Table 2. Predictive equations for basal metabolic rate used in the present study.

Predictive equations (kcal/d)		
	Males	Females
Ganpule	(0.0481×W+0.0234×H−0.0138×A−0.4235)×1,000/4.186	(0.0481×W+0.0234×H−0.0138×A−0.9708)×1,000/4.186
Japan-DRI (2010)	21.5 ×W	20.7 ×W
Harris-Benedict	66.4730+13.7516×W+5.0033×H−6.7550×A	655.0955+9.5634×W+1.8496×H−4.6756×A
Schofield	(0.048×W+3.653)×1,000/4.186	(0.034×W+3.538)×1,000/4.186
Owen	879+(10.20×W)	795+(7.18×W)
Mifflin	5+(9.99×W)+(6.25×H)−(4.92×A)	−161+(9.99×W)+(6.25×H)−(4.92×A)

W: weight (kg), H: height (cm), A: age (y). Predictive equations for 50- to 59-y old obesity subjects were used.

determined using a dry gas volume meter (Shinagawa, DC-5, Tokyo, Japan) and then converted to the volume under conditions of standard temperature, pressure, and dry gas (STPD). The gas exchange results were converted to BMR (kcal/d) using Weir's equation (*22*).

Predictive equations of BMR. Predictive BMR was calculated using the Ganpule (*18*), Japan-DRI (*23*), Harris-Benedict (*24, 25*), Schofield (*26*), Owen (*14, 15*), and Mifflin (*16*) equations (Table 2). The Japan-DRI provided the BMR standards (standard BMR per unit weight) according to age and sex category, with the data for these standards being obtained from a Japanese BMR database (*21, 23*). The Owen and Mifflin equations were developed using data obtained from adults including obese subjects.

Blood samples. Venous blood samples were collected after a fast of at least 12 h for measurement of fasting glucose, glycosylated hemoglobin (HbA_{1c}), insulin, triglycerides, and free fatty acid. The value of the internationally used HbA_{1c} (%) (HbA_{1c} [NGSP]) defined by the NGSP (National Glycohemoglobin Standardization Program), was calculated by adding 0.4% to the obtained HbA_{1c} (JDS) (%) defined by the Japan Diabetes Society (JDS) (*27*). Insulin and free fatty acids were examined using the laboratory testing services provided by SRL Inc. (Tokyo, Japan). Insulin (μIU/mL) was measured using CLEIA (Lumipulse Presto Insulin, Fujirebio Inc.), which has a minimal detection limit of 0.3 μIU/mL. Free fatty acid (mEq/L) was determined using an enzymatic assay (NEFA-SS 'Eiken,' Eiken Chemical Co. Ltd., Tokyo, Japan) with a sensitivity of 0.005 mEq/L. Other blood parameters were analyzed in the clinical laboratory of Saku Central Hospital. HOMA-R was calculated as fasting insulin (μIU/mL)×fasting glucose (mg/dL)/405.

All subjects underwent a 75-g oral glucose tolerance test. The subjects were divided into three groups according to the Diagnosis Criteria Exploratory Committee of the Japan Diabetes Society (2010) (*27*): non-diabetes (n=10), pre-diabetes (n=7), and diabetes (n=13).

Statistical analysis. The results are expressed as the mean±standard deviation (SD). Statistical significance was set at $p<0.05$. The Kolmogorov-Smirnov test was used for statistical testing of normality. HbA_{1c} and fasting insulin were log transformed as the data were not normally distributed. Differences in body composition, blood parameters, and BMR (kcal/d, kcal/kg weight/d and kcal/kg FFM/d) among the three groups were evaluated using one-way analysis of variance (ANOVA) and the Bonferroni post hoc test. Analysis of covariance (ANCOVA) with BMR as the dependent variable and FFM, FM, age, and sex as covariates was carried out. In order to examine the mechanism for differences in BMR, the blood sample measurements such as fasting glucose were added to FFM, FM, age, and sex in ANCOVA. The interaction terms with sex and body composition variables were examined in these analyses. Multiple linear regression models were also constructed using BMR as the dependent variable and FFM, FM, age, and sex as the independent variables. Gender was treated as a binomial variable (0 for male subjects, 1 for female subjects). Body height was not adjusted for, as it did not contribute significantly to BMR in the models ($p>0.05$). The relationships between the residual (measured BMR minus BMR after adjustment for FFM, FM, age, and sex) and fasting glucose, $\log_e HbA_{1c}$, $\log_e$ fasting insulin, HOMA-R, triglycerides, and free fatty acid were examined using Pearson's correlation coefficients. The statistical significance of differences between measured BMR and predicted equation BMR was analyzed by one-way ANOVA with repeated measurements and Dunnett's post hoc test, while differences between predicted and measured BMR values among non-diabetes, pre-diabetes, and diabetes were evaluated by one-way ANOVA and Bonferroni's post hoc test. The statistical analyses were performed using SPSS for Windows (version 18.0; SPSS Inc., Chicago, IL, USA).

RESULTS

No significant difference was observed in body composition among the three groups (Table 1). The subjects with diabetes had significantly higher fasting glucose and $\log_e HbA_{1c}$ levels than subjects with non-diabetes. There was no interaction between sex and diabetes diagnosis in the relationship to BMR (F=2.166, p=0.137). Moreover the interaction terms with sex and body composition variables in ANCOVA with BMR as the dependent variable were not significant. Therefore, both sexes were combined in all analyses. After adjustment for FFM, FM, age, and sex the BMR in subjects with diabetes was 7.1% higher than in non diabetic subjects (Table 3). The ANCOVA showed fasting glucose

Table 3. Basal metabolic rate in subjects with non-diabetes, pre-diabetes, or diabetes.

	Non-diabetes (n=10) Mean±SD	Pre-diabetes (n=7) Mean±SD	Diabetes (n=13) Mean±SD	ANOVA p value	ANCOVA p value
Measured BMR (kcal/d)	1,486±182	1,484±183	1,711±221[a]	0.018	—
(kcal/kg weight/d)	18.3±1.5	18.2±1.4	19.6±1.5	0.054	—
(kcal/kg FFM/d)	27.9±3.3	29.0±4.4	31.2±3.6	0.106	—
Adjusted BMR (FM, FFM, age, sex) (kcal/d)	1,531±98	1,537±95	1,648±98[b]	—	0.021
Adjusted BMR (FM, FFM, age, sex, fasting glucose) (kcal/d)	1,535±128	1,538±99	1,644±132	—	0.171

Measured BMR: measured basal metabolic rate. FFM: fat free mass. Adjusted BMR: analysis of covariance with BMR as the dependent variable and FFM, FM, age, sex, and fasting glucose as covariates was carried out. Differences among the non-diabetes, pre-diabetes, and diabetes groups were evaluated by one-way ANOVA and the Bonferroni post hoc test, [a]$p<0.05$ vs. non-diabetes, and also by ANCOVA and the Bonferroni post hoc test, [b]$p<0.05$ vs. non-diabetes.

