Recommendations

IAP National Task Force for Childhood Prevention of Adult Diseases: Insulin Resistance and Type 2 Diabetes Mellitus in Childhood

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Preamble

It is now well recognized that the constellations of conditions, which enhance the risk of cardiovascular and cerebrovascular diseases in the adult, have their origins in childhood. Indians are an ethnic group at particularly high risk for central obesity, type 2 diabetes mellitus and dyslipidemias, all resulting from a state of insulin resistance and contributing to future cardiovascular morbidity and mortality. Recent studies indicate that the prevalence of type 2 diabetes is increasing in urban Indians, and affecting younger age groups. To create awareness among pediatricians of their role in the prevention of these conditions, and to provide clear guidelines for actions to be taken by them, the Indian Academy of Pediatrics established a National Task Force on Childhood Prevention of Adult Diseases. The task force had published its review and recommendations on Childhood Physical Activity and Prevention of Adult Disease in an earlier issue of the journal. Presented here is the second review in the series, on Insulin Resistance and Type 2 Diabetes Mellitus in Childhood. The members of the task force are listed in *Annexure 1*.

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Abbreviations: DM - diabetes mellitus, IGT - impaired glucose tolerance, PCO - polycystic ovaries, BMI - body mass index, GTT - glucose tolerance test, WHR - waist hip ratio.

Abstract

Type 2 diabetes mellitus (DM) has traditionally been considered a disease of adults. However, in the last 2 decades, it is increasingly being reported in children and

adolescents. Obesity is a strong correlate, and the increasing prevalence of obesity and poor physical activity is precipitating type 2 DM at younger ages in the ethnic groups at risk. Indians and other South Asians are among the ethnic groups particularly prone to insulin resistance and type 2 DM, the other racial groups being some American Indian tribes like the Pima Indians, Mexican Americans, Pacific Islanders and African Americans, among others. The WHO has predicted that India will have the greatest number of diabetic individuals in the world by the year 2025.

Type 2 DM 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 DM (nephropathy, retinopathy, neuropathy) are brought on at an early age. In addition, type 2 DM and obesity are two components of a metabolic syndrome of insulin resistance, the other features of which include hypertension, dyslipidemia and hypercoagulability of blood. All these conditions together increase the risk for cardiovascular and cerebrovascular mortality and morbidity (*i.e.*, myocardial infarction and stroke). The resulting economic burden will be enormous.

Type 2 DM and the insulin resistance syndrome are to a large extent preventable. Adoption of a healthy eating and physical activity pattern has resulted in decreasing the development of DM in a few recent studies from various parts of the world. 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 generate a momentum towards the goal of prevention of type 2 DM and the insulin resistance syndrome in the young population of India.

Insulin resistance, type 2 DM and the metabolic syndrome

Insulin resistance means an impairment of insulin action. This is manifested by decreased insulin - stimulated glucose uptake in skeletal muscle and adipose tissue, and impaired suppression of hepatic glucose output through glycogenolysis. Insulin resistance results in compensatory increase in insulin secretion. The resulting hyperinsulinemia overcomes the insulin resistance for a while and keeps blood sugars in the normal range. However, when relative beta cell insufficiency (*i.e.*, insulin secretion insufficient for the level of hyperglycemia) also sets in, overt diabetes develops.

Type 2 DM is one component of a metabolic syndrome, also known as syndrome X, which is comprised of the following: glucose intolerance, hyperinsulinemia, obesity (particularly central obesity), hypertension and dyslipidemia (elevated triglyceride, low HDL cholesterol, increased small dense LDL)(1). Insulin resistance contributes to hypertension and the typical pattern of dyslipidemia. It is also associated with hypercoagulability of blood, due to elevated levels of plasminogen activator inhibitor. Insulin resistance, type 2 DM, dyslipidemia, hypertension and hypercoagulability together enhance the risk for cardiovascular morbidity and stroke. In addition to these macrovascular complications, type 2 DM also predisposes to microvascular complications like nephropathy, retinopathy and neuropathy(2).

