Table 2—*Microvascular and macrovascular complications in early-onset NIDDM patients who developed proliferative retinopathy before 35 years of age and those who did not*

	Group 1 (n = 135 [13%])			Group 2 (n = 930 [87%])			
	n (%, 95% CI)	Age at diagnosis (years)	Range (years)	n (%, 95% CI)	Age at diagnosis (years)	Range (years)	P value
Proliferative retinopathy	135 (100)	29 ± 5	18–35	164 (18, 15–20)	45 ± 6	36–63	<0.0001
Diabetic nephropathy	81 (60, 52–68)	31 ± 5	19–44	70 (8, 6–9)	44 ± 7	27–61	<0.0001
Renal insufficiency	42 (31, 23–39)	34 ± 6	23–48	33 (4, 2–5)	46 ± 6	32–66	<0.0001
Renal failure requiring dialysis	31 (23, 16–30)	35 ± 4	26–41	19 (2, 1–3)	48 ± 4	43–56	<0.0001
Blindness	32 (24, 16–31)	32 ± 6	21–46	5 (0.5, 0.1–1.0)	46 ± 4	42–50	<0.0001
Atherosclerotic vascular disease	14 (10, 5–15)	36 ± 7	29–42	22 (2, 1–3)	44 ± 8	28–57	<0.0001

Age at diagnosis is given as mean ± SD.

group 2. Group 1 was characterized by a significantly lower percentage of males and a significantly higher prevalence of diabetes in first-degree relatives in comparison with group 2. The prevalence of MODY was higher in group 1 than in group 2, but not significantly. Two MODY patients (one sibling) in group 1 and 14 MODY patients (7 siblings) in group 2 were related. The prevalences of diabetes in both parents were similar between the two groups.

The mean ages at the first visit to the Diabetes Center were similar between the two groups. However, 67% of the patients in group 1 (91 of 135) had developed proliferative retinopathy by the first visit. BMI was lower in group 1 than in group 2. Exclusion of obese patients with BMI >30 kg/m^2 (5 from group 1 and 97 from group 2) yielded no significant differences in BMI between the groups. Glycated hemoglobin level was significantly higher in group 1 than in group 2 ($P < 0.001$), and significantly more patients in group 1 than in group 2 were treated with insulin ($P < 0.0001$). Fasting and 2-h postprandial serum C-peptide levels in patients under insulin therapy were similar between the two groups.

Clinical outcome was obtained for a total of 7,516 person-years (1,208 person-years in group 1 and 6,308 person-years in group 2) observed at the Diabetes Center. The age (mean ± SD) at follow-up was 37 ± 7 years in group 1 and 36 ± 12 years in group 2. In group 2, 465 patients at follow-up were >35 years (mean age at follow-up, 46 ± 8 years). Microvascular and macrovascular complications in groups 1 and 2 are shown in Table 2. The patients in group 1 developed proliferative retinopathy at a mean age of 29 years and subsequent progressive complications developed in contrast to patients in group 2. Thus, 81 patients (60%, 95% CI 52–68%) developed diabetic nephropathy at a mean age of 31 years, 42 patients (31%, 23–39%) developed renal insufficiency at a mean age of 34 years, and 31 patients (23%, 16–30%) developed end-stage renal failure requiring dialysis therapy at a mean age of 35 years. Thirty-two patients (24%) became blind at a mean age of 32 years and 14 patients (10%) developed atherosclerotic vascular disease at a mean age of 36 years. Among the 31 patients who developed end-stage renal failure, 19 (61%) became blind and 9 (29%) developed atherosclerotic vascular disease at a mean age of 35 years.

CONCLUSIONS — This study revealed that patients with early-onset NIDDM are not rare in the Japanese diabetic population. A subgroup of these early-onset NIDDM patients exists who show rapid onset of proliferative retinopathy. This subgroup of patients was characterized by inadequate glycemic control, often requiring insulin therapy, and a high familial prevalence of diabetes and contained a greater proportion of women. More than half of the patients in this subgroup developed nephropathy and a quarter developed renal failure and/or blindness. These findings are serious with respect not only to their quality of life but also to diabetes care in terms of social cost-effectiveness.

A major reason for the rapid progression to severe complications may have been prolonged inadequate treatment of diabetes. Mean age at diagnosis of diabetes was only 3 years less in group 1 than in group 2. However, patients in group 1 may have had hyperglycemia of a considerably longer duration than those in group 2 in addition to poorer glycemic control as manifested by their higher glycated hemoglobin level. They were not ketosis-prone, which might have been related to the lack of regular visits by these patients. Blood glucose control was not easy for patients in group 1, since significantly more patients in this subgroup required insulin therapy. These complications could have been prevented by better metabolic control, based on the finding of the effect of metabolic control on retarding proliferative retinopathy and nephropathy in Caucasian (19) and Japanese (15) IDDM patients of comparable age.

Other possible explanations for the rapid onset of severe complications cannot be excluded. The high familial prevalence of diabetes in group 1 may indicate a genetic predisposition to diabetes in these early-onset NIDDM Japanese as a contributing factor to the development of the severe complications. The present study did not examine familial clustering of complications or genetic markers. However, clustering of diabetic vascular complications was described in some MODY families (5,6,8,14,20) and some IDDM families (21,22). Recent genetic studies have indicated that patients with MODY associated with mutations in the gene on chromosome 20q (MODY1) or chromosome 12q (MODY3) were more severe in the degree of hyperglycemia and diabetic complications than patients with MODY associated with glucokinase mutations (MODY2) (6,12,23). This supports the hypothesis that genetic factors, in addition to the severity and duration of hyperglycemia, may contribute to the vulnerability to vascular complications, though it has yet to be confirmed. A model of early-onset NIDDM Japanese with progressive complications may be useful in investigating gene-environment interactions.

in the pathogenesis of diabetes and diabetic vascular complications. The finding of female sex as a risk factor for development of proliferative retinopathy in the present study is consistent with the finding seen in young IDDM Japanese (15,24). The reason for female sex as a risk factor for proliferative retinopathy is unknown. However, difficulties of glycemic control related to menstruation cycles (25) may be one plausible explanation.

So far only a few case reports of the rapid onset of proliferative retinopathy or nephropathy in young NIDDM patients have been published (9–11). The patients in our study are likely to be comparable with those described by O'Rahilly as early-onset NIDDM (onset at 25–40 years of age) who were characterized as requiring insulin to maintain adequate glycemic control, by a high familial prevalence of diabetes, and by a tendency to develop severe complications (12), although ethnic differences between the two studies underlie the differences in clinical features such as age at diagnosis and clinical severity. Careful therapy for early-onset NIDDM would be highly important as suggested by O'Rahilly (13).

Although a clinic-based study might be insufficient to estimate the relevant prevalence of such patients, participation bias in presenting the existence of these patients and the clinical severity is unlikely. Further prospective morbidity studies are required for estimation of the incidence and the underlying risk factors.

In conclusion, we suggest the existence of young Japanese NIDDM patients who develop severe progressive diabetic complications. The existence of such a subgroup should prompt reevaluation of strategies for the worldwide care of the young diabetic population.

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文献5

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Slightly elevated blood pressure as well as poor metabolic control are risk factors for the progression of retinopathy in early-onset Japanese Type 2 diabetes

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Abstract

Not a few patients in Japan with early-onset type 2 (non-insulin-dependent) diabetes become blind due to proliferative diabetic retinopathy (PDR). However, the risk factors are poorly understood. The aim of this study was to determine the risk factors for background diabetic retinopathy (BDR) and PDR by following 394 Japanese patients with early-onset type 2 diabetes diagnosed before 30 years of age (mean age 27, mean blood pressure at entry 116/73 mm Hg). Of the 322 patients who were free of diabetic retinopathy at entry, 88 developed BDR, giving an incidence of 48.1 (95% CI 39.0–59.2)/1000 person-years. Cox proportional hazard analysis revealed mean HbA_{1c} and duration of diabetes to be significant predictors of development of BDR. Of the 160 patients with BDR, i.e., the 72 patients who had BDR at entry and the 88 who developed BDR during the follow-up, 50 developed PDR, giving an incidence of 57.7 (95% CI 55.5–60.0)/1000 person-years. Cox proportional hazard analysis indicated mean HbA_{1c} and diastolic blood pressure to be significant predictors of the progression from BDR to PDR. In conclusion, in early-onset Japanese type 2 diabetic patients, the rates of both development of BDR and of progression from BDR to PDR appear to be potentially high. Not only lifetime exposure to glycemia but also a slightly elevated blood pressure level is an important risk factor for progression to PDR.

Keywords: Early-onset type 2 diabetes; Proliferative diabetic retinopathy; Mean HbA_{1c}; Diastolic blood pressure

1. Introduction

Not a few young patients in Japan with type 2 (non-insulin-dependent) diabetes suffer from blindness due to the progression of proliferative diabetic retinopathy (PDR) (Yokoyama et al., 1997). This situation is quite different from that seen in Caucasians, because type 2 diabetes rarely develops in young non-obese Caucasian individuals. Only a few case reports of the rapid onset of PDR in young patients with type 2 diabetes have been published (Steel et al., 1976; Tymms & Reckless, 1989). No further information and no risk analysis has been reported regarding PDR in young type 2 diabetic patients. The fact that there are young patients with type 2 diabetes who become blind in their 30s due to PDR prompted us to make the present study of the risk factors for development of background diabetic retinopathy (BDR) and PDR in young Japanese individuals with type 2 diabetes. The aim of the study was to elucidate risk factors for BDR and PDR by following young type 2 diabetic patients. We discussed whether the risk and the progression rate of retinopathy in patients with early-onset type 2 diabetes are different from those in type 2 diabetic patients of other ethnicities or type 1 (insulin-dependent) diabetic patients of comparable age.

