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Resting energy expenditure is not increased in mildly hyperglycaemic obese diabetic patients

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Resting energy expenditure (REE) is believed to be increased in type 2 diabetes, an increase that is associated with deteriorating glucose tolerance during its development. Meanwhile, insulin resistance, a state linked to obesity and observed in all type 2 diabetic patients, is associated with reduced REE. Our aim was to compare REE in obese patients with and without diabetes. REE, body composition (total body water, density, percentage fat and fat-free mass: 3-compartment model) and metabolic control were assessed in fifty obese Caucasian patients with diabetes (glycated haemoglobin level 7·6 (SD 1·5) %) and fifty obese patients who were non-diabetic. Despite being more overweight and younger, obese non-diabetic patients had an absolute REE (7·73 (SD 1·44) *v.* 8·12 (SD 1·37) MJ; $P=0·17$) and percentage fat-free mass similar to those of obese diabetic patients. Even when adjusted for differences in body composition, REE remained similar in both groups. Furthermore, REE (absolute and adjusted) was unaffected by both glucose level and control (glycated haemoglobin), with fat-free mass being the only determinant of REE. We conclude that REE is not necessarily increased by the presence of diabetes in obese people.

Resting energy expenditure: Obesity: Diabetes: Fat-free mass

Being overweight or obese is strongly associated with having type 2 diabetes (Cowie & Harris, 1995). Moreover, overweight is linked with inactivity (Martinez-Gonzalez *et al.* 1999), 60–70 % of total energy typically being expended at rest. In type 2 diabetes, resting energy expenditure (REE) is thought to be even higher, with type 2 diabetic individuals within the Pima Indian community, a society synonymous with obesity, reported to have an REE 5–8 % greater than that of their non-diabetic counterparts (Bogardus *et al.* 1986, Fontvieille *et al.* 1992).

This increase probably results from rising REE during the transition from normal glucose tolerance to diabetes (Weyer *et al.* 1999). Glycaemia itself may determine REE as a 5 % higher REE is reported at a fasting plasma glucose (FPG) level of 10 mmol/l or higher (Gougeon *et al.* 2002). In most studies, however, it is only when differences in fat-free mass (FFM) are adjusted for that REE appears higher, with no difference in absolute metabolic rate otherwise being observed between those with and without diabetes (Fontvieille *et al.* 1992, Bitz *et al.* 2004, Huang *et al.* 2004). Additionally, all type 2 diabetic patients exhibit insulin resistance, a metabolic state associated with overweight and a factor associated with lowered REE (Petersen *et al.* 2003, 2004).

Given that type 2 diabetic individuals typically exhibit both hyperglycaemia and insulin resistance, factors apparently differing in their 'effect' on REE, it is questionable whether REE can differ between diabetic and non-diabetic subjects. This study compares REE in obese type 2 diabetic and obese non-diabetic patients of a similar weight.

Methods

Patients and study design

An equal number (*n* 50) of patients (BMI $\geq 30\,kg/m^2$; range 30–$62\,kg/m^2$) with and without diabetes (WHO criteria; World Health Organisation, 1999), who had been admitted to the department for 1–5 d, were recruited. Measurements, conducted at the beginning of stay, were made following an overnight fast (≥ 8 h) and in the absence of recent strenuous activity. Patients with type 1 diabetes, kidney failure, that is a creatinine clearance rate of less than 30 ml/min (Cockcroft & Gault, 1976), or aged 70 years or more were excluded. Current antidiabetic medication taken was insulin (33 %) and/or oral sulphonlyureas (66 %). Permission was granted by the hospital's ethical committee. All subjects gave their consent prior to participation.

Resting energy expenditure

REE was measured by indirect calorimetry using a ventilated hood system (Vmax Spectra; SensorMedics, Yorba Linda, CA, USA). Whole-body O_2 consumption and CO_2 production were measured from inspired and expired gas flow. The system was calibrated prior to measurements in accordance with

Abbreviations: ECW, extracellular water; FFM, fat-free mass; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; REE, resting energy expenditure; TBW, total body water.

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manufacturer's instructions. With the patient in the supine position, a 40 litre transparent Perspex hood (Sensor Medics) was placed over the head and neck, with a thin plastic apron providing a rough seal around the chest. Data were recorded every 30 s for 30 min or until such time as a 15 min steady-state period had been achieved; data were then averaged to represent measured REE.

