80年代から90年代にかけて動き出したにもかかわらず，かえって治療中断率を高くしてしまっているという皮肉な結果を示している．当センターが糖尿病専門医療施設ゆえの患者バイアスと，治療を中断する患者の減少がみられないという2つの側面から，80年代初診と比べて90年代初診の2型糖尿病患者の合併症の減少が認められなかったのであろう．

一方，1型糖尿病患者の単純網膜症頻度は80年代初診群より90年代初診群で有意に低下しており，これは医療レベルの向上の結果と考えられる．しかし1型の増殖網膜症の頻度は80年代初診群より90年代初診群が高かった．1型糖尿病では1年以上の治療中断はまず考えにくいので，当センターの専門施設ゆえの患者バイアスが原因と考えられる．さらに増殖網膜症合併患者は単純網膜症より長い罹病期間を経ていると考えられるので，日本の1型糖尿病の診療レベルの向上があった以前にすでに1型糖尿病を罹患していたことも考えられる．

今回，80年代及び90年代に当センターを初診した15歳未満発症発見糖尿病患者の合併症の状態を断面調査した．1型糖尿病は80年代より90年代の方が単純網膜症においてのみ頻度が低下していた．このことが医療の向上によるものであるならば，2000年代初診の1型糖尿病患者の合併症の頻度を調査すればさらに低下することが望まれる．2型糖尿病においては明らかな合併症の頻度の低下がみられず，治療中断例がむしろ多くなったことがその原因の一つと考えられた．日本には学校検尿システムという良いシステムがあるので，学校検尿等で糖尿病が発見されたら放置することなく医療機関に通院してもらい，合併症を予防していく必要性がさらに高まっていると考えられる．

尚，本論文の要旨は第44回日本糖尿病学会年次学術集会において発表した．

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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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DOI: 10.2337/dc07-0153

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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

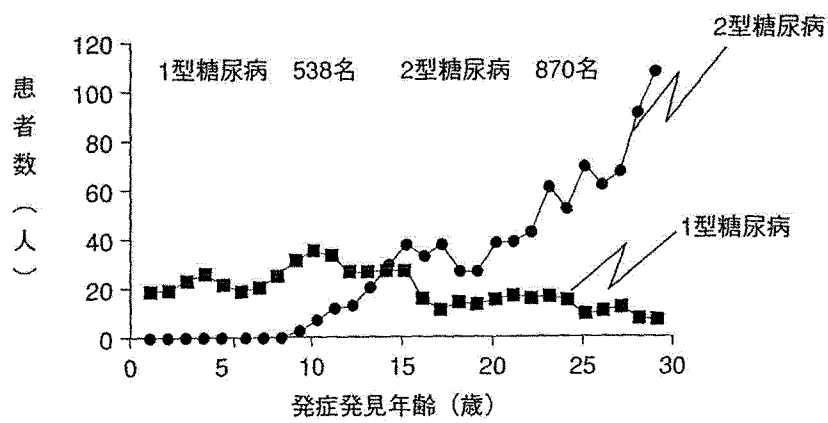
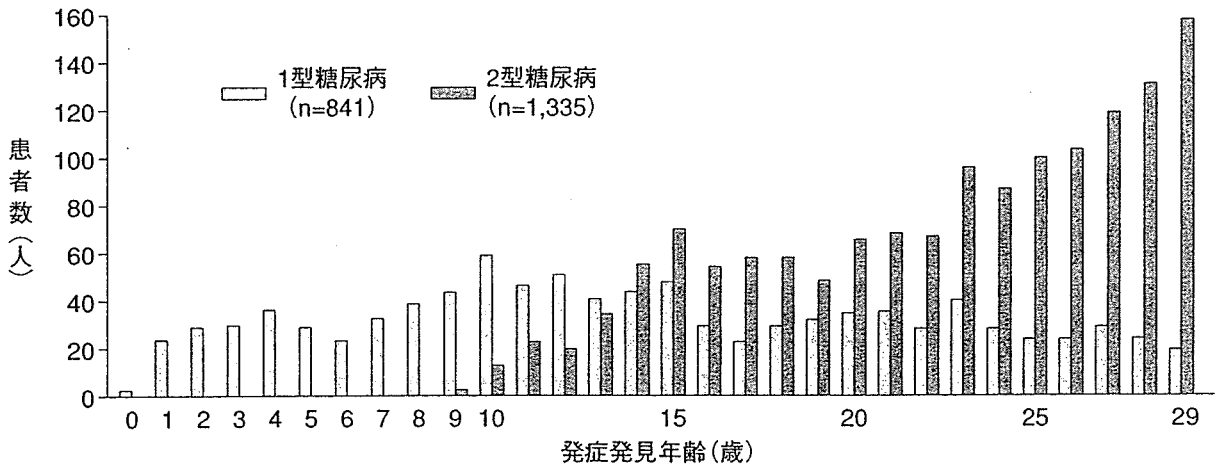