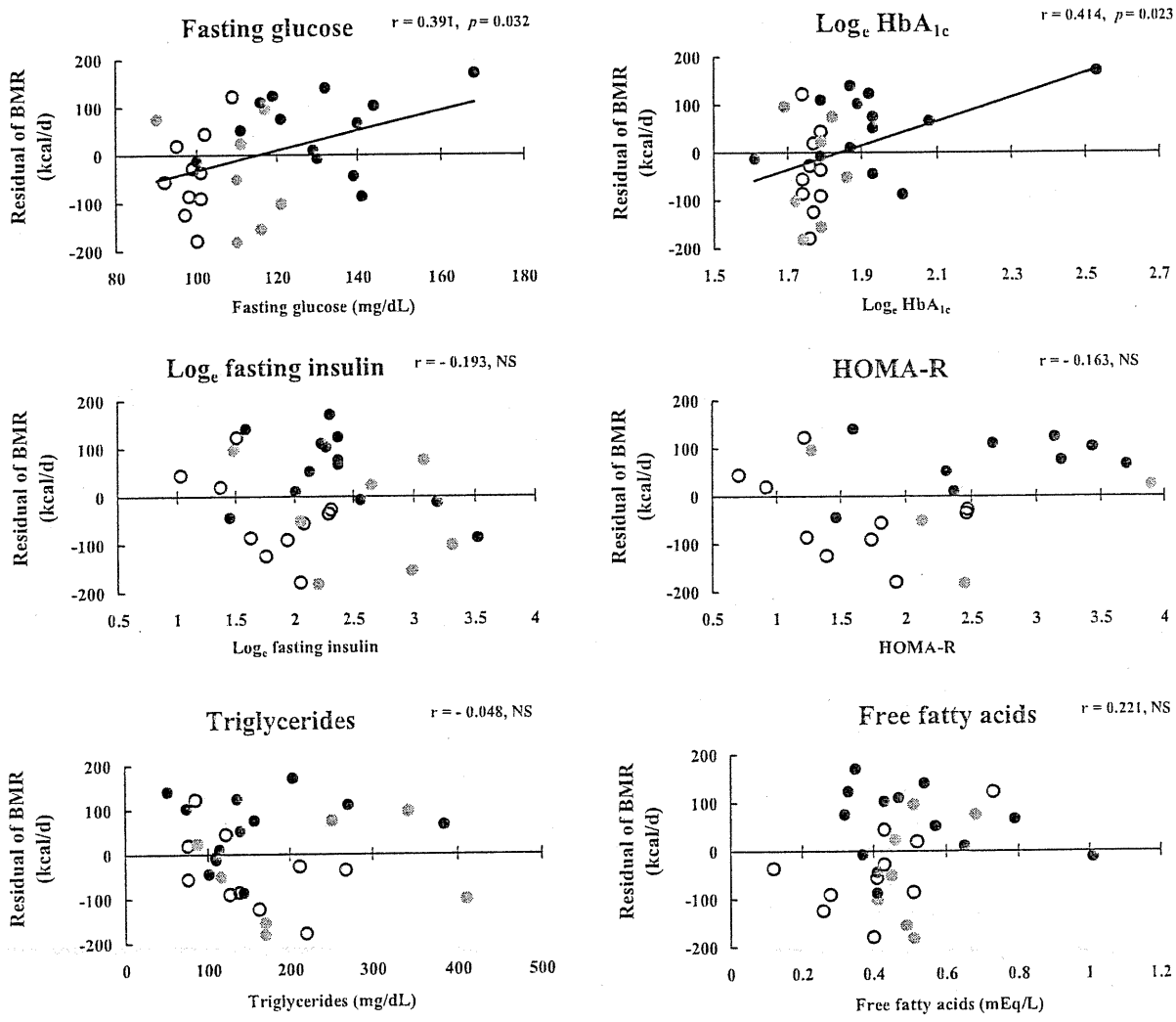

Fig. 1. Relationship between residual (measured BMR minus BMR adjusted for FM, FFM, age, and sex) and fasting glucose, log$_e$ HbA$_{1c}$, log$_e$ fasting insulin, HOMA-R, triglycerides and free fatty acids in subjects without diabetes, pre-diabetes or diabetes. HbA$_{1c}$ and fasting insulin were log transformed. Non-diabetes, white circles (○); pre-diabetes, gray circles (◍); diabetes, black circles (●). The regression lines are for all the subjects.

was an independent determinant of BMR, in addition to FFM, FM, age, and sex. After adjusting for fasting glucose in addition to FFM, FM, age and sex, there were no significant differences in BMR among the three groups. Furthermore, multiple regression analysis demonstrated 81% of the variability (R^2) in BMR was explained by FFM, FM, age, and sex, while fasting glucose as an additional independent variable explained

Table 4. Predicted basal metabolic rate in subjects with non-diabetes, pre-diabetes, or diabetes.

	Mean±SD (kcal/d)	Mean difference±SD (kcal/d)	ANOVA[a] *p* value	Post hoc test[b] *p* value	ANOVA[c] *p* value
Non-diabetes (n=10)			<0.001		
Ganpule	1,511±194	25±119		0.844	0.019[d]
Japan-DRI	1,712±175	227±117		<0.001	0.222
Harris-Benedict	1,584±196	99±127		0.002	0.061
Schofield	1,660±209	175±117		<0.001	0.068
Owen	1,548±219	62±123		0.094	0.075
Mifflin	1,499±209	13±126		0.990	0.026[d]
Pre-diabetes (n=7)			0.001		
Ganpule	1,502±214	17±148		0.977	
Japan-DRI	1,727±241	242±132		<0.001	
Harris-Benedict	1,583±210	98±159		0.111	
Schofield	1,648±222	163±185		0.002	
Owen	1,532±229	48±198		0.734	
Mifflin	1,486±226	2±167		1.000	
Diabetes (n=13)			<0.001		
Ganpule	1,601±237	−110±99		<0.001	
Japan-DRI	1,856±290	146±147		<0.001	
Harris-Benedict	1,692±253	−19±110		0.898	
Schofield	1,766±263	55±98		0.065	
Owen	1,649±264	−62±99		0.032	
Mifflin	1,585±242	−126±100		<0.001	

Mean difference: Mean of difference between predicted and measured BMR. ANOVA[a]: Significance of differences between predicted and measured BMR analyzed by one-way ANOVA with repeated measurements and Dunnett's post hoc test. Post hoc test[b]: Predicted vs. Measured. ANOVA[c]: Differences in predicted equation between non-diabetes, pre-diabetes and diabetes evaluated by one-way ANOVA and Bonferroni post hoc test. [d] $p<0.05$, Bonferroni post hoc test, non-diabetes vs. diabetes.

another 3% of the variability in BMR.

The relationships among residual BMR (measured BMR minus BMR after adjustment for FFM, FM, age, and sex) and fasting glucose, $\log_e$ HbA_{1c}, $\log_e$ fasting insulin, HOMA-R, triglycerides, and free fatty acids are shown in Fig. 1. Residual BMR correlated significantly with fasting glucose (r=0.391, p=0.032) and $\log_e$ HbA_{1c} (r=0.414, p=0.023), although there was no significant correlation between residual BMR and $\log_e$ fasting insulin, HOMA-R, triglycerides, or free fatty acid.

Table 4 shows differences between BMR predicted from six equations and measured BMR in subjects with non-diabetes, pre-diabetes, or diabetes. Predicted BMR values by Ganpule, Owen and Mifflin equations were not significantly different from the measured BMR in non- or pre diabetes. On the other hand, for diabetes there was no significant difference between measured and predicted BMR calculated by Harris-Benedict and Schofield equations. The differences between BMR predicted by Ganpule and Mifflin equations and measured BMR was significant lower in subjects with diabetes than in subjects without diabetes. The prediction error by Ganpule and Mifflin equations were similar to that calculated when BMR was adjusted for FM, FFM, age, and sex (Table 3). For the other equations, no significant differences were found between predicted and measured BMR.

DISCUSSION

This study compared BMRs among subjects with non-diabetes, pre-type 2 diabetes and type 2 diabetes in the obese Japanese population. The results showed that obese Japanese subjects with type 2 diabetes had significantly higher BMR than obese Japanese without diabetes. A similar trend has been demonstrated in previous studies. Furthermore, given the significant relationship we observed between residual BMR and fasting glucose, it is possible that fasting glucose level may be a factor in the higher BMR found in obese subjects with type 2 diabetes.

Several previous studies have examined whether or not BMR in patients with type 2 diabetes is higher than in non-diabetic subjects. Huang et al. (*28*) reported that BMR in these patients was 8.4% higher in females and 4.6% higher in males than in the corresponding non-diabetic subjects. Maiolo et al. (*29*) also reported that BMR was 35% higher in diabetic patients. It is important to note that BMR was not adjusted for body composition in these studies which may explain a large portion of the increase in BMR. On the other hand, two previous studies performed similar comparisons after adjustment for BMR. Fontvieille et al. (*3*) showed in Pima Indians that the BMR in patients with type 2 diabetes (weight: 107±33 kg, body fat: 32±9%) was 5.2% higher than in non-diabetic subjects (weight: 99±24 kg, body fat: 39±7%). Bitz et al. (*4*) also compared BMRs between subjects with or without type 2 diabetes in Caucasians and showed that BMR in the diabetic subjects (BMI: 35.5±3.7 kg/m^2) was 6.9% higher than in non-diabetic subjects (BMI: 34.1±4.7 kg/m^2). In the

present study, BMR adjusted for FFM, FM, age, and sex, was significantly higher in diabetic compared with non-diabetic subjects (7.1%) (Table 3). Surprisingly, the adjusted BMR in patients with diabetes was higher than in non-diabetic subjects. These three studies using adjusted BMR obtained similar results in different ethnicities.

Although the physiological mechanisms responsible for the increased BMR in individuals with type 2 diabetes are poorly understood, several mechanisms have been proposed to explain this increase. These include increased energy costs during hyperglycaemia, for example gluconeogenesis, protein turnover, and sympathetic nervous system activity (*3*). Bitz et al. (*4*) reported that free fatty acids may be a potential mediator in several mechanisms associated with increased BMR. Gougeon et al. (*30*) reported that BMR adjusted for weight, FFM, age, and sex was significantly higher in subjects with type 2 diabetes with a fasting plasma glucose >180 mg/dL than those with a level <180 mg/dL (*30*). They used a fasting plasma glucose level of 180 mg/dL as it represents the concentration considered to be the glycosuria threshold which reflects poor control. Gougeon et al. (*30*) also reported that fasting plasma glucose was a significant independent variable and increased the prediction of BMR by more than 3%. In the present study, we showed a significant relationship between residual BMR and fasting glucose (Fig. 1). After adjusting for fasting glucose in addition to FFM, FM, age and sex, there were no significant differences in BMR among the three groups (Table 3). Fasting glucose as an additional independent variable explained another 3% of the variability in BMR by multiple regression analysis. Therefore, the degree to which fasting glucose contributes to BMR was similar in different ethnicities. Weyer et al. (*31*) reported that a higher endogenous glucose output (EGO) was a relatively late finding in the development of type 2 diabetes and typically was not evident until the transition from impaired glucose tolerance (IGT) to diabetes. The extent to which the energy cost of EGO contributes to increased BMR is, therefore, probably less in individuals with IGT than in those with diabetes. In the present study, BMR in pre-diabetic subjects was not significantly higher than that measured in non-diabetic subjects. Fasting glucose values were also similar in non-diabetic and pre-diabetic subjects, which may have contributed to the similar BMR values we observed between the two groups. This result supports the results of Weyer et al. (*31*). In summary, higher BMR in obese subjects with type 2 diabetes may be related to fasting glucose level.