Body composition

Bioelectrical impedance analysis. Total body water (TBW) was determined by bioelectrical impedance analysis (Analycor-4; Spengler, Cachan, France). Current-inducing electrodes were placed on the right hand and receiver electrodes on the foot as previously described (Ritz, 2001). Resistance and reactance were measured at 5, 50 and 100 kHz, with extracellular water (ECW) determined at 5 kHz and TBW at the higher frequencies (see later).

Air-displacement plethysmography. Body density was determined by air-displacement plethysmography (Bod-Pod; Life Measurement, Concord, CA, USA) as described elsewhere (McCrory *et al.* 1995). Wearing underwear and a swimming cap, the patient sat within the 450 litre chamber inside the machine. Two consecutive body volume measurements (V_b), each lasting 35–45 s, were conducted. If body volume differed by more than 150 ml, a third measurement was made. Body density (D_b) was computed as: $D_b = \text{weight}/V_b$.

Metabolic markers

In addition to FPG, the level of glycated haemoglobin (HbA_{1c}) was determined by HPLC, and that of C-reactive protein by turbidimetry (Varient II; Bio-Rad, Hercules, CA, USA).

Statistical analysis and body composition calculations

Between-group comparisons were made using ANOVA, or ANCOVA where applicable. Stepwise regression analysis was conducted with individual predictors of REE found by simple correlation. Statistical significance was set at $P<0{\cdot}05$. Values are expressed as means and standard deviations. Calculations were performed using Statview statistical software (Version 4.0; Abacus Concept, Berkeley, CA, USA).

$$\text{TBW}\,(1) = 2{\cdot}896 + 0{\cdot}366 \times \text{height}^2/Z_{100} + 0{\cdot}137 \times \text{weight} + 2{\cdot}485 \times \text{gender},$$

for patients aged over 65 years, using male = 1, female = 0 (Vaché *et al.* 1998);

$$\text{TBW}\,(1) = 0{\cdot}454796 \times \text{height}^2/Z_{100} + 0{\cdot}139523 \times \text{weight} + 3{\cdot}432026,$$

for patients aged 65 years or less, regardless of gender (Segal *et al.* 1991);

$$\text{ECW}\,(1) = 0{\cdot}367 + 0{\cdot}093 \times \text{weight} + 0{\cdot}157 \times \text{height}^2/Z_5\,;$$

regardless of age or gender, with weight (kg), height (cm), density (g/cm^3), Z_5 (impedance at 5 kHz) and Z_{100} (at 100 kHz). ECW calculation was based on bromide dilution, a reference technique (Ritz, 1998), as we have previously shown that the equation usually used (Segal *et al.* 1991) induces a bias of 1·87 (SD 1·76) litres compared with bromide dilution.

Percentage fat was calculated using a three-compartmental model (Siri, 1961), a model already validated in those with type 2 diabetes (Sallé *et al.* 2005), which provides an assessment of percentage fat that is independent of FFM hydration:

$$\%\,\text{Fat}_{3-\text{comp}} = 2{\cdot}1176/\text{density} - 0{\cdot}78 \times \text{TBW}/\text{weight} - 1{\cdot}3151 \text{ (Siri, 1961)}.$$

FFM_{3-comp} was determined from weight and percentage fat mass.

Results

Table 1 summarises the characteristics of the obese diabetic and non-diabetic patients. Patients without diabetes had slightly greater adiposity, that is, lower body density, higher BMI and percentage fat mass. Patients had similar body weight, level of hydration (TBW, ECW) and FFM. The mean HbA_{1c} of diabetic patients was 7·6 (SD 1·5) %. The mean duration of diabetes was 11·3 (SD 1·7) years (range 1–46 years). The level of C-reactive protein was low and similar between groups.

Absolute measured REE was similar ($P=0{\cdot}17$) in the subjects with and without diabetes. Although REE differed ($P<0{\cdot}0001$) between men and women in each group, no difference was observed either between groups ($P=0{\cdot}45$) or when the gender × group interaction was considered: female × diabetes, 7·27 (SD 1·05) MJ/d; female × no diabetes, 7·31 (SD 1·22) MJ/d; male × diabetes, 8·60 (SD 1·31) MJ/d; male × no diabetes, 8·97 (SD 1·41) MJ/d; $P=0{\cdot}55$.

Fig. 1 displays REE after differences in FFM were accounted for. REE correlated with FFM with values of $R^2 = 0{\cdot}61$ (diabetes) and $R^2 = 0{\cdot}73$ (no diabetes). Neither the slope (0·11 (SD 0·01) *v.* 0·10 (SD 0·009) MJ/kg FFM per day; $P = 0{\cdot}87$) nor the elevation, that is, adjusted REE (kg FFM; $P=0{\cdot}91$) differed between groups.

