Original article

Resting energy expenditure prediction using bioelectrical impedance analysis in patients with severe motor and intellectual disabilities

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Running head: Resting energy expenditure prediction in patients with SMID

Key words: resting energy expenditure, indirect calorimetry, bioelectrical impedance analysis, fat-free mass, equation; Severe motor and intellectual disabilities

Abstract

Introduction: Resting energy expenditure (REE) is expected to be lower in with severe motor and intellectual disabilities (SMID) patients than in healthy subjects because of their relatively low fat-free mass (FFM). Therefore, an REE predictive equation for SMID patients may be required. The aim of this study was to validate existing REE predictive weight-based equations (Harris-Benedict, WHO, Mifflin, Owen, Schofield) and FFM-based REE equations (Mifflin, Owen and Cunningham) and to develop a new SMID patient-specific FFM-based REE equation.

Methods: Twenty-eight (22 males, 6 females) SMID patients over 18 years of age were included. The REE was measured using indirect calorimetry. FFM were measured using bioelectrical impedance analysis. A multiple linear regression analysis was used to develop a new FFM-based REE predictive equation. The accurate predictions compared the measured REE and root mean square error.

Results: The median measured REE was 950 (25^{th},75^{th} percentile :712.75, 1102.75) kcal/day. The new FFM-based equation was as follows: REE (kcal/day) =550.62 +16.62 FFM (kg). The new FFM-based REE resulted in the highest percentage of accurate predictions within 10% of measured REE (42.9%). The root mean square errors were the smallest for the new FFM-based REE and largest for Harris-Benedict (91.00 and 185.22 kcal/day).

Conclusion: For SMID patients, the REE cannot accurately be predicted using the existing weight-based REE equations. Furthermore, the existing FFM-based REE equations are less accurate with regard to the measured REE than the new FFM-based REE equation. The new FFM-based equation is advised for use in SMID patients.

1. Introduction

The presence of neurological impairment has been recognized as a critical disorder that requires intensive nutritional support due to the presence of neurological and/or metabolic disorder, and because it is associated with a high incidence of complications, such as gastroesophageal reflux disease and oropharyngeal discoordination. Patients with severe motor and intellectual disabilities (SMID) frequently require surgical procedures, such as anti-reflux surgery and tracheostomy, and pediatric surgeons face various problems in their perioperative management, most notably in management associated with these patients' nutrition, as the nutrition that they receive at the referring institution is often insufficient.

Although the accurate evaluation of these patients' nutritional status should be fundamental, it is often difficult to assess this status from physical measurements due to these patients' severe scoliosis. A nutritional assessment technique that combines the evaluation of temporal weight changes and the hematological/nutritional index has often been attempted for SMID patients. However, such techniques may be inaccurate, as the height-for-age and weight-for-age growth standards of SMID patients are lower than those of the reference population [1]. It has been proposed that a normal body weight should not be the goal for SMID patients; instead, a more appropriate goal is a ‘sufficient’ body weight, as attempts to increase the nutritional intake because of perceived undernutrition may result in the accumulation of excess body fat.

The resting energy expenditure (REE), which is measured by indirect calorimetry, is the gold standard for determining the nutritional status [2]. However, nutrition and exercise professionals do not usually have the equipment to perform calorimetry. Furthermore, indirect calorimetry is expensive and requires trained personnel to guarantee its reliability. Therefore, predictive equations are typically used to estimate the REE. The REE is expected to be relatively low in SMID patients because of their relatively low fat-free mass (FFM). REE predictive equations for SMID patients are therefore required.

We previously reported that SMID patients have a low phase angle (PhA), similar to patients with sarcopenia, and a certain proportion may also have nutritional disturbances according to bioelectrical impedance analyses (BIAs) [1]. However, no report has described the nutritional assessment of SMID patients with REEs using BIAs and indirect calorimetry.

Therefore, the aim of this study was to validate existing REE predictive equations from Harris and Benedict (Harris-Benedict) [3], the World Health Organization (WHO) [4], Schofield [5], Mifflin (one based on weight and one using FFM) [6], Owen (one based on weight and one using FFM) [7-8] and Cunningham [9] (Table 1), and to develop a new equation specifically for SMID patients. One equation was developed using FFM, since the body composition of SMID patients differ from that of the average population, and another equation was developed without FFM, as this parameter cannot always be used. We hypothesized that our new equations specifically developed for SMID patients would result in more accurate estimations of the REE than the existing equations.

2.Materials and methods

2.1 Patients

This study was conducted from June 2013 to April 2018. Twenty-eight patients (22 males and 6 females) with SMID over 18 years of age underwent measurements of their body composition by BIA and calorimetric techniques. The median age was 30 years (interquartile range 22.5-44.75 years). All of the patients were bedridden and required enteral nutrition via a nasogastric tube or gastrostomy. Regarding the causal disorders of SMID, 2 patients had a genetic anomaly, 19 had suffered cerebral damage in the neonatal period and 7 had suffered cerebral damage in infancy or later. Patients who were suffering from decompensated heart, lung, kidney or liver failure or the involuntary loss or gain of >5% body weight in the previous 3 months (which affected the BIA data) were excluded from the present study.

