ISPAD Clinical Practice Consensus Guidelines 2009 Compendium

Type 2 diabetes in children and adolescents


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Introduction

Type 2 diabetes mellitus (T2DM) in children and adolescents is becoming an increasingly important public health concern throughout the world (1–17). Because of the relatively recent recognition of the problem in this age group, many children with new onset T2DM may be misclassified as having T1DM. Conversely, as the population becomes heavier, overweight adolescents with autoimmune diabetes may be misdiagnosed as having T2DM. T2DM is often associated with risk factors for cardiovascular disease that may already be present at the time of diagnosis, making normalization of blood glucose levels and diagnosis and treatment of hypertension and dyslipidemia important (18).

Definition and classification of non-T1DM (non-immune mediated)

Type 2 diabetes (T2DM). T2DM occurs when insulin secretion is inadequate to meet the increased demand posed by insulin resistance (19). Thus, T2DM is commonly associated with other features of the insulin resistance syndrome [hyperlipidemia, hypertension, acanthosis nigricans, ovarian hyperandrogenism, non-alcoholic fatty liver disease (NAFLD)] (20). Insulin secretion depends on disease status and duration, and can vary from delayed but markedly elevated in response to a glucose challenge, to absolutely diminished (19). Adults with symptoms have 50% reduction at the time of diagnosis, and may become insulin dependent within a few years (21).

T2DM occurs:

- in youth most often during the second decade of life, with a mean age of diagnosis of ~13.5 years. This coincides with the peak of physiologic pubertal insulin resistance, which may lead to onset of overt diabetes in previously compensated adolescents.
- in all races, but at a much greater prevalence in those of non-white European descent, e.g. those of black African descent, native North American, Hispanic (especially Mexican)-American, Asian, South Asian (Indian Peninsula), and Native Pacific islanders. The SEARCH for Diabetes in Youth population-based study found the proportion of physician diagnosed T2DM among 10–19-year-olds to vary greatly by ethnicity in the US: 6% for non-Hispanic whites, 22% for Hispanics, 33% for blacks, 40% for Asians/Pacific Islanders, and 76% for Native Americans (8). In Hong Kong > 90% of young onset diabetes is
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T2DM (10), in Taiwan 50% (11) and nearly 60% in Japan (Ogawa et al. personal communication).

- in > 75% of cases in youth in the USA there is a first or second-degree relative with T2DM.
- in youth in the USA and Europe with body mass index (BMI) above 85th percentile for age and sex. In Japan, however, ~30% of T2DM are not obese (17), in Asian Indian urban children, half of those with T2DM had normal weight (< 120% ideal for height) (12), and half of Taiwanese children with T2DM were not obese (11).
- in some asymptomatic individuals in high-risk populations during medical, school, or sports examinations (22,23).
- in the presence of ketosis/ketoacidosis, one third or more of newly diagnosed patients (24). This presentation is responsible for misclassification of T2DM patients as T1DM.
- occasionally with severe dehydration (hyperosmolar hyperglycemic coma, hypokalemia) at presentation, which can be fatal (24,25)
- with a sex ratio (male:female) that varies from 1:4–1:6 in native North Americans to 1:1 in Asians and Libyan Arabs
- without associated HLA specificities.
- without associated islet cell autoimmunity (see autoimmunity T2DM).

Autoimmune T2DM

- The pathophysiology of autoimmune 'T2DM' is unclear. It most likely represents autoimmune T1DM in overweight or obese individuals with underlying insulin resistance. It has been postulated that obesity and insulin resistance may promote an inflammatory response to antigen exposure caused by apoptosis of beta cells (26).
- Youth and adults in US and Europe who are clinically diagnosed with T2DM are found to have T1DM-associated auto-antibodies in 15–40% of cases, including many who are not receiving insulin one year after diagnosis (27–30).
- Antibody positive young adult individuals with the T2DM phenotype are significantly less overweight and younger than antibody negative patients (21, 27).
- Hemoglobin (HbA1c) concentrations are significantly higher in young adults with T2DM who are antibody positive compared with those who are antibody negative (27).
- β-cell function is significantly less in antibody positive individuals, the most dramatic difference being reported in younger adult patients (25–34 years), resulting in more rapid development of insulin dependence, usually by 3 years duration (27, 30).
- The presence of islet cell antibodies (ICA) and glutamic acid decarboxylase antibodies in adults with clinically typical T2DM has been referred to as latent autoimmune diabetes of adults (27, 31). Neither the autoimmunity nor the diabetes is latent, however (26).

Atypical diabetes mellitus or “Flatbush” diabetes (32, 33)

- Atypical diabetes mellitus (ADM) occurs throughout childhood, but rarely begins past age 40. It has only been described in young people of African descent.
- There is a strong family history in multiple generations with an autosomal dominant pattern of inheritance, but an abnormal sex ratio (M : F = 1 : 3).
- ADM is not associated with HLA specificities and islet autoimmunity does not occur.
- Ketosis or ketoacidosis is typical at onset.
- Insulin secretion is present but diminished and without long-term deterioration of function. Interestingly, insulin is often not required for survival after treatment of acute metabolic deterioration, although diabetes control may be poor and ketoacidosis may recur without insulin, e.g. with illness or pregnancy.
- ADM is not associated with obesity beyond that in the general population and it is not associated with insulin resistance.

Monogenic diabetes (formerly referred to as maturity onset diabetes of the young or MODY) For more in depth information see the ISPAD Clinical Consensus Guidelines for Monogenic Diabetes (34).

- Identified in families with multigenerational diabetes; including asymptomatic individuals identified through testing of family members.
- Monogenic diabetes is not associated with obesity beyond that in the general population and it is not associated with insulin resistance.

