Table 2. Incidence density of diabetic nephropathy in patients with type 1 and type 2 diabetes diagnosed before the age of 30, by the duration of diabetes and the postpubertal duration of diabetes[a]

	Duration of diabetes *years*						
	0–4	5–9	10–14	15–19	20–24	25+	Total
Duration of diabetes *years*							
Type 1							
N new cases	0	2	32	16	5	0	55
Person-years of duration	3009	2672	1898	1077	520	181	9357
Incidence density (/1000 person-years)	0	0.75	6.86	4.86	9.62	0	5.88
Type 2							
N new cases	10	26	57	33	14	3	143
Person-years of duration	4034	3149	2012	1051	492	179	10917
Incidence density (/1000 person-years)	2.48	8.26	28.33	31.40	28.46	16.76	13.10
Rate ratio[b]							
Type 2 vs. type 1	NC	11.01	1.68	2.11	2.96	NC	2.23
95% CI		2.61–46.4	1.09–2.59	1.10–3.54	1.07–8.22		1.63–3.04
P value		0.001	0.006	0.02	0.02		0.001
Postpubertal duration of diabetes *years*							
Type 1							
N new cases	0	6	31	14	4	0	55
Person-years of postpubertal duration	2938	2572	1720	867	365	99	8560
Incidence density (/1000 person-years)	0	2.33	18.02	16.15	10.96	0	6.43
Type 2							
N new cases	10	26	57	33	14	3	143
Person-years of postpubertal duration	4034	3146	2012	1055	490	168	10905
Incidence density (/1000 person-years)	2.49	8.26	28.33	31.28	28.57	17.86	13.11
Rate ratio[b]							
Type 2 vs. type 1	NC	3.55	1.57	1.94	2.61	NC	2.04
95% CI		1.42–8.62	1.01–2.43	1.04–3.62	0.86–7.93		1.50–2.78
P value		0.005	0.02	0.001	0.07		0.001

[a]Abbreviations are: CI, confidence interval; NC, not calculated; in these patients incidence density of diabetic nephropathy in type 1 diabetic patients during the period was 0

[b]Calculated as the incidence density of diabetic nephropathy in type 2 diabetic patients divided by the incidence density in type 1 diabetic patients during the same period

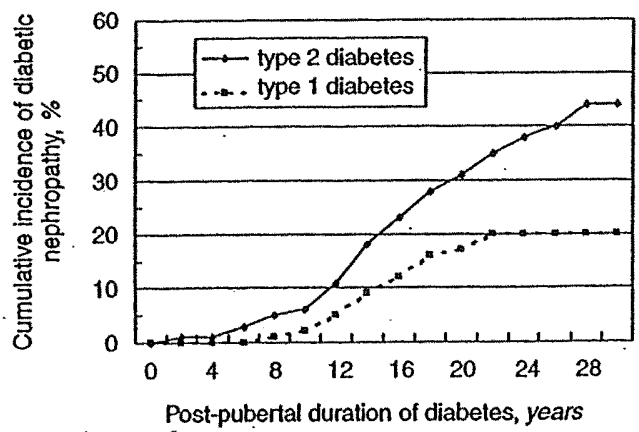

Fig. 2. Cumulative incidence of diabetic nephropathy according to postpubertal duration of diabetes in patients with type 1 (■) and type 2 (●) diabetes diagnosed before the age of 30. Patients with type 2 diabetes had a significantly higher incidence of nephropathy than those with type 1 diabetes ($P < 0.0001$).

was similar for the type 1 and type 2 diabetic patients. The distribution of patients according to the age at diagnosis of diabetes differed for the type 1 and type 2 diabetic patients. However, for three subgroups based on the decade in which diabetes was diagnosed (that is, at ages 0 to 9, 10 to 19, and 20 to 29 years), the age at diagnosis, age at first visit, age at final examination, and postpubertal duration of diabetes were comparable between the type 1 and type 2 diabetic patients. Body mass index and blood pressure levels were higher, and glycosylated hemoglobin (HbA1c) levels were lower in patients with type 2 diabetes than in those with type 1 diabetes. Thirty-six percent of the type 2 diabetic patients were treated with insulin. However, their serum C-peptide levels were apparently preserved as compared with the levels in the type 1 diabetic patients. The proportion of patients who visited with referrals was similar for the type 1 and type 2 diabetic patients (71%, 95% CI, 67 to 75% vs. 66%, 95% CI, 62 to 69%). The proportion of patients with a family history of diabetes in first-degree relatives was 24% (95% CI, 21 to 27%) in the type 1 and 56% (95% CI, 53 to 59%) in the type 2 diabetic patients.

End points of the observation

For a total of 9357 person-years in type 1 diabetes, end points of the observation were development of diabetic nephropathy for 55 patients (791 person-years), the end of follow-up without nephropathy for 447 patients (7403 person-years), death without nephropathy for 12 patients (173 person-years), and discontinued visits for 106 patients (990 person-years). For a total of 10,917 person-

Table 3. Incidence of diabetic nephropathy in young patients with type 1 and type 2 diabetes, by age at diagnosis of diabetes[a]

	Age at diagnosis of diabetes *years*		
	0–9	10–19	20–29
Type 1			
N new cases	14	25	16
Person-years of postpubertal duration	2875	3771	1914
Incidence density (/1000 person-years)	4.87	6.63	8.36
Type 2			
N new cases	2	37	104
Person-years of postpubertal duration	78	2974	7855
Incidence density (/1000 person-years)	25.53	12.44	13.24
Rate ratio[b]			
Type 2 vs. type 1 (95% CI)	5.24	1.88	1.58
95% CI	1.19–23.05	1.13–3.12	1.01–2.67
P value	0.04	0.003	0.04

[a]CI denotes confidence interval
[b]Calculated as the incidence density of diabetic nephropathy in type 2 diabetic patients divided by the incidence density in type 1 diabetic patients

Table 4. Incidence of diabetic nephropathy in young patients with type 1 and type 2 diabetes, by calendar year at onset of diabetes[a]

	Calendar year at diagnosis of diabetes			
	1965–69	1970–74	1975–79	1980–84
Type 1				
N new cases	13	18	13	7
Person-years of postpubertal diabetes	1224	1811	2058	1928
Incidence density (/1000 person-years)	10.62	9.94	6.32	3.63
Rate ratio[b] (vs. calendar year 1965–69)	1.0	0.94	0.60	0.34
95% CI		0.46–1.92	0.28–1.29	0.14–0.85
P value		NS	NS	0.002
Type 2				
N new cases	29	47	41	22
Person-years of postpubertal diabetes	1713	2208	2659	2199
Incidence density (/1000 person-years)	12.38	21.29	15.42	9.98
Rate ratio[b] (vs. calendar year 1965–69)	1.0	1.26	0.91	0.59
95% CI		1.13–1.41	0.57–1.46	0.34–1.03
P value		0.02	NS	NS
Rate ratio[c]				
Type 2 vs. type 1	1.17	2.14	2.44	2.74
95% CI	0.61–2.25	1.24–3.68	1.31–4.55	1.17–6.41
P value	NS	0.002	0.002	0.005

[a]CI denotes confidence interval; NS denotes not significant; Person-years were calculated until 20 years of postpubertal duration to compensate for the short observation of the recently diagnosed group for comparing the effect of calendar year at diagnosis of diabetes
[b]Calculated as the incidence density of diabetic nephropathy in each group (that is, calendar year at diagnosis of diabetes between 1970 and 1974, 1975 and 1979, and 1980 and 1984) divided by the incidence density of patients with diabetes diagnosed between 1965 and 1969 as reference
[c]Calculated as the incidence density of diabetic nephropathy in type 2 diabetic patients divided by the incidence density in type 1 diabetes

years in type 2 diabetes, end points of the observation were development of diabetic nephropathy for 143 patients (1867 person-years), the end of follow-up without nephropathy for 403 patients (6464 person-years), death without nephropathy for 3 patients (44 person-years), and discontinued visits for 409 patients (2542 person-years).

Incidence density of diabetic nephropathy in type 1 and type 2 diabetes

The incidence density of diabetic nephropathy was calculated for five-year periods on the basis of both the entire duration of diabetes and the postpubertal duration of diabetes (Table 2). Both calculations revealed a statistically significant and persistently high incidence of nephropathy in patients with type 2 compared with those with type 1 diabetes. The rate ratio for type 2 diabetic patients relative to type 1 diabetic patients was 2.04 (95% CI, 1.50 to 2.78).

The cumulative incidence of nephropathy after 30 years of postpubertal diabetes was significantly higher ($P < 0.0001$) for patients with type 2 diabetes (44.4%, 95% CI, 37.0 to 51.8%) than for those with type 1 diabetes (20.2%, 95% CI, 14.9 to 25.8%; Fig. 2). Provided that the type 2 diabetic patients who discontinued their clinic visits without nephropathy had no nephropathy until the final date of this study (March 1997), it still would have remained significantly higher ($P < 0.0001$) for the pa-

Table 5. Estimated cumulative incidence of diabetic nephropathy in the Poisson multivariate regression models

	Postpubertal duration of diabetes *years*			
	5	10	15	20
Type 1				
Diagnosed between 1965 and 1969				
Cumulative incidence %	0	3.4	22.4	34.2
95% CI		1.5–8.3	13.3–37.3	20.9–53.7
Diagnosed between 1980 and 1984				
Cumulative incidence %	0	1.1	7.7	12.3
95% CI		0.5–2.6	4.2–14.0	6.5–23.1
Type 2				
Cumulative incidence %	2.2	9.7	23.0	35.9
95% CI	1.4–3.7	6.8–13.8	17.3–30.3	28.1–45.3

CI denotes confidence interval. Covariates considered were sex, age at diagnosis of diabetes, calendar year at diagnosis of diabetes, observation year (postpubertal duration of diabetes). The quadratic term of observation year was necessary to get an adequate fit to data. The effect of calendar year was significant only for type 1 diabetic patients. The final model included only the linear term of observation year, the quadratic term of observation year and the calendar year of diagnosis as significant covariates.

