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Poor Agreement between Predictive Equations of Energy Expenditure and Measured Energy Expenditure in Critically Ill Acute Kidney Injury Patients

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Key Words
Acute kidney injury · Energy expenditure · Indirect calorimetry

Abstract
Background: There are multiple equations for predicting resting energy expenditure (REE), but how accurate they are in severe acute kidney injury (AKI) patients is not clear. Our aim was to determine if predictive equations for estimated REE accurately reflect the requirements of AKI patients. ***Methods:*** We included in this prospective and observational study AKI patients AKIN-3 assessed by indirect calorimetry (IC). Bland–Altman, intraclass correlation coefficient and precision (percentagem of predicted values within 10% of measured values) were performed to compare REE by equations with REE measured by IC. ***Results:*** IC was applied in 125 AKI patients. The mean age was 62.5 ± 16.6 and 65.6% were male. Mean REE measured was 2,029.11 ± 760.4 kcal/day. There were low precision, and poor agreement between measured and predicted REE by the Harris-Benedict (HB), Mifflin, Ireton-Jones, Penn state, American College of Chest Physicians, and Faisy equations. HB without using injury factor was the least precise (18% of precision). Modified Penn state equation had the best precision, although the precision rate was only 41%. For all equations, the limits of agreement range were large leading to the potential under or overfeeding of individual patients. ***Conclusion:*** None of these equations accurately estimated measured REE in severe AKI patients and most of them underestimated energy needs.

Introduction

Acute kidney injury (AKI) occurs in approximately 3–15% of hospitalized patients and can affect 30–50% of patients admitted to intensive care units (ICU). It is associated with extremely high mortality rates, ranging from 20 to 50% [1].

Previous observational studies reported that malnourished and hospitalized AKI patients have higher rates of morbidity and mortality than well-nourished patients [2, 3] and an association between cumulative caloric deficits and poor outcome in ICU patients [4, 5]. Accurate determination of energy needs is obviously important in critically ill patients because both over and underfeeding may be associated with complications and undesired consequences [6].

Underfeeding disturbs the regeneration of respiratory epithelium and causes respiratory muscle dysfunction

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which may prolong ventilator dependence. Even when subclinically present, it is responsible for reduced superficial and deep wound healing. Also, the failure to provide >25% of recommended calories significantly increases the risk of bloodstream infection [7, 8]. Similarly, the deleterious effects associated with significant overfeeding, such as poor glycemic control, altered neuroendocrine responses, increased risk of infectious complications, delayed liberation from mechanical ventilation, or even increased mortality rate, have been described [9–11].

In AKI patients, hypermetabolism and hypercatabolism may be present since it is a part of a more complex illness such as sepsis, multiple organ failure, shock, trauma, or high risk surgery [12]. Determining an appropriate method for predicting energy needs has been an area of research for many years and is essential in the treatment of these patients.

Determining energy requirements in the critically ill patient via indirect calorimetry (IC) has long been considered the gold standard [12]. Limitations for using IC include time constraints, equipment availability, staffing, and cost. Therefore, many predictive equations exist for predicting resting energy expenditure (REE), but the accuracy of these equations for estimating caloric requirements for critically ill patients is not clear [6, 13–16]. The equations include Harris-Benedict (HB) [17], Mifflin [18, 19], Ireton-Jones [20, 21], Penn state [22, 23], Faisy [13] and American College of Chest Physicians (ACCP) guidelines [24], among others. Most of the predictive equations were typically derived from studies of healthy, non-hospitalized individuals, while only a few have been validated in mechanically ventilated patients [5–13] and one has been validated for chronic dialysis patients [25], but to our knowledge, none of these equations has been validated for AKI patients.

Due to the practical limitations of routine IC as well as the absence of data to support existing predictive equations in AKI patients, we set out to determine if standard predictive equations for energy expenditure accurately reflect the energy requirements of critically ill, mechanically ventilated AKI patients.

Methods

A prospective and observational study was conducted from October 2012 to October 2014 in a university teaching hospital. This study was approved by the ethics committee. Since the participants were not able to give informed consent, the legal caregiver provided their written informed consent before entry into study.