Uncertainties of Classification

Distinguishing T2DM from T1DM or monogenic diabetes

The clinician is obliged to weigh the evidence in each individual patient to distinguish between T1DM and T2DM. The reasons for this conundrum are:

- with increasing obesity in childhood, as many as 15–25% of newly diagnosed T1DM (or monogenic diabetes) patients may be obese.
- the significant number of pediatric patients with T2DM demonstrating ketonuria or ketoacidosis at diagnosis (2).
Type 2 diabetes

- T2DM is common in the general adult population, with a random family history of \( \sim 15\% \) or greater in minority populations, reducing the specificity of a positive family history.
- Positive family history for T2DM is increased for patients with T1DM as much as threefold over the non-diabetic population and T1DM is more frequent in relatives of patients with T2DM (35, 36).
- There is considerable overlap in insulin or C-peptide measurements between T1DM, T2DM and MODY at onset of diabetes and over the first year or so. This overlap is due to the recovery phase of autoimmune-mediated T1DM (the honeymoon) and degree of glucotoxicity/lipotoxicity impairing insulin secretion at the time of testing in both T1DM and T2DM. In addition the insulin resistance of obesity raises residual C-peptide levels in obese adolescents with T1DM. Such measurements are thus relatively valueless in the acute phase.

[The role of C peptide may be more helpful in established diabetes as persistent elevation of C-peptide above the level of normal would be unusual in T1DM after 12–24 months.]

Diagnosis of type 2 diabetes

The criteria and classification of diabetes are presented in greater detail in the ISPAD Clinical Practice Consensus Guidelines: Definition, Epidemiology, Diagnosis and Classification of Diabetes (37)

**Diagnostic criteria for type 2 diabetes in childhood and adolescence.** Diagnostic criteria for diabetes are based on BG measurements and the presence or absence of symptoms (E) (38,39).

Three ways to diagnose diabetes are possible and each, in the absence of unequivocal hyperglycemia, must be confirmed, on a subsequent day, by any one of the three methods given below.

- Diabetes is diagnosed when:
  - A fasting plasma glucose (FPG) is \( \geq 7.0 \text{ mmol/l (126 mg/dl)} \)
  - The post challenge plasma glucose is \( > 11.1 \text{ mmol/l (200 mg/dl)} \)
  - performed as described by the World Health Organization (39), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.
  - or
  - Symptoms of diabetes and a casual plasma glucose \( \geq 200 \text{ mg/dl (11.1 mmol/L)} \).

- Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

- Diabetes in children, including T2DM, usually presents with characteristic symptoms such as polyuria, polydipsia, blurring of vision, and weight loss, in association with glycosuria and, in some cases, ketonuria.

- In its most severe form, ketoacidosis or hyperglycemic hyperosmolar state may develop and lead to stupor, coma, and in absence of effective treatment, death.

- The diagnosis is usually confirmed quickly in symptomatic individuals by measurement of a marked elevation of the blood glucose level. In this situation, if ketones are present in the blood or urine, treatment is urgent. Waiting another day to confirm the hyperglycemia may be dangerous in allowing ketoacidosis or hyperosmolarity to evolve.

- In the absence of symptoms or presence of mild symptoms of diabetes, hyperglycemia detected incidentally or under conditions of acute infective, traumatic, circulatory, or other stress may be transitory and should not in itself be regarded as diagnostic of diabetes. The diagnosis of diabetes, in the absence of symptoms, should not be based on a single plasma glucose concentration. Diagnosis may require continued observation with fasting and/or 2-h postprandial BG levels and/or an oral glucose tolerance test (OGTT).

- An OGTT should not be performed if diabetes can be diagnosed using fasting, random, or postprandial criteria, as excessive hyperglycemia can result using a fasting OGTT in these circumstances. (E).

- If doubt remains, periodic re-testing should be undertaken until the diagnosis is established or refuted.

**Diagnostic criteria for impaired glucose tolerance and impaired fasting glycaemia.** There are individuals whose glucose levels do not meet the criteria for diabetes, but are too high to be considered normal.

- Impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) are intermediate stages in the natural history of disordered carbohydrate metabolism between normal glucose homeostasis and diabetes (E).

- IFG and IGT are not interchangeable and represent different abnormalities of glucose regulation. IFG is a measure of disturbed carbohydrate metabolism in the basal state, while IGT is a dynamic measure of carbohydrate intolerance after a standardized glucose load.

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• Patients with IFG and/or IGT are now referred to as having ‘pre-diabetes’, indicating the relatively high risk for development of diabetes in these patients (38).
• IFG and IGT may be associated with the metabolic syndrome (MS), which includes obesity (especially abdominal or visceral obesity), dyslipidemia of the high-triglyceride and/or low-high density lipoprotein type, and hypertension.
• Individuals who meet the criteria for IGT or IFG may be euglycemic in their daily lives as shown by normal or near-normal glycated hemoglobin levels, and those with IGT may manifest hyperglycemia only when challenged with an OGTT.

Categories of fasting plasma glucose (FPG) are defined as follows:
• FPG < 5.6 mmol/L (100 mg/dL)= normal fasting glucose.
• FPG 5.6–6.9 mmol/L (100–125 mg/dL)= IFG.
• FPG ≥ 7.0 mmol/L (126 mg/dL)= provisional diagnosis of diabetes (the diagnosis must be confirmed, as described above under ‘Diagnostic criteria for type 2 diabetes’).

