Chapter 33

Clinical Approach to Diabetes in the Young in India

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ABSTRACT

According to the 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. Population-based estimates for diabetes in children and adolescents are lacking in our country. However, available data suggests that the prevalence of type 2 diabetes mellitus (T2DM) is not only increasing, but there is also a shift of age at onset of T2DM toward younger age groups. A variety of types of diabetes are seen at younger age groups including type 1 diabetes mellitus (T1DM), T2DM, maturity onset diabetes of young, fibrocalculous pancreatic diabetes, gestational diabetes, endocrine diabetes and diabetes secondary to genetic syndrome. This review describes the diagnostic algorithm and treatment approaches of different forms of diabetes in the young and emphasizes the need to classify diabetes in the young as accurately as possible.

INTRODUCTION

According to the ICMR-INDIAB national diabetes study, currently, there are an estimated 62.4 million individuals with diabetes in India.[1] This is further expected to increase to 101 million in 2030.[2] Until recently, type 1 diabetes mellitus (T1DM) was not only the most common form of diabetes seen in youth, but also perhaps the only form of diabetes seen in children and adolescents. However, this trend has started changing slowly. Type 2 diabetes mellitus (T2DM), earlier considered a disorder of middle age or elderly, is increasingly being reported among young adults and now also in adolescence and childhood, probably due to the burgeoning epidemic of childhood obesity. Indeed, the epidemic of T2DM is now spreading so rapidly, that already in some countries, like Japan; T2DM is already more common than T1DM, in children.[3,4]

Population-based estimates of T2DM in the young are lacking as screening for diabetes is not recommended in children and adolescents. Clinic-based data suggest that T2DM is increasing in the young, although this could be due to increased awareness and/or referral bias.[5,6] The ICMR-INDIAB study also showed that there is a shift of T2DM to younger age groups and that the takeoff point of prevalence of diabetes occurs at ages 25–34 years in India.[1] This could result in a huge burden not only on the patient and his family, but also on society as a whole.

TYPES OF DIABETES IN THE YOUNG IN INDIA

In India, apart from T1DM and T2DM, there are other forms of diabetes in the young including maturity-onset diabetes of the young (MODY), fibrocalculous pancreatic diabetes (FCPD), gestational diabetes mellitus (GDM), Endocrine diabetes and the rare genetic forms of diabetes. The entity called malnutrition modulated diabetes mellitus (MMDM), which was earlier described from some parts of India,[7] has largely become obsolete and is not considered here. The authors recently reported on one of the largest series of diabetes in the young (n=2,630) seen at their center, which is a tertiary diabetes center in Chennai in South India.[8] Diabetes in the young was defined as those with first diagnosis of diabetes at or below 25 years of age. The overall proportion of diabetes in the young at the authors' center rose from 0.55% during the period 1992–1995 to 2.5% in 2009. Among the total of 2,630 subjects with diabetes in the young, 1,262 (48%) had T2DM, 1,135 (43.2%) had T1DM, 118 (4.5%) had GDM and 115 (4.4%) had other forms of diabetes including FCPD and genetic syndromes of diabetes.[8] Thus at the authors' center, T2DM is already more common than T1DM. However, this may reflect referral bias in private diabetes centers. In most government hospitals T1DM is more common perhaps reflecting a socioeconomic bias due to free supply of insulin at these hospitals and the fact that T2DM in the young is mostly associated with overweight and obesity which are currently more common among the more affluent classes of society. This article will deal with various forms of diabetes in the young seen in India.

Type 1 Diabetes Mellitus

Clinical features of type 1 diabetes mellitus (T1DM) are:

- Abrupt onset of severe symptoms like polyuria, polydipsia and/or weight loss
- Usually patients are nonobese or even lean
- Family history of diabetes in parents is usually absent
- Severe diabetes with markedly-elevated glycated hemoglobin levels (HbA_{1c})
- Ketosis or ketoacidosis may be present
- C-peptide test shows absence or very low pancreatic beta-cell reserve
- GAD, IA2 or other islet cell antibodies may be present
- Patients require lifelong insulin from time of onset for survival and to maintain good health and for control of hyperglycemia.

Type 1 diabetes mellitus is further classified as immune-mediated T1DM or idiopathic T1DM based on presence or absence of autoimmune antibody markers like GAD, IA2, etc.

