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Estimating resting energy expenditure of patients on dialysis: Development and validation of a predictive equation

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ABSTRACT

Objectives: The aims of this study were to develop and validate a resting energy expenditure (REE) predictive equation in a cohort of patients on dialysis and to test the accuracy of two previously developed specific equations to estimate REE of these patients.
Methods: A database with REE measured by indirect calorimetry (IC) of 189 patients on hemodialysis and peritoneal dialysis was used to develop and validate the new equation. The sample including only patients on hemodialysis (n = 131) was used to test the accuracy of the specific REE dialysis equations by Vilar and Byham-Gray.
Results: Multiple regression analysis generated two equations:
REE (kcal/d) = 957.02 − 8.08 × age + 11.07 × body weight + 136.4 (if men) (R^2 = 0.515) (1)
REE (kcal/d) = 624.6–4.8 × age + 20.6 × fat-free, ass-fat-free mass–8.65 (if men) (R^2 = 0.512) (2)
In the validation group, REE by both equations did not differ from the REE measured by IC. No bias was found in the Bland–Altman analysis and the intraclass correlation coefficient and P20 test showed good reliability with measured REE. Vilar's equation overestimated REE; whereas REE generated by Byham-Gray's equation did not differ from measured REE. Proportional and systematic biases were significant for both equations.
Conclusions: The new equations developed showed good accuracy and can be valuable to estimate energy needs of patients on dialysis. Byham-Gray's and Vilar's equations presented low to moderate performance to estimate REE of the patients on dialysis.

Introduction

Determination of energy expenditure is an important step for the adequate prescription of energy intake, especially to chronically ill patients. Individuals with chronic kidney disease (CKD) are predisposed to several metabolic and hormonal derangements that can affect energy metabolism and energy expenditure. These include secondary hyperparathyroidism [1], insulin resistance [2,3], overt diabetes [4,5], chronic inflammation [6,7] and the dialysis procedure itself.

Indirect calorimetry (IC) is considered a reference method to determine resting energy expenditure (REE) of individuals, which is the main determinant of total energy expenditure [8]. However, the availability of this method, its high cost and the need for trained personnel makes this technique difficult for application in daily clinical practice. Predictive traditional equations, mainly Harris and Benedict [9] and Schofield [10] equations were developed for healthy individuals and their accuracy in the dialysis population is questionable. Indeed, in previous studies, REE was overestimated when such equations were applied in patients with CKD [11,12]. This emphasizes the need to develop equations based on specific characteristics of populations.

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To provide more accurate tools, two studies developed specific equations to estimate the REE of patients on maintenance hemodialysis. Vilar et al. [12] developed an equation using only easily obtainable anthropometric variables such as height, body weight, sex, and age. In addition to using anthropometric variables, Byham-Gray et al. [13] included glycosylated hemoglobin, serum C-reactive protein, and serum creatinine in the equations, based on the premise that biochemical parameters might influence REE.

In the present study, we aimed to develop and validate an easily applicable equation to estimate REE of patients on dialysis. Additionally, the accuracy of the previously available REE equations specifically developed for this population was also tested.

Methods

Participants

This was a cross-sectional study using a convenience sample that included previous databases from trials from our research group [14–16] aiming to assess the REE measured by IC from 131 patients on maintenance hemodialysis (HD) and 58 patients on peritoneal dialysis (PD) recruited from two dialysis centers—the Dialysis Unit of Oswaldo Ramos Foundation (São Paulo) and Pro-Nephron Dialysis Center (Rio de Janeiro). Inclusion criteria were >18 y of age, dialysis length >3 mo, absence of catabolic conditions, and normal thyroid function. Exclusion criteria were therapy with corticosteroid or immunosuppressive medication and presence of malignant diseases. The only differences among the samples were the exclusion of diabetes in the cohort of HD patients from the Dialysis Unit of São Paulo and exclusion of patients <60 y of age in the cohort of patients from the Dialysis Unit of Rio de Janeiro. For all patients, a daily diet containing 30 to 35 kcal/kg and 1.2 to 1.3 g/kg of protein daily had been prescribed. Written and informed consent was collected from each patient and all studies were approved by Ethics and Research Committee of the Federal University of São Paulo and Rio de Janeiro State University.

Study protocol

Patients on PD underwent IC, nutritional assessment, and fasting blood tests on the same day with emptied peritoneal cavity. In patients on HD, the IC and blood tests were carried out on a non-dialysis day and the anthropometric measurements were obtained after the dialysis session.