2. Methods

2.1. Patients

We performed a clinic-based observational longitudinal study. Patients could visit our outpatient clinic at the Diabetes Center, Tokyo Women's Medical University, without any referrals, and the charge to the patients for treatment was the same as in other hospitals. The percentage of early-onset type 2 diabetes patients (diagnosed before 30 years of age) in a large population of diabetic patients ($n=16,842$) and the

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clinical characteristics of these patients have been reported previously (Otani et al., 1990; Yokoyama et al., 1997). Briefly, out of this large population, we identified 1065 (6.3%) patients with early-onset type 2 diabetes. Of these 1065 patients, a group that fulfilled the following criteria was recruited for the present retinopathy study: (1) patients first visited the outpatient clinic between 1980 and 1989, (2) patients exhibited neither proteinuria nor proliferative retinopathy at the first visit, (3) patients were seen at the clinic for at least 1 year, (4) patients underwent fundus examination through dilated pupils by ophthalmologists at least once a year during the follow-up. A total of 527 patients did not exhibit proteinuria or proliferative retinopathy at first visit. Among them, 101 patients did not continue clinic visits, mainly because they resided outside of the Tokyo area, and 32 patients underwent fundus examination only once during the follow-up, thus leaving 394 patients for the follow-up study (Fig. 1).

2.2. Measurements

The patients were seen at the clinic every 1–3 months (an annual mean of eight visits). The baseline year was the year when a patient first visited the Diabetes Center. Diabetes was diagnosed according to the World Health Organization Criteria (Harris, 1988), and type 2 diabetes was diagnosed when patients were found not to be ketosis-prone, to be free from insulin treatment for more than 1 year after the diagnosis of diabetes and/or to exhibit preserved insulin secretion even when using insulin. Patients' profiles regarding the diagnosis of diabetes and medical treatment to control the blood glucose level were compiled from information obtained through interviews and information obtained from other hospitals visited by the patients. Blood pressure was measured using a standard sphygmomanometer and an appropriately sized cuff with the patients in a seated position. Blood pressure measurements were taken at more than four visits during the baseline year,

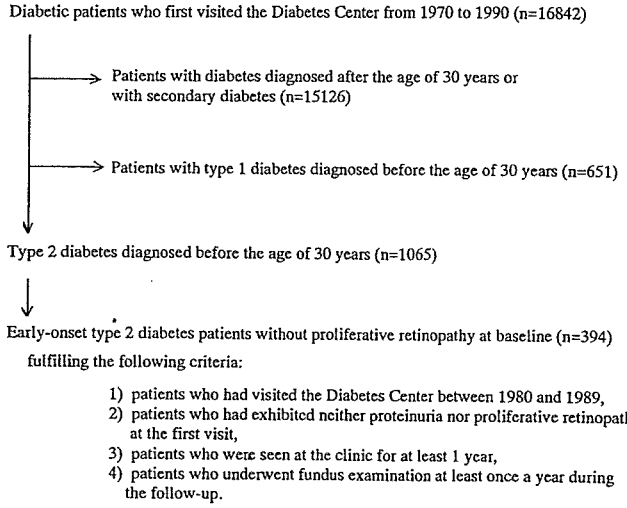

Fig. 1. Patient selection.

and the average was calculated. Patients were considered hypertensive according to the criteria of the fifth report of the Joint National Committee (JNC) on Detection, Evaluation and Treatment of High Blood Pressure (JNC, 1993) if the mean of the measurements was ≧140/90 mm Hg or if patients were taking antihypertensive drugs at baseline. Proteinuria was measured at each visit with Albustix (Miles-Sankyo, Tokyo, Japan) with a detection limit of 300 mg/dl. Fundoscopic examination with dilated pupils was performed by ophthalmologists during the baseline year, and during the follow-up it was performed at least annually for patients with no retinopathy, and every 4–6 months for patients with BDR. The findings were graded as follows: (1) no signs of diabetic retinopathy, (2) BDR, (3) PDR. BDR was defined as the presence of microaneurysms or dot hemorrhages. PDR was defined when patients had new vessels, vitreous hemorrhage, vitreoretinal traction, or retinal detachment believed to be attributable to diabetic neovascularization. In this study, we used Fukuda's (1983, 1994) classification system, which is now the most commonly used classification system for diabetic retinopathy in Japan. In this system, diabetic retinopathy is divided into benign (type A) and malignant (type B) retinopathy, and each type is subdivided into five stages. Benign retinopathy includes BDR (A1 and A2) and interrupted proliferative retinopathy (A3, A4, and A5) after photocoagulation or vitrectomy. Malignant retinopathy includes preproliferative retinopathy (B1), early (B2), advanced (B3), and end-stage (B4 and B5) proliferative retinopathy. Thus, Fukuda grades A1, A2, and B1 corresponded to BDR and the other grades to PDR in this study. The more progressive grade of the two sides was used. Data on the history of diabetes and atherosclerotic vascular disease (i.e., cerebrovascular disease, coronary heart disease, and peripheral vascular disease) in first-degree relatives was obtained from the patients by interview. Patients were classified as smokers if they were smoking >1 cigarette/day during the baseline year. Serum concentrations of total cholesterol, HDL cholesterol, and triglyceride during the baseline year were measured using an automated multianalyzer (7450: Hitachi, Tokyo). The glycated hemoglobin level was measured every 1–3 months using high performance liquid chromatography (HPLC: HA8110 until 1992 and HA8131 from 1993 on, Kyoto Daiichi Kagaku, Kyoto, Japan). The values obtained by HPLC using HA8131 (Y), which is a method standardized by the Japan Diabetes Society, were quite similar to those used in the Diabetes Control and Complications Trial (DCCT) (X) ($Y=0.972X-0.052$, $r=0.997$) (Glycohemoglobin Standardization Committee, 1997). The HbA_{1c} values in the present study were expressed as measured by the HPLC method using HA8131. The normal range of HbA_{1c} was 4.3–5.8%. The interassay coefficients of variation were 5–8% for all assays.

2.3. End points

Patients visited the Diabetes Center every 1–3 months. The study population was subdivided into two cohorts, one of

which was observed until the development of BDR (Cohort A), and the other of which was observed from the detection of BDR until the development of PDR (Cohort B). The end point of the study was (1) the development of BDR (or PDR) or (2) the last examination, if the patient was free of BDR (or PDR).

2.4. Statistical analysis

The predictive effect of independent variables for the development of BDR (or PDR) was explored using the Cox proportional hazard regression analysis. Univariate and multivariate analyses with conditional forward elimination of the independent variables were performed, and the risk ratios are given with 95% CIs. The incidence density is presented as the number of cases per 1000 person-years based on the ratio of the observed number of patients experiencing the event to the total person-years of exposure. The 95% CI was computed by a modification of the Mantel–Haenzel procedure for follow-up data (Mantel & Haenszel, 1959; Rothman & Boice, 1979; Clayton & Hills, 1996). The relationship between the mean HbA_{1c} level during the follow-up period and the incidence of PDR was explored with a χ^2 test for trend (Rothman & Boice, 1979; Fleiss, 1981; Clayton & Hills, 1996). The p values under 5% (two-tailed) were considered to be statistically significant. All analyses were performed using the personal computer statistics package SPSS for Windows version 6.0.

3. Results

3.1. Clinical features of the subjects

Table 1 shows the clinical and biochemical characteristics of the 394 patients at baseline. Age at diagnosis, sex, duration of diabetes, therapy for diabetes, HbA_{1c}, and proportion of smokers were similar for patients who participated and those who did not participate in the study. Patients who did not participate were characterized by higher BMI, higher systemic blood pressure, higher concentrations of total cholesterol and triglyceride, lower concentration of HDL cholesterol, and a lower proportion of BDR.

For the patients who participated in the study, the mean age at diagnosis of diabetes was 22.6 years, the mean age at baseline was 26.9 years, and the mean duration of diabetes was 4.4 years. The therapy for glycemic control (95% CI) at baseline was 67% (62–71%) diet, 16% (12–20%) tablets, and 18% (14–21%) insulin. Forty-nine patients were hypertensive according to the JNC-V criteria, and six of them took antihypertensive drugs. At baseline, 322 subjects were free of diabetic retinopathy and 72 subjects had BDR.

3.2. Predictors of BDR (Cohort A)

Of the 322 patients who were free of diabetic retinopathy at entry, 88 developed BDR during a mean follow-up of 5.7 years (Cohort A). The incidence density was 48.1 (95% CI 39.0–59.2)/1000 person-years. Table 2 shows the predictive effect of independent variables on the development of BDR. The known duration of diabetes, the baseline level and the mean level of HbA_{1c} during the follow-up, and the serum concentrations of total cholesterol and triglyceride had significant predictive effects (Model A). Among these, the mean HbA_{1c} level had the strongest predictive effect for development of BDR. The baseline HbA_{1c}, which was significantly correlated with the mean HbA_{1c} ($r=0.68$, $p<0.001$), had less predictive effect ($p=0.0464$) than the mean HbA_{1c}. Thus, the mean HbA_{1c} was used for subsequent multivariate analysis. The significance of the serum concentrations of total cholester-

Table 1
Baseline clinical and biochemical characteristics of the patients with early-onset type 2 diabetes who participated and those who did not participate in the study

	Subjects who participated	Subjects who did not participate
n	394	133
Percentage of men (95% CI)	54 (49–59)	57 (49–65)
Age at diagnosis of diabetes (years)	22.6±5.6	23.6±5.1
Age at baseline (years)	26.9±8.2	27.7±8.4
Known diabetes duration at baseline (years)	4.4±6.0	4.1±6.1
Percentage of patients with a given to therapy for diabetes at baseline (95% CI)		
Diet alone	67 (62–71)	72 (64–80)
Tablets	16 (12–20)	14 (8–20)
Insulin	18 (14–21)	14 (8–20)
HbA_{1c} at baseline (%)	8.5±2.2	8.5±2.6
Percentage of patients with BDR (95% CI)	18 (15–22)	9 (4–14)***
Percentage of current smokers (95% CI)	30 (26–35)	38 (30–46)
BMI (kg/m^2)	23.0±5.1	25.5±5.6**
Percentage of patients with a family history of diabetes (95% CI)	61 (57–66)	54 (46–63)
Percentage of patients with a family history of vascular disease (95% CI)	12 (9–16)	16 (10–22)
Systolic blood pressure at baseline (mm Hg)	116.4±15.3	121.2±15.6**
Diastolic blood pressure at baseline (mm Hg)	73.1±11.0	76.6±12.3***
Total cholesterol at baseline (mg/dl)	195±44	204±43***
HDL cholesterol at baseline (mg/dl)	51±17	46±12**
Triglyceride at baseline (mg/dl)[a]	107 (69–182)	122 (75–189)***

Data are means±SD, unless otherwise stated.
[a] Data are median (interquartile range).
** $p<0.01$ vs. subjects who participated.
*** $p<0.05$ vs. subjects who participated.

