High Incidence of Diabetic Nephropathy in Early-Onset Japanese NIDDM Patients

Risk analysis

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OBJECTIVE — Because early-onset Japanese NIDDM patients (diagnosed before age 30 years) can develop diabetic end-stage renal failure (ESRF) in their thirties, this study was performed to elucidate the incidence and determinants for the development of diabetic nephropathy.

RESEARCH DESIGN AND METHODS — The incidence of diabetic nephropathy and its relationship to baseline characteristics and long-term metabolic control were determined in 426 early-onset Japanese NIDDM patients who were followed for a mean of 6.8 years.

RESULTS — Of these 426 patients, 41 developed diabetic nephropathy manifested by persistent proteinuria (incidence rate [95%CI]/1,000 person-years; 14.1 [10.4–19.1]). Among patients whose mean HbA_{1c} (measured by a high-performance chromatography method that is standardized and comparable to the one used in the Diabetes Control and Complications Trial study) was around 7% or less, few developed nephropathy. The incidence of nephropathy increased with increasing mean HbA_{1c} level in a dose-dependent manner (χ^2 trend = 49.9, $P < 0.0001$). Diastolic blood pressure and duration of diabetes at entry had significant predictive effects independent of metabolic control.

CONCLUSIONS — The incidence rate of diabetic nephropathy in early-onset Japanese NIDDM patients is potentially high, similar to or higher than that in Pima Indian NIDDM or Caucasian IDDM patients of comparable age. Diabetic nephropathy in NIDDM patients aged in their thirties or forties is likely to be an early feature that leads to ESRF, and this would contribute to the marked increase in the number of new patients with diabetic ESRF in Japan. NIDDM is a serious disease if near-normal glycemia is not achieved.

The number of diabetic patients suffering from end-stage renal failure (ESRF) is increasing worldwide (1). The increase in the incidence of diabetic ESRF, which is occurring at a much higher rate than all other etiologies, is likely due to the increase in the number of patients with NIDDM-related nephropathy (2–5). Japan has the highest number in the world of patients on regular dialysis (1). The progression to ESRF is rapid and relentless once diabetic nephropathy has developed. This is the case not only for IDDM patients but also for NIDDM patients (6,7). Because prevalence of diabetes is increasing and NIDDM patients constitute 95% of the diabetic population worldwide (8), prevention of the development of diabetic nephropathy in NIDDM patients is extremely important for programs aimed at reducing the incidence of diabetic ESRF (2,9).

The incidence of NIDDM is higher in young Japanese than in young Caucasians (10,11). We have identified the existence of early-onset NIDDM patients who develop severe diabetic vascular complications such as blindness or ESRF in their thirties (12). Prevention of such severe complications is of prime importance, especially for young subjects, not only in terms of their quality of life but also for socioeconomic reasons. Diabetic nephropathy in young NIDDM patients is likely to be an early feature that leads to ESRF. However, little information regarding the impact of putative risk factors and their interaction in the development of diabetic nephropathy in NIDDM patients is available (13–16), and no such information on young NIDDM patients is available. The present study was performed to investigate incidence and risk for the development of diabetic nephropathy in early-onset NIDDM patients.

RESEARCH DESIGN AND METHODS

Patients

We performed a clinic-based observational longitudinal study. Patients can visit our outpatient clinic at the Diabetes Center, Tokyo Women's Medical College, without any referrals, and the charge for treatment to the patient is the same as in other hospitals. The percentage of early-onset NIDDM patients (diagnosed before 30 years of age) in a large population of diabetic patients (n = 16,842) and the clinical characteristics of these early-onset NIDDM patients have been reported previously (12). Briefly, out of this large population we identified 1,065 (6.3%) patients with early-onset NIDDM. Of these 1,065 patients, a group that fulfilled the following criteria was recruited for the present morbidity study: *1*) patients first visited the outpatient clinic between 1980 and 1989, *2*) patients had exhibited neither proteinuria nor proliferative retinopathy in the baseline year, and *3*) patients attended the clinic for at least 1 year. A total of 527 patients did not exhibit proteinuria or proliferative retinopathy at first visit, and 101 patients did not continue clinic visits, mainly because they reside outside of the Tokyo area, leaving 426 patients for the follow-up study (Fig. 1).