Resting energy expenditure

Measurement

REE was measured by IC using an open-circuit, ventilated, computerized, metabolic system (Vmax 29 n series Sensor Medic Corp, Yorba Linda, CA, USA). The flow sensor was calibrated with a syringe piston permitting high and low inspiratory and expiratory flow measurements. Before each REE analysis, oxygen and carbon dioxide sensors were calibrated using a reference mix of gases of known composition. Before the initiation of IC measurement, patients were asked if they had followed the instructions, in particular with regard to physical exercise and hours of fasting. Patients were advised not to fall asleep, hyperventilate, or fidget during the test; to maintain their regular medication; to abstain from physical activity for 24 h before the test; and to maintain their usual sleep routine one night before REE measurement.

Patients arrived at the clinic at 07:30 h after a 12-h overnight fast. Before initiating the test, patients rested for 30 min in a recumbent position and, afterward, were instructed to breathe for 30 min through a transparent plastic canopy placed over their heads in a quiet, dimly lit, thermo-neutral room. Oxygen consumption and carbon dioxide production were measured at 1 min intervals and the average measurement of the final 20 min was used to determine REE, using the Weir equation [17].

Predictive equations

The following REE predictive equations specific for dialysis patients were tested:

Villar et al.:

$$\mathrm{REE(kcal/d)} = -2.497 \times age \times factor_{age} + 0.011 \times height^{2.023} + 83.573 \times body\ weight^{0.6291} + 68.171 \times factor_{sex}$$

Byham-Gray et al.:

$$\text{Male REE} = 1024.41 - (4.90 \times \text{age}) + (10.21 \times \text{weight}) - (3.25 \times \text{serum creatinine [SCr]})$$

$$\text{Female REE} = 802.00 - (4.90 \times \text{age}) + (10.21 \times \text{weight}) - (3.25 \times \text{SCr})$$

Where age is in years, height in cm, body weight in kg, serum CRP (SCr) in mg/dL, factor_{age} is 1 if ages ≥65 y or 0 if not, and factor_{sex} is 0 if female and 1 if male.

Anthropometric measurements

Measurements were performed by the same observer and consisted of body weight, height and skinfold thickness. Patients' weight and height were measured using a platform manual scale balance equipped with a stadiometer (Filizola, São Paulo, Brazil) with no shoes and wearing only light clothes. Height was measured with patients standing in an upright position with chin aligned with feet. Body fat was determined as described by Durnin and Wormesley [18] by the sum of skinfolds performed at four sites (biceps, triceps, subscapular, and supra-iliac) on the nondominant arm or on the opposite side of the vascular access using a Lange Caliper (Cambridge Instrument, Cambridge, MD, USA). The average of three sets of measurements was performed for each site. Fat-free mass (FFM; kg) was calculated by the subtraction of fat mass (kg) from total body weight (kg).

Laboratory data

Blood samples were drawn just before the IC test and after a 12-h overnight fast. SCr, urea, and glucose were determined using a standard autoanalyzer. Thyroid-stimulating hormone (TSH) was determined by immunofluorometric assay and albumin by bromocresol green technique. Intact parathyroid hormone (PTH) and high-sensitivity C-reactive protein (hs-CRP) were determined by immunochemiluminescence.

Statistical analysis

From the entire cohort, 30% of patients (n = 57) were randomly selected according to age and sex and allocated in the group used for validation. The remaining 132 patients were used to develop the new predictive equation [19]. Univariate analysis was applied to screen for potential REE predictors. Selected variables were then applied to multilinear regression analysis to construct models using the enter method. Collinearity among independent variables was evaluated and when two variables showed high collinearity, the one with the strongest correlation coefficient with measured REE was used in the models. Two equations that showed the highest coefficient were selected to be tested with data from the validation group.

To test the accuracy of the predictive equations by Villar et al. [12] and Byham-Gray et al. [13], data from the sample including only patients on HD (n = 131) was used.

Shapiro–Wilk test was applied to investigate normality. Results were expressed as means ± SD, median and interquartile ranges (IQRs), or proportions. Comparisons between groups were performed using two-tailed Student's *t* test, Mann–Whitney's test or χ^2 test, as appropriate.

Accuracy of equations was evaluated through Bland–Altman graphical analysis, systematic bias was assessed using Student's *t* test for a single sample to test whether the mean differences were equal to zero. The proportional bias was evaluated by linear regression analysis to determine if the difference was influenced by the magnitude of measure, considering the difference of the values as dependent variable and the average between them as independent variable. Positive bias was considered when $P < 0.05$. Intraclass correlation (ICC) test, and P20 test (percentage of patients whose predicted REE was within 80% to 120% of the measured REE) were also performed. Statistical analysis was performed using SPSS version 18 (SPSS Inc., Chicago, IL, USA). Statistical significance was considered at $P < 0.05$.