Table 2
Predictive effect of independent variables on development of BDR (Cohort A)

Independent variable	*p* value	Hazard ratio
Model A (univariate analysis)		
Age at diagnosis of diabetes	0.13	1.03 (0.99–1.07)
Age at baseline	0.0127	1.03 (1.01–1.06)
Duration of diabetes at baseline	0.0333	1.04 (1.00–1.08)
BMI	0.82	1.01 (0.96–1.05)
Family history of diabetes	0.27	1.28 (0.83–1.98)
Family history of vascular diseases	0.74	1.11 (0.61–2.00)
Smoking	0.59	1.14 (0.72–1.80)
Mean HbA_{1c}	0.0001	1.25 (1.12–1.39)
HbA_{1c} at baseline	0.0464	1.12 (1.00–1.25)
Diastolic blood pressure	0.54	0.99 (0.97–1.01)
Systolic blood pressure	0.51	1.00 (0.98–1.01)
Total cholesterol	0.0397	1.00 (1.00–1.01)
Triglyceride	0.0214	1.00 (1.00–1.00)
Model B (multivariate analysis)		
Duration of diabetes at baseline	0.0027	1.06 (1.02–1.10)
Mean HbA_{1c}	0.00001	1.29 (1.15–1.44)

Hazard ratio (95% CI) indicates alteration of risk per unit increase in independent variables shown in Table 1.

Table 3
Predictive effect of independent variables on progression from BDR to PDR (Cohort B)

Independent variable	*p* value	Hazard ratio
Model A (univariate analysis)		
Age at diagnosis of diabetes	0.35	0.98 (0.93–1.03)
Age at baseline	0.97	1.00 (0.97–1.03)
Duration of diabetes at baseline	0.53	1.01 (0.98–1.04)
BMI	0.42	1.01 (0.97–1.09)
Family history of diabetes	0.46	1.25 (0.69–2.28)
Family history of vascular diseases	0.08	1.79 (0.93–3.44)
Smoking	0.49	1.22 (0.69–2.18)
Mean HbA_{1c}	0.00001	1.42 (1.23–1.66)
HbA_{1c} at baseline	0.0237	1.21 (1.03–1.42)
Diastolic blood pressure	0.0169	1.03 (1.01–1.05)
Systolic blood pressure	0.089	1.01 (1.00–1.03)
Total cholesterol	0.50	1.00 (1.00–1.01)
Triglyceride	0.90	1.00 (1.00–1.00)
Model B (multivariate analysis)		
Diastolic blood pressure	0.0185	1.03 (1.00–1.05)
Mean HbA_{1c}	0.00001	1.43 (1.23–1.67)

Hazard ratio (95% CI) indicates alteration of risk per unit increase in independent variables shown in Table 1.

ol and triglyceride disappeared after adjustment for the mean HbA_{1c}. Multivariate analysis (Model B) revealed that only mean HbA_{1c} and duration of diabetes were significant independent predictors of developing BDR. The impact of mean HbA_{1c} on the incidence density of BDR is shown in Fig. 2 (χ^2 trend = 21.5, $p < 0.001$). The incidence increased remarkably when the mean HbA_{1c} exceeded 8.5%.

3.3. Predictors of progression from BDR to PDR (Cohort B)

Of the 160 patients with BDR, i.e., the 72 patients who had BDR at entry and the 88 who developed BDR during the follow-up, 50 developed PDR. The incidence density for the progression from BDR to PDR, calculated on the basis of the time from the detection of BDR until the development of PDR, was 57.7 (95% CI 55.5–60.0)/1000 person-years. Table 3 shows the predictive effect of independent variables for the progression. Only the mean HbA_{1c} level and the diastolic blood pressure level were significant independent predictors of progression from BDR to PDR in multivariate analysis (Model B). The impact of mean HbA_{1c} on the progression is shown in Fig. 3. The progression rate increased markedly when the mean HbA_{1c} exceeded 8.5% (χ^2 trend = 21.9, $p < 0.001$); the highest stratum ($HbA_{1c} \geqq 10.5\%$) had a five-fold higher rate of progression than the lowest stratum ($HbA_{1c} < 6.4\%$). The impact of diastolic blood pressure levels on the progression is shown according to tertiles of diastolic blood pressure levels (Fig. 4). The high-

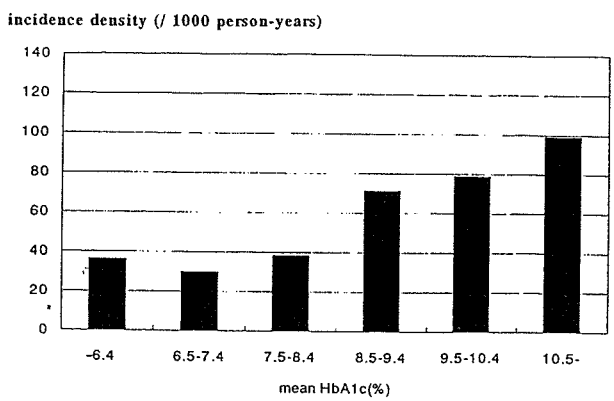

Fig. 2. Incidence density for developing BDR in Cohort A according to the stratification of the mean HbA_{1c} level during the follow-up period. Incidence density (per 1000 person-years) was calculated by dividing the number of patients who developed BDR by the observed person-years.

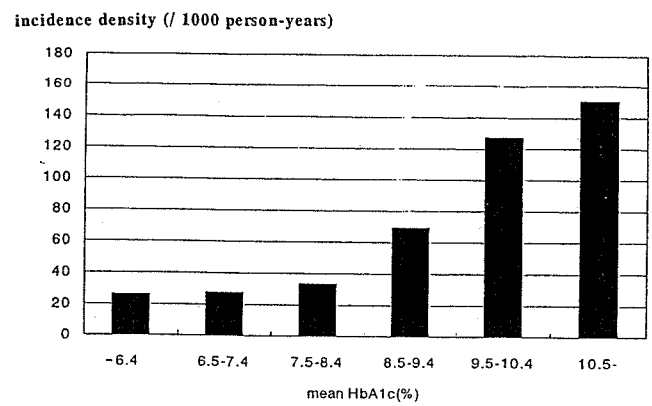

Fig. 3. Incidence density for progression from BDR to PDR in Cohort B according to the stratification of the mean HbA_{1c} level during the follow-up period. Incidence density (per 1000 person-years) was calculated by dividing the number of patients who progressed from BDR to PDR by the observed person-years.

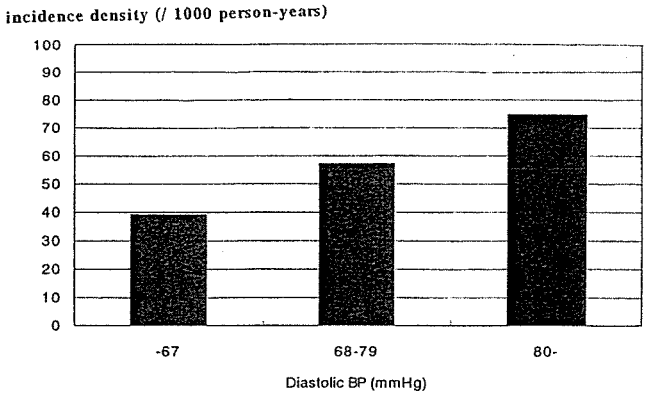

Fig. 4. Incidence density for progression from BDR to PDR according to tertiles of diastolic blood pressure levels. Incidence density (per 1000 person-years) was calculated by dividing the number of patients who progressed from BDR to PDR by the observed person-years.

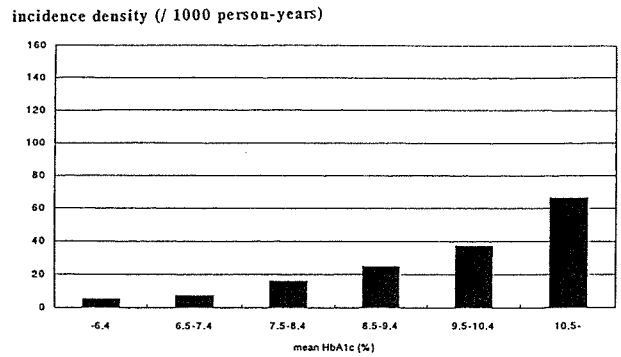

Fig. 5. Incidence density for developing PDR in the whole cohort ($n=394$) according to the stratification of mean HbA_{1c} level during the follow-up period. Incidence density (per 1000 person-years) was calculated by dividing the number of patients who developed PDR by the observed person-years.

est tertile showed a two-fold higher rate of progression than the lowest tertile.

