Table 5. Determinants of low eGFR (<60 versus ≥60; left panel) and albuminuria (micro/macroalbuminuria versus normoalbuminuria; right panel) by multiple logistic regression analysis

	eGFR<60 versus ≥60 (reference)			Micro/macroalbuminuria versus normoalbuminuria (reference)		
	Wald χ^2 score	OR (95% CI)	*P*-value	Wald χ^2 score	OR (95% CI)	*P*-value
Age (per years)	76.3	1.08 (1.06–1.10)	0.000	1.9	1.01 (1.00–1.02)	0.170
Male	0.8	0.89 (0.68–1.17)	0.386	8.3	1.31 (1.09–1.57)	0.004
BMI (per kg/m^2)	3.1	1.03 (0.99–1.06)	0.078	22.6	1.06 (1.03–1.08)	0.000
Duration of diabetes (per years)	4.4	1.02 (1.00–1.03)	0.037	0.45	1.00 (0.99–1.02)	0.504
A1C (per %)	15.3	0.79 (0.70–0.89)	0.000	29.8	1.26 (1.16–1.36)	0.000
Hypertension	10.0	1.46 (1.16–1.86)	0.002	68.7	2.12 (1.77–2.53)	0.000
Hyperlipidaemia	9.7	1.47 (1.15–1.86)	0.002	0.9	1.09 (0.91–1.31)	0.338
Smoking versus never	5.1	0.77 (0.62–0.97)	0.030	2.0	1.16 (0.95–1.42)	0.158
CVD	15.7	1.87 (1.37–2.55)	0.000	14.5	1.69 (1.29–2.29)	0.000
Retinopathy versus none						
simple	7.4	1.47 (1.11–1.91)	0.151	52.1	2.10 (1.72–2.56)	0.000
proliferative	15.9	2.11 (1.46–3.05)	0.000	80.0	3.72 (2.79–4.96)	0.000
Neuropathy (%)	1.9	1.17 (0.92–1.56)	0.174	12.3	1.45 (1.18–1.79)	0.000
Nephropathy versus normoalbuminuria				N.A.	N.A.	N.A.
Microalbuminuria	0.4	1.01 (0.83–1.45)	0.506			
Macroalbuminuria	102.1	5.56 (4.00–7.76)	0.000			
eGFR <60 versus ≥60	N.A.	N.A.	N.A.	31.1	1.91 (1.52–2.40)	0.000

Both analyses were obtained after adjustment for an effect of different clinics/hospitals.
N.A., not applicable.

type 2 diabetes can commonly progress to a significant degree of renal insufficiency while remaining normoalbuminuric [3,9]. Furthermore, we found that more than 60% of patients with normoalbuminuria and low eGFR had neither diabetic retinopathy nor neuropathy. The finding strongly suggests that non-diabetic renal disease is not uncommon in type 2 diabetic patients [2].

Clinical features of patients with normoalbuminuria and renal insufficiency

Few reports have analysed the clinical characteristics of type 2 diabetic patients with normoalbuminuria and renal insufficiency. One report compared them with those with micro/macroalbuminuria and with renal insufficiency [3]. It showed that normoalbuminuric renal insufficiency patients were characterized by female predominance, lower SBP and higher HDL, which is in accordance with our findings. Similar findings were demonstrated in type 1 diabetes [5]. We have extended their findings by demonstrating lower prevalences of smokers, CVD, retinopathy and neuropathy. Another report compared them with those with normoalbuminuria and an eGFR ≥60, where the finding was similar to ours in terms of more women, older age and higher concentrations of TC and TG [4]. Our study provides further information such as higher levels of systemic BP and PP in those with renal insufficiency and with normoalbuminuria.

