

Increased 24-h Energy Expenditure in Type 2 Diabetes

CHRISTIAN BITZ, MSC¹
SØREN TOUBRO, MD, DRMEDSCI¹
THOMAS M. LARSEN, MSC¹
HELLE HARDER, MSC²

KIRSTEN L. RENNIE, PHD³
SUSAN A. JEBB, PHD³
ARNE ASTRUP, MD, DRMEDSCI¹

OBJECTIVE — The aim of this study was to determine whether overweight and obese individuals with type 2 diabetes have higher basal and 24-h energy expenditure compared with healthy control subjects before and after adjustment for body composition, spontaneous physical activity (SPA), sex, and age.

RESEARCH DESIGN AND METHODS — Data from 31 subjects with type 2 diabetes and 61 nondiabetic control subjects were analyzed. The 24-h energy expenditure, basal metabolic rate (BMR), and sleeping energy expenditure (EE_{sleep}) between 1:00 A.M. and 6:00 A.M. were measured in whole-body respiratory chambers. Body composition was assessed by dual-energy X-ray absorptiometry (DXA).

RESULTS — No significant differences in unadjusted EE_{sleep} , BMR, and 24-h energy expenditure were observed between the type 2 diabetic group and the control group. After adjustment for fat-free mass (FFM), fat mass, SPA, sex, and age, EE_{sleep} and BMR were, respectively, 7.7 and 6.9% higher in the type 2 diabetic group compared with the control group. This was equivalent to 144 ± 40 kcal/day ($P = 0.001$) and 139 ± 61 kcal/day ($P = 0.026$), respectively. Adjusted 24-h energy expenditure was 6.5% higher in the type 2 diabetic group compared with the nondiabetic control subjects ($2,679 \pm 37$ vs. $2,515 \pm 23$ kcal/day, $P = 0.002$). In multiple regression analyses, FFM, fat mass, SPA, and diabetes status were all significant determinants of EE_{sleep} and 24-h energy expenditure, explaining 83 and 81% of the variation, respectively.

CONCLUSIONS — This study confirms reports in Pima Indians that basal and 24-h energy expenditure adjusted for body composition, SPA, sex, and age are higher in individuals with type 2 diabetes compared with nondiabetic control subjects and may be even more pronounced in Caucasians.

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The development of type 2 diabetes depends on both genetic susceptibility and environmental factors (1). An inappropriately high-energy intake and a sedentary lifestyle are well-known risk factors for obesity, and there is solid evidence that excessive fat

mass is the major cause of type 2 diabetes (2,3). Furthermore, large intervention trials have demonstrated that even a moderate, sustained weight loss in high-risk individuals can reduce the incidence of type 2 diabetes (4,5). However, genetic and disease-related differences in energy expendi-

ture may also be important etiological determinants.

A low resting energy expenditure (EE_{rest}) is a risk factor for weight gain (6). Paradoxically, cross-sectional studies have indicated an ~5% increased EE_{rest} in Pima Indians with type 2 diabetes compared with nondiabetic individuals after adjustment for age and body composition (7–9). Other studies found a decreased thermogenic response to meals (10) and insulin/glucose clamp infusions among type 2 diabetic subjects compared with nondiabetic individuals (11). Thus, the integrated effect on total 24-h energy expenditure has been reported to be similar or only slightly elevated in Pima Indians with type 2 diabetes compared with nondiabetic individuals (8,9). Studies in other ethnic groups have included only a limited number of subjects (12) or have used less reliable measurements of energy expenditure and body composition than whole-body respiratory and dual-energy X-ray absorptiometry (DXA) (12,13). The relative influence of body composition on EE_{rest} and 24-h energy expenditure in a Caucasian population that is less susceptible to obesity and type 2 diabetes and more insulin sensitive is unclear (14,15). This case-control study tested the hypothesis that overweight and obese Caucasians with type 2 diabetes have increased energy expenditure compared with nondiabetic control subjects after adjustment for body size and composition assessed by DXA.

