

Type 2 Diabetes Mellitus in Young: Need for Early Screening

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Type 2 diabetes mellitus (T2DM) has increased dramatically throughout the world in recent years. This increase has also affected the young, such that over the last decade, the rise in the number of children and youth with T2DM has been labeled an 'epidemic'. The main reason for this epidemic is the spurt in childhood obesity worldwide. This is linked to the global economic growth and changes in lifestyle and dietary habits. It is important that we recognize this epidemic of T2DM early, and institute national and global measures to contain it. T2DM in childhood can be controlled to a large extent through lifestyle modification measures. It is important that we screen this disease condition, and identify the at-risk cases.

Key words: *Acanthosis nigricans, Child, Obesity, Prevention, Type 2 diabetes mellitus.*

The economic growth and development of the past three decades have been dramatic. However, economic development has set the scene for the transformation of lifestyles, eating habits, and traditional societal and family structure. Lifestyle related non-communicable health conditions are having an increasingly negative impact on the health of many adults and children. Type 2 diabetes mellitus (T2DM), which is linked both directly and indirectly to behavioral, nutritional and environmental factors, has emerged in recent years as the leading cause of illness, disability and death. Over the past 2 decades, the incidence of T2DM in children and adolescents has markedly increased and it accounts for as many as one third of all the new cases of diabetes diagnosed in adolescents. It is a major global challenge, with India having the maximum number of cases and thus earning the dubious distinction of being termed the 'diabetic capital of world'.

One of the earliest studies to highlight this rising trend of T2DM was by Pinhas-Hamiel, *et al.* [1]. They reported a 4-fold increase in the proportion of young diabetes patients having T2DM as the etiology, between 1992 and 1994 and a 10-fold increase between 1982 and 1994. Most pediatric patients with

type 2 diabetes belong to minority communities. The SEARCH study group (a US multicenter observational study conducting population based ascertainment of cases of diabetes mellitus in individuals <20 year) found that the incidence of type 2 diabetes was highest among American Indian individuals aged 15-19 years [2], followed by Asian-Pacific Islanders and black individuals of the same age group. Studies among the Japanese, Asian-American, Indian, British, Chinese, Taiwanese, Libyan, Bangladeshi, Australian, and Maori populations have also shown increasing incidence of youth-onset T2DM during the recent past [3-10].

THE INDIAN SCENARIO

It is increasingly being recognized that Indians (and other South Asians) are an ethnic group at high risk for insulin resistance [11,12]. This is further compounded by obesity, especially of visceral fat, manifested by truncal obesity. For a similar total body fat content, Indians have higher truncal fat (subscapular, suprailiac, abdominal skin folds) than Caucasians. A similar predilection for the insulin resistance syndrome is seen in children (and adults) of other racial groups such as African Americans, Pima Indians (and some other American Indian

tribes), Hispanic Americans and Pacific islanders. Data on T2DM in Indian children and adolescents is sparse. Ramachandran, *et al.* [12,13] reported on 18 children (5 boys and 13 girls) with T2DM diagnosed below the age of 15 years at their clinic. 9 were obese and 12 had high waist hip ratio, indicating visceral obesity. Of note is the fact that 9 patients were asymptomatic and picked up on screening which was performed due to strong family history of DM and/or because of obesity. They had good glycemic control on treatment with metformin or sulphonylurea or a combination of both. In a study by Bhatia, *et al.* [11] T2DM accounted for 12% of cases (total 160 cases) of diabetes mellitus in children below 18 years of age. Few other studies have also identified the increasing prevalence of T2DM in children in India, during the last decade [14,15]. Causes for the epidemic of T2DM in children in India are as under [16]:

Changes in lifestyle (urbanisation): With improving standards of living, and availability of food in plenty, the traditional micronutrient rich foods are being replaced by energy dense highly processed, micronutrient-poor foods, which is unhealthy. Sedentary pursuits have increased; with TV and movie watching, video games, internet gazing and telephone gossip sessions becoming important activities of children. An important factor for obesity in India is the intense competition for admissions to schools and colleges with flourishing tuition classes, right from nursery levels. Children are forced to use their play time for additional studies. Games or physical training sessions are restricted or nonexistent in many schools. Some schools do not have any playgrounds at all. Also, due to unsafe roads (traffic, crime) children are discouraged from walking or cycling to school. Motorized vehicles are popular and they are perceived to be quicker and safer for transport. Erosion of open spaces for exercise and lack of parental time to supervise play are all part of new obesogenic lifestyles.

