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Type 2 *Diabetes Mellitus* in Overweight and Obese Children

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ABSTRACT. The objective of the study was to identify the incidence of Type 2 *diabetes mellitus* in overweight and obese children with *diabetes mellitus*. The period between June 2001 and September 2003, children 10-15 years-old with *diabetes mellitus* with a body mass index of more than 25 kg/m^2 who presented to the endocrinology clinics at King Abdulaziz University Hospital and Dr. Sulaiman Faqeeh Hospital were included in the study. 40 (21.5%) of 186 children with *diabetes mellitus* were identified with body mass index greater than 25 kg/m^2. Thirty (75%) of the study's patients were diagnosed to have Type 2 diabetes based on normal or high insulin, level and, C-peptide level and negative autoantibodies (glutamic acid decarboxylase antibodies, islet cell antibodies and insulin antibodies). 28 of the thirty patients showed good response to diet and oral antihyperglycemic drugs. Insulin was required for better control in 2 of them. Children diagnosed to have Type 2 *diabetes mellitus* had insidious presentation (polyurea, polydipsia) except one patient who presented with diabetic ketoacidosis. Family history of diabetes was positive in all of them and *acanthosis nigricans* was found in sixteen (53%) patients only. In conclusion, the incidence of Type 2 *diabetes mellitus* in our children is increasing. For the possibility of Type 2 *diabetes mellitus* should be considered in all diabetic children with body mass index of more than 25 kg/m^2. The recommendations of World Health Organization and American Diabetes Association should be applied.

Keywords: Type 2 *diabetes mellitus*, Children, Overweight, Obesity.

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Introduction

Until recently, immune-mediated Type 1 diabetes was the only type of diabetes considered prevalent among children, with only 1-2% of children considered to have Type 2 diabetes or rare forms of diabetes. Recent reports indicate that 8-45% of children with newly diagnosed diabetes have non-immune-mediated diabetes[1]. The variation in the percentages reported appears to depend on race, ethnicity and sampling strategy. Type 2 *diabetes mellitus* (DM) usually occurs in adults; and associated with obesity or overweight. The pathology of Type 2 DM includes insulin resistance and inadequate insulin secretions response[1, 2].

Type 2 diabetes has been described in childhood since 1979 and an increasing prevalence is now recognized associated with obesity in ethnic minority groups with family medical history of Type 2 diabetes[3-5]. It should be distinguished from maturity onset diabetes of the young (MODY), which is a rare form of diabetes associated with genetic defects in beta-cell function inherited in an autosomal dominant fashion [Table 1][4-7]. With increasing prevalence of obesity in Saudi Arabia, we expect to see more children with Type 2 diabetes.

Methods

All overweight or obese children with DM between the ages of 10 and 15 years old presented to the endocrinology clinics at King Abdulaziz University Hospital (KAUH) and Dr. Soliman Fakeeh Hospital (DSFH) in Jeddah, western province of the Kingdom during the period between June 2001 until September 2003 were investigated for Type 2 DM. American Diabetic Association (ADA) criteria to diagnose Type 2 diabetes was implemented on these diabetic children (Fig. 1). Charts of patients were recorded for height, weight, body mass index (BMI), age, sex, nationality and *acanthosis nigricans* as an evidence of insulin resistance. Insulin and C-peptide levels were measured by chemo immunoassay. All autoantibodies (glutamic acid decarboxylase antibody, islet cell antibody, and insulin antibody) were measured by radioimmunassay. Diabetic overweight or obese children who had high or normal C-peptide levels, high or normal insulin levels, with negative autoantibodies were diagnosed to have Type 2 diabetes. They were started on a diabetic diet and oral antihyperglycemic agents. Metformin was the first drug to be initiated followed by glimepiride and then insulin, if not well controlled on oral drugs. They were followed-up in the clinic initially 2 weekly then 4 weekly for the evaluation of the efficacy of the treatment clinically by symptoms of hyperglycemia, (polyurea, polydipsia and fatigability), and biochemically by blood

Table 1. Comparison of Type 1 and Type 2 diabetes and maturity onset diabetes of young in children [*Diabetes Medicine* 2000; 17: 867-781].

