Accuracy of predictive equations for evaluation of resting energy expenditure in Brazilian patients with type 2 diabetes.

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Research

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Abstract

Background Evaluation of the resting energy expenditure (REE) is essential to ensure an appropriate dietary prescription for patients with type 2 diabetes. The aim of this study was to evaluate the accuracy of predictive equations for REE estimation in patients with type 2 diabetes, considering indirect calorimetry (IC) as the reference method.

Methods A cross-sectional study was conducted in 62 patients (31 men and 31 women) with type 2 diabetes. Clinical and laboratory variables were evaluated, as well as body composition by electrical bioimpedance. The REE was measured by IC (QUARK RMR, Cosmed, Rome, Italy) and estimated by predictive equations. Data were analyzed using Bland–Altman plots, paired *t*-tests, and Pearson's correlation coefficients.

Results Patients in the sample had a mean age of 63.1 ± 5.2 years, median diabetes duration of 11 (1–36) years, and mean A1C of 7.6 ± 1.2%. Body composition analysis revealed a mean fat free mass of 35.2 ± 11.8 kg and fat mass of 29.1 ± 8.8 kg. There was wide variation in the accuracy of REE values predicted by equations when compared to those measured by IC. For women, the FAO/WHO/UNO equation provided the best REE prediction in comparison to measured REE (-1.8% difference). For men, the Oxford equation yielded values closest to those measured by IC (-1.3% difference).

Conclusions In this sample of the patients with type 2 diabetes, the best predictive equations to estimate REE were FAO/WHO/UNO and Oxford for women and men, respectively.

Introduction

Diabetes mellitus (DM) is a chronic disease that affects a significant proportion of the world population [1]. Type 2 diabetes is the most common form of DM, usually occurring in adulthood, and is associated with obesity in about 80% of cases [2]. The primary strategy for treating obese patients with type 2 diabetes is the loss of body mass through lifestyle changes [2], which has been associated with improvement in glycemic control [2]. Among these interventions, an appropriate dietary prescription with the goal of reducing body weight, taking into account each patient's daily energy needs, is essential [3]. The main component of energy requirements is the total energy expenditure (TEE); calculating the TEE requires knowledge of the resting energy expenditure (REE) [3].

The most accurate procedure for measuring REE is indirect calorimetry (IC), which is considered the reference method [3]. However, its use is limited, requires special training, and is not always available in clinical practice [3]. Thus, several predictive equations have been developed as alternative methods for REE estimation [4–14].

Variability in REE may depend on several factors, such as sex, ethnicity, age, physical activity, genetic factors, body composition, caloric intake, and the presence of diabetes or obesity [11]. Several studies have evaluated REE using predictive equations across different populations [16–18] and ethnicities [19–

26]. Studies considering sex have shown that REE is lower in women than in men [27–29]; one such study found that REE measured by IC was 23% higher in men [27]. These data contributed to a follow-up study conducted in obese men and women, which also demonstrated a significant difference (REE higher in men by approximately 335 kcal/day) [29].

In addition, the presence of diabetes is also associated with REE. Previous studies demonstrated that patients with diabetes and poor glycemic control had higher REE [9, 25, 26]. Data on the use of REE predictive equations in patients with type 2 diabetes have been described elsewhere [9, 10, 14, 21, 22, 24–26, 30–35]; however, data on Brazilian diabetic patients are still scarce [34, 35]. A cross-sectional study of obese Brazilian women with type 2 diabetes showed that some predictive equations underestimated REE by approximately − 2.6%, while others overestimated it by 10.6%, when compared with IC measurement [34]. A recent survey of Brazilian patients with type 2 diabetes of both sexes demonstrated wide variation in REE values evaluated by predictive equations. The FAO/WHO/UNO equation showed the best accuracy when compared to measured REE, but still underestimated it by -5.6% as compared to IC a difference of 100 kcal/day [35].

Considering that sex is an important variable in REE evaluation; that data in Brazilian patients with type 2 diabetes are insufficient; and that poor glycemic control has been associated with an increase in REE, evaluating the performance of predictive equations for REE in this population is essential to ensure that adequate dietary interventions are being prescribed for diabetic patients. Within this context, the aim of the present study was to evaluate the accuracy of the main predictive equations used in clinical practice for the calculation of REE in a sample of Brazilian patients with type 2 diabetes, stratified by sex, considering IC as the reference method.

Materials And Methods

Study design and patients

This cross-sectional study included 62 patients (31 men and 31 women) with type 2 diabetes. Type 2 diabetes was defined by age > 30 years at onset, no previous episode of ketoacidosis or documented ketonuria, and insulin treatment (when necessary) only 5 years after diagnosis. The inclusion criteria were not having received dietary counseling by a nutritionist in the preceding 6 months, age < 70 years, serum creatinine < 2 mg/dL, normal thyroid function tests, and absence of severe liver disease, decompensated heart failure, or any acute disease. The study protocol was approved by the Research Ethics Committee (Approval number: 15.0625), and all subjects provided written informed consent for participation.

2.2 Clinical evaluation

Blood pressure was measured with a digital sphygmomanometer (Blood Pressure Monitor, model HEM-705CP, Omron Healthcare Inc., Bannockburn, IL). Two measurements were obtained, 2 minutes apart, and the mean recorded for analysis. Patients were considered hypertensive in case of systolic blood pressure ≥ 140 mmHg on at least two occasions, history of hypertension, or current use of antihypertensive drugs.

The anthropometric parameters used to assess nutritional status were body mass (with participants barefoot and wearing lightweight clothing) and height, both measured with a calibrated anthropometric scale (Filizola®). The body mass index (BMI) was calculated as the body mass (in kg) divided by the height (in m) squared. Body composition analysis by electrical bioimpedance (InBody® 230, Seoul, South Korea) was performed for determination of fat mass (FM) and fat-free mass (FFM), both in kg.

Habitual physical activity was measured objectively by step counting with a pedometer (HJ-321, Omron Healthcare Inc.) and classified into five levels: sedentary (< 5000 steps/day), low active (5000–7499 steps/day), somewhat active (7500–9999 steps/day), active (≥ 10000–12499 steps/day) and highly active (≥ 12500 steps/day) [36]. Participants wore the pedometer for 7 days, attached to the waistband of their clothing during waking hours, except when bathing or swimming. Participants were encouraged not to alter their usual physical habits during the protocol.

