# Hypermetabolism is a reality in amyotrophic lateral sclerosis compared to healthy subjects

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# HYPERMETABOLISM IS A REALITY IN AMYOTROPHIC LATERAL SCLEROSIS COMPARED TO HEALTHY SUBJECTS

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**Authors' contribution:**

PF, PJ, PC, JCD and BM designed research; PJ, PF, YB, SW, MC, PC and JCD conducted research; PJ, PF, YB, SW, MC and JCD provided essential materials (databases); AL, PJ and PF performed statistical analysis; PF, PJ, AL, PC, JCD wrote paper; PF and PJ had primary responsibility for final content. All authors read and approved the final manuscript.

## Abbreviations

ALS: amyotrophic lateral sclerosis

BMI: body mass index

CI: confidence interval

FM: fat mass

FFM: free fat mass

IC: indirect calorimetry

IQR: interquartile range

cREE: calculated resting energy expenditure

mREE: mesured resting energy expenditure

REE: resting energy expenditure

RQ: respiratory quotient

TEE: total energy expenditure

**Abstract:**

Rationale: Hypermetabolism (HM) in Amyotrophic lateral sclerosis (ALS) is the reflection of a high energy metabolic level, but this alteration seems controversial. The main objective of the study was to confirm the existence of HM during ALS compared to healthy subjects.

Methods: A cohort of ALS patients was compared to a control group without metabolic disorder. The assessment included anthropometric criteria measurements, body composition by bioelectric impedance analysis and resting energy expenditure (REE) by indirect calorimetry. HM was defined as a variation > +10% between measured and calculated REE. Statistical analysis used Mann-Withney and Chi2 tests. Multivariate analysis included logistic regression.

Results: 287 patients and 75 controls were included. The metabolic level was higher in ALS patients (1500 kcal/24h [1290–1693] vs. 1230 kcal/24h [1000 –1455], p <0.0001) as well as the REE/fat free mass ratio (33.5 kcal/kg/24h [30.4 –37.8] vs. 28.3 kcal/kg/24h [26.1–33.6], p <0.0001). 55.0% of ALS patients had HM vs. 13.3% of controls (p <0.0001). HM was strongly and positively associated with ALS (OR= 9.50 [4.49 –20.10], p <0.0001).

Conclusions: HM in ALS is a reality, which affects more than half of the patients and is associated with ALS. This work confirms a very frequent metabolic deterioration during ALS. The identification of HM can allow a better adaptation of the patients' nutritional intake.

**Keywords:** Amyotrophic lateral sclerosis, hypermetabolism, resting energy expenditure

## INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a rare and severe neurodegenerative disease commonly diagnosed between the age of 65 to 70 years and whose incidence is 2 to 3 / 100,000 person-years (1–5). Weight loss during ALS is associated with impaired functional status and quality of life (6,7). Undernutrition affects 9 to 55% of patients (7–10) and is an independent negative factor for survivival (6). Undernutrition in ALS results from an imbalance between energy intake and total energy expenditure (TEE) (11,12). The resting energy expenditure (REE), component of the TEE, can be increased in ALS, and this increase corresponding if high, to hypermetabolism (HM) (7,13). HM is a persistent phenomenon during the course of the disease (14), and would concern 50 to 60% of patients (7,13). Only two studies, with a modest number of cases and a heterogeneous methodology, studied HM in ALS compared to a control group (13,15). Due to the disparate results of these works, the notion of HM in ALS is controversial.

In light of this controversy, the main objective of this study was to confirm the existence of HM during ALS compared to healthy subjects.

## METHODS

### Inclusion criteria

ALS patients included were followed up at the ALS Referral Centre and the Nutrition Unit of the University Hospital of Limoges (France), diagnosed between November 1996 and November 2014, according to Airlie House criteria (16). They were suffering from ALS alone

or associated with frontotemporal dementia and all were treated with riluzole. They could have a bulbar or limb onset form, a familial background (FALS) or sporadic form of ALS. Functional impairment was assessed by the ALS Functional Rating Scale (ALSFRS) or its revised form (ALSFRS-R) (17). REE was measured (mREE) by indirect calorimetry (IC), with a respiratory quotient (RQ) between 0.7 and 0.87 (7). Indeed, during an overnight fasting period from 7 to 14 hours, the RQ would be 0.68 to 0.90 (18). IC was performed less than 12 months after diagnosis and less than 1.5 months after the nutritional assessment. The body composition was to be assessed by bioelectric impedance analysis (BIA), using the validated formula for ALS patients (19).