Informed consent was obtained from the patient's families before they were enrolled in the present study. All of the patients underwent a baseline nutritional assessment that included laboratory measurements of the subjective global assessment parameters, including their age, height, weight, body mass index (BMI) (calculated as the weight [kg] divided by the height [m] squared [kg/m^2]) and the measurement of the serum levels of nutritional markers, including the albumin level, peripheral blood lymphocyte count, total cholesterol level, Onodera's prognostic nutritional index (PNI) [10] and controlling nutritional status (CONUT) score.

The PNI is a useful tool for predicting the short- and long-term postoperative outcomes in patients [10]. It is calculated based on the serum albumin concentration and peripheral blood lymphocyte count (10×serum albumin concentration [g/dL] + 0.005 × total peripheral lymphocyte count [per mm^3]). The serum albumin concentration has been reported to be easily influenced by not only the nutritional status but also by changes in the body fluid volume, such as those due to the dehydration/fluid retention status and inflammation caused by chronic disease [11]. The CONUT score is an index calculated from the following factors: the serum albumin concentration, total peripheral lymphocyte count and total cholesterol concentration. The CONUT score allows for the automatic daily assessment of the nutritional status of all inpatients that undergo a routine analysis [12]. Patients with a CONUT score > 5 and PNI < 40 were excluded from the present study.

This study was performed after obtaining informed consent from the parents according to the IRB approval by the Ethical Comittee. IRB approval was granted by the Kurume University School of Medicine (approval No.17302).

2.2 Indirect calorimetry

The REE was calculated with the manufacturer’s software program using the oxygen (O_2) consumption and carbon dioxide (CO_2) production measured by indirect calorimetry with a ventilated hood system (Vmax Encore n29; Viasys Healthcare, Houten, the Netherlands). Calibration of the equipment with two different standard gases and one standard volume was performed on a daily basis before starting the measurements. In addition, an automatic recalibration of the system was done every five minutes. The subjects remained lying down but awake. The measurement took 30 minutes. Only steady-state periods of measurement were selected according to the procedures for the ventilated hood system (<10% CV). The first 5 minutes of the measurements were discarded. The patients were studied after fasting for >2 h without parenteral nutrition. Respiratory quotients (RQs) were calculated as the ratio of the volume of CO_2 expired (VCO_2) vs. the volume of O_2 consumed (VO_2). The measured REEs were examined using the modified Weir equation: REE (kcal/day) = $[3.941(VO_2) + 1.106(VCO_2)] \times 1440$ [13].

2.3 Bioelectrical impedance analyses

The Inbody S20 (Biospace, Tokyo, Japan.) was originally used for the measurements. To prepare for the measurement, the patients were placed in the supine position under a thermoneutral environment of 28 °C. Their arms were separated from the trunk, and both legs were separated from each other. The BIA was performed with eight surface electrodes placed on the patient's thumbs, middle fingers and both sides of each ankle.

The BIA data gathered included the PhA, FFM and fat mass (FM). The PhA was determined at single frequencies (50 kHz) and calculated based on the sum of the impedance and reactance of the right arm, trunk and right leg and using the following equation: PhA (°) = (Reactance / Resistance) × (180°/π).

2.4 Statistical analyses

All data are expressed as the median (Interquartile range). All of the statistical analyses were performed using the JMP software package (SAS, Cary, NC, USA), and p values of < 0.05 were considered statistically significant. Multiple linear regression analyses were used to develop the new FFM-based REE equation. A stepwise regression approach was used with the variables FFM, FM, age, sex and a constant to verify the FFM-based REE equation. Therefore, these variables and a constant were used in a regression analysis. Variables were included when the p-value for the F-test was < 0.05.

The predicted REEs from our newly developed equation and from other commonly used equations (Table 1) were compared with the measured REE. Group differences were tested using the Mann-Whitney U test, and Spearman's correlation coefficients (r) were used to identify relationships between two variables. The accuracy was calculated as the percentage of accurate REE predictions (within 10% of the measured REE). The bias was calculated as the percentage of the predicted REE from the measured REE. The root mean squared error was calculated as the expected absolute deviation (kcal/d) of the predicted REE from the measured REE. The root mean square error is the square root of the sum of the squared differences between the measured and estimated REE values divided by the number of patients studied. The smaller root mean square error, the greater the accuracy of the equation. To quantify the degree of bias, we compared the correlation coefficients between the respective differences and means using Bland-Altman plots. The closer the correlation coefficient of the Bland-Altman plot to 0, the less the bias.