Laboratory evaluation

Blood samples were obtained after a 12-hour fast. Plasma glucose level was determined by the glucose-peroxidase enzymatic colorimetric method (Bio Diagnóstica), HbA1C by high-performance liquid chromatography (Merck-Hitachi L-9100, Merck Diagnostica, Darmstadt, Germany; reference range, 4.8–6.0%), total cholesterol and triglycerides by enzymatic colorimetric methods (Merck; Boehringer Mannheim, Buenos Aires, Argentina), and high-density lipoprotein (HDL) by a homogeneous direct method (AutoAnalyzer, ADVIA 1650). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula (LDL cholesterol = total cholesterol – HDL cholesterol – triglycerides/5).

Resting energy expenditure measurement

Objective measurement of REE was performed by IC. The IC protocol consisted of 10 min of rest on a gurney in the supine position, followed by 30 min of collection of exhaled gases using the canopy dilution technique and a coupled collection device. An open-circuit calorimeter (QUARK RMR, Cosmed, Rome, Italy) was used to determine VO_2 (oxygen consumption) and VCO_2 (carbon dioxide production). To calibrate the equipment, the volume of the turbine flowmeter was first calibrated electronically by the system, followed by calibration of the collector plates using a known gas concentration. This process was repeated for each test to standardize measurement. The first 10 min of gas collection were excluded from the analysis; thus, VO_2 and VCO_2 (L/min) obtained during the final 20 min of each collection (mean value) were used for REE calculation. The equation proposed by Weir [37], which incorporates a correction factor and thus obviates the need to consider protein metabolism, was used to obtain values in kcal/min: $[(3.9 \times VO_2) + (1.1 \times VCO_2)]$. The result in kcal/min was multiplied by 1,440 min to obtain the 24-hour REE. Subjects were asked to refrain from all moderate- or high-intensity physical activity during the 24 h preceding the test, and not to consume alcohol or caffeine. Smokers were instructed not to consume any tobacco products for at least 12 h before the day of REE measurement. Additionally, the subjects were instructed to fast for 12 h prior to the test (water freely allowed) and to have a good night's sleep (at least 8 hours). Finally, all subjects either drove or were driven to the test site to avoid any energy expenditure before determination of REE. All tests were performed between 06:30 and 08:00, in a temperature-

controlled (23 °C) and sound-controlled room, under low luminosity. All participants continued to take their usual medications during the study period; those who had morning doses to take received them after IC.

Selection of equations for estimating resting energy expenditure

The REE was estimated by eleven predictive equations, which were selected after a search of previous publications on the theme [4–14]. To be included, the equations had to have been developed for adult men and women and should be based on body weight, height, age, sex, and/or FM. Equations derived only for specific ethnic groups or for individuals with BMI ≥ 40 kg/m² were not included (**Supplement 1**).

Statistical analysis

Sample size calculation was based on a study wherein the variability of REE in relation to glycemic control, weight, age, and sex—particularly in male patients—demonstrated a multiple correlation coefficient of 0.9 [25]. Considering a study power of 80%, alpha error of 5%, and 20% attrition rate, 62 patients would be required.

REE was estimated by eleven commonly used predictive equations, according to sex and age: Harris-Benedict [4], Bernstein [5], Schofield [6], FAO/WHO/UNO [7], Mifflin-St. Jeor [8], Gougeon [9], Huang [10], Martin [11], Dietary Reference Intakes (DRIs) proposed by Institute Of Medicine [12], Oxford [13] and Ikeda [14]. The Shapiro-Wilk normality test was used to determine the distribution of the variables. The bias was calculated by subtracting the measured REE from the estimated REE. For each predictive equation, the percentage of deviation of estimated REE from measured REE was calculated as [(estimated REE − measured REE) / measured REE] × 100.

The means of estimated REE and measured REE were compared by a paired Student's t-test. Agreement between estimated and measured REE was examined graphically by plotting the differences between the predicted and the measured REE against their mean values, with 95% limits of agreement (mean difference ± 1.96 standard deviation) [38]. Pearson's correlation coefficients were used to assess the correlation between estimated and measured REE. Results are expressed as means and standard deviations or medians and interquartile ranges. Data were analyzed using SPSS version 23.0, while Bland–Altman plot values were analyzed in R version 3.3.3 (R Project for Statistical Computing, Vienna, Austria). A p value of < 0.05 was considered significant.

Results

A total of 62 patients with type 2 diabetes were included in the study (80.6% white; mean age, 63.1 ± 5.2 years; median disease duration, 11 [1–36] years; mean BMI, 30.1 ± 4.0 kg/m²). A flow diagram of patient selection is shown in Fig. 1. Men had greater body mass (89.9 ± 13.8 *vs.* 74.2 ± 11; p < 0.001) and FFM (38.6 ± 12.1 *vs.* 31.7 ± 10.7; p = 0.009) when compared to women. Regarding physical activity, the median number of steps/weeks was 5522 (1496–18097), thus classifying the majority of participants as less

active. All participants (100%) had hypertension. Most had a lipid profile within normal limits; however, fasting blood glucose and A1c levels were abnormal, as expected in a sample of patients with diabetes. All were on oral antihyperglycemic agents (100%) and antihypertensive agents (100%), while 67.7% (n = 42) also took lipid-lowering agents. The profile of the sample is described in Table 1.

Table 1
Sample profile.

