Energy Expenditure in Free-Living Japanese People with Obesity and Type 2 Diabetes, Measured Using the Doubly-Labeled Water Method

Kazuko ISHIKAWA-TAKATA1,2, Shigeho TANAKA1,3, Jonghoon PARK4, Motohiko MIYACHI5, Akemi MORITA6, Naomi AIWA7 and Shaw WATANABE8

1 Department of Nutrition and Metabolism, National Institutes of Biomedical Innovation, Health and Nutrition, Tokyo 162–8636, Japan
2 Faculty of Applied Biosciences, Tokyo University of Agriculture, Tokyo 156–8502, Japan
3 Faculty of Nutrition, Kagawa Nutrition University, Saitama 350–0288, Japan
4 Department of Physical Education, Korea University, Seoul 02841 Korea
5 Department of Physical Activity Research, National Institutes of Biomedical Innovation, Health and Nutrition, Tokyo 162–8636, Japan
6 Department of Public Health and Occupation, Mie University, Mie 514–8507, Japan
7 Department of Nutrition and Life Science, Kanagawa Institute of Technology, Kanagawa 243–0292, Japan
8 Life Science Promoting Association, Tokyo 160–0015, Japan

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Summary We determined the total energy expenditure (TEE) of healthy overweight or obese people, and those with impaired glucose tolerance and/or impaired fasting glycemia (IGT/IFG), or type 2 diabetes (T2DM) using the doubly-labeled water method. As a second purpose, we compared the measured TEE with the target energy intake recommended in the treatment guidelines for diabetes. The participants were normal glucose tolerance (NGT), and IGT/IFG (n = 11) and T2DM (n = 9) patients, who were 50–59 y and had a body mass index >25 kg/m². The median TEE/body mass (BM) values were 32.6, 33.3, and 34.4 kcal/kg BM and the TEE/target BM values (target BM: BM at a BMI of 22 kg/m²) were 43.7, 50.2, and 46.5 kcal/kg target BM for each group, respectively, and did not differ significantly among them. Obese Japanese participants with T2DM in this study had lower TEE/BM than previously studied in non-obese participants with T2DM. In IGT/IFG or T2DM patients, if 30 kcal/kg target BM was used as the energy coefficient, on the basis of the treatment guidelines, the difference between TEE and the target energy intake would be −1.174 ± 552 kcal (−38 ± 11%). When 3.5 kcal/kg target BM was used as the energy coefficient, the difference between TEE and the target energy intake would be −877 ± 542 kcal (−27 ± 13%). Thus, the energy coefficients used to estimate target energy intake during lifestyle modification in obese/overweight patients with T2DM are considered to be quite low during the first step of diet therapy.

Key Words target energy intake, treatment guideline, impaired glucose tolerance, impaired fasting glycemia, energy coefficients

Lifestyle management, including that of diet, physical activity, and smoking, is a fundamental aspect of type 2 diabetes (T2DM) care. In particular, weight management is important for overweight and obese patients. The treatment guidelines of the Japan Diabetes Society (JDS) suggest that the primary purpose of dietary therapy of T2DM is to compensate for the insulin secretory defect by optimizing energy intake (1). In addition, the correction of obesity is required to reinstate the appropriate balance between insulin demand and secretion. The dietary therapy outlined in the treatment guidelines involves the calculation of target energy intake using the energy coefficient as body mass (BM) multiplied by target body mass (target BM). Estimated as the BM at a body mass index (BMI) of 22 kg/m² for patients younger than 65 y old, and 22 to 25 kg/m² for patients with 65 y old or older. The American Diabetes Association (ADA) also suggests that weight loss achieved using a combination of caloric restriction and lifestyle modification is beneficial for overweight or obese adults with T2DM or prediabetes (2). The recommended energy intake is set to achieve a 500–700 kcal/d energy deficit, or an intake of 1,200–1,500 kcal/d for women and 1,500–1,800 kcal/d for men (3). These guidelines and a review of weight loss interventions suggest that a body mass reduction >5% has beneficial effects on glycated hemoglobin (HbA1c), lipids, and blood pressure (1, 3, 4). However, the energy intake required to achieve effective weight reduction is not clear.