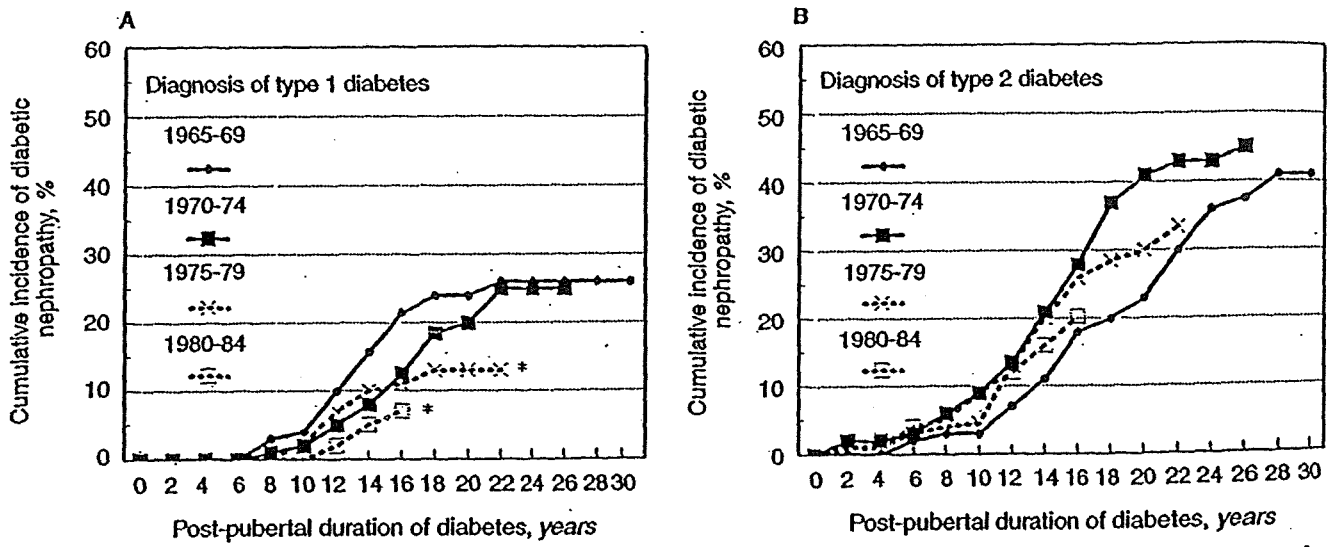

Fig. 3. Cumulative incidence of diabetic nephropathy in patients with early-onset type 1 (*A*) and type 2 (*B*) diabetes, according to the calendar year of diagnosis. Each asterisk denotes a significant difference in incidence ($P < 0.05$ with log-rank test) between the group indicated and the group with diagnosis of diabetes between 1965 and 1969.

tients with type 2 diabetes (32.9%, 95% CI, 27.3 to 38.5%) than for those with type 1 diabetes. The cumulative incidences were similar for males and females in both types. The cumulative incidences were also similar between those who visited with and without referrals and between those with and without a family history of diabetes, in both types.

Analysis of the incidence of diabetic nephropathy in three groups according to the age at diagnosis of diabetes revealed a consistently higher incidence of nephropathy in the patients with type 2 diabetes than in the patients with type 1 diabetes (Table 3).

The effect of the calendar year at diagnosis on the incidence of nephropathy is shown in Tables 4 and 5. The incidence of nephropathy among the patients with type 1 diabetes declined during the past two decades, whereas the incidence among the patients with type 2 diabetes remained persistently high. Patients who developed type 1 diabetes between 1980 and 1984 had a significantly lower incidence (3.63 out of 1000 person-years) than those who developed type 1 diabetes between 1965 and 1969 (10.62 out of 1000 person-years, rate ratio 0.34, $P = 0.002$). The rate ratio for patients with type 2 diabetes diagnosed between 1965 and 1969 relative to that for patients with type 1 diabetes diagnosed in the same period was 1.17 (95% CI, 0.61 to 2.25; Table 4). The rate ratio for the type 2 diabetic patients relative to the type 1 diabetic patients increased during the past two decades, being 2.74 (95% CI, 1.17 to 6.41) in the patients with type 2 diabetes diagnosed between 1980 and 1984 relative to the patients with type 1 diabetes diagnosed in the same period.

Table 6. Clinical features of patients who did and did not develop nephropathy

	Developed nephropathy	Did not develop nephropathy	*P* values
Type 1			
Male % (95% CI)	30.1 (19.1–44.8)	39.3 (35.2–43.3)	NS
Age at diagnosis of diabetes *years*	15.3 ± 7.1	14.0 ± 7.5	NS
HbA1c at first visit %	10.3 ± 2.0	9.4 ± 1.9	0.0002
Systolic blood pressure at first visit *mm Hg*	122 ± 16	112 ± 11	0.003
Diastolic blood pressure at first visit *mm Hg*	77 ± 10	70 ± 9	0.0001
Age at diagnosis of nephropathy or at end point* *years*	29.7 ± 7.2	29.2 ± 8.3	NS
Type 2			
Male % (95% CI)	55.2 (47.1–63.4)	55.3 (51.9–58.8)	NS
Age at diagnosis of diabetes *years*	23.1 ± 5.0	22.9 ± 5.3	NS
HbA1c at first visit %	9.6 ± 2.1	8.5 ± 2.2	<0.0001
Systolic blood pressure at first visit *mm Hg*	122 ± 19	116 ± 16	0.04
Diastolic blood pressure at first visit *mm Hg*	78 ± 11	74 ± 11	0.006
Age at diagnosis of nephropathy or at end point* *years*	36.2 ± 7.2	34.0 ± 9.9	NS

Plus-minus values are mean ± SD.
*Definition of the end point is described in the method

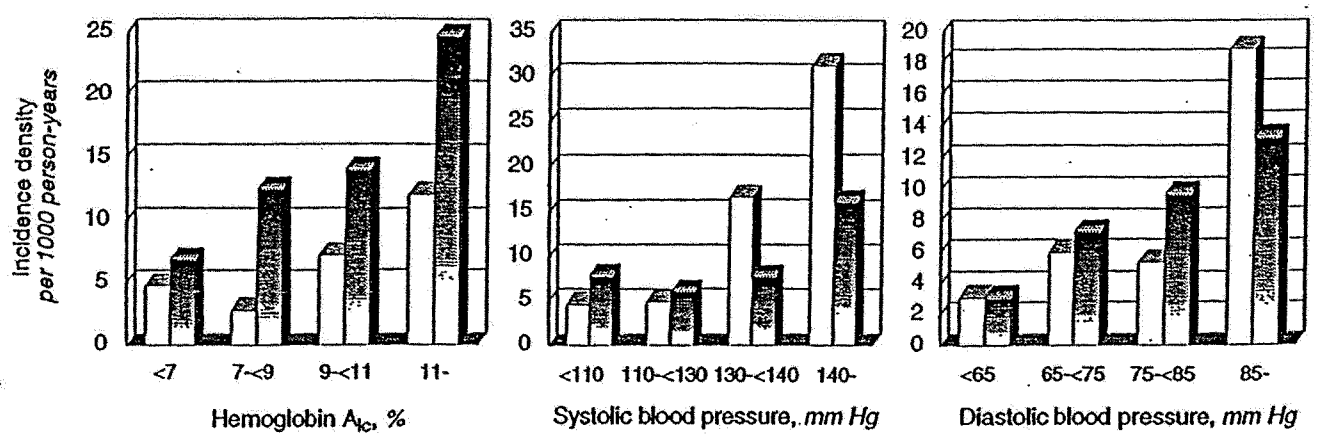

Fig. 4. Comparison of the impact of risk factors on incidence density of diabetic nephropathy between type 1 (□) and type 2 (■) diabetes.

Figure 3 showed the cumulative incidence of nephropathy in patients with early-onset type 1 (Fig. 3A) and type 2 (Fig. 3B) diabetes, according to the year of diagnosis. The cumulative incidence was significantly lower in patients with type 1 diabetes diagnosed between 1975 and 1979 and between 1980 and 1984, than in those with type 1 diabetes diagnosed between 1965 and 1969.