Although weight, FFM and adiposity correlated with measured REE, FFM was the only significant ($R^2 = 0{\cdot}67$, $P<0{\cdot}0001$) predictor of REE after stepwise regression analysis. REE did not correlate with HbA_{1c} ($R = 0{\cdot}004$, $P=0{\cdot}97$) or FPG ($R = 0{\cdot}15$, $P=0{\cdot}16$) in the combined group or the diabetic group on its own (HbA_{1c}, $R = 0{\cdot}11$, $P=0{\cdot}49$; FPG, $R = 0{\cdot}04$, $P=0{\cdot}77$). Diabetic patients separated according to HbA_{1c} level (SD 8 %) had a similar REE regardless of FFM. The WHO formula (World Health Organisation, 1985) correctly predicted REE (paired difference = 0·155 MJ/d, $P=0{\cdot}17$). Compared with equations designed to evaluate REE in obese diabetic and non-diabetic patients, combined REE differed by 0·04 MJ/d, $P=0{\cdot}67$ (Martin *et al.* 2004) and 0·31 MJ/d, $P=0{\cdot}0004$ (Huang *et al.* 2004), with no difference in measured and predicted values observed in diabetic and non-diabetic comparisons ($P=0{\cdot}55$, Martin *et al.* 2004; $P=0{\cdot}58$, Huang *et al.* 2004). REE was unaffected by HbA_{1c}, with measured and predicted values similar in uncontrolled diabetic (≥ 8 %, *n* 15), controlled diabetic (<8 %, *n* 35) and non-diabetic patients ($P=0{\cdot}67$, Huang *et al.* 2004; $P=0{\cdot}72$, Martin *et al.* 2004).

Table 1. Characteristics of patients in both subject groups

	Diabetic patients (*n* 50)		Non-diabetic patients (*n* 50)		
	Mean	SD	Mean	SD	ANOVA (*P*)*
Age (years)	55·6	11·5	43·5	14·2	<0·0001
Weight (kg)	104·4	15·5	106·9	19·2	0·47
BMI (kg/m^2)	37·5	4·9	39·8	6·5	0·04
Total body water (kg)	46·0	7·2	45·1	9·9	0·65
Extracellular water (kg)	21·0	3·9	19·9	5·4	0·27
Density (g/cm^3)	1·005	0·014	0·996	0·014	0·0012
Fat-free mass (kg)	61·2	9·5	59·3	12·4	0·39
Fat mass (%)	41·2	5·5	44·6	6·1	0·0037
Measured REE (MJ/d)	8·12	1·37	7·73	1·44	0·17
Predicted REE (MJ/d)	7·86	1·24	7·83	1·34	0·92
Respiratory quotient	0·821	0·078	0·828	0·057	0·61
Glycaemia (mmol/l)	9·5	2·6	5·6	0·8	<0·0001
C-reactive protein (mg/l)	8·3	6·8	11·4	6·6	0·20

REE; Resting energy expenditure.
* Statistical significance was defined as $P<0·05$.

Discussion

The present results suggest, first, that REE is not increased in obese people with type 2 diabetes compared with those without diabetes, either in terms of absolute metabolic rate or FFM-adjusted rate, and second, that FFM but not glycaemic level or control predicts REE.

Previously, FFM-adjusted REE has been reported to be 5–8 % higher in type 2 diabetic patients than controls without diabetes (Bogardus *et al.* 1986; Fontvieille *et al.* 1992). This elevation appears to be the result of deteriorating glycaemic control during the development of type 2 diabetes (Weyer *et al.* 1999). However, when absolute REE is considered, differences disappear (Fontvieille *et al.* 1992; Bitz *et al.* 2004; Huang *et al.* 2004). Indeed, a decrease in REE (about 5 %) is observed when antidiabetic treatment is introduced (Bogardus *et al.* 1986; Franssila-Kallunki & Groop, 1992), returning REE to its prediabetic level. In the present study, REE remained similar whether or not differences in FFM were accounted for, the body composition data having been obtained using a three-compartmental model, a highly accurate technique (Clasey *et al.* 1999).