Caron et al. have reviewed the literature regarding energy expenditure in people with diabetes mellitus (5) and shown that the resting metabolic rate (RMR) is high in patients with poorly-controlled diabetes, but that the energy expenditure associated with physical activity tends to be lower because a higher proportion of their activity is low-intensity. In addition, there is no precise
way of estimating RMR and the total energy expenditure (TEE) in free-living T2DM patients. Therefore, it is difficult to determine the most appropriate energy intake to achieve optimal BM.

Recently, two studies have measured TEE in free-living Japanese T2DM patients using the doubly-labelled water (DLW) method (6, 7). These studies showed that TEE is comparable between individuals with or without diabetes, and calculated TEE/BM values for T2DM patients of 36.5 and 36.4 kcal/kg BM, respectively. However, Yoshimura et al. studied patients with a mean age of 55 y and a mean BMI of 24.0 kg/m² (6), whereas Morino et al. studied patients with a mean age of 70.2 y and a mean BMI of 23.3 kg/m² (7). However, for healthy Japanese women, we previously indicated that TEE per day increases with increase of BMI, whereas TEE per body weight decreases with increase of BMI (8). A nationwide multicenter study conducted by the Japan Diabetes Clinical Data Management (JDDM) showed that the mean BMI of patients with T2DM increased from 24.7 to 25.4 kg/m² between 2004 and 2014 (9) and that patients younger than 65 y in particular had a significant increase in BMI. Furthermore, men younger than 54 y showed an increase in BMI from 25.9 to 27.2 kg/m².

Thus, the weight management of overweight/obese middle-aged patients is the most important component of the management of T2DM. The aims of the present study were i) to determine the TEE of overweight/obese Japanese people with or without T2DM, and ii) to compare this with the target energy intake shown in the guidelines for the treatment of T2DM.

MATERIALS AND METHODS

Participants. We studied participants in the Saku Control Obesity Program (SCOP) (10). All the 50–59 y-old obese men and women (n=30) were selected for the present study and they were allocated to normal glucose tolerance (NGT) (n=10), impaired glucose tolerance and/or impaired fasting glycaemia (IGT/IFG: impaired glucose tolerance (n=2), impaired fasting glycaemia (n=4), and a combination of impaired glucose tolerance and impaired fasting glycaemia (n=5)), and T2DM (n=9) groups on the basis of their fasting serum glucose and serum glucose concentration at the 2-h time point of an oral glucose tolerance test (OGTT) performed at the start of the SCOP, the JDS criteria, or a diagnosis made by their doctor. The diabetic patients were undergoing a diet and exercise program (n=2), taking metformin (n=1), undergoing a patient education program (n=1), or had only received advice regarding appropriate diet and exercise habits (n=5). None of the participants was administering insulin. The study was approved by the ethics committee of the National Institute of Health and Nutrition (2006.7.1) and registered in the UMIN Clinical Trials Registry (UMIN000016892). This study was conducted according to the guidelines laid down in the Declaration of Helsinki. The purpose and methodology of the study were explained in detail to all the participants and they gave their written informed consent.

Measurement of energy expenditure. TEE was measured using the DLW method, as described previously (8). The participants were asked to visit the study location for the collection of a baseline urine sample, and were then orally administered a single dose of water, some of which was labeled with $^{18}$O and $^2$H. Then, for the subsequent 2 wk, they were asked to maintain their normal diet and activity patterns, and to collect urine samples at the same time of day on eight occasions over this period. The isotopic ratios of the urine samples were analyzed using DELTA plus isotope ratio spectrometry (DELTAPlus; Thermo Electron Corporation, Bremen, Germany). TEE was calculated using the A6 equation of Schoeller et al. (11) and Weir’s equation (12). The mean food quotient, calculated using Black et al.’s equation (13) from a self-administered dietary history questionnaire (14), was used instead of the respiratory quotient. At the end of the 2-wk period, they were asked to visit the study site again after an overnight fast. RMR was measured after resting for 30 min in a supine position (15). Physical activity energy expenditure (PAEE) was calculated as TEE×0.9—RMR. Physical activity level (PAL) was calculated as TEE/RMR.

