別紙カ

B

現在30歳未満で、20歳未満発症の２型糖尿病患者調査登録用紙

貴施設でのカルテ番号＿＿＿＿＿＿＿＿＿＿（必ず記載お願いします）

該当者 姓＿＿＿＿＿名＿＿＿＿＿（生年月日19＿＿/昭和・平成＿＿年＿＿月＿＿日）
（できるだけお願いします。個人情報の取り扱いには十分に配慮します。）

記載年月日：200＿/平成1＿年＿＿月

記載した先生：医療機関名＿＿＿＿＿病(医)院（＿＿＿科）＿＿＿＿＿先生

以下登録時年所見ならびに過去のことをお聞きします。数値の記入、もしくはあてはまるものに○をして下さい。

尿糖陽性ないし血糖値から２型糖尿病と診断された(されうる)年齢 [　　]歳

1. 登録（同意取得）時年月： 200＿/平成1＿年＿＿月　　学校検尿による発見：なし／あり
2. 過去の最大体重[　　.　]kgとその時の身長[　　.　] cm（ほぼ＿＿歳時）
3. 家族歴に糖尿病が：なし／あり（２型は：父、母、祖母、祖父、姉妹、兄弟　←○で印を）、１型は＿＿＿＿に）
4. 登録時体重[　　.　]kg　身長[　　.　]cm　腹囲[　　.　] cm　血圧[　　/　　] mmHg
5. 登録時血糖:空腹時/随時[　　] mg/dl（登録時IRIがあれば空腹時/随時[　　.　]μU/ml）
   HbA1c[　　.　] %
6. 登録時治療：食事運動のみ／ SU／ﾋﾞｸﾞｱﾅｲﾄﾞ／α-GI／ﾁｱｿﾞﾘｼﾞﾝ／ｸﾞﾘﾆﾄﾞ／インスリン
   ＜薬物治療は使用しているものに丸をしてください。重複可＞
7. ｺﾚｽﾃﾛｰﾙ[　　] mg/dl 中性脂肪 [　　]mg/dl 後頸部黒色表皮症：あり／なし
8. アキレス腱反射：なし／あり／不明
9. 眼底所見：なし／単純性／前増殖性／増殖性
10. 光凝固療法（１眼でも）：なし／あり（初回実施日西暦＿＿＿＿年/平成＿＿年）
    少なくとも１眼が光覚弁以下：なし／あり（決定日西暦＿＿＿＿年/平成＿＿年）
11. Cr[　　.　]mg/dl　ｱﾙﾌﾞﾐﾝ/ｸﾚｱﾁﾆﾝ比(ACR)(尿)＿＿＿mg/gCr
    人工透析：　なし／あり（初回透析日西暦＿＿＿＿年/平成＿＿年）
    腎移植：　なし／あり（移植日西暦＿＿＿＿年/平成＿＿年）
12. 心筋梗塞:なし／あり（初回西暦＿＿＿＿年/平成＿＿年）
    脳梗塞:なし／あり（初回西暦＿＿＿＿年/平成＿＿年）
    壊疽:なし／あり（初回西暦＿＿＿＿年/平成＿＿年）
    指趾切断:なし／あり（初回西暦＿＿＿＿年/平成＿＿年、部位＿＿＿＿）
13. 最終学歴：中学卒 ／ 高校卒 ／ 専門学校卒 ／ 短大卒 ／ 大学卒 ／ 大学院卒
14. 就労状況：あり　なし（学生／主婦／その他）

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Age of onset and type of Japanese younger diabetics in Tokyo

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Summary

The age of onset of diabetes and the type of diabetes were examined in 1408 Japanese patients who were initially diagnosed as having diabetes under the age of 30 and were registered in our Diabetes Center between 1980 and 1989. Of the 1408 patients, 538 (38.2%) had insulin-dependent diabetes mellitus (IDDM) (male/female ratio of 2 : 3), and 870 (61.8%) had non-insulin-dependent diabetes mellitus (NIDDM) (male/female ratio of 5 : 4). There were significant differences of the sex ratio in both IDDM and NIDDM. The age at which the numbers in both the IDDM and NIDDM groups were almost equal was 13–14 (26 for IDDM and 23 for NIDDM at 13; 28 for IDDM and 30 for NIDDM at 14). A total of 58% of IDDM patients (22% of all patients) and only 6% of NIDDM patients (4% of all patients) were diagnosed under the age of 14 ($P < 0.01$). Of the patients with IDDM, 42% (16% of all patients) were diagnosed over the age of 14, as were 94% of NIDDM (58% of all patients). The percentage of NIDDM cases increased even more over the age of 28, and no NIDDM patients developed diabetes under the age of 9.

Key words: Insulin-dependent diabetes mellitus; Non-insulin-dependent diabetes mellitus; Juvenile-onset diabetes mellitus

Introduction

Differences in the frequency of IDDM and NIDDM have been reported between the Western and Asian countries. Many young patients with diabetes have insulin-dependent diabetes mellitus (IDDM), whereas non-insulin-dependent diabetes mellitus (NIDDM) is less common in the younger age groups in the Western countries [1–3]. In Asian countries, there have been only a few reports published about young diabetics [4–8].

Tokyo has a population of 11 770 000, accounting for 10% of the Japanese population in 1988 [9]. More than 1400 patients who were diagnosed as having diabetes under the age of 30 were referred to our department by primary-care practitioners in Tokyo. Therefore, we examined the

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age of onset and the number of younger IDDM and NIDDM patients at our diabetes center in Tokyo.

Patients and Methods

The subjects in this study were 1408 patients under the age of 30, diagnosed as having IDDM or NIDDM from 1980 to 1989. The type of diabetes was assessed 3 years after the patients had been diagnosed as having diabetes, and was classified in the following manner. The mode of onset, tendency to ketosis, dose of insulin, and blood and urine C-peptide values were taken into account in addition to the WHO diagnostic criteria to classify these patients [10]. Patients with secondary diabetes and unclassifiable diabetes were excluded.

The age when diabetic symptoms or signs first occurred, or when hyperglycemia was proven even without symptoms or signs, was taken as the age of onset.

Statistical analysis was performed using the Chi-squared test. Data on 25555000 Japanese males and 24422000 Japanese females under the age of 30 in 1988 were used to compare the sex ratio of both IDDM and NIDDM patients [9].

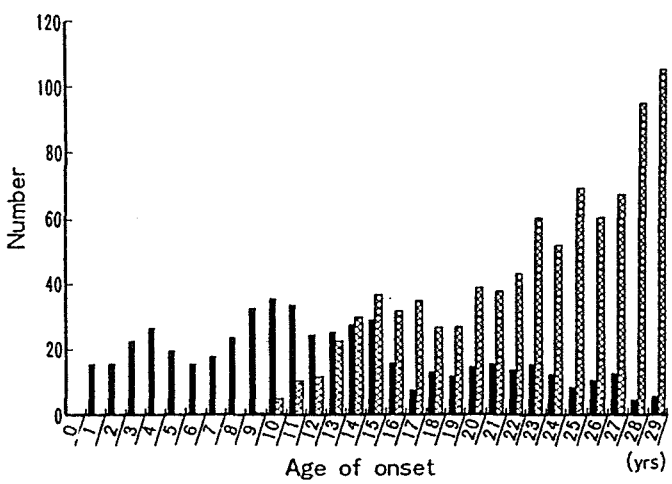

Fig. 1. Age of onset and type of diabetes among 1408 Japanese patients with the onset of diabetes under the age of 30. Solid bar, IDDM (n = 538); cross-hatched bar, NIDDM (n = 870).