One of the limitations of the present study is the relatively small sample size. In the present study, both sexes were combined. Moreover, one diabetic patient who received metformin or glibenclamide therapy and another diabetic patient who had experienced diabetes patient education program in the past were included. However, more detailed analyses with larger samples size are needed for the better understanding of the effects of sex and medication. In panticular, there is some possibility that medication affects the relationship between blood glucose and BMR through the suppression of blood fasting glucose.

As the majority of clinical facilities do not have indirect calorimetry, BMR is usually estimated from predictive equations using data such as age, sex, height, and weight (*11*). A predictive equation of BMR in obese subjects is important to provide the basis for an individualized treatment plan for weight loss (*28*). In the present study, we examined the validity of six predictive equations for BMR in Japanese subjects with non-diabetes, pre-diabetes or diabetes. The Ganpule (*18*) and Japan-DRI (*21, 23*) equations were developed based on data from Japanese subjects. The Harris-Benedict (*24, 25*), Schofield (*26*), Owen (*14, 15*), and Mifflin (*16*) equations are used internationally. The Harris-Benedict equation is the most common method for calculating BMR (*26*), while the Owen (*14, 15*) and Mifflin (*16*) equations were developed in adults including obese subjects.

Huang et al. (*28*) demonstrated that the Harris-Benedict equation overestimated BMR in diabetic males and underestimated the value in diabetic females, while Gougeon et al. (*30*) reported that BMR predicted by the Owen equations did not differ significantly from measured BMR in obese diabetic males. In the present study, the differences between BMR predicted by Ganpule and Mifflin equations and measured BMR was significant lower and negative for most predictive equations in subjects with diabetes than in subjects without diabetes. In the present study, ANCOVA showed that the differences in average prediction error of the Ganpule and Mifflin equation among the three groups were comparable to the differences obtained after adjustment for FM, FFM, age, and sex. BMR was underestimated by 110 and 126 kcal/d in diabetes, while predicted BMR was comparable to measured BMR in the non-diabetes and pre-diabetes groups. Therefore, adjustment should be made for diabetes when predicting BMR.

In conclusion, obese Japanese with type 2 diabetes have higher BMR than obese Japanese without diabetes. This phenomenon appears to be similar in different ethnicities such as Pima Indians, Caucasians, and Asians. Although the physiological mechanisms responsible for the increased BMR in subjects with type 2 diabetes remain unclear, the fasting glucose level could be a major factor contributing to this increase. Furthermore, the difference between the prediction errors of the Ganpule and Mifflin equation in subjects with and without diabetes tended to be significant and was comparable to those when BMR was adjusted for FM, FFM, age, and sex. It is therefore important to pay attention to the prediction error for BMR in diabetic patients in the clinical setting.

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ORIGINAL ARTICLE

Lower physical activity is a strong predictor of cardiovascular events in elderly patients with type 2 diabetes mellitus beyond traditional risk factors: The Japanese elderly diabetes intervention trial

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Aim: It is well known that a decline in physical activity is associated with lifestyle-related diseases including cardiovascular (CV) events. However, little is known about the association between physical activity and CV events in elderly patients, because recent accumulating reports have mainly dealt with middle-aged populations. In this study, we investigated the correlation between physical activity and CV events in Japanese elderly patients with type 2 diabetes mellitus (T2DM).

Methods: A total of 938 Japanese elderly patients with T2DM (447 men and 491 women, mean age 71.9 years) enrolled (2000–2002) in the Japanese Elderly Diabetes Intervention Trial (J-EDIT) were used in this study. Physical activity consisting of three components, work, sports and leisure-time, of their lifestyle was evaluated using the Baecke questionnaire at baseline. Total activity score (TAS) as a sum of each activity score was divided into four quartiles (Q1 to Q4).

Results: During a follow-up period of 65.2 months, 165 events and 71 deaths in total occurred. Higher TAS grade was associated with reduced risk of all events (hazard ratios: 0.82, 0.77 and 0.54 in Q2, Q3 and Q4, respectively) with statistical significance. Even after multivariate adjustment for covariates, higher TAS grade was a strong predictor of all events, and the prediction by TAS of cerebrovascular events was more effective than that

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of cardiac events. In contrast, all-cause mortality gradually decreased according to TAS grade; however, no statistical significance was found. Among the four grades of TAS, no significant change in several parameters, such as profiles of lipid and glucose metabolism, blood pressure, physical measurements, cognitive function and depression scale, was found throughout the follow-up period, suggesting that the higher level of physical activity itself was associated with the risk reduction of primary events.

Conclusion: Lower physical activity is a strong and independent predictor of all CV events in the elderly with T2DM beyond traditional risk factors. In addition to strict management of each atherosclerotic risk factor, engagement with patients to augment and maintain the level of physical activity in their lifestyle is also essential in clinical practice.
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Keywords: elderly, engagement in physical activity, Japanese Elderly Diabetes Intervention Trial study, physical activity, risk reduction, type 2 diabetes mellitus.

Background

A decline in physical activity has been shown to lead to increased risk of several cardiovascular (CV) diseases, such as cerebrovascular disease (CVD) and coronary heart disease (CHD).[1–6] In developed countries, 80% of all deaths from CV disease occur in people aged 65 years and older.[7] Unfortunately, 60% or more of USA adults are not physically active in their lifestyle.[8] Accordingly, in 1995 the Centers for Disease Control (CDC) and the American College of Sports Medicine (ACSM) recommended a moderate amount of physical activity on most days, and preferably all days, of the week.[9] However, the precise mechanisms through which physical activity lowers the risk of CV disease are not well understood.

Little is known about the crucial correlation between physical activity and CV events in elderly patients, because recent accumulating reports have mainly dealt with middle-aged populations. In fact, the evidence as a whole has been derived from studies targeting the middle-aged and the elderly combined, including three previous studies in Japan.[10–12] In addition, few studies have evaluated the association between physical activity and long-term outcomes in Japanese. The Framingham Heart Study showed an inverse association between physical activity and mortality risk as a result of CV disease, even in 285 elderly individuals.[13] However, no statistical significance was reached, possibly as a result of the limited number of events. To our knowledge, how effective and beneficial encouragement of physical activity is in the elderly is still controversial. In general, although activity has been believed to be beneficial even in the elderly,[14–16] some studies have emphasized that physical activity might be harmful to the elderly.[13,17] Therefore, it is essential to investigate the precise association of physical activity with CV events and mortality in Japanese elderly patients.

In the present study, the correlation between grade of physical activity and events (all CV events and all-cause mortality) was investigated in Japanese elderly patients with type 2 diabetes mellitus (T2DM). In addition, analysis was also carried out to address which component was more effective as a good predictor.

Methods

Study population

The subjects were participants who were enrolled in the Japanese Elderly Diabetic Intervention Trial (J-EDIT), a randomized, double-blind, recently completed trial of intensive or standard treatment of diabetes for the prevention of CV disease in elderly patients with T2DM. J-EDIT involved 1173 diabetic subjects who were aged 65 years or older (mean age 71.8 ± 4.6 years) and whose serum glycated hemoglobin A1c (HbA1c) level was >7.4% from 39 institutions and hospitals (the University of Tokyo Hospital, Kobe University Hospital, Nagoya University Hospital and Tokyo Metropolitan Geriatric Hospital etc.) in Japan. Written informed consent was obtained from all patients.

From among these patients enrolled in the J-EDIT, we selected 938 patients in whom complete data regarding physical activity (Baecke physical activity questionnaire) were obtained at baseline. We excluded participants who had difficulty communicating, dementia or serious deterioration of activities of daily living (ADL).

Physical activity assessed by Baecke questionnaire

To evaluate physical activity at enrolment in this trial, Baecke physical activity questionnaire was carried out as previously reported.[18,19] The reliability of this score has been confirmed by many previous reports. Therefore, it is suggested that it might be a valuable monitoring tool for assessing the association of multiple domains of physical activity with the metabolic syndrome (MetS) in elderly patients with T2DM, with acceptable reliability and validity. The activity score is classified into three

domains: work activity, sports activity and non-sporting leisure activity. These three components consisted of items on the frequency, duration, average amount of time spent weekly on walking, hobbies and so on, and the average amount of time spent on odd jobs and sports monthly. The types of odd jobs, sports and hobbies (e.g. dancing, gardening or fishing) were also assessed.

