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文献1

OBSERVATIONS

Proportion of Diabetes Type in Early-Onset Diabetes in Japan

Since 1990, we have reported hospital-based studies concerning Japanese patients with early-onset diabetes in our Diabetes Center, Tokyo Women's Medical University, Japan (1). Our goal is to confirm the proportion of type 1 versus type 2 diabetes in early-onset diabetes in Japan in our center with that of the Asian group in The SEARCH for Diabetes in Youth, a recent population-based study concerning the prevalence of diabetes in youth (2).

Our study consists of 4,063 Japanese patients who were initially diagnosed as having diabetes under the age of 30 years and registered in our Diabetes Center between 1960 and 2004. Of the 4,063 patients, 1,746 (43.0%) had type 1 and 2,317 (57.0%) had type 2 diabetes based on the diagnostic criteria of the Japan Diabetes Society (3), which is identical to that of the World Health Organization. Other specific types of diabetes were excluded from the study. We divided the subjects into three groups according to age at onset of diabetes, namely, 525 patients with diabetes diagnosed from 0 to 9 years, 1,382 from 10 to 19 years, and 2,156 from 20 to 29 years, to investigate the proportion of type 1 versus type 2 diabetes in each group. The proportion of type 1 versus type 2 diabetes in the three groups was 95.0 versus 5.0%, 50.9 versus 49.1%, and 25.2 versus 74.8%, respectively.

Approximately 10% of diabetic patients who resided in the Tokyo metropolitan area were registered in our Diabetes Center (4); therefore, although our study was hospital based, we believe it reflects a general trend of a proportion of diabetes type in early-onset diabetes in Japan. The SEARCH for Diabetes in Youth showed that the proportion of type 1 versus type 2 diabetes in Asian/Pacific Islander patients from 0 to 9 and 10 to 19 years of age at onset is 86.6 versus 6.7% and 58.5 versus 40.1%, respectively (2). Not only The SEARCH for Diabetes in Youth but also our study suggests that type 2 diabetes accounts for ~5–7% of Asian children with diabetes and that the proportion of type 2 diabetes is nearly half of all Asian adolescents with diabetes.

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臨床・展開研究

18. 日本人若年発症2型糖尿病の臨床的特徴

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はじめに

若者の糖尿病といえば，ちょっと昔は1型糖尿病のことを意味していた．しかし，若年発症2型糖尿病が存在する，それも最近になって存在してきたのではなく，1990年当センターからの報告[1]があるように，以前より日本には存在していた．しかし，なんの疑問もなく1型糖尿病が小児糖尿病と同意義に用いられてきたように，若年発症2型糖尿病がこれまでなおざりにされてきた感がある．今日なおざりにできない糖尿病の1群となった．

その理由は以下のごとくである．1つは，大人の2型糖尿病がそうであるように，発症時期がはっきりしない，ないし学校検尿で発見されるが体が元気なので病識に乏しい，2つに糖尿病発見後の治療がうまくいかない，つまり治療中断が多いために多くは30歳代になって重症合併症に罹患して来院することである．

このような理由で，若年発症2型糖尿病は，患者の将来のQOLの低下，就職難，医療費の高騰などが予想され，医療経済的にみても重大な問題である．また，なにかの介入余地を考えなければならない1群ともいえる．

