Postprandial Increase in Energy Expenditure Correlates with Body Weight Reduction in Patients with Type 2 Diabetes Receiving Diet Therapy

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Aim: The clinical significance of energy expenditure (EE) in the treatment of type 2 diabetes has not been fully elucidated. Here we analyzed the relationships between EE and clinical measurements in patients with type 2 diabetes receiving diet therapy.

Methods: A total of 100 patients (34 women and 66 men) with type 2 diabetes admitted to our hospital for glycemic control were enrolled. The participants received an energy-restricted diet during their hospitalization (median, 15 days). EE was measured in the fasted (FEE) and postprandial (PPEE) states using indirect calorimetry. The postprandial increment of EE (ΔEE) was calculated from the FEE and PPEE (ΔEE = PPEE – FEE).

Results: FEE, PPEE, and ΔEE were 0.997 ± 0.203, 1.104 ± 0.213, and 0.107 ± 0.134 kcal/min, respectively. Body weight decreased from 68.7 ± 16.6 to 66.8 ± 16.0 kg (p < 0.0001) during hospitalization. FEE and PPEE showed positive correlations with height, body weight, body mass index, and abdominal circumference at admission, but ΔEE was not correlated with these anthropometric measurements. On the other hand, ΔEE was inversely correlated with the body weight change. The association between ΔEE and the body weight change was independent of age, sex, and HbA1c.

Conclusions: Postprandial increase in energy expenditure may be a determinant of individual differences in weight reduction in patients with type 2 diabetes on diet therapy. As a simple surrogate for diet-induced thermogenesis, ΔEE may serve as a useful predictive marker for the efficacy of diet therapy.

Key words: Diet therapy, Energy expenditure, Type 2 diabetes mellitus

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and persists for 5–6 h after a meal; it accounts for approximately 10% of daily EE. Several, but not all, studies have indicated that DIT or glucose-induced thermogenesis (GIT) is diminished in obese individuals. A cross-sectional study reported that diminished GIT already exists at the onset of obesity. Furthermore, lower GIT in obese subjects persists even after weight reduction by diet therapy. It was also reported that the Pima population, who have a high prevalence of obesity and type 2 diabetes, show lower GIT than body weight-matched Caucasians.

Previously, we measured resting EE at 09:00 h after an overnight fast (fasting energy expenditure; FEE) and at 15:00 h in the postprandial state (postprandial energy expenditure; PEE) in hospitalized patients with type 2 diabetes to estimate daily energy expenditure using indirect calorimeter. In that study, PEE was significantly higher than FEE, and the postprandial increment in EE (ΔEE) corresponded with the estimated amount of DIT. However, the relationship between the EE indices (FEE, PEE, and ΔEE) and body weight change in type 2 diabetes has not been clarified. In the present study, we examined the associations of the EE indices with body weight change and other clinical measurements in hospitalized patients with type 2 diabetes receiving diet therapy.

**Methods**

**Subjects**

Patients with type 2 diabetes who were admitted to Nippon Medical School Hospital (Tokyo, Japan) for glycemic control during 2011–2013 were enrolled (n = 100, aged 45–65 years, 34 women and 66 men). Exclusion criteria included receiving insulin therapy before hospitalization, proliferative diabetic retinopathy, diabetic nephropathy of stage 3 or higher (urinary albumin excretion ≥ 300 mg/g Cr [spot] or ≥ 300 mg/day), ketoacidosis, liver cirrhosis, uncontrolled endocrine disease, infectious disease, malignant disease, and other systemic diseases. The study protocol was approved by the Institutional Review Board and conformed to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000), and all participants provided informed consent before enrollment.

**Clinical Measurements**

All participants underwent physical examinations including height, body weight, abdominal circumference, and blood pressure on the first and last morning of hospitalization. Blood samples were taken after an overnight fast on the second day of admission and 2 or 3 days before discharge. Fasting plasma glucose was measured using glucose oxidase method (ADAMS Glucose GA-1170; Arkray, Kyoto, Japan). Glycated hemoglobin (HbA1c) was measured using high performance liquid chromatography (ADAMS A1c HA-8160, Arkray) and is expressed as the percentage value of the National Glycohemoglobin Standardization Program according to the Japan Diabetes Society guideline. Serum and urinary C-peptide levels were measured using a chemiluminescent enzyme immunoassay (Fujirebio Inc., Tokyo, Japan).