The corresponding categories for IGT when the OGTT is used are as follows:
• 2-h postload glucose < 7.8 mmol/l (140 mg/dl)= normal glucose tolerance.
• 2-h postload glucose 7.8–11.1 mmol/l (140–199 mg/ dl)= IGT.
• 2-h postload glucose ≥ 11.1 mmol/l (200 mg/dl)= provisional diagnosis of diabetes (the diagnosis must be confirmed with additional testing, as described above).

After the diagnosis of diabetes is established, autoantibody testing should be considered when diagnosing and treating T2DM. Diabetes autoantibody testing should be considered in all pediatric patients with the clinical diagnosis of T2DM because of the high frequency of islet cell autoimmunity in otherwise “typical” T2DM. Antibodies will indicate an earlier need for insulin as well as the need to monitor for thyroid autoimmunity and to consider other autoimmune disorders associated with T1DM. (E)

Diabetes autoantibody testing also should be considered when diagnostic criteria for IFG and/or IGT are met. Diabetes autoantibody testing should be considered in overweight/obese children > 13 years of age with a clinical picture of T1DM (weight loss, ketosis/ketoacidosis), some of whom may have T2DM (E)

T2DM and the insulin resistance syndrome

Insulin resistance is an impaired response to the physiologic effects of insulin, including effects on glucose, lipid, and protein metabolism, and on vascular endothelial function. Insulin resistance occurs in most tissues including liver, muscle, and fat tissue and is influenced by sex, age, race/ethnicity, stage of sexual maturation, and total adiposity. While visceral adiposity is important in insulin resistance in adults, the specific contribution of visceral adiposity to insulin resistance in the pediatric population remains uncertain.

Several events in development may be associated with increased risk for the insulin resistance syndrome. These include premature adrenarche in girls (pubic hair appearing before the age of 8 years) and being born small for gestational age. Girls with a history of premature adrenarche are at increased risk for ovarian hyperandrogenism and PCOS and thus, insulin resistance (40). Children born small for gestational age are at increased risk for insulin resistance related to decreased intrauterine growth (41) and also at increased risk for premature adrenarche.

Diabetes is only one manifestation of the insulin resistance syndrome or the MS (22, 42–50).

Other associations include:

(i) Obesity: Obesity has deleterious associations with morbidity and cardiovascular risk independent of effects related to insulin resistance and diabetes (51–54).
(ii) Nephropathy: Albuminuria (either micro- or macro-) is present at the time of diagnosis in a substantial number of adolescents with T2DM and prevalence increases with duration of diabetes (24). Proteinuria and focal segmental glomerular sclerosis have also been reported in African-American adolescents with severe obesity, in the absence of diabetes (55).
(iii) Hypertension: Hypertension is estimated to account for 35–75% of diabetes complications, both microvascular and macrovascular (56). Diabetes or impaired glucose tolerance doubles the risk of developing hypertension (57). In addition, there is a possible genetic predisposition to hypertension in T2DM related to the associated angiotensin converting enzyme genotype (58). Hypertension in T2DM is due to volume expansion and increased vascular resistance (59) related to reduced (NO)-mediated vasodilatation and increased activity of the renin-angiotensin system.
(iv) Dyslipidemia: Hypertriglyceridemia and decreased high-density lipoprotein cholesterol are the hallmarks of T2DM dyslipidemia. Additional findings include elevated very low-density lipoprotein (VLDL), elevated LDL-c, elevated lipoprotein(a), and increased small dense LDL particles. Decreased lipoprotein lipase activity, increased lipoprotein glycation and increased lipoprotein oxidation render the lipoproteins more atherogenic. (60,61)
Ovarian hyperandrogenism and premature adrenarche (62): PCOS is being increasingly recognized in adolescents as part of the insulin resistance syndrome. Adolescents with PCOS have ~40% reduction in insulin-stimulated glucose disposal compared to body composition matched non-hyperandrogenic control subjects (59). Decreasing insulin resistance may improve ovarian function and increase fertility.

NAFLD: Hepatic steatosis is present in 25–45% of adolescents with T2DM and more advanced forms of NAFLD, such as non-alcoholic steatohepatitis, are increasingly common and associated with progression to cirrhosis (24, 64). NAFLD now represents the most common cause of cirrhosis in children and the most common reason for liver transplantation in adults in the US.

Systemic inflammation: elevated C-reactive protein, inflammatory cytokines and white blood cell counts in obese adolescents have been associated with increased risk for cardiovascular disease in adults (54).

Additional health problems related to obesity include Obstructive sleep apnea (OSA) with associated pulmonary hypertension (65), orthopedic problems resulting in diminishing physical activity (66,67), pancreatitis, cholecystitis and pseudotumor cerebri.

In adults, there is a strong association between level of hyperglycemia and increased risk of macrovascular disease. Hyperglycemia, dyslipidemia, and hypertension are contributors to the acceleration of atherosclerosis in T2DM, along with oxidative stress, glycation of vascular proteins, and abnormalities of platelet function and coagulation. Defective endothelium dependent vasodilatation is an additional factor accelerating atherosclerosis in T2DM. It is an early sign of increased risk for cardiovascular disease, and predictive of cardiovascular events (68) (B) and occurs in obese children relative to their level of obesity and degree of insulin resistance (69) (B).

The aggregation of risk factors for cardiovascular disease in the presence of insulin resistance and diabetes may result in a high risk for coronary events and increased mortality in young adulthood (A)

Testing for Co-morbidities and Complications. Co-morbidities characteristic of the insulin resistance syndrome are commonly seen at diagnosis or appear early in the course of T2DM and should be tested for sooner than in T1DM, where these disorders are complications of the diabetes rather than co-morbid conditions (70, 71) (B). A more complete discussion of testing for complications/co-morbidities is presented in the ISPAD Clinical Practice Guidelines for microvascular and macrovascular complications (72).