Results

Of the 1408 subjects registered from 1980 to 1989, 538 (38.2%) had IDDM and 870 (61.8%) had NIDDM. The IDDM patients consisted of 209 males and 329 females (male/female ratio of 2 : 3), whereas the NIDDM patients consisted of 483 males and 387 females (male/female ratio of 5 : 4). There were significant differences in the sex ratio in both the IDDM group ($P < 0.01$) and NIDDM group ($P < 0.05$) compared with the sex ratio in the general population.

The age of onset for all patients are shown in Fig. 1. The number in each group was very similar

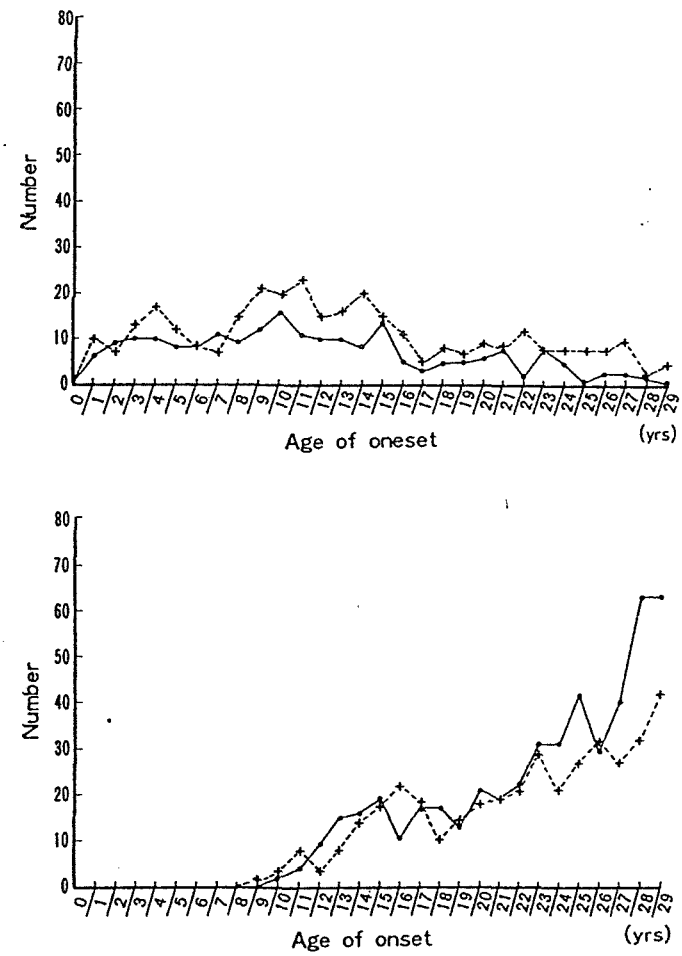

Fig. 2. Top panel, the number of Japanese patients with insulin-dependent diabetes mellitus in relation between age at diagnosis and sex. The solid line shows males (n = 209) and the broken line shows females (n = 329). Bottom panel, the number of Japanese patients with non-insulin-dependent diabetes mellitus in relation between age at diagnosis and sex. The solid line shows males (n = 483) and the broken line shows females (n = 387).

at the ages of 13–14 (26 for IDDM and 23 for NIDDM at 13; 28 for IDDM and 30 for NIDDM at 14). Of the patients with IDDM, 41.6% (15.9% of all patients) were diagnosed over the age of 14, as were 93.9% of NIDDM (58.0% of all patients). Of the IDDM patients, 58.4% (22.3% of all the patients) were diagnosed under the age of 14, and the peak age for IDDM was 10. In contrast, only 6.1% of NIDDM patients (3.8% of all the patients) were diagnosed under the age of 14 ($P < 0.01$). Over the age of 28, the percentage of NIDDM cases increased even more. None of the NIDDM patients developed diabetes under the age of 9.

Fig. 2A and B show the sex distribution of the patients in each age group. The number of female IDDM patients was generally greater than the number of male IDDM patients, while there were generally more male than female NIDDM patients. In addition, the number of male NIDDM patients showed a sudden increase over the age of 27.

Discussion

This study examined the age of onset of diabetes and the type of diabetes in young patients attending our diabetes center. Of the 1408 Japanese patients under the age of 30 in this study, 538 (38.2%) had IDDM and 870 (61.8%) had NIDDM. Another Japanese study on 67 young patients with diabetes in Tochigi prefecture also found that 40% had IDDM and 60% had NIDDM [4]. A study in southern California showed that there were racial differences in the incidence of IDDM, with a large number of cases occurring among Caucasians and only a few cases among Mexicans, Blacks and Orientals [11], although more than 90% of the younger diabetics were reported to have IDDM in Western countries [1–3]. Ramachandran et al. reported that in South India 22% of the younger diabetics had IDDM and 57.7% had NIDDM [8]. Thus, the Japanese younger diabetics are characteristic of younger Oriental diabetics.

In reports from England and Wales, the F.R.G., and Finland [2,3,12], the majority of patients developing diabetes under the age of 25 were in the IDDM group, while more patients over the age of 40 had NIDDM. Our study showed that 22.3% of all the patients with diabetes under 13 were diagnosed as having IDDM, the number of cases of IDDM and NIDDM was equal at 13–14, and 93.9% of all patients over the age of 14 were diagnosed as having NIDDM. The pattern of the age of onset in the Japanese diabetic patients was markedly different from that reported in European countries. The differences in the IDDM/NIDDM ratio and the onset-age patterns in IDDM and NIDDM in our study suggest that racial differences influence the prevalence of each type of diabetes in younger patients with this disease, as was indicated in the report from southern California [11].

Apparently 'racial' differences in the pattern of diabetes might stem not only from genetic factors but also from environmental factors. Among genetic factors, a consistent association has been found between IDDM and HLA DR3 and DR4, and this association has also been noted in all Asian populations thus far examined [13–17]. However, frequencies of the DR3 and DR4 haplotypes in the general population also vary among racial groups and tend to be higher in Western countries and lower in non-Caucasian countries [18]. The lower frequency of individuals carrying such haplotypes in non-Caucasian populations may result in a lower incidence of IDDM. Further studies including environmental factors are needed to clarify the racial differences in the incidence of IDDM in the Japanese and Caucasian populations.