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Abbreviations: DCCT, Diabetes Control and Complications Trial; ESRF, end-stage renal failure; HPLC, high-performance liquid chromatography.

Measurements

The patients attended the clinic every 1–3 months (an annual mean of 8 visits). The baseline year was established when the patients first visited the clinic without having diabetic nephropathy. Diabetes was diagnosed according to the World Health Organization criteria (17), and NIDDM 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. Patient profiles regarding 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 attended by the patients. Blood pressure was measured using a standard sphygmomanometer and an appropriately sized cuff with the patient in a seated position. Blood pressure measurements were taken on more than four visits during the baseline year, and the average was calculated. Patients were considered hypertensive according to the criteria of the fifth report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (18) if the mean of the measurements was ≥140/90 mmHg or if patients were taking antihypertensive drugs at baseline. Diabetic nephropathy was diagnosed clinically if the following criteria were fulfilled: persistent proteinuria, presence of retinopathy, and no clinical or laboratory evidence of disease other than diabetic nephropathy in the kidneys or renal tract. Proteinuria was measured at each visit using Albustix (Miles-Sankyo, Tokyo) with a detection limit of 300 mg/l, and persistent proteinuria was defined as three of four consecutive tests being positive in the absence of menstruation, urinary tract infection, or other known nondiabetic renal diseases. Onset of proteinuria was defined as the time at which the first positive test was obtained. Ophthalmoscopy with dilated pupils was carried out at least every 6–12 months by ophthalmologists. Background retinopathy was defined as the presence of microaneurysms or dot hemorrhages, and proliferative retinopathy was determined as retinal neovascularization corresponding to ≥60 in the modified Airlie House System.

Data on the history of diabetes 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.

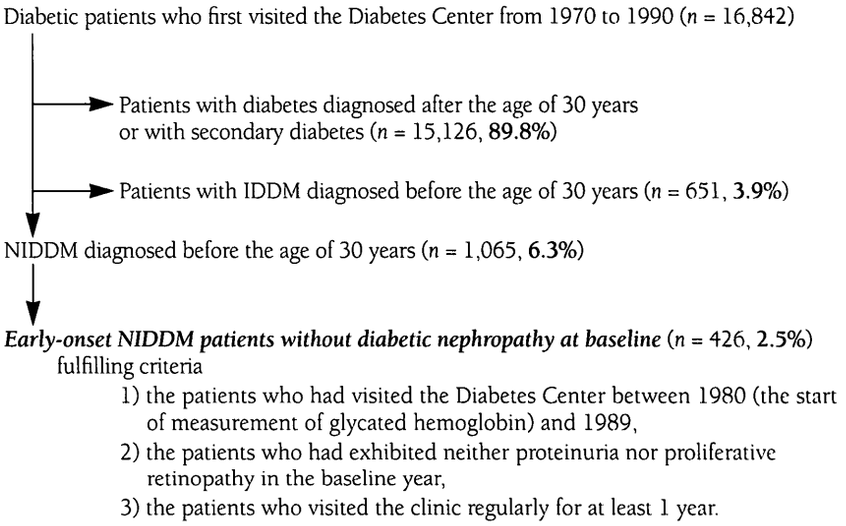

Figure 1—*Patient selection.*

Serum concentrations of total cholesterol, HDL cholesterol, and triglyceride at baseline year were measured by enzymatic colorimetric methods using an automated multianalyzer (7450; Hitachi, Tokyo). Serum C-peptide level was measured in patients who were being treated with insulin using a synthetic human C-peptide kit (C-PEPTIDE RIA; Shionogi, Tokyo) with a detection limit of 0.1 ng/ml. The glycated hemoglobin level was measured every 1–3 months (at least four times a year) by high-performance liquid chromatography (HPLC; HA8110 until 1992 and HA8131 from 1993 on, Kyoto Daiichi Kagaku, Kyoto, Japan). The values obtained by the 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]; $Y = 0.972X - 0.052$, $r = 0.997$) (19). 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.

End points

Patients were followed until the development of diabetic nephropathy or until the last examination (the end of the follow-up was up to March 1997) if they were free of nephropathy.