Inclusion criteria were AKI patients AKIN-3, defined as serum creatinine increased >300% of basal or urine output <0.3 ml/kg/h, in 24 h or anuria in 12 h; or patients requiring dialysis, independently of the serum creatinine or urine output [26] mechanically ventilated with measured IC. Patients were not on dialysis at the time of measurement REE. Those who had dialysis indication had not yet begun the procedure. Exclusion criteria were fraction of inspired oxygen (FiO_2) >0.60; positive end-expiratory pressure >10 cm H_2O; maximum airway pressure >60 cm H_2O; agitation; neuromuscular blockers; air leak in the ventilator circuit, around the endotracheal tube cuff, or from a bronchopleural fistula.

IC Was Performed Using Quark RMR (Cosmed, Rome, Italy)

The Quark RMR is designed to accurately and instantaneously measure energy requirements of either spontaneously breathing or mechanically assisted patients. In our study, the metabolic monitor has been utilized connected with a ventilator, with a turbine flow-meter placed at the ventilator outlet and the gas sampling port is inserted in line with the breathing circuit: by this way, it becomes possible to sample both inspiratory and expiratory gases. The calorimeter had a paramagnetic oxygen sensor for measuring oxygen concentrations and analyzers based on infrared absorption for carbon dioxide measurements. Gases are sampled at fixed flowrate from the ventilator circuit and drawn into the device. After that, calculate VO_2 and VCO_2. For measuring the EE, use the Weir equation [27]:

$$REE = ((3.941 \times VO_2) + (1.11 \times VCO_2)) \times 1.44.$$

IC was calibrated before each use. The protocol required that patients be inactive and undisturbed for 30 min prior to testing and for 30-minute duration of the data collection. It is recommended that patients achieve steady state during testing. Steady state was defined as a variability of <10% in the measurements of oxygen consumption and carbon dioxide production, and <5% in the respiratory quotient from minute to minute.

Parenteral and/or enteral nutrition were continued during the data collection period. Patient height was a measured value, taken at the admission, when possible, or the value documented in the medical record. Weight was measured using calibrated hospital scales, at the admission, in most patients. If the patient had edema in the moment of measure, according to the medical evaluation, the general weight maintained by the patient was obtained from family members/caregivers and used as actual weight. Body mass index (BMI, kg/m^2) was calculated. For all equations, the patient's admission body weight was used for 'actual body weight'. The predictive equations used and details of their use are summarized in table 1.

Results were expressed as numbers and percentages, means ± SDs, or medians and ranges (for data with no normal distribution). Measured and calculated REE were compared by using correlation coefficients, and Bland–Altman analysis. The intraclass correlation coefficient (ICC) was used to test the inter method reproducibility of the REE measured by the IC and the prediction equations. Coefficient values >0.4 were considered indicative of poor reproducibility, values between 0.4 and 0.75 indicative of moderate reproducibility and values <0.75 indicative of good reproducibility [28].

Bland–Altman analysis is a process used to assess the agreement between 2 methods of measurement that measure the same

Table 1. Description of predictive equations

Equation name	Calculation of REE
HB equation [13]	Men: (66.5 + (13.8 × actBW) + (5 × Ht) – (6.8 × age)) × 1.5 Women: (655 + (9.6 × actBW) + (1.8 × Ht) – (4.7 × age)) × 1.5
HB equation using an injury factor of 1.3 without an activity factor [12]	REE calculate by HB equation × 1.3
Mifflin equation [14]	Men: 5 + (10 × actBW) + (6.25 × Ht) (5 × age) Women: 161 + (10 × actBW) + (6.25 × Ht) – (5 × age)
Mifflin equation with stress factor [15]	REE calculate by Mifflin equation × 1.25
Ireton-Jones 1997 [17]	REE = (actBW × 5) – (age × 11) + (sex × 244) + (trauma × 239) + (burn × 840) + 1,784 Where sex is male (1) or female (0), trauma is traumatic injury (1) or not (0), and burn is burn injury (1) or not (0)
Penn state [18]	REE = (REE calculate by Mifflin × 0.96) + (Tmax × 167) + (VE × 31) (21) – 6,212
Modified Penn state [19]	REE = (REE calculate by Mifflin × 0.71) + (Tmax × 85) + (VE × 64) – 3,085
ACCP guidelines [20]	BMI <25: actBW × 25 BMI ≥25: IBW × 25
Faisy [9]	REE = (8 × actBW) + (14 × Ht) + (32 × VE) + (94 × Tmax) – 4,834

ActBW = Actual body weight (weight on admission in kg); Ht = height (cm); Tmax = maximum body temperature in the previous 24 h (°C); VE = minute ventilation (liters per minute) at the time of measurement read from the ventilator.

