
REVIEW ARTICLE

Urine Glucose Screening Program at Schools in Japan to Detect Children with Diabetes and Its Outcome—Incidence and Clinical Characteristics of Childhood Type 2 Diabetes in Japan

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ABSTRACT: A large number of children with type 2 diabetes have been detected by a urine glucose screening program conducted at schools in Japan since 1975. The incidence of type 2 diabetes in children has increased over the last three decades, and the incidence is estimated to be approximately 3.0/100,000/y during 1975–2000. The incidence of type 2 diabetes in junior high school children is three to six times higher than that in primary school children. More than 80% of children with type 2 diabetes are obese, and boys are more likely to be obese than girls. It is speculated that the increase in the incidence of childhood type 2 diabetes over the years may be a consequence of the increase in the frequency of obesity in school children. However, this trend of increasing incidence of childhood obesity has recently become weaker, and perhaps as a consequence, the incidence of type 2 diabetes has also decreased after the year 2000 in some cities of Japan. Improved attention to physical activity and eating habits among young people may be responsible at least in part to the decrease in the incidence of type 2 diabetes noted in recent years in big cities of Japan. (*Pediatr Res* 61: 141–145, 2007)

In the 21st century, type 2 diabetes is increasing in prevalence all over the world, and approximately 150–160 million people worldwide are currently estimated to suffer from the disease. The World Health Organization (WHO) estimated that as many as 200–300 million people worldwide would be suffering from type 2 diabetes by the end of the year 2005 (1). The majority of patients with type 2 diabetes are adults. However, various reports have indicated that the incidence of childhood type 2 diabetes has increased and continues to be on the rise (2,3). Accumulated evidence has demonstrated that the number of children with type 2 diabetes has elevated in recent years and continues increasing in young people in the United States. Currently, approximately one-third of children and adolescents in Ohio and Arkansas, and one-third of Hispanics in California have type 2 diabetes (4). It is noteworthy that some ethnic groups such as Hispanics, African-Americans, and Asians, including Japanese, have been re-

ported to be at a high risk of developing type 2 diabetes in youth as well as during adulthood (2,3).

Several Japanese studies have indicated a high incidence of childhood type 2 diabetes detected by urine glucose screening program conducted at schools in Japan (5–7). Since 1973, a program involving screening of primary 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 (8). Since 1974, the collected urine has also been tested for glucose to detect children with diabetes, and a number of school children were identified as having diabetes with minimal or no symptoms at the early stage of the disease. While the vast majority of children detected by the screening program are eventually diagnosed as having type 2 diabetes, a small number of children have also been diagnosed as having type 1 diabetes by the screening program. They showed neither symptoms of severe hyperglycemia nor those of ketosis at the time of diagnosis. This novel subtype of diabetes has been described as a slowly progressive form of type 1 diabetes (9).

The incidence of type 1 diabetes in Japanese children has been reported to be among the lowest in the world (10) and it has been estimated to be lower than that of childhood type 2 diabetes. On the other hand, the prognosis of juvenile-onset type 2 diabetes is considerably poorer in Japan possibly due to inadequate management. Yokoyama *et al.* (11) reported a higher incidence of severe diabetic complications in cases with type 2 rather than type 1 diabetes among children with early-onset diabetes. Therefore, it is important to detect children with type 2 diabetes and treat them appropriately during the early stage of the disease to prevent the occurrence and progression of the complications.

This article reviews the urine glucose screening program conducted at schools in Japan to detect children with diabetes and its outcome, *i.e.* the incidence and clinical characteristics of childhood type 2 diabetes in Japan.

Abbreviations: IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test

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METHODS

Urine glucose screening program at schools in Japan.

Together with the screening for hematuria and proteinuria to detect chronic renal disease, urine glucose testing was started in Tokyo in 1974 (5). Thereafter, some local governments and cities like Yokohama (6), Fukuoka, and Niigata (7) also adopted this screening program to detect childhood diabetes. In 1994, the school health law was revised in Japan to mandate urine screening of all primary and junior high school students for glucosuria.