ここでは，hospital-based study により，日本人若年2型糖尿病の臨床的特徴をまとめ，介入方法など，今後の治療方法を模索したい．

1型糖尿病と2型糖尿病の患者の比率

図1〜3は，糖尿病センターの前身および糖尿病センターに初診した，30歳未満発症糖尿病患者の，発症年齢，発見年齢ごとの患者数を

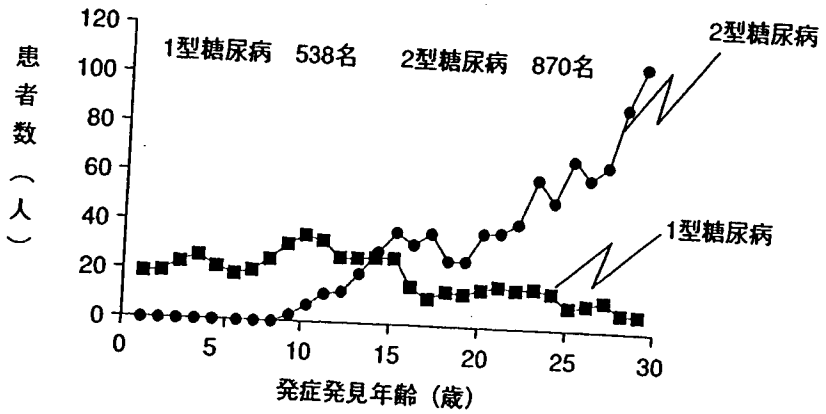
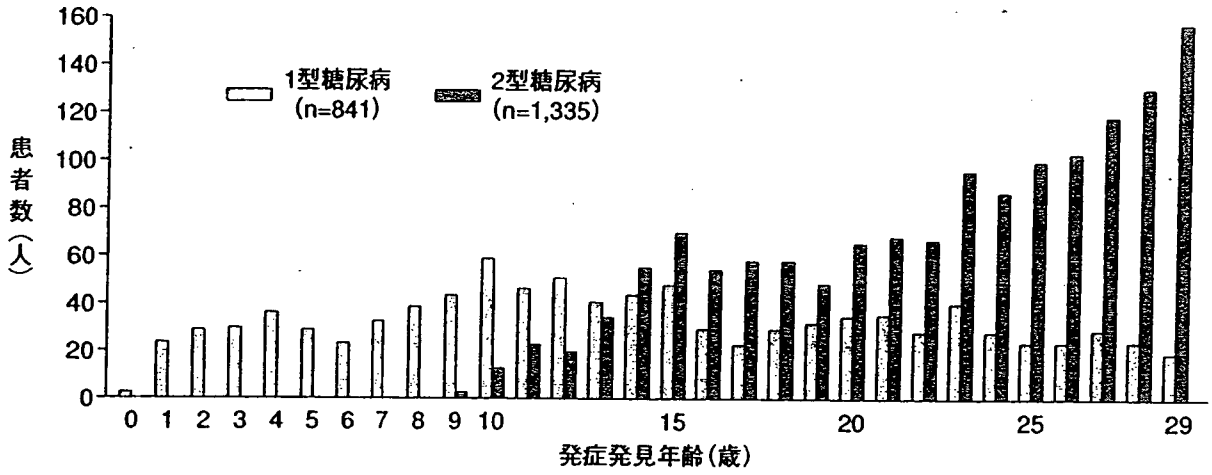


図1　東京女子医科大学糖尿病センターの30歳未満発見発症糖尿病患者の病型別および発見年齢別患者数
（大谷敏嘉・他：糖尿病　32：717，1989，Otani T et al：Diab Res Clin Prac 10：241，1990より引用）

病型別にあらわしたものである．図1[1]は1989年までに初診した患者での，図2[2]は1995年末までに初診した患者での，図3は2003年末までに初診した患者でのものである．

ここでの1型糖尿病は，ケトーシスおよびケトアシドーシスでの急性発症，過去に肥満歴がない，発症時に両親に糖尿病がない，さらに初期にはWHO分類，最近は日本糖尿病学会の病型分類によるものと定義する．2型糖尿病はそれ以外の糖尿病と定義する．