In analyses, each component was also divided into several groups as follows: three groups in "work activity" score (WAS; None: =0, Low: ≥1 and <3.25, High: >3.25), two groups in "sports activity" score (SAS; Low: <4.0, High: ≥4.0), and four groups (quartiles) in "non-sporting leisure-time activity" score (LTAS; L-Q1: <2.0, L-Q2: ≥2.0 and <2.25, L-Q3: ≥2.25 and <2.75, L-Q4: ≥2.75). Scores from each component were summed to yield total physical activity score (TAS; maximum 15 points). TAS was divided into four quartiles (Q1 to Q4) as follows: Q1: <5.7, Q2: ≥5.7 and <7.7, Q3: ≥7.7 and <10.5, Q4: ≥10.5.

Physical measurement, cognitive function, ADL and mood status

At enrolment, body mass index (BMI) was calculated by physical measurement of body height and weight. Both waist circumference and hip circumference were also measured, and waist-to-hip ratio (W/H ratio) was calculated. Cognitive function was determined by Mini-Mental State Examination (MMSE). Each basic or instrumental ADL was determined by Barthel index or Tokyo Metropolitan Institute of Gerontology (TMIG) index,[21] respectively. Mood status was checked using the Geriatric Depression Scale (GDS-15).

Blood pressure and laboratory measurements

Blood pressure (BP) was measured in the clinic. Laboratory data obtained from blood sample collection at enrolment included lipid profile (total cholesterol [TC]), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C; calculated by Friedewald equation: TC-HDL-C-TG/5), profile of glucose metabolism (fasting blood glucose; FBS, HbA1c, fasting insulin concentration [FIRI]), and renal function (serum creatinine). All parameters were obtained every year. Changes in each parameter were calculated as the difference between baseline and end of follow up.

Clinical outcomes

Patients in the present study were continuously monitored for the occurrence of all events and deaths. In this trial, the CV events according to our definition were specified clearly as cardiac events including coronary heart disease (CHD; angina pectoris and myocardial infarction), cerebrovascular disease (CVD) including transient ischemic attack (TIA), stroke and cerebral hemorrhage, peripheral artery disease (PAD), and heart failure (HF). Individual diagnoses were classified according to the 9th International Classification of Disease (ICD-9) codes. We also classified each event into diabetes-related events (CHD, CVD, coronary revascularization, heart failure, sudden death, renal death, diabetic foot) and diabetes-independent events.

Statistical analysis

Differences in baseline characteristics across the four quartiles of physical activity (Q1 to Q4) were evaluated using analysis of variance for normally distributed variables. *P*-values for sex and previous CHD/CVD were calculated based on the Cochran–Armitage trend test, and others were based on the linear contrast test. Event-free survival during the follow-up period was analyzed using Kaplan–Meier curves and log–rank test. Hazard ratios (HR) for all CV events and all-cause deaths were analyzed using a Cox proportional hazards model. HR, 95% confidence intervals (CI) and *P*-values were presented using the lowest quartile (Q1) as the reference category.

Results

Baseline characteristics

The baseline characteristics of all the eligible subjects ($n = 938$) are shown according to TAS category, which was divided into four quartiles (Q1 to Q4), in Table 1.

First, patients with higher TAS grade tended to be slightly younger. Scores of each of the three components (work, sports and non-sporting leisure time) were positively associated with TAS. No significant association between BP and TAS was observed. In the lipid profile, HDL-C and TG were positively correlated with TAS grade (*P*-value for trend: $P = 0.021$ and $P = 0.028$, respectively); however, other lipid parameters (TC and LDL-C) showed no statistical significance. In addition, serum creatinine also tended to be lower according to TAS grade; however, the difference was very slight. Each parameter of glucose metabolism showed no statistical significance between the four quartiles of TAS.

With regard to physical measurements, TAS was negatively associated with waist circumference. BMI and hip circumference also tended to be associated with TAS grade, but without statistical significance.

Cognitive function, as determined by MMSE score, was higher according to increasing TAS grade. TMIG index as instrumental ADL also showed a similar positive association; however, Barthel index as basic ADL did not (data not shown). In addition, GDS-15 score as

Table 1 Baseline characteristics of study subjects according to total physical activity score category

	All (n = 938)	TAS category Quartile 1 (n = 232)	Quartile 2 (n = 229)	Quartile 3 (n = 230)	Quartile 4 (n = 247)	P-values for linear trend
Sex (male)*	447 (47.7)	110 (47.4)	109 (47.6)	115 (50.0)	113 (45.7)	0.841
Age at baseline (years)†	71.9 (4.7)	72.7 (4.8)	72.1 (4.8)	72.1 (4.7)	70.8 (4.2)	<.0001
TAS (total)	7.7 (3.0)	3.6 (1.4)	6.6 (0.6)	9.0 (0.9)	11.3 (0.6)	<.0001
WAS (work)	2.1 (1.6)	1.1 (1.4)	2.1 (1.7)	1.7 (1.5)	3.3 (0.4)	<.0001
SS (sports)	2.8 (2.3)	0.1 (0.5)	1.8 (2.2)	4.5 (0.9)	4.8 (0.3)	<.0001
LTS (leisure-time)	2.8 (0.6)	2.4 (0.5)	2.7 (0.4)	2.9 (0.6)	3.2 (0.4)	<.0001
SBP (mmHg)†	137.1 (16.3)	137.8 (15.8)	137.2 (17)	137.2 (16.1)	136.2 (16.2)	0.310
DBP (mmHg)†	75.0 (9.9)	75.2 (10.4)	75.1 (10.1)	74.8 (10.0)	75.0 (9.1)	0.765
PP (mmHg)†	62.1 (13.6)	62.6 (14.1)	62.3 (13.5)	62.3 (13.7)	61.2 (13.2)	0.291
T-chol (mg/dL)†	203.3 (34.7)	202.4 (35.4)	205.7 (37.3)	202.8 (30.1)	202.4 (35.6)	0.770
HDL-C (mg/dL)†	56.4 (17.9)	53.3 (15.9)	56.8 (17.8)	56.3 (19.3)	58.9 (18.2)	0.002
LDL-C (mg/dL)†	121.0 (30.6)	120.8 (31.5)	123.3 (31.8)	120.9 (28.0)	119.1 (31.0)	0.393
TG (mg/dL)†	133.4 (94.1)	143.3 (86.8)	135.2 (128.9)	130.6 (79)	124.9 (72.6)	0.028
sCr (mg/dL)†	0.8 (0.3)	0.9 (0.4)	0.8 (0.4)	0.8 (0.3)	0.8 (0.2)	<.0001
FBS (mg/dL)†	167.4 (50.6)	172.9 (56.4)	168 (51.3)	168.4 (50.0)	161.1 (44.1)	0.019
FIRI (mg/dL)†	10.3 (10.4)	12.8 (13.9)	10.5 (10.2)	9.2 (8.3)	9.2 (8.3)	0.001
HbA1c (%)†	8.5 (1.3)	8.4 (1.2)	8.5 (1.3)	8.4 (1.3)	8.5 (1.2)	0.767
BMI (kg/m^2)†	23.9 (3.5)	24.5 (3.8)	24 (3.5)	23.6 (3.4)	23.5 (3.1)	0.002
Waist circumference (cm)†	84 (10.3)	86 (10.7)	84.2 (9.6)	83.4 (10.6)	82.6 (9.9)	0.0002
Hip circumference (cm)†	93.9 (8.1)	94.9 (8.5)	94.1 (7.8)	93.2 (7.9)	93.4 (7.9)	0.022
W/H ratio†	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.001
MMSE†‡	27.9 (2.6)	27.4 (3.3)	27.8 (2.4)	28.1 (2.4)	28.5 (2.1)	<.0001
Barthel index†‡	19.8 (1.1)	19.6 (1.7)	19.8 (1.2)	19.8 (0.6)	19.9 (0.3)	0.004
TMIG index†‡	11.6 (2.2)	10.5 (3.1)	11.6 (2.0)	11.9 (1.7)	12.3 (1.3)	<.0001
GDS-15†‡	4.1 (3.2)	5.3 (3.4)	4.4 (3.2)	3.8 (3.0)	3.1 (2.8)	<.0001
Previous CHD*	154 (16.4)	33 (14.2)	44 (19.2)	42 (18.3)	35 (14.2)	0.005
Previous CVD*	123 (13.1)	38 (16.4)	33 (14.4)	34 (14.8)	18 (7.3)	0.005

*n (%). †Mean (SD). ‡Mini-Mental State Examination (MMSE), Barthel index, Tokyo Metropolitan Institute of Gerontology (TMIG) index, and Geriatric Depression Scale (GDS)-15 are on a scale of 0 to 30, 0 to 20, 0 to 13, and 0 to 15, respectively. P-value for sex, previous coronary heart disease (CHD), and previous cerebrovascular disease (CVD) were calculated based on the Cochran-Armitage trend test, and others were based on the linear contrast test. BMI, body mass index; DBP, diastolic blood pressure; FBS, fasting blood glucose; FIRI, fasting insulin resistance index; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LTS, leisure-time activity score; PP, pulse pressure; SBP, systolic blood pressure; sCr, serum creatinine; SS, sports score; TAS, total activity score; T-chol, total cholesterol; TG, triglyceride; W/H ratio, waist-to-hip circumference ratio; WAS, work activity score.