図1　東京女子医科大学糖尿病センターの30歳未満発見発症糖尿病患者の病型別および発見年齢別患者数
（大谷敏嘉・他：糖尿病　32：717，1989，Otani T et al：Diab Res Clin Prac 10：241，1990より引用）

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）

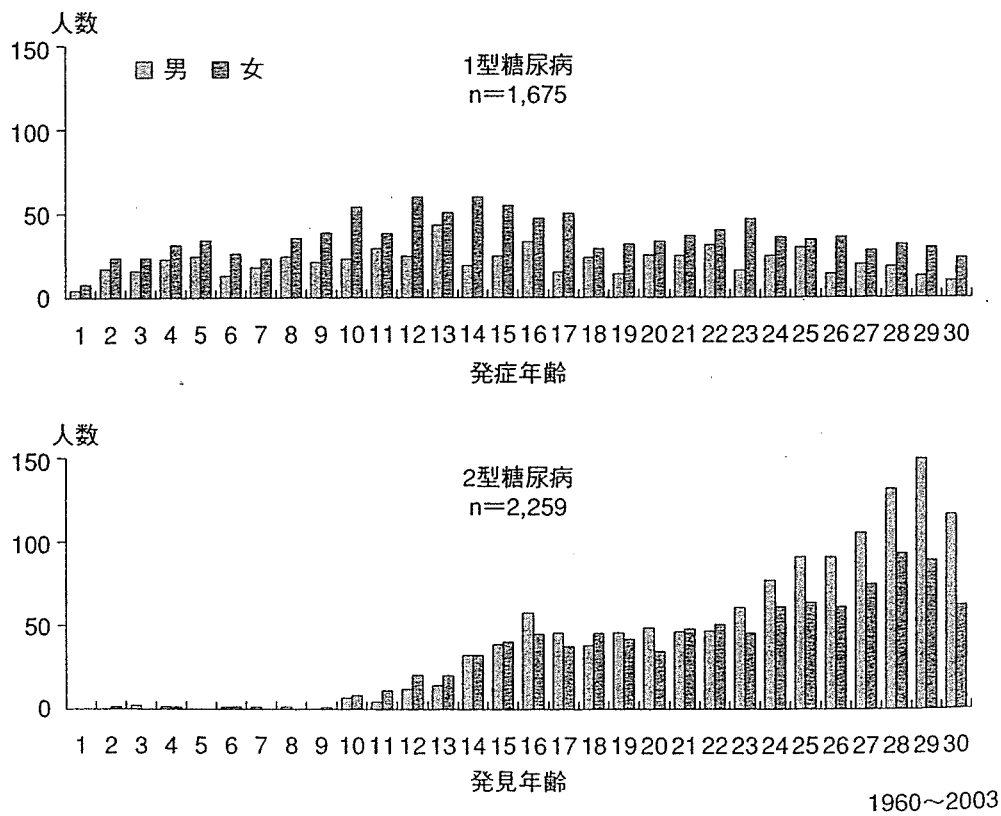


図3　30歳未満発見発症1型および2型糖尿病患者の発見発症年齢ごとの男女別人数

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	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