Table 2. Demographic, clinical and nutritional characteristics of AKI patients

Characteristics	Values
Age, years	62.5±16.6
Male	82 (65.6)
ICU	121 (96.8)
AKI	
Ischaemic	10 (8)
Mixed	2 (1.6)
Nephrotoxic	9 (7.2)
Associated with sepsis	104 (83.2)
Presence of sepsis	111 (88.8)
APACHE II	28.5±4.73
ATN-ISS	0.65±0.18
BMI, kg/m^2	28.2±7.9
Underweight (<18.5)	6 (4.8)
Normal (18.5–24.9)	40 (32)
Overweight (25–29.9)	37 (29.6)
Obese class 1 (30–34.9)	26 (20.8)
Obese class 2 (35.0–39.9)	4 (3.2)
Obese class 3 (≥40)	12 (9.6)
REE, kcal/day	2,029±760
Maximum body temperature, °C	37.7±0.9
Mortality, %	73.6

Values are expressed as n (%) and mean ± SD.

ATN-ISS = Severity scoring individual in acute tubular necrosis. REE measured by IC.

characteristic on the same scale [29]. The mean bias, which represents the difference between measured and calculated REE, is calculated by adding the differences between paired measurements and dividing the sum by the mean of paired measurements. A bias of zero represents a perfect agreement between methods (measured compared with calculated methods).

Two SDs were used to show the limits of agreement. To consider that the formula agrees with IC and assess clinical utility, in other studies [30–32], the limit of agreement was set as acceptable by ±250 kcal or ±10% of the REE measured by IC. To analyze precision, if a majority (>50%) of individual differences of REE was >10% of the gold standard, the method was considered imprecise and clinically unacceptable. p values <0.05 were considered statistically significant. All analyses were performed using Medcalc for Windows version 12.2.1 (Mariakerke, Belgium).

Results

IC was performed in 125 severe AKI patients. The mean age was 62.5 ± 16.6 (range 18–94 years) and 65.6% were male. The main etiology of AKI was associated with sepsis (83.2%), and APACHE II and individual severity score of acute tubular necrosis were 28.5 ± 4.73 and 0.65 ± 0.18, respectively. Table 2 shows the demographic, clinical and nutritional characteristics of AKI patients.

Table 3. Precision of REE measured and estimated by equation in AKI patients

	REE, kcal/day	Range, kcal/day	p value	Precision, %
IC	2,029±760	740–4,120	–	–
HB	1,501±327	995–2,685	<0.001	18
HB IF	1,951±426	1,294–3,490	0.275	36
Mifflin	1,659±292	1,077–2,569	<0.001	29
Mifflin SF	2,074±365	1,347–3,211	0.345	25
Ireton-Jones	1,875±256	1,306–2,559	0.02	27
Penn state	1,947±341	1,213–2,879	0.519	33
PSmod	1,858±299	1,244–2,728	0.04	41
ACCP	1,916±554	650–3,900	0.151	25
Faisy	1,911±307	1,081–2,681	0.072	30

Precision: number (%) of subjects within ±10% of REE measured by IC.

HB IF = HB using an injury factor; Mifflin SF = equation Mifflin with stress factor; PSmod = modified Penn state.