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文献2

Increased Incidence of Non-Insulin Dependent Diabetes Mellitus Among Japanese Schoolchildren Correlates with an Increased Intake of Animal Protein and Fat

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Tatsuhiko Urakami, MD[1]
Kuniaki Yamauchi[2]

Summary: Non-insulin dependent diabetes (NIDDM) was diagnosed in 188 of more than 7 million Tokyo schoolchildren tested between 1974 and 1994 for glycosuria followed by oral glucose tolerance testing. The incidence rate of NIDDM in youth has continued to increase since 1976. While the daily energy intake has not changed significantly, the consumption of animal protein and fat by the Japanese population has greatly increased during the past two decades, and this change in diet, with low levels of physical activity, may exacerbate insulin resistance and glucose intolerance. *Clin Pediatr.* 1998;37:111-116

Introduction

A traditional Japanese diet consists of rice, fish, soybean products, and green vegetables. Since 1955 western influences have penetrated Japanese daily life, bringing important changes to the Japanese diet and contributing to increases in the incidence of obesity, noninsulin dependent diabetes mellitus (NIDDM), and cardiovascular diseases.[1] However, reliable data concerning trends in the onset of NIDDM in children in relation to changes in dietary habits are not available.

Since 1973, a program of screening for hematuria and proteinuria in schoolchildren has been conducted by the Ministry of Education, Science and Culture in order to achieve early detection and management of chronic renal disease.[2] Since 1974, the collected urine has also been tested for glucose by our group to detect diabetes mellitus at an asymptomatic stage,[3] and we annually diagnose two to 15 cases of NIDDM in children less than 15 years of age.

This report presents the secular trends of childhood NIDDM in relation to the prevalence of obesity and changes in dietary habits in Japan.

Materials and Methods

From 1974 through 1995, 221,000 to 386,400 Tokyo schoolchildren were tested annually for glycosuria by glucose oxidase tapes to detect diabetes. Subjects collected morning urine at home in a small plastic bottle that was transferred to a screening laboratory by the school. If the first test was positive, glycosuria was confirmed in these children with an oral glucose tolerance test (OGTT) using 1.75 g/kg (maxi-

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mum 75 g). Diagnosis of diabetes was based on the WHO[4] or the United States Public Health Service diagnostic criteria.[5]

NIDDM children with low fasting blood glucose levels usually displayed a high insulin response to OGTT. Slow-onset IDDM detected by screening for glycosuria was, however, always associated with a minimal serum immunoreactive insulin (IRI) response to an OGTT.[6] In some patients, however, detection of serum islet cell antibodies (ICA) with several months' observation of glucose intolerance and pancreatic β-cell function were required to distinguish between IDDM and NIDDM. Children with IDDM detected by urine screening were usually positive for ICA or glutamic acid decarboxylase (GAD) antibodies in the serum and failed to show improvement in glucose tolerance in spite of strict dietary control and physical exercise; they also usually required insulin within 24 months of diagnosis. Some children diagnosed with NIDDM initially required insulin to achieve better glycemic control, but the time when insulin became necessary was often more than 2 years after diagnosis, and they were typically negative for ICA and GAD antibodies.

IRI or C-peptide immunoreactivity (CPR) was determined 2 hours postprandially and was measured in order to estimate the residual pancreatic β-cell function. Blood glucose and HbA_1C were measured by standard methods. IRI and CPR were measured by the double antibody procedure. Human leukocyte antigen (HLA) typing was performed by a standard microcytotoxicity test.[6] ICA were measured by an indirect immunofluorescence technique on a cryostat section of human blood group O pancreas.[7] GAD antibodies were detected by a radioimmuneassay using the Anti GAD Hoechst Kit.[8]

The prevalence of obesity in the primary and junior high school population of the Kanto area, including metropolitan Tokyo, was obtained from the School Health Statistics. The definition of obesity in our study is body weight more than 20% above the age- and height-matched ideal weight. The secular trends of nutrition in Japan are quoted from The National Nutrition Survey in Japan, which has conducted annual nutritional surveys of the nutritional status of the Japanese since 1946.

Results

From 1974 through 1995, NIDDM was diagnosed in 33 of 4,696,348 primary schoolchildren and 155 of 2,326,964 junior high school children in Tokyo who were examined for glycosuria. The male-to-female ratio was 1.0:2.1 and 1.0:1.2, respectively, in the primary and junior high school children.

The secular trends of NIDDM were estimated from the data of glucose-positive subjects who were reexamined and tested for glucose tolerance. During the periods 1976 to 1980, 1981 to 1985, and 1991 to 1995, the incidence of newly diagnosed NIDDM in primary schoolchildren was 0.2, 1.6, and 2.0, and in junior high school children was 7.3, 12.1, and 13.9 per 100,000 per year, respectively.

Table 1 and Figure 1 show the relationship between the secular

Table 1

SECULAR TRENDS IN DAILY NUTRIENT INTAKE IN JAPANESE

	1955	1965	1970	1975	1980	1985	1990	1995
Total energy (Kcal/day)	2,104	2,184	2,210	2,226	2,119	2,088	2,026	2,042
Protein intake (g/day)	69.7	71.3	77.6	81.0	78.7	79.0	78.7	81.5
Animal protein intake (g/day)	22.3	28.5	34.2	38.9	39.2	40.1	41.4	44.4
Total fat intake (g/day)	20.3	36.0	46.5	55.2	55.6	56.9	56.9	59.9
Animal fat intake (g/day)	6.5	14.3		26.2	26.9	27.6	27.5	29.8

Secular trends of daily nutrient intake are quoted from the National Nutrition Survey.

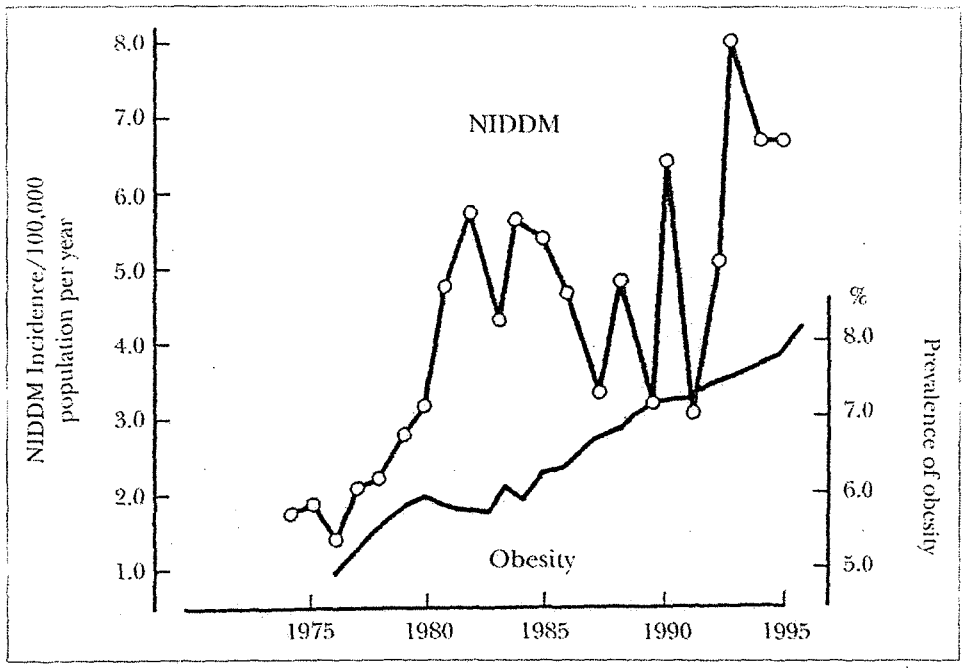

Figure 1. Yearly changes in NIDDM incidence and obesity prevalence in Japanese school children. The secular trends of NIDDM were estimated from the data of glycosuria screening in Tokyo school children. The prevalence of obesity in school children of the Kanto area, including metropolitan Tokyo, was obtained from the School Health Statistics.