In regard to the method of testing, the participants are instructed to collect midstream urine samples from the first urination in the morning at home after emptying their bladder the previous night. Urine samples are then transported in refrigerated containers to the test center for analysis of urine glucose together with that of urine protein and red blood cells. Urine glucose is determined using a glucose oxidase tape. The minimum sensitivity for positive glucose testing is 100 mg/dL or, in some areas, 50 mg/dL. Those children who are found to be positive for both glucose and ketone bodies in the urine are advised to visit a hospital for an immediate clinical evaluation to rule out diabetic ketoacidosis. If one urine sample is positive for glucose, a repeat urine test is requested on another morning. If the second test is also positive, an OGTT is performed to confirm the diagnosis of diabetes (Model A, adopted in Tokyo, etc.). In some local governments and cities, OGTT is performed even after a positive result of the first urine glucose test (Model B, adopted in Yokohama, Niigata, etc.). For the OGTT, 1.75g/kg (maximum 75g) of glucose is used, and WHO criteria (12) are currently followed for the diagnosis of glucose intolerance. The diagnostic accuracy of Model A and Model B for detection of diabetes has been reported to be almost the same by adopting either Model A or Model B (5,6). In most governments and cities, HbA1c, serum insulin, serum cholesterol, serum triglyceride, etc. are also examined at the same time. Children showing diabetic patterns on OGTT are eventually referred to a specialized hospital for detailed examination and treatment of diabetes (Fig. 1).

RESULTS

Positive Rate for Urine Glucose

The positive rate for glucosuria in the first test has been reported to be approximately 0.05–0.1% in primary school children and 0.12–0.2% in junior high school children (6,7). Thus, the positive rate in junior high school children is about

twice as high than that in the primary school children. The positive rate for glucosuria in the second test has been reported to be approximately 0.05% in both primary and junior high school children in Tokyo (7). This result indicates that a positive result cannot be reproduced in the second test in about half of the children who show a positive result in the first test. The vast majority of these children are, therefore, considered to have renal glucosuria.

Approximately 30–60% of children who show positive test for urine glucose are eventually diagnosed to have renal glucosuria. These children have no symptoms of diabetes and some have a family history of renal glucosuria. They exhibit normal glucose tolerance in the OGTT. Renal glucosuria is an isolated disorder of proximal tubular glucose transport, characterized by abnormal urinary excretion of glucose in the presence of normal blood glucose levels. Marble (13) defined renal glucosuria as a condition characterized by a normal fasting blood glucose level, normal glucose tolerance as assessed by OGTT, and a daily urinary glucose excretion of 10–100g. Laurence (14) defined renal glucosuria as a condition characterized by normal glucose tolerance as assessed by OGTT, regardless of the presence of glucosuria in the fasting state. Cases satisfying Marble's criteria appear to be few, whereas, Desjeux (15) reported that about 60% of the subjects with positive test results for urine glucose were diagnosed as having renal glucosuria in accordance with the criteria proposed by Laurence. The prevalence of renal glucosuria as determined by the urine glucose screening program is consistent with this result.

Incidence of Type 2 Diabetes as Detected by the Screening Program

Result in Tokyo. Between 1974 and 2004, a total of 9,242,259 school children including 6,225,971 primary school children and 3,016,288 junior high school children underwent urinary testing for glucosuria. Of these, a total of 236 children including 47 primary school children and 189 junior high school children were diagnosed as having type 2 diabetes through this screening program. The numbers of the target population were fluctuated according to the students' numbers residing in the Tokyo metropolitan area for each year. However, the participation rate in the urine test was scarcely changed and almost 100% of the students during the study period. The number of school children screened has decline since 1990 because of the decreased birth rate in Japan including the Tokyo metropolitan area.

The overall incidence of type 2 diabetes was estimated to be 2.55/100,000/y. Junior high school children had a significantly higher incidence of diabetes than primary school children (0.75 versus 6.27/100,000, $p < 0.0001$). Table 1 shows the annual number and incidence of type 2 diabetes as detected by the screening program for 5-y periods from 1974 to 2004 in Tokyo. The annual incidences over the six consecutive 5-y periods from 1974 to 2004 were 1.73, 3.23, 3.05, 2.90, 2.70, and 1.41/100,000, respectively. The incidence in 1974–1980 was significantly lower than that recorded in 1981–1985, 1986–1990, and 1991–1995 and tended to be lower than that

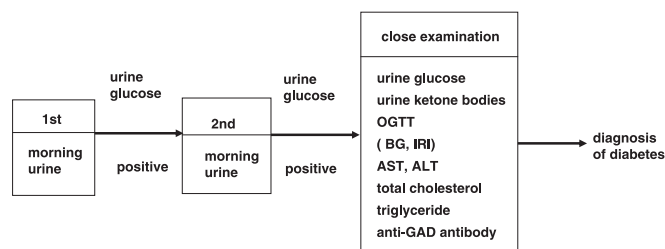


Figure 1. Urine glucose screening system at school in the Tokyo metropolitan area.

