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Original article

Resting energy expenditure equations in amyotrophic lateral sclerosis, creation of an ALS-specific equation

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SUMMARY

Introduction: Resting energy expenditure (REE) formulas for healthy people (HP) are used to calculate REE (cREE) in amyotrophic lateral sclerosis (ALS) patients. In 50–60% of ALS cases an increase of measured REE (mREE) in indirect calometry (IC) compared to cREE is found. The aims here were (i) to assess the accuracy of cREE assessed using 11 formulas as compared to mREE and (ii) to create (if necessary) a specific cREE formula for ALS patients.

Method: 315 Patients followed in the ALS expert center of Limoges between 1996 and 2014 were included. mREE assessed with IC and cREE calculated with 11 predictive formulas (Harris Benedict (HB) 1919, HB 1984, WSchofield, De Lorenzo, Johnstone, Mifflin, WHO/FAO, Owen, Fleisch, Wang and Rosenbaum) were determined at the time of diagnosis. Fat free mass (FFM) and fat mass (FM) were measured with impedancemetry. A Bland and Altman analysis was carried out. The percentage of accurate prediction ±10% of mREE, and intraclass correlation coefficients (ICC) were calculated. Using a derivation sample, a new REE formula was created using multiple linear regression according to sex, age, FFM and FM. Accuracy of this formula was assessed in a validation sample.

Results: ICC ranged between 0.60 and 0.71 (moderate agreement), and percentage of accurate prediction between 27.3% and 57.5%. Underestimation was found from 31.7% to 71.4% of cases. According to these unsatisfactory results we created an ALS-specific formula in a derivation sample (130 patients). ICC and percentage of accurate prediction increased in a validation sample (143 patients) to 0.85 (very good agreement) and 65.0% respectively, with 17.5% underestimation.

Conclusion: REE formulas for HP underestimate REE in ALS patients compared to mREE. Our new ALS-specific formula produced better results than formulas for HP. This formula can be used to estimate REE in ALS patients if IC is not accessible.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease affecting motor neurons, age at diagnosis is 65–70 years [1–4] and its incidence is stable at around 2/100 000 person years in Western populations [5]. The prognosis is severe, with a median survival in Europe of 25–30 months from onset [4].

ALS patients are at risk of malnutrition in the short and medium term (9–55% according to the literature) [1,6,7]. Causes may include increased resting energy expenditure (REE) [7–12] which if not compensated by diet, may cause weight loss. REE may be measured (mREE) with indirect calorimetry (IC) [9,10,13–16], but because of the low availability of this high-cost apparatus, and the

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Abbreviations

ALS	amyotrophic lateral sclerosis
ALSFRS	amyotrophic lateral sclerosis functional rating scale
ALSFRS-R	amyotrophic lateral sclerosis functional rating scale-revised
BIA	bioelectric impedance analysis
BMI	body mass index
CI	confidence interval
WHO/FAO	world health organization/food and agriculture organization of the United Nations
FM	fat mass
FFM	free fat mass
HB	Harris and Benedict
IC	indirect calorimetry
IQR	interquartile range
Mifflin	Mifflin St. Jeor
PA	phase angle
cREE	calculated resting energy expenditure
mREE	measured resting energy expenditure
RQ	respiratory quotient
SD	standard deviation
TEE	total energy expenditure
TSF	triceps skin fold
WSchofield	World Schofield

length of time necessary for each measurement (≥20 min), predictive formulas have been developed to provide calculated REE (cREE). The most widely used is Harris and Benedict 1919 (HB1919) [9,10,13,14,16]. The Mifflin St. Jeor (Mifflin) formula is also used [17,18]. The difference between mREE and cREE allows for the definition of energy metabolism disorder. A difference between mREE and cREE of more than 10% defines hypermetabolism, which is found in 50–60% of ALS patients [7–10,19]. REE may increase from +10 to +20% in these patients. For Sherman et al., HB 1919 is not valid when used to predict REE in ALS patients [16]. Kasarskis et al. and Shimizu et al. recently created total energy expenditure (TEE) formulas for ALS patients using HB1919 and Mifflin formulas for REE prediction. These REE formulas were constructed for healthy people [20]. Currently, no REE formulas are validated for ALS patients.

The objectives here were, in ALS patients: (i) to assess the accuracy of cREE calculated with 11 predictive formulas, commonly used in healthy patients (HB 1919, HB 1984, World Schofield (WSchofield), De Lorenzo, Johnstone, Mifflin) [20] and used in ALS studies (HB 1919, world health organization/food and agriculture organization of the United Nations (WHO/FAO), Owen, Fleisch, Wang, Rosenbaum, Mifflin) [9,10,17,21] as compared to mREE assessed using IC, and; (ii) to create, if necessary a REE formula adapted to ALS patients and suitable for use in clinical practice without IC.

2. Methods

ALS patients followed in the ALS expert center in Limoges (France) from November 1996 to November 2014 with nutritional, neurological and respiratory assessments were included. The assessments were performed after diagnosis and then regularly until the patient died. Nutritional assessment included the use of indirect calorimetry to measure REE.

2.1. Inclusion criteria

We included patients with ALS diagnosed according to Airlie House criteria (definite, probable, or laboratory-supported probable and possible) [22] and treated with riluzole. Patients could also have had ALS associated with frontotemporal dementia. The respiratory quotient (RQ) of patients by indirect calorimetry (IC) was required to be between 0.7 and 0.87 [23]. IC and the other nutritional assessments had to have been performed within 1.5 months, and IC had to be performed no more than 12 months after diagnosis.

2.2. Data collection

The data were extracted prospectively from the CleanWEB™ database of the ALS expert center, which has been validated by the Commission Nationale de l'Informatique et des Libertés (CNIL; No. 1244525). Patients gave given informed consent for data collection. The ClinicalTrial registration number is NCT03378375.