Type 2 Diabetes

Type 2 diabetes mellitus (T2DM) can be diagnosed based on the following features:

- Presence of obesity
- Presence of insulin resistance as evidenced by acanthosis nigricans

- Strong family history of diabetes (usually in one or both parents)
- Adequate pancreatic insulin reserve (good c-peptide)
- Response to oral hypoglycemic agents (OHA) for several years
- GAD and other antibodies usually absent.

Most young patients with T2DM remain asymptomatic for a long time and are detected incidentally when investigated for other problems. Classical symptoms of diabetes (polyuria, polydipsia and weight loss) are uncommon at presentation unless diagnosis is delayed for long time. Instead, they may present with unusual symptoms of tiredness, difficulty with concentration in scholastic activities, or lack of interest, thereby making diagnosis difficult unless there is a high degree of suspicion. Although fasting or random plasma glucose is recommended for diagnosing diabetes, an oral glucose tolerance test (OGTT) may be considered wherever feasible. In addition to finding diabetes in the asymptomatic individual, it also allows for the diagnosis of impaired glucose tolerance and, if this stage is detected, it offers the scope for prevention of T2DM.[9]

Although it is usually not difficult to distinguish T1DM from T2DM clinically, occasionally, there could be an overlap of clinical features. One distinguishing feature is the prevalence of cardiovascular risk factors. In a study from the authors' center, it was noted that over 40% of the children with T2DM had two or more cardiovascular risk factors, e.g. central obesity, dyslipidemia or hypertension, compared to 13.6% among T1DM subjects of similar age.[10]

MATURITY–ONSET DIABETES OF THE YOUNG

Maturity–onset diabetes of the young (MODY) is a monogenic subtype of diabetes similar to T2DM, diagnosed based on the following criteria of Tattersal and Fajans:[11]

- Onset of diabetes below 25 years of age
- Autosomal dominant inheritance (with at least three generation transmission of the disease)
- Absence of ketosis at any time
- Controllable without insulin for at least 5 years.

This clinical definition is no longer acceptable, and genetic testing is now mandatory to diagnose and classify MODY. MODY is genetically heterogenous, and there are different forms of MODY, namely MODY 1, MODY 2, MODY 3, etc. up to MODY 11 have been described so far depending on the genetic mutation detected (**Table 1**).

Studies on Genetics of MODY Done at MDRF, Chennai

At the Madras Diabetes Research Foundation (MDRF) Chennai, we have been studying MODY genes for several years. Ninety-six unrelated, 'MODY' patients who satisfied the clinical criteria of MODY given above[11] were sequenced for *HNF1A* (MODY 3) and *HNF4A* (MODY 1) genes and GCK MODY (MODY 2) with the objective of performing molecular genetic classification of MODY in these patients.[12]

All exons, the exon-intron boundaries and the promoter regions of the *HNF1A* gene were examined using denaturing high-performance liquid chromatograpy (HPLC) and direct sequencing by a 310 genetic analyzer. 9/96 subjects had *HNF1A* gene mutations. Thus, 9% of clinically-diagnosed MODY patients at our center had MODY 3. Of the remaining 87 subjects, 3 had *HNF4A* gene mutations. Thus, 3.4% of clinically-diagnosed MODY patients had MODY 1.[13] None had *GCK* MODY (MODY 2) in this series. Another study from the authors' group showed that the Ala98Val polymorphism of *HNF1A* gene (MODY 3) was associated with MODY and with an earlier age at onset of diabetes among T2DM patients.[14]

The authors recently screened 34 subjects with clinically suspected MODY 5 based on evidence of renal pathology. They found that three had known mutation and one had a novel mutation in *HNF* 1 β. Thus, 4 out of 34 clinical suspected MODY 5 patients (12%) had MODY 5 on genetic testing (Unpublished data).