**Diet and Insulin Therapy**

During the hospitalization period, dietary energy intake (kcal/day) was restricted to 27.5 kcal/kg of standard body weight (SBW) based on the recommendation of the Japan Diabetes Society. SBW was calculated from the following formula because a body mass index (BMI) of 22 is regarded as ideal for adult Japanese individuals: SBW (kg) = [height (m)]^2 × 22 (BMI, kg/m^2). The daily dietary energy intake was divided approximately equally for breakfast (08:00 h), lunch (12:00 h), and dinner (18:00 h). Each diet contained approximately 20% of energy as fat, 20% as protein, and 60% as carbohydrate. To evaluate the efficacy of the diet therapy, physical activity was maintained within the patient’s usual intensity, without a specific exercise program. If the patients were being treated with oral hypoglycemic agents at the time of admission, the agents were withdrawn on the second day of admission. On the third day, insulin therapy was initiated for all participants using the following formula for the initial daily dose: insulin (U/day) = fasting plasma glucose (mg/dL) × 0.08. The dose was divided into 3 or 4 daily insulin injections (2–6 U each): three injections of ultrarapid insulin analogue (aspart, glulisine, or lispro) before meals and, if necessary, an additional injection of long-acting insulin analogue (detemir or glargine). Thereafter, the daily insulin dose was managed appropriately until discharge.

**Evaluation of Energy Expenditure**

The assessment of EE was performed within 10 days after admission. Each participant was assessed twice: at 09:00 h (after a 14 h overnight fast) and at 15:00 h (3 h after lunch with mealtime insulin). After resting in a seated position for 15 min in a temperature-controlled (25°C) room, respiratory gas exchange was continuously measured in the supine position for 30 min with an indirect calorimeter (Aeromonitor; Minato Medical Science Co. Ltd, Osaka, Japan). The data for the last 15 min were used for analysis. EE (kcal/min) was calculated using Weir’s formula. The
EE at 09:00 h was used as the fasting EE (FEE) and that at 15:00 h as the postprandial EE (PPEE). The postprandial increment in EE (ΔEE) was calculated as follows: ΔEE = PPEE – FEE.

**Table 1. Clinical characteristics and energy expenditure indices**

| Variable | Admission | Discharge | P-value* |
|----------|-----------|-----------|----------|
| n (women/men) | 100 (34/66) |           |          |
| Age (years) | 55.6 ± 12.3 |           |          |
| Duration of diabetes (years) | 3.5 [0–8] |           |          |
| Height (cm) | 165.5 ± 9.8 |           |          |
| Body weight (kg) | 68.7 ± 16.6 | 66.8 ± 16.0 | <0.0001 |
| BMI (kg/m²) | 24.9 ± 4.7 | 24.2 ± 4.5 | <0.0001 |
| Abdominal circumference (cm) | 89.6 ± 11.8 | 86.3 ± 11.1 | <0.0001 |
| Fasting plasma glucose (mg/dL) | 175 ± 51 | 118 ± 19 | <0.0001 |
| HbA₁c (%) | 10.0 ± 2.1 |           |          |
| Serum C-peptide (mg/dL) | 1.9 ± 0.9 |           |          |
| Urinary C-peptide (µg/day) | 116 ± 71 |           |          |
| Systolic blood pressure (mmHg) | 127 ± 18 | 116 ± 14 | <0.0001 |
| Diastolic blood pressure (mmHg) | 72 ± 12 | 66 ± 9 | <0.0001 |
| Diabetic microvascular complication | 100 (34/66) | | |
| Retinopathy (n [%]) | 14 [14] |           |          |
| Albuminuria, >30 mg/g·Cr (n [%]) | 28 [28] |           |          |
| Abnormal Achilles tendon reflex (n [%]) | 19 [19] |           |          |
| Diabetes medication | 100 (34/66) | | |
| None (n [%]) | 63 [63] | 1 [1] |          |
| Oral hypoglycemic agents (n [%]) | 37 [37] | 17 [17] |          |
| Insulin (n [%]) | 0 [0] | 88 [88] |          |

Continuous variables are expressed as mean ± standard deviation or median [interquartile range]. *Differences between the values at admission and those at discharge. †Diet and exercise therapy without any hypoglycemic medications. BMI, body mass index; HbA₁c, glycated hemoglobin; FEE, fasting energy expenditure; PPEE, postprandial energy expenditure; ΔEE, postprandial increment in energy expenditure above FEE (ΔEE = PPEE – FEE).