2.3. Nutritional assessments

General data collected were: sex, date of diagnosis, date of calorimetry.

Nutritional assessment was carried out in the nutrition unit after diagnosis in the Nutrition Unit. Patients were weighed (to 0.1 kg) in underwear using a SECA® electronic balance (Vogel & Halke, Hamburg, Germany) in an upright position or on a SECA® weighing chair if they could not stand upright. Usual weight 6 months before onset of symptoms was collected allowing the calculation of the percentage of initial weight loss relative to the usual weight. Their height (in m) was measured using a SECA® gauge recording to 0.2 cm (Vogel & Halke, Hamburg, Germany) in an upright position or using the Chumlea formulas for people over 60 years who could not be verticalized [24]. BMI (in kg/m^2) was calculated using the formula: BMI (kg/m^2) = weight (kg)/ height × height (m^2). The triceps skinfold (TSF) 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 [25]. Fat free mass (FFM in kg) and fat mass (FM in kg) were calculated with the validated formula for ALS patients using weight, TSF and total body impedance at 50 kHz in bioelectric impedance analysis (BIA) Analycor® (Eugédia, Chambly, France) in supine position after 5 min of rest [26]. The impedancemetry also allowed for measurement of the phase angle (PA) marker of cellular function [27]. Measured REE (mREE in kcal/24 h) by IC was obtained with the Quark RMR® with canopy (Cosmed, Rome, Italy) after a calibration of the instrument (±0.02% on measures of expired volumes of CO_2 and inspired volumes of O_2) [23]. It was performed in the morning after 12 h of fasting, in a supine position and at rest. The patient was not physically active before the IC, and did not sleep during the exam or hyperventilate. The cREE was calculated (cREE in kcal/24 h) according to eleven predictive formulas (HB 1919, HB 1984, WSchofield, De Lorenzo, Johnstone, Mifflin, WHO/FAO, Owen, Fleisch, Wang and Rosenbaum) (Table 1). Formulas with results in kj (WSchofield, De Lorenzo and Johnstone) were converted into kcal by multiplying by 0.2388. The REE variation (bias in %) was calculated according to the formula: cREE (kcal/24 h) – mREE (kcal/24 h)/mREE (kcal/24 h) × 100. The thresholds of accurate prediction of cREE compared to mREE is of ±10%.

Table 1
Resting energy expenditure formulas tested and new formula constructed.

Harris & Benedict 1919 [38]	- Male: (Weight (kg) × 13.7516) + (Height (cm) × 5.0033) − (Age (years) × 6.755) + 66.473
	- Female: (Weight (kg) × 9.5634) + (Height (cm) × 1.8496) − (Age (years) × 4.6756) + 655.0955
Harris & Benedict 1984 [39]	- Male: (Weight (kg) × 13.397) + (Height (cm) × 4.799) − (Age (years) × 5.677) + 88.362
	- Female: (Weight (kg) × 9.247) + (Height (cm) × 3.098) − (Age (years) × 4.33) + 477.593
World Schofield [20]	- Male of 18–30 years: (0.063 × Weight (kg)) + 2.896
	- Male of 30–60 years: (0.048 × Weight (kg)) + 3.653
	- Male > 60 years: (0.049 × Weight (kg)) + 2.459
	- Female of 18–30 years: (0.062 × Weight (kg)) + 2.036
	- Female of 30–60 years: (0.034 × Weight (kg)) + 3.538
	- Female > 60 years: (0.038 × Weight (kg)) + 2.755
De Lorenzo [20]	- Male: (53.284 × Weight (kg)) + (20.957 × Height (cm)) − (23.859 × Age (years)) + 487
	- Female: (46.322 × Weight (kg)) + (15.744 × Height (cm)) − (16.66 × Age (years)) + 944
Johnstone [40]	(90.2 × FFM (kg)) + (31.6 × FM (kg)) − (12.2 × Age (years)) + 1613
Mifflin St. Jeor [41]	- Male: (9.99 × Weight (kg)) + (6.2 × Height (cm)) − (4.92 × Age (years)) + 5
	- Female: (9.99 × Weight (kg)) + (6.2 × Height (cm)) − (4.92 × Age (years)) − 161
WHO/FAO [17]	- Male of 18–30 years: (15.4 × Weight (kg)) − (27 × Height (cm)) + 717
	- Male of 31–60 years: (11.3 × Weight (kg)) + (16 × Height (cm)) + 901
	- Male of >60 years: (8.8 × Weight (kg)) + (1128 × Height (cm)) − 1071
	- Female of 18–30 years: (13.3 × Weight (kg)) + (334 × Height (cm)) + 35
	- Female of 31–60 years: (8.7 × Weight (kg)) − (25 × Height (cm)) + 865
	- Female of >60 years: (9.2 × Weight (kg)) + (637 × Height (cm)) − 302
Owen [17]	- Male: 879 + 10.2 × Weight (kg)
	- Female: 795 + 7.18 × Weight (kg)
Fleisch [17]	- Male: 24 × BSA × (38–0.073 × (Age (years) − 20))
	- Female: 24 × BSA × (35.5–0.064 × (Age (years) − 20))
Wang [17]	24.6 × FFM (kg) + 175
Rosenbaum [17]	(17.2 × FFM (kg)) + (10.5 × FM (kg)) + 375
New formula	901.34 − (5.82 × Age (years)) + (15.65 × FFM[a] (kg)) + (8.88 × FM[a] (kg)) + 145.21 if men

BSA: body surface area = 0.007184 × (Height (cm)$^{0.725}$) × (Weight (kg)$^{0.425}$); FFM: fat-free mass; FM: fat mass; WHO/FAO: world health organization/food and agriculture organization of the United Nations.
[a] Body composition measured in bioelectrical impedancemetry with Desport et al. validated formula [26].

Overestimation was >10% of measured value and underestimation was <10% of measured value [20].