Genetic/Constitutional predisposition: Modern environment may have unmasked previously silent obesogenic genes or the 'thrifty genotypes' (i.e. programming of previously malnourished populations to accumulate fat more intensely in an attempt to store for future starvation). In addition, familial

pattern of eating, exercise and behavior also contributes to increased incidence in families.

Other factors: Various other factors which contribute to increased childhood T2DM include inadequately breastfed babies and the high glycemic index of our predominantly carbohydrate diet.

THE DISEASE

T2DM spans a continuum from impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) to frank diabetes, that results from progressive deterioration of both insulin secretion and action. T2DM starting during adolescence puts the individual at risk for major morbidity and even mortality, right during the productive years of life. The microvascular complications of T2DM (nephropathy, retinopathy, neuropathy etc) are brought on at an early age. In addition, T2DM and obesity are two components of a metabolic syndrome of insulin resistance, the other features of which include hypertension, dyslipidemia, and hypercoagulability. All these conditions together increase the risk for cardiovascular and cerebrovascular mortality and morbidity (i.e. myocardial infarction and stroke). The resulting economic burden is enormous.

The major risk factors for T2DM in children include the following [1,17,18]: (i) obesity and inactivity, which are important contributors to insulin resistance; (ii) minority races: *e.g.* Native American, Black, Hispanic, Asian, and Pacific Islander; (iii) family history of T2DM in first-degree and second-degree relatives; (iv) puberty: this age coincides with relative insulin resistance that occurs due to effect of sex hormones and growth hormone; (v) low birthweight; and (vi) maternal history of gestational diabetes.

Obesity is strongly associated with T2DM in children and adolescents. 85% of children with T2DM are either overweight or obese (defined as at or above the 85th percentile of the sex-specific body mass index [BMI] for age-based growth charts) [2]. Changes in food consumption and exercise are fueling a worldwide increase in obesity in children and adolescents. As a consequence of this dramatic development, an increasing rate of T2DM has been recorded in children and adolescents around the

world. Ramachandran, *et al.* [12] studied children from six schools in Chennai, and found that the prevalence of overweight (including obese) adolescents ranged from 22% in better-off schools to 4.5% in lower income group schools. In a Delhi school with tuition fees more than Rs 2,500 per month, the prevalence of overweight was 31%, of which 7.5% were frankly obese [19]. In Pune, the figures for overweight children were 24% in a well-off school and 6% in a 'corporation' school. Family history of DM in a first degree relative is present in up to 70% of patients. The prevalence of T2DM is higher among girls than boys. The mean age of onset of T2DM is at puberty, when a physiologic state of insulin resistance develops [20-22]. In this physiologic state, T2DM develops only if inadequate beta-cell function is associated with other risk factors (e.g. obesity). Acanthosis nigricans, a marker of insulin resistance, is a velvety hyperpigmented thickening of the skin and is frequently seen on the nape of the neck and in intertriginous areas. It is found in as many as 90% of children with T2DM [2]. Polycystic ovarian syndrome (PCOS) is a reproductive disorder (characterized by hyperandrogenism and chronic anovulation), and is commonly seen in young women with T2DM. Hypertension may co-exist in children with T2DM.

The criteria for diagnosis of T2DM in children adopted by various expert agencies have been the same as in adults [23]. The glucose tolerance test (GTT) is performed after 3 days of unrestricted carbohydrate diet, after an 8 hour fast and unlimited physical activity. The subject should remain seated and should not smoke throughout the test. The glucose dose is 1.75 g per kg of anhydrous glucose (to a maximum of 75 g). It should be dissolved in about 200 mL of water and sipped over about 10 minutes to prevent nausea. The 2 hour value is from the start of ingestion of the glucose. The criteria for diagnosis are given in **Table I**.

In the absence of unequivocal hyperglycemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.

