

Clinical Pictures of Type 2 Diabetes in Thai Children and Adolescents is Highly Related to Features of Metabolic Syndrome.

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Prevalence of type 2 diabetes (T2DM) in children and adolescents has increased, paralleled to the increased prevalence of obesity around the world. The objectives of this study are (1) to identify the clinical presenting features of T2DM in Thai children and adolescents, and (2) to identify evidence of feature of metabolic syndrome in these affected. We analyzed 26 T2DM patients who were treated by Pediatric endocrinologists in our hospital.

The study showed that their mean ages (\pm SD) at diagnosis was 12.1 ± 2.3 years, all were obese and 96% had acanthosis nigricans. Fifty three percents (53%) presented with clinical signs and symptoms which included DKA (19.2%), clinical triad of polyuria, polydipsia and weight loss (15.4%), only polyuria, polydipsia (11.5%) and abnormal menstruation (7%). The rest of 46.2% had no clinical symptoms. The initial fasting or random plasma glucose found above diagnostic range in 84.5%, the rest of 15.5% were diagnosed by using oral glucose tolerance test. Dyslipidemia was found in 75%. Fifteen percents had no family history. Eighty percents had three or more than three features of metabolic syndrome.

In conclusions, clinical picture of type 2 diabetes in Thai youth varied from asymptomatic to severe illness (DKA). Almost all had clinical features of metabolic syndrome. Childhood obesity has become epidemic in our population. Such clinical picture should alert all pediatricians to be aware of chronic diseases and for making an early diagnosis and preventing long term complications in the future.

Keywords: Type 2 diabetes, Metabolic syndrome, Children and adolescents, Obesity, Acanthosis nigricans, Dyslipidemia

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Type 2 diabetes in pediatric population has increased over the last 10 years⁽¹⁾. While the exact incidence of type 2 diabetes in this age group remains unknown, recent studies demonstrated a higher incidence of pediatric diabetes than expected⁽²⁾. The major risk factors for type 2 diabetes among both children and adults include ethnicity, obesity and a family

history of type 2 diabetes⁽³⁾. Our recent publication indicated that type 2 diabetes in Thai children and adolescents increased paralleled to the increased in prevalence of obesity as in other countries^(4,5,6).

A variety of presenting symptom has been described, the most common being the classical triad of polyuria, polydipsia and weight loss which are usually found in type 1 diabetes, but varies in type 2 diabetes. The presentation of type 2 diabetes varies from asymptomatic to the life-threatening condition of diabetic ketoacidosis^(4,7,8). It also appears to be similar to the metabolic syndrome in adults which is characterized by obesity, hyperglycemia and /or insulin resis-

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tance, hypertension and dyslipidemia⁽⁸⁾. The underlying insulin resistance of obesity seems to be an important pathophysiologic event contributing to the metabolic syndrome, and this is already evident in childhood. Recent data has shown that approximately 30% of overweight children have metabolic syndrome and nine out of ten have at least one feature of the syndrome^(9,10).

The objective of this study are; (1) to identify the clinical presenting features of type 2 diabetes in children and adolescents aged under 18 years in Thai population in order to ascertain their presenting symptoms, occurrence of DKA, initial plasma glucose pattern, associated obesity, acanthosis nigricans and the frequency of a family history of diabetes, (2) to identify the evidence and feature of metabolic syndrome in these affected patients.

Material and Method

A cross-sectional review of medical record of type 2 diabetes patients who were followed at Diabetes Clinic, Department of Pediatrics, Faculty of Medicine Siriraj hospital was undertaken. Patients were informed that the data were being collected for an epidemiological study. Individual data at diagnosis included clinical symptoms, age, weight, height, family history of diabetes, physical examination, the presence of acanthosis nigricans and initial lab investigations. The

diagnostic criteria for type 2 diabetes are based on a combination of factors: absence of anti-GAD, IA2 titer, fasting insulin level, obesity, acanthosis nigricans as recommendations by American Diabetes Association.^(3,11,22) Body Mass Index (BMI) was calculated for each patient using the formula : BMI = weight(kg)/height(m²), BMISDS were then calculated using the formula and table supplied by the Thai national growth data⁽¹²⁾. Obesity was defined by BMI above 95th for Thai national growth data⁽¹²⁾.

