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Resting Metabolic rate in type 2 diabetes – accuracy of predictive equations

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RODICA DOROS[1,3*], DANIELA LIXANDRU[1,2], LAURA PETCU[1], JANETA TUDOSOIU[1], MANUELA MITU[1], ARIANA PICU[1], CONSTANTIN IONESCU-TÎRGOVISTE[1,2], CRISTIAN GUJA [1,2]

[1]National Institute of Diabetes, Nutrition and Metabolic Diseases prof. dr. N.C. Paulescu, 12 I.L. Caragiale Street, code 020045, Bucharest, Romania;
[2]University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania;
[3] National Institute of Research and Development for Food and Bioresourses IBA;
*Corresponding author Rodica Doros: phone: +40744517325; Fax : +40 212107806;
Email: rodica.doros@bioresusre.ro

Abstract

Estimation of resting metabolic rate (RMR) is the initial step for establishing caloric and nutritional needs in diabetes mellitus therapy. The aim of the present study was to assess the accuracy of RMR predictive equations in comparison with indirect calorimetry in a study group of 283 newly discovered type 2 diabetic patients. Five predictive equations were used: Harris Benedict, Owen, Mifflin, WHO/FAO/UNU (World Health Organization/ Food and Agriculture Organization / United Nations University) and Bernstein. The accuracy was estimated as the percentage of predicted RMR within ± 10%, 15% and 30% of measured RMR, the difference between predicted and measured RMR (bias) and the root mean squared prediction error (RMSE). For the entire study group, Mifflin equation had the highest accurate prediction (48.8% for ±10%, 65% for ±15% and 86.9% for ±30% of measured RMR) with the lowest bias (10.48 kcal/day) and lowest RMSE (298.3 kcal/day), followed by Harris Benedict, Owen and WHO/FAO/UNU equations with an accuracy between 43.5% and 46.3%, bias between 34.75 and 79.54 kcal/day and RMSE between 307.6 and 313.3kcal/day. After stratification by gender, body mass index and blood glucose value, Mifflin equation maintained the highest accuracy for subgroups with FPG<180mg/dl or/and HbA_{1c} <7.85.

Keywords: resting metabolic rate, type 2 diabetes, predictive equations

Abbreviations: RMR (resting metabolic rate); FPG (fasting plasma glucose); HbA_{1c} (hemoglobin A1c); RMSE (root mean squared error); WHO/FAO/UNU (World Health Organization/ Food and Agriculture Organizations/ United Nation University); BMI (Body Mass Index); FFM (fat free mass); FM (fat mass); UNL (upper normal level of laboratory)

1. Introduction

RMR represents the minimum energy expenditure for a living body in vigil state. RMR is dependent of weight, height, body mass index (BMI), fat-free mass (FFM) and it is also modified in metabolic diseases as diabetes, obesity or metabolic syndrome (Martin K., Rigalleau V & al., de Figueiredo Ferreira M. & al., Gougeon, R. &al., Buscemi, S. & al. [1-5]). Due to the scarce resources and technical limitations of indirect calorimetry technique for RMR measurement, predictive equations became an useful alternative. These equations were initially developed in healthy subjects and their results in special situations need further estimation (Schusdziarra V. & al.,Frankenfield D.C., Huang, K.C. & al. [6-8]). There is an increasing body of arguments sustaining in diabetic patients a higher RMR dependent of blood glucose and also that the introduction of antidiabetic medication as insulin or sulphonylurea decrease RMR to non diabetic value (Bitz, C. & al., Bogardus, C. & al.,

Chong, P.K. & al., Stumvoll, M. & al. [9-12]). It is also known that type 2 diabetes is associated with obesity. Adipose tissue has a lower energy expenditure but the opposite effect of increased blood glucose and increased fat tissue do not normalize RMR. The aim of this study was to investigate the accuracy of predictive equations for RMR in recently diagnosed type 2 diabetes patients with different level of metabolic control and body composition before the intervention of therapeutic modifying factors.