Table 1. Annual number and incidence of type 2 diabetes as detected by the urine glucose screening program for 5-y periods from 1974 to 2000 in Tokyo

Year	School students examined (n)	Type 2 diabetes (n)	Overall frequency of type 2 diabetes/10 ⁵	PSC examined (n)	Type 2 diabetes in PSC (n)	Frequency of type 2 diabetes in PSC/10 ⁵	JHSC examined (n)	Type 2 diabetes in JHSC (n)	Frequency of type 2 diabetes in JHSC /10 ⁵
1974–1980	2,076,767	36	1.73	1,466,801	4	0.27	609,966	32	5.25
1981–1985	1,827,870	59	3.23	1,204,262	11	0.91	623,608	48	7.70
1986–1990	1,636,969	50	3.05	1,032,514	8	0.77	604,455	42	6.95
1991–1995	1,481,518	43	2.90	992,771	8	0.81	488,747	35	7.16
1996–2000	1,296,521	35	2.70	880,199	13	1.48	416,322	22	5.28
2001–2004	922,614	13	1.41	649,242	3	0.46	273,190	10	3.66
Total	9,242,259	236	2.55	6,225,971	47	0.75	3,016,288	189	6.27

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

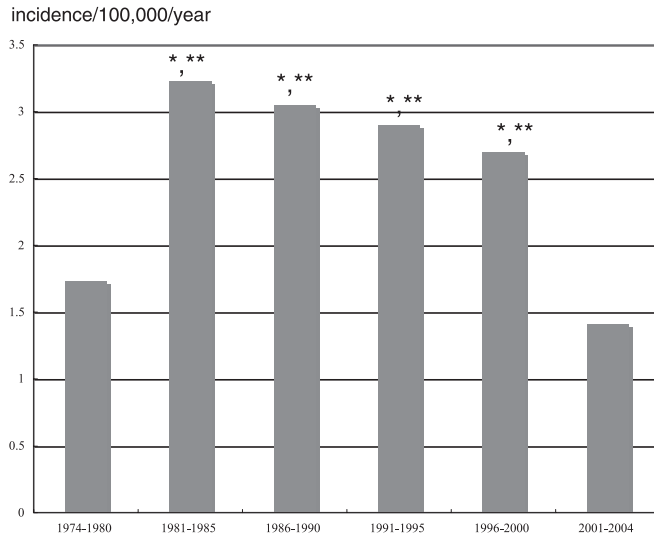


Figure 2. Overall incidence of type 2 diabetes as detected by the urine glucose screening program for 5-y periods from 1974 to 2004 in Tokyo. *The incidence in 1974–1980 was significantly lower than that recorded in 1981–1985, 1986–1990, and 1991–1995 ($p = 0.0038, 0.0091, 0.0226$, respectively) and tended to be lower than that recorded in 1996–2000 ($p = 0.0672$). **The incidence in 2001–2004 was also significantly lower than that recorded in 1981–1985, 1986–1990, and 1991–1995 ($p = 0.0056, 0.0120, 0.0194$, respectively) and tended to be lower than that recorded in 1996–2000 ($p = 0.0557$).

recorded in 1996–2000. The incidence in 2001–2004 was also significantly lower than that recorded in 1981–1985, 1986–1990, and 1991–1995 and tended to be lower than that recorded in 1996–2000 (5,16) (Fig. 2).

The annual incidence of diabetes from 1974 to 2004 in junior high school children was 5.25, 7.70, 6.95, 7.16, 5.28, and 3.66/100,000, respectively. The incidence in junior high school children in 2001–2004 was significantly lower than that recorded in 1981–1985 ($p = 0.0315$) and tended to be lower than that recorded in 1991–1995 ($p = 0.0622$). There were no significant changes in the incidence of diabetes in primary school children over the corresponding periods (16). Therefore, the overall trend of decreasing incidence of childhood type 2 diabetes in 2000–2004 was most strongly associated with the decrease in the incidence of the disease in junior high school children.