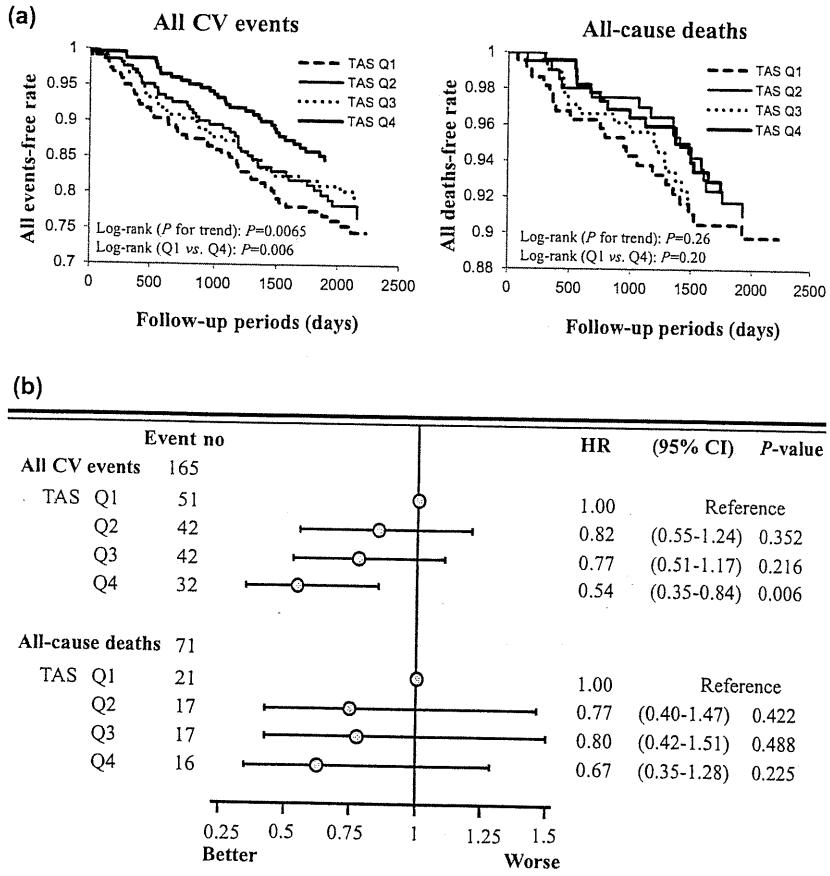

Figure 1 Kaplan–Meier analysis of incidence of all cardiovascular (CV) events and all-cause deaths, and significant risk reduction by higher total activity score (TAS) grade. (a) Kaplan–Meier analysis shows the incidence of all CV events and all-cause deaths. Few primary events of statistical significance were found in the higher TAS group. In contrast to all CV events, all-cause deaths gradually decreased according to TAS grade; however, no statistical significance was found. (b) Before adjustment, hazard ratios (HR) for all CV events and all-cause deaths using a Cox proportional hazards model showed a significant risk reduction with higher TAS grade. Q, quartile.

mood status showed an inverse association with TAS grade, suggesting an association between lower activity and depressive mood.

Regarding previous CHD, there was no significant difference among the groups. In contrast, previous CVD was less frequent in the TAS Q4 group.

Incidence of events during follow-up period

During the follow-up period of approximately 6 years (average 65.2 months), 165 all-CV events and 71 deaths in total occurred. All CV events, defined as a first event, included 45 CHD events (10 fatal and 35 non-fatal), 52 CVD events (4 fatal and 48 non-fatal), 29 diabetes-related events (9 fatal and 20 non-fatal) other than CHD and CVD, and 39 fatal diabetes-independent events. All-deaths included 11 deaths from CHD, four deaths from CVD, 11 diabetes-related deaths and 45 diabetes-independent deaths.

According to TAS grade, the incidence of these events was evaluated in all participants. As shown in Figure 1a, few all-CV events were found in the higher TAS group with statistical significance (log–rank test; $P = 0.0065$). In contrast to all-CV events, all-cause deaths gradually decreased according to TAS grade; however, no statistical significance was found. In analysis without adjustment, HR of each TAS grade were 0.82, 0.77 and 0.54 in Q2, Q3 and Q4, respectively, compared with Q1 as reference (*P*-value for trend; $P = 0.006$; Fig. 1b). In comparison between the lowest group (Q1) and highest group (Q4), a significant difference in incidence of first events was found from the early phase after randomization (log–rank test [Q1 *vs* Q4]; $P = 0.006$).

To determine how several parameters or TAS contributed to the reduction in all events, we carried out additional analysis after adjustment for several variables as potential confounders (Table 2). Among some variables except TAS, statistical significance was found for HbA1c, age and sex (female). Strikingly, TAS showed strong predictive power for all CV events. HR of each TAS grade were 0.74, 0.77 and 0.62 in Q2, Q3 and Q4, respectively, compared with Q1 as reference, and Q4 group statistically showed a significance ($P = 0.037$). However, variables including TAS except age and sex (female) were not associated with all-cause deaths. After addition of each of previous CVD or CHD to these adjusting variables, HR was 1.52 in previous CVD (95% CI 1.06–2.41, $P = 0.1006$) and HR was 1.45 in previous CHD (95% CI 1.90–2.33, $P = 0.1236$), and HR of TAS Q4 was reduced HR 0.64 (95% CI 0.35–1.17,

Table 2 Hazard ratios of all cardiovascular events and all-cause deaths after multivariate adjustment: Impact of total activity score as a strong predictor

Variants	All CV Events HR (95% CI)	*P*-value	All-Cause Deaths HR (95% CI)	*P*-VALUE
TAS				
Q1	1.00 Reference		1.00 Reference	
Q2	0.74 (0.49–1.13)	0.164	0.65 (0.33–1.29)	0.223
Q3	0.77 (0.51–1.17)	0.226	0.81 (0.43–1.54)	0.523
Q4	0.62 (0.40–0.97)	0.037	0.8 (0.41–1.56)	0.513
SBP	1.01 (1.00–1.02)	0.074	1.0 (0.99–1.02)	0.912
HbA1c	1.17 (1.00–1.38)	0.048	1.12 (0.87–1.43)	0.382
T-chol	1.01 (1.00–1.01)	0.056	1.0 (0.99–1.01)	0.886
HDL-C	0.99 (0.98–1.01)	0.333	1.0 (0.98–1.01)	0.699
TG	1.0 (1.00–1.00)	0.947	1.0 (1.00–1.00)	0.999
Age	1.06 (1.03–1.10)	0.0003	1.1 (1.05–1.16)	0.0002
Female	0.51 (0.36–0.71)	<.0001	0.53 (0.32–0.89)	0.016

CI, confidence interval; CV, cardiovascular; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; Q, quartile; SBP, systolic blood pressure; TAS, total activity score; T-chol, total cholesterol; TG, triglyceride.

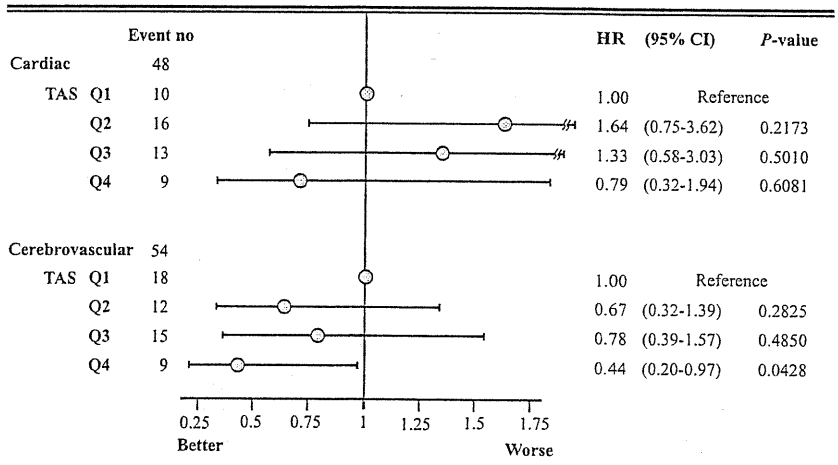

Figure 2 Predictive power for cardiac events and cerebrovascular events according to total activity score (TAS) category. HR, hazard ratio; Q, quartile.

$P = 0.1447$). In addition, in case of adjustment using previous CVD or CHD, its presence of each previous vascular event showed statistical significance (HR 1.52, 95% CI 1.06–2.41, $P = 0.1006$). Unfortunately, HR of TAS Q4 was similarly reduced HR 0.65 (95% CI 0.35–1.18, $P = 0.1549$).