Statistical analysis

The predictive effect of independent variables on the development of diabetic nephropathy 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 with 95% CIs are given. The time was calculated from the study entry (baseline) to the development of diabetic nephropathy or to the last examination if the patients were free of nephropathy. The incidence density is presented as number per 1,000 person-years based on the ratio of the observed number of patients experiencing the event (development of nephropathy) to the total person-years of exposure (at risk). The 95% CI was computed by a modification of the Mantel-Haenszel procedure for follow-up data (20–22). The relationship between mean HbA_{1c} level during the follow-up period (ordered categorical variables) and the incidence of nephropathy was explored with a χ^2 test for trend (21–23). Differences between relevant groups were tested using the Student's unpaired t test for continuous variables (with non-normally distributed variables first being logarithmically transformed) and the χ^2 test for dichotomized variables. P values under 5% (two-tailed) were taken to indicate statistical significance. All analyses were run on the personal computer statistics package SPSS for Windows version 6.0.

RESULTS

Baseline characteristics of the patients with early-onset NIDDM

Table 1 shows the patients' clinical and biochemical characteristics at baseline. Age at diagnosis, sex, diabetes duration, HbA_{1c}, therapy for diabetes, and proportion of

Table 1—*Baseline clinical and biochemical characteristics of the patients with early-onset NIDDM who participated and those who did not participate in the study*

	Subjects who participated	Subjects who did not participate
n	426	101
Percentage of men (95% CI)	55 (50–60)	53 (44–63)
Age at diagnosis of diabetes (years)	22.6 ± 5.6	23.6 ± 5.3
Age at baseline (years)	27.0 ± 8.2	27.9 ± 8.7
Known diabetes duration at baseline (years)	4.4 ± 6.0	4.3 ± 5.9
Percentage of patients according to therapy for diabetes at baseline (95% CI)		
Diet alone	67 (63–72)	70 (61–79)
Tablets	16 (12–19)	15 (9–23)
Insulin	17 (13–20)	15 (9–23)
HbA_{1c} at baseline (%)	8.4 ± 2.2	8.6 ± 2.5
Mean C-peptide level in insulin users (ng/ml) (95% CI)		
Fasting	1.3 (1.1–1.5)	1.2 (1.0–1.6)
2-h postprandial	2.6 (2.2–3.0)	2.5 (2.1–3.1)
Percentage of patients with background retinopathy (95% CI)	17 (13–20)	12 (6–20)
Percentage of current smokers (95% CI)	31 (26–35)	38 (28–48)
BMI (kg/m^2)	23.2 ± 5.1	25.4 ± 5.2*
Percentage of patients with a family history of diabetes (95% CI)	62 (57–66)	53 (44–63)
Systolic blood pressure at baseline (mmHg)	117 ± 16	121 ± 15†
Diastolic blood pressure at baseline (mmHg)	74 ± 12	76 ± 12†
Percentage of hypertensive patients (95% CI)	15 (11–18)	23 (15–32)
Total cholesterol at baseline (mmol/l)	5.07 ± 1.14	5.24 ± 1.14
HDL cholesterol at baseline (mmol/l)	1.32 ± 0.41	1.16 ± 0.31*
Triglyceride at baseline (mmol/l)‡	1.22 (0.79–2.05)	1.48 (1.00–2.16)†

Data are means ± SD or ‡median (interquartile range), unless otherwise stated. *$P < 0.01$, †$P < 0.05$ vs. subjects who participated. Hypertension was categorized if the mean of three measurements was ≥140/90 mmHg or if patients were taking antihypertensive medication, according to the fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (see METHODS).

background retinopathy and 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, and lower concentration of HDL cholesterol.

Of the patients who participated in the study, the mean duration of diabetes at baseline was 4.4 years. Therapy for glycemic control (95% CI) at baseline was 67% (63–72%) diet, 16% (12–19%) tablets, and 17% (13–20%) insulin. The HbA_{1c} level at baseline was 8.4 ± 2.2%. Six (1.4%) of 63 hypertensive patients (15%) were treated with antihypertensives, including calcium antagonists and methyldopa.

Development of nephropathy

Therapy for glycemic control (95% CI) during the follow-up period was 31% (27–36%) diet, 26% (21–30%) tablets, and 43% (38–48%) insulin. The mean HbA_{1c} level was 7.5 ± 1.9%. During the mean follow-up period of 6.8 (95% CI 6.4–7.2) years (2,908 person-years), 41 patients developed diabetic nephropathy. The incidence density for developing diabetic nephropathy was 14.1 (95% CI 10.4–19.1) per 1,000 person-years. No death was observed before the development of nephropathy. At the end of the follow-up period, mean age was 35.2 ± 9.4 years and mean duration of diabetes was 12.2 ± 6.1 years for the 41 patients who developed nephropathy. Both values were similar to those for the remaining patients at the end of the follow-up period.

