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ORIGINAL

Association between Body Mass Index and Core Components of Metabolic Syndrome in 1486 Patients with Type 1 Diabetes Mellitus in Japan (JDDM 13)

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Abstract. There is no recent study on the prevalence of overweight and obesity in patients with type 1 diabetes mellitus (T1DM) in Japan. Being overweight has a significant effect on the metabolic condition and glycemic control of such patients. In the present cross-sectional study, we investigated the effects of body mass index (BMI) on lipid profile, blood pressure, and glycemic control in patients with T1DM. In total, 1486 patients with T1DM (including 401 patients with early onset T1DM who were <20 years of age at diagnosis) were included. Patients were divided into four groups according to their BMI, and glycosylated hemoglobin (HbA1c), daily insulin dose per kg body weight, lipid profile, and blood pressure were compared between groups. We found that 15.7% of all patients were overweight (BMI ≥25.0 kg/m^2) and 2.0% were obese (BMI ≥30.0 kg/m^2), compared with 17.5% and 2.0%, respectively, in the early onset T1DM subgroup. Significant changes in lipid profiles and blood pressure were found with increasing BMI in both the entire population and the early onset T1DM subgroup. In the entire study population HbA1c and the body weight-adjusted daily insulin dose were significantly higher in patients with a BMI ≥23 kg/m^2 compared with those with a BMI <23 kg/m^2; however, this was not the case in the early onset T1DM subgroup. This difference may be due to the relatively small number of patients in that subgroup. In conclusion, the prevalence of overweight and obesity in patients with T1DM was less than that in the normal Japanese population. For patients with T1DM, being overweight was associated with higher blood pressure and dyslipidemia. Furthermore, we cannot exclude an association between being overweight and the need for higher daily doses of insulin.

Key words: type 1 diabetes mellitus (T1DM), body mass index (BMI), insulin resistance, metabolic syndrome

CLASSICALLY, diabetes mellitus has been categorized into types 1 and 2. Type 1 diabetes mellitus (T1DM) was considered an autoimmune disorder of childhood, characterized by acute onset, ketoacidosis, and insulin dependency. Conversely, type 2 diabetes mellitus (T2DM), typically diagnosed in middle-aged patients, was considered a metabolic disorder with a slow onset, for which insulin treatment was not always required. However, in recent years, the characteristics of T1DM and T2DM seem to have changed. Now, more than half the patients with T1DM present in adulthood (i.e. slow onset) and many do not develop acidosis or require insulin treatment until much later [1, 2]. At the same time, T2DM is being diagnosed more frequently in teenagers [3]. These patients

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sometimes become ketoacidotic [4, 5] and insulin dependency often ensues. The accelerator hypothesis, proposed in 2001, states that T1DM and T2DM are, in most respects, the same and can be distinguished only by the rate of β-cell loss and the accelerator responsible [6]. Furthermore, some patients may present with disease processes of both T1DM and T2DM, or develop them sequentially over time, which has been termed 'double diabetes' [7, 8].

The prevalence of overweight and obesity has increased in the US and Europe, as well as in Asian countries, such as Japan. Metabolic syndrome occurs in both nondiabetic subjects and patients with T2DM. It is a cluster of metabolically related cardiovascular risk factors, the core components of which comprise central obesity, insulin resistance, dyslipidemia, and hypertension [9–11]. There are multiple definitions of metabolic syndrome [12–14], with the most recent one being provided in the consensus statement issued by the International Diabetes Federation [15]. The presence of increased insulin resistance appears to be central to the development of metabolic syndrome. Insulin resistance is common in obesity [16], and hyperglycemia resulting from insulin resistance induces β-cell insufficiency [6]. Excessive weight gain or obesity in infancy may be associated with a higher risk of T1DM in children [17]. Although obesity is not generally considered a typical feature of T1DM, it has a similar prevalence in individuals with T1DM to that of the general population.

