PAPER

The prediction of resting energy expenditure in type 2 diabetes mellitus is improved by factoring for glycemia

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BACKGROUND: Predictive equations have been reported to overestimate resting energy expenditure (REE) for obese persons. The presence of hyperglycemia results in elevated REE in obese persons with type 2 diabetes, and its effect on the validity of these equations is unknown.
OBJECTIVE: We tested whether (1) indicators of diabetes control were independent associates of REE in type 2 diabetes and (2) their inclusion would improve predictive equations.
DESIGN: A cross-sectional study of 65 (25 men, 40 women) obese type 2 diabetic subjects. Variables measured were: REE by ventilated-hood indirect calorimetry, body composition by bioimpedance analysis, body circumferences, fasting plasma glucose (FPG) and hemoglobin A_{1c}. Data were analyzed using stepwise multiple linear regression.
RESULTS: REE, corrected for weight, fat-free mass, age and gender, was significantly greater with FPG > 10 mmol/l ($P = 0.017$) and correlated with FPG ($P = 0.013$) and hemoglobin A_{1c} as percentage upper limit of normal ($P = 0.02$). Weight was the main determinant of REE. Together with hip circumference and FPG, it explained 81% of the variation. FPG improved the predictability of the equation by > 3%. With poor glycemic control, it can represent an increase in REE of up to 8%.
CONCLUSION: Our data indicate that in a population of obese subjects with type 2 diabetes mellitus, REE is better predicted when fasting plasma glucose is included as a variable.
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Introduction

The primary strategy of treatment for obese persons with type 2 diabetes mellitus is improved glycemic control by weight loss.[1] Estimation of resting energy expenditure (REE) serves as the basis from which daily energy needs are established for the prescription of the diabetic meal plan with computation of macronutrients for weight control. An adjustment upward of 30 to as much as 300% is made to REE to account for the estimated energy expended in physical activity and the thermic effect of meals. Measuring REE as an approach to estimating total energy requirements has long been preferred to the use of dietary assessment methods because it is less time consuming, simpler and does not rely on the subjects' recall of food eaten, which often underestimates total energy needs.[3] Due to the limited access to equipment that measures REE, predictive equations have been developed using readily available variables known to affect it such as gender, weight, height and/or age.[4] Many of the published predictive equations used to estimate REE in obese persons have been developed from data collected in normal-weight individuals[5,6] or if they included persons of varying weights, did not report a separate analysis for the obese subsample.[6–10]) It has been suggested that the equations may be inaccurate in subjects with proportionately more adipose tissue.[11] Resting metabolic rates of adipose tissue are low 19 kJ/kg/day) compared with those for skeletal muscle (54 kJ/kg/day), liver 837 kJ/kg/day), brain (1004 kJ/kg/day) and heart and kidneys (1841 kJ/kg/day).[12]

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Bernstein et al[11] developed predictive equations, using a population of 202 (154 female, 48 male) obese individuals, but excluded persons requiring diabetes medication.

The most commonly used equations, published by Harris and Benedict in 1919,[6] have been shown to overestimate basal energy requirements in healthy normal-weight persons up to 15% as compared with REE measured by indirect calorimetry.[13,14]) Studies involving samples of normal-weight and obese persons combined have found an over-estimation of 5–13% by the Harris and Benedict equations.[8,10,15,16] Heshka et al[17] cross-validated 12 published predictive equations with measured REE in a sample of 126 healthy obese persons and found that most overestimated REEs and that up to 40% of the variability in measured REE remained unexplained by the variables used, ie height, weight and age. They also found that in equations using calculated body surface area in their formula, the size of the mean error was smaller. The authors suggested that, because surface area is calculated using a power term, it may reflect the smaller proportion of fat-free mass as body weight and fat mass increase.