3.4. Predictors of PDR in the whole cohort (Cohort C)

Overall, 50 out of 394 patients developed PDR during a mean follow-up of 7.1 years (Cohort C), giving an incidence density of 17.9 (95% CI 13.6–23.6)/1000 person-years. Univariate analysis (Model A) indicated that known duration of diabetes, presence of BDR, family history of vascular disease, diastolic and systolic blood pressure levels, and both the baseline and the mean HbA_{1c} levels during the follow-up had significant predictive effects (Table 4). Multivariate analysis (Model B) revealed that mean HbA_{1c}, presence of BDR at baseline, diastolic blood pressure level, and family history of vascular disease were significant independent predictors of PDR. Among patients whose mean HbA_{1c} was ≦6.4% ($n=117$) or 6.5–7.4% ($n=89$), only a few developed PDR (incidence density of 6.4 with a 95% CI from 3.3/1000 person-years to 12.3/1000 person-years) (Fig. 5). The incidence density increased with increasing mean HbA_{1c} level in a dose-dependent manner (χ^2 trend=41.7, $p<0.001$) and it was 66.4 (95% CI 38.5–114.3)/1000 person-years for patients with mean HbA_{1c} ≧10.5% ($n=31$).

Table 4
Predictive effect of independent variables on development of PDR in early-onset type 2 diabetes (Cohort C)

Independent variable	p value	Hazard ratio
Model A (univariate analysis)		
Sex (men vs. women)	0.41	1.27 (0.72–2.22)
Age at diagnosis of diabetes	0.69	1.01 (0.96–1.06)
Duration of diabetes at baseline	0.0002	1.06 (1.03–1.06)
BDR at baseline	0.00001	5.97 (3.42–10.40)
BMI	0.31	1.03 (0.98–1.08)
Family history of diabetes	0.23	1.44 (0.80–2.62)
Family history of vascular disease	0.0332	2.03 (1.06–3.88)
Smoking	0.22	1.44 (0.81–2.56)
Mean HbA_{1c}	0.00001	1.51 (1.31–1.74)
HbA_{1c} at baseline	0.0026	1.24 (1.08–1.43)
Diastolic blood pressure	0.0012	1.04 (1.01–1.06)
Systolic blood pressure	0.0192	1.02 (1.00–1.04)
Total cholesterol	0.078	1.00 (1.00–1.01)
HDL cholesterol	0.12	0.99 (0.97–1.00)
Triglyceride	0.59	1.00 (1.00–1.00)
Model B (multivariate analysis)		
Mean HbA_{1c}	0.00001	1.67 (1.41–1.97)
Family history of vascular disease	0.0156	2.28 (1.17–4.44)
Diastolic blood pressure	0.0136	1.03 (1.01–1.06)
BDR at baseline	0.00001	6.90 (3.78–12.57)

Hazard ratio (95% CI) indicates alteration of risk per unit increase in independent variables shown in Table 1.

4. Discussion

The present risk analysis first confirmed that lifetime exposure to glycemia, as revealed by the mean HbA_{1c} level during the follow-up and the duration of diabetes at baseline, was the strongest risk factor for both BDR and PDR. Secondly, we found that diastolic blood pressure was a significant risk factor in progression from BDR to PDR. Overall, the mean HbA_{1c} level during the follow-up, followed by the presence of BDR at the first visit, family history of vascular disease, and the diastolic blood pressure level, were significant risk factors for PDR.

We determined the rates of PDR and BDR according to the stratification of long-term levels of HbA_{1c}. Whether these rates are elevated or not is still difficult to interpret since few studies have ever examined the relation between the long-term HbA_{1c} levels and the incidence rate of BDR and PDR in type 2 diabetic patients. Only the DCCT study determined the incidence rate of retinopathy according to the long-term HbA_{1c} levels (Diabetes Control and Complications Research Group, 1993). The subjects in the

present study were comparable with the DCCT cohort (type 1 diabetes patients) regarding background clinical characteristics such as age (27 vs. 27 years), sex (54 vs. 54% men), diabetes duration (4 vs. 8 years), systemic blood pressure levels (116/73 vs. 116/73 mm Hg), lipid profiles (total cholesterol 195 vs. 179 mg/dl; HDL cholesterol 51 vs. 49 mg/dl; triglyceride 107 vs. 87 mg/dl), and observation period (7.1 vs. 6.5 years). The HbA_{1c} values in the present study were obtained by the method standardized by the Japan Diabetes Society and were quite similar to those used in the DCCT study (Glycohemoglobin Standardization Committee, 1997). Therefore, it should be valid to compare our cohort with the DCCT cohort. The incidences of BDR (per 1000 person-years, 95% CI) in our cohorts were 29.8 (17.3–51.4) in our Cohort A at mean HbA_{1c} level 6.5–7.4% and 71.3 (43.7–116.3) in our Cohort A at mean HbA_{1c} level 8.5–9.4%, both of which were higher than the incidence of 11.0 (7.3–16.6) in the DCCT intensive-therapy group (mean HbA_{1c} level of 7.0%) and that of 40.1 (32.7–49.2) in the DCCT conventional-therapy group (mean HbA_{1c} level of 9.0%). The incidences of progression from BDR to PDR were 27.8 (11.6–66.7) in our Cohort B at mean HbA_{1c} level 6.5–7.4% and 69.5 (34.7–138.9) in our Cohort B at mean HbA_{1c} level 8.5–9.4%, both of which were again higher than that of 11.0 in the DCCT intensive-therapy group and of 24.0 in the DCCT conventional-therapy group. These results may suggest that Japanese early-onset type 2 diabetic patients are at high risk for diabetic retinopathy.

We found a slight elevation of blood pressure to be significant for the prediction of progression from BDR to PDR, despite normal mean blood pressure levels of 116/73 mm Hg. This is consistent with the finding of Klein et al. (1984, 1989b, 1995) and Haffner et al. (1988) of the significant role of blood pressure in the progression of retinopathy exclusively in younger-onset diabetic patients, but not in older-onset diabetic patients. The recent finding by the UK Prospective Diabetes Study Group (1998) that tight blood pressure control in type 2 diabetic patients (mean age 56, mean blood pressure at entry 160/94 mm Hg) achieves a reduction in the risk of progression of diabetic retinopathy, also appears to be in agreement with our results. Interestingly, Poulsen et al. (1998) found high nocturnal diastolic blood pressure and disturbed circadian blood pressure variation in young type 1 diabetes patients with retinopathy compared to those without retinopathy. Our data are the first to demonstrate such an association in early-onset type 2 diabetic patients. It appears that exclusively in young diabetic patients, strict blood pressure control may be important in the prevention of the progression of retinopathy.

The overall incidence of PDR (17.9/1000 person-years) in early-onset Japanese type 2 diabetic patients appears to be high. It is similar to that found in early-onset Japanese type 1 diabetic patients of 19.7 (Yokoyama et al., 1994). To our knowledge, only a few studies such as the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), Oklahoma Indian study and Korean study have examined the incidence rate of retinopathy; however, all these studies examined only old-onset type 2 diabetic patients. No studies have investigating the incidence of retinopathy in early-onset type 2 diabetes have been reported. The overall incidence of PDR found in the present study was higher than or comparable to that found in old-onset type 2 diabetic patients in the WESDR (11.8/1000 person-years) (Klein et al., 1989a,b, 1994), Oklahoma Indian type 2 diabetic patients (16.1/1000 person-years) (Lee et al., 1992) and Korean type 2 diabetic patients (12.5/1000 person-years) (Kim et al., 1998). The rate of progression from BDR to PDR (57.7/1000 person-years) found here was considerably higher than that in WESDR patients (24.1/1000 person-years) (Klein et al., 1989a, 1994), Oklahoma Indian type 2 diabetic patients (46.3/1000 person-years) (Lee et al., 1992), and Korean type 2 diabetic patients (37.5/1000 person-years) (Kim et al., 1998). This suggests that Japanese early-onset type 2 diabetic patients may be at high risk for PDR once they are affected by BDR. This is consistent with the finding in Pima type 2 diabetic patients that early-onset type 2 diabetic patients are at high risk for developing PDR (Nelson et al., 1989).

We failed to find a significant effect of cigarette smoking on the development of retinopathy. Further study categorizing patients according to severity of cigarette consumption may be required since the effect is controversial in the previous reports (Muhlhauser, 1994; Muhlhauser et al., 1996; Chaturvedi et al., 1995; Moss et al., 1996).

One must account for bias due to selective referral and/or dropout. The subjects who participated in the study were selected on the basis of continuing clinic visits for more than a year. The clinical characteristics of the participants were mostly similar to those of non-participants who lived outside of the Tokyo area, while participants had slightly lower risks of retinopathy in terms of blood pressure, BDR, and lipid profiles. We tested for diabetic retinopathy until the patients' final visits to the clinic; and thus the reason for discontinuing clinic visits was not related to development of retinopathy. These facts may indicate that major bias due to selective referral was unlikely.

In conclusion, early-onset Japanese type 2 diabetic patients appear to be at high risk of developing BDR and PDR. The high risk is partly explained by long-term metabolic control and systemic blood pressure factors. Whether the excess risk is due to effects of ethnicity, age, or type of diabetes requires further investigation. Early detection of diabetes and strict control of blood glucose and blood pressure after the detection of type 2 diabetes are necessary for reducing the risk of progression of retinopathy in early-onset Japanese type 2 diabetes.