Furthermore, the intensive insulin therapy required to obtain good glycemic control and to reduce diabetic complications is itself associated with weight gain, unless it is complemented by appropriate diet therapy [18, 19]. This raises the question of how to balance the need for increasing insulin doses to maintain good glycemic control against possible weight gain, because central obesity is associated not only with insulin resistance, but also with dyslipidemia and hypertension, both of which are core components of metabolic syndrome. Thus, the aim of the present study was to investigate whether body mass index (BMI) has any effect on the core components of metabolic syndrome, including lipid profile, blood pressure, and glycemic control, in patients with T1DM in Japan.

Materials and Methods

Research design and methods

The present cross-sectional study used data obtained in 2005 from 1486 patients (645 men and 841 women) with T1DM, aged between 16 and 90 years. T1DM was diagnosed on the basis of permanent insulinopenia and being either prone to the development of ketosis (idiopathic T1DM) or positive for markers of autoimmune destruction, such as glutamic acid decarboxylase (immune-mediated T1DM). This definition of T1DM is in accordance with that of the Committee of the Japan Diabetes Society on the Classification and Diagnostic Criteria of Diabetes Mellitus [20], with the diagnosis criteria almost identical to those proposed by the World Health Organization (WHO) [21]. In the present study, data from 401 patients who were <20 years of age at the time of diagnosis of presumed T1DM were analyzed separately, as the early onset subgroup. Any patients with a primary or subsequent diagnosis of T2DM were excluded from the study. Patients were recruited at clinics and hospitals that belonged to the Japan Diabetes Clinical Data Management Study Group (JDDM; see Appendix I). Clinical data were standardized and saved using CoDiC software, as described previously [22]. Data were collected at the central analytical facility, where the information was treated anonymously and subsequently analyzed using JMP software (SAS Institute, Cary, NC, USA) [23]. The JDDM operates as an intermediate organization under the supervision of the central analytical facility and an ethics committee.

Informed consent was obtained from all patients at each institute prior to their participation in the study, in accordance with the Guidelines for Epidemiological Studies in Japan.

BMI and patient groups

Weight and height were measured using standardized techniques and equipment, with BMI calculated as weight (kg) divided by height squared (m^2). Overweight and obesity were defined as BMI ≥25.0 and ≥30.0 kg/m^2, respectively. These definitions are consistent with those of the WHO [24]. Patients were subdivided into four groups on the basis of their BMI as follows: (i) group 1, BMI <23.0 kg/m^2; (ii) group 2, 23.0 kg/m^2≤BMI<25.0 kg/m^2; (iii) group 3, 25 kg/m^2≤BMI<27.0 kg/m^2; and (iv) group 4, BMI ≥27.0 kg/m^2. Because of the small number of patients in the present study defined as obese, we did not include a separate group with BMI ≥30.0 kg/m^2 for analysis.

Measurement and standardization of data

The daily dose of insulin was normalized against body weight (U/kg body weight). Blood pressure was measured using standard techniques. Glycosylated hemoglobin (HbA1c) was measured by high-performance liquid chromatography, with the normal range defined as 4.3%–5.8%. Serum concentrations of cholesterol, triglyceride, and high-density lipoprotein (HDL) cholesterol were determined using standard techniques. The measurement of all parameters assessed in the present study was standardized across all institutions.

Statistical analysis

Statistical analyses were performed using JMP software. Triglyceride concentrations were converted to natural logarithms for analysis and are expressed as the median with interquartile ranges. Differences between groups were assessed by analysis of variance (ANOVA), followed by the Tukey-Kramer honestly significant different test for multiple comparisons with a total significance level of 5%. To assess the strength and independence of associations between either HbA1c or BMI as objective variables and other parameters as explanatory variables, multiple regression analysis was performed and standard regression coefficients with *P* values were calculated. All data, other than triglyceride concentrations, are expressed as the mean ± SD. $P < 0.05$ was considered significant.

Results

Prevalence of overweight and obese individuals

In the present study, 15.7% of all individuals (15.7% of men and 15.5% of women) were overweight (including those who were obese); 2.0% of individuals (1.7% of men and 2.0% of women) were obese. In the early onset subgroup of patients with T1DM, 17.5% of patients (20.8% of men and 15.5% of women) were overweight and 2.0% of patients (2.7% of men and 1.6% of women) were obese.

