Review

TYPE 2 DIABETES IN THE YOUNG

BK Sahay, Rakesh K. Sahay

ABSTRACT

The incidence of type 2 diabetes is increasing in the younger age groups including children. The epidemic of type 2 diabetes is a manifestation of globalization. The advent of westernization has affected the life style of both adults and children. There is an increase in physical inactivity, unhealthy food habits and obesity in children as well as adults.

Apart from type 1 diabetes, the other types of diabetes occurring in children are MODY (Maturity Onset Diabetes of the Young), MMDM (Malnutrition Modulated Diabetes Mellitus) and type 2 diabetes in the young. Hence children and young adults (<30 yrs) presenting with diabetes need to be properly classified to provide the correct modality of treatment. A precise classification in a given case may require several specialized investigations not routinely available. However, a proper history, clinical examination and routine investigations are sufficient to arrive at an appropriate diagnosis.

Absence of ketosis, a family history of diabetes with normal or elevated BMI, with presence of markers of insulin resistance like acanthosis, PCOS and/or hypertension suggests a diagnosis of type 2 diabetes. Presence of a strong family history of diabetes in three generations, an insidious onset, normal or elevated BMI favors a diagnosis of MODY, while an acute presentation with ketonuria/ketonemia without a significant family history and with a low BMI suggest the diagnosis of type 1 diabetes. Our data on the various types of diabetes seen in the young is presented.

KEY WORDS: Diabetes in young; Type 1; Type 2; MODY; MMDM.

The prevalence of type 2 diabetes is increasing the world over. This trend is being found both in the developed and developing countries. Superimposed on this disturbing trend in adults is the emerging problem of type 2 diabetes in children. This rising prevalence of type 2 diabetes in children will expose them to the risk of developing the macrovascular and microvascular complications during the prime of their life – their earning period, which will have an adverse impact on the economy.

Type 2 diabetes was hitherto common after the age of 40 years. However, in recent times individuals aged 25-40 years have been presenting with clinical features of type 2 diabetes. The incidence of type 2 diabetes in children is reported to be increasing in several parts of the world. Among the native North Americans, 30% of the new cases of type 2 diabetes occur in the second decade of life (1), while among the Japanese school children, type 2 diabetes is 7 times more common than type 1 and a similar trend is reported in the Chinese and Mexican American youth (1-3). In Pima Indians there is an increase in the incidence in the age group of 10 years and above (4). Type 2 diabetes presents a decade or two earlier in India than in the West. About 38% of type 2 diabetics are diagnosed below the age of 40 years and in about 4.8% a diagnosis is made below 25 years (5).

The distribution of patients based on the age of onset, among 4833 consecutive patients registered at Sahay's Diabetic Clinic and Research Centre, Hyderabad, during the period 1999-2002 is shown in table 1. 36.6% of the patients with type 2 diabetes had an onset below the age of 40 years and 7.5% had an onset of diabetes below the age of 30 years.

** Retd. Prof. & Head, Dept of Medicine, Osmania Medical College, Hyderabad. Sahay's Diabetic Clinic & Research Centre, Ameerpet, Hyderabad. ** Asst. Prof. of Endocrinology, Osmania Medical College and Osmania General Hospital, Hyderabad.*

Table 1: Distribution of cases based on age of onset (4833 consecutive patients registered at the Sahay's Diabetic Clinic & Research Centre, Hyderabad)

Age group (years)	n	%	Cumulative %
1-10	16	0.3	0.3
11-20	55	1.1	1.4
21-30	362	7.5	8.9
31-40	1334	27.7	36.6
41-50	1742	36.2	72.8
51-60	955	19.8	92.6
61-70	275	5.6	98.2
≥71	94	1.8	100

The epidemic of type 2 diabetes is a manifestation of globalization. The advent of westernization has resulted in a drastic change in the life style of both adults and children. There is a frightening increase in physical inactivity, unhealthy food habits and obesity in children and adults. When obesity develops in childhood years it generally continues into adulthood and frequently becomes more severe. The health consequences of obesity in adults are well established including greater rates of hyperinsulinemia, hypertension, glucose intolerance and coronary heart disease (CHD) – together also called as syndrome X by Reaven. This is often a precursor of diabetes and antedates the development of diabetes by 7-8 years (6, 7).