The criteria for metabolic syndrome (MS) include obesity, impaired glucose tolerance test or type 2 diabetes, hypertension, dyslipidemia. The definition for hypertension was described by data from the update on the Task Force for High Blood Pressure in children and adolescents⁽¹³⁾. Definition of dyslipidemia was described as cholesterol level \geq 200 mg/dl, or triglyceride level \geq 150 mg/dl, or HDL-C level \leq 35 mg/dl, as recommended by National Cholesterol Education Program (NCEP)⁽⁹⁾.

Results

Twenty-six patients who matched the diagnostic criteria of type 2 diabetes were included. Fifteen were females. Their mean ages (\pm SD) at diagnosis was 12.11 \pm 2.32 years. All were obese and ninety-six percents has acanthosis nigricans. Their demographic data are shown in Table 1. Clinical signs and

Table 1. Demographic data of Thai Type 2 diabetes in children and adolescents

	Male	Female	total
Number of case	11	15	26
Age at diagnosis (yr)(Mean \pm SD)	12.04 \pm 2.08	12.15 \pm 2.52	12.11 \pm 2.32
WtSDS	3.20 \pm 1.77	3.34 \pm 1.67	3.29 \pm 1.68
HtSDS	0.64 \pm 1.98	1.35 \pm 3.22	1.08 \pm 2.79
BMI (kg/m ²)	29.92 \pm 3.62	31.87 \pm 4.87	31.25 \pm 4.51
BMISDS	2.35 \pm 0.69	2.85 \pm 0.89	2.67 \pm 0.82
% acanthosis nigricans	94 %	100 %	96.2 %
% obesity	100 %	100 %	100 %

Table 2. Clinical presenting symptoms of Thai type 2 diabetes children at time of diagnosis

Obesity with symptoms	14/26 = 53.9 %
• Polyuria Polydipsia without weight loss	4/26 = 15.4 %
• Polyuria Polydipsia with weight loss	3/26 = 11.5 %
• Diabetes Ketoacidosis (DKA)	5/26 = 19.2 %
• Abnormal menstruation: (irregular, secondary amenorrhea)	2/26 = 7.7 %
Obesity without any compliants	12/27 = 44.4 %

symptoms of type 2 diabetes at time of diagnosis were found in 14 out of 26 patients (53.9%). The rest (46.2 %) had no clinical symptoms except obesity. Presenting symptoms included: diabetic ketoacidosis (19.2%), classical triad of polyuria, polydipsia and weight loss (15.4%), polyuria, polydipsia without weight loss (11.5%) and abnormal menstruation (7%) as tabulated in Table 2.

Results of initial laboratory investigations are tabulated in Table 3. Mean HbA1c (\pm SD) was 9.5 ± 3.7 %. Mean data of fasting plasma glucose, fasting insulin, random plasma glucose, cholesterol and trig-

lyceride were in the abnormal levels (203 ± 96 mg%, 44.7 ± 21.2 mIU/dl, 306 ± 230 mg%, 211.8 ± 33 mg%, 163.1 ± 128.1 mg%, respectively). The individual plasma glucose pattern in all cases were presented in Table 4. All symptomatic presenting patients had plasma glucose levels above the diagnostic criteria for diabetes. In asymptomatic patients, 6 cases (23.1%) had fasting plasma glucose level above the diagnostic criteria of the disease, 2 cases (7.7%) had impaired fasting plasma glucose (IFG), and the other 2 cases (7.7%) had normal fasting plasma glucose level. The diagnosis of patients (4 cases) with normal and

Table 3. Mean laboratory results at time of diagnosis of Thai type 2 diabetes children and adolescents

	Male	Female	Total
Mean HbA _{1c} (%)	9.4 \pm 4.7	9.4 \pm 3.2	9.5 \pm 3.7
Mean fasting PG(mg%)	263 \pm 130	172 \pm 55	203 \pm 96
Mean random PG(mg%)	364 \pm 288	351 \pm 204	360 \pm 230
Mean fasting insulin (mIU/dl)	30.3 \pm 21.7	48.3 \pm 20.4	44.7 \pm 21.2
Total cholesterol (mg%)	209.2 \pm 21.6	213.3 \pm 39.0	211.8 \pm 33
Total HDL-C(mg%)	38.3 \pm 22.2	47.6 \pm 12.2	44.8 \pm 15.9