図1は，1990年に若年発症2型糖尿病の存在を世界に先駆けて報告したものだが，ここで



（東京女子医科大学糖尿病センター，1960～1995年）

図2　30歳未満に発症・発見した糖尿病患者の病型別・発見年齢別人数（1995年までに初診）

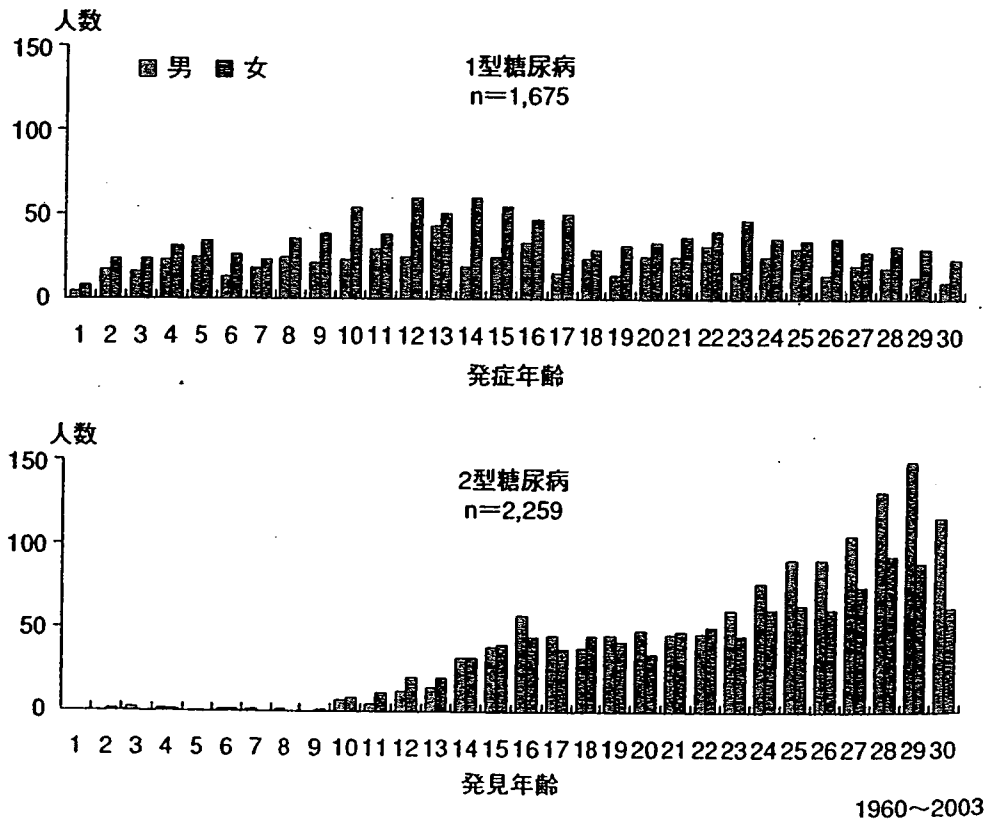


図3　30歳未満発見発症1型および2型糖尿病患者の発見発症年齢ごとの男女別人数

注目すべきは，日本人には10歳代に発見される2型糖尿病患者が1989年までの糖尿病センターには存在する，ということであった．あとで述べるが，このころの2型糖尿病はどちらかというと肥満歴のない非肥満患者が多かった．

また，図1，2および図3のどれをみても，1型および2型糖尿病患者数が10歳代の中ごろで交叉していることがわかる．

年代別の病型別比率と男女比

表1は2003年末までに初診した30歳未満発症発見糖尿病患者数を，発症発見年代を1960～1978年，1979～1988年，1989～2003年の3つの年代別に分けて，病型，性別にさらに分けてみたものである．2003年までの患者数を約3等分するように分けた．よって，初診した年代別に分けたのではない．これによって，経年的な推移が推測できる．どの年代群とも今後患者数は増加するであろうが，1989～2003年群の患者数は他の群より増加する数は多いであろう．よって1989～2003年発症した患者数は推定される数より少なくなっている．

1糖尿病専門病院という当大学糖尿病センターに初診された30歳未満発症発見糖尿病患者の，1型と2型糖尿病の比率は，各々1：1.72，1：1.24，1：1.22であった．ここで明らかにされることは，年代が下るにつれて2型糖尿病患者が1型糖尿病患者に比して爆発的に多くなっているわけではない，ということである．

昨今，若年発症2型糖尿病患者の増大がマスコミなどでいわれているが，当センターでみるかぎり“急増している”ということはみられない．これを明らかにするには，ある地域での糖尿病患者数の動きをみるpopulation-based studyをすべきである．当センターでの増大がみられなかったのは，糖尿病専門病院やクリニックの増加により，このような2型糖尿病患者も分散していることが示唆される．