Risk analysis for developing nephropathy

Table 2 shows the predictive effect of independent variables on development of diabetic nephropathy. The mean HbA_{1c} level, followed by BMI, diastolic blood pressure, known diabetes duration, systolic blood pressure, and serum concentrations of total cholesterol and triglyceride, had significant predictive effects (Model A). The baseline HbA_{1c}, which was significantly correlated to the mean HbA_{1c} ($r = 0.68$, $P < 0.001$), had a predictive effect ($P = 0.01$; hazard ratio and the 95% CI, 1.21 [1.05–1.40]) less than that of the mean HbA_{1c}. Thus, the mean HbA_{1c} was used for the risk analysis. Other variables, such as sex, age at baseline, and age at diagnosis of diabetes, had no significant effects. Adjustment for mean HbA_{1c} revealed that diastolic blood pressure ($P = 0.003$) and duration of diabetes at baseline ($P = 0.008$) had significant predictive effects, whereas the significance of BMI and serum concentrations of total cholesterol and triglyceride was abolished. Multivariate analysis revealed that mean HbA_{1c} ($P = 0.00001$), diastolic blood pressure ($P = 0.007$), and duration of diabetes ($P = 0.04$) were significant independent predictors of the development of diabetic nephropathy (Model B). Figure 2 indicates the incidence density for the development of diabetic nephropathy according to the stratification of mean HbA_{1c} levels during the follow-up period. Only a few patients developed diabetic nephropathy among those whose mean HbA_{1c} was ≤6.4% (n = 136 [32%]) or 6.5–7.4% (n = 91 [21%]). The incidence of diabetic nephropathy increased with increasing mean HbA_{1c} level in a dose-dependent manner (χ^2 trend = 49.9, df = 1, $P < 0.0001$).

CONCLUSIONS — In this longitudinal study, we performed risk analysis for the development of diabetic nephropathy in early-onset Japanese NIDDM patients. The incidence of diabetic nephropathy increased with increasing mean HbA_{1c} level in a dose-dependent manner. Only a few patients developed nephropathy when the mean HbA_{1c} during a mean follow-up of 6.8 years was ~7% or less. This supports a hypothesis that near-normal glycemia prevents the development of nephropathy. Apart from the effect of metabolic control, we found after adjustment for mean HbA_{1c} that baseline features such as the systemic blood pressure elevation and a longer duration of diabetes were significant independent predictors of diabetic nephropathy in early-onset NIDDM patients aged ~25–30 years. Risk factors such as age at diagnosis or age at baseline, which could contribute to developing nephropathy in young IDDM

Table 2—*Predictive effect of independent variables on development of diabetic nephropathy in early-onset NIDDM patients*

Independent variable	*P* value	Hazard ratio
Model A (univariate analysis)		
Sex (men vs. women)	0.34	1.38 (0.71–2.66)
Age at diagnosis of diabetes	0.85	1.00 (0.95–1.06)
Age at baseline	0.15	1.03 (0.99–1.06)
Duration of diabetes at baseline	0.01	1.04 (1.01–1.07)
Insulin treatment at baseline	0.79	1.11 (0.51–2.40)
BMI	0.003	1.08 (1.03–1.13)
Family history of diabetes	0.34	1.37 (0.71–2.66)
Smoking	0.67	1.15 (0.60–2.22)
Mean HbA_{1c}	0.00001	1.56 (1.34–1.81)
Diastolic blood pressure	0.006	1.04 (1.01–1.06)
Systolic blood pressure	0.02	1.02 (1.00–1.04)
Hypertension	0.06	2.03 (0.97–4.27)
Total cholesterol	0.03	1.01 (1.00–1.01)
HDL cholesterol	0.21	0.99 (0.97–1.01)
Log triglyceride	0.03	2.62 (1.09–6.31)
Model B (multivariate analysis)		
Mean HbA_{1c}	0.00001	1.63 (1.39–1.92)
Diastolic blood pressure	0.007	1.04 (1.01–1.07)
Duration of diabetes at baseline	0.04	1.04 (1.00–1.08)

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

patients (24,25), had no effects in the early-onset NIDDM patients.