For simultaneously analyzing the effect of multiple factors, multivariate Poisson log-linear models were fitted to the data. As covariates, sex, age at diagnosis of diabetes, calendar year of diagnosis, and observation year (postpubertal duration of diabetes) were considered. Simple models that allowed an interpretation consistent with that of a crude analysis could not be obtained if we included patients who were diagnosed before age 10 because of the complicated interaction among age at diagnosis, year of diagnosis, and observation year. We therefore deleted those patients and used the observation after 20 years for increasing the reliability of prediction based on the models. In all, 128 events in 10,791 person-years for type 2 diabetes and 44 events in 6288 person-years for type 1 diabetes were used for model fitting. The final models included only the linear term of the observation year, the quadratic term of the observation year, and the calendar year of diagnosis as significant factors, which corresponded to the results of crude analyses. The quadratic term was necessary to get an adequate fit. The effect of calendar year was significant for only type 1 diabetic patients and was included as a linear term. Models were fitted to type 1 and type 2 diabetes separately because parameters were entirely different. Predicted cumulative incidences were calculated based on fitted models, and confidence intervals were calculated using asymptomatic variance matrices of the estimated parameters.

The estimated cumulative incidence from the Poisson regression models after 20 years of postpubertal diabetes declined from 34.2% (95% CI, 20.9 to 53.7%) in the patients with type 1 diabetes diagnosed between 1965 and 1969 to 12.3% (95% CI, 6.5 to 23.1%) in those with type 1 diabetes diagnosed between 1980 and 1984, whereas it remained unchanged among the patients with

type 2 diabetes and was 35.9% (95% CI, 28.1 to 45.3%; Table 5).

Risk analysis for diabetic nephropathy in type 1 and type 2 diabetes

In both type 1 and type 2 diabetes, patients who developed nephropathy showed significantly higher levels of HbA1c and blood pressure than those who did not (Table 6). The incidence of nephropathy increased with increasing HbA1c values and blood pressure levels in both types of diabetes (Fig. 4). The incidence of nephropathy was higher in patients with type 2 diabetes than those with type 1 diabetes at every stratum of HbA1c. Patients with type 1 diabetes and the highest blood pressure levels showed a significantly higher incidence of nephropathy than those with type 2 diabetes and the same blood pressure value ($P \leq 0.05$).

DISCUSSION

This study did not aim at investigating the effects of putative risks (such as glycemic control, blood pressure, or lipid profiles on the development of diabetic nephropathy), but aimed at determining associations of the type of diabetes and year of diagnosis with the incidence of nephropathy under the conditions that: (*1*) both type 1 and type 2 diabetes occur in the young homogeneous population in Japan; (*2*) direct comparison was made within the same unit between type 1 and type 2 diabetes; (*3*) type of diabetes was carefully defined; (*4*) referral bias was evaluated; and (*5*) alternative causes of proteinuria were excluded. The study showed the incidence of nephropathy to be twice as high in the patients with type 2 as in the patients with type 1 in early-onset diabetes. The incidence of nephropathy was not influenced by gender, referral, and existence of diabetes in first-degree relatives. While the incidence of type 1 diabetes has decreased in our patient population during the past two decades, type 2 diabetes has remained persistently high. Consequently, the rate ratio for the incidence of nephropathy in type 2 diabetic patients relative to type 1 diabetic patients has become more prominent in those young, recently diagnosed diabetic patients in Japan. The increasing rate ratio for the incidence of nephropathy in type 2 diabetic patients relative to type 1 diabetic patients suggests that we will see a further increase in ESRF in patients with type 2 diabetes in the future. This situation calls for urgent, intense educational efforts in the medical community and the general population. Such efforts could save lives and lead to considerable economic savings, not only in type 1 [41] but also in type 2 diabetes.

The increased incidence of diabetic nephropathy in type 2 diabetic patients was found within 10 years after the diagnosis of diabetes. This may be explained by the systematic delay in the diagnosis of type 2 diabetes because of the lower frequencies of symptoms early in the disease. A lack of awareness of diabetes and its complications is unique to type 2 diabetes and could be responsible for such patients developing diabetic nephropathy and ESRF [17, 22, 42]. Interestingly, the incidence density of diabetic nephropathy in our patient population declined after 15 to 20 years of diabetes duration in both types of diabetes. The finding has been confirmed in type 1, but not in type 2 diabetes.

Clinical features such as sex and age at diagnosis of diabetes were different between the two types. The differences are not due to a selection bias, as other reports include more female Japanese patients with type 1 diabetes [28], and patients with type 2 diabetes were older at diagnosis than those with type 1 diabetes in a population with early-onset diabetes [16]. The high incidence of nephropathy for patients with type 2 diabetes shown in our study is unlikely to be affected by these different features, since the analysis according to the sex and age at diagnosis of diabetes showed the same results (Table 3). True duration of diabetes may be longer than the known duration in type 2 diabetes, but the difference between the two in the present study is presumed to be less than a few years because type 2 diabetes rarely occurs before the age of 15. Provided that patients with type 2 diabetes had a period of few years of diabetes before the diagnosis, it could not have accounted for the significant high incidence of nephropathy in patients with type 2 compared with those with type 1 diabetes.

Ethnicity profoundly affects the incidence of diabetes as well as its vascular complications. The results of the present study showed that type 2 diabetes occurred as early as the teens in our Japanese population, and that the incidence of diabetic nephropathy in early-onset type 2 diabetic patients was extraordinarily higher than that in type 1 diabetic patients in Japan. The high incidence of diabetic nephropathy in type 2 diabetic patients compared with type 1 diabetic patients in this study is consistent with the findings of Cowie et al [3]. They demonstrated a high and increasing incidence of diabetic ESRF among black patients with type 2 diabetes as compared with black patients with type 1 diabetes, although they neither investigated the onset of diabetic nephropathy nor included patients with type 1 and type 2 diabetes of a comparable age. That study clearly revealed an ethnic difference between whites and blacks for the incidence of diabetic ESRF, particularly in type 2 diabetes. Ethnicity may be one reason for the high incidence of diabetic nephropathy among Japanese patients with early-onset type 2 diabetes. While it appears that the incidence of diabetic nephropathy in patients with type 2 diabetes varies markedly according to ethnicity, this is not necessarily the case for type 1 diabetes.

Our study demonstrates that the incidence of diabetic nephropathy in Japanese patients with type 1 diabetes

has decreased with the increasing calendar year at diagnosis of diabetes. This confirms the finding reported by Bojestig et al that the cumulative incidence of nephropathy in type 1 diabetes has decreased substantially during the past two decades [18]. We were unable to clarify the reason for the declining incidence of nephropathy in this study; however, it is speculated that metabolic regulation and systemic blood pressure control, both of which evidently affected the development of nephropathy (Table 6 and Fig. 4), have been improved in recent years and thus reduced the incidence in patients with type 1 diabetes. The effects of these two factors on inhibiting nephropathy have been supported by prospective and/or observational studies both in type 1 and type 2 diabetes [27, 43–51]. For patients with type 1 diabetes, regular clinic visits are mandatory, which may induce better metabolic and blood pressure control; thus, this may have caused a cumulative decline in the incidence of nephropathy with increasing calendar year at diagnosis of diabetes. However, this is unlikely the case for type 2 diabetic patients, presumably because their disease is not necessarily accompanied by symptoms of hyperglycemia even without medical treatment, which may readily cause their total lifetime exposure to poor control of blood glucose and blood pressure to be longer. Interestingly, comparing these risk factors between the two types of diabetes, the incidence of nephropathy in type 2 diabetes was higher at every stratum of HbA1c value, whereas the one in type 1 diabetes was higher at the highest blood pressure level. The impact of risk factors on the development of nephropathy appears to be different between the two types of diabetes.

In a large, clinic-based population study, one must account for bias because of selective referral and/or dropout. We have looked for diabetic nephropathy until the patients' final visit to the clinic. Therefore, the reason to discontinue clinic visits was not related to development of nephropathy. Our diabetes clinic does not specialize in treating either type 1 or type 2 diabetes; the distribution of patients with type 1 and type 2 diabetes according to the calendar year at diagnosis of diabetes was similar. The proportion of patients who were referred was similar for the two types. The cumulative incidences of nephropathy were also similar between those who visited with and without referrals in both types of diabetes. Therefore, selective referral on the basis of the type of diabetes appears to be unlikely. We have excluded those who had nephropathy at first visit to the center; the present result might yield an underestimation of the incidence of nephropathy. However, an analysis including those who had nephropathy at first visit revealed the same result: the higher incidence of nephropathy for those with type 2 diabetes compared with those with type 1 diabetes ($P < 0.0001$; data not shown). Finally, when the cumulative incidence of nephropathy was calculated after first visit to the center, it was significantly higher ($P < 0.0001$) for the patients with type 2 diabetes than for those with type 1 diabetes (data not shown). This suggests that type 2 diabetes is the major cause of nephropathy in early-onset diabetes in Japan.

In conclusion, the present study demonstrates significant differences in the incidence of diabetic nephropathy according to the type of diabetes and the year of diagnosis in early-onset diabetes in Japan. Such an analysis, particularly in the non-Caucasian population, is awaited. Diabetic nephropathy and progression to ESRF in type 2 diabetes should be preventable through metabolic control [45–47], control of blood pressure [26, 48], use of angiotensin-converting enzyme inhibitors [26, 49, 50], protein restriction [51], and discontinuation of smoking [26]. The increasing prevalence of type 2 diabetes [52] and of ESRF in type 2 diabetic patients worldwide [3, 8–12, 21–25] urgently demands programs for prevention of diabetic nephropathy, especially in a high-risk population.