Proportion of patients with normoalbuminuria and with renal insufficiency

First, we should acknowledge that the proportion of patients with renal insufficiency is subject to the equation for eGFR. The proportion of 11.4% (low eGFR among those with normoalbuminuria) shown in this paper was 16.6% when the equation in the previous studies [12,15] was employed (data not shown). Secondly, one should be cautious about selection bias when calculating prevalences. The proportion of normoalbuminuria seems higher than in other cross-sectional large-scale-population-based prevalence studies [15,18], and it is possible that the included subjects had a lower prevalence of complications compared to the entire population of type 2 diabetic patients since inpatients and those who were treated solely by cardiologists/neurologists did not participate. The prevalence of renal insufficiency among those with normoalbuminuria was 12.7% (84/660) in a report from Brazil [4], which seems compatible with our finding of 11.4%. The prevalence of normoalbuminuria among those with renal insufficiency was 23.2% (20/86) in a report from Australia [3], but 42.7% (182/426) in our study: both studies performed adjustment for possible effects of the RAS inhibitor. The prevalence of 23.2% [3] was calculated at a tertiary referral clinic and the number was small. The above findings suggest that a significant proportion of type 2 diabetic patients have non-albuminuric renal insufficiency.

Factors associated for albuminuria and low eGFR

The clinical factors associated with albuminuria and low eGFR were comparable with those found in other longitudinal [5,9] and cross-sectional [3,4,6,19] studies. The UK Prospective Diabetes Study revealed that over a median of 15 years' follow-up, risk factors for development of albuminuria were male sex, TG, LDL-C, A1C, smoking and retinopathy, and those for renal insufficiency were female sex, age and neuropathy [9]. A female predilection for normoalbuminuria and renal insufficiency has been noted by other cross-sectional [3,4,6] and follow-up [5] studies, but to date the reason for this association is unknown. Lower A1C values were observed in those with low eGFR than

in those with preserved eGFR in our study, particularly in those with micro/macroalbuminuria. This could be due to a reduced erythropoietin production caused by reduced renal function [20], although our study did not collect data for haemoglobin concentrations. A decreased haemoglobin concentration has been shown to be an independent factor associated with renal dysfunction in diabetic patients [21]. Smoking is associated with albuminuria, suggesting that smoking may be an important correlate of albuminuria in the presence or absence of low eGFR. Subjects who had never smoked were more prevalent in those with low eGFR than in those with preserved eGFR among those with normo- and microalbuminuria. The same result was seen in another report [19]; however, the reason remains uncertain from these cross-sectional studies. Taken together, distinct factors associated with albuminuria and low eGFR are indicated. Indeed, no significant associations between renal insufficiency and microalbuminuria were found in multivariate analysis. These findings support the concept that albuminuria and low eGFR are not necessarily linked in type 2 diabetes [9].

Reason of low eGFR in type 2 diabetic patients

The mechanism for low eGFR in normoalbuminuric type 2 diabetic patients is still unknown, despite the involvement of non-diabetic renal disease being indicated. Among normoalbuminuric patients, greater age, longer duration of diabetes and higher prevalences of hypertension, hyperlipidaemia, diabetic neuropathy and CVD were found in those with low eGFR than in those with preserved eGFR. A lower concentration of HDL was observed in macroalbuminuric patients with renal insufficiency. These findings indicate that low eGFR could be due to age-associated senescence and interstitial fibrosis, and renal ischaemia due to intrarenal arteriosclerosis and cholesterol emboli involvements [2,22]. Lipid abnormalities by high TG and low HDL were indicated in association with progression of renal dysfunction [23]. Our finding that the prevalence of CVD was persistently twofold higher in patients with low eGFR than in those with preserved eGFR regardless of the degree of albuminuria indicates that the low eGFR is substantially associated with atherosclerotic vascular disease.