Association between BMI or HbA1c and daily insulin dose, lipid profile, and blood pressure in the study cohort

Table 1a summarizes the clinical characteristics of patients in each of the four BMI groups. Mean HbA1c was significantly higher in group 2 compared with that in group 1 (7.96 ± 1.58% vs. 7.68 ± 1.57%, respectively). Mean daily insulin doses, total cholesterol, systolic blood pressure (SBP), and triglyceride levels (median natural log) were significantly higher in groups 2–4 compared with group 1. Mean HDL cholesterol

concentrations were significantly lower, whereas diastolic blood pressure (DBP) was significantly higher, in groups 3 and 4 compared with group 1. There were no significant differences in casual plasma glucose concentrations between the four groups.

Table 1b summarizes the results of multiple linear regression analysis. A positive correlation was found between BMI and natural log triglyceride concentrations, SBP, total cholesterol concentrations, and HbA1c. However, BMI was found to be negatively correlated with age and HDL cholesterol concentrations. Positive correlations were found between HbA1c and casual plasma glucose, total cholesterol, daily insulin doses, and natural log triglyceride concentrations, whereas female sex was negatively correlated with HbA1c.

Association between BMI or HbA1c and daily insulin dose, lipid profile, and blood pressure in patients with early onset T1DM

Table 2a summarizes the clinical characteristics of the subgroup of patients with early onset T1DM according to BMI. The median natural log triglyceride concentration was significantly higher in group 4 than in groups 1–3. Mean total cholesterol concentrations and mean SBP were significantly higher in groups 3 and 4 compared with group 1. The mean HDL cholesterol concentration was significantly lower, whereas mean DBP was significantly higher, in group 4 compared with group 1. There were no significant differences in mean HbA1c, daily insulin doses, or casual plasma glucose concentrations between the four groups.

Results of multiple linear regression analysis are summarized in Table 2b. A positive correlation was found between BMI and SBP and total cholesterol concentrations. However, a negative correlation was found between BMI and HDL cholesterol concentrations. There was a positive correlation between HbA1c and total cholesterol, casual plasma glucose, daily insulin doses, and female sex.

Discussion

In Japan, the trend over the past 25 years has been for a consistent increase in the prevalence of overweight men; however, there has been, instead, a decrease in the number of overweight women in the 20–39 years age group [25]. The National Nutrition Survey of Japan, conducted in 2001 [25], revealed that 25.1% of men were overweight and 2.9% were obese, compared with 18.2% and 3.4% of women, respectively. In the US, in 2000, 64.5% of individuals (both men and women) were overweight and 30.5% were obese [26]. In European Union countries, recent estimates indicate that 17.0% of men and 18.8% of women are obese, compared with 16.5% of men and 30.8% of women in Eastern European countries [27]. Thus, the prevalence of obesity in the general population in the US and Europe is higher than in Japan.

Obesity is not generally considered a typical feature of T1DM, but the world-wide trend towards increased body weight is apparent in these patients. The negative association between BMI and age in the present study may reflect this trend. In the US, up to 25.0% of children with T1DM are overweight [28]. In the UK, the prevalence of obesity is similar in diabetic and nondiabetic children [29]. The prevalence of obesity in patients with T1DM in Italy is approximately 6.0% [30]. In the present study, the prevalence of overweight and obesity in patients with T1DM was 15.7% and 2.0%, respectively, for men and 15.5% and 2.0%, respectively, for women. These rates are less than those for the general population in Japan [25], as well as less than those reported for patients with T1DM in the US and Europe.

Of the components of metabolic syndrome investigated in the present study, even though an association was found for both lipid profile and blood pressure with BMI, only lipid profile was associated with increasing HbA1c. Although an association has been

demonstrated between HbA1c levels and both dyslipidemia and hypertension in patients with T2DM [22]. It has been suggested that metabolic syndrome impacts on advanced diabetic nephropathy in T1DM [31] and that it is associated with an increase in cardiovascular risk in T2DM [32]. Further studies are necessary to determine whether there is an association between dyslipidemia and micro- or macrovascular complications in patients with T1DM.