2型糖尿病の年代別男女比にも大きな動きはなく，どの年代も男性が女性より多い．

発症発見年齢別，年代別の，男女比を調べてみると，2型糖尿病患者は15歳以降に男性が明らかに多くなる．これは1型糖尿病の性比と明らかに異なる点である．男性が多いのは，大人の2型糖尿病における特徴と同じである．

2型糖尿病の過去の肥満歴

図4は1960～2003年に初診した30歳未満

表1 診断時年代別および発症年齢別1型および2型糖尿病患者数

1型糖尿病 n＝1,675　2型糖尿病 n＝2,259

病型	性別	発症年齢	1960～1978	1979～1988	1989～2003	合計
1	男	0～9	72	68	34	174
		10～19	57	106	79	242
		20～29	19	64	110	193
1	女	0～9	125	105	57	287
		10～19	92	178	175	445
		20～29	41	95	198	334
2	男	0～9	4	4	5	13
		10～19	84	140	115	339
		20～29	299	286	330	915
2	女	0～9	2	5	5	12
		10～19	107	120	103	330
		20～29	201	211	238	650
合計			1,103	1,382	1,449	3,934

1960～2003(内潟ら，論文準備中)

発見2型糖尿病患者の過去の肥満歴を調べたものである．これまでと同様に，3つの年代群に分けてみた．発見年齢が若いほど過去に肥満した患者パーセントは小さいが，年齢がいくにつれて男女とも過去に肥満していた．

これは，年齢が若くして発見される2型糖尿病患者ほど過去の肥満歴と関係が薄く，年齢がいくにつれて発見される2型糖尿病患者ほど過去の肥満している比率が多くなることを表している．これは，これまでのpopulation-based study[3-5]の結果と同じである．

年代別の2型糖尿病患者の家族歴

30歳未満発見2型糖尿病患者の家族歴も注目されるところである．過去の肥満歴でわけてみたが，初診時に第1度近親者に糖尿病患者がいない人は約30%強，父親に2型糖尿病がありが20%くらい，母親に2型糖尿病ありが20%弱であった．

過去に肥満歴あるほうが家族歴ありの比率が少ないのかと思っていたが，必ずしもそうではないことがわかった．30歳未満発見2型糖尿病患者が過去に肥満歴があろうがなかろうが家族歴は約70%に存在することらしい．

1988年までのデータベースを用いての若年発症2型糖尿病患者の糖尿病合併症の頻度

図5[6]は当センター小児ヤング班のYokoyamaらが報告した発症年齢をマッチさせた1型糖尿病患者と，糖尿病発症発見後の罹病期間を合わせて糖尿病腎症の累積罹患率を比較したものである．若年発症1型糖尿病患者より明らかに若年発症2型糖尿病患者のほうが腎症発症しやすいことがわかる．