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Waist circumference estimation from BMI in Japanese children

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Abstract

Waist circumference, not BMI, is one of the factors in the definition of metabolic syndrome in adults. In children, waist circumference is also a well known predictor of metabolic syndrome. However, waist circumference measurement is not as commonly recorded as weight and height measurements in physical examinations in schools. This means BMI data is available for every child, but waist circumference is not. Therefore, we investigated whether there is an alternative way to estimate waist circumference even in those children whose waist circumference measurement has not been taken. We evaluated the relationship between BMI and the waist circumference of schoolchildren using a relatively large-scale population-based cohort in Japan. There was a significant linear relationship between BMI and waist circumference noted in each age- and sex-divided group [9–10-year-old boys: waist = 13.99 + 2.63BMI ($r = 0.940$, $p < 0.001$), 9–10-year-old girls: waist = 15.09 + 2.61BMI ($r = 0.933$, $p < 0.001$), 12–13-year-old boys: waist = 23.67 + 2.22BMI ($r = 0.880$, $p < 0.001$), 12–13-year-old girls: waist = 23.83 + 2.15BMI ($r = 0.859$, $p < 0.001$)]. This means it is possible to estimate waist circumference from height and weight, at least among those age groups of children in Japan. This estimation could be an alternative way and useful in detecting childhood metabolic syndrome or obesity disease in which a waist circumference figure is necessary.

Keywords: Waist circumference; BMI; Children

Waist circumference, not body mass index (BMI), is one of the factors in the definition of metabolic syndrome in adults [1,2]. In children, waist circumference is also a well-known predictor of metabolic syndrome [3–5], although definitions for childhood metabolic syndrome are still different between studies. In Japan, a waist circumference of 80 cm has been established as one of various cutoff points for childhood obesity disease [6]. In these definitions, waist circumference is included as a means by which to detect abdominal obesity, but BMI is not. Moreover, compared to BMI, waist circumference is an even better predictor of cardiovascular disease risk factors [7].

However, in physical examinations in schools, waist circumference measurement is not as commonly recorded as weight and height measurements by which BMI can be calculated. This means BMI data is available

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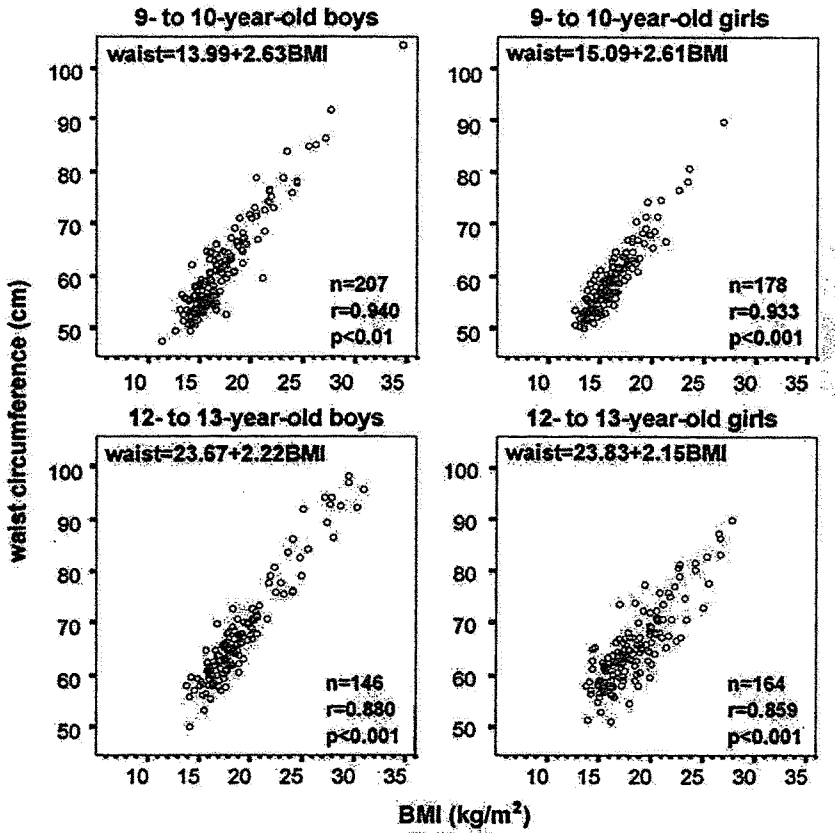

Fig. 1. The linear relationship between BMI and waist circumference in each age- and sex-divided group. *r*: Pearson's correlation coefficients.

for every child, but waist circumference is not. To know what is the waist circumference in children is becoming important, as mentioned above. Therefore, we investigated whether there is an alternative way to estimate waist circumference even in those children whose waist circumference measurement has not been taken.

We evaluated the relationship between BMI and the waist circumference of schoolchildren using a relatively large-scale population-based cohort in Japan. The participants in this study are from the 2004 health promotion plan targeted only to children ages 9–10 and 12–13 in Ina town, Saitama prefecture, located approximately 30 km north of metropolitan Tokyo: 203 boys (participation rate: 99.0%) and 174 girls (98.9%) ages 9–10, and 140 boys (95.9%) and 159 girls (98.8%) ages 12–13. The main activity involved in the health promotion plan is a detailed health examination in conjunction with annual health checks at school per Japanese school regulations. We have reported the results of this health promotion plan previously [8–10].

The children underwent physical examinations. Measurements of height, weight, and waist circumference were taken. Waist circumference was measured at the navel level, while another examiner checked verticality from the side. We then investigated the relationship between BMI and waist circumference with Pearson's correlation coefficients using the SPSS program.

The results are as shown in Fig. 1. There is a significant linear relationship between BMI and waist circumference noted in each age- and sex-divided group [9–10-year-old boys: waist = 13.99 + 2.63BMI ($r = 0.940$, $p < 0.001$); 9–10-year-old girls: waist = 15.09 + 2.61BMI ($r = 0.933$, $p < 0.001$); 12–13-year-old boys: waist = 23.67 + 2.22BMI ($r = 0.880$, $p < 0.001$); 12–13-year-old girls: waist = 23.83 + 2.15BMI ($r = 0.859$, $p < 0.001$)]. This means it is possible to estimate waist circumference from height and weight, at least among those age groups of children in Japan. Of course, the best way is to measure waist circumference itself, but in Japan it is culturally somewhat difficult to conduct waist circumference measurement that involves the raising of clothes because this activity is considered shameful. Therefore, estimation using height and weight could be an alternative way for those who do not have waist circumference data and useful in detecting childhood metabolic syndrome or obesity disease in which a waist circumference figure is necessary.

Further investigations are necessary to evaluate whether there is a similar linear relationship between BMI and waist circumference in other age groups of children and adolescents.

Acknowledgements

We are indebted to all the study participants and their parents. The authors would also like to thank all the members of the Board of Education in Ina-town in Saitama Prefecture and the Ina-town Conference for the Promotion and Operation of Childhood Lifestyle-Related Diseases Prevention Examination (Chairman: Dr. Michio Sato). This study was supported by a grant from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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Childhood obesity and its relation to serum adiponectin and leptin: A report from a population-based study

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Abstract

This study examined the relationships between serum adiponectin (AD) and leptin (LP) levels, and obesity using a population-based cohort consisted of 315 (9–10 year olds: G1) and 308 (12–13 year olds: G2) school children. Serum AD, LP and other markers were compared according to the presence of obesity.

The prevalence rates of obesity were 14.9% in G1 and 9.4% in G2. The medians of serum AD (μg/dl: non-obese/obese) were statistically lower in obese children (9.6/8.3 in G1, $p < 0.05$; 8.9/6.6 in G2, $p < 0.05$), and the medians of serum LP (ng/dl) were statistically higher in obese children (3.7/12.5 in G1, $p < 0.05$; 2.9/8.4 in G2, $p < 0.05$). The serum LP levels were significantly positively correlated with percent overweight (POW) irrespective of age and sex, and the serum AD levels were significantly negatively correlated with POW except for boys in G1. Multivariate regression analyses revealed that LP, LDL and gender in G1, and LP, AD, blood pressure and gender in G2 were significantly correlated with POW.

A large-scale, population-based study revealed that AD was lower and LP higher in obese children, and that the obese status in G2 was related to a worse metabolic profile than the case in G1.

Keywords: Children; Obesity; Leptin; Adiponectin

1. Introduction

Increasing prevalence of childhood obesity is a global problem, and especially so in Asian countries [1–3]. Obesity is a serious healthcare issue, as it is associated with hyperinsulinemia, diabetes mellitus [4], dyslipidemia hypertension and atherosclerosis [5]. Adipocytokines, including leptin and adiponectin have been proven to be one of the determinants of insulin resistance [6,7]. Obese adults are reported to have higher serum leptin and lower serum adiponectin levels, compared to non-obese subjects [8,9]. Similar findings regarding serum leptin in children have been reported from Taiwan and the United States [10,11], and regarding adiponectin have been reported by studies based on Pima Indians and Japanese children [6,12,13]. However, these results were not derived from population-based samples,

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but from relatively small population samples, and conclusions derived from this data cannot be applied to the general population. From a public health perspective, it is very important to be able to identify children in the general population who are at risk for becoming obese or developing metabolic syndrome.