TABLE 1 | Types of MODY[15,16]

Subtype	Gene symbol	Gene name	Clinical features
MODY 1	*HNF4A*	Hepatocyte nuclear factor 4 alpha	Mild-moderate fasting and postprandial plasma glucose (PG) concentrations that increase over time due to progressive decrease in insulin secretion. Respond well to sulfonylurea agents
MODY 2	*GCK*	Glucokinase	Mild fasting hyperglycemia due to impaired glucose tolerance. Less than 50% of carriers have overt diabetes mellitus, and microvascular complications of diabetes are rare
MODY 3	*HNF1A*	Hepatocyte nuclear factor 1 alpha	Same as MODY 1
MODY 4	*IPF1*	Insulin promoter factor 1	Phenotypes ranging from impaired glucose tolerance to overt diabetes mellitus; homozygous or compound heterozygous mutations of PDX1 are associated with pancreatic agenesis
MODY 5	*HNF1B*	Hepatocyte nuclear factor 1 beta	Overt diabetes mellitus in association with renal cysts
MODY 6	*Neuro D1*	Neurogenic differentiation factor 1	Rare, with phenotype characterized by obesity and insulin resistance
MODY 7	*KLF11*	Kruppel-like factor 11	Very rare; phenotype ranges from impaired glucose tolerance or impaired fasting glucose to overt DM
MODY 8	*CEL*	Bile salt dependent lipase	Very rare; associated with both exocrine and endocrine pancreatic deficiency and with demyelinating peripheral neuropathy
MODY 9	*PAX4*	Paired domain gene 4	Very rare. Crucial transcription factor for beta cells development
MODY 10	*INS*	Insulin	Very rare. Mutations in the insulin gene. Usually associated with neonatal diabetes. Rare <1% cases
MODY 11	*BLK*	Tyrosine protein kinase – B-Lymphocyte specific	By linking tyrosine kinase with effectors enzyme an important role has emerged for adapter molecules. These adapter proteins nucleate formation contributes to the qualitative and quantitative control of B-cell signaling

FIBROCALCULOUS PANCREATIC DIABETES

Fibrocalculous pancreatic diabetes (FCPD) is a unique form of diabetes seen in tropical countries secondary to non-alcoholic, chronic calcific pancreatitis.[17] Prevalence of FCPD is higher in southern India than the rest of India.[18] FCPD is a highly heterogenous condition with respect to clinical, biochemical, and histopathological features.[19-21] Ingestion of a tuber, cassava (tapioca), protein energy malnutrition and oxidative stress had been earlier implicated in the etiology of FCPD,[16] but most of these theories have now been disproved. More recently, strong evidence for a genetic susceptibility of FCPD linked the *SPINK1 N34S* gene mutation has been described.[22-24]

Patients with FCPD are generally lean, from a poor socioeconomic class, and usually present with a history of intermittent, but severe abdominal pain usually from childhood, steatorrhea (in about one-third of patients) and absence of signs of insulin resistance. Abdominal radiography shows multiple, large, dense, pancreatic calculi, while ultrasonography or computerized tomography (CT) scan shows pancreatic ductal dilatation. At the authors' center, FCPD earlier constituted about 5% of all cases of diabetes in youth but its prevalence is now declining.[25]

Mohan's Criteria for Fibrocalculous Pancreatic Diabetes (Mohan et al.[17,20])

- Patient should originate from a tropical country
- Diabetes should be present
- Demonstrable evidence of chronic pancreatitis: pancreatic calculi on X-ray abdomen or unequivocal ductal dilatation on ultrasonography/CT scan or at least three of the following:
  - Recurrent abdominal pain since childhood
  - Steatorrhea
  - Altered pancreatic morphology, e.g. increased echogenicity
  - Abnormal pancreatic function tests.
- Absence of other causes of chronic pancreatitis, i.e. alcoholism, hepatobiliary disease, primary hyperparathyrodism, etc.

GESTATIONAL DIABETES MELLITUS

Gestational diabetes mellitus (GDM) or diabetes during pregnancy is a form of diabetes, in which women without previously diagnosed diabetes exhibit higher blood glucose levels during pregnancy and considered present if hyperglycemia is detected either in the fasting state or following an OGTT. All pregnant women should receive an OGTT between the 24th and 28th week of pregnancy to screen for the condition or soon after conception those who have risk factors for gestational diabetes.[26]

The Diabetes in Pregnancy Study Group India (DIPSI) has suggested a single step procedure and a diagnostic test for diagnosing GDM due to its simplicity and economic feasibility.[27,28] The International Association of Diabetes and Pregnancy Study Groups (IADPSG) had come up with a different set of criteria as shown in **Table 2**.[29]