2.4. Statistical analysis

Statistical analysis was performed using SAS® software v9.3 (SAS Institute, Cary, North Carolina, USA) and GraphPad Prism 6.0 (GraphPad Software Inc, La Jolla, CA, USA). The threshold of significance for all statistical analyses was $p < 0.05$. We complied with the STROBE statement [28]. Quantitative variables were expressed with the median (interquartile range [IQR]) or mean ± standard deviation (SD). Qualitative variables were expressed in frequency and percentage. Normality of quantitative variables was studied using the Shapiro–Wilk test. Quantitative variables were compared using non-parametric Mann–Whitney test, and qualitative variables were compared using Chi2.

2.5. Agreement between mREE and cREE

The REE variation (bias in %) was calculated according to the formula: cREE (kcal/24 h) − mREE (kcal/24 h)/mREE (kcal/24 h) × 100. The threshold of accurate prediction of cREE compared to mREE was ±10%. Overestimation is >10% of measured value and underestimation is <10% of measured value [29]. The percentage of prediction between the 95% limit of agreement (±2 SD) and the error risk were computed. The mean percentage difference between cREE and mREE (bias in kcal/24 h and %) was calculated.

2.6. Formula derivation and validation

The entire sample was split at random into a derivation and a validation subsample. The construction of the formula for REE in ALS patients was based on the following steps using the derivation sample: (i) detection and elimination of outliers, decision based on the Cook's D influence statistics (threshold 4/n); (ii) simple linear regression analysis considering mREE as the dependent variable and the following independent variables: age, sex, height, weight, FM, FFM and PA assessed using BIA; (iii) multiple linear regression analysis considering as independent variables those with a p-value <0.20 in the simple regression, the first model was simplified step by step, confounders were checked at each step; (iv) check of the linear nature of the relation between dependent and independent variables; (v) evaluation of the normality (using Shapiro–Wilk test and Kernel and qq plot graphs) and homoscedastisticy (White test = 0.42) of the residuals of the final model; (vi) check for any misspecification of the final model (vii) check for multicollinearity among independent variables included in the final model, (viii) check for interaction between independent variables.

Based on the coefficient of the multiple linear regression, REE was estimated in the validation sample. Assessment of the agreement between mREE and REE estimated by our equation was based on the above mentioned strategy.

3. Results

3.1. Study sample

From November 1996 to November 2014, 405 ALS patients had IC. Ninety patients were excluded: 35 for a RQ < 0.7 or >0.87; 30 because the time lag between IC and nutritional assessment was over 1.5 months; and 25 because the delay between diagnosis and IC was over 12 months. The flowchart of patients included and not included is shown in Figure 1.

The 315 included patients had a median age at diagnosis of 65.9 years (56.5–73.7), with a sex ratio of 1.0. The median delay between diagnosis and nutritional assessment was 4.3 months (2.2–6.6). The median mREE with IC was of 1503 kcal/24 h (1290–1698). The nutritional, and neurological characteristics of the patients included are presented in Table 2.

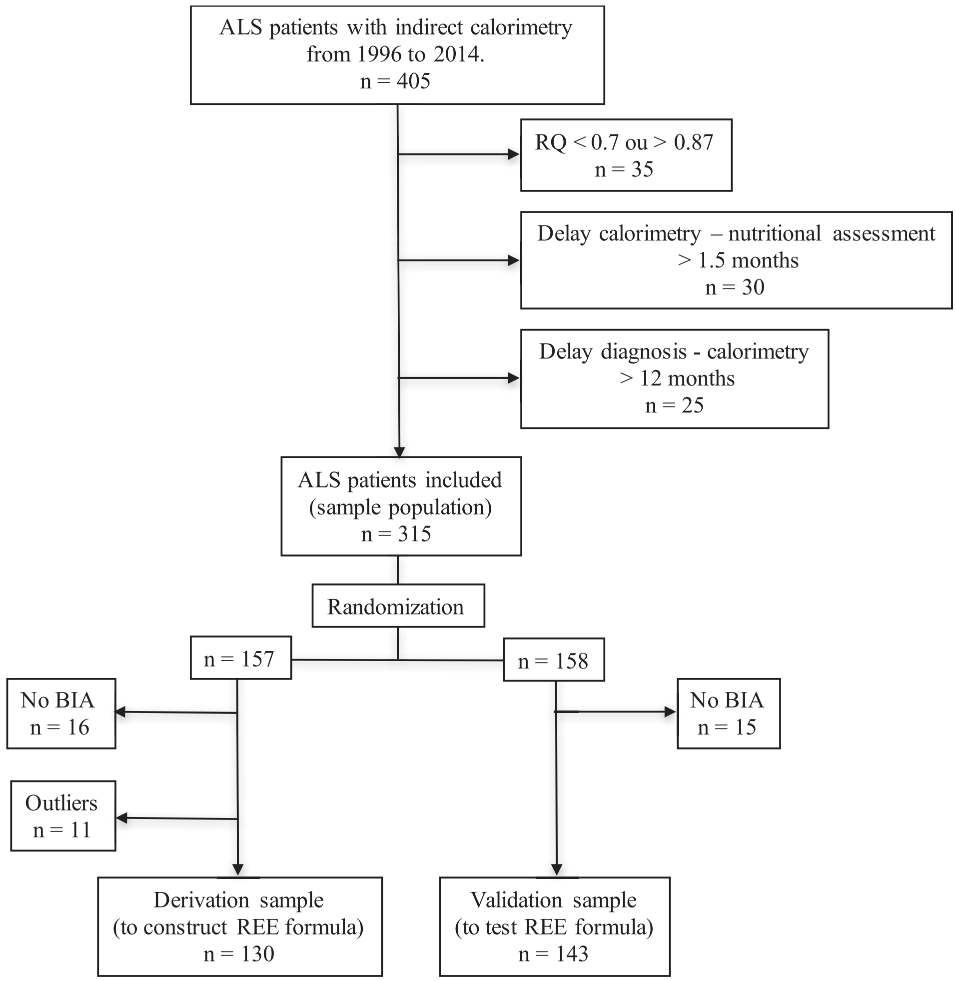

Fig. 1. Flowchart of patients with ALS included in the study. ALS: amyotrophic lateral sclerosis; BIA: body impedance analysis; n: number; RQ: respiratory quotient; REE: resting energy expenditure.

