INTRODUCTION

Diabetes mellitus is one of the commonest endocrine and metabolic diseases of childhood. Till recently, diabetes in children, adolescent and young adults was almost exclusively type 1 diabetes mellitus (T1DM), which is caused by autoimmune destruction of the insulin producing beta cells. Today this scenario has changed, as there is increased recognition of a number of different forms of "non-type 1 diabetes" in the young. This includes type 2 diabetes mellitus (T2DM), maturity onset diabetes of young (MODY), fibrocalculous pancreatic diabetes (FCPD), gestational diabetes mellitus (GDM) and diabetes due to genetic disorders. This shift to other types of diabetes that has also coincided with the increasing epidemic of T2DM along with a shift of the age at onset of T2DM, which has now started affecting the youth and even children and adolescents. This chapter will focus exclusively on the epidemiology, clinical profile and management of early onset T2DM.

EPIDEMIOLOGY

International

Although T2DM has been traditionally viewed as an adult disease, with the epidemic of T2DM spreading fast, it has now started moving to younger age groups, especially in ethnic minority populations in the developing world. Indeed, since the 1990's, there has been a striking increase in the incidence and prevalence of T2DM in children and adolescents. The potential cumulative morbidity and mortality resulting from early onset T2DM is worrisome as the period of exposure to glycaemia can be considerable, if one develops the disorder at a young age. The available data on the pathophysiology, management, complications and long-term outcomes of children with T1DM and T2DM suggests that there are important differences in the clinical profile of these two populations. The limited amount of information about the epidemiology of T2DM in children is in part due to the relatively recent recognition of its emergence in this age group and in part because screening for diabetes in children is not generally recommended.

Historically, the first cases of childhood onset T2DM were reported in 1979 and 1984 among Native Americans and Canadian First Nation People, who were regarded as homogenous groups with a greater genetic susceptibility to T2DM. The second wave of reports appeared in the mid-1990s and involved predominately ethnic minorities, namely blacks and Hispanic Americans and some white populations in the United States. At about the same time, reports began to appear from Japan as well. About a decade later, cases from Europe were reported.
The North American experience with youth-onset T2DM was reviewed by Fagot-Campagna et al. in 2000. A Table 28.1 shows the reported prevalence of early onset T2DM in North America, Europe and Africa.

From a worldwide perspective, there appears to be a close relation between rising rates of T2DM in adults and the eventual appearance of the disorder in adolescents. Indeed T2DM in children was reported earliest in those countries with the highest rates of adult T2DM. Thus attention to the epidemiology of T2DM in adult populations may be helpful in predicting the emergence of T2DM in adolescents and children. These observations appear to have great implications for screening programs for T2DM among children and adolescents.

It is estimated that as many as 15-46% of children with newly diagnosed diabetes in the United States may now have T2DM. Similar increases have been documented worldwide. The SEARCH study which is one of the largest studies on diabetes in children reports an incidence per 100,000 person years of 0.8 in the 5-9 year olds, 8.1 in 10-14 years and 11.8 in 15-19 years. Another large study from Canada, reports an incidence of 0.27 per 100,000 in children less than 10 years and 3.1 per 100,000 per year in the 10-18-year-olds. One study has reported children as young as 8 years being affected with T2DM. An excellent review on T2DM in children highlights the increasing trends and high prevalence of diabetes in the young especially in the minority groups and indigenous populations that are undergoing rapid economic and social transition.

### Studies from Asia and India

Table 28.2 presents the reports on early onset T2DM from Asia Pacific region. The prevalence of T2DM in Asia is amongst the highest worldwide and is increasing rapidly particularly in urban India. According to the national ICMR-INDIAB study, currently in India, there are an estimated 62.4 million individuals with diabetes and this is expected to increase to over 100 million by 2030. This study showed the take-off point for increasing prevalence of diabetes was at 25-34 years of age as shown in Figure 28.1. However, population based estimates for diabetes in children and adolescents are lacking in our country as most population based studies are done on adults aged 20 years and above. Available data from clinic based reports suggests that there is a shift of age at onset of T2DM towards younger age groups.
### Table 28.2: Prevalence and incidence of T2DM in children and adolescents in Asia Pacific region (Pinhas-Hamiel Op)

<table>
<thead>
<tr>
<th>Region</th>
<th>Year of Study</th>
<th>Prevalence/Incidence</th>
<th>Age Group Studied</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>1976</td>
<td>0.2/100,000</td>
<td>Primary School Children</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>1985</td>
<td>2.0/100,000</td>
<td>Primary School Children</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1995</td>
<td>13.9/100,000</td>
<td>Junior high school children</td>
<td>23</td>
</tr>
<tr>
<td>Taiwan</td>
<td>1992–1999</td>
<td>6.5/100,000</td>
<td>6–18 years</td>
<td>24</td>
</tr>
<tr>
<td>Singapore</td>
<td>1987</td>
<td>10 cases</td>
<td>12 years</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>≥ 50 cases</td>
<td>&lt; 15 years</td>
<td>26</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>1996</td>
<td>0.1/100,000</td>
<td>0–14 years</td>
<td>27</td>
</tr>
<tr>
<td>Bangkok</td>
<td>1987–1996</td>
<td>5%</td>
<td>&lt; 18 years</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>1997–1999</td>
<td>17.9%</td>
<td>Age at diagnosis–15 years</td>
<td>30</td>
</tr>
<tr>
<td>China</td>
<td>2001</td>
<td>2.4%</td>
<td>&lt; 15 years</td>
<td>31</td>
</tr>
<tr>
<td>New Zealand</td>
<td>1997–1999</td>
<td>12.5%</td>
<td>Mean age 14.2 ± 2.0 years</td>
<td>32–34</td>
</tr>
<tr>
<td></td>
<td>2000–2001</td>
<td>≥ 35.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auckland, NZ</td>
<td>1998–2007</td>
<td>0.5 to 2.5/100,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>1999–2001</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2001–2002</td>
<td>≥ 2.5/100,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangladesh</td>
<td>1995</td>
<td>5.7%</td>
<td>15–29</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>1997</td>
<td>0.04%</td>
<td>15–19</td>
<td>37</td>
</tr>
</tbody>
</table>

