

Type 2 Diabetes Mellitus in Children and Adolescents: An update

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Summary:

Childhood type 2 Diabetes Mellitus (DM) has increasingly been reported worldwide. It is commonly associated with childhood obesity. It may be presented with classical manifestation of DM such as polyuria, polydipsia, weight loss or acute complications like Diabetic ketoacidosis (DKA), Hyperglycemic Hyperosmolar State (HHS) or features of insulin resistance syndrome. Many a cases it may remain asymptomatic and hence undiagnosed. So, overweight children and adolescents who met screening criteria such as family history of type 2 DM, signs of insulin resistance, and high risk ethnics should undergo screening. Emphasis should be given on early diagnosis and optimum management plan to avoid grave consequences of it in early part of life. Diagnosis of type 2 Diabetes Mellitus in children should be done on the basis of standard diagnostic criteria such as American Diabetic Association (ADA) criteria. Both non-pharmacological and drug management are important equally. Multidisciplinary

Introduction:

Type 2 diabetes mellitus (DM) happens when the body cannot effectively use the insulin it produces. Formerly, it was called non-insulin dependent or adult onset diabetes mellitus as because, for many years it was seen only in adults. In type 1 diabetes mellitus, the body does not produce insulin and it is usually diagnosed in children and young adults. Recently, type 2 diabetes mellitus has increasingly been reported in children and

team approach including self-management plan is mandatory for obtaining optimal therapeutic goals of type 2 DM in children and adolescents. Lifestyle modification, dietary intervention, weight reduction, patient education, psychological support, and oral anti diabetic drugs and insulin therapy should be included in comprehensive diabetic management plan. Complications of type 2 DM should be minimized by all means with strict glycemic control and management of co-morbidity if any. Emphasis should also be given on prevention of type 2 DM by adopting a healthy lifestyle characterized by healthy eating behavior, regular physical activity and subsequent modest weight loss that can prevent the progression of impaired glucose tolerance to clinical diabetes mellitus.

Key words: American Diabetic Association (ADA), Diabetic Ketoacidosis (DKA), Hyperglycemic Hyperosmolar State (HHS), Overweight, Type 2 Diabetes Mellitus (DM).

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adolescents, so much so that in some parts of the world type 2 diabetes has become the main type of diabetes in children. The global rise of childhood obesity and physical inactivity is widely believed to play a crucial role¹. Currently, more than 200 children and adolescents develop the disease every day worldwide². But healthy eating and lifestyle habits are a strong defense against the disease.

Risk factors and Pathophysiology of Type 2 DM:

Type 2 DM is a complex metabolic disorder of heterogeneous etiology with social, behavioral, and environmental risk factors unmasking the effects of genetic susceptibility³. There is a strong hereditary component of the disease. The major risk factors of type 2 DM in children are: obesity and inactivity, family history of type 2 DM, age of 12-16 years, maternal gestational diabetes or type 2 diabetes, not breast feeding during infancy and ethnicity. Other factors that appear to increase risk include poor fetal growth, low birth weight and high birth weight⁴. Impaired glucose

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homeostasis is the key mechanism in type 2 DM and it depends on the balance between insulin secretion by the pancreatic β -cells and insulin action. The mean age range of onset of type 2 diabetes in youths coincides with the relative insulin resistance that occurs during pubertal development, resulting in hyper-insulinemia and play a major role in the development of type 2 DM in children and adolescents. The adverse effect of obesity on glucose metabolism is evident early in childhood. Obese children are hyper-insulinemic and have approximately 40% lower insulin-stimulated glucose metabolism compared with non-obese children⁵.