Table 4. Biases, limits of agreement, correlation coefficient and ICC between REE measured and prediction equations in AKI patients

	Bias (95% CI)	Limit of agreement	Correlation coefficient r (p value)	ICC (95% CI)
HB	528 (392 to 663)	–967.7 to 2,023.6	0.21 (0.02)	0.15 (–0.02 to 0.32)
HB IF	77.6 (–62.4 to 217.6)	–1,472 to 1,627.6	0.21 (0.02)	0.18 (0.001 to 0.34)
Mifflin	370.1 (232 to 508.3)	–1,160 to 1,900.3	0.12 (0.18)	0.08 (–0.09 to 0.25)
Mifflin SF	–44.6 (–186.7 to 97.4)	–1,617.4 to 1,528.2	0.12 (0.18)	0.09 (–0.08 to 0.27)
Ireton-Jones	153.7 (24.3 to 283)	–1,278.7 to 1,586	0.28 (0.001)	0.18 (–0.004 to 0.33)
Penn State	81.7 (–49.7 to 213.1)	–1,373 to 1,536.5	0.28 (0.002)	0.21 (0.03 to 0.37)
PSmod	170.8 (43.5 to 298.1)	–1,238.6 to 1,580.1	0.33 (<0.001)	0.23 (0.06 to 0.38)
ACCP	112.8 (–41.6 to 267.1)	–1,595.7 to 1,821.2	0.15 (0.09)	0.14 (–0.03 to 0.31)
Faisy	118.3 (–10.8 to 247.5)	–1,312.0 to 1,548.7	0.30 (<0.001)	0.21 (0.03 to 0.37)

HB IF = HB using an injury factor; Mifflin SF = equation Mifflin with stress factor; PSmod = modified Penn state.

The BMI values (11.6–57.5 kg/m^2) covered all National Heart, Lung, and Blood Institute classifications, and the mean value of the populations fell in the overweight weight range (BMI 28.2 ± 7.9 kg/m^2). Six percent of patients were underweight (BMI <18.5 kg/m^2), 32% were normal-weight patients (BMI 18.5–24.9 kg/m^2), 29.6% were overweight, 20.8% were obese class 1, 3.2% were obese class 2, and 9.6% were obese class 3.

Mean REE measured by IC was 2,029 ± 760 kcal/day. The comparison between the REE assessed by IC and by the prediction equations is shown in table 3. The measured REE was significantly higher than the REE estimated by the equations HB, Mifflin, Ireton-Jones 1997 and modified Penn state. The precision was poor for all equations. Modified Penn state equation had the best precision, although only 41% of cases had the predicted REE within 10% of their measured REE. Overall, the equations HB without using injury factor were the least precise, with only about 18% of cases having a predicted value within 10% of the measured REE. When using injury factor, this precision increased to 36%.

As shown in table 4, the ICC for the nine equations was indicative of poor degree of reproducibility with IC. It can be noted that the ICC observed for the Penn state equation (0.23) was stronger than other, however, even with poor reproducibility.

Table 4 also summarizes the correlation coefficient, limits of agreement and bias of the equations with mea-