Table 2
Nutritional characteristics of included patients.

Criteria	Entire sample Median (IQR); n (%) n = 315	MD	Derivation sample (to construct REE formula) Median (IQR); n (%) n = 130	Validation sample (to test REE formula) Median (IQR); n (%) n = 143	p
Age at diagnosis (years)	65.9 (56.5–73.7)	0	66.1 (56.5–73.9)	65.3 (56.4–72.3)	0.48
Age at calorimetry (years)	66.6 (56.9–74.1)	0	66.7 (56.9–74.3)	66.2 (57.0–73.5)	0.47
% male	161 (51.1)	0	65 (50.0)	72 (50.3)	0.95
ALSFRS-R (points)	40 (35–43)	24	36 (33–40)	34 (31–41)	0.23
Weight (kg)	65.0 (57.3–74.7)	0	64.3 (57.3–74.4)	65.0 (58.0–73.6)	0.91
BMI (kg/m^2)	24.2 (22.0–27.6)	0	24.8 (22.3–27.7)	23.6 (21.8–26.5)	**0.047**
FFM (kg)	44.4 (36.9–51.9)	28	42.7 (36.2–51.9)	44.8 (37.1–51.5)	0.63
FM (kg)	20.7 (15.2–25.4)	28	21.0 (17.0–25.5)	19.9 (13.9–24.6)	0.17
PA (°)	3.0 (2.4–3.7)	31	3.0 (2.4–3.6)	3.0 (2.4–3.7)	0.88
mREE (kcal/24 h)	1503 (1290–1698)	0	1455 (1266–1683)	1503 (1320–1678)	0.39
cREE HB1919 (kcal/24 h)	1327 (1190–1497)	0	1293 (1182–1480)	1327 (1190–1495)	0.58
cREE HB1984 (kcal/24 h)	1355 (1213–1511)	0	1338 (1215–1500)	1356 (1213–1489)	0.69
cREE WSchofield (kcal/24 h)	1350 (1217–1510)	0	1380 (1214–1500)	1345 (1230–1500)	0.95
cREE De Lorenzo (kcal/24 h)	1361 (1203–1528)	0	1346 (1191–1521)	1364 (1211–1503)	0.72
cREE Johnstone (kcal/24 h)	1317 (1158–1485)	28	1298 (1145–1481)	1326 (1161–1462)	0.73
cREE Mifflin (kcal/24 h)	1286 (1085–1453)	0	1289 (1055–1445)	1273 (1105–1438)	0.59
cREE WHO/FAO (kcal/24 h)	1378 (1256–1567)	0	1367 (1238–1553)	1385 (1275–1552)	0.55
cREE Owen (kcal/24 h)	1434 (1221–1610)	0	1435 (1221–1617)	1422 (1222–1577)	0.83
cREE Fleisch (kcal/24 h)	1392 (1242–1524)	0	1386 (1222–1520)	1386 (1259–1505)	0.59
cREE Wang (kcal/24 h)	1268 (1082–1451)	28	1226 (1065–1451)	1277 (1088–1441)	0.63
cREE Rosenbaum (kcal/24 h)	1362 (1232–1509)	28	1355 (1230–1514)	1369 (1233–1472)	0.89

BMI: body mass index; FFM: fat-free mass; FM: fat mass; HB: Harris & Benedict; IQR: interquartile range; Mifflin: Mifflin St. Jeor; PA: phase angle; mREE: measured resting energy expenditure; cREE: calculated resting energy expenditure; WHO/FAO: world health organization/food and agriculture organization of the United Nations; WSchofield: World Schofield.
Bold indicates $p<0.05$.

3.2. cREE accuracy

The results of cREE prediction with the 11 REE formulas in the entire sample (n = 315) are presented in Table 3. The analysis found moderate agreement between mREE and cREE, with an ICC range between 0.60 (−0.07–0.84) and 0.71 (0.54–0.81).

Figure 2 shows the Bland and Altman plots for the 11 formulas. With a threshold of ±10% difference between mREE and cREE, the proportion of accurate prediction ranged between 27.3% and 57.5%. An underestimation of REE (REE variation < 10%) was found in 31.7%–71.4% of cases.

3.3. ALS-specific REE formula derivation and validation

Given these results (high percentage of underestimation of REE formula in ALS patients) we attempted to create a new formula. Some patients were excluded from the derivation and validation subsamples due to lack of BIA measurement and others were excluded from the derivation because they had been detected as outliers (hence their inclusion was not desirable). Both subsamples displayed a high level of comparability only with BMI, which was slightly higher in the derivation sample compared to the validation sample: 24.8 kg/m^2 (22.3–27.7) vs. 23.6 kg/m^2 (21.8–26.5), respectively (p = 0.047) (Table 2).

After the simple linear regression analysis, age, sex, height, weight, FM, FFM and PA assessed using BIA were considered to enter the first multiple linear regression model (p-values <0.0001 for all these variables, except for FM: p = 0.0014). After a step by step simplification of the model, age, sex, FM and FFM were retained in the final model (p-values <0.0001 for all these variables, except for age: p = 0.004). The graphical evaluation of the linear nature of the relation between the dependent and the independent variables was satisfactory. The residuals of the model were considered as normally distributed (Shapiro Wilk test p = 0.58, satisfactory Kernel and qq plot graphs) and with a constant error variance (White test p = 0.42). The model was shown to be correctly specified, there was no multicollinearity or interaction between dependent variables.

