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.

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 ($P < 0.0001$).

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%

(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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