On the basis of results of multiple linear regression analysis, in the present study HbA1c appears to be associated with casual plasma glucose, the daily insulin dose per kg body weight, total cholesterol concentration, and female sex in both the entire group and the early onset subgroup. Multiple linear regression analysis did not indicate a significant association between BMI and any of these variables, except for total cholesterol, in either the entire cohort or the early onset subgroup (Table 1b, Table 2b). However, when all patients with T1DM were stratified according to BMI, it was found that the daily dose of insulin per kg body weight was greater in patients with BMI $\geq$23 kg/m^2 (Table 1a). The results suggest that patients with T1DM may develop insulin resistance that is dependent on increases in body weight.

The requirement for exogenous insulin in T1DM depends on the insulin sensitivity in target tissues, regardless of any residual β-cell function. Adolescent girls tend to be less sensitive to insulin than boys [33]. The finding in the present study that female sex was significantly correlated with deteriorations in HbA1c levels is consistent with that previous report (Table 1b,Table 2b). Insulin resistance is a prominent clinical feature of obesity in children and adults [16], as well as in patients with T2DM. In the present study, for the entire group, a higher BMI (even within the normal range) was associated with higher insulin doses and deteriorating HbA1c levels (Table 1a). Nevertheless, the possibility cannot be excluded that the small number of subjects in the early onset subgroup may have prevented some differences from reaching significance (Table 2a). Another factor in the development of insulin resistance may be hyperglycemia itself. In patients with T1DM, the action of insulin is reduced following a 24-hour period of hyperglycemia compared with that following a 24-hour period of euglycemia, suggesting that the antecedent hyperglycemia results in insulin resistance [34].

Eventually, not only hyperglycemia, but also insulin resistance may promote the development of micro- and macrovascular complications in T1DM [35–37]. In the present study, increased doses of insulin used to improve glycemic control may have caused slight weight gain in patients with T1DM (Table 1a). Increasing doses of insulin, when needed, to improve glycemic control may prevent the development of micro- and macrovascular complications of hyperglycemia. Further studies are needed to determine whether increasing insulin doses to improve glycemic control will result in excessive weight gain in patients with T1DM over a prolonged period.

In conclusion, in the present study of Japanese patients with T1DM, 15% were found to be overweight and 2% were found to be obese. These rates are less than those for the normal population in Japan, as well as less than those reported for patients with T1DM in the US and Europe. In our study population, being overweight was associated with higher blood pressure and dyslipidemia. In patients with T1DM, such metabolic changes may begin to develop even in those patients with a normal BMI. The possibility of a positive association between overweight and increased insulin doses cannot be excluded.

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Appendix I. Members of the Japan Diabetes Clinical Data Management Study Group (JDDM) who participated in the present study (listed alphabetically).

Nobuyuki Abe, Yasuko Chiba, Kazumasa Chikamori, Fumihiko Dake, Kunihiro Doi, Hiroshi Fujiya, Yoshihide Fukumoto, Atsushi Hasegawa, Yoshiyuki Hattori, Hiroshi Hayashi, Kotaro Iemitsu, Hiroshi Ishizu, Masaaki Ito, Koichi Iwasaki, Yoshio Kaku, Akira Kanamori, Azuma Kanazuka, Munemasa Kasayama, Masakazu Kato, Sumio Kato, Koichi Kawai, Kei Kawara, Katsutoshi Komori, Mikihiko Kudo, Shogo Kurebayashi, Shinichi Kuribayashi, Yoshio Kurihara, Gendai Lee, Hajime Maeda, Hideo Manaka, Naoki Manda, Kiyokazu Matoba, Masae Minami, Kazuhiro Miyazawa, Hiroshi Ninomiya, Yoko Notoya, Hisako Ogawara, Mariko Oishi, Akira Okada, Takeshi Osonoi, Sachiko Ota, Miyoko Saito, Hideo Sasaki, Hidekatsu Sugimoto, Hiromichi Sugiyama, Madoka Taguchi, Masato Takagi, Chieko Takahashi, Masahiko Takai, Hiroshi Takamura, Hiroshi Takeda, Kokichi Tanaka, Shinji Taneda, Osamu Tomonaga, Akira Tsuruoka, Takako Wada, Noriharu Yagi, Ritsuko Yamamoto, Morifumi Yanagisawa, Yoshifumi Yokomizo, Atsuyoshi Yuhara.