The formula based on the coefficient of the model from the derivation sample (130 patients) appeared as follows:

cREE (kcal/24 h) = 901.34 − (5.82 × age [years]) + (15.65 × FFM [kg]) + (8.88 × FM [kg]) + 145.21 if men. The R-square of the model was 76%.

In the validation sample, our formula was compared to the 11 other REE formulas (Table 4) and to mREE; results were the same as for the entire sample. The ICC between mREE and REE estimated using our formula was 0.85 (0.79–0.89) (i.e. very good agreement) (Table 3). Figure 3 shows the Bland and Altman plots for the 11 formulas and our new formula in the validation sample. With the threshold of ±10% of mREE, the percentage of accurate prediction was 65% (−347.7–304.4 kcal/24 h) with only 17.5% underestimation. Accurate prediction was significantly higher with our formula than eight of the other 11 formulas used, 45.5%, 49.7%, 49.0%, 51.7%, 34.3%, 26.6%, 30.1% and 43.4% for HB 1919, HB 1984, WSchofield, De Lorenzo, Johnstone, Mifflin, Wang and Rosenbaum, respectively (p = 0.0009, p = 0.0085, p = 0.006, p = 0.023, p < 0.0001, p < 0.0001, p < 0.0001 and p = 0.0002 respectively). However, though lower than our formulas, accurate prediction was not significantly different with WHO/FAO, Owen and Fleisch (55.2%, p = 0.09, 56.6%, p = 0.15 and 55.9%, p = 0.12, respectively). Underestimation was significantly lower with our formula (17.5%) than the 11 formulas used 51.0%, 46.2%, 45.5%, 44.8%, 62.9%, 71.3%, 34.3%, 33.6%, 39.9%, 66.6%, and 50.3% for HB 1919, HB 1984, WSchofield, De Lorenzo, Johnstone, Mifflin, WHO/FAO, Owen, Fleisch, Wang and Rosenbaum, respectively (p < 0.0001, p < 0.0001, p < 0.0001, p < 0.0001, p < 0.0001, p < 0.0001, p = 0.001, p = 0.002, p < 0.0001, p < 0.0001 and p < 0.0001, respectively).

4. Discussion

This study is the first to consider the accuracy of 11 REE formulas in a large sample of ALS patients (n = 315), with the creation of an ALS-specific REE formula which was validated in an independent subsample.

Assessment of the level of REE in ALS patients is important as it helps to better match the diet to the metabolic disorders present in ALS. This allows to better adapt energy intake in case of hypermetabolism, which is found in 50–60% during this disease according to HB 1919 to predict cREE [9,10]. If this adjustment is not made, patients are exposed to weight loss and accelerated development of undernutrition, which is an important risk factor for death in ALS [1,3,6]. In addition, better food intake could allow increased FM, which is a positively associated with survival [1]. The reference measurement method for REE, indirect calorimetry, is often unavailable in clinical practice due to lack of equipment. Even if it is possible, it is still time consuming. For these reasons, reliable predictive formulas are important. HB 1919 formulas are frequently used to assess energy need in various diseases including ALS [9,10,16,17,21,30–33]. Sherman et al. alone performed, in 2004, a Bland and Altman analysis to compare HB 1919 formulas with

Table 3
Prediction of calculated resting energy expenditure with the 11 formulas compared to measured resting energy expenditure in the entire sample (n = 315).

	REE		Bias		95% limits of agreement			ICC (95%CI)	Prediction		
	Mean (kcal/24 h)	SD	C-M (kcal/24 h)	%	From	to	% between limit		Accurate (±10%) (%)	Under 10% (%)	Over 10% (%)
Measured REE	1514	298.7	–	–	–	–	–		–	–	–
cREE HB1919	1356	229.2	−158.4	−9.4	−498.2	181.5	94.9	0.67 (0.18–0.84)	45.1	51.7	3.2
cREE HB1984	1377	223.3	−136.8	−7.9	−473.1	199.6	95.2	0.70 (0.30–0.84)	49.8	45.4	4.8
cREE WSchofield	1385	215.3	−129.0	−7.1	−491.6	233.6	95.6	0.67 (0.35–0.81)	43.5	43.8	6.7
cREE De Lorenzo	1377	235.8	−136.9	−8.1	−467.0	193.1	95.9	0.71 (0.30–0.86)	50.2	45.4	4.4
cREE Johnstone	1332	236.8	−181.0	−11.1	−512.6	150.7	94.4	0.66 (0.06–0.85)	36.9	60.3	2.8
cREE Mifflin	1283	252.1	−231.5	−14.8	−560.3	97.4	95.6	0.60 (−0.07–0.84)	27.3	71.4	1.3
cREE WHO/FAO	1420	222.9	−94.2	−4.9	−456.0	267.7	96.2	0.71 (0.54–0.81)	54.9	33.7	11.4
cREE Owen	1428	218.7	−86.1	−4.3	−447.6	275.3	95.9	0.71 (0.57–0.80)	57.5	31.7	10.8
cREE Fleisch	1392	197.5	−122.4	−6.7	−465.2	220.4	94.9	0.68 (0.36–0.82)	54.0	40.0	6.0
cREE Wang	1284	245.7	−229.3	−14.3	−607.7	149.1	95.8	0.56 (−0.03–0.80)	32.1	65.5	2.4
cREE Rosenbaum	1378	196.9	−135.2	−7.4	−504.1	233.8	94.8	0.64 (0.30–0.79)	46.7	46.0	7.3

CI: confidence interval; C-M: calculated REE minus measured REE; HB: Harris & Benedict; ICC: intraclass correlation coefficients; IQR: interquartile range; Mifflin: Mifflin St. Jeor; PA: phase angle; REE: resting energy expenditure; cREE: calculated resting energy expenditure; SD: standard deviation; WHO/FAO: world health organization/food and agriculture organization of the United Nations; WSchofield: World Schofield.