2. Material and Methods

The study included 283 consecutive patients (54% male), diagnosed with type 2 diabetes that had addressed to our centre in 2013-2014. An informed signed consent was obtained prior to inclusion from all subjects according to the procedures of the National Institute of Diabetes, Nutrition and Metabolic Diseases "Prof. N.C. Paulescu". Exclusion criteria were: type 1 diabetes, symptoms or signs of acute and chronic infection, malignancies, significant pulmonary disease, thyroid dysfunction, excessive alcohol consumption (>2 drinks/day). Indirect calorimetry was performed with face mask system from Quark CPET COSMED using Weir equation. For each determination, the device was warmed up for 10 min and calibrated with a certified gas composed by 16.02% oxygen, 5.02% CO_2 and nitrogen up to 100% produced by Air Liquide Healthcare America Corporation, USA. Examination was performed in the morning, after 10 hours of fasting and after 30 minutes of rest with the patient relaxed and awaked, in a thermo neutral environment. The recording length was 20 minutes after reaching the steady state. The first initial 5 minutes of registration were discharged. Weight and height were measured with subjects wearing thin clothes and without shoes. Body composition was determined by bioimpedance method using the TANITA BC 601 analyzer. The device performs single frequency bioelectrical impedance analysis with resistance and reactance measured at 50 kHz. FFM was determined as the difference between weight and fat mass (Khalil, S.F. & al. [13]). Biochemical parameters were determined the same morning, also in the fasting state using COBAS INTEGRA 400 PLUS Hitachi Roche. Prediction equations used for calculation of RMR were Harris-Benedict, Mifflin, Owen, WHO/FAO/UNU and Bernstein. Their formula is indicated in table 1. The variables analyzed in the study were: measured RMR, predicted RMR, anthropometric parameters (weight, height, waist circumference, BMI), bioelectrical impedance analysis parameters (FFM and FM), lipid and carbohydrate metabolism biomarkers (fasting plasma glucose, $HbA_{1c,}$ total cholesterol, HDL cholesterol and triglycerides). Composite indices as ratio of RMR to FFM, body weight and BMI were computed and compared. The analysis was performed on whole group, then separately on gender and subgroups based on two criteria: BMI (normal weight, overweight and obese) and glycemic level expressed as fasting plasma glucose level (below 180mg/dl and above 180mg/dl) or as HbA_{1c} level (below 133% UNL (upper normal level of laboratory) and above 133% UNL). The level of 180mg/dl was selected for its physiological importance as the renal glycemic threshold. The level of HbA_{1c} of 133% UNL corresponds in this situation to HbA_{1c} equal to 7.85 and an average plasma glucose of 178.5 mg/dl in the near proximity of renal glycemic threshold (Nathan, D.M. & al.[14]). Accuracy was calculated as percentage difference within 10%, 15% and 30% of measured RMR, bias (expressed as difference between measured and predicted mean RMR) and root mean squared prediction error (RMSE). Correlations between RMR and the other variables were performed using Pearson's test. Statistical analysis was performed using the SPSS Statistic 22. A p-value < 0.05 was considered statistically significant.

Table 1. Predictive equations

RMR predictive equation for Male	
Harris- Benedict (Frankenfield, D.C.& al. [15])	66 + (13,8x W)+ (5x H) - (6.8 x A)
Owen (Owen, O.E. & al. [16])	879 + (10.2 x W)
Mifflin St Jeor (Mifflin, M.D. & al [17])	(9.99 x W) + (6.25 x H) - (4.92 x A) + 5
Bernstein (Bernstein, R.S. & al [18])	(11 x W) + (10.2 x H) - (5.8 x A) - 1032
WHO/FAO/ UNU (*Expert Report* [19])18-30 years	15.4 x W - 27 x H + 717
WHO/FAO/ UNU (*Expert Report* [19])30- 60 years	11.3x W +16 x H + 901
WHO/FAO/ UNU (*Expert Report* [19]) > 61 years	8.8 x W +1128 x H - 1071
RMR predictive equation for Female	
Harris- Benedict (Frankenfield, D.C.& al. [15])	655 + (9.5 x W)+(1.9 x H) - (4.7 x A)
Owen (Owen, O.E.& al. [16])	795 + (7.18 x W)
Mifflin St Jeor (Mifflin, M.D. & al [17])	(9.99 x W) + (6.25 x H) - (4.92 x A) -161
Bernstein (Bernstein, R.S. &al [18])	(7.48 x W) - (0.42 x H) - (3 x A) + 844
WHO/FAO/ UNU (*Expert Report* [19])18-30 years	13.3 x W + 334 x H +35
WHO/FAO/ UNU (*Expert Report* [19])30- 60 years	8.7 x W – 25 x H +865
WHO/FAO/ UNU (*Expert Report* [19]) > 61 years	9.2 x W +637 x H -302

