated by the fact that ventilated patients were found to be hypo-metabolic, most probably due to abolishing the prior energy needs to maintain respiration by mechanical ventilation [20].

Poor energy intake, in contrast to the above-mentioned factors, may decrease REE if it does not cover energy needs. This was previously illustrated in “pure” models of starvation [7], and in anorectic patients [21]. Refeeding may, in some cases, unmask the increased needs that had been modulated by low caloric intake. In patients with Cystic Fibrosis, REE increased after weight gain which was induced by gastrostomy feeding. The increase in REE was above the expected augmentation due to the increase in LBM (as indicated by the increase in the ratio of REE/LBM) [8].

How do all these factors affect our results and how can we address the controversies in previous studies regarding the dilemma whether patients with ALS actually have increased REE? By screening our ALS clinic population at one point in time, we could assure that our group of ALS patients was highly heterogeneous in terms of disease stage. The mean REE value we report in here reflects the contributions of the different opposing components that affect REE, thus explaining why 50% of our subjects were in the normal predicted range. Since some of our patients had been diagnosed as having ALS longer than others, a decrease in muscle mass (LBM) and increased eating difficulties causing decreased caloric intake may have caused a decrease in REE. This possibility is supported by the fact that our patients consumed significantly fewer calories than their age- and sex-matched controls. In contrast to the values recorded for our study group, 67% of the Desport et al’s subjects were hypermetabolic and their REE was increased by 10–16% of the predicted [3,4] based on H-B equations and compared to healthy controls. Examining their results in greater depth, however, revealed that the LBM values did not differ between patients and controls, thus most probably indicating that these patients were in an earlier stage of their disease course, and caloric intake was not yet affected. It is reasonable, therefore, to assume that the finding of increased REE in patients with early stage disease who do not yet suffer from increased respiratory efforts or low caloric intake must reflect the contribution of the disease per se.

Highly relevant to this discussion are the findings of the study by Nau et al. [21] which indicated that a decrease in LBM replaced by an increase in body fat mass is of less clinical significance because the amount of energy stored in the body of ALS patients is preserved. We are concerned with the extra loss of muscle mass of ALS patients due to poor caloric intake, which may affect muscle function. Moreover, it is well known that death is caused by a reduction in LBM while body fat mass has still been preserved.

In order to account for the different opposing components affecting REE, we carried out a multiple regression analysis and came up with good prediction of the energy needs of ALS patients at a given point in time. This model predicts the actual measurement of REE in 86% of its variability and, therefore, very probably takes into account the inherent increase in REE due to the disease. The model explains why decreased caloric intake could affect REE and thus masks increased needs of the patients in spite of the REE measurements falling within the normal predicted values. Increasing energy intake will, therefore, increase REE and should be taken into account when nutritional intervention such as gastrostomy takes place.

We propose the following equation:

$$\text{REE measured} = 507 + 23.65 \text{FFM} + 0.186 \text{caloric intake (kcal)} - 3.6 \text{age (yr)} - 4.185 \text{FRS} + 195 \text{ (only if female).}$$

This equation can be probably only used in malnourished patients with documented reduced caloric intake compared to the predicted. The equation should be recalculated along the disease course and nutritional treatment as it may change.

In light of our results and the above considerations as well as the results of other investigators, we propose that the disease process of ALS includes an increase in REE. This increase may be caused by a mitochondrial dysfunction, as had been previously suggested [5,22]. Different factors, such as poor caloric intake and ventilation, may mask this tendency and nutritional support may unmask it and should, therefore, be taken into account when planning their nutritional needs.

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Table 3

Multivariate linear regression model for the prediction of measured resting energy expenditure (REE) (Total r-square=0.86)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>B (CI 95%)</th>
<th>Partial (R²2)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBM</td>
<td>23.65 (16.69, 30.61)</td>
<td>56.9%</td>
<td>0.015</td>
</tr>
<tr>
<td>Caloric intake</td>
<td>0.186 (0.09, 0.28)</td>
<td>14.0%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ALSFRS-R</td>
<td>-4.815 (-9.72, 0.09)</td>
<td>3.1%</td>
<td>0.054</td>
</tr>
<tr>
<td>Age</td>
<td>-3.60 (-7.36, -0.06)</td>
<td>2.4%</td>
<td>0.047</td>
</tr>
<tr>
<td>Gender (F vs. M)</td>
<td>195.74 (113.14, 310.14)</td>
<td>6.7%</td>
<td>0.002</td>
</tr>
<tr>
<td>Constant</td>
<td>5070.0 (112, 902)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LBM = Lean body mass; ALSFRS-R = Functional rating scale.
References


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