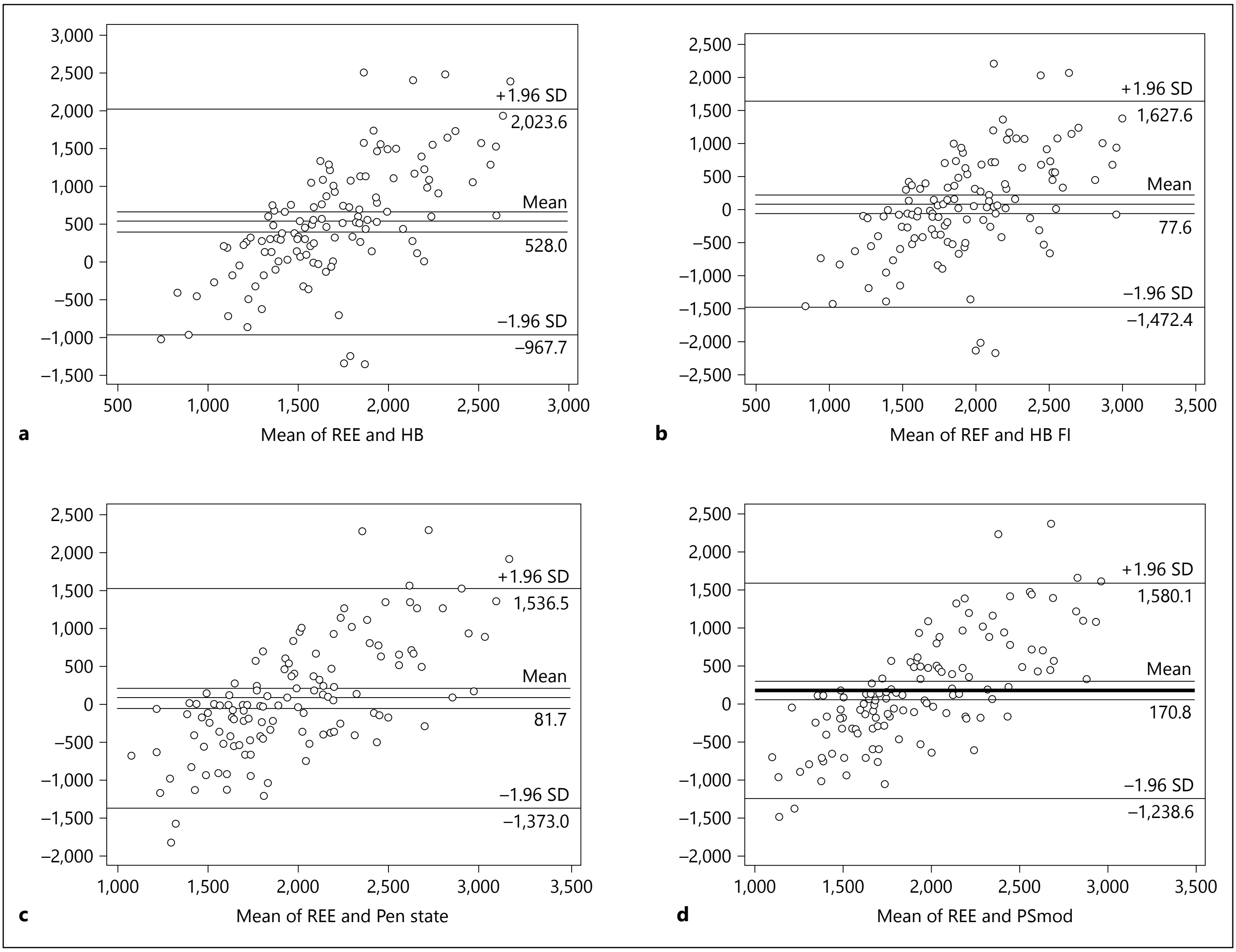

Fig. 1. Bland–Altman plots. Differences between REE measured and estimated using different prediction equations: **a** REE vs. HB equation; **b** REE vs. HB equation with injury factor; **c** REE vs. Penn state equation; **d** REE vs. modified Penn state equation. On the y-axis are plotted the values of the difference between the 2 methods measured and estimated REE, and on the x-axis, the values of average results by 2 methods. The limits of agreement were drawn (the average values of the differences + 1.96 SD and the average differences – 1.96 SD). The middle line corresponds to the bias (the average of the differences between the methods) and its CI.

sure REE. The measured REE had significant correlation with HB equation with and without using an injury factor of 1.3, Ireton-Jones equation, Penn state equation, modified Penn state equation and Faisy equation; however, these correlations were weak ($r < 0.4$).

The limits of agreement show the range of differences between the IC measurement and the REE predicted by the equations. For all equations, the limits of agreement range were large. For example, when evaluating patients using the HB equation, limits of agreement ranged from –968 kcal/day (IC less than predicted equation) to 2,024 kcal/day (IC higher than predicted equation). The large wide limits of agreement in each case highlight the potential under or overfeeding of individual patients.

The individual agreement between IC and the prediction equations are shown in figures 1 and 2 using the Bland–Altman plot analysis. An association was found between the difference (y-axis) and the average (x-axis) for all equation (HB $r = 0.69$, HB using an injury factor $r = 0.53$, Mifflin $r = 0.75$, Mifflin with stress factor $r = 0.63$, Ireton-Jones $r = 0.81$, Penn state $r = 0.68$, modified Penn state $r = 0.75$, ACCP guidelines $r = 0.31$, Faisy $r = 0.74$; all $p < 0.001$). This revealed a trend-bias for equations; that is, by increasing average, the difference rises.