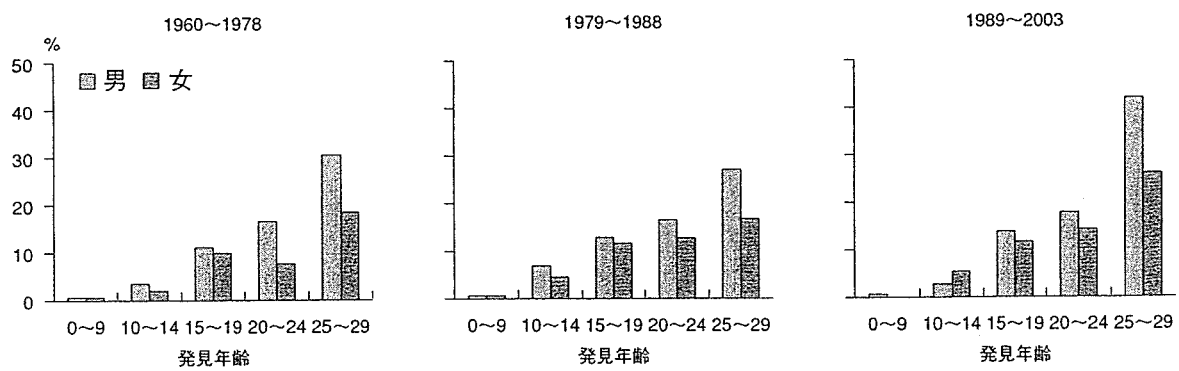


図4　過去最大BMI≧25の2型糖尿病患者の各年代ごとの各発症年齢群における男女別比率
（内潟ら，論文準備中）

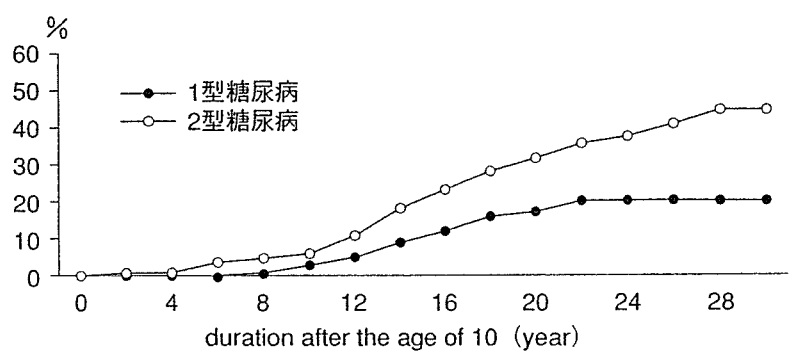


図5　Comparison of cumulative incidence of diabetic nephropathy in early onset type 1 and type 2 patients
（Yokoyama H et al：Kidney International 58：302，2000より引用）

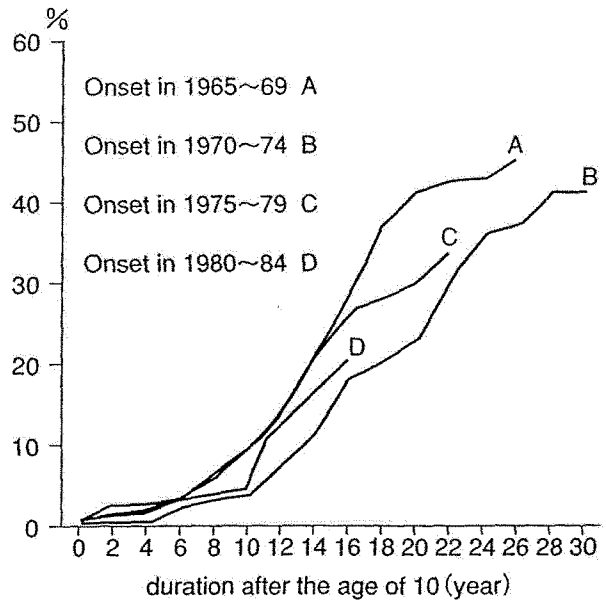


図6 Cumlative incidence of diabetic nephropathy in early onset type 2 patients
(Yokoyama H et al : Kidney International 58 : 302, 2000 より引用)

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	p
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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0031-3998/07/6102-0141
PEDIATRIC RESEARCH

Vol. 61, No. 2, 2007
Printed in U.S.A.