The wider spectrum of insulin resistance is also associated with polycystic ovarian disease and acanthosis. Acanthosis is a condition of the skin presenting as pigmentation along with verrucous hypertrophy(3). The clinical finding of acanthosis is a clue to

the presence of insulin resistance, and should prompt the performance of a glucose tolerance test to uncover asymptomatic type 2 DM or impaired glucose tolerance (IGT). Polycystic ovarian disease is seen in peripubertal girls. The presentation includes irregular menstrual cycles and hyperandrogenemia manifesting as hirsutism. Insulin resistance plays an important role in the pathogenesis of this condition and type 2 DM is more prevalent in girls and women with PCO than in the general population(see below)(4).

A detailed account of the pathogenesis of insulin resistance is beyond the scope of this review; however, the mechanisms involve defects in insulin secretion and signaling, fatty acid metabolism, skeletal muscle triglyceride and fatty acid metabolism, glucose transport across the cell membrane and glucose metabolism, among others. Adipose tissue cytokines such as adiponectin and resistin and other obesity genes may be involved(5).

Insulin sensitivity is affected by factors such as body weight, age, physical activity, ethnicity, heredity and body fat(6). Obesity is the strongest determinant of diabetes risk. In a study of 85,000 female nurses, the risk of developing DM was 40 fold higher in the highest as compared to the lowest levels of BMI. In comparison, the relative risk was 1.3 fold for smokers versus non smokers and 1.5 times for those with the lowest levels of physical activity versus those with the highest activity(7). Visceral fat is more specifically indicative of insulin resistance, as evidenced by the strong correlation of visceral fat with levels of LDL cholesterol and triglycerides and inverse correlation with HDL cholesterol in adults as well as in children. Waist circumference, a surrogate marker for visceral fat, has been shown to be strongly predictive of cardiovascular risk factors in children.

First degree relatives of type 2 DM patients have insulin resistance even when they are non obese, when compared with controls without similar family history, suggesting a strong genetic component.

What connection do these "adult" diseases have with the pediatrician?

According to a large body of epidemiological data from many parts of the world, the seeds of the insulin resistance syndrome are sown during prenatal life(8,9). Intrauterine growth retardation (IUGR), and more so IUGR followed by rapid catch up and relative postnatal obesity, have been shown to be associated with insulin resistance(10). Furthermore, studies in the Pima Indian tribe have shown that maternal gestational DM confers greater risk for insulin resistance in the offspring in comparison to family history of maternal nongestational DM or paternal DM(11).

Furthermore, puberty is a period associated with increased insulin resistance. Euglycemic hyperinsulinemic clamp studies have shown a 30% decrease in glucose disposal rates during Tanner stages 2 and 4 in comparison with prepuberty and young adulthood(12). Increased secretion of growth hormone is thought to be primarily responsible.

In addition to insulin resistance, "tracking" of other cardiovascular risk factors such as obesity, physical inactivity, hyperlipidemia, and hypertension is seen from childhood through adolescence to adulthood, as highlighted elsewhere in this review. Therefore, steps for the prevention of insulin resistance and other cardiovascular risk factors should be adopted during childhood and adolescence.

Epidemiology of type 2 DM in childhood and adolescence

Worldwide, the proportion of childhood

and adolescent DM attributable to type 2 DM is increasing(6,13-15). One of the earliest studies to highlight this trend, on a general population of whites and blacks, was by Pinhas-Hamiel *et al.* from the Greater Cincinnati Area(14). They reported a 4 fold increase in the proportion of young diabetes patients having type 2 DM as the etiology, from before 1992 to between 1992 and 1994. They also documented a 10 fold increase in incidence of type 2 DM between 1982 and 1994. Type 2 DM accounted for one third of the patients in the age group 10-19 years. Obesity was the most important associated feature, with 92% of patients having a BMI greater than 27 kg/m^2. Family history of DM in a first degree relative was present in 65% of patients.