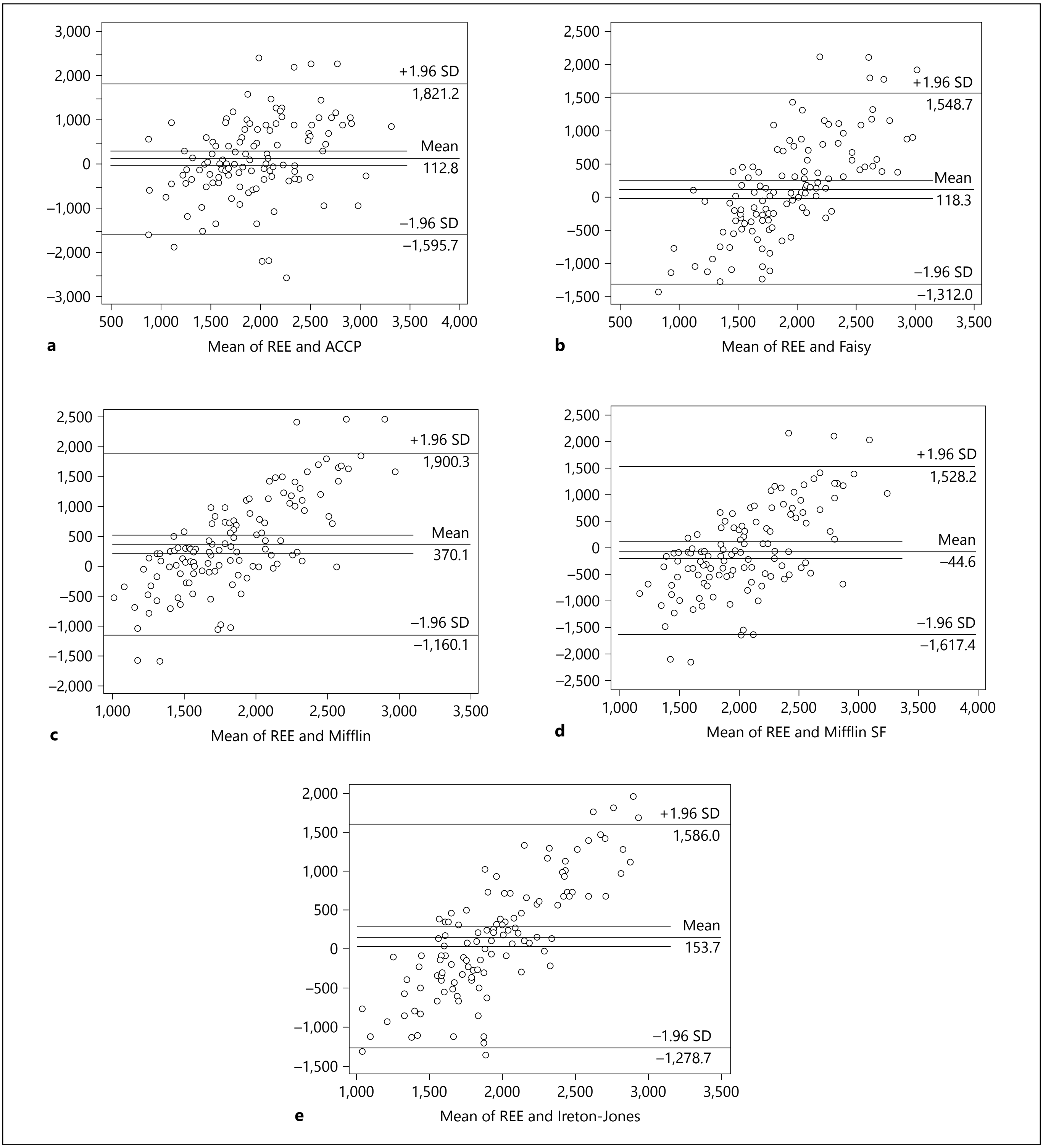

Fig. 2. Bland–Altman plots. Differences between REE measured and estimated using different prediction equations: **a** REE vs. ACCP guidelines; **b** REE vs. Faisy equation; **c** REE vs. Mifflin equation; **d** REE vs. Mifflin equation with stress factor; **e** REE vs. Ireton-Jones equation. On the y-axis are plotted the values of the difference between the 2 methods measured and estimated REE, and on the x-axis, the values of average results by 2 methods. The limits of agreement were drawn (the average values of the differences + 1.96 SD and the average differences – 1.96 SD). The middle line corresponds to the bias (the average of the differences between the methods) and its CI.