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原　著

学校検尿と治療中断が18歳未満発見2型糖尿病の合併症に与える影響

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倉繁　隆信[*2]　岩本　安彦[*1]

要約：18歳未満発見2型糖尿病の予後に学校検尿と治療中断が及ぼす影響を検討した．対象は1980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283名（男142名，女141名）である．学校検尿で発見された『学校検尿発見群』は183名おり，1974年以降この群の割合が50％を超し，1992年以降は76.5％を占めていた．『学校検尿発見群』は『学校検尿以外発見群』と比べ，治療中断の頻度および合併症の頻度，重症度のいずれにおいても差異はみられなかった．一方，糖尿病と診断されてから当センター初診までに少なくとも1年以上医療機関を受診していなかった『治療中断あり群』は91名であった．『治療中断あり群』は『中断なし群』と比べ，合併症の頻度が高く（$p<0.0001$），合併症は重症化していた（$p<0.0001$）．治療中断は罹病期間を考慮しても合併症発症に大きく影響を与えていた（$p<0.01$）．

Key words：①小児　②2型糖尿病　③学校検尿　④治療中断

〔糖尿病43（2）：131～137，2000〕

緒　言

小児期に発症する糖尿病の大部分は1型糖尿病と考えられていたが，肥満児の増加と1992年から義務付けられた学校検尿システムの導入により，昨今2型糖尿病が増加してきている[1]．2型糖尿病の多くは自覚症状に乏しい．それゆえ，唯一の早期発見方法として学校検尿システムは大変意義あるものであることは間違いなく，1974年から東京の1部の地域で行われていたこのシステムが全国的に導入されるにいたったと考えられる．

われわれは，糖尿病センターを受診した30歳未満発見2型糖尿病患者1092名の合併症を調査し，日本における若年発症2型糖尿病の予後が非常に重篤なものであることを報告した[2]．35歳までに増殖網膜症をきたした135名の約40％の患者は自分が糖尿病であることを18歳までに知っていたことも明らかになった．早期発見されたにもかかわらず重篤な合併症に陥るものが多いことが重要な問題である．

われわれは，その原因の一端を明らかにする目的で，糖尿病が学校検尿で発見された群とそれ以外の理由で発見された群の間で，合併症の頻度および程度に違いがあるか，そして成人発症糖尿病で問題にされている治療中断の問題[3]が小児期発見2型糖尿病患者においても存在するのか，治療中断が合併症にどのように影響を与えているのかを検討した．

対象と方法

1．対象

1980年から1998年までに東京女子医科大学糖尿病センターを初診し，18歳未満発見2型糖尿病と診断され，かつ罹病期間が2年以上の283名（男142名，女141名）を対象とした．2型糖尿病の診断は，従来どおり[1,2]で，1型糖尿病との鑑別にはインスリン分泌能（食事負荷試験，グルカゴン負荷試験，尿中Cペプチド），抗GAD（glutamic acid decarboxylase）抗体，ICA（islet cell antibody）などの自己抗体，病歴，家族歴，臨床経過などを参考に，総合的に判断した．対象283名の臨床像をTable 1に示す．

2．糖尿病発見様式

283名の病診録より発見様式を判定した．学校検尿

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受付日：1999年4月2日
採択日：1999年9月8日

Table 1 Clinical characeristics of type 2 diabetic patients
male/female : 142/141

onset age			6.0–17.9 y.o. (mean ± SD : 14.7 ± 2.0)		
age (year)	6–9		10–14		15–18
n	5		110		168
(%)	1.8		38.9		59.4
duration of diabetes at baseline			2.0–29.0 y.o. (mean ± SD : 5.6 ± 7.4)		
duration (year)	–5	6–10		11–15	16–
n	104	70		45	64
(%)	36.7	24.7		15.9	22.7
HbA1c at baseline			4.0–17.6% (mean ± SD : 9.4 ± 2.9)		
HbA1c (%)	–6.4	6.5–8.4	8.5–10.4	10.5–12.4	12.5–
n	44	67	70	54	48
%	15.5	23.7	24.7	19.1	17.0
Time during intermittent treatment					
Time (year)	0	1–4		5–9	10–
n	192	38		40	13
(%)	67.5	13.5		14.1	4.6
Score of complications					
score	0	1		2–3	4–6
n	191	26		24	42
(%)	67.5	9.2		8.4	14.8

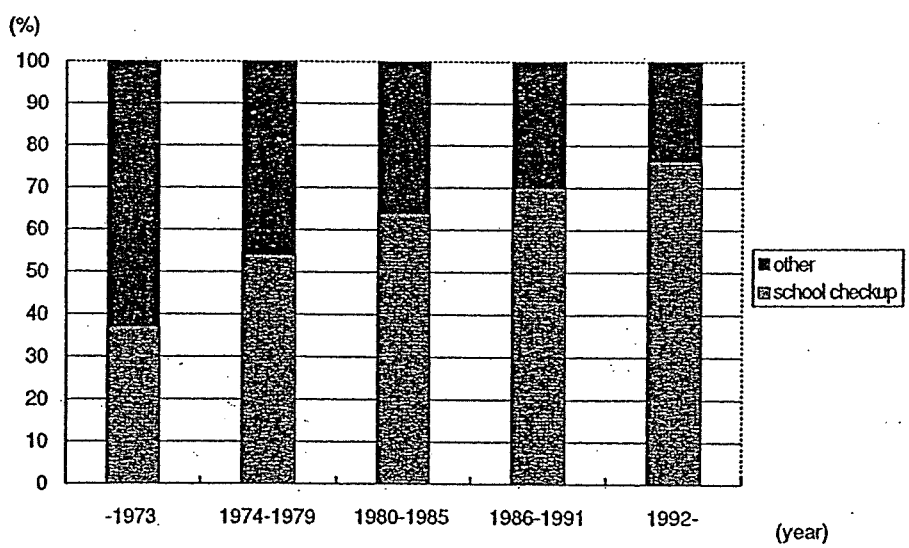

Fig. 1 Changes in the rate of patients in school checkup and other groups every 5 years

により医療機関を受診し糖尿病と診断された時，"学校検尿で発見"（以下，学校検尿発見群）とし，それ以外の理由で病院を受診し糖尿病と診断された時，"それ以外で発見"（以下，学校検尿以外発見群）とした．

3. 合併症

合併症の程度は当センター初診時の身体所見およびその後に施行された眼底検査や尿検査より判定した．網膜症，神経障害，腎症はそれぞれ以下のように3段

Table 2 Clinical characteristics of school checkup and other groups

	school checkup	other	p
n	183	100	
onset age (year)	14.8±2.1	14.7±1.9	0.6636
HbA1c (%) at the first visit	9.5±2.8	9.4±2.7	0.4079
duration of diabetes (year)	8.5±6.5	10.1±7.6	0.2010
intermittent treatment (−)/(+)	126/57	66/34	0.4752
interval of intermittent treatment			
mean (year)	4.98±3.27	5.79±3.20	0.3260
Range (year)	1〜15	1〜15	
history of hospitalization (−)/(+)	95/88	55/45	0.6189
complications (−)/(+)	128/55	63/37	0.2346
score of complications			
score 0	128	63	0.0611
1	19	7	
2	11	5	
3	4	4	
4	8	6	
5	6	3	
6	7	12	

Mean±SD

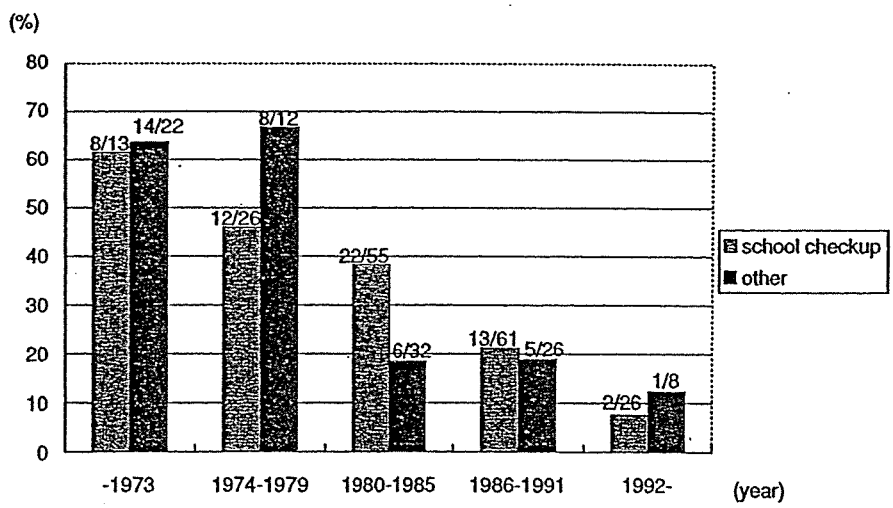

Fig. 2 Frequency of patients who had intermittent treatment in both school checkup and other groups

階に評価し，スコアの合計点数で表した（0-6点）．つまり，網膜症なしは0点，単純網膜症は1点，前増殖および増殖網膜症は2点とし，神経合併症なしを0点，症状は軽いが振動覚や神経伝導速度の低下がみられるものを1点，有痛性神経障害，自律神経障害など症状の強いものを2点とした．腎症は早期尿アルブミン/クレアチニン比が14 mg/gCr以上を1点，300 mg/gCr以上さらに透析中を2点とし，それ以外を0点とした．