Variable	Overall (n = 62)	Men (n = 31)	Women (n = 31)	*P*-value
Age (years)	63.1 ± 5.2	63.5 ± 5.5	62.6 ± 4.9	0.473[a]
Duration of diabetes (years)	11 (1–36)	12 (1–36)	10 (2–30)	0.493[b]
Ethnicity (white)	50 (80.6%)	28 (90.3%)	22 (71%)	0.307[a]
Weight (kg)	82.1 ± 14.8	89.9 ± 13.8	74.2 ± 11.2	**< 0.001**[a]
Height (cm)	164.8 ± 10.3	172.4 ± 7.6	157.2 ± 6.2	**< 0.001**[a]
BMI (kg/m²)	30.1 ± 4.0	30.3 ± 3.8	30.0 ± 4.2	0.736[a]
Fat-free mass (kg)	35.2 ± 11.8	38.6 ± 12.1	31.7 ± 10.7	**0.009**[a]
Fat mass (Kg)	29.1 ± 8.8	27.9 ± 9.3	30.3 ± 8.3	0.278[a]
Physical activity (steps/week)	5522 (1496–18097)	5190 (1496–18097)	6011(1941–14316)	0.288[a]
Hypertension	62 (100%)	31 (100%)	31 (100%)	—
Fasting plasma glucose (mg/dL)	153.3 ± 46.2	162.9 ± 45.5	143.8 ± 45.6	0.105[a]
A1C (%)	7.6 (5.2–12.0)	7.9 (5.9–12.0)	7.2 (5.2–9.2)	0.126[b]
Total cholesterol (mg/dL)	162.5 ± 40.3	158.0 ± 44.4	171.1 ± 33.7	0.197[b]
HDL cholesterol (mg/dL)	44.7 ± 13.8	39.8 ± 8.7	52.7 ± 13.8	**< 0.001**[b]
Triglycerides (mg/dL)	172 (49–681)	183 (49–681)	157 (68–342)	0.789[b]

BMI, body mass index; A1C, glycated hemoglobin; HDL, high-density lipoprotein.

Data presented as median (interquartile range), n (%), or mean ± standard deviation.

[a] Student's *t*-test; [b] Mann–Whitney *U* test; [c] Chi-square test.

— Chi-square test impossible because 100% of the sample is hypertensive, on hypoglycemic agents, and on antihypertensive agents.

Variable	Overall (n = 62)	Men (n = 31)	Women (n = 31)	*P*-value
Medications	62 (100%)	31 (100%)	31 (100%)	—
Oral antihyperglycemic agents	62 (100%)	31 (100%)	31 (100%)	—
Antihypertensive agents	42 (67.7%)	22 (71%)	20 (64.5%)	0.587[c]
Hypolipidemic agents				

BMI, body mass index; A1C, glycated hemoglobin; HDL, high-density lipoprotein.

Data presented as median (interquartile range), n (%), or mean ± standard deviation.

[a] Student's *t*-test; [b] Mann–Whitney *U* test; [c] Chi-square test.

— Chi-square test impossible because 100% of the sample is hypertensive, on hypoglycemic agents, and on antihypertensive agents.

Table 2 shows the mean and standard deviation of REE as measured by IC and estimated by the predictive equations, bias (percent deviation), and 95% limits of agreement. All variables were normally distributed according to the Shapiro-Wilk test (data not shown). The mean REE measured by IC in men and women was 1815.7 ± 262.3 kcal/day and 1473.4 ± 258.5 kcal/day respectively ($p < 0.001$). In all patients, only the Bernstein equation showed no statistically significant difference in relation to REE measured by IC. When stratified by sex, in men, the Harris-Benedict, FAO/WHO/UNO, and Oxford equations did not yield results significantly different from REE measured directly by IC. In women, only the FAO/WHO/UNO equation did not differ significantly from REE as measured by IC.

Table 2
Evaluation of measured and estimated REE in patients with type 2 diabetes.

	All (n = 62)				**Men (n = 31)**				**Women (n = 31)**			
	Mean	SD	95% limits of agreement[1]	*P*-value*	Mean	SD	95% limits of agreement[1]	*P*-value*	Mean	SD	95% limits of agreement[1]	*P*-value*
Measured REE by IC (kcal/day)	1644.6	310.6			1815.7	262.3			1473.4	258.5		

REE, resting energy expenditure; IC, indirect calorimetry; SD, standard deviation.

* Paired Student's *t*-test to compare estimated and measured REE

[1] (mean difference ± 1.96 SD of the difference)

[2] (estimated − measured) (kcal in 24 h).

[3] (difference/measured) × 100 (%).

	All (n = 62)				Men (n = 31)				Women (n = 31)			
Estimated REE (kcal/day)	1546.9	262.5	(-153.4;-41.94)	**0.001**	1734.4	231.8	(-167.8; 5.3)	0.065	1359.3	117.1	(-189.0; -39.2)	**0.004**
	-97.7				-81.3				-114.1			
	-3.5				-1.9				-3.1			
Harris-Benedict [4]												
Bias[2] (kcal/day)												
Percent deviation[3]												
Bernstein[5]	1660.1	498.9	(-105.3; 136.3)	0.799	2045.1	438.2	(22.1; 436.6)	**0.031**	1275.0	88.1	(-277.5;-119.3)	**< 0.001**
	15.5				229.4				-198.4			
Bias[2] (kcal/day)	0.2				2.2				-5.1			
Percent deviation[3]												

REE, resting energy expenditure; IC, indirect calorimetry; SD, standard deviation.

* Paired Student's *t*-test to compare estimated and measured REE

[1] (mean difference ± 1.96 SD of the difference)

[2] (estimated – measured) (kcal in 24 h).

[3] (difference/measured) × 100 (%).

	All (n = 62)				Men (n = 31)				Women (n = 31)			
Schofield [6]	1478.5	296.7	(-223.6;-108.5)	**< 0.001**	1700.1	225.9	(-203.2;-27.9)	**0.011**	1256.8	162.6	(-291.7;141.5)	**< 0.001**
Bias[2] (kcal/day)	-166.1				-115.6				-216.6			
Percent deviation[3]	-5.7				-2.6				-5.8			
FAO/WHO/UNO [7]	1603.2	257.3	(-122.6;-13.0)	**0.016**	1745.6	227.7	(-156.6;16.3)	0.108	1407.8	119.3	(-137.9;6.7)	0.074
Bias[2] (kcal/day)	-41.4				-70.1				-65.6			
Percent deviation[3]	-2.4				-1.6				-1.8			

REE, resting energy expenditure; IC, indirect calorimetry; SD, standard deviation.