Specific complications are more common in type 2 diabetes and need special attention.

- Either micro- or macro-albuminuria, may be present at the time of diagnosis and albuminuria should be evaluated at diagnosis and annually thereafter (55, 72)(E). Likewise, hypertension may be present at, or prior to diagnosis of diabetes and each individual should be evaluated at every visit for hypertension. Dyslipidemia is more common in type 2 diabetes and in family members, (60,61) and should be screened for when metabolic stability is achieved. Evaluation for NAFLD should be done at diagnosis and annually thereafter (24)(E). Inquiries about puberty, menstrual irregularities and obstructive sleep apnea should be made at diagnosis and regularly thereafter (65)(E).

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Treatment of comorbidities/complications

Additional information is available in the ISPAD Clinical Practice Guidelines on complications. (72).

Dyslipidemia, hypertension and albuminuria are more common in type 2 diabetes and may be present at diagnosis and should be assessed after blood glucose control has been optimized.

Hypertension and albuminuria.

- Confirmed hypertension (BP > 95% for age, gender and height) or albuminuria should be treated with an ACE inhibitor or, if not tolerated, an angiotensin receptor blocker (E).
- Combination therapy may be required if hypertension or albuminuria does not normalize on single agent treatment (E).

(a) Side effects are cough, hyperkalemia, headache and impotence (73). In addition, major congenital malformations have been reported with first trimester exposure to ACE inhibitors but not with other antihypertensive agents in non-diabetic women (74).

Dyslipidemia. Testing for dyslipidemia should be performed soon after diagnosis when BG control has been achieved and annually thereafter. (60,61) E

- Goal is LDL-C < 2.6 mmol (100 mg/dl) (68).
- If LDL-C is borderline (2.6–3.4 mmol; 100–129 mg/dl), or elevated (> 3.4 mmol; 130 mg/dl), repeat lipid profile should be performed in 6 months and dietary intervention to decrease total and saturated fat initiated.
• If LDL-C remains elevated after 3-6 months of attempting to optimize blood glucose control and diet, pharmacotherapy is warranted (72).
• Statin therapy has been shown to be safe and effective in children as in adults and should be the first pharmacologic intervention (72) although long term safety data are not available. Special attention should be paid to symptoms associated with muscles and connective tissues, as there is an increased risk of rhabdomyolysis (72,75).

Treatment of T2DM

Management differences Between Type 2 and Type 1 Diabetes. The emergence of T2DM in children and adolescents has required that specialists familiar with the management of T1DM in children and adolescents recognize the vast differences between the treatment challenges of these two disorders.

• Lower socioeconomic status. Whereas T1DM is distributed throughout the population proportionate to socioeconomic distribution, T2DM in North America and Europe disproportionately affects those with fewer resources, e.g. lower income levels, less educated parents, less well insured. This socioeconomic bias has not been described for Asian T2DM.
• Older age. T1DM occurs throughout childhood, when parental influence is predominant, whereas T2DM occurs typically in adolescence, when peer influence predominates.
• More family experience. Only ~5% of families with a child with T1DM have family experience with the disease, while 75% or more of families of the child with T2DM have such experience. The failure of these family members to control weight and glycemia is common, with resultant complications in the family members and a feeling of fatalism and resignation in the child.
• Different treatment priorities. In most T1DM, lifestyle modification, beyond insulin administration and glucose monitoring, is only needed for those individuals who are overweight and inactive. In all youth with T2DM, the emphasis is on lifestyle modification and secondarily on glucose monitoring and medication.
• Negative effects of technology. Technological advancements have revolutionized the management of T1DM (insulin purity and delivery systems, blood

*blood glucose values < or >130/180 (7.2/10 mmol/L) refer to self-monitoring plasma BG values of 90-130 mg/dL (5-7.2 mmol/L) fasting or preprandial and peak postprandial values of <180 mg/dL (10 mmol/L).

Fig. 1. Treatment decision tree for type 2 diabetes in children and adolescents.
glucose monitoring, insulin analogues). In contrast, technological advances in entertainment, labor saving devices, transportation, together with an economic environment that makes calorically dense food increasingly available, desirable, and inexpensive, have led to the emergence of T2DM in children and complicate its therapy.

Management Goals. Overall goals

- Weight loss
- Increase in exercise capacity
- Normalization of glycemia
- Control of comorbidities, including hypertension, dyslipidemia, nephropathy, and hepatic steatosis,

Reduction in the rate of complications may require more stringent control in insulin resistant T2DM than in T1DM, and especially diligent attention to comorbidities, as suggested by the United Kingdom Prospective Diabetes Study (21).

Education. See also the ISPAD Clinical Practice Guidelines for diabetes education (76).

Patient and family education for youth with type 2 diabetes is as important as it is in type 1 diabetes. Initial and ongoing education for T2DM will focus on behavioral changes (diet and activity). Education in insulin therapy and hypoglycemia may not be required immediately.

- Education in T2DM will place a greater emphasis on behavioral, dietary and physical activity changes than is generally required for T1DM.
- Education should be given by team members with special expertise and knowledge of the dietary, exercise, and psychological needs of youth with T2DM.
- Education should be provided in a culturally sensitive and age appropriate manner.
- Because the majority of youth with T2DM are adolescents, the ISPAD Guidelines for Adolescent Care are appropriate to the education of youth and families with T2DM.
- The entire family will need education to understand the principles of treatment of T2DM and to understand the critical importance of the lifestyle changes required to manage T2DM.
- Care providers should acknowledge that the initial uncertainty in the diagnosis i.e. type 1 vs type 2, in a minority of patients can be confusing and anxiety provoking for the youth and family. The anxiety can be minimized by emphasizing the importance of normalizing blood glucose metabolism using whatever therapy is appropriate to the metabolic circumstances of the specific individual, regardless of the ‘type’ of diabetes.