RESEARCH DESIGN AND METHODS

Data from 24-h whole-body calorimetry measurements performed from 1995 to 2002 at the Department of Human Nutrition, The Royal Veterinary and Agricultural University, Copenhagen, Denmark, were used in this study. In general, most subjects were recruited through advertisement in local newspapers, and others were referred by general practitioners for treatment of obesity. Written, informed consent was obtained from all subjects before the beginning of all studies. All protocols were approved by the Municipal Ethical

From the ¹Department of Human Nutrition, Centre for Advanced Food Research, The Royal Veterinary and Agricultural University, Frederiksberg, Denmark; ²Novo Nordisk A/S, Bagsvaerd, Denmark; and the ³MRC Human Nutrition Research, Elsie Widdowson Laboratory, Cambridge, U.K.

Address correspondence and reprint requests to Christian Bitz, Department of Human Nutrition, The Royal Veterinary and Agricultural University, Rolighedsvvej 30, 1958 Frederiksberg C, Denmark. E-mail: diabetes@christianbitz.com.

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Abbreviations: BMR, basal metabolic rate; DXA, dual-energy X-ray absorptiometry; EE_{sleep} , sleeping energy expenditure; FFA, free fatty acid; FFM, fat-free mass; EE_{rest} , resting energy expenditure; SNS, sympathetic nervous system; SPA, spontaneous physical activity.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Committee of Copenhagen and Frederiksberg, Denmark.

All subjects in the type 2 diabetic group ($n = 31$) were diagnosed according to the American Diabetes Association criteria from 1997 (16) and were enrolled in an intervention study (17). In this analysis only, baseline measurements were used. Briefly, inclusion criteria were BMI ≥ 27.0 kg/m² and HbA_{1c} for diet-treated subjects 6.5–12% and $\leq 10\%$ for sulfonylurea- or repaglinide-treated subjects in monotherapy. Furthermore, antidiabetes medication was discontinued 2 weeks before the measurements. Subjects with cardiac problems and/or treatment with any drug (except for sulfonylureas and repaglinide), which could interfere with glucose levels, were excluded. A more detailed description of inclusion and exclusion criteria is given elsewhere (17).

The control group was compiled from a historical database. Only healthy nonsmokers with body composition assessed by DXA, age >35 years, and a full dataset were included. Furthermore, lean subjects were excluded from the control group to achieve similar body size and composition as in type 2 diabetic and control groups. The final control group consisted of 61 subjects.

Chamber protocols and diets

Each subject followed a standard calorimeter protocol. In brief, subjects entered the respiration chamber the night before the study and fasted from 10:00 P.M. until the next morning. The measurement started at 9:00 A.M. and continued for 24 h. Subjects were fed an isoenergetic diet based on earlier determined equations (17–19). The carbohydrate content varied from 48 to 59%, fat from 28 to 37%, and protein was constant at 15% of energy. Meals were provided at 9:00 A.M., 1:00 P.M., and 6:00 P.M. and snacks at 11:00 A.M., 3:00 P.M., and 10:00 P.M. The scheduled exercise programs were carried out on a treadmill (75-W workload) varying from 30 to 40 min/day and as walking sequences ($2 \times 25 \times 3.5$ m) varying from 0 to 2 times/day.

Measurement of body composition

Body weight was measured to the nearest 0.1 kg using weighing scales (model 707; Seca, Copenhagen, Denmark). The weight was measured in the morning in fasting condition, with an empty bladder, without shoes, and in light clothing. Body

composition, i.e., fat-free mass (FFM), fat mass, and bone mineral content, was assessed by DXA (Lunar Radiation, Madison, WI). All scans were performed using slow mode (38–42 mm/s) (20).

Measurement of energy expenditure

The 24-h energy expenditure was measured by indirect whole-body calorimetry based on oxygen uptake, carbon dioxide production, and nitrogen excreted in the urine in one of two 14.7-m³ open-circuit respiratory chambers. The respiratory chamber is described in detail elsewhere (21). Standardized measurements of basal metabolic rate (BMR), 24-h energy expenditure, EE_{sleep}, and spontaneous physical activity (SPA) were made. The subjects were kept under 24-h surveillance by a laboratory technician during the day and by medical students during the night.