From a gradually increasing number of such reports in the last decade, the following epidemiological features are emerging:

Ethnicity

The highest prevalence of type 2 DM in children and adolescents is reported among some American Indian tribes (Pima and First Nation Indians), approximately 20-35 per 1000 population in the 10-19 year age group and 50 per 1000 in the 15-19 year age group(13). In comparison the NHANES III of USA published a general population prevalence in the same age group of 4.1 per 1000. To put these figures in perspective, the prevalence of type 1 DM in the pediatric and adolescent population is approximately 2-3 per 1000. Other ethnic groups at risk are African Americans, Mexican Americans, Japanese, Pacific Islanders and South Asians (6,15). Euglycemic hyperinsulinemic clamp studies performed in some of these racial groups have shown significantly greater insulin resistance as compared to age, sex and BMI matched adolescents of European descent(16).

Heredity

There is a strong hereditary predisposition to type 2 DM, stronger than for type 1 DM. In adults, the risk of disease in the monozygotic twin of a patient with type 2 DM is 90%, and the lifetime risk of the disease in a first degree relative is 40% (in contrast to 5% for type 1 DM)(6,13).

Obesity

The increased incidence of type 2 DM parallels an increase in obesity, as per reports from USA and Japan(17-19). Obese children are insulin resistant and have approximately a 40% lower glucose utilization rate than non obese children. Visceral fat is more harmful in this regard than subcutaneous fat. A clinic based study from Connecticut, USA, on 55 unselected obese children and 112 obese adolescents referred to an obesity clinic revealed silent DM in 4% of adolescents and IGT in 25% of children and 21% of adolescents(17).

Puberty

The peak age of presentation of childhood type 2 DM is during puberty. Puberty is characterized by a state of insulin resistance, which gradually declines at the end of puberty(12). This insulin resistance is thought to be mediated by the higher levels of growth hormone seen during puberty(6).

Polycystic ovarian disease (PCO)

PCO forms a risk factor for type 2 DM. As discussed above, women with PCO are markedly insulin resistant. Legro *et al* found 31% of women with PCO to have IGT and 7.5% to have diabetes mellitus(4). PCO itself is a common disease, and the racial predisposition appears to be similar to that for type 2 DM(4,20).

Acanthosis nigricans

This velvety, hyperpigmented skin lesion

seen in the neck and intertriginous areas such as axilla and antecubital fossa is associated with type 2 DM in upto 90% of patients(6). It is an important physical correlate of insulin resistance and proves a useful screening tool.

Indians a high risk ethnic group for type 2 DM

It is increasingly being recognized that Indians (and other South Asians) are an ethnic group at high risk for insulin resistance (21-23). This is further compounded by obesity, especially visceral fat, manifested by truncal obesity. Euglycemic-hyper-insulinemic clamp studies, the gold standard for insulin resistance experiments, have shown South Asian men to have lower glucose disposal rates per kg lean body mass as compared to Caucasian Americans(24). For a similar total body fat content, Indians had 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(25-27). Indians have been shown to have a 2 times higher risk of death from ischemic heart disease and a 3.8 times higher risk of myocardial infarction than Europeans(28).

Type 2 DM in adult Indians

In a 1998 publication, the WHO has predicted that India would experience the largest increase in type 2 diabetes in the next 25 years and would have the greatest number of diabetic individuals by the year 2025(29). A number of studies demonstrating a high prevalence of diabetes and impaired glucose tolerance both in expatriate and native Indians have led to this prediction.

DM in expatriate Indians

Expatriate Indians living in UK, South Africa, Singapore and Fiji have for long been known to have prevalence of DM greater than that in the natives of their adoptive countries. The prevalence of DM in the 40-69 year age group in Asians in London was 19% versus 4% in Europeans(21). Similarly, the age adjusted prevalence of DM in urban Fijian men of Indian origin 20 years and older was 12.9% versus 1.1% in Fijian men of Melanesian origin(30). Similar findings were also reported by Simmons, *et al.* from Coventry, UK, where the prevalence of DM in South Asian men 20 years and older was 12.4% versus 3.2% in Europeans(22).