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.

Received August 17, 2006; accepted October 6, 2006.
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DOI: 10.1203/pdr.0b013e31802d8a69

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.

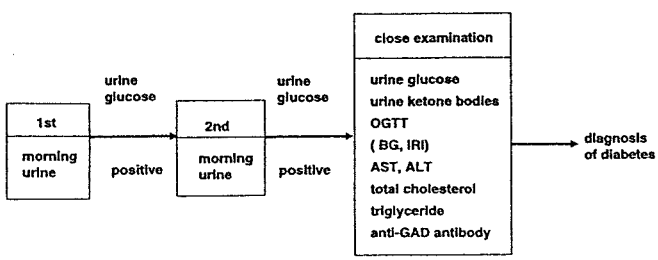

Figure 1. Urine glucose screening system at school in the Tokyo metropolitan area.

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 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.

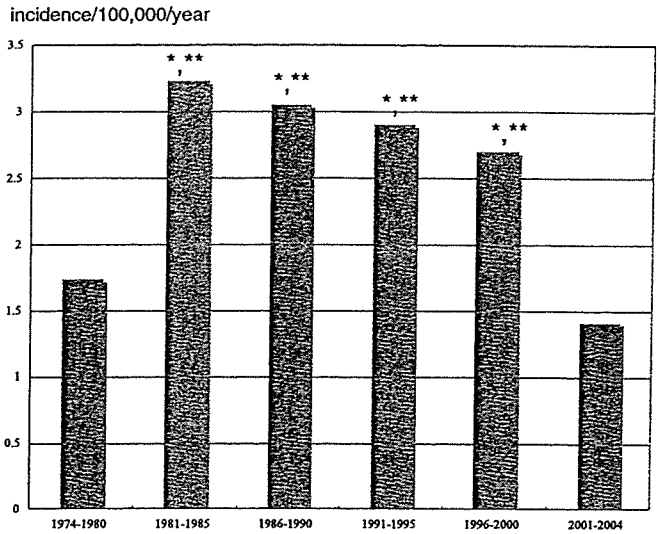

Figure 2. Overall incidence of type 2 diabetes as detected by the urine glucose screening program for 5-y periods from 1974 to 2004 in Tokyo. *The incidence in 1974–1980 was significantly lower than that recorded in 1981–1985, 1986–1990, and 1991–1995 ($p = 0.0038$, 0.0091, 0.0226, respectively) and 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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文献11

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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DOI: 10.2337/dc06-1017

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文献12

Kidney International, Vol. 58 (2000), pp. 302–311

Higher incidence of diabetic nephropathy in type 2 than in type 1 diabetes in early-onset diabetes in Japan

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Higher incidence of diabetic nephropathy in type 2 than in type 1 diabetes in early-onset diabetes in Japan.

Background. Whether the type of diabetes, race, and year and age of diagnosis affect the incidence of diabetic vascular complications is unknown. That both type 1 and type 2 diabetes occur in the young Japanese population prompted us to investigate whether the type of diabetes and the year of diagnosis are related to the incidence of nephropathy.

Methods. Of the 17,256 diabetic patients who visited the outpatient clinic at our diabetes center between 1965 and 1990, 1578 (9.1%) had early-onset diabetes (diagnosed before the age of 30); of these, 620 (39%) had type 1, and 958 (61%) had type 2 diabetes. The incidence of nephropathy was analyzed in the patients according to postpubertal duration and year of diagnosis.

Results. The cumulative incidence of nephropathy after 30 years of postpubertal diabetes was significantly higher ($P < 0.0001$) in type 2 diabetic patients (44.4%, 95% CI, 37.0 to 51.8%) than in type 1 diabetic patients (20.2%, 95% CI, 14.9 to 25.8%). The incidence of nephropathy among type 1 diabetic patients has declined during the past two decades, whereas it has not among type 2 diabetic patients. The rate ratio for type 2 diabetic patients diagnosed between 1980 and 1984 relative to type 1 diabetic patients diagnosed in the same period was 2.74 (95% CI, 1.17 to 6.41).