Results

Characteristics of the participants

Table 1 shows the demographic, clinical, and laboratory characteristics of the 189 patients studied. The majority of the patients were men, ~50 y of age, and the main cause of CKD was hypertensive nephrosclerosis. About 20% of patients had diabetes. One-third of the patients were on PD.

Development of new equations to estimate REE

As seen in Table 1, no differences in the characteristics of the patients were observed between the equation group and the validation group. In the equation group (n = 132), FFM ($r = 0.66$, $P < 0.001$), body weight ($r = 0.54$, $P < 0.001$), and height ($r = 0.44$, $P < 0.001$) had the highest correlation coefficients with REE. Among biochemical parameters, only CRP correlated with REE ($r = 0.26$, $P < 0.001$). Age was inversely correlated with REE ($r = -0.33$, $P < 0.001$) and REE differed between men and women (1431 ± 294 and 1201 ± 240 kcal/d, respectively $P = 0.001$). Because body

Table 1
Demographic, laboratory, and clinical characteristics of patients according to the groups

	Total (N = 189)	Equation group (n = 132)	Validation group (n = 57)
Men, %	62.4	63.6	58.6
Age, y	52.6 ± 16.9	52.5 ± 16.9	52.7 ± 17
Diabetes mellitus, %	19.6	20.4	17.5
CKD etiology, %			
Hypertensive nephrosclerosis	23.8	26	19.3
Diabetic nephropathy	7.4	6.1	10.5
PKD	6.9	5.3	10.5
CGN	9	8.4	10.5
Undetermined	22.2	21.4	24.3
Dialysis modality, %			
HD	69.3	69.7	68.4
PD	30.7	30.3	31.3
Dialysis length, mo	20 (10–46.5)	17.2 (9–44.7)	23 (12–49)
Anthropometrics			
Weight, kg	65 ± 13.9	65.7 ± 14.6	63.4 ± 12.1
Height, cm	162.8 ± 8.9	163.3 ± 8.6	161.7 ± 9.6
BMI, kg/m^2	24.4 ± 4.3	24.5 ± 4.4	24.3 ± 4.1
Fat-free mass, kg	47.4 ± 9.4	47.9 ± 9.6	46.3 ± 8.9
Fat mass, kg	17.5 ± 8.1	17.7 ± 8.2	17.1 ± 7.8
mREE, kcal/d	1347.1 ± 282.8	1347.1 ± 295.9	1347 ± 252.4
Respiratory quotient	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.11
Laboratory parameters			
Serum urea, mg/dL	140 (109.5–161.5)	139 (109.2–158)	141 (111.5–176)
Serum creatinine, mg/dL	9.3 (7.4–11.7)	9.4 (7.27–11.9)	9.2 (7.4–11.6)
Parathyroid hormone, pg/mL	253.5 (98.4–509)	234 (95–468)	294 (107.8–727.6)
Serum glucose, mg/dL	85 (77–97)	85 (77.2–101.5)	84 (75–95.5)
Serum albumin, g/dL	3.9 (3.6–4.2)	3.9 (3.6–4.2)	4 (3.6–4.3)
TSH, mUI/L	1.95 (1.3–3.3)	2 (1.3–3.5)	1.7 (1.3–3.2)
C-reactive protein, mg/dL	0.46 (0.2–1.2)	0.44 (0.2–1.1)	0.52 (0.2–1.2)

BMI, body mass index; CGN, chronic glomerulonephritis; DM, diabetes mellitus; HD, hemodialysis; mREE, measured resting energy expenditure; PD, peritoneal dialysis; PKD, polycystic kidney disease; TSH, thyroid-stimulating hormone.
Data are presented as mean ± SD, median and interquartile range, and frequency.