Table 4. Plasma glucose pattern in both symptomatic and asymptomatic Thai Type 2 diabetes children and adolescents at time of diagnosis

I) Patients who presented with clinical symptoms: all had PG both fasting and random PG above diagnostic range (FPG > 126%, random PG > 200 mg%)

II) Patients who presented with obesity but asymptomatic

- A) 6 cases (23.07 %) had FPG above 126mg%
- B) 2 cases had FPG between 100-126 mg%
- C) 2 cases had normal FPG (<100 mg%) at 91, 85 mg%

Patients in (B),(C) were diagnosed after oral glucose tolerance test.

Table 5. Family History of Type 2 diabetes in Thai children and adolescents

Had family History

- 1st relative (Father or Mother) 7/26 = 26.9 % only
- 2nd relative 13/26 = 50.0 % only
- 3rd relative 2/26 = 7.7 %

Do not have family History 4/26 = 15.4 %

Cases who had no family history, detail as the followings:

- Case 1: presented with mild DKA when he was admitted owing to acute asthmatic attack
- Case 2: presented with symptom of diabetes, polyuria, polydipsia and fasting plasma glucose was 211 mg%
- Case 3: presented with irregular menstruation and obese, her fasting plasma glucose was 129 mg% and confirmed by oral glucose tolerance test
- Case 4: had underlying of midline brain tumor (Geminoma), status post-operation, presented with obesity, acanthosis nigricans and glucosuria, her initial plasma glucose was 204 mg%

Table 6. The features of metabolic syndrome in Thai Type 2 diabetes children and adolescents

	Male	Female	Total
Each clinical features			
∑ Obesity	11/11 (100%)	15/15 (100 %)	26/26 (100 %)
∑ T2 DM	11/11 (100 %)	15/15 (100 %)	26/26 (100 %)
∑ Dyslipidemia	7/10 (70%)	11/14 (78.6%)	18/24 (75%)
∑ Hypertension	0/11 (0%)	2/13 (15.4%)	2/24 (8.3%)
Had only 2 features of MS: Obesity, DM	3/11 (27.3%)	2/15 (13.3%)	5/26 (19.2%)
Had 3 features of MS: Obesity, DM, Dyslipid	7/11 (63.6%)	0/11 (0%)	11/15 (73.3%)
Had 3 features of MS: Obesity, DM, HT	2/15 (13.3%)	18/26 (69.2%)	2/26 (7.7%)
Had 4 features of MS: Obesity, DM, HT, Dyslipid	1/11 (9.1%)	0/15 (0%)	1/26 (3.8%)

Table 7. Dyslipidemia in Thai Type 2 diabetes children and adolescents

	Male	Female	Total
Dyslipidemia	7/10 (70%)	11/14 (78.6%)	18/24 (75%)
Chol ≥ 200 mg/dl	6/10 (60%)	8/14 (57.1%)	14/24 (58.3%)
TG ≥ 150 mg/dl	3/9 (33.3%)	5/14 (35.7%)	8/23 (34.8%)
HDL ≤ 40 mg/dl	2/8 (25%)	2/13 (15.4%)	4/21 (19.1%)

impaired fasting plasma glucose were made by oral glucose tolerance.

Eighty-five percent of the cases had positive family history of diabetes (26.9, 50 and 7 % had positive history among 1st, 2nd and 3rd relative family history, respectively). The rest (15.4%) had no family history, their presenting symptoms are shown in Table 5, All patients had at least 2 features of MS which were obesity and diabetes. Eighty percents (21/26) has three or more than three features of MS included obesity, diabetes, hypertension and dyslipidemia as shown in Table 6 and 7.

