Etiology and Glycemic Control Among Thai Children and Adolescents with Diabetes Mellitus

Jeerunda Santiprabhob MD*,
Praewvarin Weerakulwattana MSc*, Sunattra Nunloi BSc*,
Pornpimol Kiattisakthavee BSc*, Renu Wongarn BA**,
Jirapa Wekawanich MSc***, Pairunyar Nakavachara MD*,
Katharee Chaichanwattanakul BSc*, Supawadee Likitmaskul MD**

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** Division of Endocrinology and Metabolism, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University*
*** Division of Nutrition, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University*
**** Pediatric Education and Counseling Training Program, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University*

Background: *There is little data on etiology and metabolic control in children and adolescents with diabetes in developing countries.*
Objective: *Determine the etiology of diabetes in Thai youths and to evaluate their glycemic control.*
Material and Method: *The authors retrospectively reviewed the case records of 157 patients seen at the Department of Pediatrics, Siriraj Hospital between 2003 and 2004.*
Result: *Type 1 diabetes (T1D) comprised 83%, type 2 diabetes (T2D) 13%, and other types 4%. GAD65 and IA-2 antibodies were positive in 63% and 61% of T1D patients, and 0% and 9% of T2D patients, respectively. There were an increasing number of new cases, both T1D and T2D, during the study period compared with a previous study conducted at the hospital. Mean HbA1c in T1D and T2D were 8.9 $\pm$ 2.1% and 6.2 $\pm$ 1.80%, respectively ($p < 0.001$).*
Conclusion: *Based on the present study, glycemic control appeared to be more satisfactory in T2D patients than those with T1D. Glycemic control among T1D patients was comparable to others in developed countries.*

Keywords: *Diabetes mellitus type 1 (T1D), Diabetes mellitus type 2 (T2D), Glycemic control*

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Diabetes mellitus is a chronic disease, which could lead to severe complications if patients' glucose level is not well controlled. The disease is now one of the most common non-communicable diseases globally. T1D is the most common form of diabetes among children and adolescents. The incidence of T1D varies greatly between nationalities. The incidence of T1D in a Thai population was low, 0.3-0.5 per 100,000 children per year during 1991-1995[1,2]. While T1D is common among children, T2D is the most frequent form of diabetes mellitus in all parts of the world. It is estimated that currently some 194 million people worldwide, or 5.1% of the adult population have diabetes, and the number is projected to be 333 million, or 6.3%, by 2025[3]. It is worrisome that there is also an increasing prevalence of T2D in children and adolescents associated with an increasing prevalence of obesity among this young population[4].

Since 1996, the Department of Pediatrics, Siriraj Hospital has established a multidisciplinary care team consisting of three pediatric endocrinologists, one

Correspondence to : Santiprabhob J, Division of Endocrinology and Metabolism, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, 2 Prannok Rd, Bangkok 10700, Thailand. Phone & Fax: 0-2419-7000 ext. 5676, E-mail: sijst@mahidol.ac.th

diabetic nurse educator, one full-time and one part-time nutritionists, and a psychologist[5]. The Department is the largest treatment center for children and adolescents with diabetes in Thailand. Most of the presented patients belong to the lower to middle socio-economic groups. Even though the authors provide treatment with a team approach, there are a number of problems the authors have encountered in treating patients with T1D, e.g. fear of children and their parents to take more than two injections of insulin a day, patients' non-compliance with diabetes nutrition, infrequent blood glucose monitoring due to the high cost of the glucose test strips and patients' inadequate understanding about the values of testing, etc. There are very few reports on etiology and glycemic control among Thai children with diabetes[5-7]. The objectives of the present study were to investigate the current etiology of childhood diabetes at the Institute compared to the authors' previous report[7], and to evaluate glycemic control among the presented patients. The authors wish to use the information from the present study to improve diabetes care for Thai children.

Material and Method

Subjects

The authors retrospectively reviewed the medical records of all diabetic patients (n = 157) who had been seen at the Department of Pediatrics, Siriraj Hospital between January 2003 and December 2004. The present study was approved by the Ethics Committee of Siriraj Hospital, Mahidol University.

Criteria for etiologic classification of diabetes are:[8,9]

1. T1D: describing patients whose clinical presentation was characterized by abrupt onset of symptoms, dependence on injected insulin to sustain life, and proneness to ketosis.
2. T2D: describing those patients frequently presenting with few or no symptoms, whose insulin levels were variable, and who were not ketosis-prone, and therefore did not depend on insulin to sustain life. Most patients were overweight.
3. Other types of diabetes: describing patients with other conditions and/or syndromes associated with diabetes.