In comparison with European populations, the onset of DM in South Asians is earlier. In the Coventry study, mean age of diagnosis of DM in South Asians was 48 years versus 57 years in Europeans. The mean age of the group with IGT was significantly lower for South Asians than for Europeans. The WHO meta-analysis has also shown that developing countries have the greatest diabetic patients in the 40 to 65 year age group, whereas developed countries have the greatest numbers in the age group > 65 years(29).

DM in native Indians

Data on prevalence of type 2 DM in subcontinental Indians is limited, considering the socio-economic and rural-urban disparity, and the great cultural, geographical and racial diversity of our country(23,31-35). The findings of the recently reported National Urban Diabetes Survey are worth elaborating (23). This survey was conducted on 11, 216 subjects 20 years or older, from 6 cities (Chennai, Bangalore, Hyderabad, Mumbai, Calcutta, New Delhi). The important conclusions, which also reflect the findings of other previous studies, were:

1. The prevalence of diabetes was 12%, equal in both sexes. Twenty five percent of DM was diagnosed below 40 years of age.
2. The prevalence of IGT was similar (14%), suggesting a large 'pool' of potential type 2 DM.
3. Both BMI and waist hip ratio (WHR, an index of visceral adiposity) were significantly correlated with DM and IGT. More importantly high WHR was commoner than overweight and obesity.
4. Multiple logistic regression analysis showed age, BMI, WHR, income, family history of DM, sedentary physical activity status and retired and unemployed category of occupation to all be independently associated with diabetes.

The findings of a recently published study comparing BMI and DM prevalence in Indian versus other ethnic groups are worth mentioning here. The DECODE -DECODA study group on behalf of the European Diabetes Epidemiology Group and the International Diabetes Epidemiology Group found that DM prevalence in Indians starts increasing at a BMI of 15-20 kg/m^2 compared with greater than 25 kg/m^2 in Chinese, Japanese and Europeans(36).

Secular trend and urban-rural comparisons for type 2 DM among adult Indians

In the early 1970s, a national multicentre ICMR study found DM prevalence rate among subjects 16 years and older, to be 2.1% in urban and 1.5% in rural population(31). A 1988-89 survey in the city of Chennai in subjects 20 years of age and older revealed a diabetes prevalence of 8.2% and an IGT prevalence of 8.7%(33). A 1994-95 survey in the same population (Chennai) revealed the DM prevalence had risen to 11.6% for diabetes while IGT remained similar (9.1%)(34). This increase was determined not to be due to change in the demography of the population. At the same time, the 1988-89 survey showed DM prevalence to be 4 fold lower in a rural population (2.4%). However, IGT prevalence in the rural population was 7.8% similar to that in the urban community (8.7%). The similarly high IGT prevalence in both populations could suggest the strong genetic predisposition, with urbanization providing the additional environmental insult to convert IGT to DM.

Type 2 DM in children and adolescents in India

Data on type 2 DM in Indian children and adolescents is sparse(37,38). Ramachandran et al reported on 18 children (5 boys and 13 girls) with type 2 DM diagnosed below the age of 15 years at their clinic(38). Family history of DM was present in all (in 16, first degree relatives were affected and in 2, second degree). Nine were obese and 12 of 13 had high waist hip ratio, indicating visceral obesity. The youngest age at diagnosis was 9 years. Acanthosis nigricans was present in 4, 1 was hypertensive, and one had polycystic ovarian disease. 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 our own clinic, type 2 DM accounted for 12 % (7.5%) of 160 patients with onset of DM below 18 years of age(38). Youngest age at onset was 10 years. Type 2 DM formed 10% of the etiology among patients with age at onset between 10 and 18 years. The mean BMI was 27.2 kg/m^2, significantly higher than the mean BMI of the type 1 DM group (16.2

kg/m^2). No patient presented with ketosis. Two patients required insulin for blood glucose control at initial presentation, but required insignificant doses on follow up and all are well controlled on oral hypoglycemic agents.