Discussion

Using this data set, we have demonstrated that none of the equations used to predict REE agree well with actual energy expenditure measured by IC in severe AKI patients.

It may be argued that inaccurate predictions are expected when equations developed long ago (e.g. the HB) or based on data from healthy volunteers (e.g. HB and Mifflin-St Jeor) are applied to ill hospitalized patients. The HB equation represents REE as developed from 239 mostly normal weight, white men and women evaluated in the first 2 decades of the 20th century [17]. The poor resemblance of those healthy samples to hospitalized patients seen currently includes a greater diversity in body composition, obesity, and race.

In our study, HB equation was the least precise, with poor reproducibility (ICC 0.15). Only about 18% of cases had a predicted value within 10% of the measured REE. In general, the equation underestimated REE in approximately 500 kcal/day. The limits of agreement between the equation and measured REE were large (–967.7 to 2,023.6 kcal/day), showing the low agreement between the methods.

In a systematic review, Frankenfield et al. [14] reported the results of an evidence analysis of the accuracy of metabolic rate calculation methods. HB equation presented mean differences between the resting metabolic rate measured and predicted; these differences ranged from 250 to 900 kcal/day (some individual differences may be much higher). As in our study, this equation underestimated the resting metabolic rate in critically ill patients. That work group concluded that the unmodified HB equation was not sufficiently accurate for clinical use in critically ill patients and this conclusion carries a grade of I (i.e. good evidence) [14].

Due to the inaccuracy of this equation, the correction factors were studied. Normally, the values calculated using HB equation are multiplied by correction factors to adjust energy expenditure to the current individual situation, adapting the energy expenditure to the current individual situation. There are a wide range of multiplication factors used in the published studies (injury factor, stress factor, activity factor; thermal factor, among others) [14–16]. In our study, we used HB equation × 1.3 (injury factor) and we did not use an activity factor, in an attempt to reduce the error in equation (underestimate) in AKI patients in dialysis.

In our study, using the injury factor, the HB equation had higher precision than without injury factor (36%) and the mean difference between measured and estimated REE (bias) was lower (77.6 kcal/day) showing reduction in probability to underestimate the REE. However, this equation remained with poor degree of reproducibility (ICC 0.18), and poor agreement with IC (limits of agreement large, range –1,472 to 1,627.6 kcal/day). Other studies also showed low concordance and accuracy between the equation HB and IC, even using the injury factor [6, 13, 16, 33–36].

Review studies have suggested not to use the HB equation, with or without correction factors, in critically AKI patients because it underestimated and/or overestimated REE and was inaccurate and unreliable for ICU patients [14, 37].

Similar to HB equation, the Mifflin-St Jeor equation [18] is a regression equation that combines weight, height, age, and gender to predict resting metabolic rate in healthy people. According to the published evidence, an ADA work group determined that the Mifflin-St Jeor equation was the most accurate method to predict the resting metabolic rate in healthy obese and no obese people. The use of Mifflin-St Jeor equation in critical care has been little studied [14]. We found poor agreement between REE estimated by Mifflin-St Jeor equation using or not using stress factor and measured REE by IC (limits of agreement –1,617 to 1,528 and –1,160 to 1,900 kcal/day, respectively). This equation had the lower ICC (0.08, 0.09) and precision (25, 29%) and tended to underestimate the REE when the stress factor is not used or overestimate when it is added.

In literature, Mifflin equation had poor agreement and underestimated REE in critically ill patients, in all BMI groups, and may underestimate further than the HB equation [6, 14, 38, 39].

Unlike previous equations, the Ireton-Jones, Penn state and Faisy equation were developed from REE measurements of hospitalized and critically ill patients, and dynamic variables as body temperature and minute ventilation that reflect the metabolic state of the patient were added.