The control subjects, from the Human Nutrition Unit of the University of Clermont Auvergne (France), were healthy people without ALS and not suffering from a metabolic altering disease such as inflammatory bowel disease, cancer, dysthyroidism or infectious disease. Controls were assessed by IC and BIA, according to similar procedures to those used for patients, using Kyle et al. equation for the body composition determination (20,21).

**Nutritional and metabolic assessment**

The nutritional and metabolic assessments, homogeneous and standardized in both centres, were performed according to standard procedures. Subjects were weighed in their underwear using a SECA$^{TM}$ electronic scale recording to 0.1 kg (Vogel & Halke, Hamburg, Germany) in an upright position or on a SECA$^{TM}$ weighing chair if they could not stand upright. Height was obtained using a SECA$^{TM}$ gauge recording to 0.2 cm (Vogel & Halke, Hamburg, Germany) in an upright position, or using the Chumlea formulas for people over 60 who could not be verticalized (22). Body mass index (BMI) was calculated as weight (kg) / height x height ($m^2$). Fat free mass (FFM in kg) and fat mass (FM in kg) were obtained from bioelectric impedance analysis at 50 kHz after five minutes of rest in supine position. They

were calculated using validated formulas: Desport et al. equation for ALS patients (19) with an Analycor™ device (Eugédia, Chambly, France), and Kyle et al. equation (21) for controls with BIA 101™ (RJL System, Detroit, USA). The triceps skinfold (TSF), necessary for the FFM determination according to the Desport et al. formula (19), was obtained from the average of three measurements on each side with a Harpenden caliper (Baty International, Burgess Hill, UK) according to the usual modalities (23).

IC was performed in the morning after 12 hours overnight fasting in supine position and at rest, using the Quark RMR™ (Cosmed, Rome, Italy) and the Deltatrac II™ device (DatexEngström, Helsinki, Finland), after instruments calibration (24). The mean repeatability coefficient was 7,3 +/- 2%. Harris and Benedict 1919 (HB1919) formulas were used to calculate REE (cREE) (22). The percentage of REE variation (ΔREE) was calculated using the formula: ΔREE = (mREE [kcal / 24h] - cREE [kcal / 24h]) / cREE (kcal / 24h) * 100. HM was defined as ΔREE > +10%.

**Data collection and Statistical analysis**

All data were collected prospectively and extracted from the CleanWEB™ database of the Limoges ALS Referral centre and from the Human nutrition Unit Laboratory of Clermont-Ferrand databases, validated by the French Commission Nationale de l'Informatique et des Libertés. All subjects gave their informed consent for the data collection. The study was reported at ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT03382392).

Statistical analysis was performed using SAS™ 9.3 (SAS institute NC, Cary, USA). Comparative analyses were conducted on the ALS group versus the control group using the Mann-Whitney and the Chi2 tests. To investigate the factors associated with HM, a logistic regression model was conducted and results were expressed with odds ratio (OR) and 95% confidence interval (95%CI). Adjustment variables were sex, age, BMI, FFM and FM.

158 Covariates with a significance threshold p <0.2 in univariate analysis were included in
159 multivariate analysis and a forward selection variable was used.

160

161 **RESULTS**

162 IC was performed on 405 ALS patients of which 118 were excluded: 35 for a RQ < 0.7 or >
163 0.87, 30 for a time lag between IC and nutritional assessment greater than 1.5 months, 25
164 because the delay between diagnosis and IC was over 12 months and 28 because of a lack of
165 BIA data (figure 1).

166 Seventy-five healthy controls were compared to 287 ALS patients. In ALS patients, 40.8 %
167 had a bulbar form, and 9.4% a familial form. The median delay between diagnosis and
168 nutritional assessment was 4.2 month [2.2–6.4]. The median ALSFRS-R score at inclusion
169 was 39.6 points [35-43]. Characteristics and comparisons of ALS patients and controls are
170 presented in table 1. The RQ was not significantly different between the two populations. The
171 metabolic level was higher in ALS patients (1500 kcal/24h [1290–1693] vs. 1230 kcal/24h
172 [1000 –1455], p <0.0001) as well as REE/FFM (33.5 kcal/kg/24h [30.4 –37.8] vs. 28.3 [26.1–
173 33.6] kcal/kg/24h, p <0.0001). HM was significantly more frequent in ALS patients than in
174 controls (55.0% vs. 13.3%, p < 0.0001).