Method

Data was obtained from each patient's medical record at the last visit including type of diabetes, sex, date of birth, and age at diagnosis. The characteristics of each patient (including age and duration of diabetes) and details of diabetes management (including insulin dosage and insulin regimen) were collected. Data on glycemic control was obtained using the available HbA1c level performed at each patient's last visit. Since 2002, GAD65 and IA-2 antibodies were measured in most of the newly diagnosed diabetic patients. The results of autoantibodies were recorded.

HbA1c measurement

HbA1c was performed using a Dimension® HbA1c assay kit (Dade Behring Inc., USA). The HbA1c measurement was based on a turbidimetric inhibition immunoassay (TINIA) principle (normal range 4.8-6.0%).

GAD65 and IA-2 antibodies

Autoantibodies were measured based on radioligand assays, using commercial kits, CentAK® anti-GAD65, and CentAK® anti-IA-2 (Medipan, Selchow, Germany). GAD65 and IA-2 antibodies were considered positive if levels were $\geq$ 0.9 U/ml, and $\geq$ 0.75 U/ml, respectively.

Statistical analysis

Summary statistics were expressed as means $\pm$ SD. Comparison of means was done by Student's *t*-test for normally distributed data and the Mann-Whitney *U* test for non-normally distributed data. Multiple group comparisons were done by a one-way analysis of variance. Pearson's correlation coefficient was used to assess correlations between variables with normal distribution and Spearman's correlation for non-normally distributed data. Statistical analysis was performed using SPSS version 11.5 (SPSS, Chicago, IL) for personal computers. A p-value of less than 0.05 was considered statistically significant.

Results

Etiology of diabetes

One hundred and fifty seven patients were included in the present study. One hundred and thirty one patients (83%), 61 male and 70 female, were diagnosed with T1D. Twenty patients (13%), eight male and 12 female, had T2D, and six patients (4%), four male and two female, had other types of diabetes. In this "other type of diabetes" group, three patients had Prader-Willi syndrome, one patient had Down syndrome, one patient had dyskeratosis congenita, and one patient had lymphoma.

Among 157 patients, 46 patients were newly diagnosed with diabetes during the period of study. There were an increasing number of new cases with

diabetes both T1D and T2D compared with previous studies conducted at the Institute[6,7] (Table 1).

Fifty-one patients with T1D and 11 patients with T2D had their GAD65 and IA-2 antibodies measured. Among T1D patients, 39 patients (76.5%) had at least one antibody, and 24 patients had both antibodies (47.1%). Only one patient with T2D had weakly positive IA-2 antibodies (0.76 U/mL). The frequency of antibodies to GAD65 and IA-2 in diabetic patients is shown in Table 2.

The characteristics of patients with T1D (n = 131) and T2D (n = 20) are shown in Table 3. Patients with T2D were significantly older at onset of diabetes than those with T1D. Glycemic control was better in T2D patients.

Glycemic control in T1D

Out of 131 patients with T1D, 127 patients had HbA1c measurement at the last visit. Mean HbA1c was 8.9 $\pm$ 2.1%. Only 48 patients (38%) had HbA1c < 8%. For patients who had had diabetes longer than one year (n = 114), the mean HbA1c level was 9.1 $\pm$ 2.0% and 37 patients (32%) had HbA1c < 8%.

Comparison of HbA1c levels by patient characteristics is shown in Table 4. HbA1c levels were weakly correlated with age (r = 0.27, p = 0.002) and diabetes duration (r = 0.23, p = 0.009). According to the ADA statement of care for children with T1D, the targeted HbA1c levels vary according to the ages of patients: 0-5 years of age, the targeted HbA1c is < 8.5%; 6-12 years of age, the targeted HbA1c is < 8%; 13-19 years of age, the targeted HbA1c is < 7.5%; older than 19 years of age, the targeted HbA1c is < 7%[10]. The presented data showed that patients between 0-5 years old had the highest percentage of success with the recommended glycemic control while patients in the older age groups had less success (Fig. 1).

Insulin injection regimen in patients with T1D

Out of 131 patients with T1D, 94 patients were on twice-daily insulin injections, 26 patients were on three daily insulin injections, and 11 patients were on four or more daily insulin injections (multiple daily insulin injections, MDIs). There was no statistical difference in HbA1 c levels among the three different insulin regimen groups (p > 0.05).