The only other study highlighting type 2 DM in South Asian children is from UK(15). Ehtisham, *et al*. described 8 patients with type 2 DM, from 2 counties in UK. The majority were of Indian and Pakistani origin, with a few of middle eastern origin. They presented insidiously, 5 were asymptomatic, and 4 each had acanthosis and hypertension.

Etiology and diagnosis of diabetes in children

Table 1 highlights the salient aspects of the classification of diabetes mellitus adopted by the American Diabetes Association in 1997.

Definition of DM / IGT

The cut off values of fasting and 2 hour post glucose BG for the diagnosis of DM in adults are based on the correlation with future morbidity(39). Such data are not available in children. Therefore, though normal values of BG on OGTT are different in children, the criteria for diagnosis in children adopted by various expert agencies have been the same as in adults(13). However, though the ADA in its recently revised criteria for diagnosis of DM have declared that FBG correlates very well with the 2 hour post glucose BG and is sufficient for treatment of DM, in many ethnic groups including in Indians, this is suggested to be not always true(40,41). The 2 hour value has been shown to be more sensitive in picking up diabetes. Therefore, the 2 hour value is retained as a diagnostic criterion for our patients. The GTT can help uncover glucose intolerance. Impaired fasting glucose

TABLE I– *Etiologic Classification of Diabetes.*

- Type 1 diabetes (b-cell destruction, usually leading to absolute insulin deficiency)
  - Immune-mediated
  - Idiopathic
- Type 2 diabetes
- Other specific types
  - Genetic defects of b-cell function (*e.g.*, maturity onset diabetes in young, MODY)
  - Genetic defects in insulin action (*e.g.*, lipoatrophic diabetes)
  - Diseases of the exocrine pancreas (*e.g.*, tropical calcific pancreatitis, cystic fibrosis)
  - Infections (*e.g.*, congenital rubella)
  - Uncommon forms of immune-mediated diabetes (*e.g.*, autoantibodies against the insulin receptor)
  - Other genetic syndromes sometimes associated with diabetes (*e.g.*, Prader Willi, Turner, Klinefelter, Wolfram and other syndromes)
  - Drugs (*e.g.*, glucocorticoids, pentamidine, thiazide, phenytoin)
  - Endocrinopathies (*e.g.*, Cushing syndrome, acromegaly-gigantism, hyperthyroidism, pheochromocytoma)
- Gestational diabetes mellitus (GDM)

Adapted from the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (39).

and impaired glucose tolerance are associated with increased risk of conversion to overt diabetes as compared to the general population. Therefore, efforts at prevention of DM have targeted subjects with IFG or IGT.

The 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 *Tables II* and *III*.

Patients who have typical symptoms of diabetes (polyuria, polydipsia and unexplained weight loss) do not need to undergo a GTT. A blood glucose > 200 mg/dL anytime, in the presence of symptoms, is diagnostic of diabetes.

TABLE II– *Diagnostic criteria for diabetes.*

- Symptoms of diabetes (polyuria, polydipsia, and unexplained weight loss) plus casual plasma glucose concentration ³ 200 mg/dL (11.1 mmol/L) (casual is defined as any time of day without regard to time since last meal), OR
- FPG ³126 mg/dL (7.0 mmol/L) (fasting is defined as no caloric intake for at least 8 hours) OR
- 2 hour post glucose plasma glucose value ³ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test.

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

Complications of type 2 DM in childhood and adolescence

Unlike type 1 DM, type 2 DM has an insidious onset. Many patients at the time of diagnosis therefore, have already had hyperglycemia for many years. Thus, adult type 2 DM patients are well known to have diabetes complications right at the time of diagnosis. The same has also been demonstrated in youth with type 2 DM. Twenty two percent of Pima Indian children had microalbuminuria at diagnosis. By 10 years of follow up, 60% had micro-albuminuria and 17% had macroalbuminuria (at 20-29 years of age)(18). In a report from Cincinnati on 54 children with type 2 DM, 17% had hypertension and 4% had hypertriglyceridemia(14).