175 HM was not found in 129 patients (45,0%) and 65 controls (86,7%). In subjects not
176 considered to be hypermetabolic, mREE was significantly higher in ALS patients compared
177 to healthy controls (1331 kcal/24h [1153 –1543] vs. 1210 kcal/24h [981 –1450]), p = 0.0008)
178 with a higher REE variation (1.8% [-3.5 –6.1] vs. -2.1% [-8.8 –1.4], p = 0.0001). In the
179 absence of HM, REE/ FFM ratio was higher in ALS patients (31.0 kcal/kg/24h [28.0 –35.0]
180 vs. 28.1 kcal/kg/24h [25.8 –32.8], p = 0.0004).

Factors associated with HM in univariate and multivariate analysis were presented in table 2. After adjustment, HM was positively associated with ALS ($OR_{adjusted}$ = 9.50 [4.49 –20.10], p < 0.0001) and with being a male ($OR_{adjusted}$ = 1.73 [1.10 – 2.72], p = 0.018) (table 2).

## DISCUSSION

This study highlights the existence of HM and the high level of metabolic alteration in a large cohort of ALS patients compared to healthy subjects. These metabolic alterations concern all patients, even in the absence of HM. It was essential for clinical practice to confirm the reality of HM during ALS. Indeed, these metabolic alterations can contribute to an increase in TEE (12). In the absence of adaptation of energy intake, an increase in TEE is a cause of weight loss and undernutrition, which are associated with impaired functional status, alteration of quality of life and decrease in survival (6,7,13). This reinforces the importance of metabolic assessment and nutritional care in ALS, as soon as the diagnosis is made, in order to adapt the level of dietary intake or enteral nutrition.

Our ALS patients sample is the largest in literature in this field. The original use of a logistic regression model clearly asserts a positive and strong association between ALS and HM, which has not been demonstrated previously. Indeed, Desport et al. described a higher mREE in 62 ALS patients versus 31 healthy volunteers, comparable on nutritional parameters, but the lack of multivariate analysis could not confirm the link between HM and ALS (13). Conversely, Vaisman et al. found a decrease in mREE in a modest population of 33 ALS patients compared to 33 controls: due to the disparity in weight, BMI and FFM between the two groups, and the lack of adjustment on these variables, the results were not interpretable (15).

Regardless of the relationship between HM and ALS, our study suggests a male influence on HM. Although FFM, which is proportionately higher in men (20) and the main determinant of REE (15,26), this relationship is not explained in this study by a difference in body composition by gender. Indeed, body composition parameters were not associated with HM in this work.

The causes of the HM remain unknown. Several hypotheses are mentioned: increased glucose and lipids consumption, mitochondrial alterations, hypothalamic dysfunction (6,27). Due to the high frequency of metabolic changes in ALS, HM can certainly be considered a marker of the disease. The identification of metabolic pathways and the search for biomarkers of HM would likely improve the understanding of physiopathological mechanisms and propose new therapeutic pathways targeted at metabolic phenotype in ALS.

Our study presents limitations. Despite the large number of patients followed by the ALS Referral center (88.2% of patients from our region) (7), the data were not extracted from a register and were therefore not totally exhaustive. It would have been preferable to have a larger control population from the same center and matched on the patients. We did not have such a control cohort in our center, and we used the control population which seemed to us the most suitable. So, even if patients and controls were assessed in two different centers and regions, these bordering regions (Limousin and Auvergne) had a comparable gender and age distribution ratio according to the French National Institute of Statistics (28). Moreover, nutritional and metabolic assessments were performed under standardized conditions in both center, and body composition was obtained from crude impedancemetric data (impedance and reactance), using validated formulas for each group: Desport et al. formula for ALS patients, validated versus the reference method (Dual x-ray absorptiometry) (19) and Kyle et al. formula for controls, suitable for body composition assessment in elderly subjects (21). Due to the unavailability of the same device in each center, two different devices were used for IC.

However, the mREE values of its two devices were recognized as very similar in a previous work (29). Even if age and BMI were different between patients and controls, we have taken into account these variances, which have been minimized by adjustment in multivariate analysis. We chose not to consider the subtype of ALS (clinical phenotype; familial versus sporadic form), the fasciculations and the tobacco consumption for adjustment, since previous works found no influence for these criteria on the metabolic changes (6,7,13). Finally, even if autonomic nervous abnormalities with a potential influence on the metabolic level were described in ALS, manifested for example by an increase in blood pressure or resting heart rate (30,31), we did not have such data to make an adjustment.