Significant correlation of TAS with cerebrovascular events compared with cardiac events

The association of TAS with cerebrovascular events and cardiac events (AP, MI, coronary revascularization and heart failure) was evaluated. TAS was significantly associated with cerebrovascular disease including both fatal and non-fatal events, although there was no significant association between cardiac events and TAS (Fig. 2).

Next, we compared the predictive power of TAS according to sex and age (young-elderly aged 65–74 years and old-elderly patients aged ≥75 years; Table 3). First, with regard to sex, the predictive power of TAS for all CV events was stronger in women than in men. In addition, TAS in the young-elderly significantly predicted all CV events. In the old-elderly, a similar tendency was observed; however, the association did not reach statistical significance.

Comparison of predictive power of each component in TAS

As described in the Methods section, TAS consists of three components: work activity, sports activity and non-sporting leisure-time activity. Subanalysis clearly

Table 3 Predictive power of total activity score for all cardiovascular events and all-cause death according to sex and age

	Male HR (95% CI)	*P*-value	Female HR (95% CI)	*P*-value
All CV events				
TAS				
Q1	1 Reference		1 Reference	
Q2	0.8 (0.46–1.39)	0.429	0.84 (0.45–1.56)	0.584
Q3	0.95 (0.56–1.61)	0.857	0.50 (0.25–1.03)	0.062
Q4	0.6 (0.34–1.08)	0.087	0.47 (0.24–0.93)	0.030
All-cause deaths				
Q1	1 Reference		1 Reference	
Q2	0.79 (0.33–1.91)	0.606	0.73 (0.28–1.92)	0.527
Q3	1.08 (0.48–2.41)	0.856	0.42 (0.13–1.35)	0.148
Q4	0.74 (0.31–1.78)	0.496	0.60 (0.23–1.58)	0.304
	Young-Elderly HR (95% CI)	*P*-value	Old-Elderly HR (95% CI)	*P*-value
All CV events				
TAS				
Q1	1 Reference		1 Reference	
Q2	0.70 (0.41–1.21)	0.204	1.07 (0.57–2.00)	0.839
Q3	0.81 (0.48–1.35)	0.414	0.73 (0.36–1.49)	0.387
Q4	0.58 (0.34–0.98)	0.042	0.54 (0.23–1.27)	0.158
All-cause deaths				
Q1	1 Reference		1 Reference	
Q2	0.74 (0.31–1.76)	0.498	0.8 (0.3–2.14)	0.653
Q3	0.74 (0.32–1.71)	0.478	0.95 (0.35–2.55)	0.916
Q4	0.73 (0.33–1.63)	0.448	0.68 (0.21–2.22)	0.527

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; Q, quartile; TAS, total activity score.

showed that the predictive power of "work activity" for all CV events was stronger than that of the other components (log–rank test; $P = 0.0003$) (Table 4). After adjustment, its power remained. The risk reduction of work activity was also significant, even in all-cause mortality (log–rank test; $P = 0.004$; data not shown). There was no statistical significance for sports activity. Regarding leisure-time activity, the risk reduction of it for all CV events in Q3 was strongest; however, statistical analysis did not show significance (log–rank test; $P = 0.11$).

Changes in each parameter during follow-up period

To explore which parameter contributed to the risk reduction of all primary events, the changes in values (from baseline to the end of the follow-up period) of each parameter were calculated according to TAS grade (Table 5). Among the parameters, the differences in laboratory data, including lipid parameters and glucose metabolism, BP, physical measurements, cognitive function and depression scale, between TAS grades were not significant, suggesting that a higher level of physical activity itself was important in the risk reduction of events in elderly patients with T2DM.

Discussion

Physical activity has been shown to reduce the risk of CV events; however, the biological mechanisms underlying this finding are still unclear. In the present study, the association of physical activity, as determined by TAS at baseline, with all CV events and all-cause mortality was evaluated in the J-EDIT study.

Higher TAS grade was significantly associated with a risk reduction in non-fatal all CV events; however, the association with all-cause mortality was not significant. In addition, among the three components of TAS, the predictive power of "work activity" was stronger than that of the other components – sports and leisure-time

Table 4 Comparison of predictive power for all cardiovascular events according to each component of physical activity

Component	Unadjusted			Adjusted*		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Work						
None	1 Reference			1 Reference		
Low	0.57	(0.4–0.83)	0.0029	0.72	(0.49–1.06)	0.0972
High	0.53	(0.37–0.76)	0.0007	0.68	(0.46–1.01)	0.0538
Sports						
Low	1 Reference			1 Reference		
High	0.84	(0.62–1.13)	0.2455	0.8	(0.59–1.08)	0.1425
Leisure-time						
Q1	1 Reference			1 Reference		
Q2	0.73	(0.49–1.09)	0.1236	0.75	(0.49–1.13)	0.1633
Q3	0.53	(0.33–0.83)	0.0062	0.6	(0.37–0.95)	0.0304
Q4	0.75	(0.5–1.11)	0.1502	0.79	(0.52–1.19)	0.2534

*Simultaneously adjusted for age, sex, systolic blood pressure, glycated hemoglobin A1c, total cholesterol, triglyceride, and high-density lipoprotein cholesterol at baseline. CI, confidence interval; HR, hazard ratio.

Table 5 Changes in each parameter throughout follow-up period according to total activity score category

Variables	TAS category				*P* for trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
FBS (mg/dL)	−21.2 (4.0)	−5.7 (4.4)	−11.7 (4.2)	−10.8 (3.8)	0.0649
HbA1c (%)	−0.6 (0.1)	−0.6 (0.1)	−0.5 (0.1)	−0.6 (0.1)	0.8537
T-chol (mg/dL)	−12.2 (2.5)	−16.7 (2.5)	−7.9 (2.4)	−11.3 (2.5)	0.0979
LDL-C (mg/dL)	−6.6 (2.2)	−11.3 (2.4)	−4.1 (2.3)	−7.1 (2.4)	0.1744
HDL-C (mg/dL)	−0.1 (2)	−2.4 (1)	−2.0 (1)	−1.8 (1)	0.6101
TG (mg/dL)	−15.5 (5.3)	−17.4 (7.9)	−5.2 (5)	−9.0 (4.7)	0.4164
SBP (mmHg)	−2.5 (1.1)	−1.7 (1.3)	−2.4 (1.3)	−2.2 (1.3)	0.9673
DBP (mmHg)	−4.0 (0.8)	−3.8 (0.8)	−2.6 (0.8)	−3.0 (0.7)	0.5372
PP (mmHg)	1.6 (1.0)	2.0 (1.1)	0.0 (1.1)	0.9 (1.1)	0.573
BMI (kg/m^2)	−0.2 (0.8)	−0.4 (0.2)	−0.6 (0.2)	−0.6 (0.2)	0.9353
Waist circumference (cm)	−0.8 (0.3)	−0.1 (0.4)	0.6 (0.5)	−0.1 (0.3)	0.1608
Hip circumference (cm)	0.5 (0.4)	0.0 (0.4)	0.4 (0.4)	−0.1 (0.4)	0.6398
W/H ratio	0.0 (0.0)	0.6 (0.5)	0.5 (0.5)	0.5 (0.5)	0.7671
MMSE	−0.3 (0.1)	−0.4 (0.1)	−0.4 (0.1)	−0.4 (0.1)	0.8441
GDS15	0.0 (0.1)	0.1 (0.1)	0.0 (0.1)	0.3 (0.1)	0.1087

BMI, body mass index; DBP, diastolic blood pressure; FBS, fasting blood glucose; GDS, Geriatric Depression Scale; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; PP, pulse pressure; SBP, systolic blood pressure; sCr, serum creatinine; SS, sports score; TAS, total activity score; T-chol, total cholesterol; TG, triglyceride; W/H ratio, waist-to-hip circumference ratio; WAS, work activity score.

activity. There was no significant difference in the change in almost all parameters among TAS grades throughout the follow-up period in the present trial. Therefore, we emphasize the following conclusion: (i) our data provide evidence that lower physical activity is a strong and independent predictor of CV events in the elderly with T2DM beyond traditional risk factors; (ii) in addition to routine strict management of laboratory data in clinical practice, engagement with patients to enhance and/or maintain physical activity in their lifestyle is also important. In fact, the elderly have retired from their routine jobs. The results of the present study show that they should do at least slight work routinely in their daily life, such as cooking or gardening. It might be meaningful for them to carry out some activity and continue it by themselves.