Studies involving comparisons of measured vs predicted REE in the obese population have largely excluded persons with type 2 diabetes mellitus.[8,911,18] Poorly controlled obese diabetic persons had a higher REE compared with age-, BMI- and percentage; body fat-matched control group,[19,20] which decreased to values no longer different with insulin-induced near normoglycemia.[20] Nair et al[21] reported that insulin treatment resulted in a reduction in REE in hyperglycemic individuals with type 1 diabetes, attributed partly to greater rates of protein turnover with hyperglycemia.

Therefore, given that predictive equations overestimate REE in the obese and that the effect of hyperglycemia results in elevated REE in subjects with diabetes, we sought to assess how these two opposing factors affect estimated REE in obese individuals with type 2 diabetes mellitus. We examined the validity of using predictive equations to estimate REE in that population and assessed whether diabetes control is an independent factor in determining REE. We tested whether factoring for diabetes control would improve the estimation of REE.

Subjects and methods

Data were collected from Group A: 65 (25 male, 40 female) obese subjects with type 2 diabetes mellitus involved in studies at our centre. Consent was obtained according to the Human Ethics Committee of the Royal Victoria Hospital. The subjects were weight stable at the time of testing and presented with varied levels of glycemic control, as indicated by a wide range of fasting concentrations in plasma glucose and hemoglobin A_{1c}. Thyroid function was normal and none took medications that may alter metabolic rate. In the premenopausal women, REE was measured during the follicular phase of the menstrual cycle. The subjects were non-smokers. Their characteristics are given in Table 1. To evaluate the effect of glycemic control on current predictive equations, 39 additional data points were collected from group B: seven obese diabetic (fasting plasma glucose (FPG) 7.1 ± 1.2 mM) and 32 obese nondiabetic (FPG 5.0 ± 0.1 mM) subjects (weight 100 ± 3 kg; body mass index (BMI) 37 ± 1 kg/m^2; age 45 ± 2 y; REE 7.2 ± 0.2 MJ). We used these subjects to test the equations that resulted from the stepwise multiple regression analyses done in this study.

The subjects arrived at the laboratory at 7:00 a.m., after a 12 h overnight fast. Body composition was determined and they rested in the examination room in supine position for at least 30 min prior to metabolic rate measurements.

Procedures and analytical methods. REE was measured as described earlier[20] under standardized conditions using a ventilated hood indirect calorimeter (Deltatrac[TM] Metabolic Monitor, Sensormedics Corporation, Anaheim, CA, USA). Data were collected while the subjects breathed under the plastic canopy for 20 min. The average of the last 15 min was used for calculation of 24 h REE according to the de Weir

Table 1 Subject data

	Women	Men	P
n	40	25	
Age (yrs)	52 ± 1 (34–72)	54 ± 2 (34–72)	N.S.
Weight (kg)	97 ± 2 (74–128)	111 ± 4 (34–72)	0.004
BMI (kg/m^2)	37 ± 1 (29–48)	37 ± 1 (34–72)	N.S.
Fat-free mass (kg)	52 ± 1 (40–64)	69 ± 2 (34–72)	< 0.001
Waist circumference (cm)	117 ± 2 (95–145)	121 ± 3 (104–157)	N.S.
Hip circumference (cm)	127 ± 2 (106–151)	121 ± 2 (105–148)	0.049
Waist-to-hip ratio	0.93 ± 0.01	1.00 ± 0.01	< 0.001
Fasting plasma glucose (mmol/l)	10.9 ± 0.5 (6.1–18.6)	10.0 ± 0.9 (4.1–23.4)	N.S.
Hb A_{1c} (% ULN[a])	135 ± 3 (78–180)	128 ± 4 (91–169)	N.S.
REE[b] (kJ/day)	7134 ± 165 (5732–9330)	8497 ± 274 (5962–11757)	< 0.001
REE (kcal/day)	1705 ± 39 (1370–2230)	2031 ± 65 (1425–2810)	< 0.001

Data are presented as mean $\pm$ s.e. (range).
[a] Upper limit of normal.
[b] REE, resting energy expenditure.