Another important factor, which might contribute to the increase in type 2 diabetes, is low birth weight, especially in the developing countries. A number of studies have demonstrated an association between low birth weight and the development of insulin resistance in later life (8). The thrifty phenotype hypothesis proposes that poor nutrition in fetal and infantile life is detrimental to the development and function of beta cells and insulin sensitive tissue leading to insulin resistance under the stress of obesity (9). Greater degrees of insulin resistance have been reported in Indians with type 2 diabetes as compared to other populations. Higher levels of insulin after a glucose load have been reported among Asian Indians (10).

Patients presenting with diabetes in the younger age group should be properly classified. It is apparent that a proper classification can help the physician to treat the patients correctly from the beginning. A correct treatment procedure will help the patient to lead a healthier life.

The different types of diabetes that can be seen in the young are type 1 diabetes, type 2 diabetes, malnutrition modulated diabetes mellitus, and maturity onset diabetes of the young. The diagnostic criteria and classification in children with diabetes are the same as those specified for adults (11) (Table 2). In most patients classification can be made readily on the basis of the clinical presentation and course. However, for a specific and accurate classification other investigations have to be performed - a) fasting insulin and C-peptide estimation, b) β-cell auto-antibody measurements, c) GAD antibodies and insulin antibodies.

Table 2: Etiological Classification of Diabetes

- **Type 1 diabetes** (β-cell destruction, usually leading to absolute insulin deficiency)
  - Immune mediated
  - Idiopathic
- **Type 2 diabetes** (May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
- **Gestational Diabetes Mellitus (GDM)**
- **Other specific types**
  - Genetic defects of β-cell function (e.g. MODY)
  - Genetic defects in insulin action (e.g. lipoatrophic diabetes)
  - Diseases of the exocrine pancreas (e.g. cystic fibrosis)
  - Endocrinopathies (e.g. Cushing's syndrome)
  - Drug or chemical induced (e.g. glucocorticoids)
  - Infections (e.g. congenital rubella)
  - Uncommon forms of immune mediated diabetes
  - Other genetic syndromes sometimes associated with diabetes (e.g. Praeder-Willi syndrome)

In type 2 diabetes the β-cell antibodies are absent. However, GAD antibodies have been found in a small number of type 2 diabetes patients, while in type 1 diabetes, GAD and insulin antibodies are present in 85-95% of the cases. To achieve a high degree of sensitivity a combination of tests is required.

Immune mediated type 1 diabetes has a strong HLA association. However, HLA typing is not a useful diagnostic tool. Patients with immune mediated type 1 diabetes may also have other associated autoimmune disorders – hemolytic

anemia, thyroid, adrenal diseases, vitiligo and coeliac disease.

The initial classification is based on the clinical picture at presentation. Children with immune diabetes have weight loss; they are not obese, have short duration of symptoms and 30-40% may have ketoacidosis. A significant number of those who do not present with ketoacidosis have ketonuria at onset. With treatment they may pass through the honeymoon phase (period of remission), after which they require insulin for survival. They develop ketoacidosis on withdrawal of insulin. 5% of type 1 patients may have a first or second degree relative with the same disease.

The slow onset type 1 diabetes (latent autoimmune diabetes in adults - LADA) may also affect the young but can be differentiated from true type 2 diabetes by low fasting C-peptide levels and presence of auto antibodies.

The two common non-immune forms of diabetes encountered in the young are

i. True Early Onset Type 2 diabetes
ii. Maturity Onset Diabetes of the Young (MODY)

Most children with type 2 diabetes are overweight or obese at diagnosis and present with glycosuria without ketonuria, 45-80% of these children have a family history of diabetes, with at least one parent being affected. There may be history of diabetes in first or second degree relatives also.