3. Results

The characteristics of the patients are shown in Table 2. There were no marked differences by gender. The measured REE was 950.0 (712.75-1102.75) kcal/day. Using the previously described regression analyses, the new FFM-based REE equation only included FFM (kg) and a constant. The new FFM-based equation was as follows: REE (kcal/day) = 550.62 +16.62 FFM (kg) (Figure 1). There were no significant differences between the measured REE and the new FFM-based REE equation and the mean difference was -2.219 kcal/day. There were significant differences between the measured REE and the equation-predicted REEs of the WHO (1193.6 [1011.9-1279.7] kcal/day; $p<0,001$), weight-based Mifflin (1031.9 [898.3-113.1] kcal/day; $p<0.05$), weight-based Owen (1186.0 [1085.6-1258.7] kcal/day; $p<0.001$), FFM-based Owen (773.9 [734.3-887.6] kcal/day; $p<0.01$) and Schofield (1194.4 [1045.5-1280.9] kcal/day; $p<0.001$). There were no significant differences between the measured REE and the Harris-Benedict (971.9 [838.7-1044.6] kcal/day), FFM-based Miffin (846.4 [805.5-941.0] kcal/day) and Cunningham (845.2 [792.3-948.9] kcal/day). The mean differences were the smallest for Harris-Benedict and largest for weight-based Owen (-41.598 and -225.536 kcal/day, respectively), except for with the new FFM-based REE.

The accuracy within 10% of measured REE for all equations is depicted in Figure 2A. The new FFM-based REE resulted in the highest percentage of accurate predictions (42.9%), followed by the weight-based Mifflin (35.7%), FFM-based Mifflin (32.1%) and FFM-based Owen (32.1%). All other generally used equations showed less than 30% accuracy (Cunningham, Harris-Benedict, WHO, Schofield, and weight-based Owen were 25.0%, 21.4%, 21.4%, 14.2%, 7.14%, respectively).

The bias of all equations is depicted in Figure 2B. As with the accuracy, the lowest bias was observed for the new FFM-based REE equation (100.62% [89.82%-123.13%]). The highest bias was observed with the weight-based Owen (123.99% [113.27%-141.46%]). The bias of other equations; weight-based Mifflin (108.5% [98.96%-126.2%], FFM-based Mifflin (92.71% [83.67%,113.0%]), FFM-based Owen (124.0% [113.3%-141.5%]), Cunningham (92.69% [83.87%-113.1%]), Harris-Benedict (101.7% [85.91%-136.1%]), WHO (118.9% [108.8%-132.8%]) and Schofield (110.2% [120.2%-141.4%]), respectively. the weight-based equations over-predicted measured REE, otherwise the FFM-based equations under-predicted it.

The root mean square errors were the smallest for the new FFM-based REE and largest for Harris-Benedict (91.00 and 185.22 kcal/day, respectively). The root mean square errors for other equations; FFM-based Mifflin 107.86 kcal/day, Cunningham equations 121.32 kcal/day, FFM-based Owen 121.4 kcal/day, weight-based Owen 125.04 kcal/day, Schofield 172.2 kcal/day, weight-based Mifflin 178.89 kcal/day and WHO 180.05 kcal/day, respectively. The FFM-based equations performed more equally than the weight-based equations (Figure 2C).

On Bland-Altman plots, the correlation coefficients between the mean values and differences were significant for the Harris-Benedict ($r=0.6846$, $p=0.003$), WHO ($r=0.49119$, $p<0.001$), weight-based Mifflin ($r=0.42921$ $p=0.0377$), weight-based Owen ($r=0.42576$, $p<0.001$), FFM-based Owen ($r=0.5026$, $p=0.0018$) and Schofield ($r=0.46761$, $p<0.001$) and not significant for the FFM-based Mifflin ($r=0.42921$, $p=0.0932$) and Cunningham ($r=0.4824$, $p=0.0996$) (Table 3).

4. Discussion

The purpose of this study was to validate the existing predictive equations for REE and to develop and validate new equations specifically for SMID patients. To our knowledge, the present study is the first to evaluate the REE of SMID patients using a BIA and indirect calorimetry. Our newly developed FFM-based equation provided the best prediction of the REE in SMID patients. Existing weight-based and FFM-based REE equations are less accurate with regard to the measured REE than the new FFM-based REE equation. Furthermore, although a stepwise regression approach was used for the weight-based REE equation for SMID patients with the variables of body weight, height, age and sex, variables were not included because the p-value for the F-test exceeded 0.05 in the regression analysis. According to the root mean square errors, the FFM-based REE equation performed better than the existing equations, suggesting that FFM is an important predictor of the REE in SMID patients. The Cunningham equation was developed after a systematic review of numerous studies confirming a primary correlation between the REE and FFM in adults over a broad range of body weights[9]. Mifflin[6] and Owen[7-8] used lean and obese subjects. The mean BMI in Mifflin's study was 27.5±4.1 kg/m^2 for men and 26.2±4.9

kg/m^2 for women, with a maximum of 42 kg/m^2 [6]. In Owen's study, the BMI for man was 28.2±7.5 kg/m^2 [7], and that for women was 27.8±8.6 kg/m^2 [8], with a maximum of 58.7 kg/m^2 [7]. In this study the median BMI for male SMID patients was 15.57 (13.2775-17.8775) kg/m^2, and that for female patients was 13.125 (10.375-16.925) kg/m^2. As there are some difference in the body compositions of SMID patients compared with non-SMID patients, the weight-based equations of Mifflin and Owen showed low accuracy in our population. Furthermore, the population used to develop the Schofield and WHO weight-based equations comprised a disproportionate number of Italians, who seem to have a higher basal metabolic rate than Asian people [4-5].