equation.[22] The coefficient of variation for the data used for the calculations was $4.7 \pm 0.4\%$ ($n = 65$). Weight and height were measured to the nearest 0.1 kg and 0.1 cm, with subjects dressed in street clothes and without shoes. Body circumference measurements were taken at the site giving the minimal value between the xiphoid process and the iliac crest for the waist and at the level of maximal protuberance in the trochanteric region for the hips. Body composition was measured using the bioelectrical impedance analysis method. Resistance and reactance measurements were made with a four-terminal bioimpedance analyzer (BIA-101A, RJL systems, Detroit, MI, USA) using the procedures and anatomical sites described by Lukaski et al.[23] Venous blood samples were drawn with minimal stasis in the overnight-fasted state on the morning of the REE measurement and were analyzed for glucose and hemoglobin A_{1c} by the Clinical Biochemistry Laboratory of the Hospital.

Equations. Table 2 shows the five published equations to which measured REE was compared.

Statistical analysis

The mean percent difference between calculated REE for each equation and measured REE by indirect calorimetry was evaluated by Student's paired *t*-tests. The mean difference in measured REE between groups stratified according to glycemic control was calculated by univariate analysis of variance, with weight, fat-free mass, age and gender as covariates. Linear correlations between REE and the variables of interest were calculated using the Pearson correlation coefficients. The independent associates of REE were assessed by stepwise multiple regression analysis using the SPSS/PC + program (SPSS Inc., Chicago, IL, USA); data included predictive variables that correlated ($P < 0.05$) with

Table 2 Predictive equations

Harris and Benedict
(F) $REE^a = 655 + (9.5 \times weight) + (1.9 \times height) - (4.7 \times age)$
(M) $REE = 66 + (13.8 \times weight) + 5.0 \times height - (6.8 \times age)$

Owen
(F) $REE = 795 + (7.18 \times weight)$
(M) $REE = 879 + (10.20 \times weight)$

Mifflin
$REE = (9.99 \times weight) + (6.25 \times height) - (4.92 \times age) + 166 (M) - 161$

WHO
(F) $REE = (8.7 \times weight) + 829$ (30 – 60 y)
(M) $REE = (11.6 \times weight) + 879$ (30 – 60 y)
(F) $REE = 10.5 \times weight + 596$ (> 60 y)
(M) $REE = 13.5 \times weight + 487$ (> 60 y)

Bernstein
(F) $REE = (7.48 \times weight) - (0.42 \times height) - (3.0 \times age) + 844$
(M) $REE = (11.0 \times weight) + (10.2 \times height) - (5.8 \times age) - 1032$

[a] REE, resting energy expenditure in kilocalories.

REE as dependent variable. Differences were considered significant at $P < 0.05$.

Data are presented in text and tables as means $\pm$ s.e.m.

Results

Table 3 reports the percentage differences from measured REE, of predictive REE equations calculated in obese men and women without or with diabetes stratified according to their glycemic control, defined as percentage upper limit of normal (ULN) of hemoglobin A_{1c}, based on the hospital laboratory's normal values (4.7–6.0%); percentage ULN was used rather than the absolute value of HbA_{1c}, because normal values vary with laboratories and methods of analysis. The Harris–Benedict and WHO equations overestimated

Table 3 REE predictive equations: percentage difference[a] from measured REE stratified according to glycemic control[b]