---

**Fig. 28.1:** Age- and sex-specific weighted prevalence of diabetes ICIMR INDIAB study

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The increasing trend of T2DM occurring in Asians, including Indian children and adolescents, is linked closely to the increasing prevalence of obesity and increased insulin resistance (IR) in association with low birth weight and sedentary lifestyle on a background of a strong family history of T2DM. As the prevalence of diabetes in youth increases, there is a risk that micro and macrovascular complications of diabetes may develop by early adulthood, i.e. during the height of their productivity which potentially could affect the economy of the nation apart from posing a large burden to an individual and his/her family.

We recently reported on one of the largest series of diabetes in the young (n=2630) seen at our center, which is a tertiary diabetes center in Chennai in South India. "Diabetes in the young" was defined as those with first diagnosis of diabetes at or below 25 years of age. Figure 28.2 shows that the overall proportion of diabetes in the young at our center rose from 0.55% during the period 1992–95 to 2.5% in 2009. Among the total of 2,630 subjects with diabetes in the young, 1,262 (48.0%) had T2DM, 1,135 (43.2%) had T1DM, 116 (4.5%) had GDM and 115 (4.4%) had other forms of diabetes including FCPD and genetic syndromes of diabetes. Thus at our center, T2DM is
already more common than T1DM. However, this may well reflect referral bias in private diabetes centers which not surprisingly, would attract patients from the more affluent sections of society who tend to have higher obesity rates. In most government hospitals, T1DM is still more common, again possibly reflecting a socio economic bias, due to the free supply of insulin provided at these hospitals.

Till recently, T2DM mellitus was considered rare in children. A study from Chennai published in 1995 reported a “zero” prevalence for diabetes in children after screening 3,515 school children. Other studies from Chennai have reported on type 1 as well as T2DM based on clinic data. Figure 28.3 shows that there is a gradual increase in childhood and adolescent T2DM (CAT2DM) defined as onset of T2DM at or below 19 years of age. The figures, which are presented as a proportion of the total patients registered at our center during that period show that the prevalence of CAT2DM rose from 0.01% in 1992 to 0.35% in 2009 (p for trend < 0.001). Young-onset T2DM has also been reported from other parts of India in addition to China, Korea, Malaysia and Singapore and the highest prevalence of type 2 in children has been reported from Japan. In one multicenter study from India done over a period of 2 years, 603 subjects were evaluated, of whom 535 (89%) had a diagnosis of T1DM, 36 (6%) had T2DM, 18 (3%) had FCPD and 14 (2%) had other subtypes of diabetes. Table 28.3 shows the percentage of T2DM in children and adolescents reported in India.

<p>| Table 28.3: Percentage of T2DM in children and adolescents reported in India |
|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>S. No.</th>
<th>Place, Author and Center name</th>
<th>Year or Period of study</th>
<th>Number of T2DM in children reported and given as % where applicable</th>
<th>Total sample screened</th>
<th>Age group studied</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chennai: Venkatraman et al. (Madras Medical College)</td>
<td>1979-89</td>
<td>2 (1.2%)</td>
<td>180</td>
<td>&lt; 20 years</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>Mohan et al. (Dr Mohan's Diabetes Specialities Centre)</td>
<td>1984</td>
<td>0.00</td>
<td>3515</td>
<td>5-19 years</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>Mohan et al. (Dr Mohan's Diabetes Specialities Centre)</td>
<td>2012</td>
<td>4 (0.3%)</td>
<td>1519</td>
<td>5-19 years</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>Chennai: Mohan et al. (Diabetes Research Centre)</td>
<td>1981-83</td>
<td>219 (4.8%)</td>
<td>4560</td>
<td>&lt; 20 years</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>Ramachandran et al. (Diabetes Research Centre)</td>
<td>1988</td>
<td>314 (57.7%)</td>
<td>545</td>
<td>20-29 years</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>Ramachandran et al. (Diabetes Research Centre)</td>
<td>2002</td>
<td>18 cases</td>
<td>434</td>
<td>15-19 years</td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>Mohan et al. (Dr Mohan's Diabetes Specialities Centre)</td>
<td>2006</td>
<td>16 (26.7%)</td>
<td>650</td>
<td>&lt; 20 years</td>
<td>43</td>
</tr>
<tr>
<td>8</td>
<td>Mohan et al. (Dr Mohan's Diabetes Specialities Centre)</td>
<td>1992-2009</td>
<td>1252 (48.0%)</td>
<td>2630</td>
<td>20-29 years</td>
<td>45</td>
</tr>
<tr>
<td>9</td>
<td>Mohan et al. (Dr Mohan's Diabetes Specialities Centre)</td>
<td>1992-2009</td>
<td>500 (26.8%)</td>
<td>1372</td>
<td>&lt; 20 years</td>
<td>47</td>
</tr>
<tr>
<td>10</td>
<td>Poozathagi et al. (Institute of Child Health and Hospital for Children)</td>
<td>1999-2010</td>
<td>2 (0.5%)</td>
<td>432</td>
<td>&lt; 12 years</td>
<td>56</td>
</tr>
<tr>
<td>11</td>
<td>Hyderabad: Sahay et al. (Sahay's Diabetic Clinic and Research Centre)</td>
<td>1999-2002</td>
<td>339 (7.0%)</td>
<td>4833</td>
<td>&lt; 30 years</td>
<td>57</td>
</tr>
<tr>
<td>12</td>
<td>Kokata: Banerjee et al. (NRS Medical college)</td>
<td>2004</td>
<td>13 (19.4%)</td>
<td>67</td>
<td>&lt; 20 years</td>
<td>49</td>
</tr>
<tr>
<td>13</td>
<td>New Delhi (Multisite case control study): Vikram et al. (All Indian Institute of Medical Sciences)</td>
<td>2006</td>
<td>51 cases</td>
<td>603</td>
<td>&lt; 20 years</td>
<td>48</td>
</tr>
<tr>
<td>14</td>
<td>MEDI study: Umbirshin et al. (Anurita Institute of Medical Sciences)</td>
<td>2006-2008</td>
<td>36 (6.5%)</td>
<td>603</td>
<td>&lt; 20 years</td>
<td>48</td>
</tr>
<tr>
<td>15</td>
<td>Lucknow: Khatri et al. (SGPIMS)</td>
<td>2004</td>
<td>13 (6%)</td>
<td>160</td>
<td>&lt; 18 years</td>
<td>59</td>
</tr>
<tr>
<td>16</td>
<td>Varanasi: Jyothi et al. (Institute of Medical Sciences)</td>
<td>2002</td>
<td>12 (17.11%)</td>
<td>70</td>
<td>&lt; 30 years</td>
<td>60</td>
</tr>
</tbody>
</table>
Drawbacks in present population-based and clinic-based reports on childhood and adolescent onset T2DM are:

- The age ranges studied are usually inconsistent. The age group studied by different ethnic groups varies and this leads to underestimation and a large proportion of patients may have been missed. In future, if researchers could adopt a standard age range limit like 0–11 years, 12–19 years and 20–29 years etc. it would be helpful in segregating children, adolescents, and young adults.

- Lack of uniformity in classification of diabetes types. Some of the adolescents who were originally diagnosed as having type 1 diabetes were later found to have T2DM and vice versa. When new cases of adolescents with diabetes are analyzed for classification, diagnosis could not be made initially which might be due to unavailability of glutamic acid decarboxylase (GAD) antibody and C-peptide assays. Another problem is migration of patients to other centers.

- The growing awareness of adolescent T2DM over time, among the physicians, may have affected prevalence rates. Clinicians in urban areas have become more adept at identifying and treating T2DM in children and adolescents, and hence only few of them are now being referred to academic centers. This may have led to an underestimation of T2DM in prevalence studies at diabetes centers in major teaching hospitals.

- Finally, the studies presented in Table 28.3 are almost exclusively diagnosed cases of T2DM. However, if pediatric T2DM mirrors the adult pattern of T2DM, many affected children with T2DM may be undiagnosed. This assumption is supported by a recent study of obese children, wherein asymptomatic T2DM was identified in 4% of obese adolescents at screening. A small number of population-based studies in the United States, Australia, and Canada suggest that the true prevalence T2DM in children is at least twice that of the known cases, a proportion similar to that seen in adults.

- Despite all the above limitations, one must admit that T2DM is rapidly emerging as a health problem in children and adolescents, following the same pattern as in adults. Since the life-time risk of developing diabetes-associated complications can be expected to be higher in this age group due to the long disease duration and greater duration of glycemic response, it is particularly important that appropriate screening measures be implemented to diagnose early onset T2DM at an early stage to prevent progression to the stage of complications of diabetes.

### PATHOPHYSIOLOGY OF EARLY ONSET T2DM

#### Beta Cell Function and Insulin Resistance

As the information on the pathophysiology of T2DM in the young is sparse, projections from adults becomes necessary. T2DM is characterized by disorders of insulin action and insulin secretion, either of which may be the predominant feature. The development of alterations in glucose metabolism results from a gradual deterioration of beta cell function occurring on a background of IR. T2DM is a progressive disorder and the most important factor responsible for this, is a continuing decline in beta cell function. Several studies have demonstrated that diabetes and prediabetes do not develop until the beta cells fail to compensate appropriately to the peripheral IR state. One of our study done in youth, showed both IR and beta cell function [measured by oral disposition index-(DIO)] are associated with T2DM-Y and prediabetes however only DIO remained significant after adjusting for body mass index (BMI), waist circumference and parental history of diabetes showing that it is more strongly linked with T2DM-Y and prediabetes than IR in this ethnic group. The ability of the beta cell to secrete sufficient insulin to adequately respond to the peripheral IR state depends on multiple factors including beta cell mass and secretory capacity, which are influenced by genetic and environmental factors. Indeed, although the progressive loss of beta cell function could be due to different metabolic derangements (IR, lipotoxicity) several studies have suggested that beta cell dysfunction depends also on a pre-existing, and most likely, genetically determined risk, which appears to be crucial for beta cell dysfunction to occur.