In our study, the mean BMI was 15.48 (12.335-17.793), and the mean FFM was 22.0 (19.6-26.8). In Owen's study, the FFM for men ranged from 45.2 to 97.9 kg, and that for women ranged from 34.3 to 74.7 kg. In Mifflin's study, the FFM ranged from roughly 35 to 95 kg. The BMI and FFM of the SMID patients were both extremely low in comparison to those values in healthy subjects [1]. Based on these results, the clinical condition of the SMID patients in the present study was likely to be similar to that of patients with sarcopenia. Moreover, SMID patients with obesity due to intellectual disabilities or endocrinology problems have also low fat-free mass. The patients were likely to be similar to that of patients with sarcopenia obesity. If the patients were used for the weight-based REE equation, REE would be measured excessively. The better performance of our new FFM-based REE equation over the previous weight- and/or height-based equations might have been due to differences in the body composition of SMID patients compared with the general population.

The present study is associated with some limitations due to its wide age distribution, various health conditions and the small sample size and the fact that it was a single-center study. Thus, a further multicenter study with a larger number of age- and health-matched SMID patients should be performed to verify the effectiveness of the BIA. In our study, the CONUT score, PNI score and conditions of all patients were normal. If malnutrition, respiratory disorder or chronic seizure had been complicated in any of our subjects, the energy expenditure would have been difficult to predict because of the inclusion of stress factors. Further studies are therefore needed.

This study was limited to over 18 years. The existing equations were limited adult subjects. Moreover, aspects of daily energy expenditure of children, in particular physical activity levels and growth, have greater impacts on body composition at early age, due to increase muscle mass and bone density [14]. For this reason, there has a bias of daily energy expenditure and resting energy expenditure.

In conclusion, for SMID patients, the REE cannot accurately be predicted using the existing weight-based REE equations. Furthermore, the existing FFM-based REE equations are less accurate with regard to the measured REE than the new FFM-based REE equation. Since indirect calorimetry is not always possible, and other generally used equations can fail, our newly developed FFM-based REE equation is advised for use in SMID patients.

Conflict of interest

Yushiro Yamashita has financial relationships to disclose about lecture fee from Eli Lilly and company.

5. Figure legends

Figure 1: The new FFM-based equation was as follows: REE (kcal/day) = 550.62 +16.62 FFM (kg) and the measured REE was plotted. The measured REE was significantly correlated with FFM (r^2 =0.2327, $p<0.01$).

Figure 2: Outcome measures for the REE predictive equations. (A) The accuracy percentage of all equations which are within 10% accuracy of measured REE. (B) The bias of all equations. (C) The root mean squared errors of all equations.

Table 1: Resting energy expenditure prediction equations given in their original unit and the new FFM-based REE equation (kcal/day, except Schofield (MJ/day))

