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Original Article

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 HbA_{1c}.**
***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

Introduction

Diet therapy is an essential approach for the treatment of type 2 diabetes because not only improvement of glycemic control but also reducing the risk of diabetic complications is expected[1, 2]. In clinical practice, however, there are large individual variations in the efficacy of diet therapy for body weight reduction[3, 4]. Body weight change is a result of the balance between energy expenditure (EE) and dietary energy intake. Thus, EE should be a critical determinant of individual differences in body weight change with diet therapy.

Total EE consists of three components: physical activity, basal metabolic rate (BMR), and diet-induced thermogenesis (DIT)[5]. BMR accounts for approximately 60% of daily EE[6, 7], includes the resting metabolism of all organs, and is mainly determined by muscle and fat mass[8]. Although overweight and obese subjects have higher BMR relative to healthy ones due to the increased fat mass[9], a low BMR is reported to be a potent predictor for the development of obesity[10]. DIT is due to food digestion and absorption

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and persists for 5−6 h after a meal; it accounts for approximately 10% of daily EE[6, 7]. Several, but not all, studies have indicated that DIT or glucose-induced thermogenesis (GIT) is diminished in obese individuals[11-14]. A cross-sectional study reported that diminished GIT already exists at the onset of obesity[15]. Furthermore, lower GIT in obese subjects persists even after weight reduction by diet therapy[16]. 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[17].

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; PPEE) in hospitalized patients with type 2 diabetes to estimate daily energy expenditure using indirect calorimeter[18]. In that study, PPEE 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, PPEE, 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)[19], 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 (HbA_{1c}) 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[20]. 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[21]. SBW was calculated from the following formula because a body mass index (BMI) of 22 is regarded as ideal for adult Japanese individuals[22]: 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℃) 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[23]. The

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/m^2)	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
HbA_{1c} (%)	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			
Retinopathy (*n* [%])	14 [14.0]		
Albuminuria, > 30 mg/g·Cr (*n* [%])	28 [28.0]		
Abnormal Achilles tendon reflex (*n* [%])	19 [19.0]		
Diabetes medication			
None (*n* [%]) †	63 [63.0]	1 [1.0]	
Oral hypoglycemic agents (*n* [%])	37 [37.0]	17 [17.0]	
Insulin (*n* [%])	0 [0]	88 [88.0]	
Energy expenditure indices			
FEE (kcal/min)	0.997 ± 0.203		
PPEE (kcal/min)	1.104 ± 0.213		
ΔEE (kcal/min)	0.107 ± 0.134		

Continuous valuables 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; HbA_{1c}, glycated hemoglobin; FEE, fasting energy expenditure; PPEE, postprandial energy expenditure; ΔEE, postprandial increment in energy expenditure above FEE (ΔEE = PPEE − FEE).

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.

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 admis-

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
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
HbA_{1c}	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; HbA_{1c}, glycated hemoglobin.

sion. 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 inversely with the duration of diabetes. ΔEE showed a positive correlation with diastolic blood pressure.

Relationships between Energy Expenditure Indices and Body Weight Change

Fig. 1 shows the relationships between EE indices (FEE, PPEE, and ΔEE) and percent change in body weight. ΔEE was inversely correlated with the body weight change (**Fig. 1C**), whereas no correlations were observed in FEE and PPEE (**Fig. 1A** and **B**). Multiple regression analyses of the EE indices (**Table 3**) revealed that PPEE (Model 2) and, more strongly, ΔEE (Model 3) were associated with the body weight change independently of age, sex, and HbA_{1c}.

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[24-27] but lower DIT (or GIT)[17, 28] 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 HbA_{1c}.

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℃), and free from emotional stress[29, 30]. 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[29, 31-33]. 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