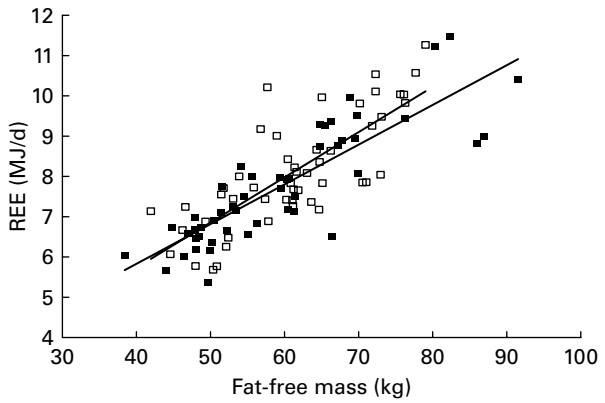

Fig. 1. Relationship between resting energy expenditure (REE) and fat-free mass. Mean REE was expressed in MJ/d adjusted per kg fat-free mass in obese diabetic patients (□, *n* 50) and obese non-diabetic patients (■, *n* 50). Neither the slope ($P=0·87$) nor the elevation ($P=0·91$) of the tendency line differed between the two groups.

Furthermore, REE was correctly predicted by the equations of the WHO (World Health Organisation, 1985) and Martin *et al.* (2004), and differed by only 3·9 % from the value given by Huang *et al.* (2004).

A number of studies have cited a relationship between glycaemic level or tolerance and REE (Gougeon *et al.* 2002; Huang *et al.* 2004; Martin *et al.* 2004). These studies concern, first, values adjusted for differences in body composition, age, sex and race, and second, patients with uncontrolled diabetes ($HbA_{1c} \geq 8$ %). Collectively, such studies do not provide an argument to suggest the existence of a common threshold above which REE is increased. In the study by Gougeon *et al.* (2002), which involved a large glycaemic range, the addition of fasting glycaemia to stepwise regression analysis added only 3 % to the variance explained by classical co-variates. The present study, which involves lower HbA_{1c} values (mean 7·6 %), did not lead to the same conclusions. It may therefore be that REE is increased in uncontrolled diabetic patients and that such an increase cannot be seen in those with better control, that is, in mildly hyperglycaemic patients. Increased energy costs during hyperglycaemia, for example gluconeogenesis, protein turnover and sympathetic nervous system activity (Fontvieille *et al.* 1992); metabolic changes more likely to occur in patients with uncontrolled rather than controlled diabetes, may play a role.

Insulin resistance, present in all type 2 diabetic patients, is linked with decreased respiration and efficiency of ATP production (Petersen *et al.* 2003, 2004), as well as impaired heart and skeletal muscle metabolism at rest (Stanley *et al.* 1997; Scheuermann-Freestone *et al.* 2003). Moreover, cardiac ATP production is negatively correlated with NEFA concentration, an indicator of insulin resistance (Scheuermann-Freestone *et al.* 2003). Indeed, increased fat accumulation in insulin-resistant elderly and type 2 diabetic offspring is associated with 30–40 % decreased mitochondrial activity and a lower REE in insulin-resistant subjects (Petersen *et al.* 2003, 2004). This is unsurprising as mitochondrial respiration represents 80–90 % of whole-body O_2 consumption (Rolfe & Brown, 1997), a significant determinant of REE. As insulin resistance correlates with overweight, its presence in our obese patients may have offset in part any increase in REE linked with diabetes.

The present data are derived from Caucasian subjects. Contrary to what is seen in Pima Indians, the subjects without diabetes in the present study generally had greater adiposity than those with diabetes, despite similar weights. With regard to antidiabetic treatment, one third of patients received insulin, the remainder receiving sulphonlyureas. This is unlikely to have affected the outcome, however, as REE is reported to be unchanged in both those on ongoing treatment and those treated up to 1–2 weeks before measurement (Huang *et al.* 2004; Bitz *et al.* 2004).

In conclusion, these results suggest REE is not elevated in obese individuals with diabetes compared with obese, non-diabetic controls of similar weight. This differs from previous reports of a higher REE in diabetic than in normal glucose-tolerant people, where REE appears high only when glycaemia is high. We acknowledge that our results may have differed had very high glycaemic levels been considered. Furthermore, REE represents the greatest proportion, approximately two-thirds, of total energy expenditure. Whether this result is also valid for total expenditure remains to be established. Collectively, studies suggest that absolute REE is similar in individuals without diabetes or with diabetes, whether treated or untreated. It is tempting to speculate that a decrease in REE, evoked as a reason for weight increase during antidiabetic treatment, may not be sufficient to explain such a gain. This warrants further investigation.

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