Physical activity is a well-established approach to reducing the risk of many chronic diseases. Most studies have shown a significant relative reduction in the incidence of CV events in physically active participants; however, the range of benefit showed considerable variation. For example, Myers *et al.* reported a marked reduction in all-cause mortality of 72% between active and inactive male participants during 6 years of follow up,[21] whereas Lee *et al.* found a risk reduction of just 13%.[22] It is clear that the risk reduction might vary depending on adjustment for important covariables, such as BP and profiles of lipid and glucose metabolism. With regard to adjustment for several relevant risk factors, a meta-analysis handling a total of 33 studies with 883 372 participants (follow-up period from 4 years to over 20 years) clearly showed an important correlation of higher physical activity with a risk reduction in CV mortality of 35% (95% CI 30–40%).[23] In addition, all-cause mortality was also reduced by 33% (95% CI 28–37%). This systematic review by meta-analysis emphasized that physical activity was associated with a marked decrease in CV and all-cause mortality in both sexes, even after adjusting for other relevant risk factors. In the present study, there was a good correlation between TAS and all CV events. However, after adjustment of previous atherosclerotic diseases, its presence of previous CVD or CHD showed a significant association with CV events during the follow-up period. Consequently, the predictive power of TAS against all CV events was slightly decreased. These observations might suggest a high risk of recurrence of CV events in T2DM patients beyond TAS grade at the baseline. Therefore, further subanalysis to simply evaluate the predictive power of TAS as primary prevention against CV events using elderly patients without both previous CVD and CHD is required. In addition, regarding all-cause mortality, TAS tended to show an association with it; however, no statistical significance was reached. One of the hypotheses to explain the relationship and discrepancy is that the sample size was relatively small and non-fatal CV events rather than fatal events might be frequently observed in all participants with T2DM at the baseline.

Next, we focused on cognitive function and depressive mood. The presence of geriatric syndrome including cognitive dysfunction has been shown to be a major factor in decline in physical activity level in the older elderly. Besides traditional risk factors, it has been clearly shown that "depressive mood" readily causes a decline in physical activity, leading to increased risk of CV disease.[24] In addition, patients with depression had a worse prognosis than those without depression after a myocardial infarction.[25,26] Prospective studies have shown that depressed people develop a more sedentary lifestyle and become less physically active.[27,28] In fact, the GDS score was higher in the lower TAS group in the present study as well. Therefore, this evidence that the importance of physical activity in the risk reduction of CV events is also associated with depressive mood is consistent with previous reports. However, the average GDS score was not so high (range 3–5 points). In addition, depressive score did not decrease, even in the lowest TAS group (Q1), throughout the follow-up period. In subanalysis, the inverse correlation between GDS and TAS was more clearly found in young-elderly patients, compared with old-elderly patients. In view of these results, especially in young-elderly patients, detailed assessment of the patient's mentality, including depressive mood, should be considered more aggressively and routinely.

The predictive power of TAS was compared between CHD and CVD. The relative risk of CVD decreased with increasing TAS, with statistical significance; however, no significance was found for CHD. In fact, we found some evidence regarding this discrepancy. Although the incidence of CHD among physically active elderly men in the Honolulu Heart Program study was less than half that in more sedentary men,[29] no clear association was observed in the Established Populations for Epidemiologic Studies of the Elderly study.[30] Compared with CHD, the correlation of physical activity with stroke has not been extensively examined for any age group.[31] However, a meta-analysis handling five epidemiological case–control studies has reported that all studies had consistent evidence showing a large advantage of higher physical activity in reducing the risk of stroke.[32]

As another interest in our data, "work activity" was the most potent predictor of first events among the three components. This suggests that, even if the patient's age is over 65 years, the fact that they are motivated to routinely try to do at least any slight work might enhance their total physical activity.

The present analysis was based on the physical activity score measured once at enrolment in the J-EDIT study. However, during the follow-up period of this trial, some patients showed a gradual decline in TAS. It is notable that new development or progression of diabetic complications, such as neuropathy and retinopathy, readily leads to a decline in physical activity. Therefore, further investigation to evaluate which factor mainly caused the decline in TAS throughout the follow-up period is necessary. This could provide supportive information on the cause–effect relationship of the associations found in this trial.

In addition, the current associations might not be extended to all populations, because the enrolled participants in the present trial were patients with T2DM. Whether the observed associations can be generalized to populations of much older ages and populations without T2DM is unknown.

This prospective follow-up study confirmed that lower physical activity is a strong independent predictor

of onset of CV events, even in Japanese elderly with T2DM. The data in the present study suggest the potential of activity to enhance overall health and well-being with aging. Ultimately, the key is to aggressively translate these findings into public health efforts.

The majority of elderly patients still have a primarily sedentary life. Numerous studies have already addressed the importance of physical activity in health management; however, unfortunately, medical staff might not have been educated about how to promote and augment the level of physical activity in elderly patients. Therefore, as well as strict management of each atherosclerotic risk factor, we should aggressively assess physical activity (especially working) and encourage elderly patients to increase or maintain their level of physical activity.

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Conflict of interest

There is no conflict of interest. The J-EDIT Study Group has not cleared any potential conflicts.

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ORIGINAL ARTICLE

Lower physical activity, but not excessive calorie intake, is associated with metabolic syndrome in elderly with type 2 diabetes mellitus: The Japanese elderly diabetes intervention trial

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Aim: A decline in physical activity has been shown to be associated with metabolic syndrome (MetS), leading to cardiovascular events. However, this is difficult to manage well in the elderly with multiple atherosclerotic risk factors. In this study, we investigated the correlation between physical activity and clinical parameters in the presence and absence of MetS in Japanese elderly subjects with type 2 diabetes mellitus (T2DM). In addition, we determined which factor, calorie intake or physical activity, mainly contributes to the prevalence of MetS.

Methods: Cross-sectional analysis of 846 consecutive Japanese elderly (408 men and 438 women, mean age 68.7 years) was carried out at the time of enrolment (2000–2002) in the Japanese Elderly Diabetes Intervention Trial. Their level of physical activity was evaluated using the Baecke questionnaire, consisting of three components: work, sports and leisure. Total activity score (TAS) as the sum of each activity score was divided into four quartiles (Q1 to Q4).

Results: After adjustment for age and sex, there was a positive association of TAS with high-density lipoprotein cholesterol, although no significant correlation between other lipid parameters and TAS was found. In addition, fasting plasma glucose, insulin level and physical measurements, such as waist circumference, waist/hip ratio and body mass index,

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were inversely associated with TAS. Although no correlation between TAS and cognitive function Mini-Mental State Examination was found, TAS was positively associated with instrumental ADL and negatively associated with geriatric depression score (GDS), suggesting that a decline in physical activity in the elderly is associated with depressed mood rather than a decline of cognitive function. Total calorie intake appeared to increase according to TAS; however, this did not reach statistical significance. In a subanalysis comparing the presence and absence of MetS, the TAS grade in the MetS group was significantly lower than that in the non-MetS group, although there was no significant difference in total calorie intake between the groups.

Conclusion: These results showed that lower physical activity, but not excessive calorie intake, is independently associated with the prevalence of MetS in the elderly with T2DM. In our routine work, encouraging physical activity might contribute to preventing MetS and subsequent atherosclerotic disease in the elderly, rather than strict management of abnormal laboratory parameters using multiple drugs. **Geriatr Gerontol Int 2012; 12 (Suppl. 1): 68–76.**

Keywords: depression, elderly, excessive calorie intake, Japanese Elderly Diabetes Intervention Trial study, metabolic syndrome, physical activity, work activity.

Background

Type 2 diabetes mellitus (T2DM) is an age-related disease with an estimated prevalence in Japan of more than 5% of the population.[1] The setting of treatment goals in medical care, especially in elderly patients, has been believed to be difficult because of several factors. In concrete terms, the purpose of treatment is not only to simply improve glucose intolerance, but also to maintain a higher quality of life (QOL) and prolong healthy longevity in parallel with prevention of diabetic complications. Several prospective intervention studies have recently shown some evidence that intensive glycemic control effectively slows the onset and progression of diabetic vascular complications associated with T2DM.[2,3] However, these epidemiological investigations did not consider the various associations with physical activity in elderly diabetic patients.

Physical activity promotes health and longevity.[4] Excess bodyweight and a sedentary lifestyle are well-established risk factors for not only T2DM, but also cardiovascular disease (CVD). Randomized trials have shown that a combination of weight loss and increased physical activity can reduce the incidence of T2DM and CVD.[5–7] In developed countries, 80% of all deaths from CVD occur in people aged 65 years and older.[8] The Framingham Heart Study has shown an inverse association between physical activity and CVD mortality risk, even in 285 elderly individuals.[9] However, this did not reach statistical significance, possibly as a result of the limited number of events. However, the precise mechanisms whereby physical activity lowers CVD risk are not well understood. In addition, it is possible that a decline in physical activity might lead to several undesirable conditions, including cognitive decline, in the elderly.

Metabolic syndrome (MetS) is loosely defined as a cluster of CVD risk factors, including disturbed insulin and glucose metabolism, hypertension, abdominal obesity and dyslipidemia. A low level of physical activity is believed to be an important determinant of this cluster of metabolic risk factors. Thus far, little is known about the association between physical activity and MetS in Japanese elderly patients with T2DM. To clarify which factors are mainly associated with the prevalence of metabolic syndrome (MetS) in the elderly with T2DM, we carried out a large-scale prospective study, the Japanese Elderly Diabetes Intervention Trial (J-EDIT), which was started in 2001.[10] To address how elderly patients with T2DM should be treated, a randomized controlled intervention study in Japanese elderly patients with diabetes has been carried out.