Behavioral Change. Lifestyle change is the cornerstone of treatment of T2DM

- The family and child should understand the medical implications of obesity and T2DM.
- Clinicians must have an understanding of the health beliefs and behaviors of the family/community to design an effective behavioral plan.
- Changes should be made in small achievable increments and with the understanding that these changes need to be permanent.
- The patient and family should be trained to monitor the quantity and quality of food, eating behavior, and physical activity.
- As in any behavioral change, a changing and sustainable reward system is essential for success.
- The education and treatment team for T2DM ideally should include a nutritionist, psychologist and/or social worker (77).

Dietary Management. Referral to a nutritionist/dietitian with knowledge and experience in nutritional management of children with DM is necessary. Dietary recommendations should be culturally appropriate, sensitive to family resources, and should be provided to all caregivers (78, 79). The family should be encouraged to make dietary changes consistent with healthy eating recommendations, including individualized counseling for weight reduction, reduced total and saturated fat intake, increased fiber intake, and increased physical activity (80). More specific dietary recommendations are given in the ISPAD Guidelines for dietary management (81).

Dietary management should include:

- Initial focus on eliminating sugar-containing soft drinks and juices in large quantities.
- Complete elimination of these drinks and substituting water, diet soft drinks, and artificial sweeteners for beverages can result in substantial weight loss and is one of the most important dietary/behavioral changes for successful weight loss.
- Lifestyle (diet and activity) modification for the entire family and for the patient in an age appropriate manner, including guidance about healthy dietary and activity habits.
- Emphasizing healthy rearing patterns related to diet and activity by teaching parental modeling of healthy habits, avoiding overly strict dieting, and avoiding using food for reward.
- Recommending that meals should be taken on schedule, in one place, with no other activity (television, studying, reading, playing), preferably as a family unit.
- Portion control. Food and snacks should be served in a plate or bowl and not eaten directly from a box or can.
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- Limiting availability of high-fat, high caloric density food and drink in the home, the reading of labels and control of purchasing.
- Encouraging positive reinforcement of minor achievement (e.g. no or minimal weight gain, reduction in high caloric drinks) and avoiding blame for failure.
- Maintaining food and activity logs as beneficial for raising awareness of food and activity issues and for monitoring progress.

Exercise management. Specific, negotiated and enjoyable exercise prescriptions should be developed for each patient and family that are sensitive to family resources and environment, and should be provided to all caregivers. A family member or friend should be identified who is available to participate in physical activity with the patient. Pedometers may be motivating to patients and family members.

Frequent follow up to determine success with the dietary and exercise changes is important to the success of the program.

Exercise management should include:

- Developing and encouraging an achievable daily exercise program is essential to breaking the vicious cycle of increased weight-increased torpor-decreased activity-increased weight. Approaches aimed primarily at reducing sedentary time, such as turning off the TV and decreasing the time spent in computer related activities, may be the most effective initially (82) (A).
- Physical activity needs to be promoted as a family. This should include daily efforts to be physically more active, such as using stairs instead of elevators, walking or bicycling to school and to shop, and doing house and yard work (E).
- Educate parents for healthy behavior reinforcement, teach them to encourage and praise physical activity, including increases in daily activities (E).

Glycemic Monitoring.

(i) Self monitoring of blood glucose (SMBG) should be performed regularly. Frequency of SMBG should be individualized, and include a combination of fasting and postprandial glucose measurements. Once glycemic goals have been achieved, several fasting values a week and daily post prandial values, taken after the biggest meal are satisfactory while the values remain within the target range (E). If values rise into the impaired glucose tolerance range, more frequent testing should be recommended for adjustment of therapy. During acute illness or when symptoms of hyper- or hypoglycemia occur, patients should perform more frequent testing and be in contact with their diabetes care team for advice (E). Patients on insulin or sulfonylureas need to monitor for asymptomatic hypoglycemia (E).

(ii) HbA1c concentration should be determined at least twice a year and quarterly if insulin is being used or metabolic control is unsatisfactory.

Pharmacologic therapy. Lifestyle change should be continued in addition to pharmacologic therapy (Fig. 1). The aim of pharmacologic therapy is to decrease insulin resistance, increase insulin secretion, or to slow postprandial glucose absorption. The first medication used should be metformin. It has the advantage over sulfonylureas of similar reduction in HbA1c without the risk of hypoglycemia. Furthermore, weight is either decreased or remains stable, and LDL-C and triglyceride levels decrease during treatment.

Failure of monotherapy with metformin over 3 months indicates the need to add a Glitazone, sulfonylurea, or insulin alone or in combination with meglitinide, amylin, a GLP-1 mimetic, or a DPP-IV inhibitor (Fig. 1).

- Patients at-risk for pregnancy should be counseled on the effects of diabetes and oral agents on conception and fetal development. No oral agent should be used during pregnancy.
- Only metformin and insulin are approved for use in children/adolescents in the majority of countries. Sulfonylureas are approved for use in children in some countries; other oral agents are described below with the understanding that some adolescents may benefit from their use.
- Thiazolidinediones may be used in older adolescents but these are not approved in those under 18 years. Combination formulations may improve compliance in these older patients.

Available hypoglycemic agents. Biguanides. Metformin acts on insulin receptors in liver, muscle, and fat tissue, with a predominant action on the liver.