Limitation of the study

The study design was cross-sectional; therefore it cannot explore causal relationships. A single measurement of serum creatinine for calculating eGFR could mislead the classification of CKD stages. Since age and female sex both reduce the MDRD equation, it cannot be denied that the association of these factors with low eGFR was generated in part by the equation. Direct measurement of GFR should be a standard clinical procedure, although it is time consuming and not feasible for screening and large-scale studies. The usefulness of eGFR has been demonstrated by several follow-up studies [24,25], and a recent validation study indicated that the difference between eGFR by MDRD and measured GFR was slight and not significant even in cross-sectional analysis of normoalbuminuric and albuminuric diabetic patients [5]. On the other hand, the strengths of this study include the large-scale population with type 2 diabetes, a nation-wide multicentre-based design and multiple measurements of ACR and blood pressure. Finally, since the subjects included in this study were recruited from practice and seemed less complicated, we cannot evaluate the prevalence of severe renal failure from this study although it is likely to be higher than we have found.

Attainment of treatment goals

The low attainment rate of treatment goals for A1C, BP and lipids may indicate that those with increasing albuminuria stages and CKD stages are refractory to standard therapy despite aggressive use of insulin, antihypertensive and lipid-lowering agents. This finding is in line with other studies [26], indicating the need for aggressive treatment of these modifiable risk factors. In diabetic patients even without albuminuria, it may be reasonable to encourage screening for low eGFR. The potential benefit of achieving current treatment goals in patients with micro/macroalbuminuria and/or low eGFR offers hope for the future reduction of CVD and end-stage renal disease if a more focused and multifactorial approach is applied.

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Conflict of interest statement. None declared.

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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

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 α<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 α<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.

Message

糖尿病データベースの構築

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Development of the data base for the diabetic patients in Japan

はじめに

糖尿病診療全体を如何に有効に導いていくかについては，検診の受診率，糖尿病患者の医療機関での受診率，糖尿病医療の質等の向上が必要であり，このためにはそれぞれの患者の継続的な診療が必要であり，現在一次予防のあり方，治療中断率抑制を目標とした診療のあり方，動脈硬化の合併症抑制のための治療のあり方などの研究が戦略研究課題(J－DOIT，1－3)として実施されている．このような介入研究の結果も重要であるが，一方では，一例一例の患者の糖尿病の発症から合併症の発症までの病歴の蓄積と治療との関係をデータとして集積し，日本人の糖尿病がどのようなものであるかを，丁寧に解析することが重要である．このようなデータベースの構築は国家的な施策として，なされるべきものと考えるが，現在行われているものは，日本糖尿病学会を中心として，日本腎臓学会，日本糖尿病眼学会，日本歯周病学会の4学会が協力して実施されている前向き大規模研究である．ここではこの研究の概略と進捗状況を述べ，その意義と問題点などを概説する．

I. 研究の背景と糖尿病データベースの必要性

糖尿病の合併症を予防するには糖尿病の医療の質の客観的なデータを収集し，その解析から実態を把握し，どのような治療が合併症抑制に有効であるかを明らかにすることが必要である．これまで，全国的なデータとしては，筆者らが中間法人糖尿病データマネジメント研究会(JDDM)として，全国の糖尿病専門医が75,000人の患者からCoDiCというソフトで得たものがあり[1]，その解析により種々の日本における糖尿病診療の医療の質を報告している．例えば，図1に示すよう日本において専門医の診療の質を表すものとして，治療内容別のHbA_{1c}の値を報告し[2]，欧米と比較しても比較的優れた結果を報告している[3]．これらの結果は，HbA_{1c}，血糖，血圧などの臨床データと薬物などの治療内容を網羅したものであり，多くの患者のデータよりその信用度が高い．しかし，合併症などのデータになるとその標準化の問題などがあり，慎重に収集・解析する必要がある．またこれらの患者は，糖尿病専門医の患者のデータであり日本の糖尿病を代表するものであるかどうかも慎重に吟味する必要がある．専門医は全体の糖尿病患者の20%程度しか診療していない現実から，かかりつけ医が診療しているあとの80%についてのデータも検討する必要がある．かかりつけ医のデータに関しては，多くの非専門医のかかりつけ医のカルテから直接抽出したものは現在まで見られず，最近著者らが行った戦略研究J－DOIT2の非専門医のかかりつけ医を対象にしたパイロット研究で得たものしか存在しない．他には，JDCSや久山町研究などもあるが，前者は専門医が主治医であり[4]，後者はある町のポピュレーションを対象にしたものであり[5]，多くのデータベースで満足すべきものは未だ見ない．さらに，厚生労働省では，4疾患5事業の計画の中にも患者登録とそのデータの蓄積が重要であるとし，その結果を糖尿病医療の質の向上にむけ活用する必要があるとしている[6]．このような症例の登録は，図2に示すように個々の症例の治療のあり方がいかに合併症などに対して影響があるか，どのような治療が合併症を予防できるか，糖尿病治療のガイドラインや厚生施策の資料となるものと考えられる．