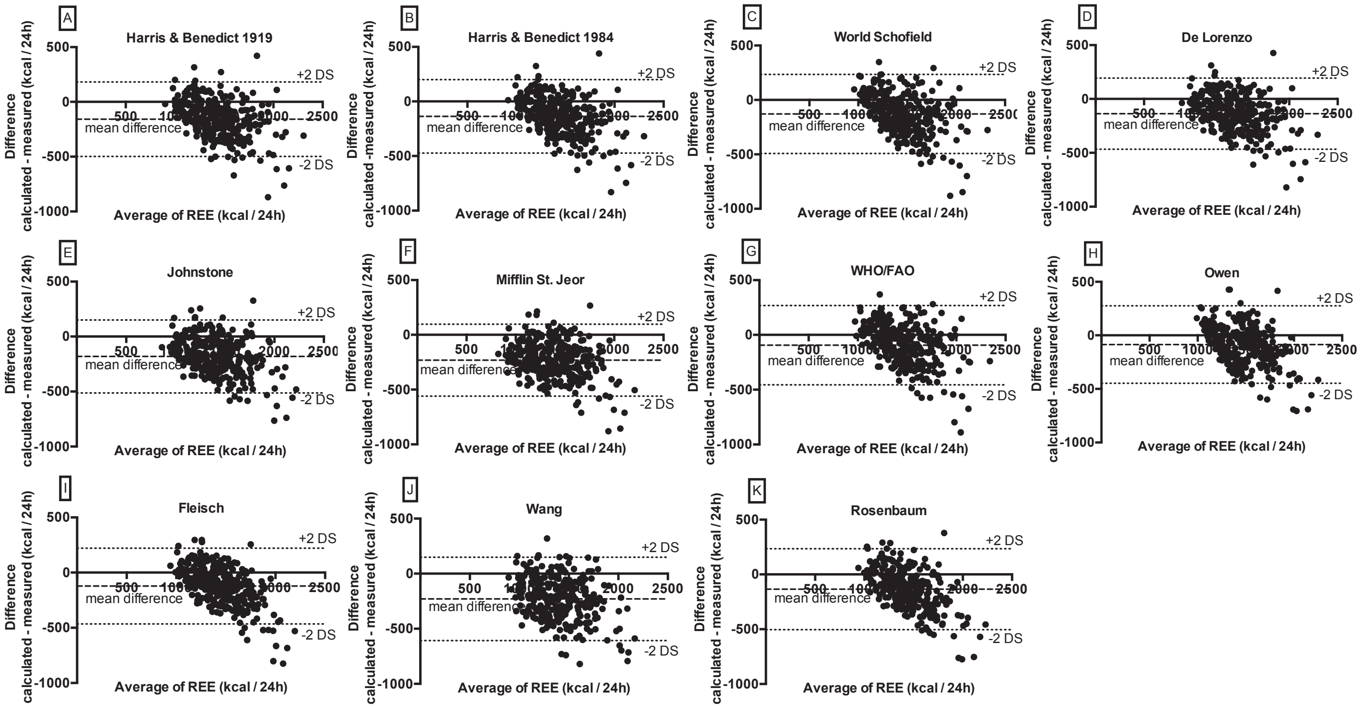

Fig. 2. Bland and Altman graphics between calculated resting energy expenditure with the 11 formulas and measured resting energy expenditure in the entire sample (n = 315). Panel A: Harris and Benedict 1919, panel B: Harris and Benedict 1984, panel C: World Schofield, panel D: De Lorenzo, panel E: Johnstone, panel F: Mifflin St. Jeor, panel G: WHO/FAO (world health organization/food and agriculture organization of the United Nations), panel H: Owen, panel I: Fleisch, panel J: Wang and panel K: Rosenbaum. REE: resting energy expenditure; SD: standard deviation.

Table 4
Prediction of calculated resting energy expenditure with the 11 formulas and the constructed formula compared to measured resting energy expenditure in the validation sample (n = 143).

	REE		Bias		95% limits of agreement			ICC (95%CI)	Prediction		
	Mean (kcal/24 h)	SD	C-M (kcal/24 h)	%	From	to	% between limits		Accurate (±10%) (%)	Under 10% (%)	Over 10% (%)
Measured REE	1514	373.2	–	–	–	–	–		–	–	–
cREE HB1919	1356	222.2	−158.1	−9.6	−497.8	181.5	95.1	0.70 (0.20–0.86)	45.5[a]	51.0[a]	3.5[a]
cREE HB1984	1375	212.8	−139.3	−8.2	−473.4	194.8	95.1	0.72 (0.32–0.87)	49.7[a]	46.2[a]	4.2[a]
cREE WSchofield	1381	207.1	−133.7	−7.7	−493.1	225.7	97.2	0.69 (0.38–0.83)	49.0[a]	45.5[a]	5.6[a]
cREE De Lorenzo	1376	224.9	−138.4	−8.3	−465.0	188.2	95.1	0.74 (0.30–0.88)	51.7[a]	44.8[a]	4.9[a]
cREE Johnstone	1326	215.5	−187.9	−11.6	−516.5	140.7	95.1	0.70 (0.05–0.88)	34.3[a]	62.9[a]	2.8[a]
cREE Mifflin	1285	241.6	−229.4	−14.7	−561.2	102.4	95.1	0.62 (−0.07–0.86)	26.6[a]	71.3[a]	2.1[a]
cREE WHO/FAO	1421	213.2	−93.7	−5.1	−443.1	255.6	97.2	0.68 (0.48–0.80)	55.2	34.3[a]	10.5
cREE Owen	1418	206.9	−96.2	−5.1	−464.6	272.3	95.8	0.65 (0.45–0.77)	56.6	33.6[a]	9.8
cREE Fleisch	1398	189.0	−120.9	−6.8	−448.8	207.0	95.1	0.66 (0.31–0.81)	55.9	39.9[a]	4.2[a]
cREE Wang	1281	224.0	−233.5	−14.5	−618.9	151.8	95.8	0.48 (−0.06–0.75)	30.1[a]	66.6[a]	3.5[a]
cREE Rosenbaum	1369	178.0	−145.0	−8.2	−500.1	210.2	95.1	0.58 (0.17–0.77)	43.4[a]	50.3[a]	6.3[a]
cREE Constructed Formula	1492	236.3	−21.6	−0.5	−347.7	304.4	95.1	0.85 (0.79–0.89)	65.0	17.5	17.5