Glycemic control in T2D

Seventeen out of 20 patients with T2D had HbA1c measurement at the last visit. The mean HbA1c was 6.2 $\pm$ 1.8%. Fourteen patients (82%) had HbA1c < 7%. Nineteen out of 20 patients were on medications.

Table 1. Etiology and number of patients with new onset diabetes at different study periods

	Jan 1987 – Dec 1996[6] (10 years)	Jan 1997 – Dec 1999[7] (3 years)	Present study Jan 2003 – Dec 2004 (2 years)
Total number (%)	59 (100)	39 (100)	46 (100)
T1D (%)	55 (93)	28 (72)	32 (70)
T2D (%)	3 (5)	7 (18)	13 (28)
Other type (%)	1 (2)	4 (10)	1 (2)
	(-thalassemia major)	(Prader-Willi syndrome [1], SLE [1], leukemia [2]	(Down syndrome)
Total cases/year	5.9	13	23
T1D cases/year	5.5	9.3	16
T2D cases/year	0.3	2.3	6.5

Table 2. Frequency of antibodies to GAD65 and IA-2 in diabetic patients

Type of diabetes	Number of patients tested for antibodies	GAD65	IA-2
T1D	51	32 (63%)	31 (61%)
T2D	11	0 (0%)	1 (9%)

Table 3. Comparison of characteristics between patients with T1D and T2D

Characteristics	T1D n = 131	T2D n = 20	p-value
Age (years)	12.2 ± 4.6	14.4 ± 2.6	0.003
Age at onset (years)	7.7 ± 4.0	12.7 ± 2.8	<0.001
Duration (years)	4.5 ± 3.6	1.8 ± 1.8	<0.001
Weight (kg)	41.4 ± 5.8	78.3 ± 22.9	<0.001
Height (cm)	143.4 ± 19.4	159.5 ± 10.5	<0.001
BMI (kg/m^2)	19.3 ± 3.7	30.4 ± 6.4	<0.001
HbA1c (%)	8.9 ± 2.1	6.2 ± 1.8	<0.001

Table 4. Comparison of HbA1c results by patient characteristics in T1D (n = 127)

Characteristics	N (%)	Mean	p-value
Gender			
Male	60 (47)	8.9 ± 1.9	0.847
Female	67 (53)	8.8 ± 2.2	
Age (years)			
0-5	11 (9)	8.1 ± 0.9	0.014
6-12	56 (44)	8.3 ± 1.8	
13-18	49 (38)	9.5 ± 2.4	
19+	11 (9)	9.5 ± 2.0	
Duration			
0-12 months	13 (10)	6.8 ± 1.2	<0.001
13 months - 4 years	64 (51)	8.9 ± 1.8	
5 years+	50 (39)	9.4 ± 2.3	