The GTT can help uncover glucose intolerance. IFG and IGT are associated with increased risk of conversion to overt diabetes as compared to the general population. Therefore, efforts at prevention

TABLE I DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS

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- Symptoms of diabetes (polyuria, polydipsia, and unexplained weight loss) plus casual plasma glucose concentration ≥ 200 mg/dL (11.1 mmol/L) (casual is defined as any time of day without regard to time since last meal), OR
 - Fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L) (fasting is defined as no caloric intake for at least 8 hrs), OR
 - 2 hour post-glucose plasma glucose value ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test.
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of DM have targeted subjects with IFG (FPG between 100-126 mg/dL) or IGT (PPG between 140-200 mg/dL). IGT is commonly present in obese children, and is considered as prediabetic state. Amongst obese children, the prevalence of T2DM and IGT is 1.3% and 18.2%, respectively [24]. In an earlier study from Delhi, IGT of 24.8% has been reported amongst overweight and obese children 5-18 years of age [25]. In a longitudinal study of an 'obese African-American girl' who progressed from NGT to IGT and later to T2DM over a 5-year period, Saad, *et al.* [26] demonstrated that although insulin resistance was the pre-existing abnormality, it was the marked decline in insulin secretion that finally led to the development of diabetes. In a study of 117 obese individuals, aged 4-18 years, 84 (71.7%) had NGT whilst 33 (28.2%) had IGT at baseline [27]. Over a mean duration of 20 months, 24% of the patients with IGT developed diabetes, 30% remained glucose intolerant, whilst 45% reverted to NGT. The children with IGT who progressed to T2DM had significantly higher BMI scores at baseline and they continued to gain weight during the follow-up period. The study showed that glucose tolerance in obese youth is highly dynamic and can deteriorate rapidly. It appears that the rate of deterioration of beta cell function is faster in children with IGT, compared to similar adults.

SCREENING AND PREVENTION

Earlier diagnosis of diabetes may prevent or slow the development of complications if active treatment is implemented early. As children may have no symptoms or mild symptoms, T2DM in children can remain undiagnosed for a long time. Evidence-base suggests that intensive treatment as early as possible in the pathophysiology of T2DM reduces the associated morbidity and mortality [28-30]. T2DM and the insulin resistance syndrome are to a large

extent preventable, if intervened during the pre-diabetes (IGT) state.

American Diabetes Association (ADA) recommends opportunistic screening of at-risk asymptomatic children [31]. Since Indians are a high ethnic risk group, this is to be interpreted as follows: all Indian children >10 years in age, who are overweight, and have any one of the risk factors (**Table II**) should be screened for DM. The aim of screening and early detection of at-risk cases is to start preventive measures early and to prevent onset/progression of the disease. Prevention can be planned at two levels [32].

Primary prevention: Efforts at prevention of T2DM have mainly focused on diet and exercise therapy i.e. lifestyle modification. The most well known studies which assessed the effectiveness of lifestyle modification on the development of T2DM were in adults (Da-Qing study and the Finnish Diabetes Prevention Study). Primary prevention efforts can focus on the prevention of obesity in children and the promotion of breastfeeding. Weight loss programs with the best results combine exercise and dietary components with behavior modification. It is important to maintain healthy components of traditional diets (i.e., micronutrient rich food such as fruits, vegetables and whole grain cereals) and guard against heavily marketed energy dense fatty and salty foods (e.g. prepackaged snacks, ice-creams and