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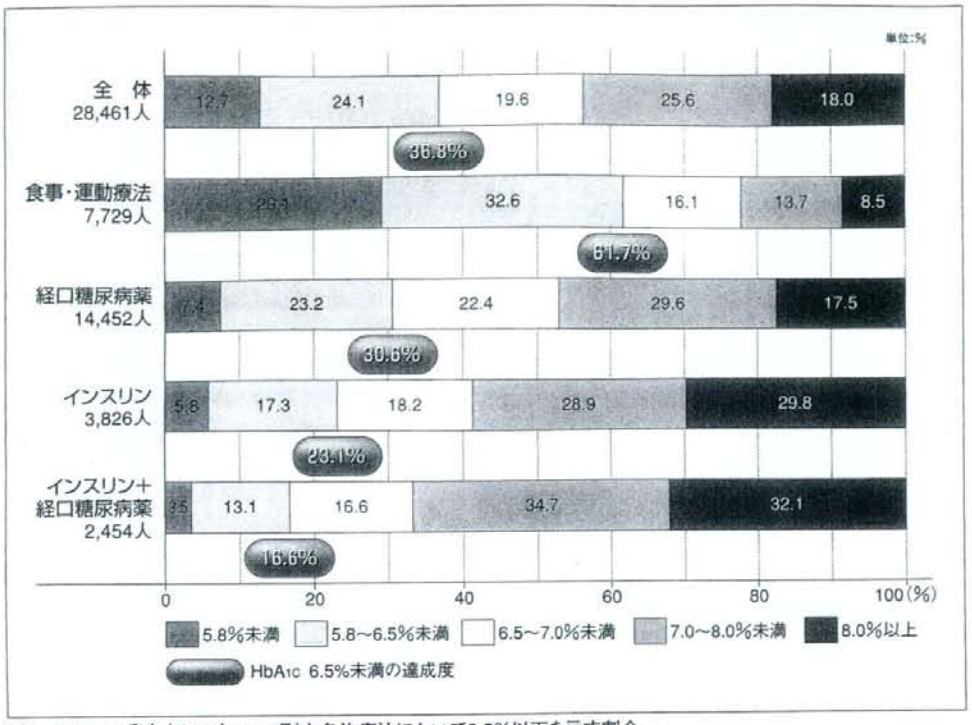