* Paired Student's *t*-test to compare estimated and measured REE

[1] (mean difference ± 1.96 SD of the difference)

[2] (estimated – measured) (kcal in 24 h).

[3] (difference/measured) × 100 (%).

	All (n = 62)				Men (n = 31)				Women (n = 31)			
Mifflin–St.Jeor [8]	1454.9 -189.7	264.4	(-243.7;-135.6)	**< 0.001**	1663.5 -152.2	181.7	(-235.3;-69.0)	**0.001**	1246.3 -227.1	138.7	(-298.5;155.7)	**< 0.001**
Bias [2] (kcal/day)	-7.0				-3.7				-6.4			
Percent deviation [3]												
Gougeon et al. [9]	1547.1 -97.5	248.0	(-156.5;-38.3)	**0.002**	1715.4 -100.3	196.5	(-188.8;-11.7)	**0.028**	1378.8 -94.6	167.2	(-178.1;-11.1)	**0.028**
Bias [2] (kcal/day)	-3.2				-2.3				-2.3			
Percent deviation [3]												

REE, resting energy expenditure; IC, indirect calorimetry; SD, standard deviation.

* Paired Student's *t*-test to compare estimated and measured REE

[1] (mean difference ± 1.96 SD of the difference)

[2] (estimated − measured) (kcal in 24 h).

[3] (difference/measured) × 100 (%).

	All (n = 62)				Men (n = 31)				Women (n = 31)			
Huang et al. [10]	2052.6	369.8	(337.6; 478.4)	**< 0.001**	2248.5	345.0	(324.6; 541.0)	**< 0.001**	1856.7	282.4	(287.5; 478.9)	**< 0.001**
Bias[2] (kcal/day)	408				432.8				383.3			
Percent deviation[3]	11.5				8.1				8.1			
Martin et al. [11]	1330.6	236.7	(-382.6; -245.2)	**< 0.001**	1428.2	228.0	(-491.9; -283.0)	**< 0.001**	1233	205.6	(-327.4;-153.3)	**< 0.001**
Bias[2] (kcal/day)	-314				-387.5				-240.4			
Percent deviation[3]	-9.1				-7.5				-5.6			

REE, resting energy expenditure; IC, indirect calorimetry; SD, standard deviation.

* Paired Student's *t*-test to compare estimated and measured REE

[1] (mean difference ± 1.96 SD of the difference)

[2] (estimated − measured) (kcal in 24 h).

[3] (difference/measured) × 100 (%).

	All (n = 62)				Men (n = 31)				Women (n = 31)			
Dietary Reference Intakes [12]	2086.8 442.2 13.3	372.5	(375.9; 508.4)	**< 0.001**	2395.4 579.7 14.0	228.0	(495.3; 664.0)	**< 0.001**	1778.1 304.7 7.8	186.7	(-225.6; 383.7)	**< 0.001**
Bias[2] (kcal/day)												
Percent deviation[3]												
Oxford [13]	1556.1 -88.5 -3.2	271.6	(-143.3; -33.6)	**0.002**	1761.7 -54 -1.3	218.9	(-138.4; 30.3)	0.201	1350.4 -123 -3.4	121.3	(-195.8;-50.1)	**0.002**
Bias[2] (kcal/day)												
Percent deviation[3]												

REE, resting energy expenditure; IC, indirect calorimetry; SD, standard deviation.

* Paired Student's *t*-test to compare estimated and measured REE

[1] (mean difference ± 1.96 SD of the difference)

[2] (estimated – measured) (kcal in 24 h).

[3] (difference/measured) × 100 (%).

	All (n = 62)				Men (n = 31)				Women (n = 31)			
Ikeda et al. [14]	1381.7 -262.9	151.8	(-321.9; -203.7)	**< 0.001**	1458.6 -357.1	147.6	(-436.1; -278.0)	**< 0.001**	1304.8 -168.6	113.4	(-246.7;-90.5)	**< 0.001**
Bias[2] (kcal/day)	-8.8				-9.2				-4.4			
Percent deviation[3]												

REE, resting energy expenditure; IC, indirect calorimetry; SD, standard deviation.

* Paired Student's *t*-test to compare estimated and measured REE

[1] (mean difference ± 1.96 SD of the difference)

[2] (estimated − measured) (kcal in 24 h).

[3] (difference/measured) × 100 (%).

According to percent variation, the predictive equations that most underestimated REE as compared to IC was that of Ikeda in men (-9.2%) and Mifflin St-Jeor in women (-6.4%). The equation proposed by Bernstein underestimated the measured REE in men (-5.1%) and overestimated it in women (2.2%). The equations that presented the best accuracy were Oxford for men (-1.3%) and FAO/WHO/UNO for women (-1.8%), with a precision of 54 kcal and 65.6 kcal/day, respectively.

Figure 2 shows the differences in mean REE measured by IC and that estimated by the predictive equations. The Bland–Altman plots suggest poor correlation between measured and estimated REE, with broad concordance limits. The lower and upper limits are always higher in men, indicating that REE variation is greater in this group. Positive, significant correlations were observed in both sexes between IC-measured REE and with most of the predictive equations. In men, only Bernstein's proposed equation showed no correlation with IC-measured REE measured by IC. Correlation analysis also showed a significant association ($p < 0.001$) between dependent and independent variables in both sexes. In women, REE correlated positively with weight ($r = 0.538$), height ($r = 0.516$), and FFM ($r = 0.492$). In men, REE correlated with weight ($r = 0.557$), BMI ($r = 0.545$), and FM ($r = 0.482$). We did not observe significant correlations between REE and glycemic control in this group of patients.

Discussion

Few studies have compared REE values measured by IC versus those estimated by predictive equations in Brazilian patients with type 2 diabetes [34, 35]. The REE values predicted by the Oxford and FAO/WHO/UNO et al equations, in men and women respectively, were those closest to IC-measured REE in our sample. Our results are consistent with those of a previous study conducted in Brazilians with type 2 diabetes, in which the FAO/WHO/UNO equation had the best performance for REE prediction, underestimating it by -5.6% as compared to IC [35]. In healthy Chilean individuals of both sexes, the Oxford equation also seems to be the best alternative for calculation of REE [39].