Discussion

During the past decade, incidence of childhood and adolescents diabetes in Thailand especially type 1 diabetes has been reported to be low^(14,15,16,17). However there was a relatively high prevalence of type 2 diabetes in adult⁽¹⁸⁾, leading to an estimated increase of diabetes in our population to 1.65 fold in the year 2025⁽¹⁹⁾. Our previous study reported that the prevalence of type 2 diabetes increased and was associated with increasing prevalence of obesity, similar to observations in several countries^(4,5,6). This study demonstrated variation of clinical presentation of our type 2 diabetes which ranged from asymptomatic case to those with serious symptoms as diabetic ketoacidosis. Nearly fifty percents of patients presented with obesity and

acanthosis nigricans without any symptoms of diabetes. In symptomatic cases, only thirty percents of cases had either typical clinical triad of diabetes or diabetes ketoacidosis at the time of diagnosis. Twenty percents presented with mild clinical symptoms which were only polyuria, polydipsia without weight loss and abnormal menstruation in girls. The clinical picture of type 2 diabetes in our children and adolescents are quite similar to reports in other ethnicities^(8, 20, 21). Young patients diagnosed as having type 2 diabetes in many countries were generally overweight, had strong family history of type 2 diabetes and often had sign of insulin resistance^(5, 6, 7, 8, 20, 21). Our data demonstrated the same features with the exception of the family history. We found that only 26.9% had diabetic parents, 50 % had positive history in the 2nd generation and 7.7% in the 3rd generation. This information reminds us that we may have to interview patient's family history up to the third generation in Thai population. From the author's experience, diagnosis among parents were made after the diagnosis of the index case. Among the four cases without family history, three presented with obvious clinical signs and symptoms while one had underlying cause of post hypothamic tumor which led to severe obesity and glucosuria (as shown in Table 5). Due to a high incidence of adult type 2 diabetes in Thai population, we should screen all individuals who are obese as recommended by ADA

and WHO^(3,11,22), both in children and adults in order to recognize pre-diabetes condition such as impaired fasting glucose, impaired oral glucose tolerance test. The recommendation includes that overweight children who reach the age of 10 years or start puberty, if one either has sign of insulin resistance such as acanthosis nigricans, hypertension, abnormal menstruation, hirsutism, or had family history need to carefully review clinical signs and symptoms of diabetes and screening for either fasting plasma glucose or oral glucose tolerance test as physician decision. Education and counseling for prevention of medical consequences in childhood obesity especially those at risk includes intensive controlled regarding diet, and modification of lifestyle and behavior.

By the criteria for metabolic syndrome, we found that eighty percents of 26 patients had three or more criteria while twenty percents had two criteria. In adults, the MS is a risk factor for type 2 diabetes and cardiovascular disease that is associated with increased mortality. Although no studies to date have directly explored the impact of the metabolic syndrome on disease outcomes in childhood, autopsy report among children have shown that cardiovascular risk factors (including obesity, high blood pressure, high triglyceride, low HDL-C) are related to the early stages of coronary atherosclerosis^(24,25). Several large population studies have established the prevalence of the metabolic syndrome during childhood^(9,23, 26). Our data demonstrated that there was a relatively high rate of features of metabolic syndrome in our patients. The definition and management guideline of MS in overweight children is still in debatable. However, some experts⁽⁹⁾ advocated the creation of a definition and comprehensive screening of MS in overweight children in order to prevent and treatment of disease associated with the MS based on current pediatrics guideline. Due to our findings, we would need a recommendation for our pediatric practice in order to prevent these serious chronic diseases in teenagers. The applied comprehensive screening of MS in overweight children include (1) recognize overweight/obese children,(2) follow up and recommend family for lifestyle, diet modification, (3) record blood pressure and waist circumference on every visit and (4) if an obese child ages more than 10 years has any sign of insulin resistance either acanthosis nigricans, hypertension, dyslipidemia or abnormal menstruation in girl, they would require yearly check up for FBG and/or oral glucose tolerance test. Several studies have shown that changes in lifestyle and diet modification can improve CHO metabolism among

obese subjects.^(27,28) Our previous study⁽²⁹⁾ also demonstrated similar findings, i.e., impaired glucose tolerance in obese children can be reversed to normal glucose tolerance after one year of team approach for diet education and changes in lifestyle management.

In the past, Thailand witnessed a low incidence of diabetes in children and adolescents. Our pediatricians may not be used to the diagnosis and management of this diseases. This clinical picture of type 2 diabetes and their related figure of metabolic syndrome should alert our pediatric clinical practice to make an early diagnosis. Until then, we would be able to prevent the disease by successfully encouraging overweight children and parents to change their daily lifestyle and modify their diet. This study also reminds us in making attempt to differentiate type 1 and type 2 diabetes, as both can present with or without DKA as a presenting manifestations especially in teenagers.