The volume of the outgoing air from the chamber was measured by the principle of differential pressure (AVA 500; Hartmann & Braun, Frankfurt, Germany). The carbon dioxide concentration of the outgoing air was measured by infrared analysis (Uras 3G; Hartmann & Braun), and the oxygen concentration was measured by the paramagnetic principle (Magnos 4G; Hartmann & Braun). The 24-h energy expenditure was measured from 9:00 A.M. to 9:00 A.M. the following morning, and the EE_{sleep} was measured between 1:00 A.M. and 6:00 A.M. Basal metabolic rate (BMR) was measured for 1 h from 8:00 A.M. to 9:00 A.M. on the second morning after 12 h of fasting, while subjects were awake but still lying prone in bed.

The EE_{sleep} has a coefficient of variation (CV) $<3\%$ on repeated measurements in the same subject (>2 weeks apart) compared with a CV of 4% on BMR (22).

SPA was assessed by two microwave radar detectors (Sisor Mini-Radar; Static Input System SA, Lausanne, Switzerland), which continuously emitted and received a signal. When the radar detected a moving object, a signal was generated and received by the transceiver. The SPA measurements indicated the percentage of time the subjects were active to a detectable degree.

Variables and statistics

Variables that were not normally distributed were either log transformed or categorized as appropriate. The main outcome

variables were EE_{sleep}, BMR, and 24-h energy expenditure. Univariate regression was used to examine associations among FFM, fat mass, SPA, sex, and age and EE_{sleep}, BMR, or 24-h energy expenditure. Variables that were significantly associated were then entered into multiple regression analyses using a forward stepwise model. In all analyses, the significance level was set at 0.05.

General linear modeling was used to compare EE_{sleep}, BMR, or 24-h energy expenditure between the type 2 diabetic and the control groups after adjustment for body composition, sex, and age. Statistical analyses were performed with SPSS for Windows version 11.0.1 (SPSS, Chicago, IL).

RESULTS— The physiological characteristics of the 31 type 2 diabetic subjects and the 61 nondiabetic subjects are presented in Table 1. Sixty-one percent of the subjects in both groups were women. The mean age of the type 2 diabetic group was significantly higher than in the nondiabetic group (59 ± 9 vs. 43 ± 6 years, $P < 0.001$). No significant differences in body weight and composition were observed. The median of duration of diabetes was 2.5 years (range 0.3–26.6) in the type 2 diabetic group.

In univariate analyses, FFM was the major predictor of EE_{sleep}, BMR, and 24-h energy expenditure, explaining 57.5, 64.2, and 70.1% of the variation, respectively. Associated determinants of EE_{sleep}, BMR, and 24-h energy expenditure were added to stepwise multiple regression analyses, and the prediction equations were as follows:

$$1) \text{ EE}_{\text{sleep}} (\text{kcal/day}) = 408.7 + 16.5 \cdot \text{FFM} (\text{kg}) + 7.9 \cdot \text{fat mass} (\text{kg}) + 147.3 \cdot [\text{SPA}_{\text{sleep}} (\%)] + 89.7 \cdot [\text{diabetes status} (0,1)] + 106 \cdot \text{sex} (0,1)$$

$$2) \text{ 24-h energy expenditure (kcal/day)} = 389.7 + 22.2 \cdot \text{FFM} (\text{kg}) + 7.2 \cdot \text{fat mass} (\text{kg}) + 52.7 \cdot [\text{24-h SPA} (\%)] + 124.9 \cdot [\text{diabetes status} (0,1)] + 129.2 \cdot \text{sex} (0,1)$$

$$3) \text{ BMR (kcal/day)} = 541.9 + 18.2 \cdot \text{FFM} (\text{kg}) + 7.7 \cdot \text{fat mass} (\text{kg}) + 185.4 \cdot \text{sex} (0,1)$$

Diabetes status was defined as nondiabetic (0) and type 2 diabetes (1). Sex was defined as women (0) and men (1).