図6[6]は同様に，同じデータベースの2型糖

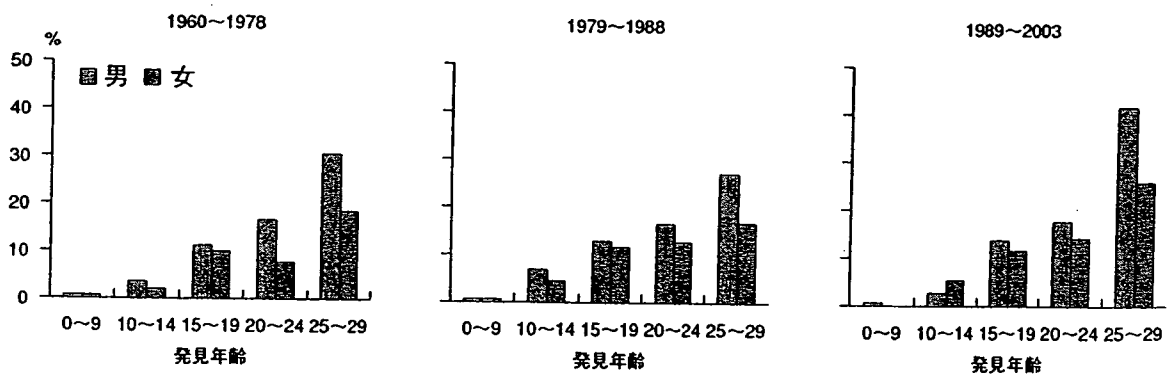


図4　過去最大BMI≧25の2型糖尿病患者の各年代ごとの各発症年齢群における男女別比率
（内潟ら，論文準備中）

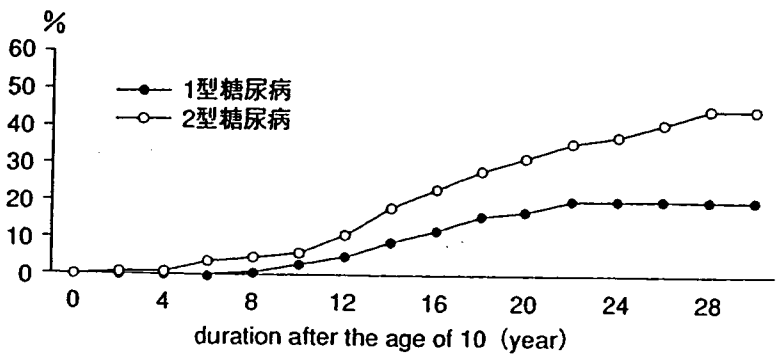


図5　Comparison of cumulative incidence of diabetic nephropathy in early onset type 1 and type 2 patients
（Yokoyama H et al：Kidney International 58：302，2000より引用）

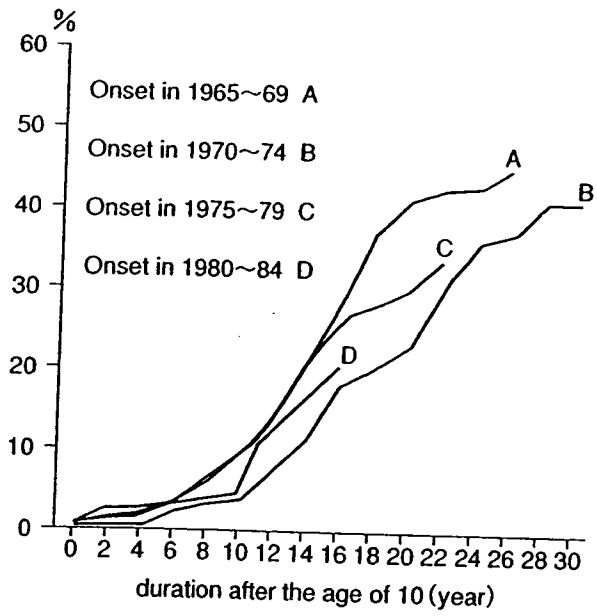


図6 Cumlative incidence of diabetic nephropathy in early onset type 2 patients
(Yokoyama H et al : Kidney International 58 : 302, 2000 より引用)

尿病患者の，発見年代ごとに分けて糖尿病腎症罹患率が，年代とともにどのようになっているかを調べたYokoyamaらの結果である．年代が下っても罹患率の低下はみられなく，これは同様の1型糖尿病患者を用いた同様の調査では明らかに腎症発症の低下がみられる[6]のと比較して，糖尿病治療の進歩の影響を受けていないといえる．これは，合併症が発症してはじめて医療機関を受診するといった患者が2型糖尿病に多く，1型糖尿病はインスリン治療のために確実に医療機関を受診しているというこの差が大きな原因と思われる．

◪細小血管症を進展させる因子を分析する

1. 網膜症なしから単純網膜症の発症

これは当センター小児ヤング班のOkudairaらによってすでに調査されている[7]．1970～1990年データベースを用いた調査により，univariate analysisでは調査期間内の平均HbA_{1c}，調査時年齢，調査時までの罹病期間，調査時HbA_{1c}，調査時中性脂肪，調査時コレステロールなどがあがってきたが，multivariate analysisでは，調査期間内の平均HbA_{1c}，調査時までの罹病期間の2因子が独立して挙げられた．単純網膜症発症は調査期間内の平均HbA_{1c}とは正の相関で関連していた[7]．