**Statistical Analysis**

Continuous variables are expressed as mean ± standard deviation or median [interquartile range] for variables with a normal or skewed distribution, respectively. Differences in clinical measurements between admission and discharge and in EE between fasting and postprandial states were analyzed using paired t-test. Correlations between EE indices (FEE, PPEE, and ΔEE) and other continuous variables were examined using Pearson correlation analysis. A multivariate regression model was used to evaluate the relative significance of each EE index for the body weight change. A p-value < 0.05 was considered significant. All analyses were performed using JMP 11 software (SAS Institute Inc., Cary, NC, USA).

**Results**

**Clinical Characteristics and Energy Expenditure**

Clinical characteristics of the participants at admission and discharge and their EE indices are shown in Table 1. PPEE was significantly higher than FEE (p < 0.0001). The ΔEE was 0.107 ± 0.134 kcal/min. During hospitalization (15 [14–16] days), all participants received diet therapy (1647 ± 167 kcal/day) and intensive insulin treatment to improve glycemic control, thereby fasting blood glucose was decreased significantly. In total, 88% of the participants continued insulin treatment until discharge. No severe adverse effects were observed during the hospitalization period. Body weight, BMI, abdominal circumference, FPG, and systolic and diastolic blood pressure decreased significantly during the hospitalization with diet therapy.

Table 2 shows the Pearson correlation coefficients of each EE index with clinical measurements at admi-
FEE and PPEE showed positive correlations with height, body weight, BMI, and abdominal circumference, and C-peptide levels, whereas they correlated inversely with age. FEE was also correlated positively with the duration of diabetes. ΔEE showed a positive correlation with diastolic blood pressure.

### Discussion

Most of the previous studies on EE in type 2 diabetes have focused on a comparison between patients and healthy individuals. They have demonstrated that patients with type 2 diabetes have higher BMR but lower DIT (or GIT) as compared to healthy individuals. These findings have contributed to our understanding of dynamic changes in EE under diabetic conditions. On the other hand, there have been few reports on individual differences in EE and their influence on treatment outcomes in patients with type 2 diabetes. Since type 2 diabetes is a heterogeneous disease, patients are supposed to have a wide range of EE. In the present study, we analyzed the relationships between EE indices (FEE, PPEE, and ΔEE) and clinical measurements in hospitalized patients with type 2 diabetes on diet therapy. Although FEE and PPEE were correlated with anthropometric parameters (height, body weight, BMI, and abdominal circumference) at admission, ΔEE was not correlated with these variables. On the other hand, ΔEE was inversely correlated with the body weight change independently of age, sex, and HbA1c.

The measurement conditions for FEE in the present study fulfilled the requirements for the measurement of BMR, which generally require that the subject be completely rested, lying down, fully awake, fasted for 10–12 h, in thermo-neutral conditions (22–26°C), and free from emotional stress. Thus, FEE in the present study reflects the BMR of the participants. Indeed, FEE was correlated with age and anthropometric parameters as reported in BMR. In the present study, FEE was also correlated positively with serum and urinary levels of C-peptide, a marker of endogenous insulin secretion. To our knowledge, there are few reports regarding the association between BMR and C-peptide; however, the positive correlation seems reasonable because both BMR and endogenous insulin secretion generally increase with obesity. In the present study, both FEE and C-peptide levels were actually correlated with BMI, and the association between FEE and C-peptide disappeared after adjustment for BMI (data not shown). PPEE was also correlated with age, anthropometric parameters, and C-peptide levels. Similar associations of FEE and PPEE with the clinical measurements are not unexpected because