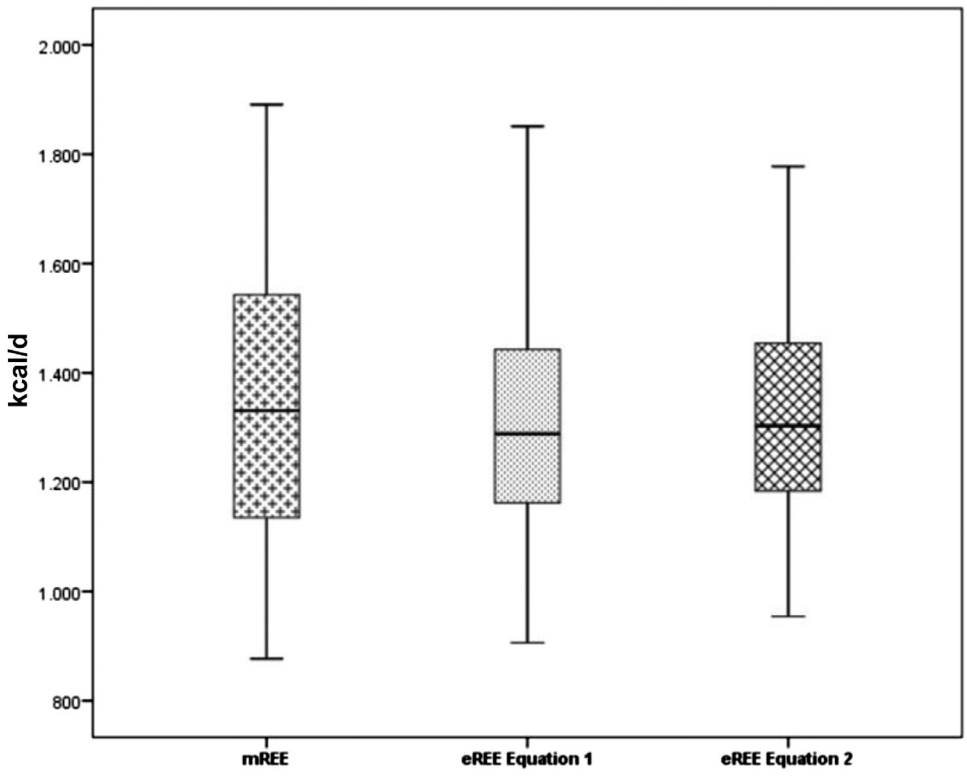

Fig. 1. Resting energy expenditure measured by indirect calorimetry (mREE) and estimated (eREE) by Equation 1 and Equation 2 in the validation group (n = 57). $P > 0.05$.