CI: confidence interval; C-M: calculated REE minus measured REE; HB: Harris & Benedict; ICC: intraclass correlation coefficients; IQR: interquartile range; Mifflin: Mifflin St. Jeor; PA: phase angle; REE: resting energy expenditure; cREE: calculated resting energy expenditure; SD: standard deviation; WHO/FAO: world health organization/food and agriculture organization of the United Nations; WSchofield: World Schofield.
[a] Comparison cREE CF vs other cREE formulas $p < 0.05$.

mREE in IC in a small sample of 34 ALS patients with and without ventilation [16]. HB 1919 are not adapted to predict REE of ALS patient. Other studies published focused on mREE and cREE are presented in Table 5.

In our study we found a mREE in IC of 1514 ± 283 kcal/24 h in agreement with the literature [9,10,15,17]. Sherman et al. reported slightly lower results in 16 non-ventilated patients [16]. This discrepancy may be due to differences in the IC apparatus used. Our study shows that, in a large population of ALS patients, the 11 predictive formulas used are not adapted to ALS patients. The main problem with these formulas is underestimation of the energy requirement in 31.7%–71.4% of patients, with a real risk of inadequate energy intake, which can lead to weight loss and undernutrition. Reasons for this maladjustment are probably diverse. The main issue is the absence of validation of these REE formulas in ALS patients with alteration of the body composition. Indeed, ALS, patients lose FFM and increase their FM [1,9,10]. In addition, the numbers of ALS patients to whom these equations were applied were sometimes low, and patient characteristics may be very different [13,15,16]. Given these difficulties, we created a new formula that allows for better prediction and less underestimation of REE in ALS patients. This formula integrates body composition data (FFM and FM) obtained with impedancemetry according to a validated method which is easy, fast and noninvasive for ALS patients

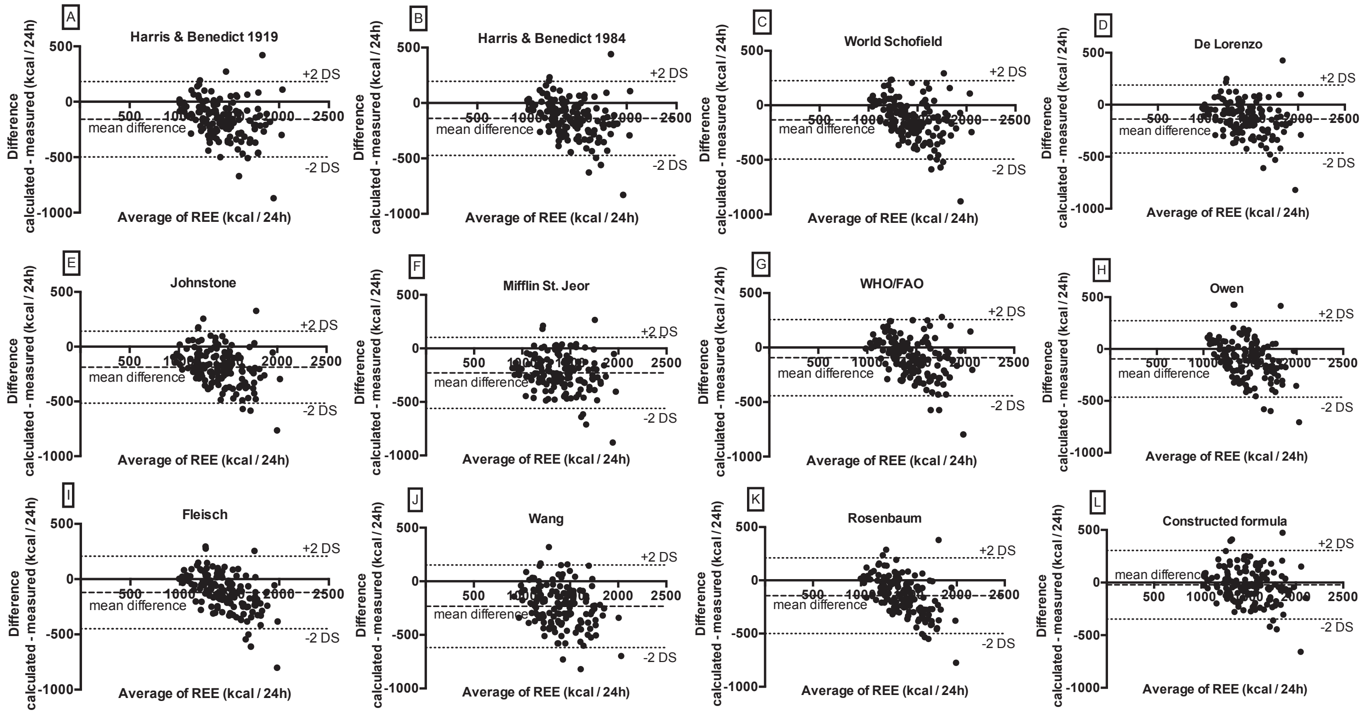

Fig. 3. Bland and Altman graphics between calculated resting energy expenditure with the 11 formulas and the constructed formula and measured resting energy expenditure in the validation sample (n = 143). Panel A: Harris and Benedict 1919, panel B: Harris and Benedict 1984, panel C: World Schofield, panel D: De Lorenzo, panel E: Johnstone, panel F: Mifflin St. Jeor, panel G: WHO/FAO (world health organization/food and agriculture organization of the United Nations), panel H: Owen, panel I: Fleisch, panel J: Wang, panel K: Rosenbaum and panel L: constructed formula. REE: resting energy expenditure; SD: standard deviation.