Although they are intended for use in critical patients, in our population of AKI patients, all these formulas had poor agreement with measured REE by IC.

Frankenfield et al. [15] compared energy expenditure equations to measurements by IC in 202 mechanically ventilated critically ill patients divided into <60 or >60 years and BMI <30 or >30 kg/m^2. Seventeen equations were evaluated and the Penn state equation was the most accurate (precision 67%).

Kross et al. [6] evaluated the energy expenditure equations in a total of 927 patients, including 401 obese patients. They found there was poor agreement between REE measured by IC and REE predicted by the HB, ACCP, Mifflin, and the Ireton-Jones equations. In all cases, except using Ireton-Jones, the predictive equations underestimated measured REE.

Review studies also suggest that Ireton-Jones, Penn state, Faisy and ACCP equation has no sufficient accuracy and agreement with measured REE in critically ill patients and should not replace the use of IC [14, 30, 40, 41].

In our study, these equations underestimated the REE measured by IC (Ireton-Jones 154 kcal/day less than measured REE, Penn state 82 kcal/day; Penn state modified 171 kcal/day; Faisy 118 kcal/day and ACCP 113 kcal/day). Although, Penn state modified equation has presented a higher precision (41%) and ICC (0.23), it is not enough as an indication of use in critically ill AKI patients. Using universal prediction equations to critical ill AKI patients, errors of prediction can occur and lead to overfeeding or underfeeding if they are used to guide the feeding regimen of these patients [14].

The reason why these equations are not accurate in these patients is not clear. The kidneys are responsible for many regulatory functions, such as acid–base balance, fluid and electrolyte balance, gluconeogenesis, the secretion of erythropoietin and conversion of vitamin D3 to its active form. While the kidneys are responsible for only 10% of energy expenditure, metabolic disorders, and proinflammatory state associated with renal failure, the underlying disease process and comorbidities could alter energy expenditure [12]. However, energy expenditure is not apparently increased by AKI. There is only one study on AKI population, and it showed that the REE was around 130% of normal, calculated by the HB equation, in patients with sepsis and AKI [42].

Some limitations should be recognized. First, the use of weight on admission can overestimate the actual weight due to pre-ICU procedures (such as resuscitation). However, as we are evaluating patients with severe AKI, the current weight probably offer a greater error due to edema. Moreover, in some cases, the patient's weight at admission was not available, and therefore, the weight information collected from patients' caretakers was used instead. The same was done with height and can lead to an incorrect estimate of REE.

Second, we were not able to examine all the predictive equations currently used in practice because we were unable to obtain some pieces of clinical information needed to perform them. For example, we were unable to calculate the Swinamer equation, commonly used to predict the energy needs for ventilated patients because we could not obtain information on tidal volume. However, the equations that we evaluated contain clinical information readily available to practitioners, making them clinically useful equations for critical care clinicians to use. Third, we did not have information about treatments that might influence energy expenditure and carbon dioxide production, including type of nutrition and energy intake, catecholamine, neuromuscular blocking agents, and opioids.

Another limitation is that we only have REE measure at one moment. Day-to-day variations in energy expenditure of between 4 and 56% have been reported [43]. Because of this variability in REE, one measurement, which is then extrapolated to represent several days may introduce significant error. Thus, REE measured is representative of that moment, and the same for REE estimated in the equations. For the monitoring of patients, further measures REE must be made of both the IC, as the equations.

Finally, because we studied a select population of patients, those with severe AKI, our findings may not be generalizable to all AKI, or critically ill patients and, finally, only 1 IC measurement was performed, whereas repeated measurements are recommended to cope with the dynamic alterations of energy metabolism during the course of critical illness.

Despite limitations, this is the largest study to reports that predictive equations do not accurately estimate REE in critically ill AKI patients. None of the prediction equations evaluated in this study had accuracy higher than 50%, and may result in such a high value as 80% of patients receiving inadequate or excessive energy intakes. Our findings support the need to conduct a controlled prospective study to develop an appropriate prediction equation to assess energy needs for critically ill AKI patients. Alternatively, because of the limitations of the predictive formula, IC may be required to assess the energy needs in severe AKI patients requiring dialysis.

Acknowledgments

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