Treatment of Type 2 DM in childhood

Goals of therapy include:

1. Normalisation of blood glucose values.
2. Control of associated problems of obesity, hypertension, dyslipidemia.
3. Appropriate counseling regarding diet and physical activity.
4. Education of patient and family.
5. Monitoring for microvascular complications such as retinopathy, nephropathy, neuropathy and foot care.

TABLE III–*Diagnostic categories of venous plasma glucose on oral glucose tolerance test.*

Plasma glucose	Normal	Impaired fasting glucose	Impaired glucose tolerance	Diabetes
Fasting	< 110 mg %	³ 110 and < 126 mg%	< 126 mg %	³ 126 mg %
2 hour post glucose	< 140 mg %	< 140 mg %	140 - 200 mg %	³ 200 mg %

For details of diabetes management in children, the reader is referred to more detailed reviews(42).

Pharmacological therapy

While insulin is the only form of therapy in type 1 DM, it is usually not necessary in the treatment of type 2 DM in the early years. Exceptions may occur if the patient presents with acute complications like diabetic ketoacidosis or hyperosmolar non ketotic coma. In a well patient with new onset diabetes, the clues to the etiology being type 1 DM (for which insulin must be started) are the history of acute onset polyuria and polydipsia, significant weight loss, absence of obesity, presence of ketones and presence of autoantibodies in the blood. Clues to the etiology being type 2 DM (for which oral medication can be started) include obesity, acanthosis, strong family history of DM and absence of the above features of type 1 DM. However these compartments are not watertight. Type 2 DM may present with significant weight loss and ketones. Type 1 DM may often present with absent ketones and have a family history of type 2 DM. Autoantibodies, even in recent onset type 1 DM, are not as frequent in Indian children as in Caucasians(43). Thus, when in doubt, it is better to start insulin. If after the first year of DM the insulin dose requirement is negligible (less than about 0.2 or 0.3 units/kg/body weight), type 2 DM becomes the likely diagnosis and oral hypoglycemic agents (OHA) may be tried.

Oral agents for diabetes

The groups of oral agents for diabetes are as follows:

(*a*) Biguanides (metformin): decrease hepatic glucose output and improve peripheral glucose uptake.

(*b*) Sulphonylureas (glibenclamide, glipizide, gliclazide, *etc.*) increase insulin secretion.

(*c*) Meglitinide (repaglinide): enhance short term glucose stimulated insulin secretion.

(*d*) a glucosidase inhibitors (acarbose): slows carbohydrate absorption from the gut.

(*e*) Thiazolidenediones (troglitazone which is now withdrawn due to serious side effects, rosiglitazone, pioglitazone) enhance peripheral insulin sensitivity.

Of these, metformin is the agent of first choice in children if diet and exercise therapy have not been sufficient to control glycemia(13). It should not be used in renal or hepatic dysfunction, or during alcohol abuse. Pregnancy and severe infection warrant the use of insulin.

If metformin alone is not able to produce good glucose control, another oral agent or insulin can be added. Of the other oral agents, the maximum experience is with sulphonylureas. Troglitazone is known to produce fatal hepatic failure, and is no longer used. Large prospective studies like the DCCT for type 1 DM and the UKPDS and Kumomoto study for type 2 DM have confirmed that good blood glucose control delays and minimizes long term microvascular complications (2,44,45). The UKPDS also provided strong evidence that tight blood pressure control minimizes long term macro and microvascular complications in adults with type 2 DM(46).

Monitoring for complications

A fundus examination for retinopathy by a retina specialist and a urinary microalbumin test should be performed yearly. In contrast to type 1 DM, complication screening begins at onset of DM in type 2 DM. Examination for neuropathy, blood pressure and the feet should be done twice a year.

Prevention of diabetes in childhood and adolescence

Prevention can be planned at two levels. Primary prevention consists of measures instituted to prevent or delay the onset of diabetes. Secondary prevention includes measures that are employed to delay or prevent the occurrence of complications of diabetes.