Conclusions. The incidence of nephropathy has declined in Japanese patients with type 1 but not in those with type 2 diabetes. In young Japanese patients, because of the higher incidence of nephropathy in type 2 diabetes and the higher prevalence of type 2 than type 1 diabetes, type 2 diabetes is likely the major cause of diabetic nephropathy.

The relationship of the type of diabetes to the risk of diabetic vascular complications has not been studied in detail [1–3]. Type 1 (insulin-dependent) diabetes mellitus has been recognized as an important cause of diabetic nephropathy, leading to diabetic end-stage renal failure (ESRF) and early death [4–7]. However, several reports have identified an increasing incidence of ESRF in patients with type 2 (non–insulin-dependent) diabetes, especially in minorities such as African Americans, Mexican Americans, and Pima Indians [3, 8–14].

Ethnic differences likely lead to differing incidences of diabetes as well as differing incidences of the accompanying vascular complications [3, 10, 12, 14]. Type 2 diabetes is not rare in the young Japanese population [15, 16]. We have recently reported that Japanese patients with early-onset type 2 diabetes can develop severe diabetic vascular complications, such as blindness or ESRF, when in their thirties [17]. On the other hand, a recent report in young Swedish patients with type 1 diabetes indicated a declining incidence of diabetic nephropathy [18], although whether the decline is universally independent of ethnicity or nationality is a matter of debate [19, 20].

The incidence of diabetic ESRF is rising at a much faster rate than ESRF because of all other etiologies worldwide [21, 22], that is, in the United States [23], in some European countries [24], and in Japan [25]. The progression to ESRF is relentless unless treated intervention occurs not only for type 1 but also for type 2 diabetic patients [26, 27], and regular hemodialysis treatment costs between $50,000 and $100,000 US per person annually. The rising incidence of diabetic ESRF, therefore, has prompted the re-evaluation of patients at risk for developing diabetic nephropathy according to race, type of diabetes, and year at diagnosis of diabetes. Because both types of diabetes occur in the young Japanese population, we investigated whether the type of diabetes and the year of diagnosis are related to the incidence of diabetic nephropathy.

Key words: insulin-dependent diabetes, noninsulin-dependent diabetes, childhood diabetes, end-stage renal failure, proteinuria, retinopathy.

Received for publication August 12, 1999
and in revised form January 19, 2000
Accepted for publication February 1, 2000

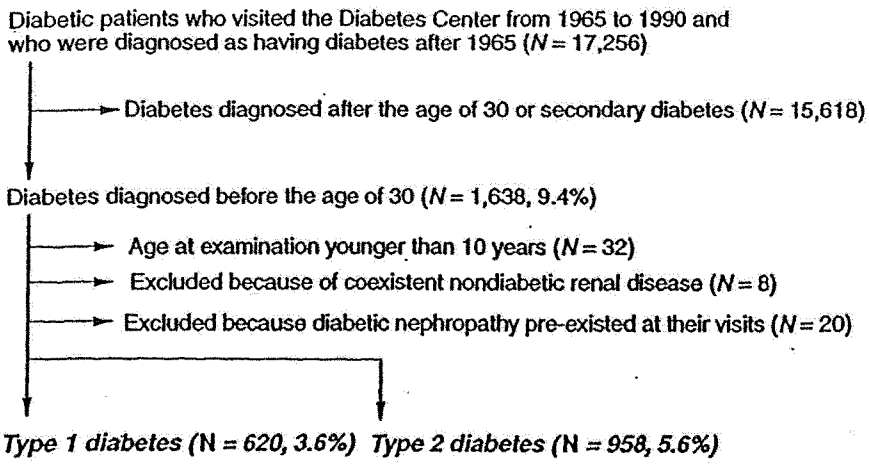

Fig. 1. Patient selection.