図1 HbA_{1c}の分布(2004年5~7月)と各治療法において6.5%以下を示す割合

II. 糖尿病データベース構築研究の経過と概要

糖尿病学会において，平成16年10月に第1回糖尿病データベース構築委員会が開催され，各委員から専門的な立場から現在までの取組状況(腎症，大血管障害，神経障害，1型糖尿病，網膜症，死因など)が説明され，また，疫学的な見地から種々検討された．その結果，次のようなcohort studyを立ち上げることとなった．すなわち，約10,000症例の糖尿病患者を登録し，これらの症例を全数調査する．合併症の発症をエンドポイントとして，後ろ向き，前向き研究(historically prospective study)を行う．エンドポイントとなるのは，腎症：透析，網膜症：光凝固・失明，脳梗塞：半身麻痺などの臨床所見，心血管障害：CABG，PCI，心不全，Amputation，などとする．これらの症例はルーティンの診療でフォローしている患者とし，できるだけ，多くの患者を登録するためには，臨床データの必要とする記録を最小限で必須なもののみとする．5年程度で結果の解析を行う．この集団において，死因の調査も行い，従来のアンケート調査との比較なども行う．年に1回，登録した患者のデータの記録を行う．さらに重要なことは，登録患者の記録には標準化が必要であるが，これをあらかじめ明確にし，参加者にその旨徹底する．例えば，網膜症の分類には，福田の分類は用いず，単純・前増殖性網膜症・増殖性網膜症などにする．このような考えから，各委員の専門的な立場から必須項目を挙げ，それをまた委員会で最小必須項目の絞り込み作業をした．専門家としては，どうしても多くの項目を挙げる傾向にあったが，委員会全体でこれをなるべく抑える方向に考えた．また，最小限必要な項目と一部詳細にデータを収集する項目を考え，後者には例えば，末梢神経障害の診察にC128の音叉による振動感覚の診察は入れるが，爪楊枝による診察

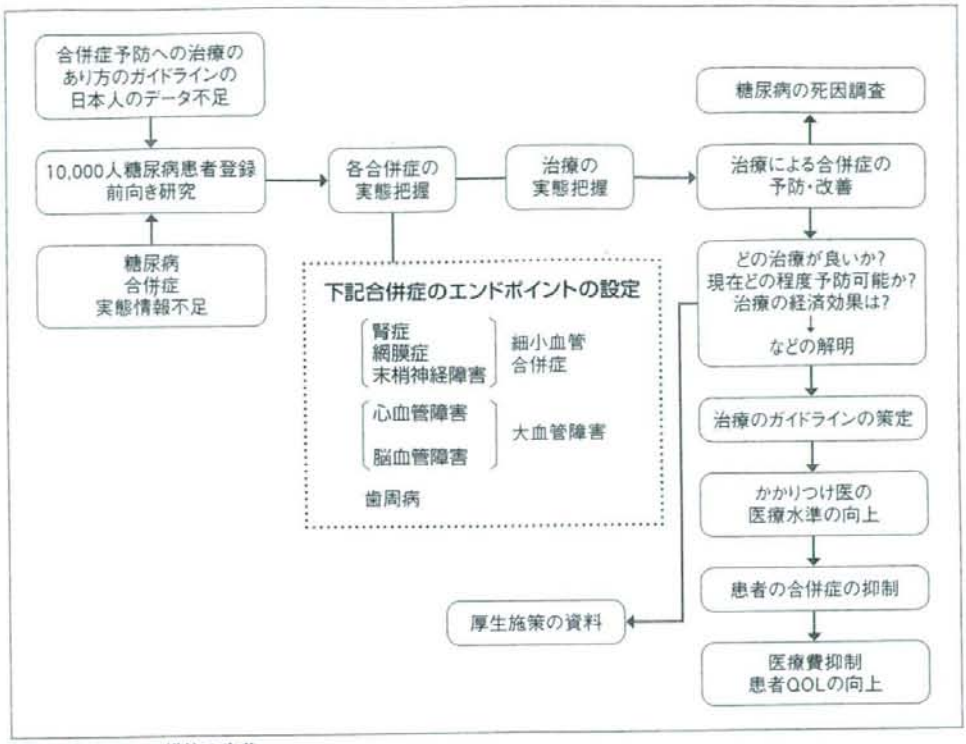

図2　データベース構築の意義

は入れないことや，検査値の中でも随時血糖は入れるが空腹時血糖やインスリン値は入れないことなどを決めた．このような，項目の決定には相当な時間を要し，最後にはできるだけ少ない方向で決まった．ただし，詳細なデータを要する場合は，それぞれ専門家の考えを入れ，データが入った患者のみを集計し，別に統計解析をすることとした．