Primary prevention

As is foreseeable from the understanding of the role of obesity and physical inactivity in enhancing insulin resistance and the risk of type 2 DM in the genetically predisposed individual, efforts at prevention of type 2 DM have focused on (*a*) diet and exercise therapy *ie*, lifestyle modification and (*b*) pharmacotherapy for decreasing insulin resistance. Early screening for IGT in individuals at risk provides, in some individuals, a window of time in which to institute these measures before the onset of clinical symptoms.

Who should be screened, how and how often?

As per the American Diabetes Association consensus statement on childhood type 2 DM published in the year 2000, all overweight children greater than 10 years in age who have any 2 of the risk factors for DM (of which ethnicity is one), should be screened(13). Since Indians are a high risk group, this is to be interpreted as follows: *All Indian children >10 years in age, and are overweight (BMI >85th centile for age or weight >120% of the 50th centile weight for height by national standards), and have any one of the following risk factors, should be screened for DM: family history of type 2 DM in first or second degree relative, polycystic ovaries, acanthosis, dyslipidemia or hypertension.* Furthermore, it is recommended that clinical judgment be used to test for diabetes in high-risk patients who do not meet these criteria (for example in a morbidly obese patient without any other risk factor). A predisposing condition like Turner, Klinefelter, Prader Willi or Cushing syndromes warrants screening irrespective of the presence of obesity.

Pending the availability of good Indian nationally representative standards for BMI in childhood, the definition for overweight and obesity worldwide, provided by the International Obesity Task Force of the WHO, may be used(47). These charts and tables provide percentiles for boys and girls aged 2 to 18 years that at 18 years pass through the widely used adult cut-offs for overweight and obesity, 25 and 30 kg/m^2. These were pooled from longitudinal nationally representative large bodies of height and weight data from 6 countries: USA, Great Britain, Brazil, Singapore, Hong Kong and Netherlands. The "overweight" percentile, which passes through 25 kg/m^2, can be used in place of 85th centile mentioned above.

Screening has been recommended by a fasting BG by the American Diabetes Association. However, in Indians, for reasons discussed above, fasting as well as 2 hour post glucose values are recommended. The method of carrying out a GTT is described above, and the interpretation in *Table III*. If the values are found normal, screening should be repeated 2 yearly.

Life style modification

The most well known studies which assessed the effectiveness of lifestyle modification on the development of type 2 DM were in adults, the Da Qing study and the Finnish Diabetes Prevention Study(48,49). In the former, 126 Chinese men with IGT were assigned to get dietary and exercise intervention and 133 were followed as controls. Over 6 years, 32% less DM occurred

in the intervention group. In the latter study 522 overweight subjects with IGT were randomized to receive intensive supervised diet and exercise intervention, or to receive standard written and verbal counseling regarding diet and exercise, at baseline and at every year. Significant weight loss occurred in the former group vis-à-vis the latter, both at the end of 1 year as well as 2 years. The incidence of DM over 4 years was 11% in the former versus 23% in the latter group. No study has directly looked at the effectiveness of this prevention method for DM in children/ adolescents, though numerous studies have looked at the effectiveness in reducing obesity and insulin resistance, as discussed elsewhere in this review.

Pharmacologic therapy

The most commonly used medication for prevention of type 2 DM is metformin. While studies in children and adolescents(50) have demonstrated decrease in insulin resistance with metformin compared with placebo, studies in adults have gone one step ahead and demonstrated decrease in incidence of DM in IGT patients taking metformin versus placebo. The Diabetes Prevention Program is the most well known, where 3234 overweight subjects with IGT or IFG were given standard lifestyle modification instructions with placebo or metformin and a third group received intensive lifestyle modification advice with no medication. The third group was the most effective in decreasing the rate of conversion of IGT to DM followed by the metformin group, both significantly lower than the placebo group(51).