Although the pathophysiological mechanisms of T2DM are not commonly understood, it is clear that IR plays an important role in its development. Evidence for this comes from longitudinal studies demonstrating that IR occurs 10–20 years before the onset of the disease and that it is the best predictor of whether or not an individual will develop diabetes later. In addition, IR, by placing an increasing demand on the beta cell to hypersecrete insulin, influences the progressive beta cell failure of T2DM. The precise mechanism by which IR leads to beta cell failure remains unknown. A possible hypothesis is that the cause of IR is also directly responsible for the beta cell failure (i.e. lipotoxicity). Flow chart 28.1 summarizes the pathophysiology and risk factors of T2DM in youth.
Clinical Presentation of Early Onset of T2DM

As in adults, T2DM is largely asymptomatic in children, and often is diagnosed during routine clinical examination or when complications develop. The early symptoms include polyuria, nocturia, polydipsia, polyphagia, weight loss and fatigue. Often the child complains of frequent infections, excessive tiredness and irritability or injuries take a long time to heal. Although these symptoms are very typical, the possibility of diabetes is often not considered because of a lack of awareness. A family history of diabetes is a strong pointer to T2DM. Acanthosis nigricans (AN) and skin tags are other important clues. An adolescent girl with polycystic ovarian syndrome (PCOS) is highly likely to be having glucose intolerance or even overt T2DM.

The clinical features distinguishing early onset T2DM, T1DM and MODY are summarized in Table 28.4.

Algorithm for Differential Diagnosis of Diabetes in Youth in India

Using a simple questionnaire, which involves family history of diabetes, response to therapy, presence of ketosis, and abdominal X-ray, we have evolved an algorithm (Flow chart 28.2) by which the majority of cases of youth-onset diabetes in India can be classified into different groups. In addition, C-peptide, insulin antibodies, and ultrasonography of the abdomen are all useful. It must be emphasized that it is difficult to classify some patients into a distinct type, for example, those with overlap of features of T1DM and T2DM so-called “double diabetes” or “hybrid diabetes”. Flow chart 28.2 summarizes the diagnostic approach to classify diabetes in youth in India.

RISK FACTORS OF EARLY ONSET T2DM

Ethnicity

Ethnicity/race is an important non-modifiable risk factor in the development of T2DM in adults. The influence of this appears to be even stronger among youth onset T2DM. However, high prevalence rate have been noted in Asians, Hispanics, indigenous peoples (USA, Canada, Australia) and African Americans, with the highest rates in the world being observed in Pima Indians. A number of studies comparing African-American and European-American children suggest a genetic basis for the apparently greater susceptibility to T2DM in certain ethnic groups. It has been known for several years that Asian Indians, despite having lower body mass index and lower prevalence of traditional risk factors for diabetes, are more insulin resistant and more susceptible to T2DM, than whites.
Table 28.4: Clinical features differentiating between type 1, early onset T2DM and MODY

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Early onset, T2DM</th>
<th>Type 1 DM</th>
<th>MODY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity</td>
<td>Hispanic, African American, Asians, Native Americans</td>
<td>Caucasians</td>
<td>Caucasians</td>
</tr>
<tr>
<td>Parents affected</td>
<td>Usually both (45–80%)</td>
<td>5–10%</td>
<td>Either one or both affected (90–100%)</td>
</tr>
<tr>
<td>Age of onset</td>
<td>At Puberty</td>
<td>Throughout childhood</td>
<td>&lt; 25 years</td>
</tr>
<tr>
<td>Obesity</td>
<td>Common</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Acanthosis Nigricans</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Family history of DM</td>
<td>Yes</td>
<td>Less common</td>
<td>Yes (Autosomal dominant)</td>
</tr>
<tr>
<td>Onset of DM</td>
<td>Chronic, insulin required to correct glucotoxicity</td>
<td>Acute, severe insulin required</td>
<td>Subtle, insulin not required</td>
</tr>
<tr>
<td>Severity of DM</td>
<td>Mild</td>
<td>Severe</td>
<td>Mild</td>
</tr>
<tr>
<td>Ketosis/Coma</td>
<td>Unusual</td>
<td>Yes</td>
<td>Unusual</td>
</tr>
<tr>
<td>Causative factor</td>
<td>Insulin resistance</td>
<td>β cell destruction leading to insulin deficiency</td>
<td>Insulin secretion</td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

(T2DM: Type 2 diabetes mellitus; DM: Diabetes mellitus; MODY: Maturity onset of diabetes)

Flow chart 28.2: Algorithm for differential diagnosis of diabetes in youth (Mohan et al.)*

![Flow chart image]

(QHA: Oral hypoglycemic agents; MODY: Maturity onset of diabetes; GDM: Gestational diabetes mellitus; DM: Diabetes mellitus; FCPD: Fibrocalculus pancreatic diabetes)
Puberty and Polycystic Ovarian Syndrome

Polycystic ovarian syndrome is being increasingly recognized in adolescents as part of the IR syndrome. Adolescent females with T2DM should be assessed for symptoms and signs of PCOS-like menstrual irregularities and hirsutism. The mean age at diagnosis in all studies of T2DM in children is approximately 13.5 years corresponding to the time of peak adolescent growth and development. A significant percentage of girls develop T2DM before the age of 15 years in different ethnic groups. Our clinic based study revealed that girls 10–14 years old have a much higher risk of developing diabetes than boys even after adjusting for BMI, parental history, serum cholesterol and blood pressure. A recent population based study from our group, shows that the prevalence of glucose intolerance among girls was higher (4.2%) when compared to boys (3.2%). Approximately, 30% of adolescent girls with PCOS have been found to have impaired glucose tolerance (IGT), with 4% having T2DM. It is well known that the onset of puberty leads to increased IR and that hormonal change due to puberty could be a triggering factor for developing T2DM in girls. IR in youth typically occurs during puberty and is thought to coincide with occurrence of T2DM. Pancreatic beta cells of some adolescents cannot overcome the physiologic rise in IR and therefore a relative insulin deficiency develops, eventually leading to T2DM.