TABLE 2 | Criteria for diagnosis of GDM (IADPSG criteria[29])

Measure of glycemia	Values
Fasting plasma glucose	≥92 mg/dL (OGTT) Overt diabetes if ≥126 mg/dL
1 hour plasma glucose	≥180 mg/dL (OGTT)
2 hour plasma glucose	≥153 mg/dL (OGTT)
Glycated hemoglobin (%)	Overt diabetes if ≥6.5%
Random plasma glucose	Overt diabetes if ≥200 mg/dL

Note: GDM if one or more values equals or exceeds indicated in above table

ENDOCRINE DIABETES

The hyperglycemia resulting secondary to over production of counter regulatory hormones due to endocrine disorders are called endocrine diabetes. It is important to make the diagnosis of endocrine diabetes, because many of these entities can be successfully treated early and failure to detect a secondary cause of diabetes may make the control of blood glucose difficult or even impossible. Some of these conditions are Cushing's syndrome, acromegaly, pheochromocytoma, glucagonoma and hyperthyroidism.

Genetic Syndromes often associated with diabetes mellitus in the young are Down syndrome, Klinefelter's syndrome, Turner's syndrome, Laurence-Moon-Biedl syndrome, Friedreich's ataxia, etc.

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, the authors have evolved an algorithm 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 help to refine the process. 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". **Flow chart 1** summarizes the diagnostic approach to classify diabetes in youth in India.

TREATMENT AND MANAGEMENT OF DIABETES IN THE YOUNG

Type 1 Diabetes Mellitus

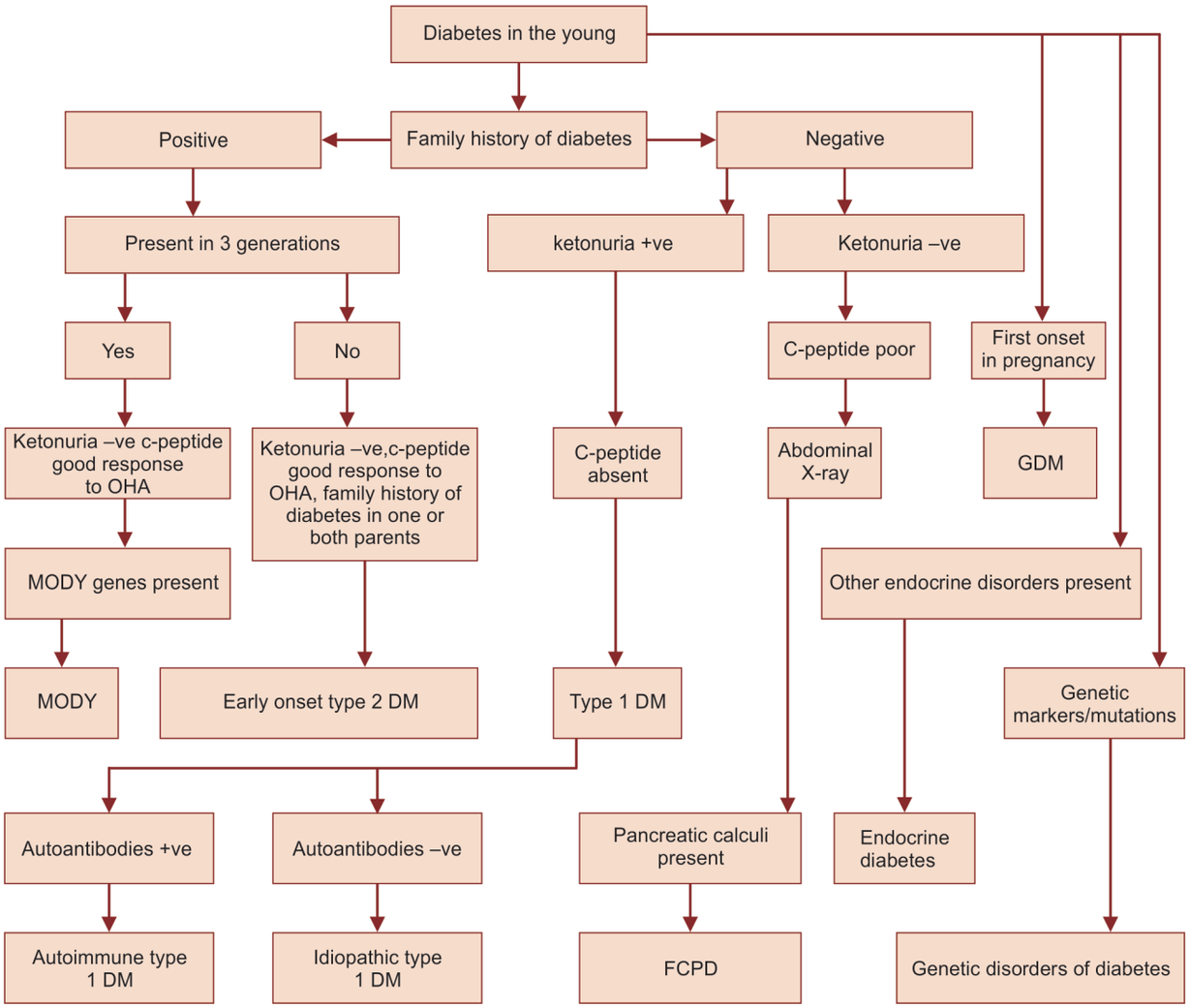
In type 1 diabetes mellitus (T1DM), since the pancreas can no longer produce insulin, patients are required to take insulin daily, either by injection or via an insulin pump. Other methods to deliver insulin are being investigated. Children with T1DM are at risk for long-term complications (damage to the cardiovascular system, kidneys, eyes, nerves, blood vessels, skin, gums and teeth).