Epidemiology of Type 2 DM in children and adolescents:

Type 2 DM in youth appears to be emerging as a serious clinical issue. Its prevalence in the United States (USA) is approximately 12:100,000, while it is still rare in Europe⁶ (approx. 2.5:100,000). In Bangladesh the exact prevalence of Type 2 DM is not known. But in a study among 2152 students volunteers in Bangladesh, Abu Sayeed et al⁷. observed that the prevalence of type 2 DM and impaired fasting glucose (IFG) appears to be 1.8% and 3.4% respectively. The majority of USA young people diagnosed with type 2 diabetes are found in specific ethnic subgroups such as African-American, Hispanic, Asian/Pacific Islanders and American Indians being highest in Pima Indians (22.3/1000 in 10-14 year old children). Furthermore, the great majority of the children are obese. Screening studies in obese adolescents have reported a prevalence of 0.4% up to 1% of type 2 diabetes in obese children⁸ 12 years⁸.

Clinical presentation of Type 2 DM:

The presentation of type 2 DM in children and adolescents varies according to the disease stage. Early in the disease, before diabetes diagnostic criteria are met, insulin resistance predominates with compensatory high insulin secretion, resulting in normoglycemia and the patient likely to be asymptomatic⁹. At this stage, the disease may only be detected by abnormal blood glucose concentrations identified during screening. Obesity is the hallmark of type 2 diabetes in children and adolescents. Most children are obese or extremely obese at diagnosis and present with glycosuria without ketonuria, absent or mild polyuria and polydipsia, and little or no weight loss. In its severest form, the child presents with polyuria, polydipsia, and weight loss. Up to 33% in particular ethnic groups have ketonuria at

diagnosis and 5%-25% ketoacidosis at presentation¹⁰. Vary rarely, type 2 diabetes mellitus manifest with a hyperglycemic hyperosmolar state (HHS). Acanthosis nigricans and polycystic ovarian syndrome (PCOS), disorders associated with insulin resistance and obesity, are common in youth with type 2 DM¹¹. Children with type 2 diabetes frequently have a positive family history, and 74%-100% first or second degree relative have type 2 DM. Some syndromes such as Klinefelter syndrome, Bardet Biedl Syndrome, Prader Willi Syndrome and Alström Syndrome are also associated with type 2 DM. They all are associated with mental retardation and frequently to extreme obesity¹².

Differential Diagnosis:

Patients with type 2 DM may have clinical presentations indistinguishable from those of patients with other types of diabetes mellitus¹¹. It is important to classify diabetes mellitus in children and adolescents correctly, so that appropriate therapy may be instituted. Typically, children with type 1 diabetes mellitus are not overweight and have recent weight loss, polydipsia, and polyuria. They have a short duration of symptoms and frequently have ketoacidosis at presentation¹¹. Type 2 diabetic children and adolescents may represent a form of early-onset latent autoimmune diabetes mellitus similar to that described in adults (LADA). These patients with LADA share insulin resistance with that of type 2 diabetes mellitus patients but display a more severe defect in β -cell capacity¹². Following the terminology 'latent autoimmune diabetes mellitus in adulthood, LADA', the non-insulin dependent diabetic children and adolescents with β -cell autoantibodies could be named 'latent autoimmune diabetes mellitus in youth' (LADY)¹³. Double diabetes mellitus or type 1.5 diabetes mellitus are other proposed names for this entity¹³. Maturity-onset of diabetes mellitus of the young (MODY) is another rare form of diabetes mellitus in children that includes several disorders caused by monogenic defects in β -cell function¹⁴. MODY 2 and MODY 3 (defect in glucokinase and HNF1 α respectively) are the most frequent types of MODY. Patients with MODY have a dominant genetic trait, usually are non-obese and have low fasting insulin levels. Recent studies suggest that the clinical presentation of MODY is broad, ranging from asymptomatic hyperglycemia to a severe acute presentation¹³.

Diagnostic criteria for Type 2 Diabetes Mellitus:

Diagnosis of type 2 Diabetes Mellitus in children and adolescents can be made on the basis of American Diabetic Association (ADA) revised diagnostic criteria (Table 1)¹⁵ or any other diagnostic criteria. In the absence of unequivocal hyperglycemia, random, fasting or two-hour blood sample should be confirmed by repeat testing. Other tests may be necessary in difficult cases for diagnosis of type of DM, such as fasting insulin or C-peptide determination and occasionally, β -cell autoantibodies measurements. C-peptide levels are elevated in individuals with type 2 diabetes mellitus in contrast to patients with type 1 diabetes mellitus or MODY diabetes.