In our study, most predictive equations underestimated REE when compared to the reference criteria (-9.1 to -2.4% difference). In addition, we found a wide difference between measured and estimated REE, since the equations cannot estimate values with the same consistency and magnitude as IC. Similar discrepancies were also observed in other studies of patients with type 2 diabetes [34, 35].

Sex is a factor that has been associated with REE [27–29]. When comparing the FAO/WHO/UNO equation in men and women, we found that it underestimated REE in both (-1.6% vs. -1.8%, respectively). Conversely, in a study of French patients with type 2 diabetes, this equation overestimated REE in both sexes [30]. In another study of Brazilian women with type 2 diabetes, the equation also overestimated REE when compared to IC [34].

The Harris-Benedict equation is that most used in clinical practice to determine energy requirements [4]. However, studies have shown that it may not be appropriate to estimate REE in both sexes [40, 41]. In men and women without diabetes, the equation overestimated REE by 9% [40] and 14% [41], respectively. In our sample of individuals with diabetes, however, this equation underestimated REE in both men and women (-1.9% vs. -3.1%, respectively). These findings are consistent with those of other studies which evaluated the accuracy of this equation in patients with type 2 diabetes [10, 31, 35].

The American Dietetic Association (now the American Academy of Nutrition and Dietetics) previously recommended use of the Mifflin-St. Jeor equation to estimate REE in overweight and obese individuals [42]. However, in our study, this equation was the one that most underestimated REE in men and women, with a difference of 152 kcal and 227 kcal/day, respectively. Similarly, the Schofield equation underestimated REE in both sexes (-2.6% vs. -5.8%), while the Bernstein equation underestimated REE only in females (-5.1%). These findings suggest that energy restriction calculations based on these equations may be insufficient to facilitate glycemic control and weight loss or maintenance in this population.

Most of the equations evaluated in this study were originally developed in healthy, eutrophic populations [4, 6–8, 10]. Thus, the differences we observed may have been due to the presence of obese patients (BMI > 30 kg/m²) in our sample, as well as to the fact that, in individuals with diabetes, insulin resistance is associated with abnormal metabolic reactions [43]. In fact, the presence of diabetes per se influences REE [9, 10, 14, 26, 33]. Studies conducted in Japan have shown that obese individuals with type 2

diabetes have a higher REE than their obese counterparts without type 2 diabetes, and that fasting blood glucose levels can be one of the main determinants of this increase [14, 26]. More recently, a study also performed in Japanese patients with type 2 diabetes showed that REE correlated significantly with plasma glucose and HbA1c [33]. The reasons for this phenomenon are not yet well established, but factors such as increased gluconeogenesis [9], increased protein turnover [44], increased glycosuria [9], and elevated levels of glucagon [45] may all influence REE in patients with diabetes.

In 2002, Gougeon et al evaluated the REE of women with type 2 diabetes and proposed an equation for predicting REE that included plasma glucose, HbA1c, and FM as independent variables [9]. As already noted, studies have shown that the presence of diabetes is an important variable that must be considered when evaluating REE [9, 25, 26]. In our study, however, these variables did not correlate significantly with REE in patients of either sex. Moreover, the equation proposed by Gougeon et al underestimated REE by 2.3% in both sexes. Other equations developed in patients with diabetes were also evaluated in our study. The equation by Huang et al. [10] overestimated REE with an 8.1% bias in both sexes. Martins et al. underestimated by -7.5% in men and – 5.6% in women [11]. Different results were found in a study with Brazilian women with type 2 diabetes, in which the Gougeon equation overestimated REE by 2.8% and Hugan et al. equation underestimated by 11.2% [34].

The results of our study indicate that the DRIs equations to predict REE do not have an acceptable level of precision when applied to Brazilian patients with type 2 diabetes. In our study, these equations estimated higher REE values when compared to the values measured by IC, overestimating in men and women by 14.0% and 7.8% respectively. In a recent study carried out with the elderly, this equation had a bias of -7.2% in men and – 6.6% in women [46]. Other study she was reported as accurate to estimate REE in men and women [47, 48].

The mean REE in the sample as a whole, measured objectively by IC, was 1644.6 ± 310 kcal/day. We found that men with type 2 diabetes had a higher REE (≅ 324 kcal/day) when compared to women. This corroborates previous studies conducted in obese individuals, which also demonstrated a higher REE in men [27–29]. It is well established that body composition differs significantly between men and women [49], and the variability in REE found between the sexes is probably because men have greater overall body mass and FFM than women. In our sample, we found significant correlations ($p < 0.001$) of REE with FM and FFM. REE correlated, albeit weakly, with FM in men (0.482) and with FFM in women (0.492). Studies have shown that including body composition (FM and/or FFM) in REE predictive equations does not improve their accuracy [32]. This is a relevant finding, because equations based on anthropometric parameters (weight and height) are more viable in clinical practice than equations based on body composition.

Our study had some limitations. Seasonality may influence REE, and our protocol was carried out over a 1-year period, thus including all seasons. However, we standardized the temperature and humidity of the environment where IC was performed so as to mitigate any seasonal influence on REE. Patients' use of antidiabetic agents may have been a limitation, as these medications are known to induce metabolic

alterations in individuals with type 2 diabetes. This effect was minimized by instructing the patients to take their first dose of the day only after REE measurement had been performed. On the other hand, this is the first study performed in Brazilian patients with type 2 diabetes to include sex stratification. According this, in the absence of IC, we suggest for clinical practice the use of the Oxford equations (≅ 54 kcal/day) and FAO/WHO/UNO (≅ 65.6 kcal/day), for men and women, respectively.

Conclusions

Our findings suggest there is wide variability in the accuracy of predictive equations for REE. We recommend that, in Brazilian patients with type 2 diabetes, the Oxford equation (for men) and the FAO/WHO/UNO equation (for women) are the best options to estimate REE in clinical practice when IC is unavailable or otherwise infeasible.