Table 2: Patient characteristics

Table 3: Agreement between measured and predicted REEs

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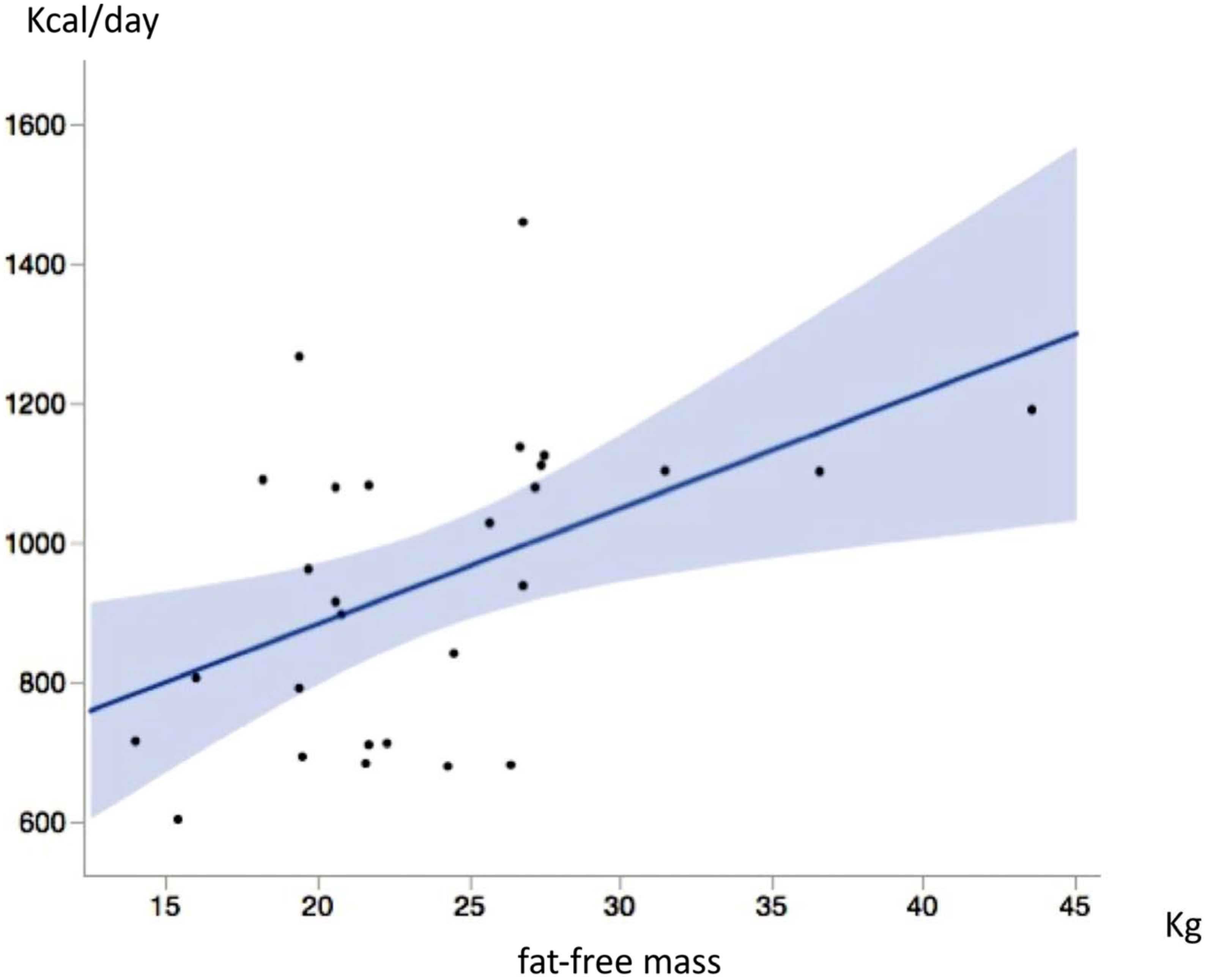
Figure 1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