4. 治療中断

治療中断は，糖尿病と診断されてから東京女子医科大学糖尿病センター初診までの間に，少なくとも1年以上いずれの医療機関へも受診していないことと定義した．

5. 過去の入院歴

糖尿病発見時に教育入院ないしは教育目的に入院を経験していないかどうかを診療録より調査した．

6. マッチドペア分析

まず性，発見年齢，罹病期間が一致したペアを選び，

Table 3 Comparison of clinical characteristics between intermittent treatment and continuous treatment groups

	intermittent	continuous	p
n	91	192	
onset age (year)	14.5±2.2	14.9±2.0	0.4537
male/female	42/49	100/92	0.3514
HbA1c (%)	9.5±3.0	9.4±2.9	0.5576
duration of diabetes (year)	12.0±7.8	3.2±5.0	<0.0001
history of hospitalization (−)/(+)	44/47	104/84	0.2804
complication (−)/(+)	19/72	172/20	<0.0001
treatment at the first visit			
insulin and OHA	29	118	
insulin	19	30	
OHA	21	24	
Diet	22	20	
score of complications			
score 0	19	172	<0.0001
1	15	11	
2	13	3	
3	7	1	
4	13	0	
5	7	2	
6	17	3	

OHA; oral hypoglycemic agents
Mean±SD

次に一方は治療中断あり，他方は治療中断なしのペアを選出する．選出された何組みかのペアを用いて，中断歴の有無と合併症の発症との関係を検討した．

7. 統計処理

カテゴリー変数に対してχ二乗検定，パラメトリック連続変数に対してt検定，ノンパラメトリック連続変数にはMann-Whitney U検定とSpearmanの順位相関係数を，また，マッチドペア分析に対してMcNemar法を用いた．いずれも$p<0.05$を有意とした．

結 果

1. 対象患者の臨床像

Table 1は全対象患者283名の臨床像である．6歳未満発見の2型糖尿病患者はいなかった．15〜18歳発見患者は約60%を占めた．発見から当センター初診までの罹病期間は5年以下が37%を占めたが，16年以上という長期罹病患者も23%を占めていた．初診時HbA1c値は6.4%から12.5%までバラツキがみられ，治療中断例は32%に，合併症も32%に存在した．

2. 学校検尿発見群とそれ以外発見群

発見様式の割合の年次推移

Fig. 1に学校検尿発見とそれ以外発見という発見様式の割合の年次推移を示す．1974年から東京の1部の地域で学童の糖尿病検尿が開始され[4]，学校検尿発見群の割合は50%を超すようになり，1992年に全国的に学校検尿における糖尿測定が義務付けられてからは，1992年以降発見者のうち学校検尿発見者が76.5% (26/34) に達していた．

2群間の臨床的特徴

Table 2に『学校検尿発見群』と『学校検尿以外発見群』の臨床的特徴を示した．発見年齢および当センター初診時のHbA1cには統計的有意差はなかった．治療中断の有無においても2群間に差異はなく，それは1974年以降も，また1992年以降の患者に限ってみても，治療中断率には差はみられなかった (Fig. 2)．中断期間にも2群間において有意な差異はみられなかった．次に，初診時の合併症について調べた．合併症の有無および合併症スコアに関しても2群間に有意な差異はみられなかった ($p=0.0611$)．

『学校検尿以外発見群』の発見理由

283例中100例が学校検尿以外の理由で発見されていた．発見理由には，多飲，多尿，口渇，体重減少などの糖尿病症状が69.6%と最も多く，次いで他の疾患罹病時に発見された者が続いた (17.7%)．その他，家族や知人に糖尿病の人がいてたまたま検尿をした (6.3%)，意識障害 (2.5%)，トイレ臭，くみとり (2.5%) などであった．

3. 『治療中断あり群』と『治療中断なし群』の特徴の比較

2群間の合併症に関する特徴

過去の中断歴の有無が合併症に影響を与えたかどうかを次に検討した（Table 3）．283名のうち治療中断ありは91名で，192名は過去に治療中断をしていなかった．この2群間には，発見年齢，性および当センター初診時のHbA1cに有意差はみられなかった．しかし，当センター初診時までの罹病期間には有意な差異がみられた．『治療中断なし群』は『あり群』に比べ，糖尿病発見早期に当センターを初診していた（$p<0.0001$）．そして，合併症の有無および合併症スコアに関しても2群の間には著しい有無差が認められた（$p<0.0001$）．『学校検尿発見群』が増加した1974年以降においても『治療中断群』に合併症を発症している者が多く，かつ合併症スコアが高得点であった（$p<0.0001$）．

マッチドペアによる検討

治療中断の影響をさらにしらべるために，当センター初診までの罹病期間をそろえた患者間の合併症の状況を次に調査した．まず性，発見年齢，罹病期間が一致したペアを選び，次に一方は治療中断あり，他方は治療中断なしのペア42組を選出できた（マッチドペア解析）．「中断ありかつ合併症あり」と「中断なしかつ合併症なし」のペアは23組，「中断ありかつ合併症あり」と「中断なしかつ合併症あり」のペアは7組，「中断ありかつ合併症なし」と「中断なしかつ合併症なし」のペアは12組あり，「中断ありかつ合併症なし」と「中断なしかつ合併症あり」のペアは1組もみられなかった．マッチドペアによる解析を行ったところ，明らかに治療中断ありが合併症ありと有意に相関した（McNemar法，$p<0.01$）．

治療内容の比較

インスリン治療患者および経口血糖降下薬治療患者は『中断なし群』に有意に多かった（$p=0.0001$, $p=0.0014$）．しかし，2種類の薬物治療の相違は治療中断の有無とは関連しなかった．また，インスリンも経口血糖降下薬も単独使用より併用使用した患者が『中断なし群』に多かった（$p=0.0072$, $p=0.0003$）．

4. 発見時の入院歴の有無と治療中断歴の有無の検討

糖尿病発見時に入院している患者が133名（47%）いた．しかしそのうち49名（36.8%）が治療を中断していた．一方，入院せず外来通院のみの患者は150名（53%）おり，治療中断者は46名（30.7%）であった．入院歴の有無と中断歴の有無には関連はみられなかった（$p=0.2804$）．この傾向は経年的にみられても変動はなかった．

Table 4 Reasons for dropout and hospital visit after dropout

(1) reasons for dropout (n=91)	
①think it not a problem to dropout	16(17.6%)
②easy improvement	16(17.6%)
③no symptpms	11(12.1%)
④dislike of admission therapy	10(11.0%)
⑤diet	10(11.0%)
⑥translocation, graduation	10(11.0%)
⑦aversion to insulin injection	8 (8.8%)
⑧busy	4 (4.4%)
⑨change of doctor	4 (4.4%)
⑩hypoglycemia by oral hypoglycemic agent	2 (2.1%)
(2) reasons for hospital visit after dropout (n=91)	
①other disease	26(28.6%)
②visual disturbance	18(19.8%)
③medical checkup	18(19.8%)
④symptoms (weight loss, polyuria etc.)	13(14.3%)
⑤pregnancy	9 (9.9%)
⑥concerned about diabetic complications	4 (4.4%)
⑦coma	3 (3.2%)

5. 中断および再受診の理由

Table 4に診療録から得た治療中断の理由および再受診した理由を示した．成人の場合と同様，病識に乏しいためと思われる中断理由が多かった．中断後の再受診理由には，眼合併症による視力障害や，妊娠に関連したものが多かった．

考　察

2型糖尿病人口の増加とその重要性により，検尿システムが学校や企業にて全国規模でおこなわれるようになった．しかしながら，今日の医療施設への低い受診率および高頻度の合併症の存在は，検尿システムのながれを再検討する必要性をわれわれに促していると考えられる．本研究においても，対象患者の学校検尿発見率が経年的に増加していることから，学校検尿が2型糖尿病の早期発見に大きく貢献していることは明白である．しかし，治療中断率の経年的変化が学校検尿で発見されてもされなくてもほぼ同様であった．経年的に治療中断しにくくなった理由として，学校検尿システムとともに社会全体として糖尿病に対する意識が高まってきたことが大きく影響していると考えられる．1992年以降の患者の治療中断率が低いのはまだ罹病期間が短いためと考えられる．

われわれは学校検尿システムが治療中断阻止や合併症の発症阻止に影響を与えるのではないかと考え，『学校検尿発見群』と『学校検尿以外発見群』の2群を比較した．しかし，治療中断および合併症発症のいずれ

にも学校検尿するだけでは有効ではなかった．

小児医療では新生児マススクリーニングをはじめとして予防医学が進歩してきた．その結果，重篤な症状に陥る症例が減少し，かつ医療経済上も効果的であることが証明された[5]．1992年全国で学校検尿での尿糖測定が義務付けられると，同様に学校検尿というスクリーニングによる糖尿病の早期発見，早期治療の意義が期待された．しかし，学校検尿で早期発見しても，『学校検尿以外発見群』と同様，治療を中断し合併症を発症している事実が存在していた．糖尿病はマススクリーニングだけでは早期発見の有効性が現れなかった．

その理由として，糖尿病発見後の治療，教育が適切に行われていないことがあげられる．2型糖尿病は，特に18歳未満発見例に関しては薬物療法が必要となることは極めて少ない．食事および運動など生活習慣の是正のみで血糖コントロールはすみやかに改善する．1型糖尿病のように毎日インスリンを注射しなければいけないわけではない．しかし，そのことが病識を低下させ，糖尿病の重大さを認識せず，治療中断してしまうことが理由のひとつに考えられた．

中断者に関する問題は，すでに成人において検討されており[3,6,7]，その治療方針に難渋している．しかし，入院歴のある者の方が外来通院のみの者より治療中断率が明らかに低かった[3]ことから，正しい認識を持った医師および医療従事者が時間をかけて丁寧に教育を行えば，治療中断率が減少することが期待される．しかし，今回の小児での検討では，初期入院歴の有無と中断歴の有無のあいだにはまったく関連がなかった（P＝0.2804）．また，成人例ではみられなかった，入院治療がいやだったという中断理由が小児では多かったことを考えると，学校検尿で発見された者に対する初期教育が正しく行われているかどうかに疑問が残る．

学校検尿で発見された患者に対し，いかに治療を中断させないようにできるかが合併症防止の有効な手段であることに注目し，その方法をみつけることが今後の課題であると考えられた．

本研究の一部は平成10年厚生省科学研究（子ども家庭総合研究事業）小児糖尿病生活習慣病の発症要因，治療，予防に関する研究（班長：松浦信夫）と平成10年度文部省科学研究費奨励研究（A）によるものである．

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Abstract

Influence of Urine Glucose Screening for School Chidren and Intermittent Treatment on Diabetic Complications in Early-onset Type 2 Diabetic Patients

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The influence of urine glucose screening for school children and intermittent treatment of diabetes was investigated in early-onset diabetic patients. A total of 283 patients (142 male, 141 female) were recruited, who were diagnosed with type 2 diabetes mellitus before 18 years of age and were registerd in the Diabetic Center of Tokyo Wemen's Medical School of Medicine from 1980 to 1998. A total of 183 cases (64.7%) were diagnosed as diabetes mellitus by urine glucose screening test for school children (school urine group). After 1992, 76.5% were diagnosed by the urine glucose screening. There were 57 cases in the school urine group who entered the intermittent treatment group. School urine screening had no effect on protecting against diabetic complications at the visit to our center. However, comparison with the intermittent group (91 cases) and continuous treatment group showed that the intermittent treatment group had a significant increase in development and deterioration of diabetic complications. After consideration of the diabetic duration, intermittent treatment was found to render the diabetic complications severe.