Acanthosis Nigricans

Acanthosis nigricans is a cutaneous marker characterized by velvety hyperpigmented patches typically seen at the base of neck, in the axilla (Figs 28.4A and B) and anogenital area. It is a well established clinical sign of IR and is reported to occur in up to 60–90% of youth with T2DM. However in our study, only 21.2% had this marker and it is also uncommon in Japan. One study showed that apart from AN, other phenotypic markers like buffalo hump and double chin are associated with metabolic syndrome in adult Asian Indians. Thus, even though occurrence of AN when present is a useful clue to suspect T2DM, it cannot be relied on as a diagnostic marker of IR and T2DM.

Obesity

The rising occurrence of T2DM has been attributed to the increasing rates of obesity in children. Obesity is the most important modifiable risk factor for the development of IR, independent of sex, age and ethnic background. Overweight and obesity are now becoming major problems in adolescents around the world. Secular increases in the prevalence of obesity in children have also been recorded in China, Hong Kong, the UK and Australia. The problem of obesity now also extends to developing nations, particularly in relatively affluent urban areas. In India, a study conducted in 2002 found that the age adjusted prevalence of "overweight" among 13–18 years old was 18% in boys and 16% in girls correlating positively with age and socioeconomic status and negatively with physical activity. Another Indian study showed an increasing trend in prevalence of overweight and obesity in urban Asian Indian adolescents associated with male gender and high socio economic
status. In children, as in adults, visceral fat appears to be the best predictor of T2DM. The presence of both obesity and IR confer greater risk for cardiovascular disease (CVD) in young type 2 diabetic patients compared with that expected with either obesity or IR alone.

**Diet and Physical Activity**

Obesity is linked to recent changes in the diets of children. Fast foods and high fat/high carbohydrate/high sugar consumption has increased, while the concept of family meals has declined in many societies. While diet composition may contribute to obesity, it is likely that the most important aspect in the development of IR and type 2 in youth is excess calorie intake which is not on par with the expenditure of calories. This imbalance between excess intake and reduction in the energy expenditure coupled with large portions and high-calorie diets with a sedentary lifestyle have led to an epidemic of obesity among youth. Indeed, physical inactivity has been identified as an important predictor of excess weight gain and evolution of the T2DM epidemic.

**Family History of Diabetes**

Many studies show a strong family history among affected youth with 45-80% having at least one parent with diabetes and 74-100% having a first or second degree relative with T2DM. History of diabetes in one or both parents was seen in over 80% of our T2DM in children and adolescents in our clinic and it corroborates a previous study done in children, adolescents and young adults from North India. Parental history of T2DM mellitus increases the risk of not only glucose intolerance, but also other cardiometabolic risk factors like overweight, low high-density lipoprotein, high cholesterol and high blood pressure in Asian Indian adolescents.

**In Utero Exposure to Undernutrition**

Undernutrition in fetal and infant life followed by over nutrition later in life have been shown to predispose individuals to diabetes and the metabolic syndrome. India is one of the countries with the highest incidence of infants with low birth weight. This is most likely due to poor maternal nutrition. A particular pattern of being born small for gestational age (SGA), followed by accelerated weight gain in early childhood has been associated with increased risk for both IGT and T2DM in adulthood.

**Systemic Inflammation**

Several inflammatory markers, such as interleukin 6, C-reactive protein, other cytokines and acute-phase reactants, such as fibrinogen and plasma activator inhibitor-1 (PAI-1), have been associated with T2DM and its metabolic precursor, IR. Elevated C-reactive protein, inflammatory cytokines and white blood cell counts in obese adolescents have been associated with increased risk for CVD in adults. Adiponectin, a hormone released by adipocytes, has insulin sensitizing, anti-inflammatory and anti-atherogenic properties. Adiponectin levels are decreased in obese individuals. One study has reported that insulin-sensitive obese adolescents have higher levels of adiponectin as compared with insulin-resistant obese adolescents. In addition, adiponectin levels decrease in parallel to progression through puberty, with pubertal stage being the strongest independent predictor of adiponectin levels in adolescent boys. Therefore low levels of adiponectin in obese individuals may play a critical role in the development of T2DM. We have recently showed that adiponectin levels can be used as a marker to differentiate T1DM and T2DM with a cut off value of 5.1 μg/mL.

**Genetics**

Understanding the genetics of childhood T2DM poses a challenge owing to a relatively low prevalence of disease, large variation in the ethnic background and the underlying complex genetic traits of diabetes. Recently, genome wide association studies in adult onset T2DM have contributed substantially to our understanding. It is of interest that of the 24 genetic loci that have been associated with T2DM, the majority of genes effect insulin secretion rather than sensitivity. There is a paucity of studies examining T2DM susceptibility genes in children and adolescents. The TC7L2 gene has recently been
implicated in the development of IGT in obese children. The only gene mutation confirmed to increase the risk of T2DM in children and adolescents is the unique single-nucleotide polymorphism (SNP-G319S) in hepatocyte nuclear factor (HNF) 1α gene, which has been described in the Oji-Cree population in Canada. We have also shown that the Ala98 Val polymorphism of HNF 1α gene is associated with MODY and with earlier age at onset of T2DM. More genetic studies of T2DM in children and adolescents are urgently needed.

Diagnostic Criteria
Testing for T2DM in asymptomatic children.

CRITERIA

A consensus panel of the American Diabetes Association (ADA) recommended that individuals who are overweight (as defined below) and with any of the other risk factors indicated below should be tested every 3 years, starting at age 10 or at the onset of puberty, if that begins earlier. Overweight is defined as (BMI ≥ 85th percentile for age and sex, or weight for height ≥ 85th percentile, or weight ≥ 120% of ideal for height).