chocolates), and the sugary cold drinks. A simple Indianised message based on recommendations of AHA could be – “Think of a day’s food composition as a Thali, wherein 50% (half) is full of vegetables, salads and fruits. A quarter (25%) should be made up of cereals such as rice and/or chapattis and the remaining quarter should be protein based (dal/milk/egg/animal protein)” [16]. Children should be encouraged to be active not only for weight control but for general well being. WHO recommends at least 30 minutes of cumulative moderate exercise (equivalent to walking briskly) for all ages; plus for children, an additional 20 minutes of vigorous exercise (equivalent to running), three times a week. These recommendations are basically for prevention of CHD; prevention of obesity may require more physical exertion. In general, moderate to vigorous activities for a period of at least one hour a day may be a more practical recommendation for all school going children. Also, sedentary habits like television watching, computers and tuition classes should be restricted to 1-2 hours daily. Pharmacologic therapy to decrease weight is not recommended for children until more safety and efficacy data are available. The most commonly used medication for prevention of T2DM is metformin. Studies in children and adolescents have demonstrated decrease in insulin resistance with metformin compared with placebo [29]. Very low-calorie diets and high protein diets are contraindicated, except in a well-controlled research setting. Quick-fix weight loss programs are unsafe for children and rarely result in long term weight control; furthermore, they do not promote lasting, healthful eating behaviors. Preventing obesity in women of childbearing age is another primary prevention goal, because exposure to the environment of a diabetic pregnancy places the fetus at increased risk of future onset of diabetes.

Secondary prevention includes measures that are employed to delay or prevent the occurrence of complications of diabetes. Excellent glycemic control, blood pressure control, timely screening for long term complications, diabetes education, and psychological and social support are the pillars of secondary prevention.

RECOMMENDATIONS

The role of controlling the risk factors, and

TABLE II TESTING FOR TYPE 2 DIABETES IN ASYMPTOMATIC CHILDREN

Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)

Plus any two of the following risk factors:

- Family history of type 2 diabetes in first- or second-degree relative
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small for gestational-age birthweight)
- Maternal history of diabetes or GDM during the child’s gestation

Age of initiation: Age 10 years or at onset of puberty, if puberty occurs at a younger age

Frequency: Every 3 years

importance of lifestyle-modification has been amply proven beyond doubt [33-35]. However, there is no clear policy and guidelines for controlling the disease in children. Considering the existing recommendations worldwide and the Indian scenario, the following guidelines are recommended for controlling T2DM in children and adolescents, in our country:

A concerted, multipronged effort is needed, involving the general public, pediatricians and general physicians, teachers and schools, the media, the government and professional medical bodies, to create awareness and generate a momentum towards the goal of prevention of T2DM in the young population of India. The various channels of interventions recommended are [12,16,35]:

(a) *Community* - Community prevention activities should be developed on the basis of each community's unique needs and resources. Development and implementation of these activities should have the endorsement of appropriate local authorities. Ideally, these activities should be multidisciplinary (e.g. medical, nutrition, public health, nursing, health education) and include media, government, schools, parents and specially created 'task forces'. Health care professionals should play a crucial role in their communities by raising community awareness about the importance of programs and facilities for physical activity and resources for healthy nutrition and lifestyle. Community recreation programs should encourage youth to participate in events that require physical activity.

(b) *Schools* - Schools are probably the ideal medium of intervention as they are central to children's lives and information can be relatively quickly dissipated through this channel. Pediatricians and other health care professionals should advocate for school policy that requires daily physical activity/sports for every child and for physical fitness programs in the school. Various aspects to be considered are: (i) training of teachers in lifestyles, nutrition and activity, (ii) introduction of ideal school meals or provision of canteens offering only healthy options based on Indian

foods (iii) introduction of 'nutrition and physical education' in school curriculum and compulsory inclusion of their marks to the total grade (iv) after school games to be encouraged and keeping the school playgrounds open on weekends and holidays, (v) obese children not to be teased, targeted, bullied or isolated, and (vi) regular school health checkups be conducted.

(c) *Health centers/Doctors/Other professionals* - regular screening of high-risk cases, early case detection and creating awareness in community.

(d) *Media* - regular and positive coverage of importance lifestyle modification measures.

(e) *Governmental authorities* - Both health and infrastructural authorities should be responsible for devising national strategies, encouraging food outlets/restaurants to serve healthy choices, providing safe exercise opportunities, regulate advertisements aimed at children and insist on food labeling and consider taxation on 'fatty food' or alternatively reduce taxation/promote production of fresh food and vegetables.

Suitable screening programs be started for high-risk children in the community, especially in schools. There is a hard-felt requirement of having a definite national guideline/program for screening and early detection of T2DM in children. Till then, regular and opportunistic screening of high-risk children as per ADA guidelines of 2011 can be adopted [31].

Funding: None.

Competing interests: None stated.

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