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原　著

80年代と90年代に初診した15歳未満発見糖尿病患者の合併症頻度の比較

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要約：小児期発症糖尿病患者の合併症頻度を，病型及び初診年によるcase control studyにて比較した．対象は15歳未満発見2型糖尿病患者のうち80年代(1980～1988年)初診群42名，90年代(1989～1998年)初診群42名であり，各々1988年，1998年に網膜症及び腎症の断面調査を施行し，糖尿病発症発見年齢と断面調査時の罹病期間を一致させた1型糖尿病患者(80年代初診群104名，90年代初診群91名)と比較した．いずれの年代でも単純網膜症は1型の方に多く，増殖網膜症は2型の方が多い傾向にあった．両型とも増殖網膜症及び腎症の頻度は時代が下るとともにむしろ増加している傾向にあったが，1型の単純網膜症頻度だけは有意に低下していた($p<0.005$)．また90年代初診2型群の約半数例に治療中断歴があり，これらの患者に特に高率に合併症が認められた．

Key words：①若年発症糖尿病　②網膜症　③腎症　④断面調査
〔糖尿病47(7)：521～526, 2004〕

緒　言

欧米では小児の糖尿病といえばほとんどが1型糖尿病であり[1]，20歳以下の2型糖尿病の発症は数%にすぎない．一方，日本では欧米に比べて小児期発症2型糖尿病患者が多いという特徴がある．例えば，東京女子医科大学糖尿病センターに通院中の15歳未満発見糖尿病患者の約2割は2型である[2,3]．1974年から導入された学校検尿(尿糖検査)が1992年には義務化され，小児に対しても糖尿病のスクリーニングが徹底されるようになった[4]ことと，近年，生活スタイルの変化により，小児期発症2型糖尿病患者数が増加してきていると考えられる[5]．しかし，症例の把握や有病率の推定が困難であることから小児期発症の2型糖尿病に関する疫学調査の報告は極めて少ない[6,7]．

我々は，若年発症2型糖尿病患者は若くして重篤な合併症に陥ることが多いことをこれまで報告してきた[8～11]．そこで，小児期に発見された2型糖尿病患者がどのような経過をたどっているかを明らかにする一環として，80年代初診と90年代初診の15歳未満発見2型糖尿病患者の合併症の頻度を断面調査し，80年代から90年代になって合併症頻度の低下がみられるか，また同年代発症の1型糖尿病患者と比較して合併症頻度に差異が認められるかどうかをcase control studyにより検討した．

対　象

〈80年代初診群〉

1980年から1988年に当センターを初診した15歳未満発見2型糖尿病患者のうち推定罹病期間が2年以上で，1988年に網膜症及び尿蛋白の検査を施行することができたもの42例を対象とした．そして，彼らと糖尿病の発見年齢，調査時の罹病期間を一致させた1型糖尿病患者104例を選出した．

〈90年代初診群〉

1989年から1998年に当センターを初診した15歳未満発見2型糖尿病患者のうち推定罹病期間が2年以上で，1998年に網膜症及び尿蛋白・尿中アルブミン検査を施行することができたもの42例を対象とした．

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Table 1 Patient profiles

Group / Type	80s 2(n=42) (a)	80s 1(n=104) (b)	90s 2(n=42) (c)	90s 1(n=91) (d)	p
%male(n, %)	18(42.3)	40(38.5)	9(21.5)	34(37.4)	ns
onset age(years)	12.7±1.4	12.1±1.6	12.5±1.6	12.0±1.6	ns
family history of DM(n, %)	25(59.5)	20(19.2)	26(61.9)	11(12.1)	<0.0001[1]
At study(1988 or 1998)	in 1988		in 1998		
duration(years)	12.1±6.9	12.0±6.1	12.9±6.4	12.8±6.0	ns
follow-up(years)	4.4±2.7	4.9±2.5	4.0±2.5	4.4±2.9	ns
HbA1c(%)	8.7±2.3	9.5±2.1	7.0±1.7	7.6±1.5	[2]
BMI(kg/m^2)	22.8±4.4	21.6±2.1*	22.8±3.3	22.8±2.9	<0.05
treatment(n, %)					
diet	8(19.0)		4(9.5)		
OHA	12(18.6)		11(26.2)		ns[3]
insulin	22(52.4)	104(100)	27(64.3)	91(100)	

[1] (a) vs(b), (c) vs(d) [2] (a) vs(b), (c) vs(d) : p<0.005 (a) vs(c), (b) vs(d) : p<0.0005 [3] (a) vs(c)

そして，彼らと糖尿病の発見年齢，調査時の罹病期間を一致させた1型糖尿病患者91例を選出した．

方 法

糖尿病の診断は1985年のWHOの診断基準により判定し，病型鑑別についてはインスリン分泌能，膵島関連自己抗体，発症形式，家族歴，ケトーシス傾向の有無，臨床経過等を可能な限り調べて総合的に判断した．

80年代初診群については1988年に，90年代初診群については1998年に各々網膜症及び腎症の断面調査を施行した．網膜症は，眼科専門医による眼底精密検査によりScott分類及び福田分類に基づき判定を行い，網膜症なし，単純網膜症及び増殖網膜症に分類した．腎症は80年代については尿定性検査により，90年代については尿定性に加えて早朝尿アルブミン・クレアチニン比(ACR)も評価し，臨床経過と合わせて判定した．ACR 14 mg/g.Cr以上を潜在性腎症とし，ACR 300 mg/g.Cr以上または尿定性にて尿蛋白100 mg/dl以上が持続している場合に顕性腎症とした．合併症あり群は網膜症か腎症がある群であり，合併症なし群はいずれもない群である．

また2型糖尿病患者については治療中断歴の有無と合併症との関係を調査した．糖尿病と診断されてから1年以上継続通院が滞った場合に治療中断歴ありとした．

統計処理は，4群間の検定は分散分析のポストホックテスト，合併症頻度に関してはχ^2検定を用いた．

結 果

1. 対象患者の臨床像

80年代初診群(以後，80年代と略す)及び90年代初診群(以後，90年代と略す)の2型，1型糖尿病患者の臨床的特徴をTable 1に示した．糖尿病発症発見年齢は12.0～12.7歳と4群間で有意差を認めなかった．第一度近親者内における糖尿病家族歴は80年代の2型は59.5%，90年代の2型は61.9%と両年代とも1型に比べて有意に高率であった．

断面調査時(1988年及び1998年)において，罹病期間は12.0～12.9年，当センター通院期間は4.0～4.9年であり，いずれも4群間で有意差を認めなかった．この時点でのHbA1cは両年代とも2型より1型が有意に高値であり，また両病型とも90年代初診群より80年代初診群の方が有意に高値であった．BMIは80年代初診群の1型が他の群より小さかったが，いずれも肥満傾向は認めなかった．調査時点の治療状況については，80年代2型の52.4%，90年代2型の64.3%がインスリン治療になっていたが，食事療法，経口薬治療を含めた治療法の割合は80年代と90年代の両群間で有意差はなかった．

2. 網膜症の頻度

80年代初診群については1988年時の，90年代初診群については1998年時における網膜症の頻度をFig. 1に示した．2型糖尿病の80年代初診群の単純網膜症の頻度は23.8%(10例)，増殖網膜症の頻度は21.4%(9例)であり，1型糖尿病の80年代初診群の単純網膜症の頻度は34.6%(36例)，増殖網膜症の頻度は16.4%(17例)であった．一方，2型糖尿病の90年代初診群の単純網膜症の頻度は9.5%(4例)，増殖網膜症の頻

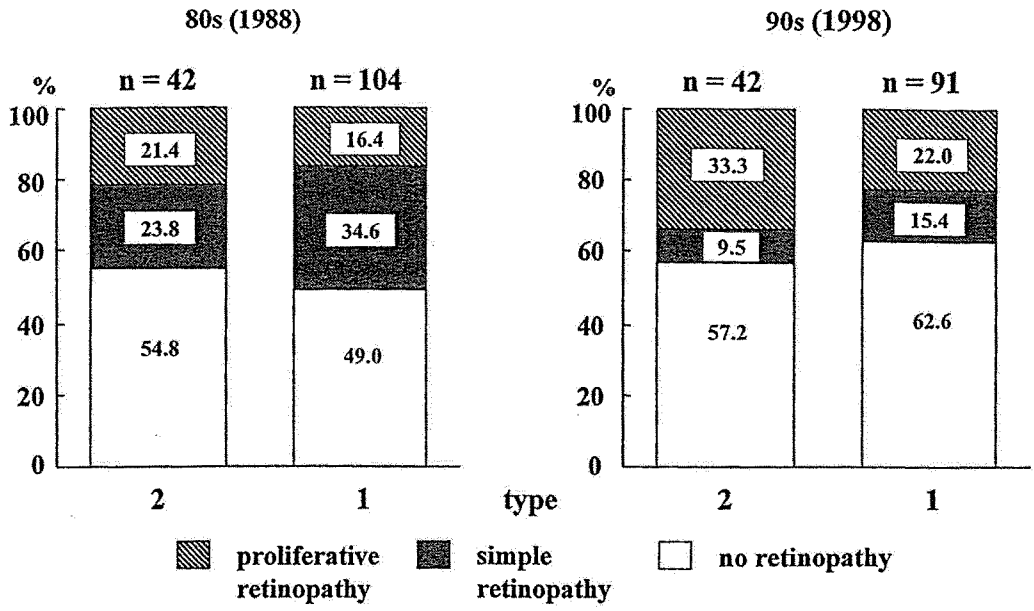

Fig. 1 Prevalence of retinopathy in patients with type 2 and 1 diabetes diagnosed before the age of 15 and visiting in the 1980s (80s group) and 1990s (90s group). Results of the 80s group were obtained in 1988 and those of the 90s group in 1998.