METHODS

Study population

We performed a clinic-based epidemiologic observational study. Patients can visit the outpatient clinic at the Diabetes Center, Tokyo Women's Medical University, without any referrals, and the charge for treatment paid by the patient is the same as in the other hospitals. A large population of diabetic patients (N = 17,256) who resided in the Tokyo metropolitan area (about 5400 km^2) attended the outpatient clinic between 1965 and 1990, which corresponds to approximately 10% of diabetic patients attending to a medical clinic in the metropolitan area. Among them, 1638 (9.4%) had early-onset diabetes (diagnosed before the age of 30; Fig. 1). Thirty-two early-onset diabetic patients were excluded because they were prepubertal (younger than 10 years old) at examination. Eight patients were excluded because of coexisting nondiabetic renal disease, and 20 patients were excluded because they already had nephropathy before their visits to our clinic. Of the remaining 1578 (9.1%) patients with early-onset diabetes, 620 (39%) with type 1 and 958 (61%) with type 2 diabetes were included in the study. The proportion of male sex in each type was consistent with previous reports in a young Japanese diabetic population [16, 17, 28].

The diagnosis of diabetes and classification of diabetes type (type 1 or type 2) was made according to the World Health Organization criteria [29]. Briefly, type 1 diabetes was defined as the patient being prone to ketosis and requiring insulin therapy within one year after the diagnosis. Type 2 diabetes was diagnosed if the patient was found not to be ketosis prone, did not require insulin therapy for more than one year after the diagnosis, and/or exhibited preserved insulin secretion even when treated with insulin. Type 2 diabetes was diagnosed because of symptoms (27%), other complaints (28%), or screening tests (45%). To confirm the diagnosis of the diabetes type, serum C-peptide levels were measured in patients treated with insulin using a synthetic human C-peptide kit (C-PEPTIDE RIA; Shionogi, Tokyo, Japan). The limit of detection of the kit was 0.1 ng/mL, and interassay and intra-assay coefficients of variation were 6.4 and 6.7%, respectively.

The patients visited the clinic every one to three months (8 visits per annum on the average). Blood pressure was measured using a sphygmomanometer and an appropriately sized cuff with the patient in a seated position. Glycosylated hemoglobin (HbA1c) was measured by high-performance liquid chromatography (HPLC; HA8110; Kyoto Daiichi Kagaku, Kyoto, Japan). The normal range of HbA1c by HPLC was 4.8 to 6.4%. An average of the HbA1c values during a year at first visit was calculated. For the patient who had no data on HbA1c at the first visit (before 1980, HbA1c measurement had not been instituted), the average of the first available year for HbA1c was used. Patient profiles regarding the diagnosis of diabetes and medical treatment to control the blood glucose level were compiled from information obtained through interviews and data obtained from other hospitals attended by the patients. Data on the history of diabetes (any type of diabetes) in first-degree relatives were obtained from patients by interview.

Outcome measures

In accordance with suggestions by Parving et al, diabetic nephropathy was diagnosed clinically if the following criteria were fulfilled: persistent proteinuria, presence of diabetic retinopathy, and absence of clinical or laboratory evidence of disease other than diabetic nephropathy in the kidneys or renal tract [30]. Proteinuria was measured at each visit (every 1 to 3 months) using Albustix (Miles-Sankyo, Tokyo, Japan), which has a detection limit of 300 mg/L. The onset of proteinuria was

defined as the time when the first positive test was obtained.

Statistical analysis

The incidence density and cumulative incidence were used as measures of the frequency of diabetic nephropathy. The incidence density is presented as the number per 1000 person-years based on the ratio of the observed number of patients experiencing the event (cases) to the total person-years of exposure (at risk). The 95% CI was computed by a modification of the Mantel and Haenzel procedure for follow-up data [31–33]. The association of covariates with the risk of an event (developing diabetic nephropathy) was assessed through the computation of rates with stratification and regression models. Log-linear Poisson regression models using SAS-GENMOD were used to assess the effects of covariates on the absolute risk and to estimate the cumulative incidence [34–36]. A comparison of the incidence density with the rate ratio was performed using the score chi-squared test, and the normal approximation after log-transformation was used for the calculation of confidence intervals [33, 35]. The rate ratio was calculated by dividing the incidence density of diabetic nephropathy in type 2 diabetic patients by that in type 1 diabetic patients. The cumulative incidence was plotted using the Kaplan–Meier method with the log-rank test statistic.