trends of NIDDM and yearly changes in the dietary habits of the Japanese. While daily energy intake per capita (mean value of 2,026–2,226 Kcal/day) has not changed, intake of animal fat and total fat increased 4.0 and 2.7 times, respectively, between 1955 and 1975. In addition, the intake of eggs, meat, and milk, including dairy products, increased approximately 3.6, 5.4, and 7.3 times, respectively, between 1955 and 1975. Since 1975, animal fat and protein in the diet have not increased significantly. Although there was a difference of 10 years between the increase in the incidence of NIDDM and increased consumption of animal fat and protein, the pattern of the secular trends of NIDDM and pattern of change in diet among the Japanese are similar.

The yearly increase in NIDDM incidence in schoolchildren seems more closely related to the increase in animal fat and protein consumption than to an increase in energy intake or the prevalence of obesity. As shown in Table 2, NIDDM is more common in nonobese female patients than in nonobese males but is more common in severely obese males than females.

NIDDM was known in first-degree relatives in 36% (65/180) of patients and in first- and second-degree relatives in 53% of patients. No significant difference was found between frequencies of familial NIDDM in male vs female patients.

Discussion

In 1983 we reported that in Japan the incidence and prevalence of NIDDM in youth is higher than the incidence and prevalence of IDDM.[9] This report notes increasing incidence rates since then (Figure 1). A similar increase of NIDDM in Hispanic-American youths and youths from other ethnic groups has been reported.[10-12] The increase in the prevalence of this disorder in adults is thought to be related to dietary changes and the increasing prevalence of obesity. There are no reliable data, however, concerning the cause for the increase of NIDDM in Japanese children.

The secular trends of NIDDM in Japanese schoolchildren were

Table 2

DISTRIBUTION OF OBESITY RATE IN MALE AND FEMALE PATIENTS

Obesity rate*	Males (%)	Females (%)	Total (%)
~19.9	5 (6.4)	25 (24.3)	30 (16.6)
20.0~39.9	20 (25.6)	42 (40.8)	62 (34.3)
40.0~59.9	27 (34.6)	21 (20.3)	48 (26.5)
60.0~	26 (33.3)	15 (14.6)	41 (22.6)
Total	78 (99.9)	103 (100.0)	181 (100.0)

*Obesity rate (%) = $\frac{\text{weight} - \text{age- and height-matched idea weight}}{\text{age- and height-matched ideal weight}} \times 100$

similar to the patterns of increased consumption of animal fat and protein in the diet during the period 1955 to 1975.

It is known that administration of amino acids such as arginine, leucine, or histidine and the intake of meat such as beef produce an increase in insulin release.[13] The intake of foods containing saturated fatty acids induces insulin resistance and an increased insulin response to oral glucose tolerance.[14] Therefore, the increase in NIDDM incidence in Japanese children during the last two decades may be related to the increase in the consumption of animal protein and fat, which may help accelerate insulin resistance. Since 1975, the prevalence of obesity in schoolchildren has been increasing in spite of the absence of significant changes in total energy intake and nutrient consumption. This increase in obesity may be related to physical inactivity in Japanese schoolchildren.

Glaser et al[11] reported a high prevalence rate of NIDDM in Mexican or Mexican-American children, and 67% of those affected have a history of NIDDM in first-degree relatives. In our study, 36% of the patients have a history of NIDDM in first-degree relatives, which is lower than that reported in Mexican-American children with NIDDM.

NIDDM in nonobese children with a slightly impaired insulin secretion is more common in females than in males. The distribution of age at diagnosis shows a peak at puberty with a slightly earlier peak in females.[15] The prevalence ratio in males to females is 1.0:1.3. These results suggest that puberty accelerates preexisting glucose intolerance[16] and that this phenomenon is more pronounced in females.

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文献3

Annual Incidence and Clinical Characteristics of Type 2 Diabetes in Children as Detected by Urine Glucose Screening in the Tokyo Metropolitan Area

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OBJECTIVE — This study investigates the annual incidence and clinical characteristics of type 2 diabetes among school-aged children as detected by urine glucose screening from 1974 to 2002 in the Tokyo metropolitan area.

RESEARCH DESIGN AND METHODS — In total, 8,812,356 school children were examined for glucosuria. Morning urine was used for the analysis. When the urine was positive for glucose, an oral glucose tolerance test was carried out to confirm diabetes.

RESULTS — In all, 232 students were identified to have type 2 diabetes. The overall annual incidence of type 2 diabetes was 2.63/100,000. The annual incidence after 1981 was significantly higher than that before 1980 (1.73 vs. 2.76/100,000, $P < 0.0001$). The annual incidence was significantly higher for junior high school students compared with primary school students (0.78 vs. 6.43/100,000, $P < 0.0001$). The overall male-to-female ratio of students with type 2 diabetes was 1.0:1.19 ($P = 0.296$), but it was 1.0:1.56 ($P = 0.278$) for primary school students. Overall, 83.4% of children with diabetes were obese (≥20% overweight). However, nonobese girls (<20% overweight) with diabetes accounted for 23.0% of the patients, whereas markedly obese boys (≥40% overweight) accounted for 61.5% of the patients. The frequency of a family history of type 2 diabetes in second- and first-degree relatives was 56.5%.

CONCLUSIONS — We confirmed that the incidence of young people with type 2 diabetes increased after 1981 in the Tokyo metropolitan area. The increase in the frequency of this disorder seemed to be strongly related to an increasing prevalence of obesity. Age and genetic susceptibility may be associated with the occurrence of type 2 diabetes.

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Information about the epidemiology of type 2 diabetes in children and adolescents is limited because of the relatively recent recognition of its importance in this age-group. Accumulated evidence suggests that the number of children with type 2 diabetes has increased in recent years and continues to do so in the U.S. (1–6). Currently, approximately one-third of all children and adolescents in Ohio and Arkansas and one-third of Hispanic children in California have type 2 diabetes (1). It is noteworthy that several racial and ethnic groups, such as the Pima Indians (7), Navajo Indians (8), people from the Arab Emirates living in the U.S. (9), Cree-Ojibway aborigines in Canada (10), an indigenous population in Australia (11), and Asian populations (12–14) are reported to be at a particularly high risk of developing type 2 diabetes.

In Japan, we previously demonstrated that from 1974 to 1995, the annual incidence of childhood type 2 diabetes was estimated at ~3–5/100,000 school children in the Tokyo metropolitan area, as detected by urine glucose screening (15). A similar trend was noted in the cities of Yokohama and Osaka (16). Several studies have indicated that the possible explanations for the emergence of type 2 diabetes in children and adolescents are the increased rate of obesity and decreasing physical activity in this age-group (1–6). Some environmental factors and genetic susceptibility may also be associated with the development of type 2 diabetes (1–6,15).