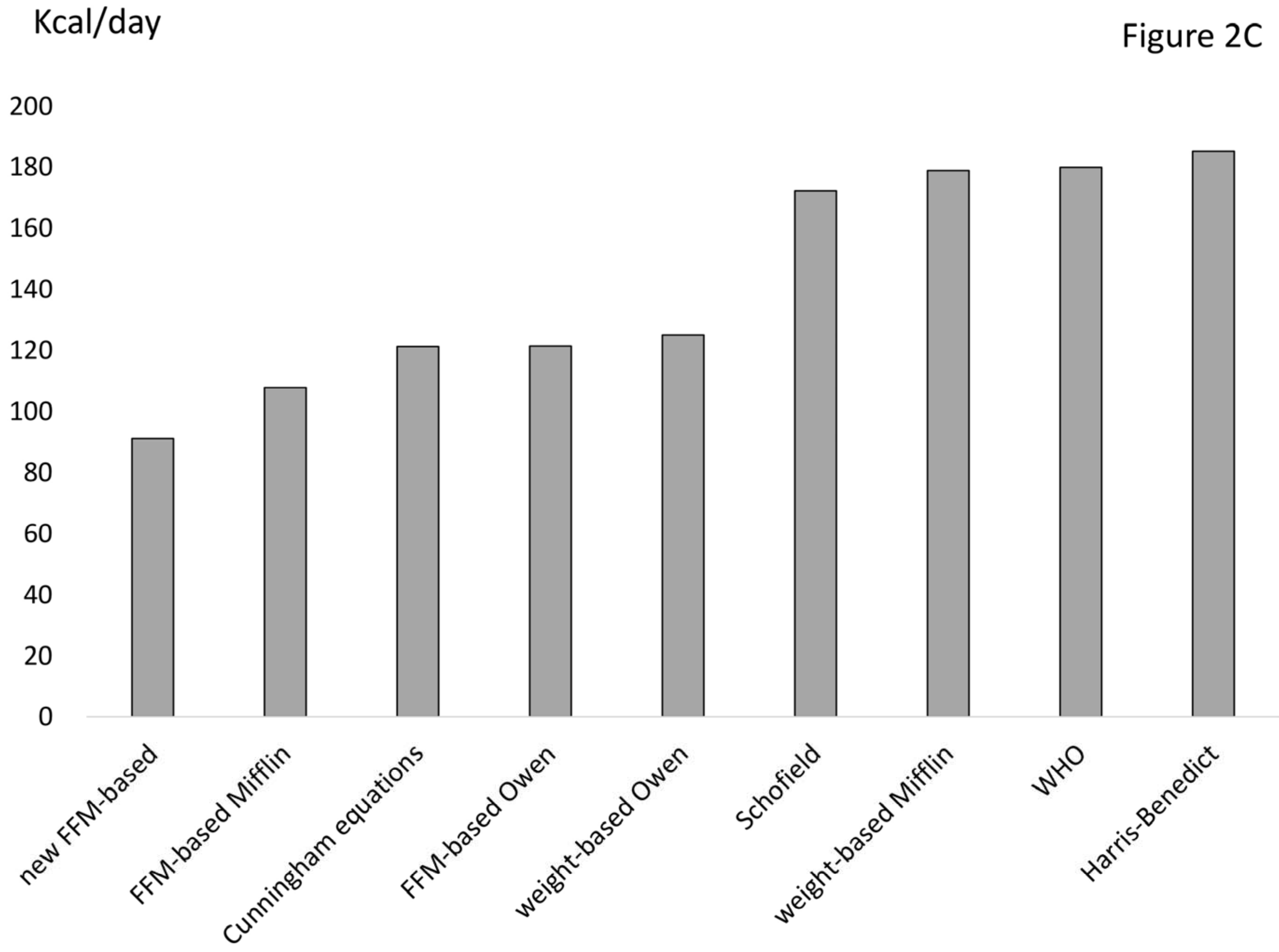
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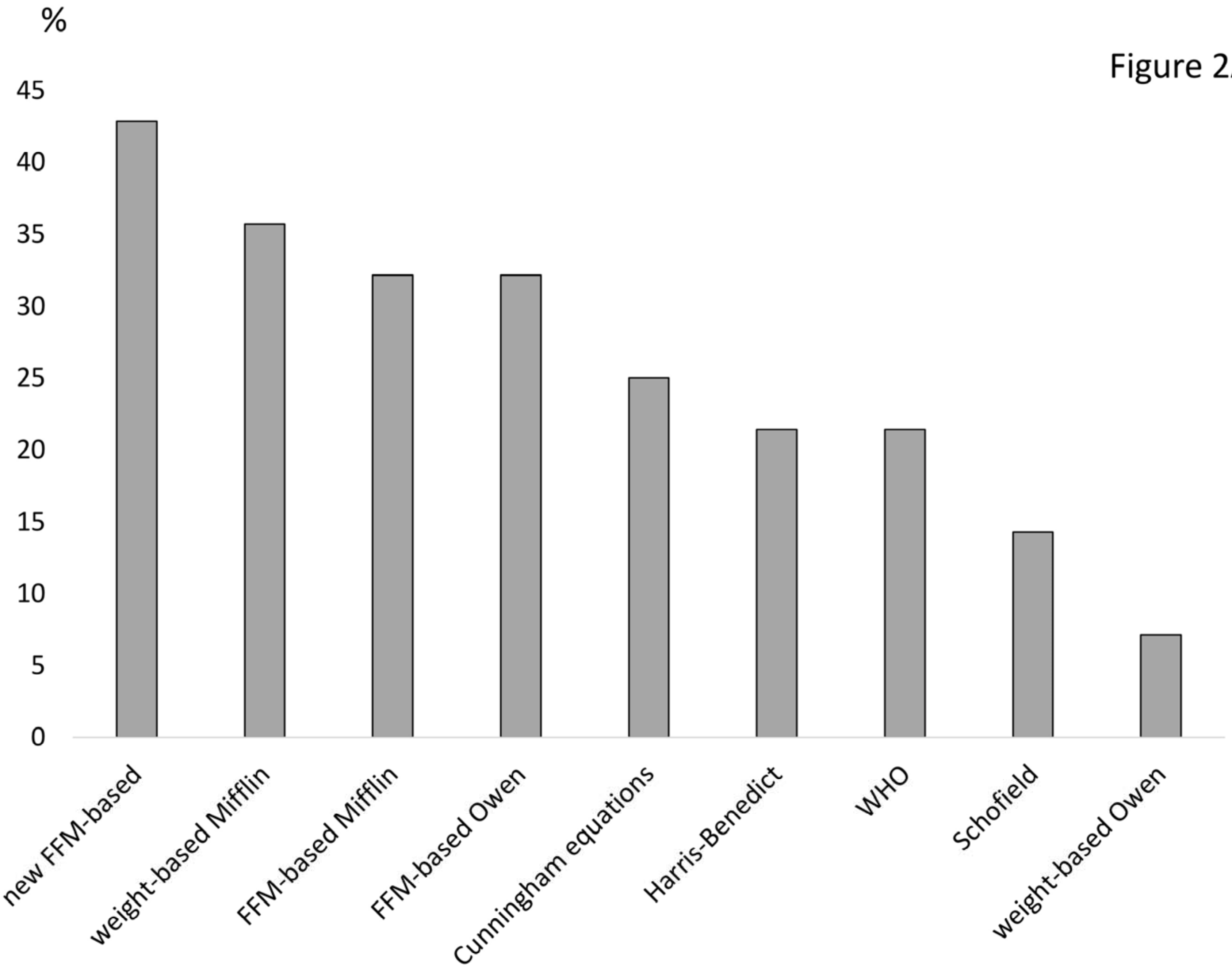
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weight-based Owen