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Table 1a. Clinical characteristics of all study subjects

	Normal Weight		Overweight		*p* value of ANOVA	Significant Differences Between Groups
	Group 1 (BMI<23kg/m^2)	Group 2 (23kg/m^2≦BMI<25kg/m^2)	Group 3 (25kg/m^2≦BMI<27kg/m^2)	Group 4 (BMI≧27kg/m^2)		
No. subjects (%)	943 (63.45)	310 (20.86)	131 (8.81)	102 (6.86)		
Age (years)	44.63 ± 16.00	43.85 ± 16.76	44.47 ± 15.93	42.96 ± 15.90	0.715	
Sex					0.289	
% Female (n)	58.00 (547)	52.58 (163)	53.44 (70)	59.80 (61)		
% Male (n)	42.00 (396)	47.42 (147)	45.56 (61)	40.20 (41)		
HbA1c (%)	7.68 ± 1.57	7.96 ± 1.58	7.89 ± 1.63	8.10 ± 1.46	0.005	a
Daily insulin dose (U/kg)	0.68 ± 0,29	0.73 ± 0.30	0.75 ± 0.32	0.76 ± 0.30	0.0035	a,b,c
Duration of diabetes (years)	11.68 ± 8.91	13.42 ± 9.34	13.89 ± 9.97	13.92 ± 7.56	0.0011	a,b
Casual plasma glucose (mg/dL)	173.36 ± 86.80	183.50 ± 92.22	172.08 ± 87.74	175.55 ± 86.61	0.38	
Total cholesterol (mg/dL)	191.49 ± 34.94	200.14 ± 34.96	203.67 ± 39.07	211.16 ± 43.63	<0.0001	a,b,c,e,
HDL-cholesterol (mg/dL)	72.97 ± 18.73	69.66 ± 18.21	66.91 ± 17.46	62.16 ± 21.00	<0.0001	b,c,e,
Ln [triglyceride]*	1.8388 (1.7160-1.9868)	1.9294 (1.7924-2.1399)	2.0170 (1.8256-2.2253)	2.0393 (1.8851-2.2049)	<0.0001	a,b,c,e
SBP (mmHg)	119.89 ±16.69	125.03 ± 16.34	128.38 ± 16.37	131.24 ± 14.94	<0.0001	a,b.c.e
DBP (mmHg)	71.45 ±10.18	73.18 ± 10.29	75.54 ± 9.93	77.45 ± 10.40	<0.0001	b,c,e,

* Data show the median concentration [ln(mmol/L)]with the interquartile range given in parentheses. Other data are presented as the mean ±SD, unless indicated otherwise.

Stastical comparisons are as follows: a, group 1 vs. group 2; b, group 1 vs. group 3; c, group 1 vs. group 4; d, group 2 vs. group 3; e, group 2 vs. group 4; f, group 3 vs. group 4 (all $\alpha<0.05$).

BMI, body mass index; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.

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Table 1b. Results of multiple linear regression analysis of all study subjects

Explanatory variables	BMI		HbA1c	
	standard regression coefficient	*p* value	standard regression coefficient	*p* value
Age	-0.115	0.002	-0.071	0.059
Sex (Female)	-0.049	0.135	-0.073	0.024
Daily insulin dose (U/kg)	0.055	0.119	0.151	<0.001
Duration of diabetes	0.061	0.055	-0.037	0.251
BMI			0.033	0.325
Casual plasma glucose	-0.030	0.362	0.288	<0.001
HbA1c	0.034	<0.001		
Total cholesterol	0.168	<0.001	0.221	<0.001
HDL-cholesterol	-0.194	<0.001	-0.013	0.748
Ln[triglyceride]	0.134	<0.001	0.090	0.022
SBP	0.219	<0.001	-0.050	0.290
DBP	0.068	0.120	0.027	0.534

BMI, body mass index; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.