Table-I*Diagnostic criteria for type 2 DM¹⁵*

- Symptoms of diabetes mellitus such as polydipsia, polyuria, and unexplained weight loss plus
- Random glucose concentration ≥ 200 mg/dL (11.1 mmol/L) in venous plasma,
- Fasting glucose ≥ 126 mg/dL (7.0 mmol/L) in venous or capillary plasma,
- Or two-hours glucose during oral glucose tolerance test (oGTT) ≥ 200 mg/dL (11.1 mmol/L) in venous plasma or capillary whole blood sample And
- Hemoglobin A1c (HbA1c) $\geq 6.5\%$

Screening for Type 2 Diabetes Mellitus:

Most of the children and adolescents with type 2 diabetes remain asymptomatic at diagnosis. So screening for it is necessary¹⁶. It is found that unrecognized hyperglycemia contributes to both microvascular and macrovascular risk in later life¹⁷. However, at the present time, a general screening for type 2 DM in youth is unlikely to be cost effective and so a targeted screening is necessary. The ADA recommends a screening in overweight children and adolescents at onset of puberty in high risk patients (Table 2). Screening test should be performed every 2 years starting at the age of 10 years or at onset of puberty. It should be done by testing fasting glucose or oGTT¹⁸.

Table-II*Criteria for screening tests for type 2 DM in children and adolescents¹⁸*

Overweight (BMI > 90 percentile) plus one of the following risk factors:

- Family history of type 2 DM in 1^o or 2^o relative;
- Race/ethnicity (Asian, American Indian, African-Americans, Hispanics);
- Signs of insulin resistance; or conditions associated with insulin resistance such as acanthosis nigricans, hypertension, dyslipidemia, polycystic ovarian syndrome (PCOS);
- Extreme obesity (BMI > 99.5 percentile).

Complications of Type 2 Diabetes Mellitus:

The chronic complications of type 2 DM in children and adolescents are macrovascular diseases like accelerated development of cardiovascular disease leading to stroke and myocardial infarction, and microvascular diseases like nephropathy, retinopathy and neuropathy leading to end-stage renal disease, loss of visual acuity, and limb amputations. Microvascular disease is the hallmark of hyperglycemia diagnosed at a younger age. As because the complications of DM are related to the duration of disease itself, risks of complications more common in children and adolescents as compared to adult diabetics¹⁹. All of these complications contribute to the excess morbidity and mortality in individuals with diabetes mellitus. Young people with type 2 DM appear to be at a much higher risk of developing early diabetes associated complications than those with type 1 diabetes mellitus²⁰. This higher level of risk does not appear to be related to overall levels of glycemic control or duration of disease but to occurrence of hypertension and dyslipidemia.

Management of Type 2 Diabetes Mellitus:

The ideal goal of management (Table 3)²¹ of type 2 diabetes in children and adolescents is normalization of blood glucose values, HbA1c and to decrease the risk of diabetes related acute and chronic complications. Successful control of the associated comorbidities, such as hypertension and dyslipidemia, is also important¹¹. The American Academy of Pediatrics has, very recently,

published the management guidelines for children and adolescents with type 2 diabetes mellitus²².

Table-III

Therapeutic goal of type 2 DM in children and adolescents²¹

- Before breakfast sugar: 90–130 mg/dL (5.0–7.2 mmol/L);
- Before bed/ overnight sugar 90–150 mg/dL (5.0–8.3 mmol/L);
- Target HbA1C <7%;
- Target blood pressure consistently, <90th percentile for age, sex, and height;
- Target LDL cholesterol value, 100 mg/dL (2.6 mmol/L).