The use of HB1919 formulas, established for healthy subjects, can be another bias. Indeed, it is possible that the ΔREE demonstrated was related to an inappropriate use of these equations in ALS patients. Nevertheless, in a recent work, Jesus et al. compared the mREE and cREE by 12 predictive formulas, including HB1919 equations (32): This work highlighted that ALS patients had a mREE higher than cREE whatever the formula used, and therefore that the increase in REE was not related to the inappropriate use of HB1919 equations. Thus, these formulas seem to be relevant as a reference value to search for an ΔREE. Furthermore, other authors have validated, for ALS patients, the use of equations comprising sex and age, such as HB1919 or Mifflin-St Jeor formulas, both for the REE measurement (33), but also in models allowing to estimate the TEE (12).

Our study focused specifically on the REE assessment, which is not sufficient on its own to define the energy requirements of patients. We didn't studied the TEE, which is a basis for estimating energy requirements. Thus, in a previous work, Kasarskis et al. proposed models for estimating the TEE, which can be used in current practice, taking into account body composition and physical function, making it possible to adapt food or enteral intakes (12).

At last, this study cannot specify when the metabolic changes appear. It could be of interest to measure REE in the presymptomatic stage in descendants of ALS familial form patients, in order to detect a possible HM before onset of the first symptoms and to set up early nutritional care.

## CONCLUSION

The concept of HM during ALS is a reality and could not be controversial: HM affects more than half of the patients and is positively and strongly associated with ALS. This work confirms a very frequent metabolic alteration during ALS, contributing to the deterioration of nutritional status, a factor of poor prognosis. This reinforces the importance of HM screening, which should be systematic, to provide early and appropriate nutritional care: diet advice, oral supplementation or enteral nutrition. The causes of HM are still unknown. The identification of the mechanisms involved could improve patient management.

## Conflicts of interest

The authors have no conflict of interest to disclose

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## Figure legend

Figure 1: Flowchart of ALS patients included in the study.

ALS: amyotrophic lateral sclerosis; RQ: respiratory quotient

**Figure 1:**

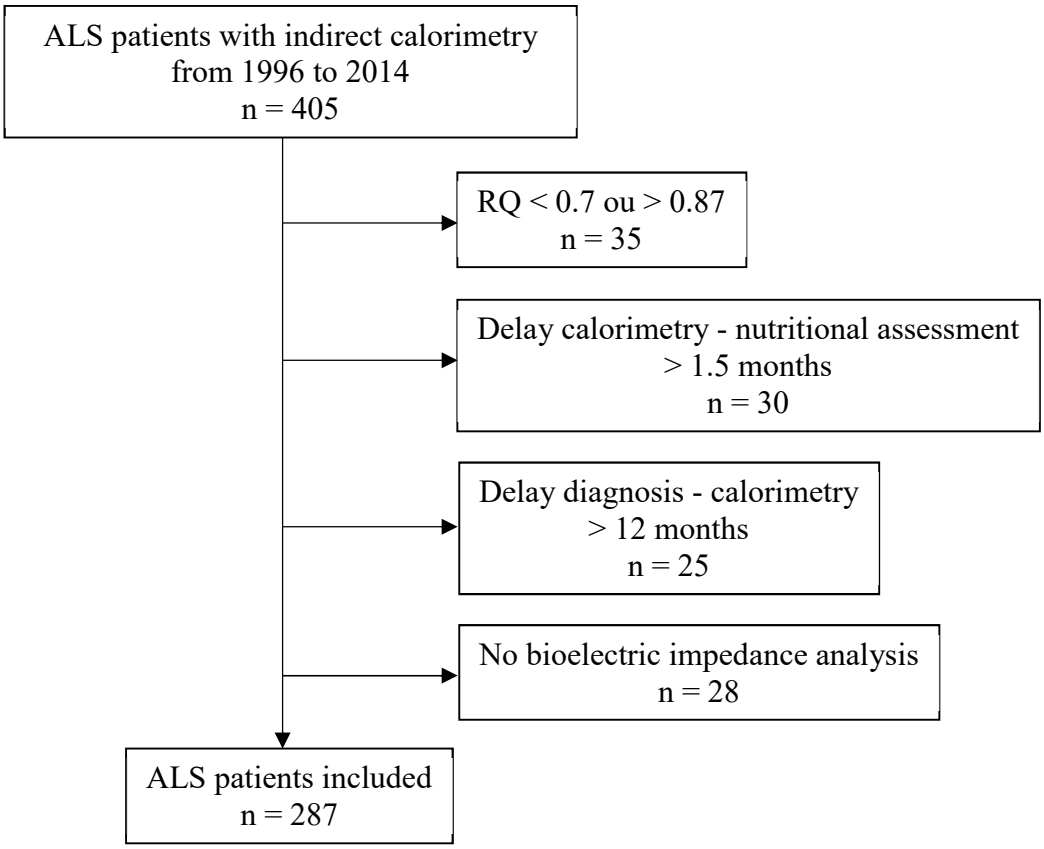
ALS patients with indirect calorimetry
from 1996 to 2014
n = 405
RQ < 0.7 ou > 0.87
n = 35
Delay calorimetry - nutritional assessment
> 1.5 months
n = 30
Delay diagnosis - calorimetry
> 12 months
n = 25
No bioelectric impedance analysis
n = 28
ALS patients included
n = 287