Conclusion

Clinical pictures of childhood type 2 diabetes varied from asymptomatic cases to those with severe illnesses as diabetic ketoacidosis. All our type 2 diabetes children were obese and most had acanthosis nigricans. Almost all (80%) had at least 3 features of metabolic syndrome (obesity, diabetes, hypertension or dyslipidemia). Such clinical picture should alert all pediatricians and physicians to the diagnosis of type 2 diabetes. The conclusive criteria and management guideline of MS in children has not yet been fully described. Further epidemiologic studies, research of management and prevention of type 2 diabetes and metabolic syndrome in the young are urgently needed.

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อาการ และอาการแสดงของเบาหวานชนิดที่ 2 ในเด็กและวัยรุ่นไทย มีความสัมพันธ์กับกลุ่มอาการเมตาบอลิกอย่างไร

สุภาวดี ลิขิตมาศกุล, จิรันดา สันติประภาพ, ไพรัชยา สวัสดิ์พานิช, นวพร นำเบญจพล, คัทธี ชัยชาญวัฒนากุล

เบาหวานชนิดที่ 2 ในเด็กและวัยรุ่น มีอุบัติการณ์เพิ่มขึ้นสัมพันธ์กับโรคอ้วนทั่วโลก ได้ศึกษาผู้ป่วยที่วินิจฉัยเป็นเบาหวานชนิดที่ 2 จำนวน 26 รายของภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล โดยมีวัตถุประสงค์เพื่อศึกษาถึงอาการและอาการแสดงเมื่อเริ่มวินิจฉัย อุบัติการณ์ของภาวะเลือดเป็นกรดดีเคเอ ภาวะอ้วน อะแคนโทโรสสินิกิริแคนส์ ประวัติครอบครัว และศึกษาถึงความชุกของลักษณะของกลุ่มอาการเมตาบอลิก (Metabolic syndrome) ในผู้ป่วยกลุ่มนี้

ผลการศึกษา ผู้ป่วย 26 ราย มีอายุเฉลี่ย 12.1 ± 2.3 ปี อ้วนทุกราย ร้อยละ 98 มีอะแคนโทโรสสินิกิริแคนส์ ร้อยละ 53.8 มีอาการและอาการแสดงของเบาหวานได้แก่ ดีเคเอ (ร้อยละ 19.2) ลักษณะเฉพาะของเบาหวาน ปัสสาวะบ่อย ดื่มน้ำมาก น้ำหนักลดและไม่ลด (ร้อยละ 26.9) และประจำเดือนผิดปกติในเพศหญิง (ร้อยละ 7) ที่เหลือร้อยละ 46.2 ไม่มีอาการผิดปกติใดๆ ผลการตรวจน้ำตาล พบว่า ร้อยละ 15.5 ไม่สามารถวินิจฉัยโรคจากการ ตรวจน้ำตาลก่อนและหลังอาหาร ต้องวินิจฉัยโดยการทำ oral glucose tolerance test , ร้อยละ 75 มีค่าไขมันผิดปกติ และ ร้อยละ 15.4 ไม่มีประวัติครอบครัว ความชุกของกลุ่มอาการเมตาบอลิกที่มีอาการเท่ากับ 3 หรือมากกว่า 3 ข้อขึ้นไป คิดเป็น 80 % ของผู้ป่วยทั้งหมด

เบาหวานในเด็กและวัยรุ่นไทยมีอาการและอาการแสดงแตกต่างกันตั้งแต่ไม่มีอาการจนถึงมีอาการรุนแรงเป็นดีเคเอ และเกือบทุกรายมีอาการเข้ากับกลุ่มอาการเมตาบอลิก ดังนั้นกุมารแพทย์และแพทย์ทั่วไปควรให้ความสนใจเฝ้าระวัง และให้การวินิจฉัยโรคเรื้อรัง เบาหวานชนิดที่ 2 และกลุ่มอาการเมตาบอลิกในเด็กและวัยรุ่นที่อ้วน เพื่อให้การรักษาตั้งแต่แรก และป้องกันโรคแทรกซ้อนต่อไป