Insulin therapy should be initiated for children and adolescents with type 2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between type 1 and type 2DM is unclear; and, in usual cases: who have random venous blood or plasma sugar concentration ≥ 250 mg/dL; or whose HbA1c is $>9\%$. In all other instances, lifestyle modification program, including nutrition and physical activity, and Metformin should be started as first-line therapy at the time of diagnosis of type 2DM²². Despite of severe manifestation, initial management of obese children and adolescents with type 2 DM should consist of behavior modification strategies for lifestyle change such as decreasing high-caloric high-fat food choice and sedentary behavior, while increasing physical activity. Lifestyle changes should not be imposed and self-motivation is necessary²³. Treatment options of type 2 DM include:

Diet: Balanced macronutrient diets at 900 to 1200 kcal per day are associated with both short and long-term (e² 1 year) improvements in weight status and body composition in children 6 to 12 years of age²⁴. These calorie management are to be incorporated with lifestyle changes, including increased activity and medication. Restrictions of no less than 1200 kcal per day in adolescents 13 to 18 years old result in improved weight status and body composition²⁵.

Physical activity: It is an integral part of weight management for prevention and treatment of type 2DM.

Children and adolescents are encouraged to engage in 'moderate-to-vigorous' exercise for at least 60 minutes daily and to limit non-academic 'screen time' to less than 2 hours a day. Screen time contributes to a sedentary lifestyle, especially when the child or adolescent eats while watching television or playing computer games²⁶.

Patients education: All children with type 2 diabetes mellitus should receive comprehensive self-management education which include teaching self-monitoring of blood glucose, performed as needed and during periods of acute illness or when symptoms of hyper- or hypoglycemia occur²⁷.

Pharmacological treatment: If treatment goal with nutrition education and exercise is not met, pharmacological therapy is indicated. Metformin and insulin are the only anti-diabetic agents currently recommended for use in children. Thiazolidinediones and incretins are occasionally used in adolescents younger than 18 years²⁸. Metformin, a biguanide, is the most appropriate starting point for pharmacological treatment in children with type 2 diabetes mellitus if insulin therapy is not indicated. The effectiveness has been proven for adolescents in clinical trials. Metformin decreases hepatic glucose output and enhances primarily hepatic and also muscle insulin sensitivity without a direct effect on β -cell function. It has the advantage of weight reduction, decrease in lipids without the risk of hypoglycemia. Because of concerns about lactic acidosis metformin is contraindicated in patients with impaired renal function and should be discontinued with the administration of radiocontrast material or hypocaloric diet. Metformin should not be used in patients with known hypoxic conditions, severe infection, hepatic disease, or alcohol abuse. The most common side effects of metformin are gastrointestinal disturbances. The dose of metformin should be increased up to 2 gm in split doses, unless there are gastrointestinal side effects. Metformin has a good safety record, but should not be given if there is any doubt at all about the nature of diagnosis. Rosiglitazone, a thiazolidinedione has been studied in some randomized trial in adolescents compared to lifestyle intervention and metformin and found some effects. However, rosiglitazone has been withdrawn from the market due to its side effects and is not available any more¹³.

If monotherapy with metformin is not successful over a reasonable period of time (3-6 months), insulin treatment will often be the only feasible way of controlling hyperglycemia. There is no specific contraindication to insulin in children. Any type of insulin and analogs can be used. Insulin regimes should be adopted that are carefully tailored to lifestyle such as bedtime insulin alone, twice-a-day insulin or multidose insulin regimes¹³. Basal insulin is provided through either the use of long acting, relatively peak-free insulin by needle or via an insulin pump. Bolus insulin doses are given at meal-time, using one of the rapid-acting insulin analogs. The bolus dose is calculated by using a correction algorithm for the premeal blood sugar concentration as well as a "carb ratio," in which 1 unit of a rapid-acting insulin analog is given for "X" grams of carbohydrates ingested (For example, see Table 4)¹⁵.