Anthropometric measurements. BM was measured on the day of dosing and on the day of RMR measurement at the end of the 2-wk TEE measurement period, to the nearest 0.1 kg, and height was measured to the nearest 0.1 cm using an automatic scale (Tanita, BF-220, Tokyo, Japan). Fat-free mass (FFM) was calculated as the dilution space assessed at the time of TEE measurement, divided by 0.732. Fat mass (FM) was calculated as the mean BM before and after the TEE measurement period, minus FFM. BM was calculated by dividing the mean BM by height squared. Target BM was calculated as the BM at a BMI of 22 kg/m², calculated using the measured height.

Statistical analysis. Because most of the data were not normally distributed, they are summarized using medians and the 25th and 75th percentiles. The three groups were compared using the Kruskal-Wallis test. In addition, to exclude the effect of the differences in sex distribution and age among the three groups, sex- and age-adjusted means and standard errors were calculated for TEE and PAEE using analysis of covariance (ANCOVA). The data are expressed as adjusted means and 95% confidence intervals. Spearman’s rank correlation coefficients for the relationships between BMI and TEE/BM or TEE/target BM were calculated. In addition, partial correlation coefficients adjusted for age and sex or age, sex, and the number of steps taken, were also calculated. The significance level was set at p<0.05. Statistical analysis was conducted using SPSS ver.22 (IBM, Inc., Armonk, NY, USA).

RESULTS

The physical characteristics of the participants are presented in Table 1. There were no significant differences among the groups, except with regard to fasting serum glucose and serum glucose at the 2-h time point.
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of the OGTT: the T2DM group had significantly higher fasting and 2-h serum glucose concentrations than the NGT and IGT/IFG groups. In the whole group of participants, BMI ranged from 27.6 to 39.1 kg/m², with a median of 29.7 kg/m². Sixteen participants were classified as overweight and 14 were classified as obese, according to the World Health Organization criteria (https://www.who.int/westernpacific/health-topics/obesity).

RMR, TEE, and PAEE were not significantly different among the groups, regardless of whether they were expressed as kcal, kcal/kg BM, kcal/kg FFM or kcal/kg target BM. The median TEE/BM values were 32.6–34.4 kcal/kg BM and the median TEE/target BM values were 43.7–50.2 kcal/kg target BM across all the participants (Table 2, Fig. 1a). The means and standard deviations of TEE/BW and TEE/target BM for the entire sample were 34.1±4.2 kcal/kg BM and 48.3±8.0 kcal/kg target BM, respectively. The PAL and mean number of daily steps were similar in each group.

The sex- and age-adjusted TEE and PAEE are compared in Table 3. The adjusted TEE and PAEE were similar in each group. TEE/BM, with or without adjustment for sex and age, were comparable, and the adjusted means were 33.4–34.6 kcal/kg BM.

Figure 1 compares the relationship of BMI with TEE/BM and TEE/target BM. TEE/BM did not correlate with BMI (r=0.129, p=0.496), but there was a relatively

Table 1. Characteristics of the participants.