Since 1973, a program involving screening of primary school children and junior high school children for hematuria and proteinuria using a morning urine specimen has been conducted by the Ministry of Education, Science, and Culture for an early detection of chronic renal disease (17). Since 1974, the collected urine has also been tested for glucose to detect childhood diabetes, and we have detected a number of school children with type 1 and type 2 diabetes with minimal or no symptoms at the early stage of the disease (18).

In the present study, we investigated the annual incidence and the clinical characteristics of childhood type 2 diabe-

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Abbreviations: OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

tes detected by the urine glucose screening program from 1974 to 2002 in the Tokyo metropolitan area.

RESEARCH DESIGN AND METHODS

The study subjects were diagnosed as having diabetes by a urine glucose screening program. We have annually screened primary school children aged 6–12 years and junior high school children aged 13–15 years residing in the Tokyo metropolitan area for glucosuria concomitant with proteinuria and hematuria since 1974. The annual participation rate in the urine test was almost 100%. Urinalysis was carried out using glucose oxidase tapes in a morning urine specimen. If a urine test was positive (urine glucose ≥100 mg/dl), a subsequent urine test was requested on another morning. An oral glucose tolerance test (OGTT) was performed when positive results were obtained on both the initial and the second urine tests to confirm diabetes. For the OGTT, 1.75 g/kg (maximum 75 g) of glucose was used and the U.S. Public Health Service criteria (19) and/or World Health Organization criteria (20–23) for the diagnosis of glucose intolerance were followed.

In all, ~30–60% of the subjects who showed positive results for urine glucose in the first and second screening test and exhibited normal glucose tolerance by OGTT were considered to have renal glucosuria. They had no symptoms of diabetes, and some of them had a family history of renal glucosuria. After the diagnosis of renal glucosuria, we followed them and confirmed that they never developed diabetes. Renal glucosuria is an isolated disorder of proximal tubular glucose transport, characterized by abnormal urinary excretion in the presence of normal glucose levels. Marble (24) defined renal glucosuria as a condition characterized by normal fasting blood glucose level, normal glucose tolerance as assessed by an OGTT, and a daily urinary glucose excretion of 10–100 g. Laurence (25) defined this condition as the existence of glucosuria with normal glucose tolerance as assessed by an OGTT, regardless of the presence of glucosuria in the fasting state. The subjects who fulfilled Marble's criteria were few. However, Desjeux (26) reported that about 60% of the subjects with positive results for urine glucose were diagnosed as having renal glucosuria in accordance with the criteria proposed by Laurence. Our finding with respect to the prevalence of renal glucosuria in the screening is in accord with this result.

In general, children diagnosed with type 2 diabetes by the screening test showed minimal or no symptoms of diabetes and displayed a high insulin response to an OGTT at diagnosis (18). However, some patients (~5%) showed severe symptoms of the disease (such as ketosis at diagnosis) and low insulin secretion because of glucose toxicity. All the patients diagnosed with type 2 diabetes were negative for diabetes-related autoantibodies. On the other hand, we have also detected a small number of children with type 1 diabetes by the screening program. They showed low levels of serum insulin from the time of diagnosis. All the patients initially showed neither severe symptoms nor ketosis but they required insulin therapy for glycemic control and to prevent ketoacidosis from the time of diagnosis or within 15 months after diagnosis. All of these patients were nonobese at diagnosis. More than 80% of the children were positive for diabetes-related autoantibodies at the time of diagnosis. This novel subtype of diabetes is recognized as a slowly progressing form of type 1 diabetes (18,27).

To evaluate obesity in children and adolescents, percent overweight is commonly used in Japan as an index instead of BMI. Percent overweight is calculated based on the age- and height-matched ideal weight as (current weight − age- and height-matched ideal weight)/(age- and height-matched ideal weight) × 100%. Patients whose percent overweight is ≥20.0% are classified as obese (28).

To detect diabetes-related autoantibodies including islet cell antibodies, anti-GAD antibodies, and insulin autoantibodies, serum samples were collected from the patients at the time of diagnosis and stored at −70°C until the determinations were performed. Islet cell antibodies were detected by the indirect immunofluorescence method (27). Anti-GAD antibodies and insulin antibodies were measured by radioimmunoassay.

Statistical analysis

Frequency was analyzed using Fisher's exact probability test to detect differences among the groups. $P < 0.05$ was considered significant.

RESULTS

From 1974 to 2002, we annually screened 220,622–386,398 school children residing in the Tokyo metropolitan area. The number of school children screened started to decline in 1990 because of the decreased birth rate in this area. A total of 8,812,356 school children (5,918,758 primary school children and 2,893,598 junior high school children) were examined for glucosuria using a morning urine specimen. Type 2 diabetes was diagnosed in a total of 232 school children (106 male and 126 female). The overall male-to-female ratio was 1.0:1.19, and there was no significant predominance in sex ($P = 0.296$).

Table 1 shows the annual number and incidence of childhood type 2 diabetes from 1974 to 2002. We have annually diagnosed type 2 diabetes in 3–13 children in this screening program. The overall annual incidence of type 2 diabetes during the 29-year period was 2.63/100,000.

We compared the incidence of type 2 diabetes every 5 years from 1974 to 2002. The annual incidences of type 2 diabetes were 1.73, 3.23, 3.05, 2.90, and 2.46/100,000 in 1974–1980, 1981–1985, 1986–1990, 1991–1995, and 1996–2002, respectively. The incidence from 1981–1990 was significantly higher than that in 1974–1980 (1981–1985, $P = 0.0038$; 1986–1990, $P = 0.0091$; 1991–1995, $P = 0.0226$). There was no significant difference in the incidence of type 2 diabetes between 1996 and 2002 and 1974 and 1980 ($P = 0.1182$). The average annual incidence after 1981 (2.76/100,000) was significantly higher than the incidence in 1974–1980 (1.73/100,000; $P < 0.0001$). There was no statistical change in the incidence of type 2 diabetes from 1981 to 2002.

The annual number and incidence of type 2 diabetes in primary school and junior high school students from 1974 to 2002 is shown in Table 1. Of the 232 children with type 2 diabetes detected by the screening system, 46 (19.8%) were primary school students and 186 (80.2%) were junior high school students. The annual incidences of type 2 diabetes in primary school and junior high school students were 0.78/100,000 and 6.43/100,000, respectively. Junior high school students showed a significantly high incidence of type 2 diabetes compared with primary school children ($P < 0.0001$).