Table-IV

Calculation of Basal Bolus Insulin Regimen¹⁵

- If an adolescent has a blood glucose of 250 mg/dL, is to consume a meal containing 60 gm of carbohydrates, with a carbohydrate ratio of 1:10 and an assigned correction dose of 1:25 > 125 the mealtime bolus dose of insulin would be as follows:
 $60 \text{ gm}/10 = 6 \text{ units rapid-acting insulin for meal}$
 plus
 $(250 - 125)/25 = 125/25 = 5 \text{ units rapid-acting insulin for correction};$ Thus, total bolus insulin coverage at mealtime is: 11 Units (6 + 5)
- Note: Insulin sensitivity-25; Target blood glucose level-125mg/dl, 'carb ratio'-10.

Monitoring of Diabetes Mellitus and treatment of complications:

All children and adolescents with newly diagnosed type 2 DM, regardless of prescribed treatment plan, should perform finger-stick blood glucose monitoring before meals and at bedtime until reasonable metabolic control is achieved²⁹. Once blood glucose concentrations are at target levels, the frequency of monitoring can be modified depending on the medication used, the regimen's intensity, and the patient's metabolic control. Monitoring of HbA1c concentrations every 3 months and intensification of treatment is required if treatment goals for blood sugar and HbA1c

concentrations are not being met. Patients on insulin should also be monitored periodically for asymptomatic hypoglycemia. To monitor retinopathy, dilated eye examinations should be performed regularly. Screening for microalbuminuria should be performed yearly²⁶. Angiotensin converting enzyme (ACE) inhibitors are the agents of choice in children with microalbuminuria. Control of hypertension in children with type 2 diabetes mellitus is mandatory. If normotension is not achieved by ACE inhibitors, combination therapy with α -blockers, calcium antagonists or low-dose diuretics may be needed. It is unclear whether foot examinations are important in children. Testing for and treating lipid abnormalities are necessary to avoid macrovascular complications³⁰.

Psychological impacts of Type 2 DM in children and adolescents:

Adolescents with type 2 diabetes mellitus rate lower 'Quality of Life' scores than their peers with type 1 DM and the burden of neuropsychiatric disorders in young people with type 2 DM is high, with as many as one in five experiencing either psychiatric illness or neurodevelopmental/behavioral problems. It is found that psychosocial factors represent a significant barrier to optimum self-management in adolescents with type DM, often leading to a vicious circle of spiraling poor self-management and increasing psychosocial problems. Poor psychosocial health may also be physiologically related to poorer glycemic control. Therefore psychologists should be the core component of care of children and adolescents with type 2 diabetes mellitus¹³.

Prevention of Type 2 Diabetes Mellitus:

Prevention of Type 2 Diabetes Mellitus should start very early in life, even before birth. Primary prevention has proven to be difficult or impossible in most societies. A multidisciplinary team approach is needed to develop and secure preventive strategies. Good nutrition and modest exercise for pregnant women as well as monitoring of intrauterine growth of the fetus are mandatory. After birth, rapid weight gain should be avoided and the principles of good nutrition and physical activity are to be taught at all ages. Breastfeeding should be strongly recommended. Children's food choice can be influenced by early intervention and guidance¹⁸. Teacher training, modification of school meals and physical education are effective in reducing

risk factors for obesity which is the hallmark of type 2 DM in children. Recent intervention studies have convincingly demonstrated that adoption of a healthy lifestyle characterized by healthy eating behavior, regular physical activity and subsequent modest weight loss can prevent the progression of impaired glucose tolerance to clinical diabetes mellitus. The use of metformin is not effective to prevent type 2 DM in obese adolescents with impaired glucose tolerance³¹.

Conclusion:

Type 2 diabetes mellitus is emerging as a new clinical problem within pediatric practice. Clinicians should be aware of the frequent mild or asymptomatic manifestation of type 2 diabetes mellitus in childhood. Therefore, a screening seems meaningful especially in high risk groups such as children and adolescents with obesity, relatives with type 2 diabetes mellitus, and clinical features of insulin resistance. Emphasis should be given on early diagnosis and comprehensive management plan to avoid grave consequences of it in early part of life. All efforts should be given on prevention of type 2 DM such as, healthy eating, physical activity, and modest weight reduction. Collaborative efforts from all corners of the modern society can efficiently combat against this emerging disease.

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