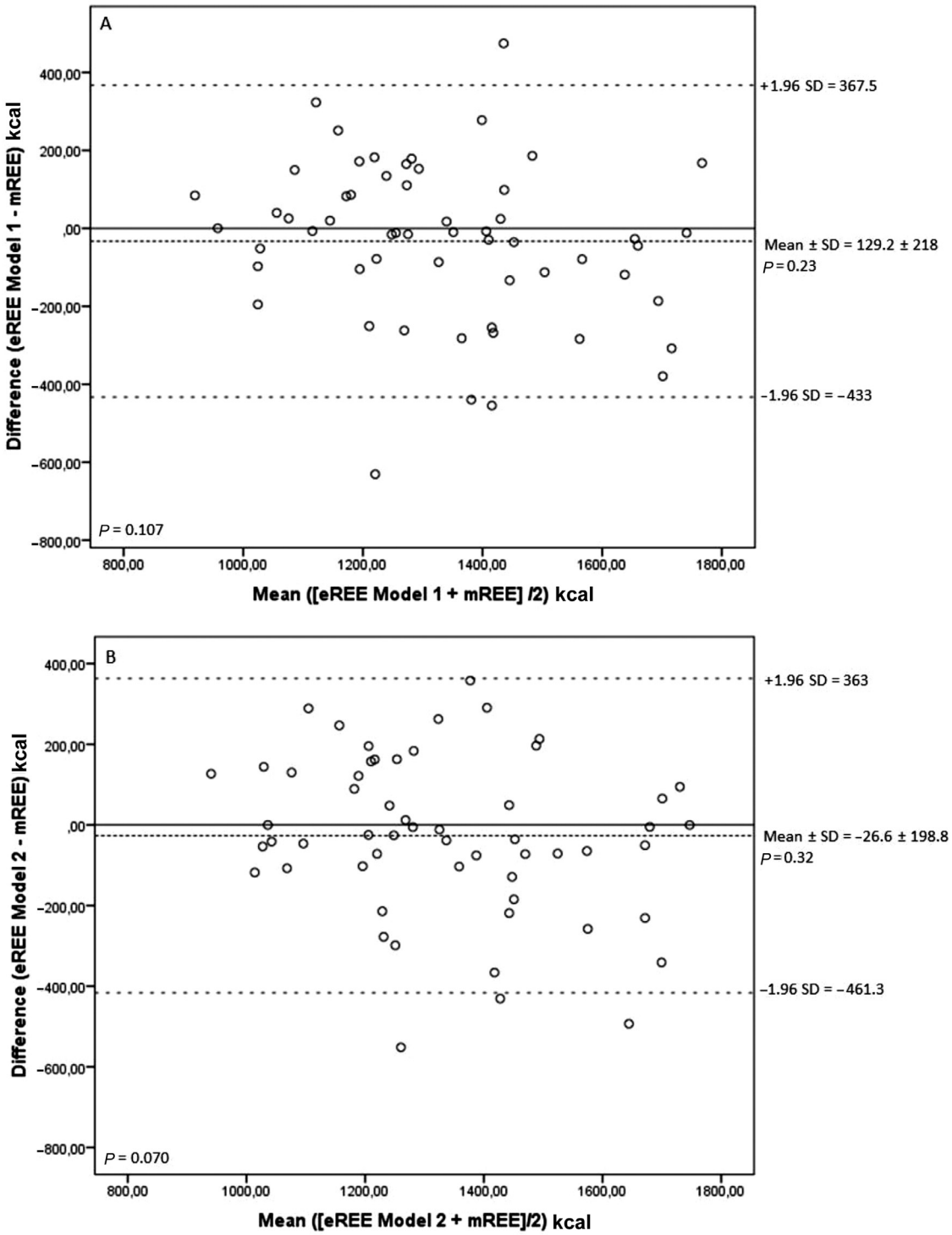

Fig. 2. Bland-Altman analysis of measured (mREE) and estimated REE (eREE) by Equation 1 (**A**) and Equation 2 (**B**). *P*-value on the bottom left of each plot refers to the proportional bias.

weight and height showed high collinearity, only body weight was used in the equation.

Multiple regression analyses resulted in two equations described as follows:

$$\left(R^2 = 0.515\right)$$
$$\text{REE(kcal/d)} = 957.02 - 8.08 \times \text{age} + 11.07 \times \text{body weight} + 136.4(\text{if men}) \quad (1)$$

$$\left(R^2 = 0.512\right)$$
$$\text{REE(kcal/d)} = 624.6 - 4.8 \times \text{age} + 20.6 \times \text{FFM} - 8.65(\text{if men}) \quad (2)$$

where age is in years, body weight and FFM in kg.

Inclusion of CRP in both regression models improved the model by only 5% and because this variable often is unavailable in daily clinical practice, it was not included in the equations.

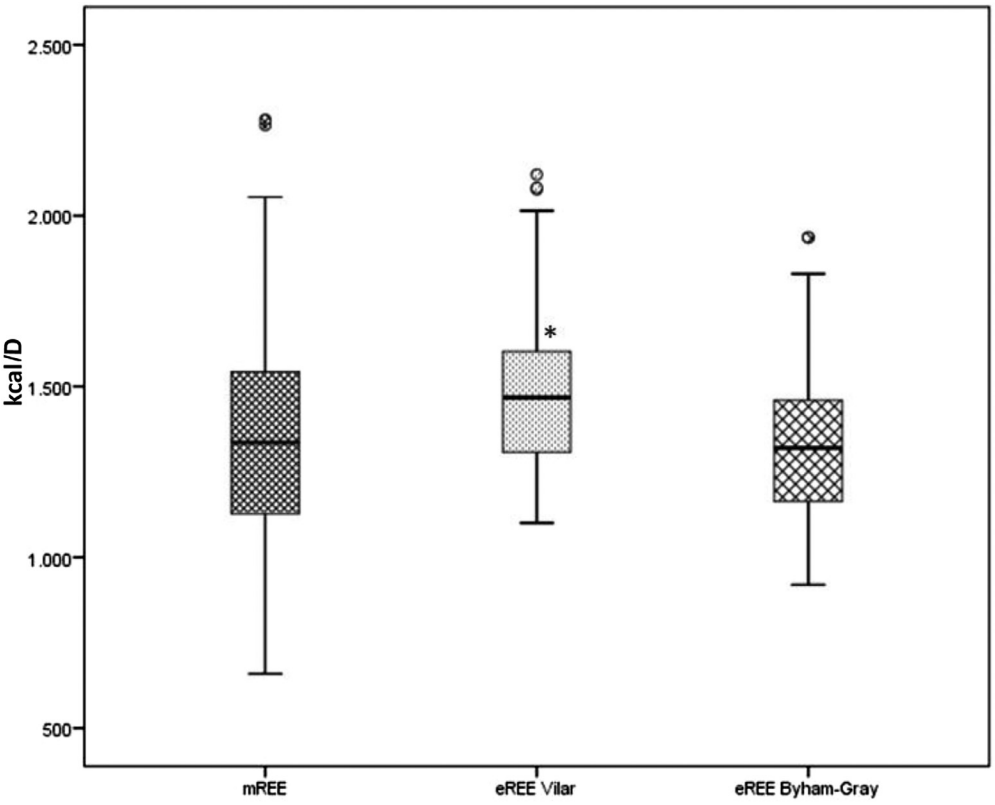

Fig. 3. Resting energy expenditure measured by indirect calorimetry (mREE) and estimated (eREE) by Vilar and Byham-Gray predictive equations.