Other risk factors for T2DM:

- Family history of T2DM in first- or second-degree relative
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
- Signs of IR or conditions associated with IR (AN, hypertension, dyslipidemia, polycystic ovary syndrome PCOS or SGA birth weight)
- Maternal history of diabetes or GDM during the child's gestation.

Criteria for the Diagnosis of Diabetes

1. HbA1c more than or equal to 6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay
2. Fasting plasma glucose (FPG) more than or equal to 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.
3. Two-hour plasma glucose more than or equal to 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT). The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water, or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose more than or equal to 200 mg/dL (11.1 mmol/L).

TREATMENT AND MANAGEMENT

Treating T2DM in children and adolescents can be as (or even more) challenging than treating type 1 diabetes, because the cornerstone of therapy is lifestyle modification achieved through diet and physical activity. In developed countries, pediatric T2DM disproportionately affects segments of the population with fewer resources, both at the family and community levels, to implement these changes. Conversely, in developing countries, at present, the more affluent groups tend to get childhood onset T2DM. The goals of treatment are weight loss plus normalization of glucose, blood pressure and lipids. These goals are best accomplished through a combination of education, medical nutrition therapy, exercise and pharmacotherapy. Behavior change is critical to the management of T2DM in children and it is important to impress on the whole family unit regarding need for healthy food choices and the benefits of increasing physical activity.

Lifestyle modification includes attainment and maintenance of a healthy bodyweight, increased exercise levels, normalization of blood glucose levels, minimization of hypoglycemia and the prevention of not only the complications of diabetes but also, hypertension, hyperlipidemia and non-alcoholic fatty liver disease. Education should be age-appropriate and culturally sensitive, and must focus on lifestyle and health behaviors of the entire family in order to be effective. This should be continued in addition to pharmacologic treatment, the primary aim of which is to decrease IR, preserve insulin secretion, or to slow postprandial glucose absorption.

Type 2 diabetes mellitus can be controlled with oral hypoglycemic agents (OHA) at least for the first 2-5 years. Treatment should be started with metformin and monitored frequently until control is achieved. If control is not achieved with metformin, a sulphonylurea can be added. Very often, insulin may be required at least in the early stages to control symptoms and later, if secondary failure to OHA develops.

Biguanides

Metformin is the drug of choice for children and adolescents with T2DM. Metformin acts on insulin receptors

*In the absence of unequivocal hyperglycemia, criteria 1-3 should be confirmed by repeat testing.
in liver, muscle and fat tissue with a predominant action on the liver. The following are some of the effects of metformin:

- Hepatic glucose production is reduced by decreasing gluconeogenesis.
- Insulin-stimulated glucose uptake is increased in muscle and fat.
- An initial anorexic effect may promote weight loss.
- Long-term use is associated with a 1-2% reduction in HbA1c.
- Gastrointestinal side effects (transient abdominal pain, diarrhea, nausea) may occur. These can be eliminated in most patients with slow dosage titration over 3-4 weeks and instructions to always take the medication after food. The side effects may also be attenuated by the use of extended-release formulations.
- The risk of lactic acidosis with metformin is extremely low. Metformin should not, however, be given to patients with renal impairment, hepatic disease, cardiac or respiratory insufficiency, or who are receiving radiographic contrast materials. Metformin should be temporarily discontinued during any acute illness.
- Metformin may normalize ovulatory abnormalities in girls with PCOS and thereby increase pregnancy risk.
- Metformin should be started at a low dose (either 250 or 500 mg twice daily depending on their glycemic levels along with meals) and slowly titrated to reach a total daily dose of 2 g.

**Insulin**

Despite hyperinsulinemia and IR, relatively small doses of supplemental insulin are often effective to achieve euglycemia in T2DM. If there is inadequate glycemic control on oral agents, a long-acting insulin analogue without a peak action may provide satisfactory therapy without meal-related therapy. Metformin should be continued to improve insulin sensitivity. If postprandial hyperglycemia persists, rapid or short-acting insulin can be substituted. The side effects of insulin are hypoglycemia and weight gain, which could be a substantial problem if dietary measures and physical activity are not attended to.

Sulfonylurea agents (glibenclamide, gliclazide, glipizide or glimepiride) may be used to control diabetes. However, other class of drugs, such as glinides (repaglinide and nateglinide), glucosidase inhibitors (acarbose) and thiazolidinediones compounds (glitazones like pioglitazone) are not approved in childhood onset T2DM. Indeed, with the recent reports of bladder cancer with prolonged use of pioglitazone, this drug should be avoided in children. Among the newer therapeutic options that may prove beneficial for pediatric patients with T2DM are the incretin-based therapies like GLP-1 analogues (Exenatide and Liraglutide) and dipeptidyl peptidase-4 inhibitors (DPP4) like sitagliptin, vildagliptin, saxagliptin and linagliptin. However, data in pediatrics is almost nonexistent and their approval for use in children is awaited once the ongoing trials are completed.

**Complications of Early Onset of T2DM**

Type 2 diabetes mellitus in children and adolescents may place the individuals at risk for increased morbidity and mortality during their most productive life years, however only limited long-term studies on follow-up were available on secondary complications.