The current study, therefore, assesses the relationship between adipocytokines and obesity in children in general, using a population-based cohort in Japan.

2. Methods

The current health promotion plan was initiated in 1994 for the promotion of a healthy lifestyle in children who live in Ina-town, Saitama Prefecture [14,15]; this area hosts a population of approximately 35,000 and is located approximately 30 km north of metropolitan Tokyo. Occupations of the residents range from farming through to commuting to work in Tokyo. The main activity involved in the health promotion plan is a detailed health examination – including blood sampling and lifestyle intervention, if necessary – in conjunction with annual health checks at school as per Japanese School Law. The subjects of this study were participants in the health promotion plan, which was conducted in September 2002; the subjects comprised 169 boys (participation rate: 98.3%) and 146 girls (99.3%), aged 9–10 years (i.e., fourth-graders), from all three public elementary schools in Ina-town, and 158 boys (98.8%) and 150 girls (97.4%) aged 12–13 years (i.e., first-graders) from all three public junior high schools in Ina-town. The participants represented almost the entire children of the same age in the town.

The children underwent physical examinations consisting of venous blood sampling to measure serum levels of total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL), plasma glucose (PG), leptin and adiponectin. Measurements of height, weight and systolic blood pressure were also taken.

TC, TG, LDL and PG were measured with routine automated laboratory methods. The levels of LDL were determined by Cholestest-LDL kit (Daiichi Pure Chemicals, Japan) [16]. Adiponectin levels were determined with commercially available ELISA kits (Otsuka Pharmaceutical Co Ltd., Japan) with intra- and inter-assay coefficients of variation below 10%, which was reported in a paper by Arita et al. [17]. Leptin levels were measured using commercially available RIA kits (Linco Research Inc.) with intra- and inter-assay coefficients of variation below 10%, as described previously [18]. Blood collection was usually performed 2 to 3 h after eating breakfast because of recommendations by the Institutional Review Board (IRB).

Blood pressure was measured in the right arm with a standard mercury sphygmomanometer, with the subjects sitting in a relaxed state.

Obesity, for purposes of this study, was defined as a body weight at least 120 percent overweight (POW) compared to the sex- and age-matched ideal standardized body weights for Japanese children [19].

Serum adiponectin, leptin and other markers for obese children were compared to non-obese subjects. The correlation between leptin, adiponectin and POW was examined by univariate regression analyses. Step-wise multivariate regression analyses were employed to assess the potential predictors of POW with the independent variables of adiponectin, leptin, LDL, TG, PG SBP and sex.

As leptin and adiponectin distributions were skewed, each variable was expressed as a median and intraquartile range in parentheses. Non-parametric analyses using the Wilcoxon rank sum test were employed for comparison. Spearman's correlation coefficients were employed for univariate regression analyses. Statistical analyses were conducted using the SPSS program and SAS software.

The study protocol was approved by the two independent IRB at Jikei University School of Medicine and Showa University School of Medicine. Written informed consent was obtained from all participants and their parents.

3. Results

3.1. Prevalence of obesity

The prevalence rates of obesity were 17.8% for boys and 11.6% for girls in the 9–10-year-old group, and 12.0% for boys and 6.7% for girls in the 12–13-year-old group. The highest prevalence was observed in boys aged 9–10 years.

3.2. Adiponectin and leptin levels according to obesity status

The levels of serum adiponectin were statistically lower in obese children compared to non-obese, with the exception of girls in the 12–13-year-old group (Table 1). The levels of serum leptin were statistically higher in obese children compared to non-obese, irrespective of age and gender (Table 1).

3.3. Clinical variables according to obesity status

Regarding TC, TG, LDL, PG and SBP, 9–10-year-old obese boys and girls had higher levels in all variables with the exception of PG Obese boys aged 12–13 years had higher levels in TG and SBP, and 12–13-year-old obese girls had higher levels in TC and SBP compared to non-obese subjects (Tables 1 and 2).

3.4. Regression analyses

The serum leptin levels were significantly positively correlated with POW irrespective of age and sex, and the serum adiponectin levels were significantly

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Table 1
Percent overweight (POW), systolic blood pressure (SBP), and serum adiponectin and leptin according to age, sex and obesity status

	9–10 years old			12–13 years old		
	Obesity −	Obesity + (%)	Total	Obesity −	Obesity + (%)	Total
N						
Boys	139	30 (17.8)	169	139	19 (12.0)	158
Girls	129	17 (11.6)	146	140	10 (6.7)	150
Total	268	47 (14.9)	315	281	29 (9.4)	308
POW (%)						
Boys	−2.5 (−8.5–4.5)	32.8 (26.8–45.2)	0.2 (−7.2–14.3)	−2.6 (−9.2–4.0)	27.4 (23.2–38.9)	−1.5 (−8.4–8.1)
Girls	−2.5 (−8.0–7.1)	34.9 (28.7–38.4)	−1.1 (−7.4–9.7)	−6.1 (−13.8–3.7)	30.5 (24.7–46.6)	−5.0 (−13.5–4.4)
Total	−2.5 (−8.5–6.0)	33.2 (27.0–40.5)	−0.3 (−7.4–11.8)	−4.5 (−10.9–3.8)	29.0 (24.0–38.9)	−2.5 (−10.3–7.0)
SBP (mmHg)						
Boys	110 (102–118)	119 (114–130)*	112 (104–120)	104 (99–116)	120 (106–131)*	106 (100–117)
Girls	108 (102–116)	118 (110–126)*	110 (102–118)	105 (98–115)	117 (112–124)*	106 (98–116)
Total	110 (102–118)	118 (114–126)*	110 (103–120)	104 (98–115)	120 (112–125)*	106 (99–116)
Adiponectin (ng/dl)						
Boys	9.7 (7.2–12.0)	7.6 (5.6–10.2)*	9.5 (6.9–11.6)	8.5 (6.8–11.0)	6.4 (5.3–10.8)*	8.3 (6.6–10.8)
Girls	9.6 (7.5–11.9)	8.3 (5.8–8.7)*	9.2 (7.3–11.5)	9.5 (7.7–12.1)	8.3 (5.9–9.4)	9.4 (7.6–12.1)
Total	9.6 (7.3–12.0)	8.3 (5.6–9.9)*	9.3 (7.0–11.6)	8.9 (7.3–11.2)	6.6 (5.8–9.4)*	8.7 (7.0–11.1)
Leptin (ng/dl)						
Boys	2.8 (2.1–5.0)	10.6 (8.3–14.9)*	3.7 (2.2–7.3)	2.0 (1.5–2.8)	7.0 (5.3–10.8)*	2.2 (1.6–3.4)
Girls	4.1 (3.2–6.2)	13.0 (10.4–18.5)*	4.5 (3.3–7.1)	4.6 (3.0–6.2)	13.3 (9.2–15.5)*	4.7 (3.1–6.8)
Total	3.7 (2.4–5.5)	12.5 (8.6–16.4)*	4.1 (2.5–7.1)	2.9 (1.9–5.0)	8.4 (6.8–11.8)*	3.2 (2.0–5.9)

Values are expressed as median and intraquartile range in the parenthesis. The obese status was defined as a body weight at least 120 percent overweight compared to the sex- and age-matched ideal standardized body weights for Japanese children according to ref. [19].
* $p < 0.05$ by Wilcoxon rank sum test.

negatively correlated with POW with the exception of 9–10-year-old boys (Fig. 1).

Multivariate regression analyses revealed that the higher level of leptin and LDL, and male gender in the 9–10 age group and the higher levels of leptin and SBP, the lower level of adiponectin and male gender in the 12–13 age group were the significantly correlated with POW (Table 3).

4. Discussion

The prevalence of childhood obesity is increasing worldwide. Nonetheless, information regarding childhood obesity and its relationship to adipocytokines in children is still limited. This is the first study to observe adiponectin and leptin levels in groups with or without obesity, within a population-based cohort of children in Japan.

As was reported in adult and childhood populations [6,10–13], the serum leptin level was higher and the adiponectin level was lower in obese children, irrespective of age and sex, as compared to those in the current study who were not obese.

Regarding the age-specific levels of these adipocytokines, several reports have been published. The level of serum leptin increased with age, with a peak noted at 16–20 years [20]; the levels of serum adiponectin do not change with age in 18–80-year-old women [21]. In the current study, the serum leptin and adiponectin levels in girls were the same between 9–10 years and 12–13 years. In contrast, both values in the 12–13-year-old boys group were lower than those in the 9–10-year-old boys group. Similar findings have been reported in Germany and in Ohio, USA, with adiponectin values of post-pubertal children lower than in pre-pubertal children, especially in boys [22,23]. These studies indicate that the low adiponectin level in adolescent boys was significantly related with plasma androgen levels [23]. Regarding leptin, Huang et al. reported that the plasma leptin levels were significantly higher in girls than boys aged 10–19 years old, possibly due to a stimulatory effect of estradiol on leptin concentration in girls and a suppressive effect of testosterone on leptin concentration in boys [24].