2. 単純網膜症から増殖網膜症への進展

1970～1990年データベースを用いたOkudairaら[7]による調査では，調査期間内の平均HbA_{1c}，調査時拡張期血圧，調査時HbA_{1c}などがあげられたが，multivariate analysisでは，調査期間内の平均HbA_{1c}，調査時拡張期血圧の2因子が独立して挙げられた．調査時拡張期血圧が高くなるほど正の相関をもって増殖網膜症を発症することも明らかとなった．

3. 糖尿病腎症(持続性蛋白尿)への進展

これは1960～1990年データベースを用いてYokoyamaら[6]がすでに報告している．調査期間内平均HbA_{1c}，調査時拡張期血圧，調査時BMI，調査時までの罹病期間，調査時中性脂肪があがってきたが，multivariate analysisでは，調査期間内の平均HbA_{1c}，調査時拡張期血圧，調査時までの罹病期間の3因子が独立して挙げられた．調査期間内の平均HbA_{1c}は糖尿病腎症発症と正の相関関係を示した．

4. 糖尿病合併症を発症させる因子

以上より，1型糖尿病で報告されているように，糖尿病網膜症ないし糖尿病腎症発症には罹病期間内のHbA_{1c}が最も大きな影響を与えることが明らかになった．さらに拡張期血圧も大きな因子となることが明らかになったが，これは1型糖尿病では大きな影響を与える因子としてはあがってこない因子である．これは，2型糖尿病における細小血管合併症発症の特徴的なことといえる．

◢重症合併症を発症する若年発症2型糖尿病患者の存在

1970～1990年データベースを用いてYokoyamaらは，まだ若くして重症の細小血管合併症と大血管障害合併症を併発する若年発症2型糖尿病患者が存在することを報告した[8]．30歳未満発見2型糖尿病患者のうち，35歳までに増殖網膜症を発症した135名を抽出した（表2）ところ，表3にみられように他の重症合併症も併発していることを示した．糖尿病腎症，透析，失明，壊疽および心筋梗塞がおもなものであるが，発症年齢がいずれも30歳代であった．このように重症合併症で苦しむ30歳代の2型糖尿病患者の約40%は，18歳までに自分が糖尿病を発症していることを知っていた．このことは注目に値する．

表2　Micro-and macro-vascular complications in early onset type 2 patients with PDR before the age of 35 at the first visit

male(n)	63/135(47%)
onset age(y.o.)	19.5 ± 5.7 (8-29)
onset age＜18 y.o.(n)	53/135(40%)
MODY	11/135(8%)
age at the first visit(y.o.)	29 ± 6
BMI at the first visit	21 ± 3.8
HbA_{1C}(%) at the first visit	11.7 ± 2.9
Tx at the first visit, Diet：OHA：insulin	12%：15%：73%

（Yokoyama H et al：Diabetes Care 20：844, 1997 より引用）

◢では学校検尿システムはどのように作動しているか

岡田ら[9]は当センターの1980～1998年データベースを用いて，学校検尿システムが若年発症2型糖尿病の合併症予防にどのように介入しているかを調査した．上記のデータベース内に18歳未満で発見された2型糖尿病患者283名を対象に，当センター初診時の合併症の状況を調査することによって行われた．

表4は対象を糖尿病発見が学校検尿群とそれ

表3　Micro-and macro-vascular complications in 135 early onset type 2 patients with PDR before the age of 35

complications	No.of patients(%)	age at diagnosis(year)
proliferative retinopathy	135(100)	29(range 18-35)
diabetic nephropathy	81(60)	31(range 19-44)
dialysis	31(23)	35(range 26-41)
blindness	32(24)	32(range 21-46)
gangrene & AMI	14(10)	36(range 29-42)