Figure 2A

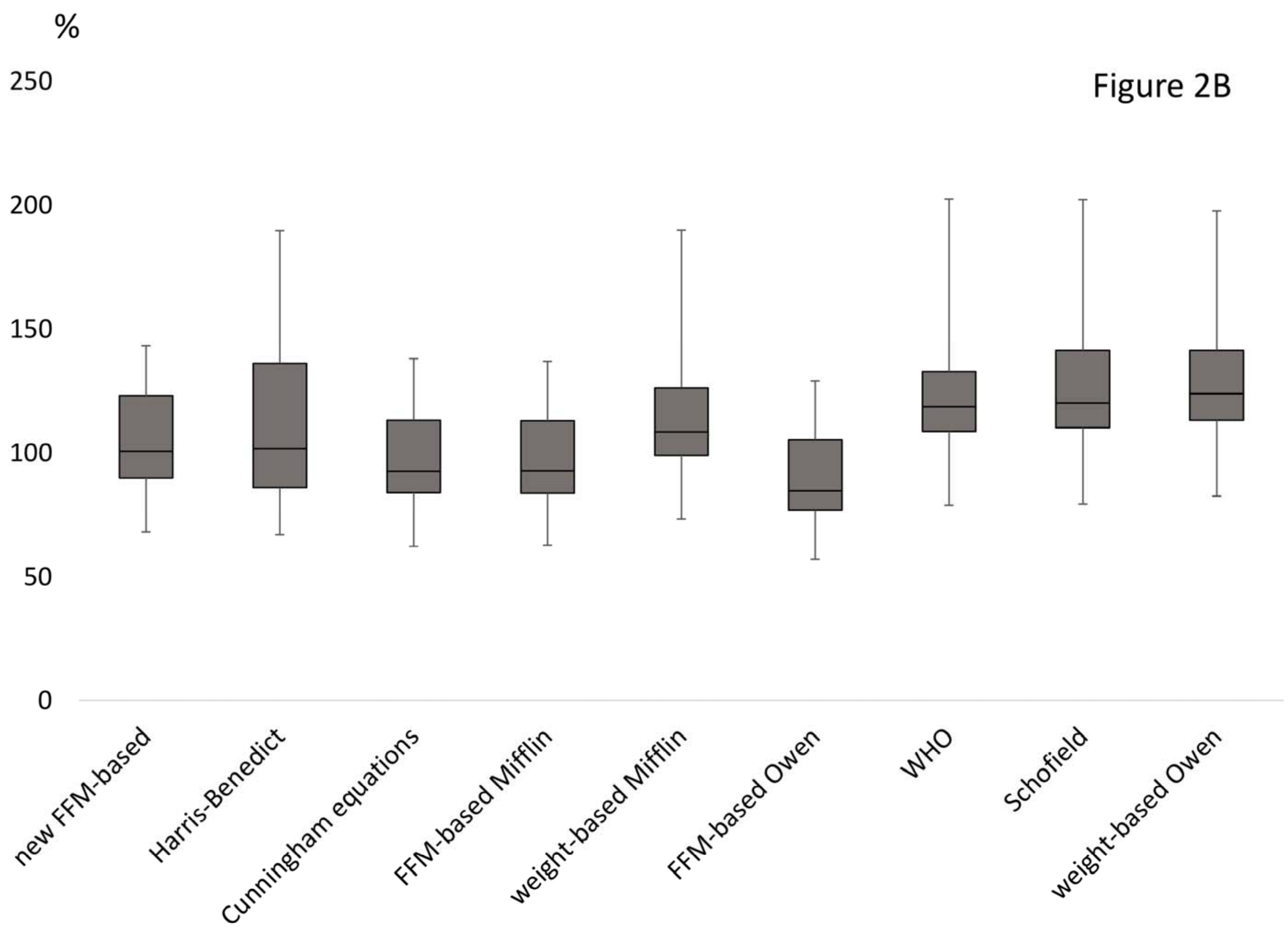

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Figure 2B
new FFM-based
Harris-Benedict
Cunningham equations
FFM-based Mifflin
weight-based Mifflin
FFM-based Owen
WHO
Schofield
weight-based Owen

Table1:Resting energy expenditure prediction equations given in their original unit and the new FFM-based REE equation (kcal/day, except Schofield* (MJ/day))