- Hepatic glucose production is reduced by decreasing gluconeogenesis.
- Insulin stimulated glucose uptake is increased in muscle and fat.
- An initial anorexic effect may promote weight loss.
- Long-term use is associated with a 1–2% reduction in HbA1c.
- Intestinal side effects (transient abdominal pain, diarrhea, nausea) may occur. These can be eliminated in most patients with slow dosage titration over 3–4 weeks, and instructions to always take the medication with food. The side effects may be attenuated by the use of extended release formulations.
• The risk of lactic acidosis with metformin is extremely low. Metformin should not be given to patients with renal impairment, hepatic disease, cardiac or respiratory insufficiency, or who are receiving radiographic contrast materials. Metformin should be temporarily discontinued during a gastrointestinal illness (A).

• Metformin may normalize ovulatory abnormalities in girls with PCOS and increase pregnancy risk (A).

**Insulin.** Despite hyperinsulinemia and insulin resistance, relatively small doses of supplemental insulin are often effective. If there is inadequate glycemic control on oral agents, a long-acting insulin analogue without peak effects may provide satisfactory therapy without meal related therapy. Metformin should be continued to improve insulin sensitivity. Thiazolidinediones are not recommended in combination with insulin because of increased risk for fluid retention with the combination.

• If post-prandial hyperglycemia occurs, pre-meal meglitinide is a good initial choice. If post-prandial hyperglycemia persists, rapid or short acting insulin can be substituted.

• The side effects of insulin are hypoglycemia, which has not been common in T2DM treated with insulin, and weight gain, a substantial problem in this population if dietary measures are not attended to.

• In adults with inadequately controlled T2DM from multiple centers in Europe and Australia, a single daily injection of insulin glargine, a long acting (24 hours) analog with little or no peak action, was almost as effective as three times a day rapid insulin analog (83).

Sulfonylurea and meglitinide/repaglinide (may not be approved for use in those < 18 years)

• Increase insulin secretion; thus most useful when there is residual beta cell function

• Sulfonylureas bind to receptors on the K+ /ATP channel complex causing K+ channels to close, resulting in insulin secretion

• Meglitinide and repaglinide bind to a separate site on the K+ /ATP channel complex

• Sulfonylurea sites equilibrate slowly and binding persists for prolonged periods; thus, traditional sulfonylureas have prolonged effects

• Meglitinide/repaglinide have an intermediate equilibration and binding duration and are, thus, used for rapid enhancement of insulin secretion, e.g. before meals

• Major adverse effects of sulfonylureas are hypoglycemia, which can be prolonged, and weight gain.

**TZDs (only approved for use in adults).** Clinical trials have been, or are underway in children with this class of drugs.

• TZDs increase insulin sensitivity in muscle, adipose, and liver tissue, with a greater effect on muscle glucose uptake than biguanides.

• TZDs bind to nuclear proteins, activating peroxisome proliferator activator receptors (PPAR gamma), which are ubiquitous orphan steroid receptors particularly abundant in adipocytes. This activation ultimately increases formation of proteins involved in the nuclear based actions of insulin, including cell growth, adipose cell differentiation, regulation of insulin receptor activity, and glucose transport into the cell. The binding of the thiazolidinediones to PPARgamma receptors is ubiquitous, affecting muscle cell growth and migration in response to growth factors, including arterial walls smooth muscle.

• Long-term treatment in adults is associated with a reduction in HbA1c of 0.5–1.3%.

• Thiazolidinediones have differing effects on lipid profiles.

• Side effects include edema, weight gain, anemia, and possible increased risk of heart disease in adults (84,85).

• Liver enzyme elevations were found in ~1% of those taking the original member of this group, troglitazone, with fatalities resulting in its withdrawal. The newer thiazolidinediones (rosiglitazone and pioglitazone) appear not to have hepatotoxicity in adults.

Glucosidase inhibitors (these drugs are only approved for use in adults)

Alpha glucosidase inhibitors (acarbose, miglitol) reduce the absorption of carbohydrates in the upper small intestine by inhibiting breakdown of oligosaccharides, thereby delaying absorption in the lower small intestine. This reduces the postprandial rise of plasma glucose.

• Long-term therapy is associated with 0.5-1% reduction in HbA1c (86).

• The frequent side effect of flatulence makes these agents unacceptable to most adolescents.

Amylin (amylin is not approved for those under 18 years, and is only approved for use in the US for patients with T1DM and T2DM who are taking insulin)

• Amylin is administered by subcutaneous injection before meals.
Amylin peptide is co-secreted with insulin from pancreatic beta cells in response to food. It lowers BG by decreasing glucagon release, slowing gastric emptying and decreasing food intake. The principal adverse effects are hypoglycemia and nausea, prompting the manufacturer to recommend decreasing the insulin dose by 50% when treatment with amylin is initiated (87).

- Treatment produces mild reductions in HbA1c.
- Modest weight loss or weight stabilization is generally seen with amylin treatment.
- There is a reported study of amylin use in children with T1DM (88)

Incretin mimetics (glucagon-like peptide-1 receptor agonists) (exenatide) (89) (these drugs are only approved for use in adults)

- Incretin mimetics are given as a twice-daily subcutaneous injection, usually with breakfast and dinner. In normal physiology, GLP-1 is rapidly secreted by L-cells in the small intestine into the circulation in response to food, increasing insulin secretion proportionate to BG concentrations, suppressing glucagon, prolonging gastric emptying, and promoting satiety. They are rapidly degraded by dipeptidyl peptidase-IV (DPP-IV); both native GLP-1 and the injected mimetic have a half life of 2 minutes.
- Clinical trials in adults have shown reduced fasting and post-prandial BG, weight loss, and lower HbA1c. Adverse effects include nausea, vomiting, diarrhea, with nausea occurring in up to 44% of patients; and infrequent dizziness, headache, and dyspepsia. The nausea decreases over time.