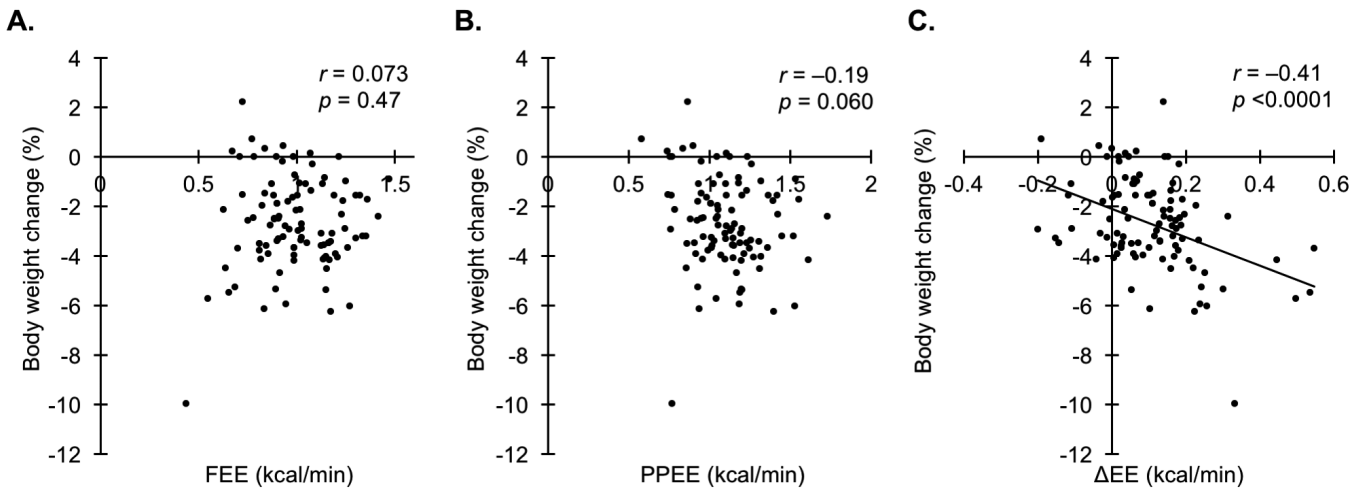

Fig. 1. Relationships between energy expenditure indices and body weight change

Correlations of (A) FEE, (B) PPEE, and (C) ΔEE with percent change in body weight. Pearson correlation coefficient is shown in each panel. FEE, fasting energy expenditure; PPEE, postprandial energy expenditure; ΔEE, postprandial increment in energy expenditure above FEE (ΔEE = PPEE − FEE).

ΔEE accounted 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. ΔEE 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[34-36]. 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, ΔEE 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[14, 36]. In the present study, whereas no correlations were seen between ΔEE and anthropometric or glycemic measurements, ΔEE 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 ΔEE because beta-adrenergic blockade largely decreases GIT[37]. In rodents, SNS activity-induced DIT has been considered mainly due to thermogenesis in brown adipose tissue (BAT)[38, 39]. SNS activation stimulates cAMP-protein kinase A pathway in BAT thorough $\beta 3$ adrenergic receptor, leading to increased expression of peroxisome proliferator-activated receptor-γ coactivator-1α and uncoupling protein-1[40]. 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[41]. Intriguingly, Lee *et al*.[42] reported that SNS activation by cold exposure induces BAT accumulation accompanied by DIT increase in humans. Saito[43] also suggested that EE increase after food intake is more obvious in BAT-positive than -negative individuals. Further research into the relationships between ΔEE and clinical parameters relating to SNS activity or BAT may reveal the endogenous determinant of ΔEE.

There are several potential mechanisms underlying the relationship between ΔEE and the efficacy of diet therapy. With respect to body weight change, ΔEE, 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[37], ΔEE 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[44]. ΔEE 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*.[45]

Table 3. Multiple regression models for predicting body weight change

	Model 1			Model 2			Model 3		
	$r^2=0.11$		$p=0.028$	$r^2=0.14$		$p=0.0049$	$r^2=0.27$		$p<0.0001$
	β-coefficient	t-value	p-value	β-coefficient	t-value	p-value	β-coefficient	t-value	p-value
Age	0.015	0.13	0.89	−0.17	−1.51	0.13	−0.094	−1.04	0.30
Sex (women)	0.24	2.21	0.030	0.086	0.82	0.41	0.19	2.16	0.033
HbA_{1c}	0.23	2.31	0.023	0.26	2.69	0.0086	0.24	2.65	0.0094
FEE	0.14	1.19	0.24						
PPEE				−0.28	−2.35	0.021			
ΔEE							−0.43	−4.84	<0.0001

Data are expressed as β-coefficient (estimated partial regression coefficient) and t- and p-values for the association of percent change in body weight with energy expenditure indices (FEE [Model 1], PPEE [Model 2], and ΔEE [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; ΔEE, postprandial increment in energy expenditure above FEE (ΔEE=PPEE−FEE).

recently reported that cold- or capsaicin-induced BAT recruitment could reduce body fat mass in healthy individuals. We recently reported that miglitol, an α-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 β3 adrenergic receptor−cAMP−protein kinase A pathway and upregulated uncoupling protein-1 in BAT[48]. Overall, the SNS-BAT-DIT axis underlying ΔEE may be a potential therapeutic target for improving the efficacy of diet therapy.

Several reports have also suggested the significance of DIT for body weight reduction in surgical treatment of severe obesity. For instance, augmentation of DIT partly accounts for weight loss after gastric bypass surgeries both in rats[49] and humans[50]. Postprandial increase in EE persisted for as long as 9 years after Roux-en-Y gastric bypass, resulting in a favorable effect on long-term body weight maintenance[51]. Since DIT partly depends on food digestion and absorption processes, morphological changes of gut after the gastric bypass (e.g., an increase in intestinal wall thickness, a lengthening of the gut, or an increased mass) might increase the energy demands for the processes[52]. At the same time, the gastric bypass increases postprandial levels of gut hormones (peptide YY and glucagon-like peptide-1)[53] and changes a composition of intestinal microbiota[54], which have a potential to modulate energy expenditure[55, 56]. Further research into the involvement of those intestinal factors in DIT is now of great interest for better understanding the mechanism of body weight regulation.

The present study has several limitations. First, whereas ΔEE 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 ΔEE with conventional multipoint analysis of DIT. Second, since EE is closely related to body composition[9, 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 ΔEE 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 ΔEE as a predictor of body weight reduction on diet therapy. Last, the cause of individual differences in ΔEE 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 ΔEE 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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