FFM ($P < 0.001$), fat mass ($P < 0.001$), SPA_{sleep} ($P < 0.001$), diabetes status ($P = 0.002$), and sex ($P = 0.030$) were all significant predictors of EE_{sleep}. Similarly, FFM ($P < 0.001$), fat mass ($P <$

Table 1—Physiological characteristics of 31 Caucasians (61% women) with type 2 diabetes and 61 nondiabetic control subjects (61% women)

	Type 2 diabetes	No diabetes	Mean difference
n	31	61	
Age (years)	59.1 ± 8.8 (39–75)	43.4 ± 5.6 (35–57)	+15.7 (+36.1%)*
Body weight (kg)	101.8 ± 13.8 (69.0–123.9)	101.6 ± 17.4 (61.5–144.7)	+0.2 (+0.2%)
Height (cm)	169 ± 10 (150–193)	172 ± 8 (157–189)	–3 (–1.7%)
BMI (kg/m ²)	35.5 ± 3.7 (28.2–42.6)	34.1 ± 4.7 (25.1–47.8)	+1.4 (+4.1%)
FFM			
kg	59.7 ± 11.1 (39.4–79.4)	62.4 ± 9.6 (37.4–80.0)	–2.7 (–4.3%)
%	59.0 ± 6.9 (45.6–70.5)	60.8 ± 7.7 (44.2–81.9)	–1.8 (–3.0%)
Fat mass			
kg	41.3 ± 8.7 (28.1–63.4)	40.0 ± 12.4 (14.8–71.7)	+1.3 (+3.3%)
%	41.0 ± 6.9 (29.6–54.5)	39.2 ± 7.7 (18.1–55.8)	+1.8 (+4.6%)

Data are means ± SD (range). Significant difference between groups: * $P < 0.001$. No asterisk means no significant difference ($P > 0.05$).

0.001), 24-h SPA ($P < 0.001$), diabetes status ($P = 0.001$), and sex ($P = 0.030$) were significant predictors of 24-h energy expenditure.

FFM ($P < 0.001$), fat mass ($P < 0.001$), and sex ($P = 0.010$) were significantly associated with BMR. Age was not significantly associated with BMR, EE_{sleep} , or 24-h energy expenditure when adjustment for sex and body composition was made. The duration of diabetes did not contribute to the explained variation in any energy expenditure parameters. The explained variations in the models were 82.9, 81.4, and 70.0%, respectively (Eqs. 1, 2, and 3).

No significant differences in unadjusted EE_{sleep} , BMR, and 24-h energy expenditure, respectively, were observed between the type 2 diabetic and the control groups. Furthermore, unadjusted BMR was 7.6% higher ($+145 \pm 20$ kcal/day) than EE_{sleep} in the control group compared with 3.6% ($+72 \pm 27$ kcal/

day) in the type 2 diabetic group ($P = 0.031$).

When adjusted for FFM, fat mass, SPA, sex, and age, the mean EE_{sleep} was 7.7% higher in the type 2 diabetic subjects compared with the nondiabetic control subjects ($2,023 \pm 29$ vs. $1,879 \pm 18$ kcal/day, $P = 0.001$). After the same adjustment, BMR was 6.9% higher in the type 2 diabetic group than in the control group ($2,140 \pm 45$ vs. $2,001 \pm 28$ kcal/day, $P = 0.026$). Furthermore, 24-h energy expenditure adjusted for FFM, fat mass, SPA, sex, and age was 6.5% higher in the type 2 diabetic group compared with the nondiabetic control group ($2,679 \pm 37$ vs. $2,515 \pm 23$ kcal/day, $P = 0.002$) (Table 2). The effect of diabetes status between 24-h energy expenditure and FFM adjusted for fat mass, sex, and age is illustrated in Fig. 1. During the chamber stay, the control subjects were in energy balance, whereas the individuals with type 2 diabetes were in negative en-

ergy balance (7 ± 35 vs. -234 ± 48 kcal/day, $P < 0.001$). When 24-h energy expenditure was adjusted for energy balance, the difference between the type 2 diabetic group and the control group was reduced to 4.0% (96 ± 49 kcal/day, $P = 0.052$).