Equation validation

Data from the validation group (n = 57) were used to test the two new equations. As shown in Figure 1, the estimated REE by equation 1 (1314.7 ± 212.5 kcal/d) and by equation 2 (1320.1 ± 208.8 kcal/d) was not different from measured REE (1347.1 ± 283.3 kcal/d) and showed no difference between each other ($P = 0.53$). REE accuracy (80–120%) was observed in 84.2% of patients with equation 1 and 82.5% with equation 2. ICC analysis revealed that estimated REE (eREE) by Equation 1 (ICC = 0.76; 95% confidence interval [CI], 0.59–0.86) and Equation 2 (ICC = 0.77; 95% CI, 0.62–0.82) had good reliability with measured REE (mREE). As shown in Figure 2, biases were −32.3 ± 204.2 kcal/d and −26.6 ± 199 kcal/d, for Equation 1 and Equation 2, respectively, and did not differ from zero ($P = 0.23$ and $P = 0.32$, respectively).

Performance of Vilar and Byham-Gray equations to estimate REE

As both equations were developed including only patients on HD, we excluded the patients on PD and performed the analysis with the sample of patients on HD (n = 131). In this cohort, the majority of patients were men (65%), 13.7% had diabetes mellitus, and mean age was 53.1 ± 17.2 y. Body mass index was 23.2 kg/m^2 (21.2–26.3 kg/m^2), dialysis length was 24 mo (10–52 mo), CRP was 0.46 mg/dL (0.22–1.01 mg/dL), serum parathyroid hormone was 192.2 mg/dL (70.5 - 430.5 mg/dL), serum albumin was 4 g/dL (3.7–4.3 g/dL), and SCr was 9.9 ± 3.14 mg/dL. As shown in Figure 3, estimated REE by Vilar equation (1478.1 ± 212.3 kcal/d) was higher when compared with mREE (1345.2 ± 297.8 kcal/d; $P < 0.001$); whereas Byham-Gray equation (1323.2 ± 216.6 kcal/d) showed no difference from mREE ($P = 0.118$). According to ICC analysis, the agreement of Vilar equation (ICC = 0.64; 95% CI, 0.54–0.74) and Byham-Gray equation (ICC = 0.69; 95% CI, 0.59–0.77) were equal, and both were considered moderate. Considering the range of 80% to 120% (P20), the equations correctly predicted mREE in 71.7% (Vilar) and 81.7% (Byham-Gray) of the patients. According to the Bland–Altman test, the mean bias was 132.8 ± 217.2 kcal/d using Vilar's equation and −13.9.6 ± 100.7 kcal/d using Byham-Gray's equation, and both were different from zero ($P < 0.001$) Proportional bias was significant for both equations (Fig. 4).

Discussion

In the present study, we aimed to develop and validate two equations using variables such as age, body weight, and FFM, which easily can be obtained to estimate REE of patients on dialysis. We also tested the reliability of two dialysis-specific predictive equations to estimate REE.

There are a number of equations to estimate REE, but most of them were derived from healthy individuals and may be inaccurate when applying to individuals with chronic and catabolic diseases such as CKD. Indeed, when testing the accuracy of traditional and widely used equations of Harris–Benedict [9] and Schofield [10] in patients with CKD, studies have found overestimation [11,20] depending on the stage of the disease and on the characteristics of the studied population. Therefore, it is clear that CKD-specific formulas should be developed and tested to provide a more reliable estimation of REE in an attempt of better appraisal of the energy needs of patients on dialysis.