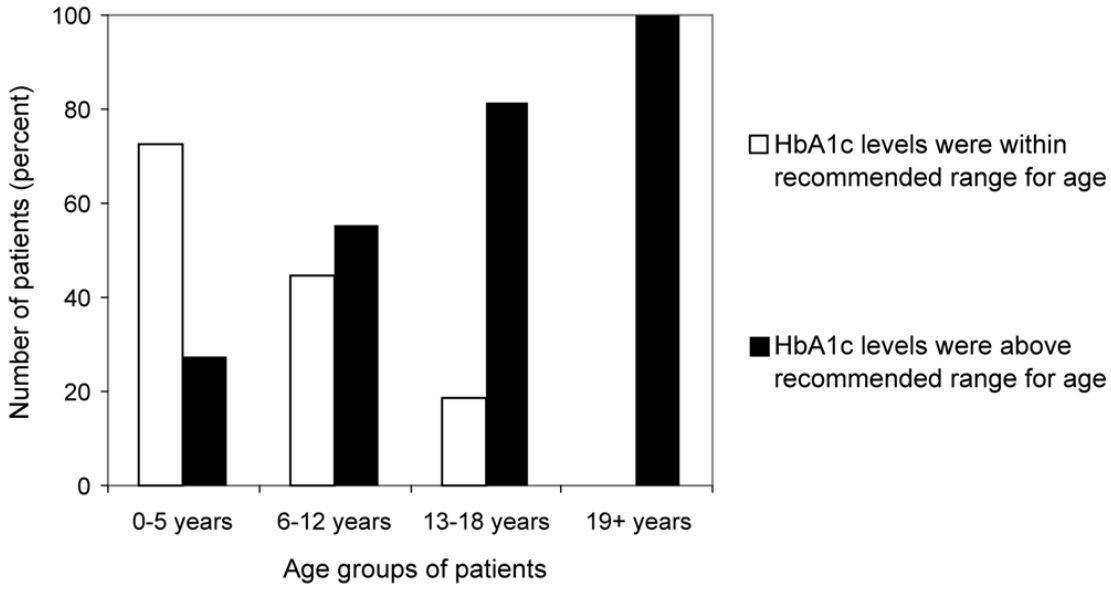

Fig. 1 Percentage of patients with T1D achieving recommended HbA1c levels by age group

Sixteen of them were on only metformin, one patient was on metformin and acarbose, one patient was on metformin, sibutramine, and orlistat, and one patient was on sibutramine.

Discussion

The present study reported an increasing number of new patients with diabetes compared to previous studies conducted at the Institute[6,7]. The increase in T1D among Thai children is similar to the reports from other parts of the world[11-13]. T2D was previously considered a disease of adults, however, there have been an increasing number of children and adolescents with T2D in recent years[14-16]. It is estimated that T2D represents 8-45% of patients with diabetes currently diagnosed in many US pediatric centers[17]. Like Western countries, an increasing number of T2D is seen among Asian children and adolescents[18,19] along with an increased incidence of overweight[20]. At the Institute, the percentage of patients with T2D has increased dramatically in two decades from 5%[6] to 28%. A previous report from the Institute also supported the finding that an increasing number of children with T2D are associated with an increasing prevalence of obesity[7]. This emerging epidemic obesity among children and adolescents is worrisome. It is important for all healthcare providers to detect children with obesity and provide early intervention to prevent them developing T2D.

Since 2002, the authors started measuring GAD65 and IA-2 antibodies in newly diagnosed diabetic patients. Of 51 T1D patients, antibodies to GAD65 and IA-2 were found in 32 (63%) and 31 (61%), respectively. The frequencies of these antibodies in Thai youth were similar to that found in Australians[21], Americans[22], and Japanese[23]. The frequencies of GAD65 antibodies in the presented patients were higher than that found in Korean (30%)[24] and Chinese (40%)[25] patients. Thus, there are variations in prevalence of autoantibodies among people of different Asian ethnic backgrounds.

Out of 11 patients with T2D, only one patient had weakly positive IA-2 antibodies. Whether this patient had latent autoimmune diabetes of adulthood (LADA) would require a long-term follow-up of his clinical course to determine.

In the present study, patients with T2D had more satisfactory glycemic control than those with T1D. This finding was not unexpected since patients with T1D needed to be compliant with diabetes self-management skills, which are difficult tasks, in order to achieve good blood glucose control while T2D patients could have optimal glucose control with lifestyle intervention and oral medications. Our T2D patients had a relatively short duration of disease, a longer follow-up is required to determine their long-term glycemic control. The mean HbA1c of 8.9% in the presented patients with T1D is comparable to other studies from North India[26], France[27], Scotland[28], Northern Ireland[29], and multinational studies from 18 countries[30] (mean HbA1c measured using a HPLC method were 8.4%, 9.0%, 8.9%, 8.8%, and 8.6%, respectively). The difficulty in achieving targeted glycemic control in young patients worldwide is similar to the Diabetes Control and Complications Trial study, which reported that HbA1c levels were decreased to only 8.1 ± 0.1% in adolescents who were under intensive management[31]. The correlations between HbA1c level and age and between HbA1c level and diabetes duration in the present study are consistent with previous large cross-sectional studies[27,29,30]. These results confirm that blood glucose control is poorest during puberty and among patients with a long duration of diabetes. The fact that adolescents with diabetes are more independent, less supported by the family, and have more important things in life (e.g. studies, peers, loving relationship etc.) than young children with diabetes, can lead to a worsening of glycemic control. In addition, patients with a long duration of diabetes, and a lack of continuous and repeated education on diabetes self-management skills could explain the poor glycemic control. On the other hand, the lower HbA1c level seen in patients having diabetes less than a year is likely to result from endogenous insulin secretion. Most of the presented patients (72%) were on twice-daily insulin injections. MDIs with glargine insulin were introduced to the presented patients two years ago and only 8% of patients were using this regimen. It has been difficult to initiate MDIs because of the patients' physical and psychological discomfort from multiple injections, the inconvenience of carrying insulin to school, and the high cost of glargine insulin. In the present study, the authors did not find any significant difference in glycemic control among patients with different insulin regimens.