As with adults, it can be expected that youth with T2DM will also develop diabetes-related complications. Long-term complications may be microvascular (retinopathy, nephropathy, and neuropathy) or macrovascular (ischemic heart disease, peripheral vascular disease and stroke). Microvascular complications may develop in puberty or early adulthood whereas macrovascular complications usually occur in later years. The longer the duration of diabetes, the greater the risk of complications, which increase significantly following puberty. The risk of developing complications may also be increased by poor glycemic control, hypertension, dyslipidemia and behavior such as smoking, in addition to genetic factors.

**Retinopathy**

Dilated eye examinations and retinal photography should be performed in adolescents with T2DM according to the ADA’s standards of medical care. Even though overall retinopathy remains more frequent in patients with type 1 diabetes (matched for duration), it may be present in adolescents with T2DM at the time of diagnosis, and hence the need for screening at the time of diagnosis itself.

The earliest sign of diabetic eye disease is the development of background or non-proliferative diabetic retinopathy (NPDR), which consists of microaneurysms and hemorrhages with exudates which do not involve the macula. NPDR is usually asymptomatic and does not damage vision. It may stabilize, regress with improved glycemic control or progress if poor control continues. NPDR however may progress to proliferative diabetic retinopathy (PDR). This can be successfully treated in its early stages with laser photocoagulation therapy. Macular
edema is the result of fluid accumulation in the retina secondary to capillary leakage and/or microaneurysms and can develop at all stages of retinopathy. Cataract is very rare under the age of 20 years.

Up to 9% of patients diagnosed with T2DM before age 30, have evidence of retinopathy at diagnosis and nearly 13% develop proliferative retinopathy before age 35. In our study the prevalence of retinopathy rose from 4.2% among those with diabetes duration of less than or equal to 5 years to 81.5% in those more than 15 years duration. According to one study, retinopathy was less common in youth onset than in adult onset groups at all durations of diabetes.

Nepihathy

Screening for microalbuminuria should be done at diagnosis and at yearly intervals thereafter. Nepihathy is preceded by the development of persistent microalbuminuria which affects approximately 10% of children and adolescents. Microalbuminuria is defined as an albumin excretion rate of 30–300 mg/24 hours in two out of three timed collections. Timed collections may be difficult to collect in children and an alternative screening tool is the measurement of the Albumin creatinine ratio in the first voided morning urine sample which has been shown to correlate closely with the timed overnight albumin excretion rate. Nepihathy was equally common in all the age groups and was not related to age of diabetes onset (at < 5 years duration of T2DM, nepihathy incidence per 1,000 person years was 13/1,000 youth, 8/1,000 young adults and 7/1,000 older groups). In our clinic based study, the prevalence of microalbuminuria increased from 8.7% in those with diabetes duration of less than or equal to 5 years to 29.5% in those more than 15 years, whereas the prevalence of overt nepihathy increased from 9% in those with diabetes duration of more than 5 to less than or equal to 10 years to 34.4% in those with duration of more than 15 years.

Neuropathy

The earliest symptoms include numbness and paresthesia of the feet or hands with evidence of decreased vibration sense, loss of ankle jerk reflexes and a diminution in sensation to pinprick on clinical examination. Clinical neuropathy in adolescence is rare, although subclinical neuropathy demonstrated by abnormalities of vibration perception threshold have been reported in 20–57% of adolescents with diabetes. The prevalence of neuropathy was 3% in those with diabetes duration of less than 5 years and increased to 49.2% (30 of 61) in those with more than 15 years duration in our study. Limited data suggest that rates of peripheral and autonomic neuropathy do not differ among adolescents with type 1 and T2DM, although, adolescents with T2DM appear to develop neuropathy at a more rapid rate. Prevalence of diabetes complications in early onset T2DM is detailed in Table 28.5. Prevalence of microvascular complications in childhood and adolescent onset at our center stratified by duration of diabetes is presented in Figure 28.5.

Metabolic risk factors or other characteristics of the IR syndrome are commonly seen at diagnosis or appear early in the course of T2DM and should be tested for sooner than in type 1 diabetes, as in the latter these disorders are complications of the diabetes, rather than comorbid conditions. Thus, dyslipidemia and hypertension should be assessed at the time of onset of diabetes itself, in early onset T2DM.

Hypertension

Blood pressure should be monitored and treated aggressively with angiotensin converting enzyme (ACE) inhibitors, if either the systolic or diastolic pressure is above the child's usual percentile or above the 85th percentile for age and sex. In our study, raised blood pressure was seen among 27.2% of boys and 21.4% of girls. Hypertension is estimated to account of 35–75% of both microvascular and macrovascular complications. Diabetes or IGT doubles the risk of developing hypertension. Confirmed hypertension or albuminuria should be treated with an angiotensin receptor blocker or an ACE inhibitor. Combination therapy may be required if hypertension or albuminuria does not normalize on a single agent.

Dyslipidemia

Hypertriglyceridemia and decreased high density lipoprotein (HDL) cholesterol are the hallmarks of T2DM dyslipidemia. We found 40.3% boys and 36.2% girls have hypertriglyceridemia, while 61.1% and 69.2% respectively have low HDL cholesterol. Dyslipidemia is very common, with raised cholesterol and triglyceride concentrations in 33–60% of younger adults aged less than 18 years with T2DM. These rates are higher than those found in non-diabetic obese individuals, suggesting that the presence of diabetes has an additive impact on dyslipidemia.
Table 28.5: Diabetes complications in early onset T2DM