Results in Other Governments and Cities in Japan. The incidences of childhood type 2 diabetes detected by the urine glucose screening program in Tokyo and other cities in Japan

are shown in Table 2. Taking into account these results, it is speculated that the overall incidence of childhood type 2 diabetes in Japan is approximately 3.0/100,000/y. The incidence in junior high school children is three to six times higher than that in primary school children.

Kikuchi *et al.* (6) reported the annual incidence of type 2 diabetes in Yokohama city during the 5-y periods 1987–1991 and 1992–1996 were significantly higher than the incidence recorded in 1982–1986. However, Yokota *et al.* (17) demonstrated that the incidence in 1997–2001 was lower than that in 1992–1996 for the same population in Yokohama city. In Fukuoka city, the incidence of type 2 diabetes in junior high school children has been steadily decreasing after 1999 (7). Taking into account these findings and the results obtained in the Tokyo study, it may be deemed that the incidence of childhood type 2 diabetes in big cities of Japan has somewhat decreasing in recent years.

Impaired glucose tolerance. Among children who showed positive test results for urine glucose, a few were diagnosed as having IGT by OGTT. In the Tokyo study, a total of 16 children were identified as having IGTT. Of these, six children finally progressed to type 2 diabetes. In the Yokohama study, 33 children with IGT were found by the screening program, and one third of them developed to type 2 diabetes after 5 y from diagnosis. Obese children showed significantly high incidence of developing diabetes, and all of the diabetic patients showed worsening of obesity at the point of onset of diabetes (18).

Clinical Characteristics of Type 2 Diabetes as Detected by the Screening Program

Gender. Rosenbloom *et al.* (2) reported that gender is an important predisposing factor in the occurrence of type 2 diabetes, with analysis of a large number of studies revealing that girls are 1.7 times more likely to develop diabetes than boys. However, there appears to be no statistically significant gender difference in the incidence of type 2 diabetes among Japanese children (5–7).

Age. The majority of children with type 2 diabetes are junior high school children with the usual pubertal age of 13–15 y at diagnosis (5–7). Puberty is an important risk factor leading to hyperglycemia. Insulin sensitivity decreases by 30% during puberty and is associated with a compensatory increase in the insulin secretion (19,20).

Table 2. Incidence of type 2 diabetes as detected by the urine glucose screening program in various areas of Japan

References	Incidence/100,000/y
Tokyo (1974–2004) (5,16)	Overall: 2.55 (PSC: 0.75; JHSC: 6.27) 1974–1980: 1.73; 1981–1985: 3.23; 1986–1990: 3.05; 1991–1995: 2.90; 1996–2000: 2.70; 2001–2004: 1.41
Yokohama (1982–2001) (6,17)	Overall: 3.19 (PSC: 1.50; JHSC: 6.65) 1982–1986: 1.89; 1987–1991: 3.19; 1992–1996: 4.97; 1997–2001: 4.56
Niigata (1982–2003) (7)	Overall: 3.57 PSC: 1982–1988: 0; 1989–1993: 1.7; 1994–1998: 1.3; 1999–2003: 2.8 JHSC: 1982–1988: 0; 1989–1993: 6.0; 1994–1998: 14.6; 1999–2003: 13.4
Fukuoka (1989–1998) (7)	Overall: 2.77 (PSC: 1.62; JHSC: 5.05)

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

Obesity. Various studies have reported that greater than 80% of Japanese children with type 2 diabetes are obese at the time of diagnosis (5–7). In the Tokyo study (5), 83.4% were more than 20% overweight and 48.7% had severe obesity defined as more than 40% overweight. On the other hand, some studies have indicated that obesity is significantly more prevalent among males with childhood type 2 diabetes; *e.g.* in the Tokyo study (5), boys showed a higher frequency of obesity than girls (91.5 versus 77.0%). Sugihara *et al.* (21) also reported a higher frequency of obesity in males (78% versus 63%) based on the results of a survey conducted with the participation of major pediatric departments in Japan. Besides severe obesity being more prevalent among males with childhood type 2 diabetes, nonobesity has also been reported to be more prevalent among females with type 2 diabetes (5,21). This may suggest gender difference in the pathogenesis of type 2 diabetes, whereas obesity, which causes insulin resistance, is highly likely to be involved in the development of hyperglycemia in males, other mechanisms may be involved in females with diabetes.