The present study does have limitations. The retrospective nature of the present study did not allow the authors to obtain other important data that might contribute to glycemic control. For example, the frequency of self-monitoring of blood glucose, presence of family support, patients' socio-economic status, and number of clinic attendances were not reported. To

improve care for children with diabetes, the authors need a prospective study to determine risk factors associated with poor glycemic control as well as data on acute and chronic complications among the presented patients. Although the authors have provided a multidisciplinary care team approach for children with diabetes, the authors have not been successful in treating them. The HbA1c in most T1D patients did not meet the recommended target levels. The authors have recognized the importance of continuing diabetes education, thus the authors have provided a 30-minute session on various topics of diabetes at the diabetes clinic and recently established the diabetes call center to provide close telephone communication between patients and the care team. Future research on the influence of regular contact between the team and patients on glycemic control will need to be determined. In addition, improvements in health care at the national level are required. For example, these include having the test strips being paid for by health insurance (thru a government program or private insurance), having a policy for referring patients to an experienced diabetes center for proper education, and having more information on diabetes and its complications available for laypeople to increase their awareness of this disease.

In conclusion, the authors have found an increasing number of children with diabetes both T1D and T2D. Although the glycemic control appeared to be satisfactory among children with T2D, the percentage of children with T1D achieving optimal glycemic control was less than satisfactory.

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สาเหตุและผลการควบคุมระดับน้ำตาลในผู้ป่วยเบาหวานเด็กและวัยรุ่นไทย

จีรันดา สันติประภพ, แพรววริญญ์ วีรกุลวัฒนา, สุเนตรา นุ่นลอย, พรพิมล เกียรติศักดิ์ทวี, เรณู วงษ์อาน, จิราภา เวคะวนิชย์, ไพรัลยา นาควัชระ, คัทรี ชัยชาญวัฒนากุล, สุภาวดี ลิขิตมาศกุล

ข้อมูลเกี่ยวกับสาเหตุและผลการควบคุมระดับน้ำตาลในผู้ป่วยเด็กและวัยรุ่นที่เป็นโรคเบาหวานในประเทศที่กำลังพัฒนานั้นยังมีจำนวนน้อย วัตถุประสงค์ของการศึกษานี้เพื่อศึกษาถึงสาเหตุและผลการควบคุมระดับน้ำตาลในผู้ป่วยเด็กและวัยรุ่นไทย โดยเป็นการศึกษาย้อนหลังในผู้ป่วยจำนวน 157 ราย ที่ได้รับการรักษาที่ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล ระหว่างปี พ.ศ. 2546 - พ.ศ. 2547 พบว่าผู้ป่วย ร้อยละ 83 เป็นเบาหวานชนิดที่ 1 ร้อยละ 13 เป็นเบาหวานชนิดที่ 2 และร้อยละ 4 เป็นเบาหวานชนิดอื่น ๆ ผู้ป่วยเบาหวานชนิดที่ 1 ตรวจพบ GAD65 antibody และ IA-2 antibody ร้อยละ 63 และ 61 ตามลำดับ ในขณะที่ผู้ป่วยเบาหวานชนิดที่ 2 ตรวจไม่พบ GAD65 antibody และพบ IA-2 antibody ร้อยละ 9 เมื่อเปรียบเทียบกับการศึกษาในอดีต พบว่ามีจำนวนผู้ป่วยเบาหวานใหม่เพิ่มขึ้นทั้งเบาหวานชนิดที่ 1 และ 2 ค่าเฉลี่ย HbA1c ในผู้ป่วยเบาหวานชนิดที่ 1 และ 2 เท่ากับ 8.9 $\pm$ 2.1% และ 6.2 $\pm$ 1.80% ($p < 0.001$) ตามลำดับ จากการศึกษานี้ผู้ป่วยเบาหวานชนิดที่ 2 มีการควบคุมระดับน้ำตาลอยู่ในเกณฑ์ดีกว่าผู้ป่วยเบาหวานชนิดที่ 1 ผู้ป่วยเด็กไทยที่เป็นเบาหวานชนิดที่ 1 มีผลการควบคุมระดับน้ำตาลใกล้เคียงกับผู้ป่วยในประเทศที่พัฒนาแล้ว