Equation	Subset of subjects	Formula
HB	Male	REE=66.43+13.7516BW+500.33Ht-6.755Age
	Female	REE=655.1+9.56BW+185Ht-4.68Age
Miffin	Male	REE=9.99BW+6.25Ht-4.92Age+5
	Female	REE=9.99BW+6.25Ht-4.92Age-161
Miffin (FFM)	All subjects	REE=19.7FFM+413
WHO	18-30(yr)	
	Male	REE=15.4BW-27Ht+717
	Female	REE=13.3BW+334Ht+35
	30-60(yr)	
	Male	REE=11.3BW-16Ht+901
	Female	REE=8.7BW-25Ht+865
Owen	Male	REE=10.2BW+879
	Female	REE=7.18BW+795
Owen (FFM)	Male	REE=22.3FFM+290
	Female	REE=19.7FFM+334
Schofield*	18-30(yr)	
	Male	REE=63BW-42Ht+2953
	Female	REE=48BW-11Ht+3670
	30-60(yr)	
	Male	REE=62BW+1148Ht+411
	Female	REE=34BW+6Ht+3530
Cunningham (FFM)	All subjects	REE=21.6FFM+370
The new FFM-based REE equation	All subjects	REE=550.62 +16.62 FFM

FFM: Fat free mass, BW: Body Weight (kg), Ht: Height (m), Age:year (y)
*Equation for values in MJ/day, 1MJ=238.9kcal

Table2:Patient characteristics

	All (n=28)	**Male (n=22)**	**Female (n=6)**	**p value**
Age (y)	30 (22.5, 44.75)	32 (24.75, 46.0)	23 (18.75, 34.75)	n.s
Height (m)	1.46(1.37, 1.55)	1.46(1.39, 1.56)	1.45(1.39, 1.56)	n.s
Body Weight (kg)	30.6(25.25, 37.225)	25.25(22.65, 28.4)	32.1(27.5, 38.15)	n.s
Body Mass Index (kg/m2)	15.48(12.335, 17.793)	15.57(13.2775, 17.8775)	13.125(10.375, 16.925)	n.s
Controlling nutritional status	1(1, 2)	1(1, 2)	1(0.75, 2.5)	n.s
0-1 (n)	16	12	4	
2 (n)	7	6	1	n.s
3~4 (n)	5	4	1	
Prognostic nutritional index	48.46(44.44, 52.94)	48.32(44.70, 53.94)	49.52(44.24, 52.41)	n.s
>/=50 (n)	11	8	3	
41</=PNI<50 (n)	17	14	3	n.s
<40 (n)	0	0	0	
FFM (kg)	22.0(19.6, 26.8)	24.4(20.37, 27.25)	18.8(15.05, 23.4)	n.s
FM (kg)	5.75(2.6, 12.25)	5.9(2.75, 13.1)	4.8(2.3, 12)	n.s
Phase Angle (˚)	3.852(2.756, 4.48)	3.673(2.785, 4.47)	4.260(2.482, 5.028)	n.s
REE (kcal/d)	950(712.75, 1102.75)	1053.5(828.5 1105)	713.5(663, 888.75)	n.s
RQ	0.885(0.835, 0.92)	0.885(0.845, 0.9225)	0.875(0.7775, 0.9125)	n.s

FFM: Fat free mass, FM: Fat mass, REE: Rest energy expanditure, RQ:Respratry quotient

Table3: Agreement between measured and predicted REE

	REE (kcal/d)	R	Difference (measured-estimated: mean)	r (p value)
Measured	950.0 (712.75, 1102.75)			
HBE	971.9 (838.7, 1044.6)	-0.04	-41.598	0.6846 (0.0003)
WHO	1193.6 (1011.9, 1279.7)***	0.3892*	-202.679	0.49119 (<0.0001)
Miffin	1031.9 (898.3, 113.1)*	0.3780*	91.0368	0.42921 (0.0377)
Miffin (FFM)	846.4 (805.5, 941.0)	0.5129**	61.778	0.5021 (0.0932)
Owen	1186.0 (1085.6, 1258.7)***	0.3825*	-225.536	0.42576 (<0.0001)
Owen (FFM)	773.9 (734.3, 887.6)**	0.5062**	123.97	0.5026 (0.0018)
Schofield	1194.4 (1045.5, 1280.9)***	0.3816*	-213.721	0.46761 (<0.0001)
Cunningham (FFM)	845.2 (792.3, 948.9)	0.4857**	-61.9843	0.4824 (0.0996)
FFM-based REE	916.3 (881.8, 996.0)	0.5144**	-2.219	0.50215 (0.7227)

R:Spearman`s correlation coefficient for Measured REE

r, correlation coefficient between the mean values of measured and estimated REE and difference between measured and estimated REE on Bland-Altman plot.

*p<0.05, **p<0.01, ***p<0.001 vs Measured at Mann-Whitney U test