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Table 2a. Clinical characteristics of the study subjects with early onset type 1 diabetes mellitus

	Normal Weight		Overweight		*p* value of ANOVA	Significant Differences Between Groups
	Group 1 (BMI<23kg/m^2)	Group 2 (23kg/m^2≤BMI<25kg/m^2)	Group 3 (25kg/m^2≤BMI<27kg/m^2)	Group 4 (BMI≧27kg/m^2)		
No. subjects (%)	232 (58.10)	99 (24.69)	37 (9.23)	33(8.23)		
Age (years)	28.61 ± 8.17	28.61 ± 8.31	27.97 ± 8.11	27.73 ± 6.61	0.916	
Sex					0.275	
% Female (n)	66.95 (156)	58.59 (58)	56.76 (21)	54.55 (18)		
% Male (n)	33.05 (77)	41.41 (41)	43.24 (16)	45.45 (15)		
HbA1c (%)	7.86 ± 1.46	7.98 ± 1.96	8.54± 2.04	8.44 ± 1.67	0.057	
Daily insulin dose (U/kg)	0.87 ± 0.32	0.92 ± 0.32	0.94 ± 0.39	0.94 ± 0.57	0.306	
Duration of diabetes (years)	16.36 ± 9.17	17.04± 8.70	16.57 ± 8.38	16.57 ± 6.47	0.938	
Casual plasma glucose (mg/dL)	179.10± 89.15	192.21 ± 98.85	181.75 ± 107.56	176.78 ± 75.53	0.685	
Total cholesterol (mg/dL)	187.37 ± 35.69	190.17 ± 34.64	214.00 ± 56.85	237.50 ± 59.98	<0.0001	b,c,d,e,
HDL-cholesterol (mg/dL)	73.68 ± 16.83	69.83 ± 16.57	73.67 ± 21.22	62.63 ± 20.30	0.0442	c
Ln [triglyceride]*	1.8129 (1.7076-1.9542)	1.9111 (1.7763-2.0700)	1.8976 (1.7362-2.0801)	2.0492 (1.8967-2.4385)	<0.0001	c,e,f
SBP (mmHg)	114.82 ±15.06	118.57± 13.62	121.858 ± 15.70	125.664 ± 13.14	<0.0001	b.c
DBP (mmHg)	69.53 ± 9.61	69.67± 9.77	75.36 ± 9.99	74.66 ± 9.24	0.0175	c

* Data show the median concentration [ln(mmol/L)]with the interquartile range given in parentheses. Other data are presented as the mean ±SD, unless indicated otherwise.

Stastical comparisons are as follows: a, group 1 vs. group 2; b, group 1 vs. group 3; c, group 1 vs. group 4; d, group 2 vs. group 3; e, group 2 vs. group 4; f, group 3 vs. group 4 (all $\alpha<0.05$).

BMI, body mass index; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.

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Table 2b. Results of multiple linear regression analysis of early onset type 1 diabetes mellitus

Explanatory variables	BMI		HbA1c	
	standard regression coefficient	*p* value	standard regression coefficient	*p* value
Age	-0.145	0.228	-0.102	0.369
Sex {Female}	0.015	0.822	0.173	0.004
Daily insulin dose (U/kg)	0.014	0.840	1.193	0.002
Duration of diabetes	0.050	0.667	0.070	0.520
BMI			-0.025	0.702
Casual plasma glucose	0.054	0.407	0.287	<0.001
HbA1c	-0.028	0.702		
Total cholesterol	0.399	<0.001	0.247	0.002
HDL-cholesterol	-0.273	<0.001	0.037	0.605
Ln[triglyceride]	0.078	0.316	0.141	0.054
SBP	0.268	0.003	-0.145	0.095
DBP	-0.005	0.954	0.145	0.072

BMI, body mass index; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.