（Yokoyama H et al：Diabetes Care 20：844, 1997 より引用）

表4　学校検尿発見群とそれ以外発見群での比較

		学校検尿発見	それ以外発見	
人数	(人)	183	100	
発見年齢	(歳)	14.8 ± 2.1	14.7 ± 1.9	0.6636
HbA_{1C}	(%)	9.5 ± 2.8	9.4 ± 2.7	0.4079
罹病期間	(年)	8.5 ± 6.5	10.1 ± 7.6	0.2010
中断なし/あり	(人)	126/57	66/34	0.4752
中断期間	(年)	4.98 ± 3.27 (1-15)	5.79 ± 3.20 (1-15)	0.3260
初期入院歴なし/あり	(人)	95/88	55/45	0.6189
合併症なし/あり	(人)	128/55	63/37	0.2346
スコア	0点	128	63	
	1点	19	7	
	2点	11	5	
	3点	4	4	0.0611
	4点	8	6	
	5点	6	3	
	6点	7	12	

（岡田ら：糖尿病　43：131，2000 より引用）

以外群に分けての臨床背景である．発見年齢，初診までの罹病期間，初診までの治療中断歴などにこの2群間に相違はない．また，初診時の合併症の有無，重症度にも，2群間に相違はみられなかった．

しかし，この対象283名を初診までに治療中断がある群，なし群で分けて，初診時合併症の状況を調べてみた．ここでの治療中断は，糖尿病が発見されてから当センター初診までに医療機関を1年以上受診していないことと定義した．この2群で初診時合併症の有無と重症度を調べたところ，治療中断歴あり群のほうが合併症発症頻度が高いことがわかった．

2型糖尿病は発見されてからきちんと受診して食事・運動療法だけであっても，経口血糖降下薬ないしインスリン治療であっても，中断してもすぐに症状が出現しないために，受診がなおざりになりやすい．その結果，合併症を併発してのちに当センターを受診している患者が多いといえる．

この現象は，奥平らが15歳未満発症1型糖尿病患者と2型糖尿病患者から1980年代当センター初診群と1990年代初診群を抽出して，両群の合併症頻度を比較して報告した[10]．2型糖尿病患者において10年間の時差があってもなんら合併症頻度の良好化と結びついていないことが明らかとなった．

学校検尿システムは1992年から全国で義務化されたが，最初の章で述べたように，若年発症2型糖尿病患者が肥満患児の増加とともに全国レベルでは増加していることが考えられるので，介入する方法としてはすばらしい方法なので，是非2型糖尿病患者の合併症をおこさないように，学校検尿システムが作動していってほしいと願うばかりである．

おわりに

小児期・思春期糖尿病は1型でも2型でも，血糖コントロールが簡単に悪化じやすく，また，小児期にはなにもおこらなく思春期後からはじめて糖尿病合併症が発症してくる．

思春期をうまくのりこえれば，つまりよい血糖コントロールの下にこの時期を過ぎれば，合併症の発症が低頻度に抑えられるともいえる．

今後，患者数の増大化は大人の糖尿病患者と同じく進む．患者QOLのためにも，医療経済面においても，合併症予防に全力で立ち向かいたいものである．

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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) 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.

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

(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

Recent Trend Toward Decrease in the Incidence of Childhood Type 2 Diabetes in Tokyo

We previously reported that the annual incidences of children with type 2 diabetes as detected by urine glucose screening at school in Tokyo during 1981–1995 were significantly higher than the incidence in 1974–1980 (1). We evaluated recent changes in the annual incidence of childhood type 2 diabetes in Tokyo. The results were analyzed using Fisher's exact probability test.

From 1974 to 2004, a total of 9,242,259 school students were tested for glucosuria to detect diabetes. A total of 236 children were diagnosed as having type 2 diabetes through this screening program. Overall, 83.9% of children with diabetes were obese. The overall incidence was 2.55 per 100,000 per year. Junior high school children had a significantly higher incidence than primary