	Diabetes Type		
	Type 1	**Type 2**	**MODY**
Ethnic Groups	Reported in all races / ethnicities	Hispanic, African - American, Indian, Australian Aborigines, Maoris, Japanese, Asian	Reported in all races / ethnicities
ICA	70 - 80% Positive	Negative	Negative
GAD Antibody	85 - 95% Positive	Can be Positive	
Beta-Cell	Failure	Dysfunction and Insulin Resistance	Dysfunction
Overweight at diagnosis	< 24%	> 85%	Non-obese
Family Medical History of Diabetes	5%	45% - 80% in a parent 74% - 100% in a 1st / 2nd degree relative	Autosomal dominant family history
Ketoacidosis at Presentation	30 - 40%	5% - 25%	< 5%
Insulin Use	100%	17% - 37%	Variable
Ratio of Gender	Equal sex ratio	80% female	Equal sex ratio
Onset Age Adult	10 - 14 years old	12 - 14 years old	Childhood / Adolescence / Young
HLA	95% HLA - DR 3/4	Unknown	No Association
Prevalence	0.17% in US residents 0 - 19 years old	Population 0.1% - 5.1% in US studies	Unknown

ICA = islet cell antibodies; GAD = glutamic acid decarboxylase

glucose levels and HbA1C. Glycosylated hemoglobin (dimension technique) was measured at the beginning of the study then at three and six months intervals.

Results

One hundred and eighty six (186) children were diagnosed to have DM according to ADA criteria. Forty (21.5%) of these children had BMI of ≥ g/m^2. Thirty (75%) of overweight or obese children fulfilled the criteria of Type 2 DM according to the ADA criteria (Fig. 1). Thirteen (43.3%) of the children diagnosed to haveType 2 were overweight, (BMI, > 25 < 30 kg/m^2) and seventeen (56.6%) were obese (BMI > 30 kg/m^2). All the children who were diagnosed to have Type 2 DM had normal or high fasting C–peptide and insulin levels; but were negative for islet cell antibody and glutamic acid decarboxylase antibody. The remaining of the forty (25%) diabetic overweight or obese children had low C–peptide and insulin levels; whereas, antibodies against islet cell, and glutamic acid decarboxylase were found in four (40%) of them.

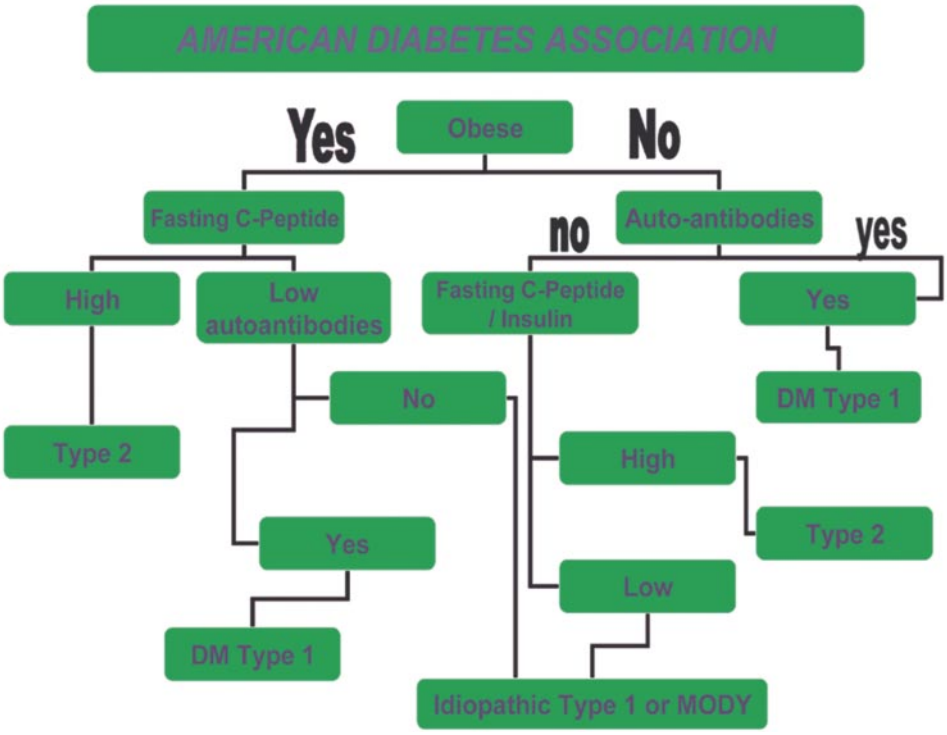

Fig. 1. The criteria diagnosed to have Type 2 *diabetes mellitus* (ADA recommendation)[7,13,21].

All children diagnosed to have Type 2 diabetes had strong family history of diabetes where either the mother or the father or both were diabetic. All of them were symptomatic presenting with polyuria and polydipsia, and only one was admitted with diabetic ketoacidosis (DKA) (Table 2).

Table 2. Clinical characteristics of the patients.