Abbreviations

DM - Diabetes mellitus

TEE – Total Energy Expenditure

REE - Resting Energy Expenditure

IC - Indirect Calorimetry

VO_2 - Oxygen Consumption

VCO_2 - Carbon Dioxide Production

References

1. World Health Organization. Global Report on Diabetes. Geneva: World Health Organization; 2016. pp. 1–88.
2. American Diabetes Association (ADA). Standards of medical care in diabetes: lifestyle management. Diabetes Care. 2020;48(Suppl 1):38–65.
3. Compher C, Frankenfield D, Keim N, Roth-Yousey L. Best practice methods to apply to measurement of resting metabolic rate in adults: a systematic review. J Am Diet Assoc. 2006;106:881–903. doi:10.1016/j.jada.2006.02.009.
4. Harris J, Benedict FG. A biometric study of human basal metabolism. *Proc Natl Acad Sci* USA. 1918;4(12):370–3. doi:10.1073/pnas.4.12.370.
5. Bernstein RS, Thornton JC, Yang MU, Wang J, Redmond AM, Pierson RN Jr, et al. Prediction of the resting metabolic rate in obese patients. Am J Clin Nutr. 1983;37(4):595–602. doi:10.1093/ajcn/37.4.595.

6. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr. 1985;39(1):5–41.
7. FAO. Energy and protein requirements: Report of a joint FAO/ WHO/UNO expert consultation. Geneva: World Health Organization; 1985.
8. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr. 1990;51(2):241–7. doi:10.1093/ajcn/51.2.241.
9. Gougeon R, Lamarche M, Yale JF, Venuta T. The prediction of resting energy expenditure in type 2 diabetes mellitus is improved by factoring for glycemia. Int J Obes Relat Metab Disord. 2002;26(12):1547–52. doi:10.1038/sj.ijo.0802178.
10. Huang KC, Kornas N, Steinbeck K, Loughnan G, Caterson ID. Resting metabolic rate in severely obese diabetic and nondiabetic subjects. Obes Res. 2004;12(5):840–5. doi:10.1038/oby.2004.101.
11. Martin K, Wallace P, Rust PF, Garvey WT. Estimation of resting energy expenditure considering effects of race and diabetes status. Diabetes Care. 2004;27(6):1405–11. doi:10.2337/diacare.27.6.1405.
12. Institute of Medicine. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington (DC): National Academy Press; 2005.
13. Cole TJ, Henry CJ. The Oxford Brookes basal metabolic rate database-a reanalysis. Public Health Nutr. 2005;8(7A):1202–12. doi:10.1079/phn2005806.
14. Ikeda K, Fujimoto S, Goto M, Yamada C, Hamasaki A, Ida M, et al. A new equation to estimate basal energy expenditure of patients with diabetes. Clin Nutr. 2013;32(5):777–82. doi:10.1016/j.clnu.2012.11.017.
15. Hagedorn T, Poggiogalle E, Savina C, Coletti C, Paolini M, Scavone L, et al. Indirect calorimetry in obese female subjects: Factors influencing the resting metabolic rate. World J Exp Med June. 2012;20(20):2(3):58–64. doi:10.5493/wjem.v2.i3.58.
16. Krüger RL, Lopes AL, Gross JS, Macedo RC, Teixeira BC, Oliveira AR. Validation of predictive equations for basal metabolic rate in eutrophic and obese subjects. Rev Bras Cineantropom Desempenho Hum. 2015;17(1):73–81. doi:10.5007/1980-0037.2015v17n1p73.
17. Poli VFS, Sanches RB, Moraes AS, Fidalgo JPN, Nascimento MA, Andrade-Silva SG, et al. Resting energy expenditure in obese women: comparison between measured and estimated values. Br J Nutr. 2016;116(7):1306–13. doi:10.1017/S0007114516003172.
18. Ruiz JR, Ortega FB, Rodríguez G, Alkorta P, Labayen I. Validity of resting energy expenditure predictive equations before and after an energy-restricted diet intervention in obese women. PLosOne. 2011;6(9):e23759. doi:10.1371/journal.pone.0023759.
19. Weijs PJM. Validity of predictive equations for resting energy expenditure in US and Dutch overweight and obese class I and II adults aged 18–65 y. Am J Clin Nutr. 2010;88(4):959–70. doi:10.1093/ajcn/88.4.959.
20. Weijs PJM, Vansant GA. Validity of predictive equations for resting energy expenditure in Belgian normal weight to morbid obese women. Clin Nutr. 2010;29(3):347–51.

doi:10.1016/j.clnu.2009.09.009.