W- weight; H-height; A-age

3. Results and Discussion

The analyzed parameters were similar for both sexes regarding fasting plasma glucose, HbA_{1c}, total cholesterol and triglycerides. Female patients with diabetes were older (61± 0.81 versus 57.3± 0.8 years; $p<0.05$) and with higher BMI (32± 0.5 versus 30.6 ± 0.3 kg/m^2; $p<0.05$) than male. Regarding BMI subgroups, 9.2% from patients were normal weight, 35% from patients were overweight (female 30.5% and male 38.7%) and 55.8% from patients were obese (female 58.5% and male 53.5%). No significant differences were found regarding the distribution of genders on BMI classification ($p<0.292$). Mean measured RMR was 1577.1± 395.4 kcal/day. The clinical and biochemical parameters for studied diabetic patients are indicated in table 2. Separately by gender, the mean measured and predicted RMR were tested with t - paired test and statistical significant difference was observed, excepting for Owen and Mifflin equation in female and Mifflin and WHO/FAO/UNU in male. The results are presented in table 3. The differences between measured RMR and RMR calculated with Harris, Owen, Mifflin, WHO/FAO/UNU and Bernstein prediction equations were tested with one sample t test against the value 0. We found statistically significant difference for Harris ($p<0,001$), Owen ($p=0.009$), Bernstein ($p<0,001$) equations and consequently we excluded these equations from Bland Altman analysis. The differences between determined RMR and predicted RMR with Mifflin and WHO/FAO/UNU were not statistical significant ($p=0.555$, accordingly $p=0.062$) therefore we continued to construct the Bland Altman plot. For Mifflin and WHO/FAO/UNU equation, we used linear regression to test if there is a level of agreement between the two measures, but the $t=8.26$, $p<0.001$, unstandardized $B=0.432$, respectively $t=10.98$, $p<0.001$, unstandardized $B=0.594$, so we have to reject the null hypothesis. Bland Altman analysis results indicated the existence of a higher level of agreement with a proportional bias for Mifflin and WHO/FAO/UNU equations. Measured RMR was correlated with age, weight, waist circumference, height, BMI and FFM ($p<0.01$). RMR adjusted for gender, age and weight correlates with fasting plasma glucose ($r=0.176$; $p=0.014$) and HbA_{1c} level ($r=0.159$; $p=0.018$). Correlation indices increased when adjustment for fat-free mass was added. Positive correlation was determined between RMR/ BMI ratio and FPG both for female, $r(128)=0.212$, $p<0.05$ and male, $r(155)=0.269$, $p<0.005$. Positive correlation was found between RMR/BMI ratio and HbA_{1c} both in female, $r(128)=0.206$, $p<0.05$ and male, $r(155)=0.241$, $p<0.05$. In comparison with other equations, Mifflin equation has the highest accurate prediction (48.8%) the lowest bias (10.48 kcal/day) and lowest RMSE (298.31kcal/day). The results before stratification are displayed in table 4.