Multivariate regression analyses revealed that higher levels of SBP and lower levels of adiponectin were significantly correlated with POW only in the 12–13-year-old group, not in the 9–10-year-old group. The results indicate that the obese status in the 12–13-year-old group was related to a worse metabolic profile than

Table 2
Plasma glucose (PG), Total cholesterol (TC), Triglyceride (TG), LDL cholesterol (LDL) according to age, sex and obesity status

	9–10 years old			12–13 years old		
	Obesity −	Obesity +	Total	Obesity −	Obesity +	Total
N						
Boys	139	30 (17.8)	169	139	19 (12.0)	158
Girls	129	17 (11.6)	146	140	10 (6.7)	150
Total	268	47 (14.9)	315	281	29 (9.4)	308
PG (mg/dl)						
Boys	92 (88–95)	93 (88–98)	92 (88–95)	90 (84–95)	92 (88–95)	90 (84–95)
Girls	88 (86–93)	92 (89–95)*	89 (86–94)	88 (83–92)	91 (88–97)	88 (84–92)
Total	90 (87–94)	93 (88–97)*	91 (87–95)	89 (84–94)	92 (88–95)*	89 (84–94)
TC (mg/dl)						
Boys	169 (155–186)	186 (172–200)*	172 (157–190)	161 (145–176)	162 (150–191)	161 (145–177)
Girls	170 (152–193)	183 (172–205)*	171 (155–195)	172 (159–187)	157 (134–171)*	171 (158–187)
Total	170 (155–189)	185 (172–205)*	172 (157–192)	167 (151–182)	159 (143–189)	166 (151–183)
TG (mg/dl)						
Boys	64 (43–89)	97 (63–138)*	69 (46–99)	50 (37–74)	67 (47–177)*	52 (38–79)
Girls	69 (53–98)	113 (73–126)*	73 (54–103)	60 (42–83)	66 (44–88)	60 (42–84)
Total	67 (48–95)	103 (66–138)*	71 (50–101)	54 (39–78)	67 (44–130)*	55 (40–83)
LDL (mg/dl)						
Boys	92 (81–109)	114 (83–130)*	95 (81–114)	92 (77–105)	102 (90–114)	93 (78–105)
Girls	95 (81–113)	117 (105–127)*	97 (83–117)	103 (89–116)	89 (74–118)	103 (89–116)
Total	94 (81–110)	115 (91–129)*	96 (82–115)	97 (83–110)	94 (84–114)	97 (83–111)

Values are expressed as median and intraquartile range in the parenthesis. The obese status was defined as a body weight at least 120 percent overweight compared to the sex- and age-matched ideal standardized body weights for Japanese children according to ref. [19].
* $p < 0.05$ by Wilcoxon rank sum test.

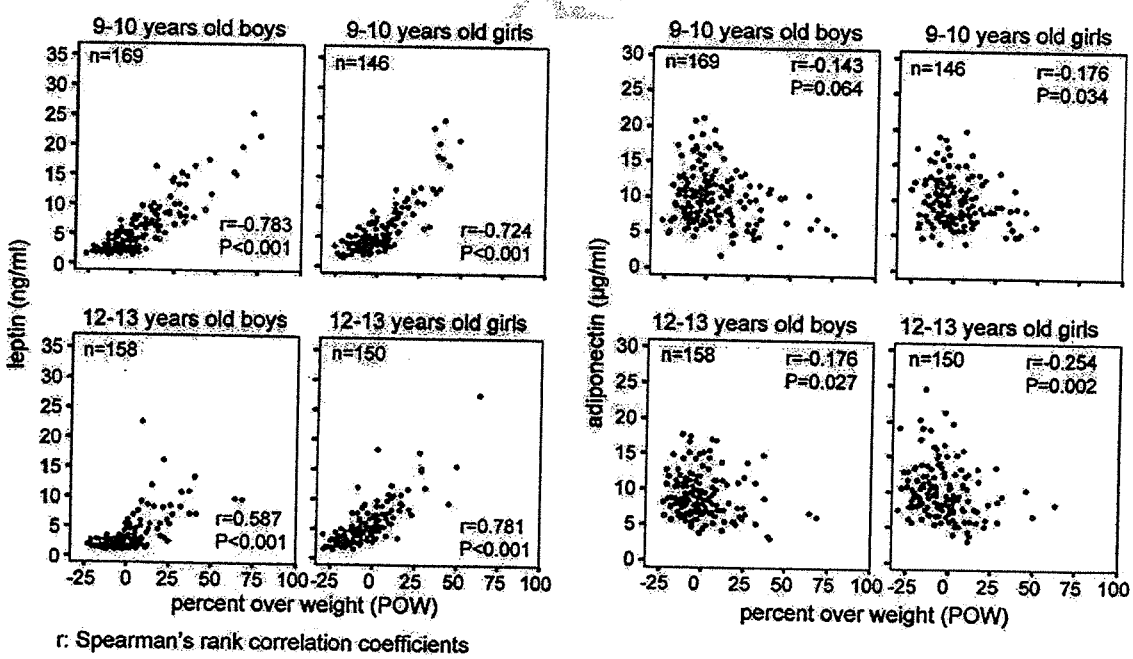

Fig. 1. Correlation between percent overweight (POW) and serum leptin/adiponectin levels in children according to age and sex from a population-based cohort. r: Spearman's rank correlation coefficients.

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Table 3
Factors associated with percent overweight (POW), assessed by the step-wise multiple regression analyses by age

9–10 years old			12–13 years old		
Independent variables	β	p	Independent variables	β	p
Leptin	0.824	<0.001	Leptin	0.692	<0.001
Sex (girls/boys)	−0.139	<0.001	Sex (girls/boys)	−0.321	<0.001
LDL	0.066	0.041	SBP	0.198	<0.001
			Adiponectin	−0.088	0.023

Variables included in the model: adiponectin, leptin, plasma glucose (PG), low density lipoprotein cholesterol (LDL), triglyceride (TG), systolic blood pressure (SBP), sex.

that seen in the 9–10-year-old group, probably due to increased secretion of gonadal hormones after puberty [23,24].

A limitation of this study was that it was based on cross-sectional data, and not as a follow-up study. Therefore, markers in 9–10-year-old children were not necessarily predictors for 12–13-year-old children. We plan on following the participants of this study who were aged 9–10 years for the next three years, to identify possible predictors of obesity status and adipocytokines.

Another limitation is that we did not obtain markers for puberty status (e.g., Tanner's stage) of the study participants. However, there are more than 600 children participating in the study and it is technically impossible to obtain information from all participants.

The current study indicates that serum leptin level is higher and serum adiponectin lower in obese children than those in non-obese children, within a population-based cohort in Japan. A follow up study is warranted, especially regarding the values of adipocytokines and the levels and types of obesity in the study participants.

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文献15

第109回日本小児科学会学術集会
教育講演

小児の2型糖尿病—今昔—

東京女子医科大学糖尿病センター
内　潟　安　子

キーワード：1型糖尿病，2型糖尿病，肥満，家族歴

小児2型糖尿病は新興疾患か？

小児にも大人型の糖尿病が発症することに，いまなおけげんに思われている読者は少なくないのではないだろうか．少なくとも私の学生時代は，小児糖尿病といえばそれはインスリン依存型糖尿病とイコールであると思われていた．いまなお小児の糖尿病といえばインスリン依存型糖尿病だけではないか，と思われているふしがある．

インスリン依存型糖尿病は，1999年に日本糖尿病学会から診断基準と病名に関する報告（糖尿病，診断基準）[1]が出されて以来，その発症形式ならびに病態から，「1型糖尿病」と呼ばれるに至っている．

さて，最近，新聞その他に，小児肥満児の問題や肥満から発症する将来の生活習慣病への進行に関連した，警告を発する記事が目に付く．アメリカ糖尿病学会の会長講演においても，毎回といっていいほど，小児思春期の若者に対する警告が発せられる．図1は3年前の2003年7月のタイム誌の表紙である．もう個人や1地域，1国家の問題ではなくなってきていて，全世界的な問題として小児思春期の肥満や糖尿病を取り扱っていることがわかる．AIDS/HIVと同じレベルの問題として考える時にきたといえる．

2006年12月に南アフリカ連邦で開催される国際糖尿病連合（IDF）に先立って，次期IDF会長シリンク博士（国際小児思春期糖尿病研究会の前会長，シドニー大学小児内分泌学教授）は「Unite for Diabetes」キャンペーンを開始したが，これは糖尿病が10秒ごとに1人を殺すサイレントキラーであることを再度十分に認識しよう，いまがこれに対して団結して戦う時がきた，というキャンペーンである．いろいろな戦略構想がなされるはずであり，最終的には国連決議にまで持っていく予定である．著者も世界的規模での委員会のメンバーとして，これに関わっている．

日本人の小児期発症糖尿病ないし，若年時に診断された糖尿病については，全国規模での実態調査もおこなわれていない．平成14年に行われた糖尿病実態調査（図2）はもっとも最近のものであるが，この調査でも