21. Fontvieille AM, Lillioja S, Ferraro RT, Schulz LO, Rising R, Ravussin E. Twenty-four-hour energy expenditure in Pima Indians with type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia. 1992;35(8):753–9. doi:10.1007/bf00429096.
22. Bitz C, Toubro S, Larsen TM, et al. Increased 24-h energy expenditure in type 2 diabetes. Diabetes Care. 2004;27(10):2416–21. doi:10.2337/diacare.27.10.2416.
23. Liu HY, Lu YF, Chen WJ. Predictive equations for basal metabolic rate in Chinese adults: a cross-validation study. J Am Diet Assoc. 1995;95(12):1403–8. doi:10.1016/S0002-8223(95)00369-X.
24. Miyake R, Tanaka S, Ohkawara K, Ishikawa-Takata K, Hikihara Y, Taguri E, et al. Validity of predictive equations for basal metabolic rate in Japanese adults. J Nutr Sci Vitaminol. 2011;57(3):224–32. doi:10.3177/jnsv.57.224.
25. Ikeda K, Fujimoto S, Goto M, Yamada C, Hamasaki A, Shide K, et al. Impact of endogenous and exogenous insulin on basal energy expenditure in patients with type 2 diabetes under standard treatment. Am J Clin Nutr. 2011;94(6):1513–8. doi:10.3945/ajcn.111.017889.
26. Miyake R, Ohkawara K, Ishikawa-Takata K, Morita A, Watanabe S, Tanaka S. Obese Japanese adults with type 2 diabetes have higher basal metabolic rates than non-diabetic adults. J Nutr Sci Vitaminol. 2011;57(5):348–54. doi:10.3177/jnsv.57.348.
27. Arciero PJ, Goran MI, Poehlman ET. Resting metabolic rate is lower in women than in men. J Appl Physiol. 1993;75(6):2514–20. doi:10.1152/jappl.1993.75.6.2514.
28. de Luis DA, Aller R, Izaola O, Romero E. Prediction equation of resting energy expenditure in an adult Spanish population of obese adult population. Ann NutrMetab. 2006;50(3):193–6. doi:10.1159/000090740.
29. Paul DR, Novotny JA, Rumpler WV. Effects of the interaction of sex and food intake on the relation between energy expenditure and body composition. Am J Clin Nutr. 2004;79(3):385–9. doi:10.1093/ajcn/79.3.385.
30. Ryan M, Sallé A, Guilloteau G, Genaitay M, Livingstone MB, Ritz P. Resting energy expenditure is not increased in mildyhyperglycaemic obese diabetic patients. Br J Nutr. 2006;96(5):945–8. doi:10.1017/bjn20061744.
31. Rigalleau V, Lasseur C, Pécheur S, Chauveau P, Combe C, Perlemoine C, et al. Resting energy expenditure in uremic, diabetic and uremic diabetic subjects. J Diabetes Complications. 2004;18(4):237–41. doi:10.1016/S1056-8727(03)00077-1.
32. Sun MX, Zhao S, Mao H, Wang ZJ, Zhang XY, Yi L. Increased BMR in Overweight and Obese Patients with Type 2 Diabetes may Result from an Increased Fat-free Mass. J Huazhong Univ Sci TechnolMed Sci. 2016;36(1):59–63. doi:10.1007/s11596-016-1542-6.
33. Tabata S, Kinodhita N, Yamada S, Matsumoto H. Accuracy of basal metabolic rate estimated by predictive equations in Japanese with type 2 diabetes. Asia Pac J Clin Nutr. 2018;27(4):763–9. doi:10.6133/apjcn.102017.05.

34. de Figueiredo Ferreira M, Detrano F, Coelho GM, Barros ME, Serrão Lanzillotti R, Firmino Nogueira Neto J, et al. Body composition and basal metabolic rate in women with type 2 diabetes mellitus. J Nutr Metab. 2014;2014:574057. doi:10.1155/2014/574057.
35. Steemburgo T, Camila L, Farinha JB, Paula TP, Oliveira AR, Azevedo MJ. Basal metabolic rate in Brazilian patients with type 2 diabetes: comparison between measured and estimated values. Arch Endocrinol Metab. 2019;63(1):53–61. doi:10.20945/2359-3997000000103.
36. Tudor-Locke C, Hatano Y, Pangrazi RP, Kang M. Revisiting "how many steps are enough? Med Sci Sports Exerc. 2008;40(7):537-43. doi:10.1249/MSS.0b013e31817c7133.
37. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol. 1949;109(1–2):1–9. doi:10.1113/jphysiol.1949.sp004363.
38. Bland J, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986;327(8476):307–10.
39. Galgani JE, Castro-Sepulveda M, Pérez-Luco C, Fernández-Verdejo R. Validity of predicture equations for resting metabolic rate in healthy humans. Clin Sci. 2018;132(16):1741–51. doi:10.1042/CS20180317.
40. Owen OE, Kave E, Owen RS, Craig ES, Polansky M, Smalley KJ, et al. A reappraisal of caloric requirements in helth men. Am J Clin Nutr. 1987;46(6):875–85. doi:10.1093/ajcn/46.6.875.
41. Owen OE, Kave E, Owen RS, Polansky M, Caprio S, Mozzoli MA, et al. A reappraisal of caloric requirements in helth women. Am J Clin Nutr. 1986;44(1):1–19. doi:10.1093/ajcn/44.1.1.
42. Seagle HM, Strain GW, Makris A, Reeves RS. Position of the American Dietetic Association: Weight management. J Am Diet Assoc. 2009;109(2):330–46. doi:10.1016/j.jada.2008.11.041.
43. Weyer C, Bogardus C, Pratley RE. Metabolic factors contributing to increased resting metabolic rate and decreased insulin-induced thermogenesis during the development of type 2 diabetes. Diabetes. 1999;48(8):1607–14. doi:10.2337/diabetes.48.8.1607.
44. Consoli A, Nurjhan N, Capani F, Gerich J. Predominat role of gluconeogenesis in increased hepatic glucose prodution in NIDDM. Diabetes. 1989;38(5):550–57. doi:10.2337/diab.38.5.550.
45. Bursztein S, Elwyn DH, Askanazi J. Energy, Metabolism. Indirect Calorimetry and Nutrition. Baltimore: Willians e Wilkins; 1989. 266p.
46. Ndahimana D, Go NY, Ishika-Takata K, Park J, Kim EK. Validity of the dietary reference intakes for determining energy requirements in older adults. Nutr Res Pract. 2019;13(3):256–62. doi:10.4162/nrp.2019.13.3.256.
47. Kim EK, Kim JH, Kim MH, Ndahimana D, Yean SE, Yoon JS, et al. Validation of dietary reference intake equations for estimating energy requirements in Korean adults by using the doubly labeled water method. Nutr Res Pract. 2017;11(4):300–6. doi:10.4162/nrp.2017.11.4.300.
48. Tooze JA, Schoeller DA, Subar AF, Kipnis V, Schatzkin A, Troiano RP. Total daily energy expenditure among middle-aged men and women: the OPEN Study. Am J Clin Nutr. 2007;86:382–7. doi:10.1093/ajcn/86.2.382.

49. FAO/WHO/UNO. Report of Joint FAO/WHO/UNU Expert Consultation. Rome: Human Energy Requirements; 2004.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Research Ethics Committee of the Hospital de Clinicas de Porto Alegre #protocol number 1506.25, and all subjects provided written informed consent for participation.