	Harris – Benedict	Mifflin	Owen	WHO	Bernstein
			Men		
Obese nondiabetic ($n = 9$)	$14.5 \pm 3.0^*$	4.5 ± 3.0	3.4 ± 3.9	$10.2 \pm 4.3^*$	$-8.8 \pm 2.1^*$
Obese diabetic					
$<115\%$ ULN[c]$*$ $n = 9$)	$5.7 \pm 2.2^*$	-3.2 ± 1.7	0.5 ± 1.7	4.7 ± 2.7	$-16.4 \pm 1.7^*$
115 – 140% ULN $n = 12$)	1.5 ± 1.2	$-4.4 \pm 1.3^*$	2.2 ± 2.2	$6.9 \pm 2.0^*$	$-22.6 \pm 1.0^*$
$>140\%$ ULN ($n = 6$)	1.7 ± 3.0	$-8.8 \pm 2.7^*$	-6.1 ± 2.7	1.7 ± 2.9	$-20.1 \pm 2.9^*$
			Women		
Obese nondiabetic ($n = 23$)	$5.7 \pm 1.8^*$	-0.1 ± 1.4	$-4.7 \pm 2.0^*$	$6.7 \pm 2.2^*$	$-13.1 \pm 1.6^*$
Obese diabetic					
$<115\%$ ULN ($n = 6$)	-1 ± 2.8	$-6.3 \pm 2.4^*$	$-10.7 \pm 3.3^*$	-0.2 ± 3.6	$-18.8 \pm 2.5^*$
115 – 140% ULN ($n = 23$)	-1.2 ± 2.3	$-5.5 \pm 2.2^*$	$-10.3 \pm 2.2^*$	-0.3 ± 2.4	$-19.0 \pm 1.9^*$
$>140\%$ ULN $n = 14$)	$-5.4 \pm 1.9^*$	$-10.7 \pm 1.8^*$	$-13.1 \pm 2.1^*$	-3.6 ± 2.0	$-22 \pm 1.6^*$

$*$ $P < 0.05$ vs 0.
[a] Percentage difference was calculated as predicted REE minus measured REE divided by measured REE and multiplied by 100.
[b] Optimal glycemic control was defined as $<115\%$ upper limit of normal ($HbA_{1c} < 6.9\%$); 115 – 140% referred to HbA_{1c} of 7 – 8.4% and $>140\%$ referred to $HbA_{1c} > 8.4\%$.
[c] ULN, upper limit of normal of HbA_{1c}.

REE in the nondiabetic obese subjects and improved their estimate as glycemic control worsened, in the obese diabetic groups. REE predicted by Mifflin equations did not differ significantly from measured REE for obese nondiabetic men and women nor did that by Owen for men. Owen's equation underestimated measured REE in obese nondiabetic women. Those equations and that of Bernstein increasingly underestimated measured REE as diabetes control worsened in the obese diabetic subjects.

Table 4 presents the data of the diabetic subjects divided into two groups according to whether their fasting plasma glucose was below or above 10 mmol/l when REE was measured. We used 10 mmol/l because it is the concentration considered as the threshold above which patients experience glycosuria, and reflects poor control. REE was significantly greater in the group with the high glucose values when corrected for weight, fat-free mass (FFM), age and gender.

Using Pearson correlation analysis, REE related strongly to weight, height, BMI, FFM, waist and hip circumferences ($P < 0.001$); to waist-to-hip ratio ($P = 0.015$); and to age ($P = 0.029$). REE did not correlate with fasting plasma glucose ($P = 0.075$), nor with hemoglobin A_{1c} expressed as percentage upper limit of normal ($P = 0.202$), except when controlling for weight, FFM, age and gender ($P = 0.013$ for glucose and $P = 0.021$ for hemoglobin A_{1c}). Stepwise multiple regression analysis was carried out to identify the significant independent factors that could be determinants of REE among these variables. Five models emerged. Weight explained 72% of the variation in REE; weight and fat mass, 77%; weight, fat mass and fasting plasma glucose, 80% (Table 5, model 3). When hip circumference entered the equation, fat mass was no longer a significant determinant. Eighty-one percent of the variation was explained by weight, glucose and hip circumference (Table 5, model 5). There was no effect of sex or age.

Table 6 shows percentage difference between REE measured in Group B and predicted by the equations given in Tables 2 and 5. The percentage differences from measured REE did not differ significantly from zero for both equations presented in Table 5 nor for those from Mifflin in Table 2, for both genders, and from Owen for men. By contrast, the equations from Harris and Benedict and that from WHO overestimated, on average, measured REE by ~12% in men and ~5% in women, while that from Owen underestimated it by ~5% in women and those from Bernstein by 13% for both genders.