|                     | NGT (n=10) | IGT/IFG (n=11) | T2DM (n=9) | p     |
|---------------------|------------|----------------|------------|-------|
| Male/female         | 5/5        | 6/5            | 5/4        | 0.649 |
| Age (y)             | 53.8 (51.2, 57.6) | 53.4 (50.4, 56.4) | 51.7 (50.7, 55.5) | 0.686 |
| Body mass (kg)      |            |                |            |       |
| Before              | 78.6 (77.6, 87.5) | 87.0 (77.5, 92.7) | 82.4 (77.4, 93.3) | 0.622 |
| After               | 78.9 (76.5, 86.8) | 87.5 (76.2, 92.4) | 81.3 (76.2, 93.1) | 0.543 |
| Difference           | −0.4 (−0.9, 0) | 0 (−0.4, 0.4) | −0.6 (−1.1, 0.3) |       |
| Height (cm)         | 165.5 (156.1, 174.0) | 163.8 (155.7, 169.4) | 168.6 (156.5, 172.7) | 0.871 |
| BMI (kg/m²)         | 29.4 (28.7, 30.7) | 30.6 (29.5, 35.1) | 30.3 (28.5, 33.5) | 0.309 |
| Fat-free mass (kg)  | 49.9 (42.3, 56.8) | 54.2 (43.9, 65.7) | 53.5 (44.3, 64.8) | 0.998 |
| Fat mass (kg)       | 31.7 (27.5, 35.0) | 30.9 (26.1, 34.0) | 29.7 (24.6, 37.0) | 0.300 |
| Body fat (%)        | 40.0 (32.9, 44.3) | 37.3 (28.4, 42.9) | 39.4 (30.1, 41.3) | 0.624 |
| Fasting glucose (mg/dL) | 100 (97, 101) | 111 (110, 119) | 139 (130, 143) | <0.001 |
| Serum glucose after 2 h of the OGTT (mg/dL) | 120 (107, 133) | 155 (124, 192) | 244 (212, 280) | 0.025 |

NGT: normal glucose tolerance, IGT/IFG: impaired glucose tolerance and/or impaired fasting glycemia, BMI: body mass index, OGTT: oral glucose tolerance test.

*p<0.001 vs. NGT, †p=0.025 vs. IGT/IFG, ‡p=0.003 vs. IGT/IFG.

Data are median (25th percentile, 75th percentile).

Body mass before the day of the doubly-labeled water dosing and after the last day of urine sampling, and the difference between body mass before and after the measurement period were shown.

Table 2. Resting metabolic rate, total energy expenditure, physical activity, and energy expenditure in the three groups.

|                     | NGT (n=10) | IGT/IFG (n=11) | T2DM (n=9) | p     |
|---------------------|------------|----------------|------------|-------|
| RMR (kcal/d)        | 1,488 (1,395, 1,700) | 1,469 (1,408, 1,858) | 1,686 (1,488, 1,765) | 0.303 |
| (kcal/kg BM)        | 18.6 (16.7, 20.6) | 17.4 (16.7, 19.6) | 21.2 (18.0, 22.2) | 0.231 |
| (kcal/kg FFM)       | 32.2 (27.3, 34.2) | 27.7 (24.6, 30.9) | 34.1 (27.2, 35.9) | 0.460 |
| (kcal/kg target BM) | 25.0 (22.2, 29.4) | 24.9 (23.2, 31.7) | 27.2 (24.3, 32.1) | 0.476 |
| TEE (kcal/d)        | 2,672 (2,532, 3,030) | 2,901 (2,552, 3,556) | 2,742 (2,494, 3,257) | 0.610 |
| (kcal/kg BM)        | 32.6 (31.9, 34.8) | 33.3 (31.4, 39.7) | 34.4 (32.1, 36.5) | 0.557 |
| (kcal/kg FFM)       | 54.1 (49.2, 58.0) | 57.3 (47.8, 61.3) | 53.7 (50.8, 60.2) | 0.991 |
| (kcal/kg target BM) | 43.7 (42.0, 47.0) | 50.2 (43.4, 57.5) | 46.5 (44.2, 55.5) | 0.325 |
| PAEE (kcal/d)       | 998 (768, 1,137) | 1,094 (477, 1,675) | 851 (649, 1,123) | 0.515 |
| (kcal/kg BM)        | 11.5 (9.4, 13.3) | 13.5 (6.6, 18.1) | 9.8 (7.4, 14.3) | 0.641 |
| (kcal/kg FFM)       | 18.6 (14.4, 21.2) | 20.3 (11.4, 28.5) | 15.9 (12.2, 22.0) | 0.632 |
| (kcal/kg target BM) | 15.3 (12.4, 17.8) | 18.0 (8.9, 27.7) | 13.2 (11.0, 19.1) | 0.450 |
| Walking steps/d     | 7,672 (7,241, 9,868) | 7,688 (4,871, 9,198) | 7,485 (5,976, 10,030) | 0.617 |
| PAL                 | 1.83 (1.59, 1.99) | 2.00 (1.55, 2.31) | 1.63 (1.53, 1.89) | 0.360 |