The basic elements of T1DM management are insulin administration, nutrition management, physical activity, self-monitoring of blood glucose (SMBG), and the avoidance of hypoglycemia. Algorithms are used for insulin dosing based on blood glucose level and food intake. Children receiving fixed insulin doses of intermediate-acting and rapid-acting insulins can plan their meal timings at the time of peak action of the insulin. Children receiving a long-acting insulin analog or using an insulin pump receive a rapid-acting insulin analog just before meals, with the amount of premeal insulin based on carbohydrate content of the meal using insulin: carbohydrate ratio and a correction scale for hyperglycemia. Further adjustment of insulin or food intake may be made based on anticipation of special circumstances such as increased exercise and intercurrent illness. Children on these regimens are expected to check their blood glucose levels routinely before meals and at bedtime.[30]

Type 2 Diabetes Mellitus

Lifestyle change is the cornerstone of T2DM management. This includes attainment and maintenance of a healthy bodyweight, regular physical activity, normalization of blood glucose levels, minimization of hypoglycemia and the management and the prevention of complications including hypertension, hyperlipidemia, nephropathy and nonalcoholic 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.[31]

Flow chart 1: Algorithm for differential diagnosis of diabetes in youth (Mohan et al.[10])



Type 2 diabetes mellitus can be controlled with OHA for several years. The American Diabetes Association (ADA) and International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines recommend metformin as the first-line oral antidiabetic drug.[32] Treatment should be started with metformin and if control is not achieved, sulfonylureas (like glibenclamide, glimepiride or gliclazide) or other OHAs can be added. Patients should be monitored frequently, and doses of drugs adjusted until normoglycemia are achieved. Glycated hemoglobin (HbA_{1C}) should be done at 3 months' interval. Metformin is associated with side effects, like diarrhea and abdominal pain, whereas sulfonylureas are associated with hypoglycemia and weight gain. Metformin should not be given to patients with renal impairment, hepatic disease, cardiac or respiratory insufficiency or when receiving radiographic contrast materials, whereas sulfonylureas should not be given to those who have impairment of liver and kidney function. Very often, insulin may be required in the early stages to control symptoms and later in the natural history if secondary failure to OHA develops.[32]

Other classes of drugs, such as glinides (repaglinide and nateglinide, short-acting insulin secretagogues), glucosidase inhibitors (acarbose) and thiazolidinediones compounds (glitazones like pioglitazone and rosiglitazone) which are available for adults[32] are not yet approved in childhood onset T2DM. Among the newer therapeutic options that may prove beneficial for pediatric patients with T2DM are the incretin-based therapies like GLP-1 analogs (exenatide and liraglutide) and dipeptidyl peptidase-4 inhibitors (DPP4) like sitagliptin, vildagliptin, saxagliptin and linagliptin. Here again, data in pediatrics is almost nonexistent and their approval for use in children is awaited once the ongoing trials are completed.