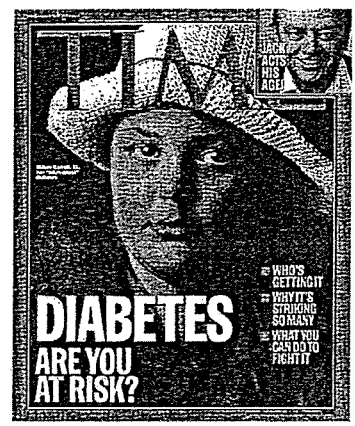


図1

最年少群は20～29歳である．より年少者の糖尿病人口の割合は不明のままである．

小児思春期発症の2型糖尿病患者が存在することは，1990年世界に先駆して日本に東京女子医科大学糖尿病センターでの調査によりあきらかにされた（図3）．30歳未満で発見・発症し，当センターを初診した糖尿病患者数を，病型別に，診断時年齢ごとに，プロットしたものが図3である．この時代はIDDM, NIDDMという言葉を使用しているが，これは今の1型糖尿病と2型糖尿病（MODYなど遺伝子異常による糖尿病も含む）のことである．

図4は2003年末までに初診した同様の30歳未満で発症・発見された糖尿病患者数を，病型別，発症年齢別にプロットしたものである．図3と図4を比較すると，この13年間に1型糖尿病関数は870名から1,675名（1,93倍増）に，2型糖尿病患者数は538名から2,259名（4.20倍増）に増加している．

この図であきらかなように幼少時は1型糖尿病が主体であるが，10歳代の中盤で1型糖尿病と2糖尿病の患者数は交差し，その後は2型糖尿病の患者数が圧倒的に多くなる．このパターンは昔も今も変わらない．

このことより，9歳未満の糖尿病はほとんど1型糖尿病であるが，9～18歳では1型：2型の比率は54：

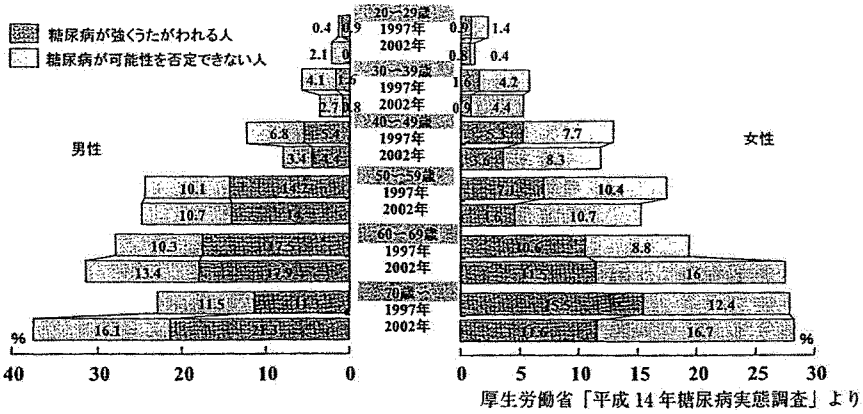
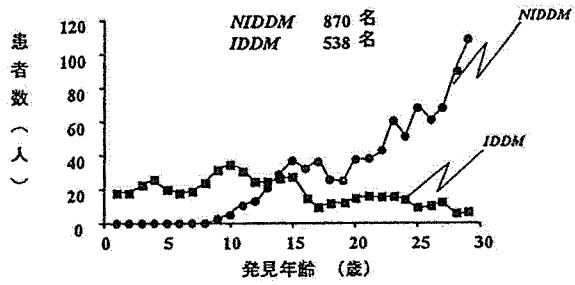


図2　性・年齢層別の「糖尿病が強くうたがわれる人」と「糖尿病の可能性を否定できない人」の割合の推移



(大谷敏嘉ら糖尿病 32：717, 1989, & Otani T, et al. Diab Res Clin Prac 10：241, 1990)

図3　東京女子医科大糖尿病センターの30歳未満発見発症糖尿病患者の病型別糖尿病発見年齢別人数

46と，ほぼ同数となる．

また，日本の1型糖尿病はどの年齢においても女児が多い．2型糖尿病においては，どの年齢においても逆に男児が多くなる．

日本の小児2型糖尿病の昔と今を比較する

1．1型糖尿病と2型糖尿病の患者数の比率

上記のような，1型糖尿病と2型糖尿病の患者数の比率は，古い年代，新しい年代ではどのような違いがあるのだろうか．1960～1978年代診断群，1979～1988年代診断群，1989～2003年代診断群の3年代で分けて，各々の年代の発症年齢群の1型：2型の比率をみてみる．

1960～1978年代から最近の年代になるほど，1型糖尿病の各年齢群の比率は，幼少時高値%からしだいに10歳台後半から20歳台にかけての%が増加してくる．一方，2型糖尿病の年齢群の%は1960～1978年代から1979～1988年代にかけて10歳台での発症%が増加してきて，その後の1989～2003年代になると，下火になってくる傾向がある．これは，1979～1988年代になって急に大人の肥満率が急増することと関係しているのかもしれない．1989～2003年代はバブル崩壊後にあたり，その傾向にすこし歯止めがかかったのかもしれない．

もちろん，上記のことは1糖尿病センターという医療機関での年代的推移を調査したものであって，日本全体にも同じ流れがあるかどうかには，この結果からは言及できない．最近，Uratamiらは1980年を境にした小児期発症2型糖尿病の増加を報告した[2]．

当センターにおける同様の検討は，1995年までに初診した30歳未満発症糖尿病患者データベースを用いてすでに報告してある[3]ので，こちらも参照されたい．

2．2型糖尿病の過去の肥満歴の年代別推移

30歳未満発症2型糖尿病患者を上記で示したような3つの年代群に分類し，発症年齢0～9歳，10～14歳，15～19歳，20～24歳，25～29歳の各群にさらに細分し，年齢を考慮せずに，過去の肥満歴をBody mass index (BMI) ≧25に該当する患者%を用いて表してみた（図5）．

成長期の肥満をBMIで診断することには異論があろうが，BMI≧25という日本人としてはだれが見ても肥満と判断する範疇の患者%を知りたかったので，今回はBMI≧25を取り上げた．

どの発症年代においても，発症年齢が高齢化するほど，肥満患者%が増加することが明らかになった．また肥満患者%は3つの年代群間には大きな違いはみられず，唯一1989～2003年代群の25～29歳発症群で，肥満患者%が男女とも大きくなっていた．

この結果からいえることは，日本の若年発症2型糖尿病患者は過去に肥満歴を有するのは10%くらいで，のこりは過去に肥満歴がない2型糖尿病患者である，過去に肥満歴を有する%は1960～1978年代も最近の1989～2003年代でも大きく異なることはない，ただし

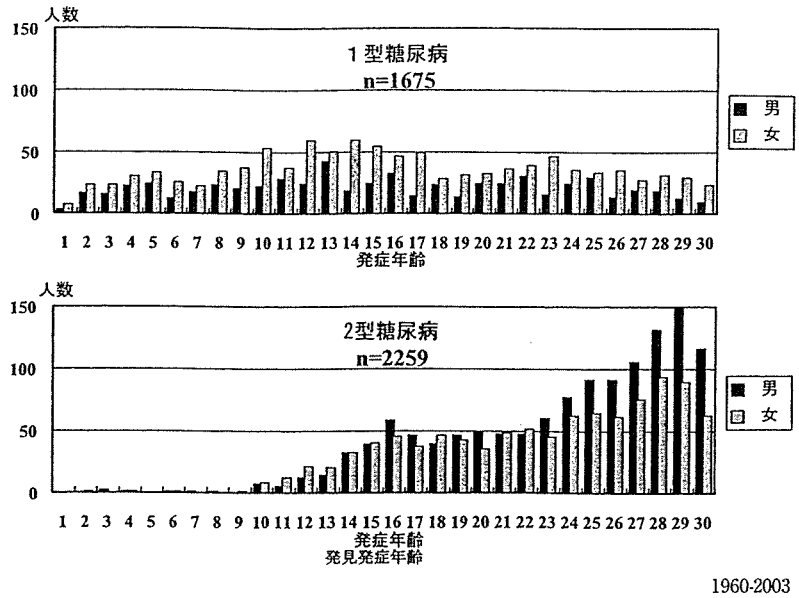


図4　30歳未満発見発症1型及び2型糖尿病患者の発見発症年齢ごとの男女別人数

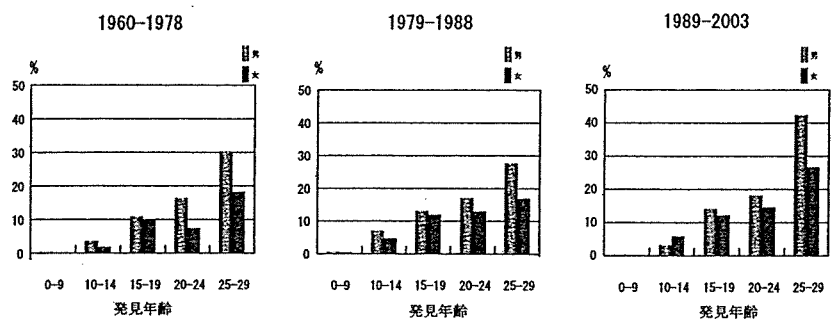


図5　過去最大BMI≧25の2型糖尿病患者の各年代ごとの各発症年齢群における男女別比率

発症年齢が30歳に近付くほど過去に肥満歴を有する患者%が大きくなり，特に1989～2003年代に多く存在する，といえる．

さらに，日本人の若年発症2型糖尿病は大人発症2型糖尿病と同じく，また欧米人2型糖尿病と異なり，肥満の後に発症しているのではない，非肥満2型糖尿病患者が相当存在することである．それは発症年齢が幼少ほど多い．幼少時に発症する2型糖尿病患者ほど糖尿病発症に関与する遺伝的素因が強く反映している可能性が浮かび上がってくる．