DPP-IV Inhibitors (89) (these drugs are only approved for use in adults)

- DPP-IV inhibitors inhibit the enzyme that breaks down GLP-1, resulting in higher concentrations of GLP-1 producing effects similar to those of GLP-1 mimetics.
- Unlike GLP-1 mimetics, they have no effect on gastric emptying, satiety or weight loss.
- They are administered orally with metformin or a thiazolidinedione once daily.

Initial medical treatment:

Initial treatment modality is determined by symptoms, severity of hyperglycemia, and presence or absence of ketosis/ketoacidosis. As in T1DM, those with symptoms, particularly vomiting, can deteriorate rapidly and need urgent assessment and treatment (E).

1. If metabolically stable, metformin is the treatment of choice (E)
   a. Begin with 250 mg daily x 3–4 days, if tolerated, increase to 250 mg BID, titrate in this manner over 3–4 weeks until the maximal dose of 1000 mg BID is reached.
2. Insulin may be required for metabolic stabilization (A)
3. Transition from insulin to metformin can usually be made over 2-6 weeks beginning when metabolic stability is reached, usually 1-2 weeks after diagnosis (E)
4. Transition can usually be achieved safely by titration of the metformin as in # 1 above. Insulin may be decreased by 10–20% each time the metformin is increased with a goal of eliminating insulin therapy (E)
5. Blood glucose testing may be decreased to twice a day, fasting and 2-3 hours after the largest meal, when insulin is eliminated (E)
6. If at any time during the insulin taper, the glucose values rise into the impaired range, the taper should be slowed until values stabilize. If the glucose values are in the diabetic range, the diagnosis of T2DM should be reconsidered and lifestyle changes reinforced (E)

GASTRIC SURGERY

- Bariatric surgery may be considered for adolescents with obesity-related comorbidities, including T2DM (90).
- Gastric bypass, the traditional surgical procedure for weight loss, can have significant complications including nutrient malabsorption and even death. Newer techniques, which appear to be safer, include gastric banding and vagal nerve stimulators. A Swedish study of over 2000 subjects undergoing a variety of bariatric surgery procedures found persistence of weight loss after 10 years and reduced mortality compared to conventionally treated obese patients (91).
- A randomized controlled trial of gastric banding versus conventional treatment for recent onset T2D in a small population of obese individuals from Australia achieved a 73% remission rate which correlated with weight loss and lower baseline HbA1c, without serious complications (92).
- Although the morbidity and mortality rates in adults have decreased over the last 5 years, this treatment is still uncommon in children and should be undertaken only in centers with an established program designed to collect outcome data (E).
Testing (case finding) for T2DM

Justification for case finding in a population at risk (93):

- **The condition tested for is sufficiently common to justify the investment.** A large screening program identified only < 1% of high risk children with type 2 diabetes (22). (B) Whether this is sufficiently frequent in adolescents to justify testing those with high-risk ethnicity or family history is still unclear (E).
- **The condition tested for is serious in terms of morbidity and mortality.** unquestionably true of T2DM in adolescents because of the association with increased cardiovascular risk factors and renal dysfunction.
- **The condition tested for has a prolonged latency period without symptoms, during which abnormality can be detected.** Impaired glucose tolerance in youth has been detected in asymptomatic adolescents, but albuminuria and dyslipidemia may already be present, indicative of a period of dysmetabolism and potentially a long latency period for overt type 2 diabetes, as in adults.
- **A test is available that is sensitive (few false negatives) and accurate with acceptable specificity (minimal number of false positives).** The fasting plasma glucose and 2-hour plasma glucose have been applied to high risk populations and are exceptionally sensitive and specific. Random opportunistic glucose measurements may be appropriate, and are likely to be sensitive. The cost of this if the yield is low must be considered in any screening program.
- **An intervention is available to prevent or delay disease onset or to more effectively treat the condition detected in the latency phase.**

In the face of an apparent rapid increase in type 2 diabetes in US youth, The American Diabetes Association issued a Consensus Statement in 2000, recommending screening youth for type 2 diabetes based broadly on known risk factors (2) (E). Concerns have been raised about these recommendations as more information has accumulated since this publication.

Concerns about these criteria are:

- they were established without a database and, therefore, not evidence-based
- although the fasting plasma glucose was considered preferable because of lower-cost and greater convenience, sensitivity is compromised because the 2-hour plasma glucose increases earlier in the course of development of T2DM
- while some ethnicities may be overrepresented in populations of affected individuals, not being a member of such a group is not protective and therefore may be a spurious basis for selection of individuals to be tested

Studies in the 7 years following publication of these criteria, from Europe, the US, Japan, Taiwan, India, and Israel, have provided a data base for refining case-finding recommendations (11,22, 23, 43–49, 94) (C)

- These studies emphasize the limitation of fasting glucose determination for testing purposes in obese youngsters.
- Studies of large numbers of school children in Japan and Taiwan, using urine tests for initial screening indicate a very low yield (~0.02%) of diabetes and an unjustifiable cost-benefit ratio in most populations (11, 93).
- Some studies demonstrate a relatively low yield of identifying cases even in high risk populations using an OGTT, 0.1% were found to have a 2 hour post glucose > 200 mg/dl (11 mmol/l) in a primarily non-white, predominantly overweight US population (22) and 0.4% had diabetes in a Native American population (23). In these studies 2–3% had impaired glucose tolerance or impaired fasting glucose.
- Several studies, including all ethnicities have also noted the high frequency of detection of non-glycemic features of the insulin resistance syndrome in children and youth with BMI greater than 85th percentile (95).