Timely diagnosis and treatment of T2DM can prevent or delay the onset of diabetes complications. Ongoing efforts to prevent and treat T2DM in children will require collaborative involvement of health care providers, research organizations, school personnel, community institutions and government agencies working together.

Maturity–Onset Diabetes of the Young

Treatment of maturity–onset diabetes of the young (MODY) varies depending on types of MODY. Most respond to diet therapy, exercise and/or sulfonylurea treatment. With longer duration, those with

TABLE 3 | Management of diabetes in the young

Types of diabetes	Type of treatment
T1DM	Should be treated only by insulin. Usually adjustable daily doses are needed
T2DM	Can be controlled with oral hypoglycemic agents (OHA). Very often, insulin may be required at least in the early stages to control symptoms and later if secondary failure to OHA develops
MODY	Mostly respond to diet therapy, exercise and/or sulfonylurea treatment. With longer duration insulin might be needed
FCPD	Only few can be controlled by OHA, eventually need insulin for control of diabetes
GDM	Diet in mild cases. Add insulin if there is overt diabetes [if fasting plasma glucose is ≥7.0 mmol/L (126 mg/dL) and/or random plasma glucose is ≥11.1 mmol/L (200 mg/dL) or if OGTT 2 hour plasma glucose is ≥153 mg/dL or if HbA_{1c} is ≥6.5%]
Endocrine diabetes	Treatment for diabetes and endocrine disorders
Genetic syndromes	Treatment for diabetes + attention to other genetic defects

MODY 1 and MODY 3 may require insulin therapy. MODY 2 run a benign course throughout life and rarely requiring drug therapy.

Fibrocalculous Pancreatic Diabetes

For FCPD, oral hypoglycemic agents may be useful in a few patients with mild diabetes and relatively early in the course of the disease. However, the majority of patients eventually need insulin for control of diabetes and to improve their general health and sense of well-being. Replacements of large doses of pancreatic enzymes help to improve digestion and general health. Surgical intervention is indicated only for severe intolerable pain. There are some reports which suggest that after surgery the mean daily insulin requirement may decrease but this is a controversial issue. FCPD is a premalignant condition and hence screening for pancreatic adenocarcinoma should be done particularly if there is history of weight loss or jaundice **Table 3** summarizes the management strategies for diabetes in the young.

Unfortunately, there is no single formula to manage diabetes in all children. Blood glucose targets, frequency of blood glucose testing, type, dose and frequency of insulin, use of insulin injections with a syringe or a pen or pump, use of oral glucose-lowering medication and details of nutrition management all may vary among individuals. Indeed, combination therapies may be needed in some. Diabetes care teams should determine the regimen that best suits each individual's characteristics and circumstances and involve the family members as well in planning the management schedule.

POINTS TO REMEMBER

- All youth with diabetes need not have T1DM
- Accurate clinical history, detailed pedigree chart, few biochemical tests and simple physical signs and use of an algorithm can help to classify the diabetes in the young to thus give the appropriate treatment
- Type 1 diabetes mellitus (T1DM) requires lifelong insulin and the regimen should be altered to the child's need
- Even though screening of at-risk youth for T2DM remains controversial, we should target and screen the young with risk factors like overweight/obesity, family history of diabetes in parents and presence of signs of insulin resistance like acanthosis nigricans and PCOS
- Treatment and management of T2DM in the young requires lifestyle changes (more physical activity, appropriate food intake) plus addition of oral hypoglycemic agents whenever indicated. If these measures fail, insulin should be instituted
- Awareness, education and intensive counseling among the community and families will go a long way in prevention of T2DM in the young
- Maturity–onset diabetes of the young (MODY) if suspected needs genetic testing and treatment based on type of MODY
- Fibrocalculous pancreatic diabetes (FCPD) needs, in addition to antidiabetic drugs, pancreatic enzyme replacement, surgery in some cases and a surveillance for pancreatic cancer
- Gestational diabetes mellitus (GDM) should be managed following established GDM guidelines
- Endocrine diabetes and diabetes secondary to genetic syndromes will need treatment of the primary condition as well, as in addition to diabetes.

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