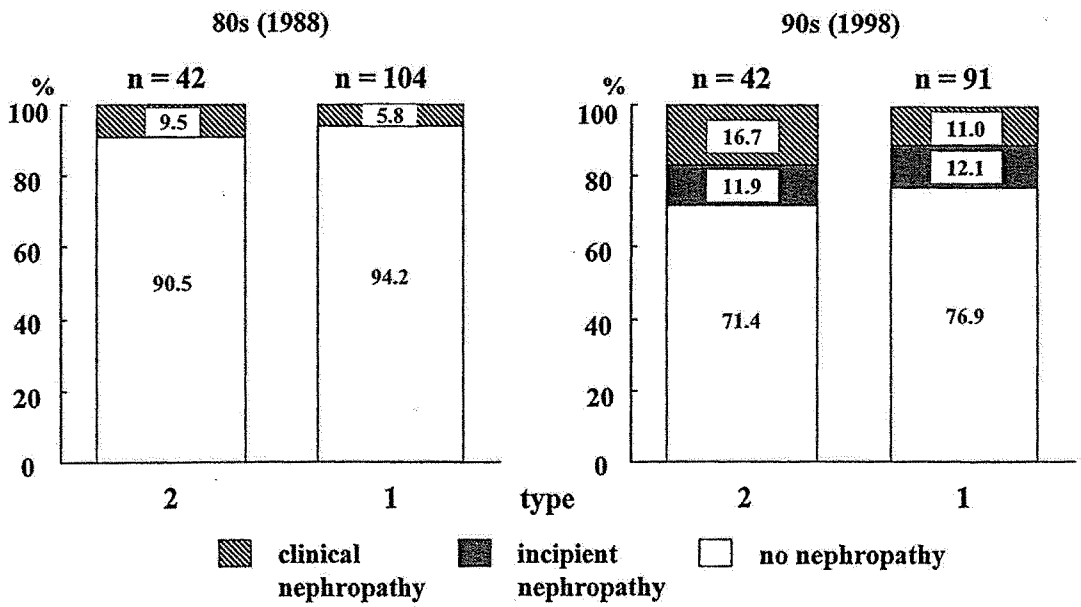

Fig. 2 Prevalence of nephropathy in patients with type 2 and 1 diabetes diagnosed before the age of 15 (other factors the same as in FIg. 1)

度は33.3%(14例)であり，1型糖尿病の90年代初診群の単純網膜症の頻度は15.4%(14例)，増殖網膜症の頻度は22.0%(20例)であった．両年代とも単純網膜症は1型の方が頻度が高く，増殖網膜症は2型の方が頻度が高い傾向が認められたが，統計学的に有意差はなかった．

次に，網膜症の頻度の年代による差を検討した．両型とも80年代に比べて90年代の方が増殖網膜症の頻度は増加し，単純網膜症の頻度は減少している傾向が認められた．特に1型の単純網膜症の頻度は34.6%から15.4%と有意に低下していた($p<0.005$)(Fig. 1)．

3. 腎症の頻度

80年代初診群については1988年時の，90年代初診群については1998年時における腎症の頻度をFig. 2に示した．80年代初診群の顕性腎症の頻度は2型で

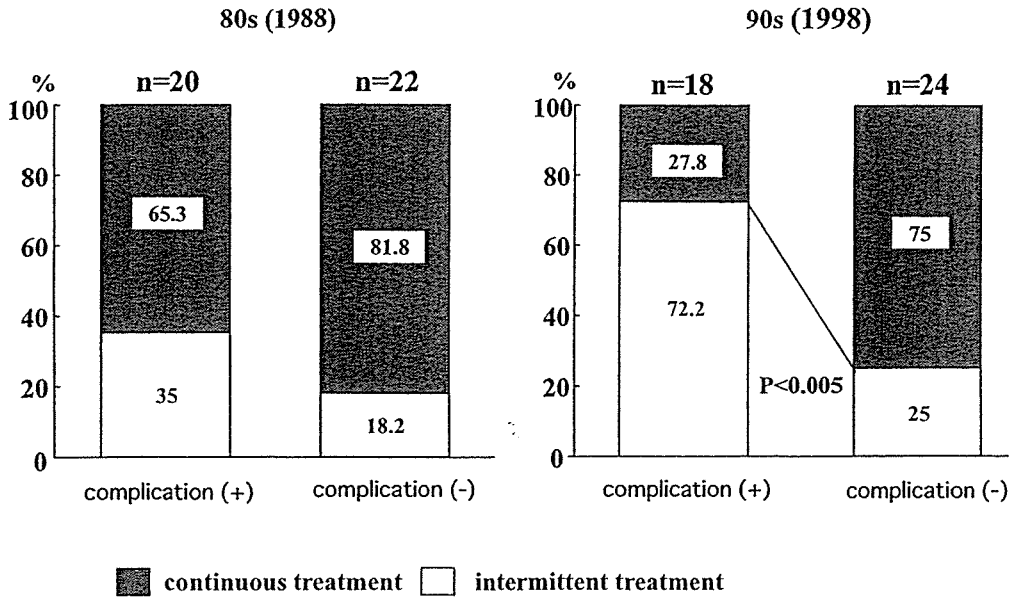

Fig. 3　Relationship between history of intermittent treatment and diabetic complications in patients with type 2 diabetes who visited in the 1980s(80s group) and 1990s(90s group).

9.5%(4例)，1型で5.8%(6例)であった．90年代初診群については潜在性腎症の頻度は2型で11.9%(5例)，1型で12.1%(11例)であり，顕性腎症の頻度は2型で16.7%(7例)，1型で11.0%(10例)であった．両年代とも顕性腎症の頻度は2型の方がわずかに高い傾向がみられた．

次に，顕性腎症の頻度の年代による差を検討した．2型，1型とも80年代に比べて90年代の方がやや増加している傾向が認められた(Fig. 2)．

4. 2型糖尿病患者における合併症と治療中断歴の関係

治療中断歴は80年代初診群の2型糖尿病患者42名中11名(26.2%)に，90年代初診群の2型糖尿病患者42名中19名(45.2%)に認めた．90年代の方が中断歴を有するものがむしろ増加していた．Fig. 3ではそれぞれの年代において，2型の合併症がある群とない群で中断歴を有する患者の占める割合を比較した．両年代とも合併症あり群はなし群に比べて中断歴を有する患者の頻度が高かった．特に90年代においては合併症あり群の72.2%に中断歴が認められ，有意に高率であった($p<0.005$)．

考　察

80年代初診群，すなわち1980年から1988年に当センターを初診した15歳未満発症発見糖尿病患者の1988年における合併症頻度の断面調査の一部はすでに大谷らが報告している[12]．今回は90年代初診群，すなわち1989年から1998年に当センターを初診した15歳未満発症発見糖尿病患者の合併症頻度の1998年における断面調査を同様に行い，経時的変化の検討を加えた．

糖尿病センター通院中の15歳未満発見2型糖尿病患者は，糖尿病の発見年齢及び調査時における罹病期間を一致させた1型糖尿病患者と比較して，80年代初診群も90年代初診群もともに増殖網膜症の頻度が高いことが明らかになった．以前我々は1990年までに当センターを初診した30歳未満発見糖尿病患者の腎症累積発症率を調査し，2型糖尿病患者の方が1型糖尿病患者より有意に高いことを報告した[10]が，本結果は1990年以降も同様の現状が存在することを示唆している．

80年代から90年代になると1型，2型とも初診時の増殖網膜症及び腎症の頻度はむしろ増加している傾向がみられた．当センターは糖尿病専門施設であるため合併症出現後に他院から紹介される患者が多く，初診時にすでに増殖網膜症，腎症を有する患者も多い[8]．また，2型糖尿病患者においては90年代初診群の方が治療中断歴を有するものが多く，高率に合併症が発症していた．我々は以前に18歳未満発見2型糖尿病患者の予後に学校検尿及び治療中断歴が与える影響を検討し，治療中断が合併症発症ならびに重症化に大きな影響を与えることを明らかにした[13]．同調査において若年発症2型糖尿病患者の中断理由を調べているが，中断することを問題と思わなかった，容易に改善した，自覚症状がない等，病識に乏しいためと思われるものが多かった．本調査で80年代初診群より，90年代初診群の方が治療中断歴を有する2型糖尿病患者の頻度が高かったということは，学校検尿システムが