NGT: normal glucose tolerance, IGT/IFG: impaired glucose tolerance and/or impaired fasting glycemia, RMR: resting metabolic rate, TEE: total energy expenditure, BM: body mass, FFM: fat-free mass, target BM: target body mass; calculated as the body mass at a BMI of 22 kg/m². PAL: physical activity level; calculated as TEE divided by RMR. PAEE: physical activity energy expenditure; calculated as TEE×0.9–RMR.
strong correlation between BMI and TEE/target BM ($\rho=0.650$, $p<0.001$). Adjustment for age and sex did not alter these relationships (BMI and TEE/BM: $\rho=0.195$, $p=0.321$; BMI and TEE/target BM: $\rho=0.666$, $p<0.001$).

When IGT/IFG or T2DM participants were classified according to the PAL of dietary reference intakes (DRI) for Japan (16), the median TEE/target BM values were 34.9, 50.0, and 58.3 kcal/kg target BM in inactive (PAL<1.6, $n=3$), moderately active (1.6<PAL≤1.9, $n=13$), and very active (PAL>1.9, $n=4$) individuals. In the IGT/IFG or T2DM participants, the target energy intakes were estimated to be 1,485±149, 1,782±179, and 2,080±209 kcal/d using energy coefficients of 25, 30, and 35 kcal/kg target BM, respectively. The differences between the TEEs and the target energy intakes were −1,471±563 kcal (−48±9%), −1,174±552 kcal (−38±11%), and −877±542 kcal (−27±13%) for the
energy coefficients of 25, 30, and 35 kcal/kg target BM, respectively.

**DISCUSSION**

In the present study, we measured the TEE in overweight/obese Japanese people with or without diabetes and found that TEE/BM was similar among people with normal glucose homeostasis and those in the IGT/IFG and T2DM groups. However, the measured TEE/BM values were lower than those measured in previous studies of Japanese non-obese diabetic patients. In addition, when we used the energy coefficients in the JDS’s guidelines for the treatment of diabetes, the calculated target energy intakes were quite low compared with the actual TEE.

The participants in the present study were similarly or slightly more active than the healthy Japanese population as a whole. The mean number of steps taken was 7,485–7,688/d, which is similar to the number counted in the National Survey of Health and Nutrition, Japan (17), which indicated that the mean number of steps taken by people aged 50 were 7,670 and 6,857/d for men and women, respectively. When we compared the PALs, calculated as the TEE divided by RMR, the participants in the NGT and IGT/IFG groups were shown to be more active than in our previous study (18), by factors of 1.71 and 1.77 for men and women, respectively.

In the present study, the median TEE/BM values for the IGT/IFG and T2DM groups were 33.3 and 34.4 kcal/kg BM and the median BMIs were 30.6 and 30.3 kg/m², respectively. These values were slightly lower than those in previous studies for Japanese diabetic patients that were of a similar age, but not obese (36.5 kcal/kg BM) (6) and those of older non-obese Japanese diabetic patients (37.8 kcal/kg BM) (7). If TEE/BM is calculated using the data of Chong et al. (19), values of 41.3, 36.6, and 31.8 kcal/kg BM for normal, overweight, and obese diabetic participants are obtained using the DLW method. In addition, another study by Chong et al. (20) found that the TEE/BM of diabetic patients taking metformin, who had a mean BMI of 33.4 kg/m², was 32.3 kcal/kg BM. The TEE/BM values for obese diabetic patients (21) and obese diabetic patients using metformin (20) were lower than those of Japanese diabetic patients in previous studies (6, 7), but similar to those calculated in the present study. Our previous study (8) of healthy Japanese women also showed that TEE/BM was significantly negatively associated with BMI. However, there was no significant relationship between BMI and TEE/BM among participants in the present study, who had BMIs of 27.6–39.1 kg/m².