Table 4 Measured REE stratified according to fasting plasma glucose (FPG)

	n	REE (kJ/day)	REE (kJ/day) adjusted for weight, fat-free mass, age and gender
FPG < 10 mmol/l	21 female, 15 male	7385 ± 211	7481 ± 106
FPG > 10 mmol/l	19 female, 10 male	7998 ± 258	7879 ± 118*

* $P = 0.017$ vs FPG < 10 mmol/l.

Table 5 Multiple regression models to predict resting energy expenditure in obese diabetic persons (in kilojoules)[a]

Variable	Slope	Beta	P
Model 3[b]			
Intercept	374.9 ± 490.5		0.448
Weight	85.3 ± 7.2	1.18	< 0.001
Fat mass	−48.3 ± 11.5	−0.42	< 0.001
Fasting plasma glucose	62.9 ± 22.0	0.17	0.006
r^2		0.802	
Model 5[c]			
Intercept	4043.7 ± 806.3		< 0.001
Weight	79.2 ± 5.7	1.09	< 0.001
Fasting Plasma Glucose	77.5 ± 21.9	0.21	0.001
HIP circ.	−42.6 ± 9.0	−0.38	< 0.001
r^2		0.813	

[a] Factors included in the models were: weight, height, fat-free mass, fat mass, body mass index, waist and hip circumferences, waist-to-hip ratio, age, gender, fasting plasma glucose, % ULN hemoglobin A_{1c}.
[b] REE = 375 + (85 × weight in kg) − (48 × fat mass in kg) + (63 × FPG in mM).
[c] REE = 4044 + (79 × weight in kg) + (78 × FPG in mM) − (43 × hip circumference in cm).

Discussion

Our results strongly indicate that, in obese type 2 diabetic subjects, fasting plasma glucose is an independent determinant of resting energy expenditure, beyond measures of body compartments. We used fasting plasma glucose concentration and percentage ULN of HbA_{1c} as indicators of glycemic control. Fasting plasma glucose was the significant independent variable and it increased the prediction of REE by more than 3%. Although the range in values for both HbA_{1c} and glucose was large and comparable, it is conceivable that the fasting plasma glucose value predicted REE better because blood samples were taken on the day when REE was measured. By contrast HbA_{1c} reflects glycemic con-

Table 6 Percent difference from measured REE of predictive equations from Table 2 and those of Table 5 using data from group B only ($n = 39$)

	Harris–Benedict	Mifflin	Owen	WHO	Bernstein	Model 3	Model 5
Men ($n = 12$)	11.6 ± 2.6*	1.8 ± 2.6	2.3 ± 2.9	8.7 ± 3.3*	−11.6 ± 2.1*	−0.5 ± 2.1	−1.5 ± 2.9
Women ($n = 27$)	4.8 ± 1.6*	−0.7 ± 1.3	−5.3 ± 1.8*	5.9 ± 1.9*	−13.9 ± 1.5*	1.6 ± 1.3	1.9 ± 1.4
Range[a] ($n = 39$)	−8 to 30	−11 to 22	−18 to 24	−8 to 33	−26 to 4	−13 to 16	−16 to 18

* $P < 0.01$ vs 0.
[a] For both sexes together.

trol of the past 3 months. Higher REE has been reported in moderately hyperglycemic diabetic persons compared with nondiabetic subjects, matched by BMI.[19,24] We found that insulin therapy sufficient to improve glycemia decreased REE by 3[20] to 8%[25], the magnitude of change relating to that of the hyperglycemia and/or the intensity of the therapy.[26] The greater REE with poor diabetes control has been attributed to increased glucose production rates that reflect elevated rates of gluconeogenesis,[24] and to higher protein turnover,[27,28] two processes recognized as energy requiring. The greater REE in the group of diabetic subjects with fasting plasma glucose > 10 mmol/l, once adjusted for body composition, further confirmed that the state of glucose control influences REE.