### Table 2. Pearson correlation coefficients between energy expenditure indices and other continuous variables at admission

| Variable                  | FEE       |        |        |        | PPEE     |        |        |        |        | ΔEE      |        |        |
|---------------------------|-----------|--------|--------|--------|----------|--------|--------|--------|--------|----------|--------|--------|
|                           | r         | p-value| r      | p-value| r        | p-value| r      | p-value| r      | p-value  |
| Age                       | −0.45     | <0.0001| −0.51  | <0.0001| −0.12    | 0.23   |
| Duration of diabetes      | −0.21     | 0.040  | −0.16  | 0.12   | 0.061    | 0.54   |
| Height                    | 0.69      | <0.0001| 0.66   | <0.0001| 0.0098   | 0.92   |
| Body weight               | 0.78      | <0.0001| 0.81   | <0.0001| 0.11     | 0.29   |
| BMI                       | 0.55      | <0.0001| 0.60   | <0.0001| 0.12     | 0.24   |
| Abdominal circumference    | 0.55      | <0.0001| 0.59   | <0.0001| 0.098    | 0.33   |
| Fasting plasma glucose    | 0.0033    | 0.97   | −0.046 | 0.65   | −0.078   | 0.44   |
| HbA1c                     | 0.17      | 0.10   | 0.17   | 0.10   | 0.014    | 0.89   |
| Serum C-peptide           | 0.34      | 0.0006 | 0.34   | 0.0005 | 0.030    | 0.77   |
| Urinary C-peptide         | 0.41      | <0.0001| 0.48   | <0.0001| 0.15     | 0.13   |
| Systolic blood pressure   | −0.053    | 0.60   | 0.035  | 0.73   | 0.14     | 0.17   |
| Diastolic blood pressure  | 0.052     | 0.61   | 0.17   | 0.084  | 0.20     | 0.049  |

FEE, fasting energy expenditure; PPEE, postprandial energy expenditure; ΔEE, postprandial increment in energy expenditure above FEE (ΔEE = PPEE − FEE); BMI, body mass index; HbA1c, glycated hemoglobin.
peroxisome proliferator-activated receptor-γ coactivator-1α and uncoupling protein-1. In humans, BAT had been thought to involute throughout childhood and adolescence; however, recent studies using positron emission tomography revealed the existence of metabolically active BAT in adults. Intriguingly, Lee et al. reported that SNS activation by cold exposure induces BAT accumulation accompanied by DIT increase in humans. Saito also suggested that EE increase after food intake is more obvious in BAT-positive than -negative individuals. Further research into the relationships between EE and clinical parameters relating to SNS activity or BAT may reveal the endogenous determinant of EE.

There are several potential mechanisms underlying the relationship between EE and the efficacy of diet therapy. With respect to body weight change, EE, but not FEE, was inversely correlated with the body weight change, suggesting that DIT rather than BMR is an important factor for individual differences in body weight change on diet therapy. Although DIT accounts for only approximately 10% of PPEE; i.e., the predominant component of PPEE is considered to be BMR.

The only difference in the measurement of PPEE from that of FEE was consumption of breakfast and lunch (with mealtime insulin) before the measurement. DIT is therefore considered to reflect DIT. In several studies evaluating 24 h EE in participants who consumed three meals a day, three different peaks of DIT were observed at approximately 2–3 h after breakfast, lunch, and dinner. PPEE at 15:00 h (3 h after lunch) in the present study should therefore include a certain part of the DIT peak after lunch. Collectively, DIT in the present study, a simple calculation from the two-point measurement of EE (FEE and PPEE), may be a convenient and useful index for estimating DIT. In addition to total energy or protein content (or both) in the diet, various endogenous factors have been proposed as determinants for DIT, including lean body mass, glucose tolerance, insulin resistance, and sympathetic nerve system (SNS) activity. In the present study, whereas no correlations were seen between DIT and anthropometric or glycemic measurements, DIT was positively correlated with diastolic blood pressure. The positive correlation may be due in part to the SNS activity. SNS activity is postulated as a major endogenous determinant of DIT because beta-adrenergic blockade largely decreases GIT. In rodents, SNS activity-induced DIT has been considered mainly due to thermogenesis in brown adipose tissue (BAT). SNS activation stimulates cAMP-protein kinase A pathway in BAT thorough β3 adrenergic receptor, leading to increased expression of peroxisome proliferator-activated receptor-γ coactivator-1α and uncoupling protein-1. In humans, BAT had been thought to involute throughout childhood and adolescence; however, recent studies using positron emission tomography revealed the existence of metabolically active BAT in adults. Intriguingly, Lee et al. reported that SNS activation by cold exposure induces BAT accumulation accompanied by DIT increase in humans. Saito also suggested that EE increase after food intake is more obvious in BAT-positive than -negative individuals. Further research into the relationships between DIT and clinical parameters relating to SNS activity or BAT may reveal the endogenous determinant of DIT.