Table 2. Clinical, biochemical, calorimetric and bioelectrical impedance data of study group with comparison between genders

Study group	Women (n=128)	Men (n=155)	p-value
Age (years)	61 ±0.9[1]	57.3 ±0.8	p<0.05
Weight (kg)	82.4 ±1.5	92.6 ±1.2	p<0.05
Height (cm)	160.3±0.5	173.6±0.5	p<0.05
BMI (kg/m^2)	32 ±0.5	30.6 ±0.3	p<0.05
Waist circumference (cm)	103.5±1.2	108.2±0.9	p<0.05
Fasting plasma glucose (mg/dl)	170±5.7	176±5.7	ns
HbA_{1c}	7.6±0.1	7,5±5.7	ns
RMR (kcal/day)	1383.8 ±25	1736.6 ±32.4	p<0.001
Fat-Free mass (kg)	46.7 ±0.5	64.3 ±0.6	p<0.001
Fat mass(kg)	35.1 ±1	28±0.7	p<0.05
RMR/kg Fat-Free Mass	29.6±.4	26.9±.4	p<0.05
RMR/kg body weight	17.1±0.3	18.9±0.3	p<0.05
RMR/BMI	44.1±0.8	57±1	p<0.05
Cholesterol (mg/dl)	221.2 ±4.9	212.9 ±3.9	ns
HDL-Cholesterol(mg/dl)	49.3 ±1	42 ±0.8	p<0.05
Triglycerides (mg/dl)	160.3 ±8.9	180.1 ±8.3	ns

1-mean±standard error; ns – not significant (p>0.05, independent t test)

Table 3. Comparison between measured and predicted RMR

	mRMR[1]	Harris[3]	Owen	Mifflin	WHO[4]	Bernstein
Female	1383.8±25[2]	**1456.1±17**[*]	1387±11	1364.7±8	**1461.8±16**[*]	**1210.3±12.7**[*]
Male	1736.5±32	**1819.8±20**[*]	**1821.6±12**[*]	1731.6±5	1734.5±16	**1425.37±18.9**[*]

1-measured RMR using indirect calorimetry; 2 - Data are presented as mean ± standard error; 3 - Harris Benedict equation; 4- WHO/FAO/UNU equation;*-statistically significant, p<0.05 (t-paired test) comparing to measured RMR;

Also Mifflin equations had equal proportions of over predictions and under predictions. After the study group was split by gender, Owen equation had the best accuracy within ± 10% (49.2% for female and 61.3% per male) and Mifflin equation had the highest accurate prediction within ±15% and ±30% of measured RMR (67.2% - 90.65% for female and 63.3% - 83.8% for male). The equation with the highest accuracy within ±10% for subgroups of gender, BMI, FPG and HbA_{1c} are provided in table 5. The analyzed equations maintain similar accuracy for the same subgroups of gender and BMI regardless if the threshold for hyperglycemic state was FPG> 180mg/dl or HbA_{1c} > 7.85. Separately by gender and subgroups of BMI, FPG and HbA_{1c}, in accuracy range of ±10% from measured RMR, Mifflin equation provide the most accurate results from 42.9% -72% for overweight women and obese patients of both sexes with HbA_{1c}<7,85 or FPG <180mg/dl and Harris Benedict equation provide more accurate results 43.1- 80% for men in normal weight regardless of glycemic level, overweight with HbA_{1c}<7,85 or FPG<180mg/dl and obese with HbA_{1c}> 7.85 or FPG>180mg/dl. Harris Benedict equation had the highest over prediction rate 39.6% when estimated accuracy was ±10%. For both sexes for obese with metabolic imbalance HbA_{1c}>7.85 or FPG> 180mg/dl Harris Benedict and WHO/FAO/UNU had the highest accuracy. Bernstein equation had the lowest accuracy in this study group and under predicted as a rule. When accuracy was considered as ±10% of measured RMR the under prediction of Bernstein equation was 62%. As RMR prediction is a cornerstone of diabetes management the most accurate predictive equation for a certain interval of HbA_{1c} or blood glucose level is

of particular interest. The specificity of this study group as treatment naïve diabetic patients excludes also potential bias of antidiabetic medication as confounder for analysis.