Thus, factoring for glucose control significantly improved the prediction of REE beyond weight. In a state of poor control, this factor can amount to 8% more energy spent at rest, ie > 600 kJ/day, and lead to error in planning regimens with a deficit in energy. As has been reported previously,[10,15–18], we found that the commonly used predictive equations, those of Harris and Benedict[6] and WHO,[7] overestimated REE in obese nondiabetic subjects. In the diabetic subjects, as glycemic control worsened, as indicated by an increase in percentage upper limit of normal of HbA_{1c}, the mean percentage differences between REE from those two predictive equations and that from measurement were no longer significantly different. In the obese diabetic women with worse control (percentage ULN of $HbA_{1c} > 140\%$), the Harris and Benedict equation actually significantly underestimated REE (Table 3), again indicating that, as glycemic control deteriorates, REE increases. The same observations apply to Bernstein's, Mifflin's and Owen's equations whose underestimations increased on the average as percentage above upper limit of normal HbA_{1c} increased. Karhunen *et al*[29] found no effect of blood glucose concentration on REE in nondiabetic obese women, a factor for which the variability was small compared with that found in our group, decreasing the strength of its contribution in their study. By contrast, they found that fasting serum insulin concentration made a significant independent contribution to REE, and suggested that it could partly be explained by insulin's stimulating effects on the sympathetic nervous system activity.[30] Their population was characterized by a large variability in insulin concentrations, thereby increasing the strength of its contribution. Obisesan *et al*[31] also reported that fasting plasma glucose was an independent predictor of REE in a population of 40 older men with heart failure whose glucose values ranged from 3.4 to 20.4 mmol/l. In these subjects, predictive equations underestimated REE on the average by 10%, such that adding fasting glucose to body weight as predictive variables increased the cumulative r^2 from 0.55 to 0.74.

Age had no independent effect on REE. This could be partly explained by a standard deviation of only 8.6 y in our population. Age-related declines in REE, independent of changes in body composition, have been reported.[32,33] For instance, Hunter *et al*[33] included lean and fat tissue partitioning in the analyses of the relation of age and REE and showed that in normal weight and sedentary women, varying in age but less so in lean body mass, the estimation of REE by age was improved when trunk lean mass and leg fat mass were included as variables in the model. We have not measured regional lean and fat tissues. Our obese population was characterized by upper body obesity and equal proportions of whole-body fat mass and fat-free mass such that weight was a better predictor of REE than fat-free mass. Fat-free mass has been identified as the strongest determinant of REE, accounting for 49[29] to 90%[34] of the variation in REE, depending upon the heterogeneity of the cohorts studied. In our subjects, weight was largely contributed to by the upper body as indicated by elevated waist circumferences and waist-to-hip ratios, which is the area where organ mass with high metabolic activity is located.[12,32] Others have reported strong correlations between trunk lean mass and REE.[33–36]

There was no independent effect of gender in our model but a negative one of hip circumference. The latter may have reflected a lower REE in women who were characterized by greater hip circumferences and lower fat-free mass. Others have shown, but only in women, that there is an association between visceral fat and REE[37] and waist-to-hip ratio and REE,[29] indicating greater REE with greater abdominal obesity. These findings support the negative effect of hip circumference (gluteo femoral obesity) on REE that we found. Furthermore, when tested using a different group of obese persons that included a few subjects with diabetes, the equations derived from multiple regression analysis, presented in Table 5, predicted the measured REE with mean percent differences that were not statistically different from zero.

Conclusions

We found that in a population of obese persons with type 2 diabetes mellitus, glycemic control indicated by fasting plasma glucose is an independent determinant of resting energy expenditure that explains more than 3% of the variation in REE. Including fasting plasma glucose in an equation for REE derived from a larger number of obese subjects with type 2 diabetes, would improve its predictability.

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