In the J-EDIT study, we investigated the correlation between physical activity and MetS in the elderly with T2DM. In particular, we focused on the association of oral calorie intake with physical inactivity in the presence or absence of MetS.

Methods

Study population

Participants were enrolled in the J-EDIT, which is a recently completed trial of intensive or standard treatment for diabetes in the primary prevention of CVD in the elderly. J-EDIT included 1173 diabetic patients who were aged 65 years or older (mean age 71.8 ± 4.6 years) and whose serum glycated hemoglobin A1c (HbA1c)

level was >7.4% from 39 institutes and hospitals (Tokyo University Hospital, Kobe University Hospital, Nagoya University Hospital and Tokyo Metropolitan Geriatric Hospital etc.) in Japan. Patients with chronic renal failure (serum creatinine > 1.5 mg/dL), severe heart failure or symptomatic cerebral infarction were also excluded from the present study. Written informed consent was obtained from all patients.

From these patients enrolled in the J-EDIT, we selected 846 patients with T2DM (mean age 71.9 ± 4.6 years, 408 men (mean age 71.5 ± 4.5 years) and 438 women (mean age 72.2 ± 4.7 years) in whom complete data on baseline physical activity (Baecke questionnaire) and nutritional survey were obtained at entry. We excluded patients who had difficulties in communicating, dementia or serious deterioration of activities of daily life from the present study.

Physical activity assessed by Baecke questionnaire

At enrolment in the present study, physical activity was evaluated by a self-administered validated Baecke physical activity questionnaire, as previously reported.[11] Baecke physical activity score is classified into three domains: work activity, sports activity and non-sporting leisure activity. These three components consisted of items on the frequency, duration, and pace of walking and bicycling during the previous week, the average amount of time spent weekly on hobbies and gardening, and the average amount of time spent monthly on odd jobs and sports. Types of odd jobs, sports and hobbies (e.g. dancing or fishing) were also assessed. Many previous reports have confirmed the reliability of this score in many individuals, suggesting that it might be a useful monitoring tool for assessing the association of multiple domains of physical activity with MetS in elderly patients with T2DM, with acceptable reliability and validity. In analyses, total activity score (TAS; maximum 15 points) was divided into four quartiles (Q1 to Q4) as follows; Q1: <5.7, Q2: ≥5.7 and <7.7, Q3: ≥7.7 and <10.5, Q4: ≥10.5.

Comprehensive geriatric assessment

To perform comprehensive geriatric assessment (CGA), we carried out several evaluations. Mini-Mental State Examination (MMSE) was used to assess cognitive function.[10] Geriatric Depression Scale (GDS) was used to assess depression status. We also checked basic activities of daily life (bADL) and instrumental activities of daily life (iADL), as determined by the Tokyo Metropolitan Institute of Gerontology (TMIG) index of competence.[12]

Physical measurements

Height, weight, waist circumference and hip circumference were measured at enrolment. Body mass index (BMI) and waist-to-hip ratio (W/H ratio) were calculated using these parameters.

Nutritional assessment of dietary calorie intake

Calorie intake was assessed using a self-reported questionnaire that has been previously shown to be valid and reliable.[13] Nutritional habit was evaluated every trimester through 7-day food records. Each energy intake, such as protein, carbohydrate and fat, and total calorie intake were calculated in all patients.

Laboratory measurements and blood pressure

Blood samples were obtained at the time of enrolment and stored in vapor-phase liquid nitrogen (−170°C). Glycemic metabolism, such as fasting plasma glucose and HbA1c; lipid parameters, such as total, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG); and renal function, such as serum creatinine, were measured. Blood pressure (BP) was measured in the non-dominant arm after 5 min of sitting quietly in accordance with the current recommendations for clinic blood pressure of each hospital.

Metabolic risk factor criteria

In the present study, MetS was defined according to the criteria proposed by the Japanese Society of Internal Medicine (JSIM), the International Diabetes Federation (IDF) and the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III).[13–16]

Statistical analysis

Analyses of covariance (ANCOVA) was used to assess independent associations between our two indices of habitual physical activity (daily step count and daily duration of activity at an intensity >3 MetS) and the presence or absence of MetS and five individual diagnostic criteria (BMI, TG, HDL-C, systolic BP and/or diastolic BP, and glucose and/or HbA1c), after controlling for age and sex. We divided the patients arbitrarily into four quartiles of physical activity (Q1: lowest group to Q4: highest group). In addition, pre-existing illness (such as cerebrovascular disease, ischemic heart disease, diabetes and retinopathy) at baseline was also considered. The χ^2-test for linear trends was used to analyze independent associations between habitual physical activity and the metabolic syndrome in adjusted models. Data are presented as mean ± standard deviation (SD), with all statistical comparisons made at the 0.05 level of significance.

Results

Comparison of parameters according to physical activity

Cross-sectional analysis of 846 consecutive Japanese elderly (408 men and 438 women; mean age 68.7 years) was carried out at the time of enrolment (2000–2002) in the J-EDIT study, a randomized, double-blind, recently completed trial of intensive or standard treatment for the prevention of CVD in elderly diabetics.

An index of physical activity was calculated using the Baecke score, including three components (work, sports and leisure). TAS was divided into four quartiles (Q1 to Q4). The baseline characteristics of patients according to their TAS grade are shown in Table 1. Regarding lipid parameters, HDL-C was positively associated with TAS, although there was no significant correlation between other lipid parameters and TAS. A negative correlation of fasting plasma glucose and plasma insulin level with TAS was found. Regarding the association between BP and TAS, no significant tendency was found.

There was a negative association between TAS and physical measurements, such as BMI, waist circumference, hip circumference and W/H ratio. In particular, high significance was observed especially in the young elderly (data not shown). However, there was no significant association with each component of TAS.

Comparison of CGA according to physical activity

Regarding comprehensive geriatric assessment (CGA), TAS was positively associated with TMIG index as instrumental ADL and negatively associated with geriatric depression score (GDS; Table 1). In contrast, there was no significant correlation between TAS and cognitive function, as determined by MMSE. These results suggest that a decline in physical activity in the elderly is associated with a depressive tendency rather than cognitive dysfunction.

Comparison of calorie intake according to physical activity

Next, we measured oral calorie intake. The calorie intake from protein and lipid were positively associated with TAS; however, there was no correlation with calorie intake from carbohydrate (Table 1). Total calorie intake tended to increase according to TAS grade, but the tendency did not reach statistical significance. Next, the total calorie intake was compared according to TAS grade in each group, divided by sex and age (Fig. 1). There was no significant difference between total calorie intake and TAS in all subgroups.

There was no significant difference between both sexes (Fig. 2a). TAS in the old elderly was significantly lower than that in the young elderly in both sexes. Comparing pre-existing illness, there was a correlation between TAS grade and cerebrovascular disease, but not coronary heart disease or diabetic retinopathy (Fig. 2b).

Impact of lower physical activity, but not excessive calorie intake, in elderly with MetS

It is well known that there is a correlation between a sedentary lifestyle and obesity. Even in the elderly, it is possible that the prevalence of MetS is associated with not only excessive calorie intake, but also their behavior. Therefore, next, we examined which factor, excessive calorie intake or physical inactivity, mainly contributes to the prevalence of MetS. First, we divided all the patients into two groups, MetS and non-MetS, using the definition of MetS of the Japanese Society of Internal Medicine (JSIM).

First, calorie intake from several types of food was compared between MetS and non-MetS (Table 2). Calorie intake from protein and fat in MetS was higher than that in non-MetS. However, for carbohydrate-derived and total calorie intake, no significant difference was found between both groups. Furthermore, in addition to the JSIM criteria, we divided the patients into two groups, MetS and non-MetS, using other clinical definitions, IDF and NCEP-ATP III. Even with each definition, TAS grade in the MetS group was lower than that in the non-MetS group (Fig. 3a). Interestingly, there was no significant difference in total calorie intake between both groups. Among the three components of TAS, work activity showed a more significant correlation with the prevalence of MetS than the other components, sports or leisure activity (Fig. 3b).

Discussion

The present study analyzed the possible association between lower physical activity and prevalence of MetS in Japanese elderly patients with T2DM who were enrolled in the J-EDIT study. The present study had two aims: (i) to evaluate the association between TAS as total physical activity and clinical parameters in the diabetic elderly; and (ii) to determine which factor, total calorie intake or physical activity, mainly contributes to the presence of MetS in the elderly with T2DM. In the present study, physical activity was assessed by the Baecke questionnaire,[11] because this is an easy, fast and valid tool for the assessment of physical activity in epidemiological studies concerning elderly populations.

The present study showed several results, as follows: TAS grade as total physical activity level in the young elderly was higher than that in the old elderly. No significant difference in TAS was found between both sexes. The presence of cerebrovascular disease in the