Table 2 shows yearly changes in the

Table 1—*Annual number and frequency of type 2 diabetes detected by the urine glucose screening program in the Tokyo metropolitan area from 1974–2002*

Year	School students examined (*n*)	Type 2 diabetes (*n*)	Frequency of type 2 diabetes/10^5	PSC examined (*n*)	Type 2 diabetes in PSC	Frequency in PSC/10^5	JHSC examined (*n*)	Type 2 diabetes in JHSC	Frequency in JHSC/10^5
1974	220,622	6	2.72	157,492	0	0	63,130	6	9.5
1975	225,089	3	1.33	160,609	0	0	64,480	3	4.65
1976	228,104	4	1.75	162,637	1	0.61	65,467	3	4.58
1977	343,146	3	0.87	242,740	0	0	100,406	3	2.99
1978	359,086	6	1.67	252,026	1	0.4	107,060	5	4.67
1979	362,766	7	1.93	256,761	1	0.39	106,005	6	5.66
1980	338,090	7	2.07	234,536	1	0.43	103,554	6	5.79
1981	386,398	12	3.11	264,266	2	0.76	122,132	10	8.19
1982	381,508	13	3.41	254,697	3	1.18	126,811	10	7.89
1983	367,220	10	2.72	241,793	2	0.83	125,427	8	6.38
1984	352,744	11	3.12	228,851	1	0.44	123,893	10	8.07
1985	340,059	13	3.82	214,655	3	1.4	125,404	10	7.97
1986	339,624	13	3.83	210,563	1	0.47	129,061	12	9.3
1987	345,284	7	2.03	213,617	0	0	131,667	7	5.32
1988	328,400	11	3.35	205,669	4	1.94	122,731	7	5.7
1989	319,717	6	1.88	204,940	1	0.49	114,777	5	4.36
1990	303,994	13	4.28	197,725	2	1.01	106,269	11	10.35
1991	319,457	4	1.25	210,832	0	0	108,625	4	3.68
1992	307,855	8	2.6	204,306	2	0.98	103,549	6	5.79
1993	295,049	12	4.07	198,283	2	1.01	96,766	10	10.33
1994	284,468	9	3.16	192,697	2	1.04	91,771	7	7.63
1995	274,732	10	3.64	186,653	2	1.07	88,079	8	9.08
1996	278,839	4	1.43	188,782	2	1.06	90,057	2	2.22
1997	263,928	9	3.41	178,134	2	1.12	85,794	7	8.16
1998	257,464	9	3.5	174,119	4	2.35	83,345	5	6
1999	250,432	7	2.8	170,539	3	1.76	79,893	4	5
2000	245,893	6	2.44	168,625	2	1.19	77,268	4	5.18
2001	249,455	4	1.6	172,505	1	0.58	76,950	3	3.9
2002	242,933	5	2.06	169,706	1	0.59	73,227	4	5.46
Total	8,812,356	232	2.63	5,918,758	46	0.78	2,893,598	186	6.43

PSC, primary school children; JHSC, junior high school children.

patient numbers and ratio of primary school children and junior high school children having type 2 diabetes every 5 years from 1974 to 2002. The ratio of primary school children with diabetes before 1995 was <20.0%. However, it exceeded 30.0% in 1996–2002 and from 1996 to 2002 it was significantly higher than that from 1974 to 1980 (34.1 vs. 11.1%, $P = 0.019$). The male-to-female ratio in primary school students was 1.0:1.56 ($P = 0.278$) and 1.0:1.10 ($P = 0.654$) in junior high school students.

Table 3 shows the distribution of the percent overweight in children with type 2 diabetes. In all, 83.6% of children with diabetes were ≥20.0% overweight and were judged to be obese. Of the girls, 23.0% were <20.0% overweight and thus were considered nonobese. Only 8.5% of boys were nonobese. Severe obesity, defined as ≥40.0% overweight, was more frequent in boys (65.1%) than in girls (48.7%). The percentages of subjects who were 40.0–60.0% overweight (28.3%) and ≥60.0% overweight (36.8%) were significantly higher than the percentages of subjects <20.0% overweight (8.5%) ($P = 0.0059$ and $P < 0.0001$, respectively).

Regarding first-degree relatives, 39.2% of the diabetic children had a family history of type 2 diabetes. When considering second- and first-degree relatives, 56.5% had a family history of type 2 diabetes. In all, 35.0% of the diabetic boys and 42.9% of the diabetic girls had first-degree relatives with type 2 diabetes, whereas 51.9% of the diabetic boys and 60.3% of the diabetic girls had second- and first-degree relatives with type 2 diabetes. There was no significant difference in the frequency of family history of type 2 diabetes between males and females.

CONCLUSIONS — Several recent studies have indicated that type 2 diabetes is becoming an increasingly prevalent disorder in young people all over the world (1–3). The estimated prevalence of type 2 diabetes among American children and adolescents younger than 19 years is 1.0–50.9/1,000 (2). Pima Indians, American Indians, Hispanics, and African Americans are reported to show a higher prevalence of childhood type 2 diabetes compared with whites in the U.S. (2,4–6). Young Asian people are also considered to be at a considerable risk of

Table 2—*Yearly changes in the patient ratio every 5 years from 1974 to 2002 in primary school children and junior high school children with type 2 diabetes*

Year	*n*	Primary school children	Junior high school children
1974–1980	36	4 (11.1)*	32 (88.9)
1981–1985	59	11 (18.6)	48 (81.4)
1986–1990	50	8 (16.0)	42 (84.0)
1991–1995	43	8 (18.6)	35 (81.4)
1996–2002	44	15 (34.1)*	29 (65.9)
Total	232	46 (19.8)	186 (80.2)

Data are *n* (%). *P = 0.019, percentage of primary school children in 1974–1980 vs. 1996–2002.

developing type 2 diabetes. A 10-country study done in Asia showed that ~10% of children with diabetes attending major pediatric centers had type 2 diabetes (29). The incidence of type 2 diabetes increased from 5% in 1986–1995 to 17.9% in 1986–1999 among children and adolescents in Thailand with newly diagnosed diabetes (13). The annual incidence of childhood type 2 diabetes is estimated at 4–7/100,000 in Taiwan as detected by urine glucose screening (14). The number of children with type 2 diabetes may be underestimated in these Asian countries because of difficulties in research, underdiagnosis, and misclassification of type 2 diabetes by pediatric endocrinologists (3,29).

In the present study, we investigated the annual incidence of type 2 diabetes in children aged 6–15 years in the Tokyo metropolitan area from 1974 to 2002 by urine glucose screening at school. We confirmed that the overall annual incidence of childhood type 2 diabetes during the past 29 years in Tokyo was 2.63/100,000 and the incidence from 1981 to 1995 was significantly higher than that from 1974 to 1980. There was no significant increase and change in the incidence of childhood type 2 diabetes in Tokyo since 1981.

We have also detected children with type 1 diabetes who show a slowly progressing form of the disease (18,27) through this screening program. In total, 46 students with type 1 diabetes were detected with minimum symptoms of the disease, and the overall annual incidence of this form of diabetes was 0.52/100,000. Consequently, type 2 diabetes was more frequently detected than type 1 diabetes ($P < 0.0001$). There was no significant change in the incidence of type 1 diabetes detected by the screening program. The annual incidence of type 1 diabetes, including abrupt and slowly progressing forms, in Japanese children has been reported to be almost 2/100,000 (30,31). Therefore, the incidence of type 2 diabetes is considered to be higher than that of type 1 diabetes among Japanese children.