Acanthosis nigricans and polycystic ovarian syndrome (PCOS) associated with insulin resistance are common among them. Velvety hyperpigmented patches predominantly seen on the nape of the neck, axilla and groin (intertrigenous areas) characterize acanthosis. Presence of acanthosis in a diabetic is a hallmark of type 2 diabetes. Majority of these children (90%) are diagnosed between the ages of 10-18 years (12).

Puberty appears to play a major role in the development of type 2 diabetes mellitus. The increased growth hormone secretion during this period is responsible for the insulin resistance during puberty (13). In those with a genetic predisposition for insulin resistance, the environmental factors may tilt the balance towards development of type 2 diabetes during this period. 5-25% of the patients of type 2 diabetes may also have ketonuria at onset. These patients may get the label of type 1 diabetes at the onset and subsequent C-peptide and antibody studies will frequently help in classifying them under the right category.

MODY is another form of diabetes occurring in children. It includes several genetic disorders (at least 6) caused by monogenic defects in the beta cell function and inherited in an autosomal dominant fashion. Their presentation may be variable – commonly insidious with mild hyperglycemia. Sometimes they may also present acutely. These patients are generally not very obese and do not have evidence of acanthosis. They have a strong family history of diabetes running into three generations. Molecular diagnostic testing is required to identify and classify them accurately. Such facilities are usually available in research laboratories only.

Of the 423 young diabetics seen by us, detailed analysis of the data was done for 382 patients. Initial classification of these patients was done on the basis of the clinical presentation, anthropometric data, and family history. All these patients were managed with insulin for control of hyperglycemia. Subsequent investigations were also done to assess C-peptide levels. Patients identified to be having type 2 diabetes or MODY were shifted to oral hypoglycemic agents, while patients with type 1 diabetes were continued on insulin therapy. Table 3 gives the distribution of these patients into various types of types. All patients below the age of 10 years were type 1 diabetics. Type 2 diabetes and MODY were the predominant type in the age group of 21-30 years. 19 patients of these were seen in the age group of 11-20 years. One of the patients with type 2 diabetes initially presented with ketosis and was labeled as type 1 diabetes. After recovery, the C-peptide estimation was done and she was reclassified as type 2 diabetes and has been maintaining good glycemic control with oral hypoglycemic agents for past two years.

Table 3: Types of Diabetes in the Young

Age group	Type 1 DM	Type 2 DM	MODY
0-5	3	0	0
6-10	5	0	0
11-15	9	0	5
16-20	11	2	12
21-25	9	81	22
26-30	6	151	66
Total	43	234	105

Patients with type 1 diabetes presented with osmotic symptoms with weight loss and ketonuria. However, only 17 presented with ketoacidosis. 31 out of the 43 patients had a BMI <19 kg/m^2, the remaining 12 had a normal BMI (table 4). Family history of diabetes was present in only 13. All of them showed very low C-peptide levels.

Table 4: BMI among the Different Types of Diabetes in the Young

BMI (kg/m2)	<19	19-25	26-28	>28
Type 1	31	12	0	0
Type 2	19	110	78	27
MODY	13	55	23	14

The clinical picture in type 2 diabetes and MODY was similar. Most cases were of insidious onset, had a family history of diabetes in parents, siblings, grandparents or first degree relatives (table 5). Their BMI was normal or greater than 25. Most of these patients presented with osmotic symptoms, weight gain, tingling and numbness in hands and feet, visual disturbances, balanitis, vulvovaginitis or periarthritis. However, a significant number were totally asymptomatic (38%). Presence of acanthosis nigricans and features of the metabolic syndrome such as abdominal obesity, hypertension helped in differentiating patients with type 2 diabetes from those with MODY. The most characteristic feature of MODY was the presence of a strong family history running into three generations.

Table 5: Comparison of Family History between Type 1 and Type 2 Diabetes in the Young

	Type 1 DM	Type 2 DM
None	30 (69.8)	68 (29.0)
Father	5 (11.6)	39 (16.7)
Mother	-	42 (17.9)
Both Parents	-	44 (18.8)
Grandparents	7 (16.3)	26 (11.1)
Siblings	1 (2.3)	15 (6.5)
Total	43	234

** Figures in paranthesis are percentages*

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