There are several potential mechanisms underlying the relationship between DIT and the efficacy of diet therapy. With respect to body weight change, DIT, but not FEE, was inversely correlated with the body weight change, suggesting that DIT rather than BMR is an important factor for individual differences in body weight change on diet therapy. Although DIT accounts for only about 10% of daily EE, the amount would contribute to individual differences in total EE. At the same time, since DIT is supposed to be largely influenced by SNS activity, DIT may in part represent SNS activity influencing body weight regulation. In fact, the relationship between SNS activity (assessed by postprandial norepinephrine concentration) and the efficacy of diet therapy has been reported in obese Caucasians. DIT may also represent amount or activity of BAT. To our knowledge, there has been no direct evidence for the involvement BAT in the efficacy of diet therapy; however, Yoneshiro et al. accounted for only approximately 10% of PPEE; i.e., the predominant component of PPEE is considered to be BMR.
recently reported that cold- or capsaicin-induced BAT recruitment could reduce body fat mass in healthy individuals. We recently reported that miglitol, an a-glucosidase inhibitor, is preferable not only for improving glycemic control but also for promoting body weight reduction in patients with obese type 2 diabetes\(^{46}\). In rodents, miglitol increased energy expenditure and attenuated diet-induced obesity\(^{47, 48}\). Intriguingly, miglitol stimulated increased mass\(^{46}\); in rodents, miglitol increased energy expenditure indices (FEE [Model 1], PPEE [Model 2], and \(\Delta EE\) [Model 3]) and clinical covariates (age, sex, and HbA\(_1c\)). Total \(r^2\) and \(p\) values for the entire model are shown. HbA\(_1c\), glycated hemoglobin; FEE, fasting energy expenditure; PPEE, postprandial energy expenditure; \(\Delta EE\), postprandial increment in energy expenditure above FEE (\(\Delta EE = PPEE - FEE\)).

The present study has several limitations. First, whereas \(\Delta EE\) was calculated from the two-point measurement of EE (FEE and PPEE) in the present study, DIT is commonly calculated from the area under the curve above BMR with multipoint measurement of EE, e.g., every 30 min for 24 h using respiratory chamber\(^{34}\). The two-point analysis using indirect calorimetry may have an advantage at least in terms of convenience, i.e., readily applicable to clinical use; however, it would be preferable to validate the compatibility of \(\Delta EE\) with conventional multipoint analysis of DIT. Second, since EE is closely related to body composition\(^5, 14\) and various metabolic factors including insulin\(^28, 57\), stricter control of the potential confounding factors at the time of EE measurement (e.g., the amount of weight loss and the length of insulin treatment until the measurement) might provide more convincing data. In addition, the information on \(\Delta EE\) changes and their association with body weight changes during diet therapy may provide additional insights into the role of DIT in body weight regulation. Third, the study period (15 [14–16] days) is too short to attain obvious body weight reduction. A long-term follow-up after strict diet control (e.g., after discharge in the present study) will be necessary to strengthen the potential of \(\Delta EE\) as a predictor of body weight reduction on diet therapy. Last, the cause of individual differences in \(\Delta EE\) still remains to be elucidated. The elucidation of the individual differences may open new therapeutic avenues for body weight control.

### Conclusions

In the present study, we demonstrated that \(\Delta EE\) was inversely correlated with the body weight change
in patients with type 2 diabetes receiving energy-restricted diet. Postprandial increase in energy expenditure may therefore be a key determinant of individual differences in body weight change on diet therapy. As a simple surrogate measure of DIT, ΔEE may serve as a useful predictive marker for the efficacy of diet therapy for weight reduction.

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Conflicts of Interest

None of the authors have any conflicts of interest associated with this manuscript.

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