Characteristics	Patients'
Age	10 - 15 years old
Sex	10 males; 20 females
Race	13 African; 9 Saudi (black); 6 Saudi (non-black), 1 Qatari; 1 Kuwaiti
Polyurea - polydipsia	100%
DKA	Only one
Family History	100%
BMI	13 patients > 25 kg/m^2 < 30 kg/ m^2, and 17 patients > 30 kg/m^2
Acanthosis Nigricans	53%
Blood Glucose Average	241 - 483 mg/dl 290 ±
HbA1C	9.7 - 13.9% SD 11.72% ± 1.24

DKA = diabetic ketoacidosis; BMI = body mass index; HbA1C = glycosylated hemoglobin; SD = standard deviation.

Twenty females and 10 males (2:1) between the ages of 10 to 15 years were overweight or obese and their BMI was ≥ 25 kg/m^2. One patient was from Kuwait, one from Qatar, thirteen from Africa, 15 (50%) Saudis (nine black color and six non-black). Random venous blood glucose levels ranged from 241 mg/dl to 483 mg/dl with mean glucose concentration of 290 mg/dl; whereas, glycosylated hemoglobin was high in all of them (8–13.9%). Sixteen children (53.33%) with Type 2 DM had evidence of insulin resistance in the form of *acanthosis nigricans*. All the children with Type 2 diabetes were started on oral antihyperglycemic agents except one child who presented to the Emergency Department with DKA. This child was treated with insulin then shifted to metformin. When the goal of control of blood glucose level was not achieved on metformin, sulfonylurea was added.

During the follow-up after two weeks, all the children demonstrated an improvement in their symptoms and blood glucose levels except two children who required additional insulin injections for better control. Three months later, blood glucose levels were controlled and simultaneously, their weight also improved. Statistical analysis of the random blood sugar and glycosylated Hb (HbA1C) at diagnosis, three and six months later revealed significant improvement in the P

value less than 0.001. Statistical analysis was done by one-way analysis of variance followed by using Tukey–Kramer multiple comparison tests.

Discussion

Type 2 DM in children is an emotionally chargeable issue and an emerging public health problem. DM is one of the most common and increasingly prevalent chronic disease in children[8,9]. Type 2 DM is characterized by insulin resistance and a relative decrease in insulin secretion. It is traditionally a disease of adult onset, but over the last two decades it is being increasingly recognized in childhood[3,7]. All children with Type 2 diabetes in our study were overweight or obese, but in reports from different countries only 85% were overweight or obese, this difference could be related to patient's selection[3,8,10]. Glycosuria, polyuria, polydipsia with little or no weight loss was the main presentation. Children with Type 2 diabetes in the present study had a strong family history of Type 2 diabetes (all of them 100%); whereas, other studies showed positive history in 45-80% in either parent and 74-100% in the first or second degree relatives[4]. Type 2 diabetes in young age should be differentiated from Type 1 and Maturity Onset Diabetes of Young (MODY). The comparisons of Type 1 diabetes, Type 2 diabetes, and MODY are shown in Table 1[4-7].

Type 2 diabetes is more common in the ethnic minority populations and has been described in American and Canadian Indians, Hispanics, African Americans, Japanese and Middle Eastern children[4]. Twenty-two (73.3%) of the children diagnosed to have Type 2 DM in the study were black with more preponderance in females (2:1). The prevalence of Type 2 diabetes varies with the population being studied, but ranges from 1 to 51 per 1,000 in the United States and Canada, the highest prevalence being in the Pima Indians, Hispanics and African-Americans[5]. Type 2 diabetes in childhood now accounts for 8–45% of new cases of diabetes in children in some pediatric diabetic clinics in the US and has shown to outnumber the new cases of Type 1 diabetes diagnosed annually in Japanese children[11]. The present study revealed that 16% of the children age 10 -15 years diagnosed to have DM had Type 2 DM. Obesity was one of the most common predisposing factor to Type 2 DM. We found that all children diagnosed to have Type 2 were either overweight or obese (BMI > 25 kg/m^2). Physicians should have the awareness that Type 1 diabetes is not the only form of diabetes in children. Type 2 diabetes is frequently asymptomatic and should be considered in obese children, high-risk ethnic groups and children with strong family history of DM[8,12]. Since these Type 2 diabetic children can present with diabetic ketoacidosis they can erroneously be diagnosed as Type 1 DM and put on insulin therapy for life if the condition is not correctly diagnosed by the treating physician[11].

A raised C-peptide or insulin level and negative autoantibodies to insulin or glutamic acid decarboxylase (GAD) with obesity, overweight, or a positive family medical history and signs of insulin resistance can help to distinguish between Type 1 and Type 2 diabetes[7,13]. Up to 90% of the children with Type 2 diabetes have *acanthosis nigricans* which has been reported in American, Japanese, Pacific Islander, Asian, and Middle Eastern children[14]. In the present study in Saudi Arabia, only 53.33% had *acanthosis nigricans*.