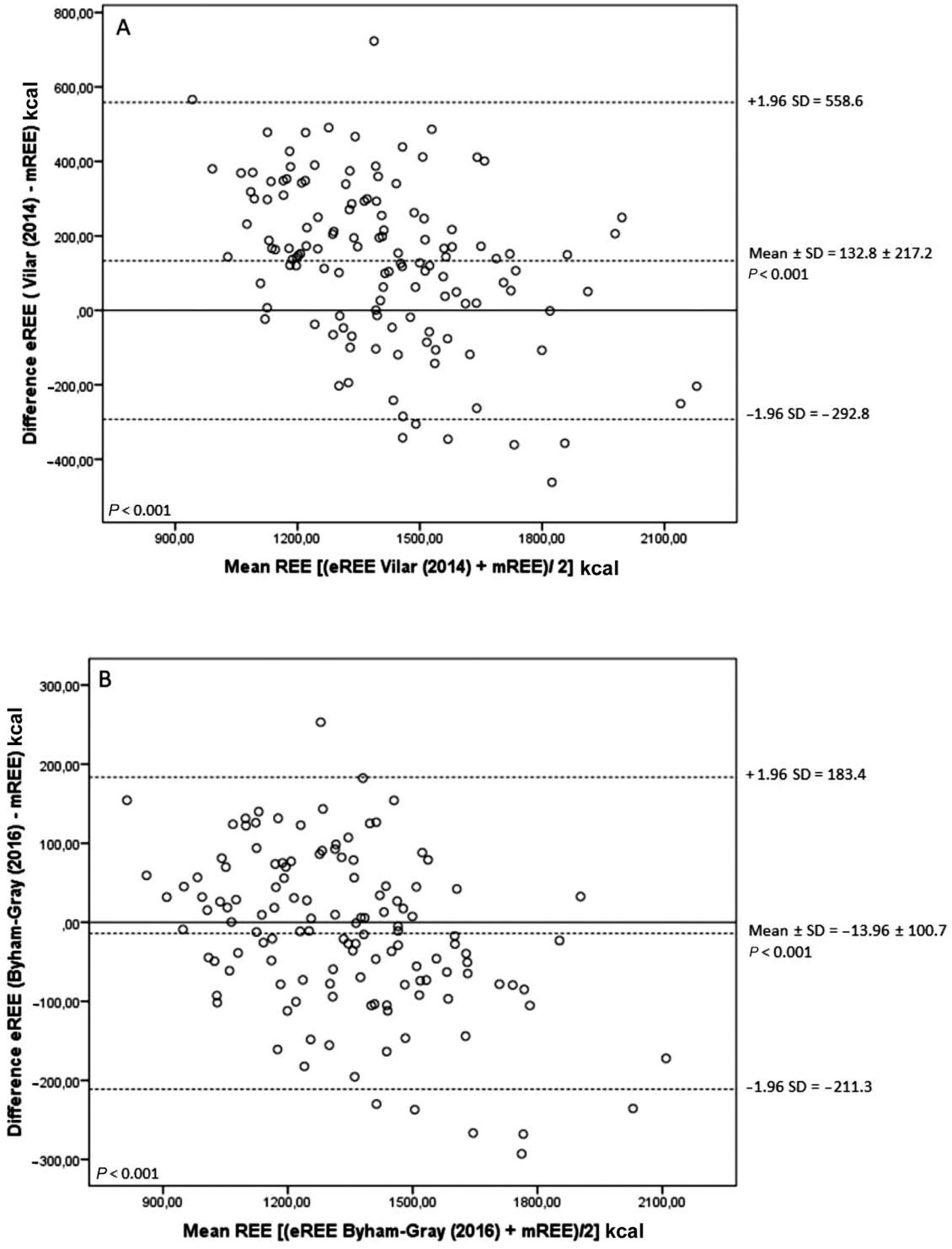

Fig. 4. Bland-Altman analysis of measured (mREE) and estimated REE (eREE) by Vilar (**A**) and Byham-Gray (**B**) equations. *P*-value on the bottom left of each plot refers to the proportional bias.

Considering the need to develop an equation more suitable to the dialysis population, we developed two REE equations using a cohort of 132 patients. It is of note that for both equations developed herein, the variables that best predicted REE (age, sex, weight, and FFM) explained about 50% of the variations in REE. This is quite low when compared with studies in healthy populations. Based on the FFM and fat mass of 213 healthy individuals, Nelson et al. [21] derived a model that explained 98% of the REE's variation. A high level of REE predictability (76.8%) also was found in a cohort of 109 healthy Korean men and women considering body weight, FFM, and age [22]. However, our result is not markedly different from the studies of Vilar et al. [12] and Byham-Gray et al. [13], as described previously. The lower performance of REE equations

when developed with patients on dialysis cannot be clearly elucidated. Nevertheless, we can speculate that the diverse spectrum of components involved in such complex disease as CKD may exert influence on energy expenditure and cannot be captured when only simple variables are used in the model.