The 24-h SPA, adjusted for duration of exercise, was significantly lower (-10.5%) in the type 2 diabetic subjects compared with the nondiabetic subjects (7.5 ± 0.2 vs. $8.5 \pm 0.2\%$, $P = 0.003$). Conversely, the mean SPA_{sleep} was 40% higher in the type 2 diabetic group compared with the nondiabetic group but did not reach significance (0.93 ± 0.11 vs. $0.66 \pm 0.08\%$, $P = 0.056$). No interactions between the predicting variables were found.

CONCLUSIONS—The present study demonstrates that overweight and obese Caucasians with type 2 diabetes have a 7% higher 24-h energy expenditure after

Table 2—Whole-body indirect calorimetry

	Type 2 diabetes	No diabetes	Mean difference
n	31	61	
24-h energy expenditure (kcal/day)	2,587 ± 61	2,563 ± 43	+22 ± 74 (+0.9%)‡
Adjusted 24-h energy expenditure (kcal/day)*	2,679 ± 37	2,515 ± 23	+164 ± 31 (+6.5%)§
BMR (kcal/day)	2,060 ± 59	2,042 ± 42	+18 ± 73 (+0.9%)‡
Adjusted BMR (kcal/day)*	2,140 ± 45	2,001 ± 28	+139 ± 61 (+6.9%)
EE_{sleep} (kcal/day)	1,989 ± 51	1,897 ± 37	+92 ± 63 (+4.8%)‡
Adjusted EE_{sleep} (kcal/day)*	2,023 ± 29	1,879 ± 18	+144 ± 40 (+7.7%)§
24-h SPA (%)†	7.6 ± 0.2	8.5 ± 0.2	–0.9 ± 0.3 (–10.5%)§
Sleeping SPA (%)†	0.93 ± 0.11	0.66 ± 0.08	+0.27 ± 0.14 (+40.9%)‡

Data are means ± SE. *Adjusted for FFM, fat mass, SPA, sex, and age; †adjusted for duration of exercise on bike. No significant difference between groups: ‡ $P > 0.05$. Significant difference between groups: § $P < 0.01$; || $P < 0.05$.

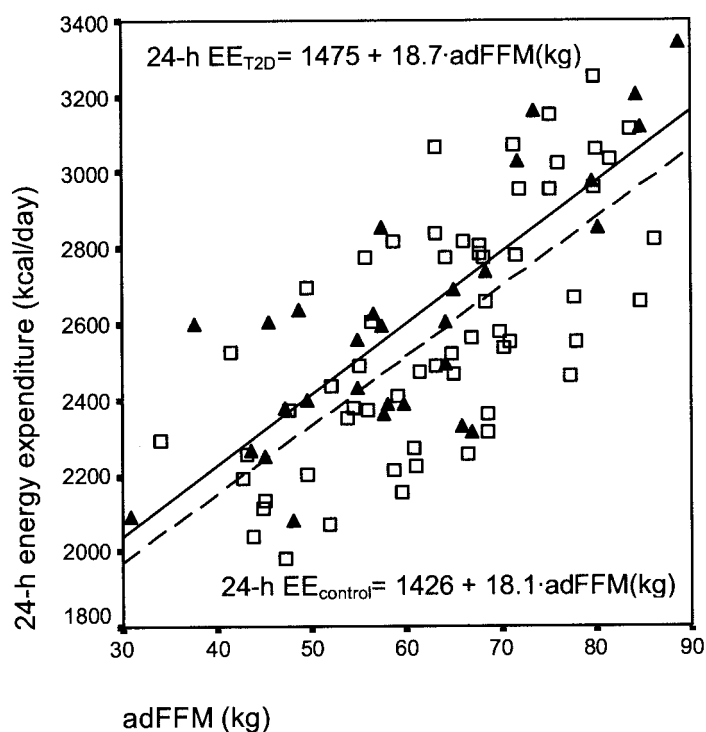


Figure 1—24-h energy expenditure as a function of FFM adjusted for fat mass, sex, and age (adFFM). \blacktriangle , Individuals with type 2 diabetes; \square , nondiabetic individuals. Regression lines: —, type 2 diabetic subjects ($P < 0.001$); - - -, control subjects ($P < 0.001$).