Several studies have indicated that the increase in childhood type 2 diabetes is a result of the increased frequency of obesity in young people (1–3). Insulin resistance originates from obesity, and it is related to glucose intolerance and development of diabetes (32). In the present study, we found that >80% of children with type 2 diabetes are obese. The prevalence of obesity in Japanese school children has increased in the past 20–30 years. The frequency of obese Japanese school students in 2000 was approximately three times higher than that in 1970 (33). Currently ~10% of Japanese school children are obese (33). Since the 1970s, lifestyle and eating habits of the Japanese, especially those of children, have become Westernized (33). A reduction in energy expenditure due to a decrease in physical exercise associated with a prolongation of television viewing is a possible contributor to the increasing rate of obesity in Japanese children (34). Increased intake of animal protein and fat in recent years may correlate with the increase in the prevalence of obesity and the incidence of type 2 diabetes among Japanese school children (15). The yearly increase in the prevalence of obesity since 1980 in school children of the Kanto area, including the Tokyo metropolitan area, is possibly related to the increase in the incidence of childhood type 2 diabetes (15,34).

In the present study, the majority of children with diabetes were junior high school students with a usual pubertal age of 13–15 years. Puberty is considered to be an important risk factor leading to glucose intolerance. Insulin sensitivity decreases by ~30% during puberty, and it is associated with a compensatory increase in insulin secretion (35,36). The peak age of pediatric patients at diagnosis of type 2 diabetes is between 12 and 16 years (2). On the other hand, we found that the incidence of type 2 diabetes in primary school children tended to increase in recent years. Most primary school children in whom type 2 diabetes was diagnosed were 10–12 years old and obese. Obese children tend to enter puberty at a younger age. The recent increase in the percentage of primary school students with diabetes may be influenced by the early occurrence of puberty.

It is interesting to note that among Japanese children with type 2 diabetes, the girls more commonly had a normal weight, whereas the boys were more frequently markedly obese. In the case of Japanese junior high school students, the prevalence of obesity increased regardless of sex, but boys showed a higher prevalence of obesity than girls (7.6 vs. 7.6% in 1989–1990, 12.3 vs. 10.8% in 2001–2002) (37). The risk of developing type 2 diabetes due to obesity was much higher in men than in women in a Japanese adult population–based study (38). Poor eating habits, which are notable in older boys and adult men, may be one of the reasons for the high frequency of type 2 diabetes in men (37,38). On the other hand, most of the studies in children indicate a higher frequency of type 2 diabetes in girls (2). Rosenbloom et al. (1) reported that girls were 1.7 times more likely to have type 2 diabetes than boys. Femininity may play an important role in the development of type 2 diabetes, which excludes insulin resistance associated with obesity.

We demonstrated a high frequency of type 2 diabetes among Japanese children with a family history of type 2 diabetes. The frequency of a family history of type 2 diabetes in second- and first-degree relatives is reported to range from 74 to 100%

Table 3—*Distribution of children with type 2 diabetes by percent overweight*

% overweight	Boys	Girls	Total
n	106	126	232
<20%	9 (8.5)	29 (23.0)	38 (16.4)
20–39	28 (26.4)	51 (40.5)	79 (34.1)
40–59	30 (28.3)*	27 (21.4)	57 (24.6)
≥60%	39 (36.8)**	19 (15.1)	56 (24.1)

Data are *n* (%). Percent overweight is calculated based on the (current weight − age- and height-matched ideal weight)/(age- and height-matched ideal weight) × 100 (%). Patients whose percent overweight is ≥20.0% were judged to be obese. *<20% overweight vs. 40–59% overweight (P = 0.0059); **<20% overweight vs. ≥60% overweight ($P < 0.0001$).

(2). In the present study, we investigated the children's family history at the time of diagnosis, when the patients were <15 years of age. The frequency of a family member with type 2 diabetes may increase after children are diagnosed with diabetes. In any case, genetic susceptibility is strongly associated with the occurrence of type 2 diabetes.

We think that urine glucose screening for all school children is useful in detecting childhood diabetes at the early stages of the disease (i.e., before they develop ketoacidosis). However, it costs ~$3 U.S. per subject for urinalysis using a glucose oxidase tape and ~$500 U.S. to diagnose one subject with diabetes in this screening program, including OGTT and the measurement of HbA_{1c}. It may not be appropriate to recommend this screening program for all children, and it may be necessary to target only high-risk subjects for screening. The American Diabetes Association and the American Academy of Pediatrics recommend a testing age of >10 years or at the onset of puberty for children with a BMI >85th percentile, with second- and first-degree diabetic relatives, in an at-risk race or ethnic group, and with signs of insulin resistance (2,3).

We confirmed that the annual incidence of type 2 diabetes among school children in the Tokyo metropolitan area increased after 1981. Japanese children are considered to be at a considerably high risk of developing type 2 diabetes. Age, sex, and genetic susceptibility may be associated with the occurrence of type 2 diabetes. However, an increasing prevalence of obesity associated with changes of lifestyle in this group seems to be a major cause of the increase in the frequency of this disorder. Therefore, improvement of lifestyle by increased physical activity and reduced caloric intake and consumption of animal proteins and fat are necessary to decrease the prevalence of childhood obesity and thereby prevent the development of type 2 diabetes (1–3,39).

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文献4

Existence of Early-Onset NIDDM Japanese Demonstrating Severe Diabetic Complications

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OBJECTIVE — To identify the clinical characteristics of early-onset NIDDM patients with severe diabetic complications.

RESEARCH DESIGN AND METHODS — The clinical cases of a large number of diabetic patients who visited a diabetes center within the period 1970–1990 were reviewed. Of a total of 16,842 diabetic patients, 1,065 (6.3%) had early-onset NIDDM (diabetes diagnosed before 30 years of age). These 1,065 patients were divided into two groups, those who developed proliferative retinopathy before the age of 35 (n = 135) and those who did not (n = 930). Development of proliferative retinopathy, nephropathy, renal failure, blindness, and atherosclerotic vascular disease were compared between the two groups.

RESULTS — The subgroup of 135 patients was characterized by poor glycemic control, often requiring insulin therapy and a higher familial prevalence of diabetes, and contained a greater proportion of women than the subgroup of 930 patients. Of the 135 patients, 99 (67%) developed proliferative retinopathy before the first visit. The 135 patients developed severe progressive complications in contrast to the 930 patients. A total of 81 patients (60%) developed diabetic nephropathy at a mean age of 31 years, 31 (23%) developed renal failure requiring dialysis at a mean age of 35 years, 32 (24%) became blind at a mean age of 32 years, and 14 (10%) developed atherosclerotic vascular disease at a mean age of 36 years.

CONCLUSIONS — Some Japanese early-onset NIDDM patients develop severe diabetic complications in their youth. Most of them had no symptoms nor regular treatment regarding diabetes until they were noticed to have developed severe diabetic complications. Although the relevant prevalence and the pathogenetic mechanism underlying the rapid onset of the complications remain to be determined, prolonged inadequate treatment of and familial predisposition to diabetes may be contributing factors. Careful diabetes care in the twenties, not only for IDDM but also for NIDDM patients, is warranted.