The incidence density for developing diabetic nephropathy was 14.1/1,000 person-years (95% CI 10.4–19.1). It indicates that the incidence of diabetic nephropathy is high in early-onset Japanese NIDDM patients, particularly when near-normal glycemia is not achieved. Possible reasons for the high incidence are discussed below.

The finding that longer duration of diabetes at baseline, in addition to higher HbA_{1c} levels during the follow-up, affected the subsequent development of nephropathy is consistent with those of other studies on NIDDM (26–30) and IDDM (31–33). It may support the notion that total lifetime exposure to glycemia is a key function of the risk of complications (34).

Ethnic differences are likely to lead not only to differing incidences of diabetes but also to differing incidences of the accompanying vascular complications. The present study showed that NIDDM occurs as early as the teens in the Japanese population and that the incidence of diabetic nephropathy in early-onset Japanese NIDDM patients is high. Previous reports indicated that the incidence of diabetic nephropathy in NIDDM patients varies considerably depending on race. Minorities, such as African-Americans, Mexican-Americans (2,27,35,36), and Pima Indians (26,30,37), are at higher risk of developing NIDDM-related nephropathy and ESRF than are elderly Caucasian NIDDM patients (28). Nelson et al. (30) investigated incidence of nephropathy in a morbidity study similar to the present design. They showed that of the 456 Pima Indian NIDDM patients aged ~40 years with a mean diabetes duration of 6 years, 20 patients developed overt nephropathy (urinary albumin excretion ≥300 mg/g) during a follow-up of 4.7 years, yielding the incidence density of overt nephropathy of 9.3/1,000 person-years (95% CI 6.0–14.5). The results of the present study may indicate that young Japanese NIDDM patients are at an even higher risk of developing diabetic nephropathy than are the Pima Indian NIDDM patients.

Plausible explanations given for these differences between races were degree of hyperglycemia (26) and differences in blood pressure (27) in addition to the genetic effect per se. To compare the pure effect of ethnic difference on the incidence of nephropathy, assessment of the degree of glycemia in terms of mean HbA_{1c} level during the long-term follow-up period is required. However, no such data are available from these previous studies (2,26–28,30,35,36). The HbA_{1c} values in the present study were obtained through the method standardized by the Japan Diabetes Society and were quite similar to those used in the DCCT (19). The subjects in the present study are comparable with the DCCT cohort (38) with respect to sex (55 vs. 54% men), age (27 vs. 27 years), diabetes duration (5 vs. 8 years), systemic blood pressure levels (117/74 vs. 116/73

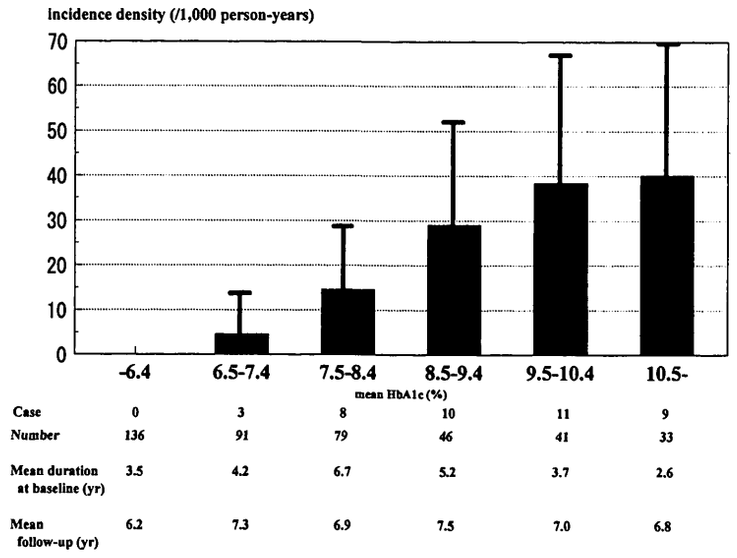

Figure 2—*Incidence density for developing diabetic nephropathy according to the stratification of mean HbA_{1c} levels during the follow-up period. Incidence density (per 1,000 person-years) was calculated by division of number of patients who developed diabetic nephropathy by the observed person-years. Bars indicate 95% CI. Case indicates the number of patients who developed diabetic nephropathy. Number indicates the total number of patients in each range of mean HbA_{1c} level.*