school children (0.75 vs. 6.27 per 100,000; $P < 0.0001$). The annual incidences over the 5-year periods from 1974 to 2004 were 1.73, 3.23, 3.05, 2.90, 2.70, and 1.41 per 100,000, respectively. The incidence in 1974–1980 was significantly lower than those in 1981–1985, 1986–1990, and 1991–1995 ($P = 0.0038$, 0.0091, and 0.0226, respectively) and tended to be lower than that in 1996–2000 ($P = 0.0672$). The incidence in 2001–2004 was also significantly lower than those in 1981–1985, 1986–1990, and 1991–1995 ($P = 0.0056$, 0.0120, and 0.0194, respectively) and tended to be lower than that in 1996–2000, as well ($P = 0.0557$). The annual incidences of junior high school children from 1974 to 2004 were 5.25, 7.70, 6.95, 7.16, 5.28, and 3.66 per 100,000, respectively. The incidence of junior high school children in 2001–2004 was significantly lower than that in 1981–1985 ($P = 0.0315$) and tended to be lower than that in 1991–1995 ($P = 0.0622$). For the same periods, there was no significant change in the incidence of primary school children. Therefore, the overall trend toward decrease in the incidence of childhood type 2 diabetes in 2000–2004 was most strongly associated with the decrease in that among junior high school children.

After the 1970s, the tendency toward childhood obesity rapidly increased in the 8- to 14-year age-group in Japan, contributing to the increase in childhood type 2 diabetes (2). However, this trend has recently seemed to be weakened. The Ministry of Education, Culture, Sports, Science and Technology of Japan reported a recent trend toward a decrease in the prevalence of obesity among junior high school children (3). Recently, significant concern regarding childhood obesity and associated metabolic disorders has spread in the Japanese population, especially among children and adolescents residing in cities (3). They are likely to ingest fewer sugar-sweetened beverages and snacks as well as fat-rich foods than in the past. In addition, they tend to limit sedentary activities and participate in various sports (3). These lifestyle changes may contribute to the decrease in the incidence of type 2 diabetes in 2001–2004 in the Tokyo metropolitan area.

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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 reported 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.

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

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.

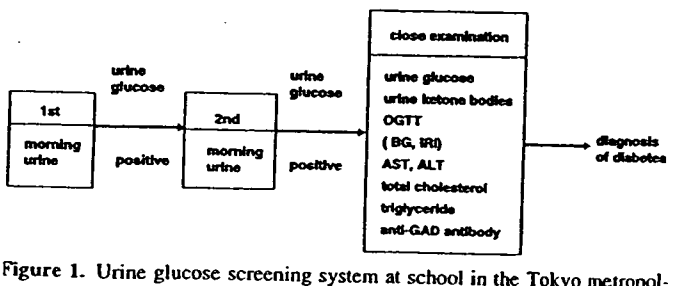

Figure 1. Urine glucose screening system at school in the Tokyo metropolitan area.

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

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

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.

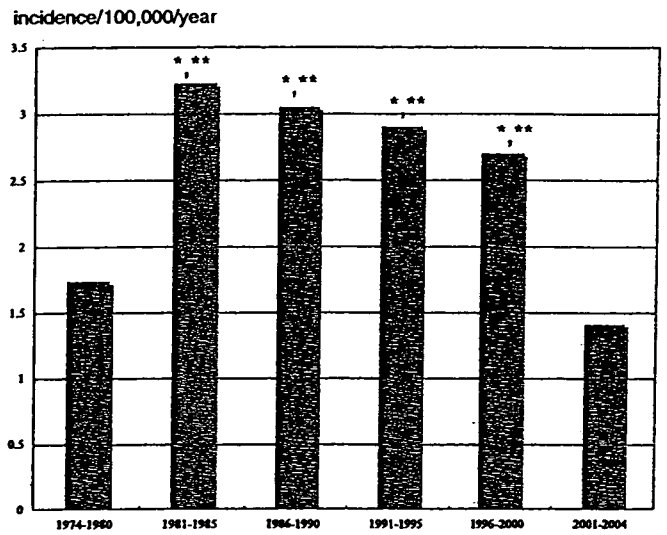

Figure 2. Overall incidence of type 2 diabetes as detected by the urine glucose screening program for 5-y periods from 1974 to 2004 in Tokyo. *The incidence in 1974–1980 was significantly lower than that recorded in 1981–1985, 1986–1990, and 1991–1995 ($p = 0.0038, 0.0091, 0.0226$, respectively) and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