Table 4. Mean predicted RMR, accuracy, bias and RMSE obtained with the targeted equations

n = 283	RMR predicted	Bias[2] kcal/d	Accuracy[3] (±10%)	Accuracy[4] (±15%)	Accuracy[5](±30%)	RMSE kcal/d
Harris[6]	1656.61±293.4[1]	-79.54	46.3	62.9	85.5	307.61
Owen	1626.09±261.5	-49.03	43.8	59.7	86.2	316.05
Mifflin	1566.58±274.8	10.48	48.8	65.0	86.9	298.31
WHO[7]	1611.82±240.7	-34.75	43.5	58.7	85.5	313.32
Bernstein	1328.09±226	248.96	28.3	41.8	83.3	394.93

1-Mean ± standard deviation; 2-Difference between mean measured RMR and mean predicted RMR; 3-The percentage of subjects with predicted RMR within 10% of the measured RMR; 4-The percentage of subjects with predicted RMR within 15% of the measured RMR; 5- The percentage of subjects with predicted RMR within 30% of the measured RMR; 6 - Harris Benedict equation; 7 - WHO/FAO/UNU equation

Table 5. Equation with highest accuracy for study subgroups 1-6

accurate equation within 10%	Subgroup 1	Subgroup 2	Subgroup 3	Subgroup 4	Subgroup 5	Subgroup 6
female	Owen	WHO**	Mifflin	Mifflin	Mifflin/Owen	Harris, WHO
male	Harris*	WHO, Harris, Mifflin	WHO, Harris	Owen	Mifflin	Harris, WHO

*- Harris Benedict equation;**-WHO/FAO/UNU equation; Subgroups:**(1) normal weight**, HbA_{1c}<133%UNL (n=9), FPG<180mg/dl (n=8); **(2) normal weight**, HbA_{1c}>133%UNL (n=5), FPG>180mg/dl (n=6); **(3) overweight** HbA_{1c}<133%UNL (n=25), FPG<180mg/dl (n=25); **(4) overweight** HbA_{1c}>133%UNL (n=14), FPG>180mg/dl(n=14);**(5) obese** HbA_{1c} <133%UNL (n=57) FPG<180mg/dl(n=58); **(6)obese** HbA_{1c}>133%UNL (n=18), FPG>180mg/dl (n=17);

Even if the carbohydrate metabolic thresholds for subgroups are very close numerically, corresponding to 180mg/dl fasting plasma glucose and 178.5mg/dl average estimated glucose for a HbA_{1c} = 7.85, their clinical significance is different. Fasting plasma glucose expressed the glucose value in the day of calorimetric determination, while HbA_{1c} expressed an average plasma glucose from the previous 3 month, possible different from fasting plasma glucose value simultaneous with calorimetric measurement. It could be taking into consideration that fasting plasma glucose at the onset of disease increased slowly with disease progression and their glycemic variability is lower than in than in diabetic patients with severe β cells dysfunction and therapeutic intervention. The results from this study sustained the idea that the selection of the optimum equation could use interchangeable these 2 criteria. This is also a possible argument that modification of RMR in diabetic milieu is induced rather by chronic hyperglycemic state than acute glycemic increase. In conclusion, accuracy of predictive equations was different depending of gender, BMI and glycemic level subgroups, recommending that the selection of specific equation should take into consideration these anthropometric and metabolic factors. In newly diagnosed type 2 diabetes patients analyzed as a homogenous group, Mifflin equation had the best predictive value. Additional arguments from stratified analysis sustained that for normal or overweight diabetic patients, Mifflin and Owen equations is recommended for women and Mifflin, WHO/FAO/UNU and Harris Benedict equations for men. For obese patients that represent 55.8% of this cohort, Mifflin

equations maintained its predictive value in diabetic patients with FPG < 180mg/dl or HbA_{1c} < 7.85 but not in obese patients with FPG>180mg/dl or HbA_{1c} > 7.85. For the association diabetes mellitus, obesity and FPG>180 or HbA_{1c} > 7.8, Harris Benedict and WHO/FAO/UNU equations predict more accurate.

4. Aknowledgements

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