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Country, Author and Centre name</th>
<th>Year or period of study</th>
<th>Age at onset in years (Duration of diabetes in years)</th>
<th>Retinopathy n (%)</th>
<th>Nephropathy n (%)</th>
<th>Neuropathy n (%)</th>
<th>Ref no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>India</td>
<td>1985</td>
<td>≤ 25 (≥ 15)</td>
<td>28/60 (43.3%)</td>
<td>12/60 (20%)</td>
<td>27/60 (45%)</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>· Mohan et al. (Diabetes Research Centre)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>· Ramachandran et al. (Diabetes Research Centre)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>· Mohan et al. (Dr Mohan's Diabetes Specialities Centre)</td>
<td>2011</td>
<td>≤ 25 (≥ 15)</td>
<td>100/139 (71.9%)</td>
<td>38/172 (22.1%)</td>
<td>57/165 (34.5%)</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>· Mohan et al. (Dr Mohan's Diabetes Specialities Centre)</td>
<td>2012</td>
<td>≤ 20 (&lt;15)</td>
<td>44/54 (81.5%)</td>
<td>21/61 (34.4%)</td>
<td>30/61 (49.2%)</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>· Jeytsna et al. (Institute of Medical Sciences)</td>
<td>2002</td>
<td>≤ 30</td>
<td>41%</td>
<td>—</td>
<td>—</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>South African Indians</td>
<td>1996–2008</td>
<td>≤ 30 (15)</td>
<td>37/103 (35.9%)</td>
<td>16/103 (15.5%)</td>
<td>—</td>
<td>134</td>
</tr>
<tr>
<td>3</td>
<td>USA</td>
<td>2001–2003</td>
<td>—</td>
<td>1/40 (2.5)</td>
<td>9/40 (22.5%)</td>
<td>—</td>
<td>135</td>
</tr>
<tr>
<td></td>
<td>· Farah et al.</td>
<td></td>
<td>—</td>
<td>—</td>
<td>ESRD-25 cases/1,000 person years</td>
<td>—</td>
<td>136</td>
</tr>
<tr>
<td></td>
<td>· Pevkov et al. (given as age sex adjusted incidence rate)</td>
<td>—</td>
<td>&lt;20 (decades of age)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>133</td>
</tr>
<tr>
<td></td>
<td>· Krakoff et al.</td>
<td>2003</td>
<td>≤ 20 (15–20)</td>
<td>9 cases</td>
<td>—</td>
<td>10 cases</td>
<td>131</td>
</tr>
<tr>
<td>4</td>
<td>UK</td>
<td>2009</td>
<td>32 (10–20)</td>
<td>65 (9.5)</td>
<td>—</td>
<td>51 (32.9)</td>
<td>137</td>
</tr>
<tr>
<td>5</td>
<td>Japan</td>
<td>1965–1993</td>
<td>&lt;30 (15–19)</td>
<td>—</td>
<td>31.4/1,000 person years</td>
<td>—</td>
<td>138</td>
</tr>
<tr>
<td></td>
<td>· Yokoyama et al. (given as incidence density)</td>
<td>1997</td>
<td>—</td>
<td>9.3%</td>
<td>—</td>
<td>—</td>
<td>130</td>
</tr>
<tr>
<td>6</td>
<td>Malaysia</td>
<td>1999</td>
<td>≤ 30 (≥ 10)</td>
<td>82/191 (42.9%)</td>
<td>57/197 (28.9%)</td>
<td>—</td>
<td>139</td>
</tr>
</tbody>
</table>

The hyperlipidemia could improve with exercise, weight loss and glycemic control. Nutritional changes include a reduced fat diet and changing to complex carbohydrates. However, should such attempts to normalize lipids fail after 6 months of intensive efforts, use of lipid lowering medications would be indicated. The most commonly used lipid lowering agents are the HMG CoA reductase inhibitors (statins).

**PREVENTION OF T2DM IN CHILDREN**

In high-risk cases, e.g. those with strong family history, obesity, acanthosis nigricans or polycystic ovarian disease, screening for diabetes seems to be justified in youth. Early detection and treatment are the cornerstones to reduce morbidity and mortality due to youth-onset T2DM.⁵
The increasing prevalence of T2DM in the young may be arrested by increasing physical activity and following traditional dietary habits. Interventional programs should be considered to address the underlying cause, with an emphasis on diet, weight, exercise and lifestyle issues. It is far better to put our public health efforts on primordial and primary prevention of diabetes, rather than dealing with diabetes and its late stage complications. Lifestyle modification should be encouraged and implemented for all children and adolescents at the school level.

Physical activity plays a critical role in the prevention of early onset T2DM. Increased physical activity results in improved insulin sensitivity and increased glucose uptake at the level of the muscle and a decreased need for insulin therapy.  

What can be Done to Prevent the Epidemic of T2DM in Children?

1. Screening methods should target the high-risk youth population which can be identified by simple clinical clues: presence of overweight or obesity and a positive family history of diabetes/AN and/or polycystic ovarian disease. An OGTT is ideal in these children. If this is not feasible, at least FPG should be done, which however, has a much lower sensitivity.

2. We should find ways to help people to be more physically active and eat healthier diets. This requires an integrated approach, and should involve other sectors outside of health, for example those that influence urban design.

3. Policy-makers need to integrate plans for the prevention of diabetes into national health systems. Countries have to find ways to make economic progress in a way that it does not affect the health of the children. This requires an inter-sectoral approach with multiple stakeholders.

4. Education imparted to diabetic patients, their families and the community at large will go a long way in achieving this goal.

5. Regular follow-up and constant motivation is required to ensure that these preventive measures are followed over a number of years.

All the above factors can be integrated into the Government of India’s National Program for the Prevention and Control of Diabetes CVD and Stroke which is currently being rolled out across the country. This can help to stem the tide of a potential epidemic of T2DM in children and adolescents in India.

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FURTHER READING

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