**Table 1:** Comparison of demographic, nutritional characteristics and resting energy expenditure (REE) between ALS patients and healthy controls

| Variables | ALS Patients Median [IQR] or n (%) (n = 287) | Healthy controls Median [IQR] or n (%) (n = 75) | p |
|---|---|---|---|
| Male | 145 (50.5) | 40 (53.3) | 0.66 |
| Age at IC (years) | 66.4 [56.7–73.1] | 75.0 [68.5–86.0] | **<0.0001** |
| Weight (kg) | 64.9 [57.9 –74.2] | 66.0 [54.5 –75.0] | 0.25 |
| BMI (kg/m$^2$) | 24.3 [22.0 –27.5] | 26.2 [23.2 –28.4] | **0.026** |
| FFM (kg) | 44.4 [36.9 –51.8] | 40.7 [30.9 –54.8] | 0.15 |
| FM (kg) | 20.7 [15.2 –25.4] | 20.5 [16.8 –26.9] | 0.56 |
| mREE (kcal/24h) | 1500 [1290 –1693] | 1230 [1000 –1455] | **<0.0001** |
| cREE (kcal/24h) | 1327 [1195 –1496] | 1262 [1023 –1460] | **0.0015** |
| ΔREE (%) | 11.5 [3.6 –19.3] | -1.2 [-7.5 –5.3] | **<0.0001** |
| Hypermetabolism | 158 (55.0) | 10 (13.3) | **<0.0001** |
| REE/weight (kcal/kg/24h) | 22.9 [20.9 –25.0] | 19.2 [17.4 –20.9] | **<0.0001** |
| REE/FFM (kcal/kg/24h) | 33.5 [30.4 –37.8] | 28.3 [26.1–33.6] | **<0.0001** |

*ALS: amyotrophic lateral sclerosis; BMI: body mass index; FFM: free fat mass; cREE: calculated resting energy expenditure; ΔREE: percentage of REE variation; FM: fat mass; IC: indirect calorimetry; IQR: interquartile range; mREE: measured resting energy expenditure; n: number*

**Table 2:** Factors associated with hypermetabolism

| Variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | $OR_{crude}$[95%CI] | p | $OR_{adjusted}$[95%CI] | p |
| ALS patients vs. controls | 7.96 [3.93 – 16.12] | **<0.0001** | 9.50 [4.49 – 20.10] | **<0.0001** |
| Male vs. female | 1.50 [0.99 – 2.28] | 0.054 | 1.73 [1.10 – 2.72] | **0.018** |
| Age (+ 1 year increment) | 0.98 [0.97 – 1.00] | 0.061 | 1.01 [0.99 ; 1.03] | 0.250 |
| BMI (+ 1 point increment) | 0.96 [0.92 – 1.00] | 0.070 | | |
| FFM (+ 1 kg increment) | 1.02 [1.00 – 1.04] | 0.064 | | |
| FM (+ 1 kg increment) | 0.97 [0.95 – 1.00] | **0.023** | | |

OR: odds ratio; CI: confidence interval; ALS: amyotrophic lateral sclerosis; BMI: body mass index; FFM: free fat mass; FM: fat mass