mmHg), lipid profiles (total cholesterol 5.07 vs. 4.63 mmol/l; HDL cholesterol 1.32 vs. 1.27 mmol/l, triglyceride 1.22 vs. 0.98 mmol/l), and observation period (6.8 vs. 6.5 years). True duration of diabetes may be longer than the known duration in NIDDM, but the difference between the two in the present study is presumed to be less than a few years because NIDDM rarely occurs before the age of 15 (11). Therefore, it may be allowed to compare our cohort with the DCCT cohort. The incidence of diabetic nephropathy was 14.0/1,000 person-years (95% CI 9.9–19.8) in patients of the DCCT secondary intervention cohort receiving conventional therapy who exhibited a mean HbA_{1c} level of 9.0%. This incidence is the same as the level of our 426 subjects, including those with near-normal glycemia. Our subjects who had the similar mean HbA_{1c} level of 9.0% exhibited a higher incidence of 29.0/1,000 person-years (25% CI 15.6–53.8) compared with the DCCT cohort. Acknowledging the shortness of the estimated duration at baseline, it still appears that incidence of nephropathy in early-onset Japanese NIDDM patients is high, similar to, or even higher than that in Caucasian IDDM patients of comparable age, implying an ethnicity-related vulnerability to the development of diabetic nephropathy or an effect of difference of diabetes type.

The systemic blood pressure and the serum concentrations of cholesterol and triglyceride, both of which were mostly within the normal range in the young subjects, were associated with an increased risk of development of diabetic nephropathy. The serum concentrations of cholesterol and triglyceride were related to metabolic control, and thus the significance was abolished after adjustment for the mean HbA_{1c} level. A drawback in this study was the lack of information regarding the urinary albumin excretion rate. Slight elevation of albuminuria may have been associated with the poor metabolic control, high blood pressure, and high concentrations of cholesterol and triglyceride. However, the finding that after adjustment, diastolic blood pressure remained predictive of development of nephropathy is in agreement with other studies that have indicated systemic blood pressure elevation to be an independent risk factor for an increase of albuminuria (30,39) and for the progression of diabetic nephropathy (6,15,40). That we found the slight elevation of blood pressure to be significant in the prediction of the development of nephropathy, despite a mean level of 117/74 mmHg, may be due to the fact that the role of blood pressure was not obscured because only a few patients (1%) were treated with antihypertensive medications.

The subjects who participated in this study were selected on the basis of exhibiting no proteinuria at study entry and continuing clinic visits for at least a year, and they had lower risks for nephropathy at baseline in terms of blood pressure and lipid profiles than did those who did not participate. We looked for diabetic nephropathy up until their final visits to the clinic, and no death occurred before developing nephropathy. Therefore, the present result might have been an underestimation of the prevalence of nephropathy in early-onset Japanese NIDDM patients, even if a bias due to referral or patient selection had occurred. Because NIDDM patients are not ketosis-prone and are not necessarily accompanied with symptoms at the diagnosis of NIDDM and because, in contrast, insulin therapy in IDDM patients has been improved using multiple insulin injections, the total lifetime exposure to glycemia could readily become longer in NIDDM patients than in IDDM patients. In addition, young subjects are, as a rule, not concerned about their health condition if they are not suffering any symptoms. Actually, not a few NIDDM patients progress to diabetic ESRF before recognition of the onset of diabetes and/or of the onset of the vascular complications (12). We believe that diabetic nephropathy seen in the NIDDM patients aged in their 30s or 40s is an early feature that leads to ESRF, contributing to the compelling increase in numbers of new patients with diabetic ESRF. Thus, NIDDM appears to be a stronger risk for the development of long-term complications than IDDM in the Japanese population.

In conclusion, early-onset Japanese NIDDM patients are at high risk of developing nephropathy when near-normal glycemia is not achieved. The mean HbA_{1c} level, the diastolic blood pressure, and duration of diabetes were significant predictors of nephropathy. In addition to a lifetime exposure to glycemia as a key function of the risk of nephropathy, ethnicity and type of diabetes may play an important role for the development to diabetic nephropathy.

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