adjustment for FFM, fat mass, SPA, sex, and age than overweight and obese individuals without diabetes. Our result is higher than earlier reports of 2–5% higher 24-h energy expenditure in diabetic Pima Indians (8,9). However, it has been reported that healthy Pima Indians have higher adjusted 24-h energy expenditure than Caucasians (23). Therefore, the relative increase in 24-h energy expenditure when developing type 2 diabetes may be less in Pima Indians. Thus, overall our findings are in agreement with other studies where individuals with type 2 diabetes under a strict but low physical activity level have a higher 24-h energy expenditure than healthy nondiabetic individuals (6–9,12,13).

It is notable that the nondiabetic subjects were younger than the type 2 diabetic subjects. However, this is unlikely to have any effect on the results, because age was not an independent determinant of energy expenditure in this study after adjustment for body size, composition, and sex. This is in agreement with most studies, apart from Weyer et al. (23), who reported a marginal but significant effect of age on 24-h energy expenditure, with a

decrease of 2 kcal/day per year. Our finding of a 165-kcal/day higher 24-h energy expenditure in type 2 diabetic subjects exceeds the variation in 24-h energy expenditure, which could be explained by the Weyer estimate (–32 kcal/day). Because the difference in mean age between the groups was significant, age was included as a covariate in the analyses. However, this did not alter the results.

EE_{sleep} and BMR were 7–8% higher in the type 2 diabetic subjects compared with the control group. Previous results of an ~5% higher EE_{rest} in type 2 diabetes have been reported in Pima Indians (7–9) and in a single study in Caucasians (13). This suggests that the diabetic state may induce an increase in EE_{rest} . This is supported by a longitudinal study in a group of 17 Pima Indians in whom glucose tolerance deteriorated from normal glucose tolerance to impaired glucose tolerance to type 2 diabetes. EE_{rest} (adjusted for FFM and fat mass) increased by 4.2% from normal glucose tolerance to impaired glucose tolerance and by another 2.6% with progression to type 2 diabetes (9). Therefore, EE_{rest} may increase early during the development of type 2 diabetes, and this

may be mediated by other physiological factors than changes in body composition.

Several potential physiological mechanisms may be responsible for the increased EE_{rest} in type 2 diabetes. Fasting blood glucose is an independent determinant of EE_{rest} (24) explained partly by an elevated rate of hepatic glucose production in individuals with type 2 diabetes (9,13). A 5% reduction in BMR has been found when fasting glucose was lowered by 5.9 mmol/l (24), so that the glycemic control may be an important determinant of EE_{rest} .

The necessary energy for the energy-consuming process of hepatic glucose production may be provided by an increased rate of lipid oxidation (13). Furthermore, a high rate of lipolysis leading to an elevated level of plasma free fatty acids (FFAs) has been associated with impaired insulin-mediated suppression of hepatic glucose production (25), impaired glucose uptake in skeletal muscle (26), increased synthesis of VLDL (27), and stimulation of mitochondrial uncoupling proteins (28). Thus, FFAs may be a potent mediator in several mechanisms associated with increased EE_{rest} .

There is limited evidence that sympathetic nervous system (SNS) activity is increased in hyperinsulinemic individuals with type 2 diabetes compared with body- and age-matched nondiabetic control subjects (29). Furthermore, SNS activity increases with advancing age in healthy adults (30). Our data clearly demonstrate that 24-h energy expenditure was higher in the older and type 2 diabetic subjects after adjustment for body composition, SPA, sex, and age, and we suggest that the effect of chronic increases in SNS activity might partly be responsible. However, the discontinuation of antidiabetes medication may also have caused temporal further elevation in glucose and insulin levels, which also could contribute to differences in 24-h energy expenditure between the groups.