Consent for publication

The manuscript has not been published (in full or in part) before and is not being considered for publication in any other journal while under consideration for Nutrition & Metabolism. The authors understand that, if accepted, this manuscript must not be published elsewhere in similar form, in any language, without the consent of this Journal.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contribution

TS and TG contributed to the conception and design of the research; TS, TG and TPP contributed to the design of the research; TG, MMF, FPB, and ARO contributed to the acquisition and analysis of the data; LVV and TS contributed to the interpretation of the data; TG and TS drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Figures

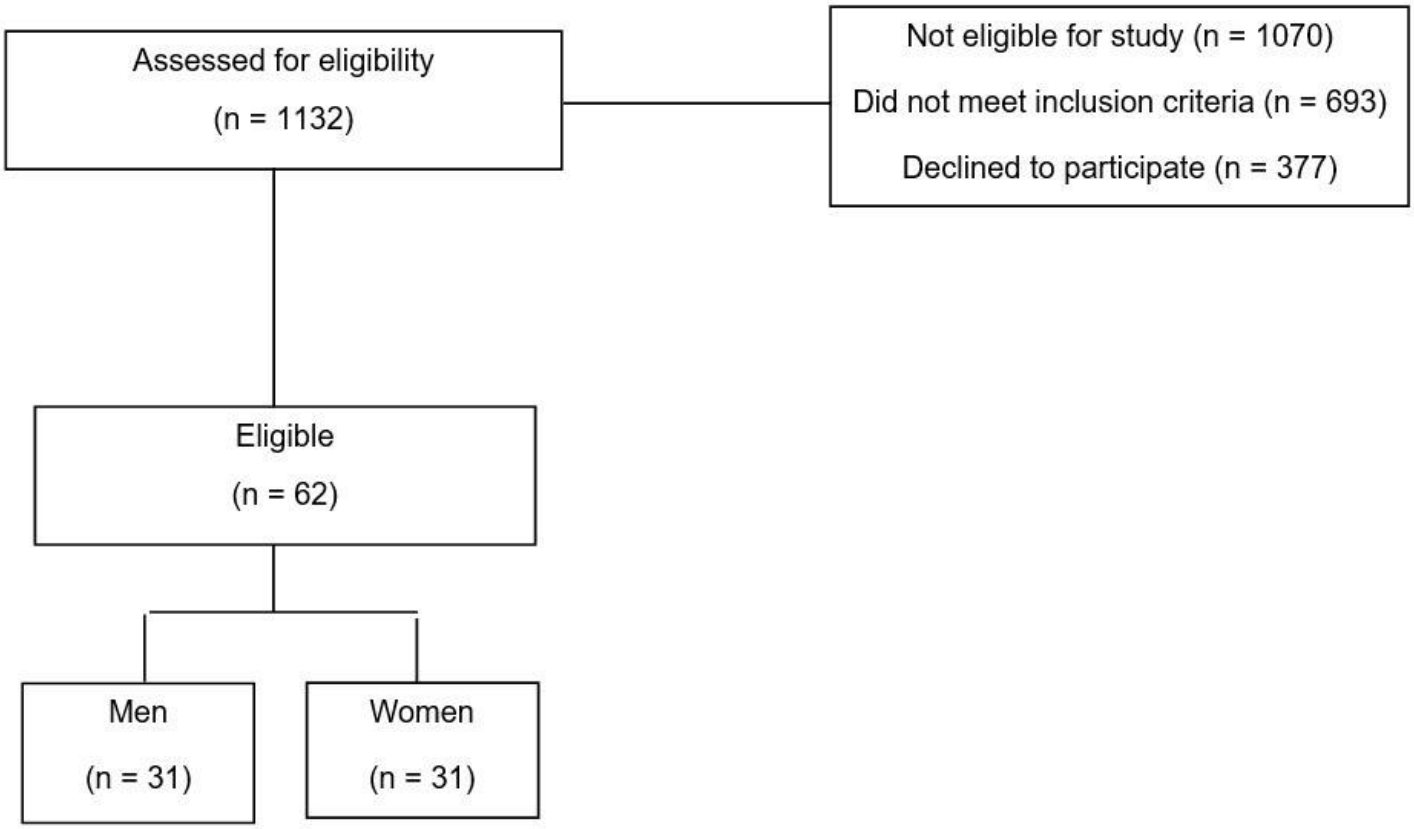

Figure 1

Flowchart of patient selection.

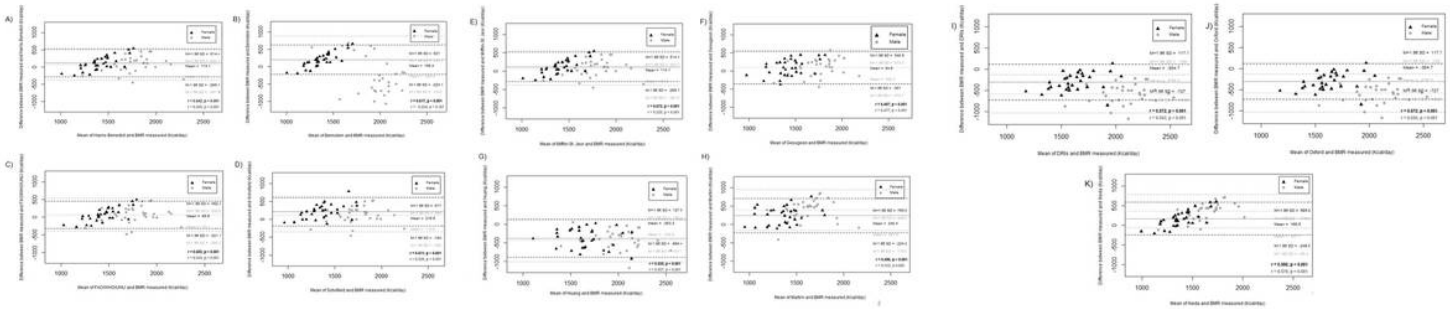

Figure 2

Bland–Altman plots comparing indirect calorimetry (IC) and the following predictive equations for resting energy expenditure (REE) in patients with type 2 diabetes: A) Harris-Benedict [4]; B) Bernstein [5]; C) FAO/WHO/UNO [6]; D) Schofield [7]; E) Mifflin–St.Jeor [8]; F) Gougeon et al [9]; G) Huang et al [10]; H) Martin et al [11]; I) Dietary Reference Intakes [12]; J) Oxford [13]; and K) Ikeda et al [14].

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