Interestingly, in the present study, the influence of FFM on REE was not greater than that of body weight, as would be expected. Geisler et al. [23] studied the influence of FFM on the REE of healthy adults according to age and observed a percentage of explanation ranging from 54% in individuals >70 y to 64.5% in those 18 to 39 y of age. In another study, FFM measured by five methods explained 70% of REE variation in 104 overweight individuals [24]. Conversely, in the present study, FFM explained only 43% of the variation in REE. This is in accordance with Avesani et al. [4], who noticed that FFM (measured by dual-energy x-ray absorptiometry) explained 36% of the variation in REE of patients with non–dialysis-dependent CKD. Several disturbances involved in the physiopathology of CKD, such as increased muscle protein catabolism, can contribute to reduction in muscle mass and to altered metabolism of this tissue with consequent influence on energy output [25–27]. Moreover, the suppressed cellular oxygen consumption by mitochondrial abnormal activity seen in these patients also may influence this imbalance [28]. Finally, although some studies in healthy individuals have shown that fat mass has some contribution in explaining REE [24], this was not significant in the present study ($R^2 = 0.031$). This finding may probably explain the similarity between the correlation coefficient of the two equations by using body weight or FFM.

Inflammation is a well-recognized factor that influences REE in several clinical conditions [29] including CKD [30]. In the present study CRP was positively correlated with REE, but when applied to the model, REE equation predictability was improved by only 5%. A couple of studies [30,31] observed that CRP levels >0.6 and 1.05 mg/dL could influence REE of patients on dialysis and therefore it seems that CRP may affect the energy expenditure of patients with CKD at levels that are higher than the ones observed in the present study (median CRP = 0.44 mg/dL). Considering that CRP measurements are not routinely available in most clinical settings, CRP was not included in the equations.

Vilar et al. sought to develop a simple equation based on parameters easily obtained in clinical practice. Height, body weight, age, and sex explained 66.3% of the variation in REE in the cohort of 200 patients on maintenance dialysis that was used to derive the equation. Byham-Gray et al. observed that in addition to anthropometric and demographic parameters, the inclusion of biochemical variables such as SCr, CRP, and glycosylated hemoglobin provided a better fitting model indicating that such serum markers, whenever available, should be considered when estimating REE of patients on HD. Although in that study three predictive equations were developed, we chose to evaluate the performance of the equation using SCr, a variable usually available in clinical settings. In this equation, body weight, age, and SCr explained 66% of the variation in REE of 116 patients used to develop the model.

We tested both equations in our cohort of patients and found low to moderate accuracy with large ranges of limits of agreement. On average, Vilar et al.'s equation overestimated REE and Byham-Gray et al.'s equation did not differ from mREE. However, in both equations there was a systematic bias and a proportional bias, indicating that differences observed were influenced by the magnitude of the measure. Although a number of factors and conditions may have influenced the relatively poor performance of both equations in the present sample, differences in patient demographic and clinical characteristics may, at least partly, explain this result.

For instance, in our cohort, patients with diabetes were underrepresented compared with the Vilar et al.'s study (27.1%). In fact, studies have shown that poorly controlled diabetes may cause an average 7.7% increase in REE in the absence of CKD [5] and 12.3% when associated with CKD [4]. Differences in body weight and body composition also might have accounted for the REE overestimation. Although the Vilar cohort comprised mainly overweight individuals, the mean body mass index in the present cohort was within the normal range. Additionally, mean FFM is normally higher in overweight individuals compared with those of normal weight [32]. It is well known that FFM is the main determinant of REE, accounting for >70% of the REE variability in healthy individuals [33]. Surprisingly, most of the mentioned conditions that may have played a role in the overestimation of REE by the Vilar equation were also present in the Byham-Gray et al.'s cohort; however, no overestimation was found. It is possible that other non-identified variables related with decreased REE might have compensated the REE increase due to those conditions.

Finally, methodological differences among the studies might have influenced the results. The patients used to develop Vilar et al.'s equation were submitted to the IC test on the dialysis day and after only 2 h of fasting, which may prevent the exclusion of the thermic effect of food and might have influenced the final result.

Some limitations of this study should be acknowledged. The present cohort was comprised mainly by relatively young and clinically stable patients on dialysis, which may not be representative of the general dialysis population. This might have affected the reliability of the REE predictive equations when applied to patients with more serious complications such as severe hyperparathyroidism, poorly controlled diabetes, or overt inflammatory condition. The standardized methodology for measurement of REE, the sample size, and the validation of both equations are important strengths of the present study.

Conclusion

The predictive REE equations developed from the present cohort, using simple variables, proved to be valid with good accuracy. The equations developed by Byham-Gray et al. and Vilar et al. presented low performance when used to estimate the REE of the present cohort of patients. This finding highlights the importance of identifying the characteristics of the population used to develop the REE predictive equation before applying it to a different population.

Conflict of interest declaration

We have read and understood Nutrition policy on disclosing conflicts of interest and declare that we have none.

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