そして，高齢になるほど過去の肥満歴を有する患者%が多くなることから，肥満したことが2型糖尿病発症により影響を与えていることが考えられる．

3. 糖尿病家族歴の年代別推移

次に，それでは糖尿病家族歴はどうなっているだろうか．上記で推測したことが支持されるであろうか．

過去のBMIによって，BMI≧25，20≦BMI<25，BMI>20の各群に分けて，初診時の糖尿病家族歴を調査した．結果はどの群も，「家族歴なし」が約30%，父親が約20%，母親が約20%であった．特に非肥満群に糖尿病家族歴を有する患者が多いということはいえなかった．反対に過去に肥満歴を有する群では，糖尿病家族歴を有する患者が少ないということもいえなかった．

これは，こどもも両親のどちらかに糖尿病疾患感受性遺伝子を有していても，子どもが糖尿病を発症している時に両親がかならずしも糖尿病をまだ発症していないこともありうる．子どものほうが両親よりジャンクフードを食べるチャンスが多いことや，幼少時代から両親より体重あたり高カロリーのものを食することが多いことも考えられる．そのために，糖尿病家族歴の調査では上記のことが必ずしも支持されなかった事が考えられる．

表1　学校検尿発見群とそれ以外発見群での比較

		学校検尿発見	それ以外発見	p
人数	(人)	183	100	
発見年齢	(歳)	14.8±2.1	14.7±1.9	0.6636
HbA1c	(%)	9.5±2.8	9.4±2.7	0.4079
罹病期間	(年)	8.5±6.5	10.1±7.6	0.2010
中断なし/あり	(人)	126/57	66/34	0.4752
中断期間	(年)	4.98±3.27 (1～15)	5.79±3.20 (1～15)	0.3260
初期入院歴なし/あり	(人)	95/88	55/45	0.6189
合併症なし/あり	(人)	128/55	63/37	0.2346
スコア	0点	128	63	
	1点	19	7	
	2点	11	5	
	3点	4	4	0.0611
	4点	8	6	
	5点	6	3	
	6点	7	12	

学校検尿システムはどのように役立ってきたか？

2型糖尿病は「サイレントキラー」ともいわれている．なぜなら，発症時期が明確に患者自身にもわからず，なんの症状もなくじわじわと血糖が上昇してきて，おかしいなと気が付いたらそれは合併症の症状であるというのが，2型糖尿病患者の一般的な既往歴である．

日本では1974年から東京の一部の地域で早朝尿を用いた学校検尿システムがおこなわれていた．そして，学校検尿システムは1992年から全国の小中学校でおこなうことが義務化されて今日に至っている．尿タンパクの検出に尿糖検査も附随してきたことはご存知の通りである．

ひるがってみるに，日本では乳幼児健診があり，3歳児健診があり，6歳児健診，就学時健診，学校検尿があり，入学時健診，入社時健診，定期健診，市民健診，老人検診，と生まれてから死ぬまで多くの健診があり，どの年齢であっても，どれかの健診がカバーするようになっている．尿糖検査もほとんどの健診でなされているはずである．このように，健診システムが一生の間に整備されている国は世界にない．

しかし，世界の糖尿病人口の増加ともに，日本人の2型糖尿病人口も増加している．この原因はおもに健診以外のことである．もちろん，健診システムが多少の歯止めとなるうることはあろうが，健診システムが有効に活用されていても糖尿病人口の増加はありうる．

しかしながら，糖尿病性合併症を有する人口の増加は健診システムが有効に作動しているかどうかと関係する．健診システム，その後のフォローシステムが整備および完備していれば，糖尿病性合併症の予防に直接繋がっていく．日本では，たとえば学校検尿システムが1974年から整備されていても，生徒の糖尿病罹患率の抑制にはつながっておらず[2]，かつ，糖尿病性合併症の発症抑制ないし重症化への抑制にも繋がっていなかったことが明らかにされた[4]．

岡田ら[4]は，1960年から1998年までに東京女子医科大学糖尿病センターを受診した18歳未満発見2型糖尿病患者282名について，初診時の糖尿病性合併症の程度と過去の治療中断歴の有無を調査した．表1は，282名を学校検尿で糖尿病発見された群（学校検尿発見群）とそれ以外で糖尿病を発見された群（それ以外群）の2群にわけて，この2群の臨床的特徴を比較したものである．

なお，合併症の重症度は，糖尿病に特徴的な合併症である3大細小血管合併症(神経障害，網膜症，腎症)について，軽度，中等度，重度の3段階に分類してスコア化した．3大合併症とも重度であれば最大点数のスコア6点となる．

表1の特徴的なことは，糖尿病センターに初診時のHbA1cは両群とも9.5%と悪く，また糖尿病性合併症の有無ならびに重症度も両群間に差異がなかったことである．我々は学校検尿において発見されるということは糖尿病状態を早期に発見することであるから，その後は合併症も発症することなく単に血糖コントロールだけの目的の通院でうまくいっているのではないかと仮定し，この調査を計画した．しかし，結果は，糖尿病センターに初診する20歳以降になると学校検尿で早期に発見されようがすでに合併症を発症していることも少なくないことがわかった．もちろん，糖尿病

表2　治療中断歴の有無による比較

		中断あり	中断なし	p
人数	(人)	91	192	
発見年齢	(歳)	14.5±2.2	14.9±2.0	0.4537
男/女		42/49	100/92	0.3514
HbA1c	(%)	9.5±3.0	9.4±2.9	0.5576
罹病期間	(年)	12.0±7.8	3.2±5.0	< 0.0001
入院歴なし/あり	(人)	44/47	104/84	0.2804
合併症なし/あり	(人)	19/72	172/20	< 0.0001
スコア	0点	19	172	
	1点	15	11	
	2点	13	3	
	3点	7	1	< 0.0001
	4点	13	0	
	5点	7	2	
	6点	17	3	

センターへの転院であるので合併症の治療目的に紹介されることも多いので，このような結果になった可能性もある．しかし，両群間に有意差がなかったのは事実なので，学校検尿で早期発見されても，これが合併症予防対策には現状はなっていないといえる．

治療中断と合併症の有病率の関係

これまで外来診療していて，治療中断者に合併症の頻度が高くかつ重症者が多い印象をもっていたので，治療中断の有無が当センター初診時の合併症の状況とどのように関係しているか，調査した．

表2がその結果である．282名を過去の治療中断歴(定義は，糖尿病と診断されて後継続通院が1年以上滞ったことがあった，健診で糖尿病と診断されても医療施設への初診までに1年以上あった）ありなしで2群に分類した．糖尿病教育の意味も兼ねた過去の初期入院の有無は，その後の治療中断の防止にはなっていないことがわかった．そして，治療中断あり群のほうが，圧倒的に合併症を有する患者が多くかつ重症化していたことが明らかになった．

この調査では治療中断歴の長さと合併症の重症度との関連は明らかにされなかった．同じ調査を当センター初診される通常の糖尿病患者においておこなってみたのが図6である[5]．

図6は治療中断（この定義はこれまでの治療中断の定義と同じ）の長さと合併症の重症度との相関をみた結果である．統計的有意に正の相関があることがわかった．つまり，治療中断の期間が長ければ長いほど重症の合併症を発症して初診されることがわかった．

治療中断の理由も調べたが，取り立てて特別な理由はなかった．たいしたことではないと思った，すぐに良くなった，症状がなかった，入院治療が嫌だ，食事療法のみでよいといわれた，などなどである[4]．

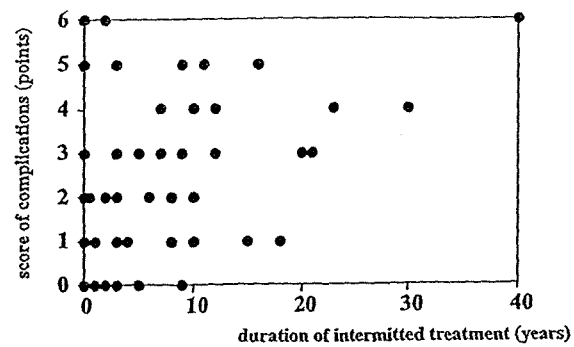


図6　Relationship between the duration of intermitted treatments and the severity the diabetic complications ($p < 0.0001$).

1型糖尿病と2型糖尿病の糖尿病性腎症累積罹患率の比較

それでは，罹病期間をマッチさせてみたら，1型糖尿病と2型糖尿病ではどちらが合併症を発症しやすくなっているのであろうか．

図7は当センターの30歳未満発症の1型糖尿病患者と2型糖尿病患者の，10歳以降の罹病期間を横軸にして，糖尿病性腎症の累積罹患率を縦軸にしてプロットした図である[6]．明らかに，2型糖尿病のほうが糖尿病性腎症を発症しやすくなっていることがわかる．2型糖尿病の治療が糖尿病センターにおいても困難だからこのように合併症を発症しているという意味ではなくて，合併症を発症して受診されるのである．

1型糖尿病はいろいろな事情があってもインスリン治療を欠かすことができない．よって，いやがおうにもどこかの医療機関を受診することになる．ある意味