In theory, the higher energy expenditure should promote a negative energy balance and thereby weight loss in obese type 2 diabetic patients. Together with urinary glucose, this may serve as a defense mechanism against further weight gain. However, it is well established that type 2 diabetic patients are often more resistant than matched nondiabetic individuals to losing weight on weight management programs, independent of

whether the intervention is conventional or pharmaceutical assisted (31). Therefore, the higher energy expenditure may be less important than other pathophysiological abnormalities involving appetite regulation in type 2 diabetic subjects.

However, the higher 24-h energy expenditure of subjects with type 2 diabetes needs to be addressed to estimate individual energy requirements for clinical purposes. We observed a larger deficit on 24-h energy balance in the diabetic group compared with the nondiabetic group, which may be due to using nondiabetes prediction equations to estimate energy requirements. Energy imbalance is known to influence substrate oxidation (32) and, over longer periods of under- or overfeeding, also EE_{rest} (33). In addition, urinary glucose excretion has been reported to be 3.1% of 24-h energy expenditure (103 ± 112 kcal/day) in obese type 2 diabetic individuals on treatment (34), which would contribute to an even higher energy deficit. The energy losses would most likely increase further in type 2 diabetic patients off treatment. To our knowledge, only two prediction equations of EE_{rest} in individuals with type 2 diabetes have been developed, and they used less accurate measurements of EE_{rest} and body composition (35,36). Therefore, more accurate prediction equations for individuals with type 2 diabetes are needed for clinical purposes and trials.

We found a significant smaller positive difference between BMR and EE_{sleep} in the type 2 diabetic individuals compared with the nondiabetic subjects. This may partly be explained by disturbed sleep caused by need for thirst or urination among the type 2 diabetic subjects (37), supported by their markedly higher level of SPA_{sleep} . This phenomenon could be more pronounced as antidiabetes medication was ceased 2 weeks before the chamber stay. A significant lower level of 24-h SPA was observed in the type 2 diabetic group compared with the nondiabetic group. Recent studies have shown a high correlation between the standardized physical activity in the chamber and the habitual physical activity in free-living conditions measured over several days by the double-labeled water method (38). However, lower SPA has not been reported in other studies, and it is not known whether it can be generalized to all patients with type 2 diabetes. More studies using the double-labeled water method, allowing

measurements of free-living energy expenditure, are needed to test this hypothesis.

Finally, our results confirm that FFM, which reflects the metabolically active tissue, is the major determinant of energy expenditure (19,21,39). Furthermore, fat mass was significant and independent of FFM associated with energy expenditure. The energy requirements of various organs (respiration, heart, liver, and kidney) are likely to be increased by the enlarged fat mass, and more energy is required to carry and move the larger body (21). However, several potential modulators of energy expenditure, which may have contributed to the explained variation, were not assessed in the present study. These include the level of various hormones (such as thyroid hormones) (39), cytokines and peptides (such as leptin, adiponectin, and tumor necrosis factor- α secreted from the fat cells) (40), uncoupling proteins (28), and SNS activity (29). Another cause of variation is the lack of metabolic uniformity in the FFM, which is connected with the interindividual differences in components of highly active tissues and organs (41). Thus, different ratios of high-versus low-energy-requiring organs may explain some of the residual interindividual variation in energy expenditure. Taken together, genetic variations leading to interindividual differences in the above may be important determinants of energy expenditure.

In conclusion, the present study confirms the previous reported alterations in 24-h energy expenditure in Pima Indians with type 2 diabetes and may be even more pronounced in Caucasians. Basal, resting, and 24-h energy expenditure, independently of body composition, sex, and age, were found to be 7–8% higher in overweight and obese Caucasians with type 2 diabetes compared with healthy control subjects. Under a standardized but low physical activity level, the higher 24-h energy expenditure in type 2 diabetic patients clearly shows that the higher BMR is quantitatively more important than the lower physical activity and postprandial thermogenic response. Currently, it is not clear whether the observed metabolic impairments are factors or adaptational responses to the diabetic state. Longitudinal studies are necessary to elucidate the metabolic abnormalities and underlying mechanisms associated with the developing of type 2 diabetes.

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