Ethnic differences may lead to different incidences of diabetes. The incidence of IDDM is, for instance, lower in Japanese than in Caucasians. However, the incidence of NIDDM in young Japanese is not low (1,2). NIDDM in the young is a heterogeneous metabolic disease where a genetic susceptibility may play a role in the pathogenesis of developing diabetes and/or its vascular complications (3). A subset of NIDDM in the young has been described as maturity-onset diabetes of the young (MODY), which is characterized by an early age of onset, usually before 25 years of age, and by autosomal dominant inheritance (3–6). Vascular complications seem to be rare in young NIDDM patients (7), but severe vascular complications have been reported in some cases or families (e.g., MODY3) (6,8–14). Whether heredity of NIDDM is associated with vulnerability to diabetic vascular complications is important not only for investigation of the pathogenesis of vascular complications but also for the prevention in the young diabetic population (12).

For several years, we have recognized that some young NIDDM patients develop severe vascular complications rapidly. In most of cases, we have found that these patients did not regularly visit a medical clinic until they suffered from visual disturbance or leg edema. In this report, we extend these observations and describe a group of patients who developed severe vascular complications in comparison with young NIDDM patients who did not develop complications. We did not confine early-onset NIDDM to MODY in this study, since *1*) the age at onset of diabetes cannot be equated with the age at diagnosis and *2*) the term MODY might lead to the unwarranted assumption that all cases of NIDDM in the young have the same etiology and prognosis.

RESEARCH DESIGN AND METHODS

— Of a total of 16,842 diabetic patients who visited the Diabetes Center, Tokyo Women's Medical College, from 1970 to 1990, 1,065 (6.3%) were early-onset NIDDM patients who were diagnosed as having diabetes before 30 years of age (Fig. 1). Early-onset IDDM patients and their complications have been described elsewhere (15,16). For characterization of early-onset NIDDM associated with the rapid development of severe vascular complications, the 1,065 patients were divided into two groups, those who developed proliferative retinopathy before 35 years of age (group 1, n = 135) and those who did not (group 2, n = 930). Patient profiles regarding diagnosis of diabetes, medical treatment to control blood glucose, family history of diabetes, and diagnosis of proliferative retinopathy and other complications were investigated through patient records, together with information from other hospitals. Diabetes was diagnosed according to the World Health Organization criteria (17), and NIDDM was defined as being not ketosis-prone and free from insulin for >1 year after diagnosis of diabetes and/or having

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MODY, maturity-onset diabetes of the young.

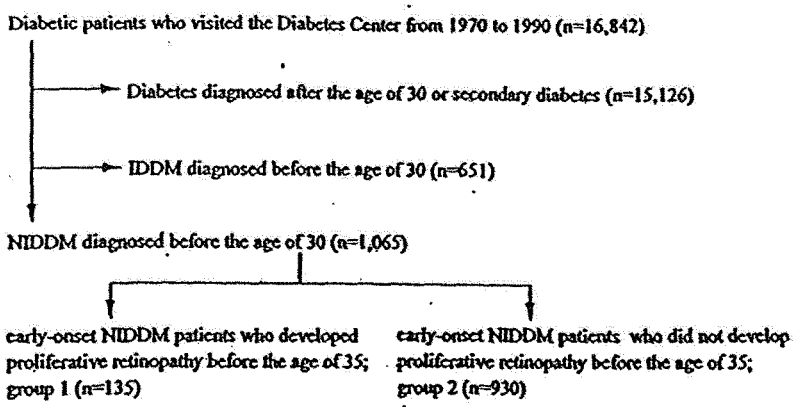

Figure 1—*Patient selection.*

preserved insulin secretion even when using insulin. To ensure the diagnosis of NIDDM, the serum C-peptide level was measured, and the endogenous insulin secretion in patients who were under insulin treatment was evaluated. MODY was defined as NIDDM characterized by an age at diagnosis of <25 years and an autosomal mode of inheritance (3,4,6). Proliferative retinopathy was determined as retinal neovascularization in accordance with the modified Airlie House System (18).

Clinical outcome was reviewed up to July 1996 regarding diabetic nephropathy, blindness, and atherosclerotic vascular disease. Diabetic nephropathy was defined as the onset of persistent proteinuria checked monthly by dipsticks. Renal insufficiency was defined as elevation of serum creatine level to >1.5 mg/dl (normal range, 0.7–1.3 mg/dl). Blindness was defined as visual acuity ≤5/200. Atherosclerotic vascular disease included coronary heart disease, cerebrovascular disease, and peripheral vascular disease manifested by intermittent claudication. Patients were defined as having coronary heart disease when resting electrocardiogram, investigated yearly, showed signs of probable myocardial infarction (Minnesota codes 1.1-2) or possible myocardial ischemia (Minnesota codes 1.3, 4.1-4, 5.1-3, or 7.1) or when clinical heart disease as defined above was present. Glycated hemoglobin at the first visit to the Diabetes Center (or the one examined in 1980 for patients who visited before 1980) was measured by high-performance liquid chromatography (normal range, 5.5–8.5%). Serum C-peptide level was measured in patients who were under insulin treatment by a synthetic human C-peptide kit (C-peptide radioimmunoassay, Shionogi). The detection limit of the measurement was 0.1 ng/ml, and inter- and intra-assay variation were 6.4% and 6.7%, respectively. Statistical analysis was performed using SPSS Windows version 6.0 with the unpaired *t* test or χ^2 test for comparison between the groups.

RESULTS — Table 1 shows clinical characteristics of early-onset NIDDM patients divided into two groups, those who developed proliferative retinopathy before the age of 35 (group 1) and those who did not (group 2). Age at diagnosis of diabetes was younger in group 1 than in

Table 1—*Clinical characteristics of early-onset NIDDM patients (n = 1,065) who developed proliferative retinopathy before 35 years of age and those who did not*

	Early-onset NIDDM		
	Onset of proliferative retinopathy before 35 years of age (group 1)	No onset of proliferative retinopathy before 35 years of age (group 2)	*P* value
n	135 (13%)	930 (87%)	
Background features			
Percent male	47 (39–56)	58 (55–61)	<0.05
Age at diagnosis of diabetes (years)	20 ± 5	23 ± 5	<0.001
Percent diabetes in first-degree relatives	66 (58–74)	56 (53–59)	<0.05
Percent MODY	8.1 (3.5–11.7)	4.4 (3.1–5.7)	NS
Percent diabetes in both parents	7.4 (3.0–11.8)	7.1 (5.5–8.7)	NS
Clinical characteristics at first visit			
Age at first visit (years)	29 ± 6	29 ± 10	NS
BMI (kg/m^2)	21.7 ± 3.8	23.2 ± 5.2	<0.05
Glycated hemoglobin (%)	11.7 ± 2.9	9.9 ± 2.3	<0.001
Therapy for diabetes (%, 95% CI)			
Diet only	12 (7–18)	50 (49–52)	<0.0001
Tablets	15 (9–21)	19 (16–21)	
Insulin	73 (65–80)	30 (27–33)	
Serum C-peptide level in insulin-users (ng/ml, mean, 95% CI)			
Fasting	1.3 (1.1–1.5)	1.2 (1.1–1.3)	NS
2-h postprandial	2.6 (2.2–3.0)	2.5 (2.3–2.7)	NS

Data are means ± SD, unless otherwise indicated; 95% CI given in parentheses.