Table 5
Studies on patients with amyotrophic lateral sclerosis with measured and calculated resting energy expenditure and bias.

First author/ years	Number of patients	Age (years) Mean ± SD or median (IQR)	Weight (kg) Mean ± SD or median (IQR)	FFM (kg) Mean ± SD	Height (cm) Mean ± SD or median (IQR)	mREE (kcal/24 h) Mean ± SD or median (IQR)	cREE (kcal/24 h) Mean ± SD or median (IQR)	Bias (%) Mean ± SD or median (IQR)
Sherman et al./ 2004 [16]6)	Ventilated: 18	67.2 ± 3.2	70.6 ± 15.6	–	172.0 ± 10.0	1654.9 ± 362.9	HB 1919: 1461.0 ± -	−10.1 ± 17.6
	Non ventilated: 16	56.2 ± 14.5	76.2 ± 26.6	–	169.6 ± 10.8	1340.8 ± 471.6	HB 1919: 1505.0 ± -	18.6 ± 24.9
Desport et al./ 2005 [9]9)	168	–	64.5 ± 13.9	43.8 ± 10.7*	162.5 ± -	1521.9 ± 307.5	HB 1919: 1334.0 ± 234.7	−12.3 ± -[a]
Bouteloup et al./2009 [10]0)	61	64.3 ± 9.9	–	43.8 ± 11.6*	–	1449.0 ± 300.7	HB 1919: 1315.5 ± 242.2	−9.2 ± -[a]
Siirala et al./ 2010 [21]4)	Ventilated: 5	55 (50–76)	83 (58–98)	–	177 (155–192)	1060 (960–1480)	HB 1919: 1580 (1190 –2020)	49.1 (–)[a]
							WHO/FAO: 1656 (1374 –2039)	56.2 (–)[a]
							Mifflin: 1557 (1399–1909)	46.9 (–)[a]
							Owen: 1726 (1183–1879)	62.8 (–)[a]
							Fleisch: 1630 (1210–1938)	53.8 (–)[a]
Kasarskis et al., 2014	80	58.7 ± 11.9	80.1 ± 16.8	50.7 ± 11.1*	171.9 ± -	1539.0 ± 366.0	HB 1919: 1596.0 ± 283.0	3.7 ± -[a]
							Mifflin: 1523.0 ± 283.0	−1.0 ± -[a]
							Rosenbaum: 1508.0 ± 203.0	−2.0 ± -[a]
							Wang: 1315.0 ± 264.0	−14.6 ± -[a]
							Owen: 1589.0 ± 250.0	3.2 ± -[a]

FFM: fat-free mass (*: in bioimpedance analysis); HB: Harris and Benedict; IQR: interquartile range; Mifflin: Mifflin St. Jeor; REE: resting energy expenditure; mREE: measured resting energy expenditure; cREE: calculated resting energy expenditure; SD: standard deviation; WHO/FAO: world health organization/food and agriculture organization of the United Nation.
[a] Bias not calculated in the study, a posteriori calculation with mean or median cREE and mREE.

[26]. Moreover, body composition is a better reflection of nutritional status than weight and height used in several REE predictive formula. REE is therefore related to FFM. The recent ESPEN guidelines for ALS, propose to use HB 1919 equations to assess energy needs in the absence of IC [34]. But because of the poor agreement of HB 1919 formulas in ALS, an ALS-specific formula seems necessary. In absence of IC, this new formula could be used easily in clinical practice to diagnose hypermetabolism at onset of the disease and to adapt energy needs in ALS during follow up.

However, there are several limitations to our study. Although the ALS referral center follows 88.2% of ALS patients in our region, this population is not totally representative of patients in the region and country [2]. There is therefore a selection bias. Moreover, it would be desirable to validate the new formula in a sample of ALS patients from another center and in a population-based setting if possible. This new formula found a poor REE prediction for 35% of patients, suggesting that other elements determining REE of ALS patients were not taken into account (R^2 of the model was 76%). These remain to be discovered [35], as it is known that neither the intensity of the fasciculations, smoking, nor any inflammatory or infectious condition is implicated [9,10,35]. Cortical hyperexcitability could be related to metabolic dysfunction in ALS and could increase glucose metabolism in the brains of ALS patients [36,37]. However, there is currently no recognised link between REE in indirect calorimetry and brain hypermetabolism. It is therefore difficult to integrate this parameter into a REE predictive formula used in daily practice. We did not calculate the sample size a priori but verified that the power was sufficient given the size of the study. For example, the linear regression used for formula derivation was at least of 80% even considering an independent variable that would be weakly correlated to the dependent variable ($r = 0.25$, e.g.).

5. Conclusion

When REE formulas for healthy people are used in ALS patients, they provide an accurate prediction of REE (±10% of mREE) in less than 58% of cases, with a high level of underestimation up to 71% of cases. These formulas are not adapted to predict REE in ALS patients, and their use can lead to underestimation of energy need with weight loss and malnutrition, which are important prognosis factors in ALS. The creation of an ALS-specific REE formula using body composition allows prediction of REE in 65% of cases with only 17.5% underestimation. Agreement between mREE and estimated REE using the formula was very good (0.85). This formula can therefore be used to predict REE in clinical practice in ALS patients if indirect calorimetry is not available. Validation in another independent sample of ALS patients is required.

Authors' contributions

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

Conflict of interest

Authors had no financial or personal relationships with companies or organizations sponsoring the research at the time it was carried out.

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