Among other medications, troglitazone has been shown to delay DM in a group of women who had previously had gestational diabetes(52). However, this medicine is now withdrawn because of serious side effects. Data of the use of the newer thiazolidenediones (pioglitazone and rosiglitazone) is not ready yet either in adults or in children.

Other pharmacotherapy which have been claimed to delay DM in adults are acarbose(53), the ACE inhibitor ramipril(54) and the lipid lowering agent pravastatin(55). In the latter 2 studies, DM prevention was a secondary outcome measure. More studies are required to corroborate these findings before these agents can be brought into clinical use for diabetes prevention.

At the time of writing, even metformin has not yet been recommended for DM *prevention* in children (or adults) by any consensus workshop or bodies like the American Diabetes Association. Lifestyle modification measures, the details of which can be found elsewhere in this review, must certainly be used, though proven feasibility and effectivity in delaying or preventing DM in childhood or adolescence is yet to be documented.

Secondary prevention

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. For a detailed description of these aspects, the reader is referred to more detailed reviews(42).

Targets for primary prevention of insulin resistance

I. The Pediatrician

A. Pick up patients who need screening for DM by looking for risk factors

(*i*) Yearly growth (height, weight and weight for height / BMI) charting 3 to 6 monthly from birth to 5 years of age and 6 to 12 monthly thereafter

(*ii*) Eliciting family history of DM, hypertension, obesity

(*iii*) History and physical examination for blood pressure in all from age 3 years, and acanthosis and polycystic ovaries after 10 years of age.

(*iv*) Two yearly screening of blood glucose (see above for how to screen) in those at risk, after age 10 years. Lipid profile in children age > 2 years with family history of dyslipidemia or premature cardio-vascular disease, or anytime in children with family history unknown but with any risk factor for insulin resistance. If diagnosis of DM or hyperlipidemia is made, refer to specialized centre for diabetes / other initial education and initiation of the plan of management.

(*v*) Recommend lifestyle modification for overweight / obese children and also children who are not yet overweight but are crossing BMI percentiles upwards.

B. Disseminate awareness by

(*i*) Educating patients, parents and grand-parents about the importance of healthy lifestyle.

(*ii*) Distributing literature to patients' families.

(*iii*) Lectures in school and community.

II. Teacher / School / School Boards / College

(*i*) Daily 20 minutes of compulsory physical education time.

(*ii*) School snacks to be "healthy".

(*iii*) Curriculum to include chapters on healthy lifestyle: diet, exercise, smoking.

(*iv*) Yearly height and weight charting.

(*v*) Yearly health check up, including urine sugar from 10 years onwards.

(*vi*) Achievement in sport to be given more importance by boards / college.

III. Government

(*i*) Facilities for exercise for adults and children.

(*ii*) Reimbursement for preventive health measures.

IV. Media

(*i*) Knowledge dissemination.

(*ii*) Advocacy (*e.g.*, Target advertising in childrens' programs).

V. Parents

(*i*) Be good role models for healthy lifestyle.

(*ii*) Encourage exercise, discourage TV watching and computer games by setting examples.

(*iii*) Encourage children to help with household chores.

(*iv*) Quit smoking if doing so, to set example.

VI. Task force / IAP

(*i*) Provide nationally relevant growth and BMI charts and height measuring equipment.

(*ii*) Provide literature for pediatricians and parents on obesity, DM, food pyramid, *etc.*

(*iii*) Advocacy: school boards and colleges, media, government, food regulatory authorities, bring in funding for research.

Recommendations for research

1. Generation of new data on growth, BMI, waist and hip circumference, and skin folds in Indian children.
2. Prevalence of obesity in India, SE groups at risk, predisposing factors.
3. Prevalence of type 2 DM and IGT in children and adolescents in India, especially in the obese.
4. Acceptability and effectiveness of yoga,

conventional exercise techniques and drugs in tackling obesity and type 2 DM.

5. Effectiveness of school based lifestyle modification programs in India.

REFERENCES

*(References with a * symbol are either landmark studies or those of more interest to pediatricians).*

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Annexure I

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