These new data indicate that screening to identify diabetes in asymptomatic youth has a low yield and further research is required to determine the optimal strategy for testing, including the frequency of testing. (C/E) In populations with high incidence of T2DM, if resources are available, currently some clinicians may favor screening while awaiting more information on optimal screening strategies. However, in many populations screening outside of a research setting is not cost effective.

Because abnormal glucose tolerance may be present in 2–3% of high risk groups and additional findings of insulin resistance may be also be present prior to overt diabetes, a high index of suspicion should be maintained and at risk children should be advised on approaches to prevent T2DM (see subsequently). Children at risk for T2DM diabetes and metabolic syndrome include (C/E):

- Children with BMI 85–95th percentile:
- if there is an immediate family history of T2DM, early cardiovascular disease, or
- if there are signs of insulin resistance (acanthosis nigricans, dyslipidemia, hypertension, PCOS)

Asian children regardless of BMI, if history of abnormally low or high birth weight (89), or family history of diabetes (90).

Children with BMI > 95th percentile, regardless of family history or associated features.
Prevention of T2DM

- Worldwide, obesity is increasing in all segments of the population. The epidemic of obesity and its complications accounts for a substantial and increasing proportion of direct and indirect health care costs. Prevention of T2DM requires prevention of obesity in those who are not overweight and treatment of obesity in those who have a BMI > 85th percentile (or even less in non-European populations) (11, 95). (A)
- Primary prevention of T2DM is directed toward the obesity pandemic and involves reversing eating and entertainment trends in homes, schools, and communities that have resulted in excess caloric intake and marked decrease in energy expenditure by children and adults; optimizing the fetal environment in pregnancy; and the promotion of breast-feeding.
- Studies have shown that relatively minimal weight loss can decrease rate of diabetes in at risk populations (96,97) (A,C)
- Intervention in adult populations reflects difficulty in altering lifestyle and dietary habits (98).
- The challenge is huge, of countering eating and entertainment trends that provide popular social outlets and are highly attractive, ubiquitous, and heavily promoted (E).
- The societal changes required are of such magnitude that enormous community and governmental commitment is required (E).

Recommendations:
Autoantibody testing when diagnosing and treating T2DM:
- Diabetes autoantibody testing should be considered in all pediatric patients with the clinical diagnosis of T2DM because of the high frequency of islet cell autoimmunity in otherwise “typical” T2DM:
  - Antibodies will indicate an earlier need for insulin. (E)
  - Antibodies will indicate the need to check for thyroid autoimmunity and to consider other associated autoimmune disorders. (E)
- Diabetes autoantibody testing should be considered in overweight/obese children > 13 years of age with a clinical picture of T1DM (weight loss, ketosis/ketoacidosis), some of whom may have T2DM (E)
- C–peptide measurements should be considered in overweight/obese children > 13 years of age who have worsening levels of control on oral agents to confirm those requiring insulin therapy and to reconsider the diabetes classification.(E)
- Because of the multitude of cardiovascular risk factors associated with insulin resistance, T2DM is likely to be associated with earlier severe complications than T1DM in childhood (E).
- The insidious onset in much of T2DM, the lipid dysmetabolism, and the unknown duration of IGT preceding diagnosis may, as in adults, be associated with micro- and macrovascular disease already present at diagnosis (E).

Recommendation for initial medical treatment of type 2 diabetes* (98):
  * Preadolescent children are unlikely to have T2DM, even if obese (8)
  * Overweight adolescents should have both T1DM and T2 DM considered in the diagnosis (4,8)
  * Antibody determination is the only way to definitively determine the presence of autoimmune diabetes (T1DM)

Initial treatment modality is determined by symptoms, severity of hyperglycemia, and presence or absence of ketosis/ketoacidosis. As in T1DM, those with symptoms, particularly vomiting, can deteriorate rapidly and need urgent assessment and appropriate treatment. (E).

Lifestyle changes in diet and exercise are essential and should be recommended for all individuals with T2DM
Complication testing specific to T2DM in young people:
- Testing for either micro- or macro-albuminuria, should be performed at the time of diagnosis and annually thereafter (55, 72) (E).
  - Elevated levels of urine albumin should be confirmed on 2 of 3 samples
- Blood pressure should be monitored at every visit according to standardized techniques specific for children ( (72), E) On-line instructions are available at:  www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf
  - Elevated BP should be confirmed on 2 additional days. Hypertension is defined as an average systolic or diastolic BP ≥ 95 percentile for age, sex and height percentiles, with high normal BP being 90 to < 95percentile.
  - Normal BP levels for age, sex, and height are available at the above website.
- Testing for dyslipidemia should be performed soon after diagnosis when BG control has been achieved and annually thereafter (60,61) E
- Evaluation for NAFLD should be done at diagnosis and annually thereafter (24) (E).
- Inquiries about puberty, menstrual irregularities and obstructive sleep apnea should be made at diagnosis and regularly thereafter (65) (E).
Examination for retinopathy should be performed at diagnosis and annually thereafter (E).

Recommendations for case finding:

- Case finding for research purposes should determine abnormal glucose tolerance, IFG and IGT in a standardized manner by blood glucose level obtained fasting before an oral glucose load of 1.75g/kg body weight up to 75 g, and 2 hours following ingestion of the glucose (E).

- For longitudinal research purposes, frequency of testing at risk individuals may be annually (E).

- The clinical diagnosis of T2DM in an asymptomatic individual requires at least two abnormal glucose values, diagnostic of diabetes, on 2 separate days (E).

Recommendation for prevention:

- The societal, family, community, and personnel resources required to prevent, or delay, the development of T2DM and the other serious manifestations of the insulin resistance syndrome are daunting and need to be addresses (E).

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