In the present study we did not find any significant difference in TEE among the NGT, IGT/IFG, and T2DM groups, which is consistent with the findings of previous studies that measured TEE in individuals with and without T2DM using the DLW method (6, 7, 21).

In the present study, the sex- and age-adjusted PAEE and TEE were similar among the groups. The review by Caron et al. (5) reported that PAEE is lower in patients with diabetes, which was attributed to a lower overall level of daily physical activity, owing to a high proportion of low-intensity physical activity being performed. However, the studies quoted in this review were mostly of non-Japanese populations and the characteristics of the participants, including their degree of obesity and lifestyle, were different from those of the present participants.

The treatment guidelines published by the JDS established target energy intakes for T2DM patients using energy coefficients of 25–30, 30–35, and >35 kcal/kg target BM for light (almost sedentary), moderate (mostly sedentary, except for commuting, housework, and light exercise), and heavy (regularly participating in heavy muscular work and/or vigorous exercise) physical activity; and multiplied these by the target BM, calculated as the BM at a BMI of 22 kg/m² for patients younger than 65 y old. However, in the present study, the TEE/target BM was 50.2 kcal/kg target BM for participants in the IGT/IFG group and 46.5 kcal/kg target BM for those in the T2DM group. In addition, when we classified the participants according to their PAL, the TEE/target BM values were 36.6, 50.0, and 58.3 kcal/kg target BM for light, moderate, and heavy physical activity, respectively. These values are much higher than the energy coefficients used by the JDS. The “Standards of Medical Care in Diabetes” published by the ADA recommends lifestyle interventions, including a 500–750 kcal dietary energy deficit. However, when 30 kcal/kg target BM is used to calculate target energy intake, the difference between the measured TEE and the calculated target energy intake is −1,174±552 kcal (−38±11%), which is nearly double the deficit in energy intake recommended by the ADA. In the present study, TEE/BM did not significantly correlate with BMI, but participants with a higher BMI had higher TEE/target BM values. Thus, the difference between the measured TEE and the target energy intake was greater among participants with high BMIs. Therefore, we contend that the energy coefficients suggested by the JDS are quite low for the first step of dietary therapy for obese/overweight patients. The JDS’s treatment guidelines also recommend that these energy coefficients should be used flexibly, and our data indicate that care should be taken when prescribing energy intake for patients whose actual BM differs substantially from the target BM.

The most notable limitation of this study was the number of participants. Because the number in each group was low, this might have affected the statistical power of the analysis. However, the cost and effort involved in such studies are high; therefore, the previous studies quoted herein studied similar numbers of people. Furthermore, even with a much larger number of participants, the conclusion of the present study that the TEE of patients with T2DM is much larger than the calculated target energy intake in the current Japanese guidelines would not be changed. In addition, the participants in the present study were recruited in one rural area in central Japan; therefore, their lifestyles are likely to be dissimilar to those of Japanese people living in an urban area.
In conclusion, TEE was comparable among obese/overweight Japanese subjects with or without T2DM. However, overweight/obese Japanese people with impaired fasting glycemia and/or impaired glucose tolerance, or T2DM have lower TEE/BMs than those previously published for non-obese T2DM patients. In people with a BMI over 27.6 kg/m², TEE/BM does not correlate with BMI. In addition, the energy coefficients used to estimate target energy intake during lifestyle modification in T2DM are quite low compared with the actual TEEs. However, further studies are needed to definitely establish the most appropriate target energy intakes for lifestyle modification in T2DM.

**Authorship**

The SCP study was designed and conducted by M.M., A.M., and N.A.; and S.W., K.IT., and J.P. measured the total energy expenditure and analyzed the data. S.T. participated in the measurement of the resting metabolic rate. K.IT. drafted the manuscript and all authors reviewed the manuscript.

**Disclosure of state of COI**

No conflicts of interest to be declared.

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