Goals of treatment were to normalize the fasting plasma glucose and HbA1C levels, as this has shown to reduce the risk of acute and chronic complications[15,16,20]. It is also important to treat concomitant hypertension and dyslipidemia[9,16]. Initial treatment depends on the clinical presentation. Insulin therapy was needed if the presentation was with ketoacidosis or dehydration[15]. With an indolent presentation, treatment with diet and exercise to achieve weight reduction was more appropriate[12,19]. However, as these patients (children) do not perceive themselves as ill, compliance with lifestyle modification is limited. The standard oral antihyperglycemic agents may have a role in therapy although their relative benefit is uncertain. Insulin therapy was often necessary in some patients who required it intermittently to overcome periods of increased insulin resistance (*e.g.,* glucocorticoid therapy or pregnancy)[4,13,15,19]. Two patients in this present study required additional insulin to control their diabetes.

Follow-up data was scarce to locate, but serious complications of diabetes are known to occur within 10 years of diagnosis and in the early 3rd decade of life[15,16,20]. Type 2 diabetes in children fulfills the WHO criteria for screening and there is an urgent need for community based programs and for studies on primary and secondary prevention of complications[16-19].

The ADA recommends screening for Type 2 diabetes in overweight or obese individuals who have two of the following risk factors: 1) A positive family medical history of Type 2 diabetes in a first or second degree relative; 2) Ethnic origin: US Indians, African-Americans, Hispanics, Asians, South Pacific Islanders; 3) Signs of insulin resistance or conditions associated with it (*acanthosis nigricans*, hypertension, dyslipidemia, polycystic ovarian syndrome). The ADA also recommended testing every two years from the age of 10 years old or onset of puberty by fasting plasma glucose or 2-h post-prandial glucose (Table 3)[7,13,21].

Conclusion

Type 2 diabetes is an important precursor to future morbidity from cardiovascular or renal disease. Early recognition and appropriate treatment may

delay the onset of complications. A case finding study is urgently required to estimate the size of the problem and establish the safest modalities of treatment and prevention in the pediatric age group in Saudi Arabia.

TABLE 3. Testing for Type 2 diabetes in children (from ADA recommendation)[7,13,21].

Criteria	Plus *Any two of the following risk factors:*
Overweight (BMI > 85th percentile for age and sex of weight for height > 85th percentile, or > 120th percentile of ideal for height).	Family history of Type 2 diabetes in first- or second degree relative.
	Race / ethnicity (American Indian, African-American, Hispanic, Asian / Pacific Islander).
	Signs of insulin resistance or conditions associated with insulin resistance (*acathosis nigrcans*, hypertension, dyslipidemia, PCO).
	Age of initiation: age 10 years or at onset of puberty if puberty occurs at a younger age.
	Frequency: every 2 years.
	Test: FPG preferred.

ADA = American Diabetes Association; BMI = body mass index; PCO = polycystic ovarian syndrome; FPG = fasting plasma glucose.

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مرض السكري (النوع الثاني) لدى الأطفال

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المستخلص . النوع الثاني من مرض السكري عند الأطفال مشكلة صحية عالمية ، وحيث إنه لم يسبق وأن تمت دراسة هذا المرض بالنسبة للأطفال في المملكة العربية السعودية ، لذا تم عمل فحوصات مخبرية لمرضى أطفال من عمر ١٠ – ١٥ سنة مصابين بمرض السكري ويعانون من زيادة في الوزن ، وذلك لقياس معدل الأنسولين في الدم ، أو لمعرفة ما إذا كانت هناك أجسام مضادة ضد خلايا البنكرياس أو الأنسولين. ولقد تم التعرف على ٤٠ طفلا يعانون من زيادة الوزن مع السكري من ١٨٦ طفل يعانون من مرض السكري في الفترة من يونيو ٢٠٠١ إلى سبتمبر ٢٠٠٣، ووجد أن ٣٠ طفلاًمنهم – الذين يعانون من مرض السكري مع زيادة في الوزن – كانت الأجسام المضادة لخلايا لانجرهانز سلبية لديهم ، كما أن معدل الأنسولين في الدم طبيعي ، لذا تم تشخيصهم من النوع الثاني ، وعلاجهم عن طريق الحمية والعقاقير الطبية التي أثبتت جدواها في التحكم في معدل السكر في الدم . فقط اثنان من المرضى احتاجا إلى إضافة الأنسولين. ومن هذا المنطلق يجب الفحص وعمل الفحوصات لتشخيص النوع الثاني من مرض السكري لدى الأطفال المصابين بهذا المرض ، وخاصة الذين يعانون من زيادة في الوزن .