このような作業が進んでいるところで，日本歯周病学会にも参加していただき，日本糖尿病学会，日本腎臓学会，日本糖尿病眼学会とあわせて4学会がこれに参画し，平成18年度厚生科研の募集があり，応募をした．その結果厚生労働省には「糖尿病における失明，歯周病，腎症，大血管合併症などの実態把握とその治療に関するデータベース構築による大規模前向き研究」という題名で小林正(日本糖尿病学会)，堀田　饒(日本糖尿病学会)，田嶼尚子(日本糖尿病学会)，岩本安彦(日本糖尿病学会)，山田信博(日本糖尿病学会)，門脇　孝(日本糖尿病学会)，槙野博史(日本腎臓学会)，北野滋彦(日本糖尿病眼学会)，野口俊英(日本歯周病学会)の研究者の名で応募し，受理された[7]．実際はこれらの研究者のほか，疫学研究者として吉池信男，また合併症や食事療法，運動療法のワーキングチームの研究者としてそれぞれの学会員が分担して各問題にあたった．この研究の各学会から提出された各追跡項目に関しては，既に述べたごとく必須項目以外に，各合併症ごとにさらに十分なデータを得るために，「可能ならば」取得できるデータを設定し，これらのデータからより信頼度の高い解析結果を得ることにした．例えば，眼底写真4方向や，歯周病の病態を明らかにするレントゲン写真(オルソパントモ)の取得などである．また，倫理的な考慮として，患者登録に関し，患者情報保護を徹底し，施設番号，中央番号にて表

すことにした．患者には研究の概要を十分説明し，書面による研究参加の承諾の署名を得ることにした．プロトコールを完成し，糖尿病学会の倫理委員会にて承認された．平成19年4月から登録が始まった．

III. 追跡項目について

追跡項目については，できるだけ必須項目のみにし，標準的なものにまとめた．患者基本情報としては，氏名，ID番号を示さず，中央の登録番号が入るようにすることで，個人情報も保護されるようになっている．既往歴，家族歴等も✓印で示されるように簡単に形式を整え，また病型も簡単に示すようにした．空腹時血糖，中性脂肪など空腹時に採血を要するものは必須項目とせず，これらは「可能ならば」採取するということにした．高感度CRPも同様で肥満や動脈硬化の指標の一つとして重要と考えられているが日常診療の検査としては必須項目とはしないことにした．腎症の微量アルブミン尿の所見を随時尿の1回目のみ必須とし，2回目を「可能ならば」とした．眼科の所見は，眼科の所見標準化し，眼底写真に関しては必須とせず，日常診療範囲でのデータで十分であるとした．神経障害の症状とアキレス腱反射，C128音叉による振動覚，CV_{RR}を必須とし，爪楊枝による痛覚検査は「可能ならば」とした．歯科に関する追跡情報では，問診のみが必須で歯科受診は日常診療では困難との判断で「可能ならば」受診しその所見を記入することにした．治療に関しては，食事に関しては当初BHDQによるチェックシートを考えていたが，質問事項の多すぎること，多忙な外来や患者への説明などを考慮するとその取得は困難であるとし，「可能ならば」取得することになった．治療薬は薬品名でなく，どのカテゴリーの薬品かをチェックすることにした．

図3 登録期間の延長を伝えるポスター

このように，できるだけ簡素にしてもある程度の時間を要するが，糖尿病学会の認定教育施設であればこの程度の記入は年1回可能であろうと思われる．最小でしかも十分であるという条件が，10,000症例という患者数の登録に必要であり，このような観点から今回の追跡情報は標準的なものであるものと考えられ，この種の大規模試験を企画する場合には十分使用できるものと考えられる．

IV. エンドポイントの設定

エンドポイントの設定は，次に示す状態をエンドポイントとするhistorically prospective studyを行う．

①腎症：アルブミン尿の出現(尿中アルブミン/クレアチニン比が30mg/gCr以上)，顕性蛋白尿の出現(尿中アルブミン/クレアチニン比が300mg/gCr以上)，血清クレアチニン値の2倍