Person-years were primarily accumulated from the diagnosis of diabetes. The incidence density was calculated for five-year periods using two types of observation periods: the entire duration of diabetes and the postpubertal duration of diabetes. The observation based on postpubertal duration of diabetes is considered more relevant in this study since (*1*) the duration of diabetes before puberty does not contribute much to the risk of diabetic nephropathy [37–40], and (2) it can compensate for the considerable differences in age at diagnosis between type 1 and type 2 diabetic patients. Patients who developed diabetes before the age of 10 years were entered into the calculation of postpubertal diabetes when they reached age 10. For patients who developed nephropathy, the contribution of person-years was accumulated until the year of onset of nephropathy. Those who remained free from nephropathy or those who deceased without developing nephropathy contributed to person-years until the last examination (the end of follow-up up to March 1997). Those who had no nephropathy and discontinued visits, presumably because they went outside of the Tokyo area, contributed to person-years until the last clinic visit. Differences between relevant groups were tested using the Student's unpaired *t*-test for continuous variables and the chi-squared test for dichotomized variables. *P* values under 5% (two-tailed) were taken to indicate statistical significance. Analyses were run on a personal computer using SPSS for Windows, version 6.0, and SAS for Windows, version 6.11.

Table 1. Clinical characteristics of patients with type 1 and type 2 diabetes diagnosed before the age of 30

Characteristic	Diabetes	
	Type 1 (N = 620)	Type 2 (N = 958)
Male sex *N of patients (%)*	239 (39)	530 (55)
Calendar year at diagnosis of diabetes		
N of patients (%)		
1965–69	67 (11)	94 (10)
1970–74	104 (17)	137 (14)
1975–79	137 (22)	195 (20)
1980–84	165 (26)	250 (26)
1985–90	147 (24)	282 (30)
Age at diagnosis of diabetes		
N of patients (%)		
Diabetes diagnosed at 0–9 years	205 (33)	5 (1)
Diabetes diagnosed at 10–19 years	257 (41)	278 (29)
Diabetes diagnosed at 20–29 years	158 (26)	675 (70)
Age at first visit		
Diabetes diagnosed at 0–9 years	15.4 ± 6.2	20.1 ± 7.8
Diabetes diagnosed at 10–19 years	20.1 ± 4.8	20.6 ± 6.3
Diabetes diagnosed at 20–29 years	27.6 ± 5.1	30.7 ± 6.7
Body mass index *kg/m²*	19.8 ± 2.9	23.0 ± 5.2
HbA1c at first visit %	9.5 ± 2.0	8.7 ± 2.2
Systolic blood pressure at first visit *mm Hg*	113 ± 12	117 ± 16
Diastolic blood pressure at first visit *mm Hg*	71 ± 9	74 ± 12
Diabetes in first-degree relatives % (95% CI)	24 (21–27)	56 (53–59)
Therapy for diabetes at first visit		
N of patients (%)		
Diet only	0 (0)	431 (45)
Tablets	0 (0)	182 (19)
Insulin	620 (100)	345 (36)
Serum C-peptide levels in insulin users *ng/mL*		
Fasting		
Mean	0.1	1.2
95% CI	0–0.2	1.1–1.3
Two hours postprandial		
Mean	0.1	2.5
95% CI	0–0.2	2.3–2.7
Age at final examination		
Diabetes diagnosed at 0–9 years	24.6 ± 7.7	29.2 ± 7.3
Diabetes diagnosed at 10–19 years	29.6 ± 6.5	27.6 ± 8.1
Diabetes diagnosed at 20–29 years	37.2 ± 7.0	38.5 ± 9.0
Postpubertal duration at examination *years*	15.7 ± 7.2	12.4 ± 8.4

Plus-minus values are mean ± SD. CI denotes confidence interval.

RESULTS

Clinical features of patients with type 1 and type 2 diabetes diagnosed before the age of 30

Clinical and biochemical characteristics of the patients with early onset diabetes are shown in Table 1. Thirty-nine percent of the type 1 diabetic patients and 55% of the type 2 diabetic patients were male. The distribution of patients according to the calendar year at diagnosis