Several studies have indicated that the observed increase in the incidence of childhood type 2 diabetes is a result of increased frequency of obesity among young people (2–4). The prevalence of obesity in Japanese school children has increased significantly over the past three decades. The prevalence of obesity among Japanese school children in the year 2000 was reported to be approximately 10%, three times as high as the prevalence recorded three decades ago (22). Since the 1970s, the Japanese people, especially Japanese children, have become westernized in relation to their lifestyles and eating habits. Increase in the prevalence of a sedentary lifestyle (watching television and playing TV games) and nutritional problems, such as increased intake of animal protein and fat (23,24), possibly contribute to the increased prevalence of obesity and development of type 2 diabetes among Japanese school children. However, this trend of increasing incidence of childhood obesity appears to have become weaker recently. The Ministry of Education, Culture, Sports, Science and Technology of Japan reported in recent years of a decreasing prevalence of obesity among junior high school children (25). This could be related to the significant increase in awareness and concern regarding childhood obesity and associated metabolic disorders has spread in the Japanese population, especially among children and adolescents residing in big cities. These children, therefore, appear to take sugar-sweetened beverages and snacks as well as high-fat foods less frequently than before. In addition, they seem to

have emerged from sedentary lifestyles to actively participate in various sports activities (25). These lifestyle changes may contribute to the decrease in the incidence of type 2 diabetes observed in recent years in big cities of Japan.

Family history of type 2 diabetes. In regard to the role of a family history of diabetes, 56.5% of children with type 2 diabetes in the Tokyo study (5) and 69% of the patients reported by Sugihara *et al.* (21) had a family history of type 2 diabetes in second- and first-degree relatives. The frequency of a positive family history of type 2 diabetes in second- and first-degree relatives has been reported to range from 74 to 100% in Caucasian population (2–4). The frequency of detection of type 2 diabetes in family members may possibly increase after children are diagnosed as having diabetes. Therefore, the family history plays a crucial role in the majority of children developing type 2 diabetes.

Future Prospects

In 1994, when urine glucose screening at schools was made obligatory, no further budgets were allocated for the formation of committees to evaluate cases with positive results. Consequently, no committee for the diagnosis and follow-up of cases showing a positive urine glucose screening test results have been established yet in many governments and cities in Japan (17). In Tokyo, however, all the participants of screening programs with positive test results have undergone adequate evaluation at a unique examination institute and follow-up system established by pediatric diabetes specialists with the support of the Tokyo Health Service Association (5). It is important to constitute such committees composed of pediatric diabetologists for the establishment of a system for confirmation of the diagnosis, treatment and follow-up of cases showing positive screening test results in all areas of Japan.

The major purpose of urine glucose screening is to diagnose the disease in the early stage in children with type 2 diabetes and provide appropriate treatment. However, no guideline for the management of childhood type 2 diabetes has been established as yet in Japan. Moreover, the Japanese government has not approved most of the oral hypoglycemic agents available currently for use in the pediatric population. It is, therefore, extremely important to establish appropriate strategies for the treatment of type 2 diabetes among children at the earliest.

Ritchie *et al.* (26) reviewed the possibility of prevention of type 2 diabetes among youth, and concluded that this disease can be potentially prevented or delayed by improvement of the

eating habits and physical activity among children (27,28). Several clinical trials in adults have shown that even moderate weight loss can reduce the risk of development of type 2 diabetes (29–31). However, the efficacy of dietary and exercise programs in the prevention of type 2 diabetes among youth still remains to be studied. A recent study by Urakami *et al.* (16) reported a reduction in the incidence of type 2 diabetes in Tokyo during 2001–2004, possibly due to a decreased frequency of childhood obesity associated with improved eating habits and physical activity among children. An interventional trial of the effect of lifestyle alterations should be begun in obese children residing in all areas of Japan to establish its efficacy in the prevention of type 2 diabetes as well as the so-called metabolic syndrome in children.

SUMMARY

The increase of childhood type 2 diabetes is observed not only in Japan but is also reported in various countries including the United States, especially among young people with risk factors for type 2 diabetes (*i.e.* pubertal age, obesity, family history of type 2 diabetes, high-risk racial or ethnic group, etc.) (2–4). It is, therefore, principal to establish a screening program to detect children with having type 2 diabetes at the early stage and create a strategy for prevention and treatment of the disease during childhood worldwide.

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