

Glycemic Abnormalities in Adolescents

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Abstract

Glycemic abnormalities including prediabetes and Type 2 diabetes mellitus (T2DM) are emerging clinical problems in children and adolescents. Increased insulin resistance during pubertal development appears to uncover glycemic abnormalities. Pediatricians and physicians should be knowledgeable and conscious about the prevalence and progression of prediabetes to T2DM, the frequent mild or asymptomatic manifestation of T2DM in children and adolescents and the high risk of complications in these patients. Screening for glycemic abnormalities seems useful in high risk groups such as children and adolescents with obesity, family history of T2DM, and with clinical features suggestive of insulin resistance (hypertension, dyslipidemia, polycystic ovarian syndrome, or acanthosis nigricans). Modification of life style and reduction of obesity is still the prime target of prevention and early management of early glycemic abnormalities. However, use of hypoglycemic drugs is indicated when these measures fail to achieve adequate glycemic control.

Keywords: Adolescents; Diabetes; Prediabetes; Diagnosis; Monitoring

Physiological Changes in Insulin Secretion and Glycemic Control in Healthy Adolescents

During puberty insulin levels are higher compared to the prepubertal and post pubertal (adulthood) periods. Direct evidence of increased pubertal insensitivity to insulin has been proven using *in vivo* experiments. In healthy adolescents there is a decrease in insulin-stimulated glucose uptake compared with pre-pubertal children. This puberty-related insensitivity to insulin is compensated by an increase in insulin secretion [1-3]. A large cross-sectional study of children and adolescents without diabetes found that insulin sensitivity was lowest at age 12 to 14 years (Tanner stage 3 of puberty) in both sexes, across all ethnic groups, returning to almost pre-pubertal levels in young people above 16 years of age (Tanner's stage 5). A significant correlation has been demonstrated between the speed of growth and an increase in fasting serum insulin in pubertal adolescents without diabetes [4-7].

The major hormonal changes that are associated with the onset of puberty include a two-fold increase in the secretion of Growth Hormone (GH), increase in insulin-like growth factor-I (IGF-I), and an increase in the sex steroids that lead to the remarkable increase in height, development of secondary sexual characteristics and change in body composition. The secretion of GH increases during puberty and declines after the pubertal growth spurt is completed. GH is known to be an important factor in reducing insulin sensitivity and insulin-stimulated glucose metabolism has been correlated negatively with GH and/or IGF-I levels [4,5].

The significance of these physiological changes in metabolism and insulin sensitivity for adolescents with type 2 and type 1 diabetes mellitus

1. Type 2 diabetes mellitus (T2DM) appears to be a substantial and growing problem among adolescents. Increased insulin insensitivity due to puberty as well as due to obesity in adolescents diagnosed with type 2 diabetes are important pathophysiologic mechanisms in all ethnic groups. Adolescents with T2DM2 have deterioration of glycemic control during this pubertal period [8-12].

2. In adolescents with Type 1 DM (T1DM), it is now apparent that because of increased insulin insensitivity, insulin action decreases by between 30% and 50%. Therefore, healthcare providers should be aware that insulin requirements increase by between 30% and 50% during puberty. If this fact is overlooked, an adolescent's blood glucose control and HbA1c levels will deteriorate [8-12].

Prevalence of Prediabetes in Adolescents and Its Potential Risks

Prediabetic states are prevalent among children and adolescents. The prevalence of prediabetes depends on the definition used. Significant differences in prevalence can depend on whether prediabetes is defined by Impaired Fasting Glucose (IFG), Impaired Glucose Tolerance (IGT), or using HbA1C criteria as well as considering the age and ethnicity of the patients. In adolescents, the prevalence of IFG ranges from 13% to 40% and of IGT, from 2% to 5%, whereas approximately 20% have HbA1c levels of 5.7%-6.4%. The prevalence of prediabetes using IFG and IGT (in 2005-2006) among adolescents in the US aged 12-19 years, using the ADA criteria, showed that 13.1% had IFG, 3.4% had IGT and 16.1% had both IFG and IGT [13]. Moreover, the prevalence of prediabetes has increased markedly over recent decades [14,15]. Among 3,400 adolescents in the US aged 12 to 19 (from the NHANES survey) the prevalence of prediabetes/diabetes increased significantly, from 9 percent to 23 percent between 1999 and 2008 [16].

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The prevalence of prediabetes is significantly higher among obese pubertal children with a positive family history of T2DM. In the Studies to Treat or Prevent Pediatric Type 2 Diabetes (STOPP-T2D), conducted in 2003 in 8th-grade students (mean age, 13.6 years), 40.5% had fasting glucose levels ≥ 100 mg/dL. In those with a body mass index (BMI) at the 95th percentile or higher, the prevalence increased to 47%. 36.5% of students with normal BMI (< 85th percentile) also had fasting glucose levels ≥ 100 mg/dL [17]. In a multiethnic cohort study conducted between 2005 and 2010, 1156 obese children and adolescents (40% boys) underwent an Oral Glucose Tolerance Test (OGTT) and HbA1c measurement. In 21% of these patients, HbA1c levels were 5.7%-6.4%. Among children classified as being at increased risk for diabetes on the basis of their HbA1c values, only 47% were categorized as being at increased risk on the basis of their OGTT results. Moreover, 27% of children with HbA1c levels below 5.7% were diagnosed with prediabetes on the basis of OGTT results [18].

Agreement is poor between HbA1c levels and OGTT results. It is not clear which of these measures will more closely predict long-term complications. HbA1c alone is a poor diagnostic tool for prediabetes in obese children and adolescents. The ADA panel, when recommending HbA1c for diagnosis in adults, acknowledged that concordance is not perfect among HbA1c, fasting plasma glucose, and 2-hour fasting plasma glucose levels. Nevertheless, long-term data on HbA1c elevation and risk for retinopathy, combined with practical considerations on the use of HbA1c, led the ADA to recommend its use [19,20].

Among adults, prediabetes is a recognized risk factor for both T2DM and cardiovascular disease and is associated with retinopathy, a 2-fold increased incidence of micro albuminuria, and neuropathy. Concerns have been raised about the potential effect of prediabetes on morbidity in adolescents. However, no available data that describes the impact of prediabetes on morbidity in children [20-22].

Identified Risk Factors for Prediabetes

Obesity, family history of diabetes especially parental diabetes and male sex pose high risk rate of prediabetes. Adolescents aged 12-15 years have a significantly higher rate of prediabetes than those aged 16-19 years. This may be related to the peak of pubertal insulin resistance that occurs during early adolescence. Adolescents with 2 or more cardio metabolic risk factors (hypertension, dyslipidemia, and hypertriglyceridemia) have a 2.7-fold higher rate of prediabetes than those with no cardio-metabolic risk factors. Similarly, adolescents with hyper-insulinemia have a 4-fold higher prevalence than those without cardio-metabolic risk factors [23-27].

The Fate of Prediabetes and Predictors of Progression from Prediabetes to T2DM?

The story of developing T2DM from normal glucose tolerance entails many successive stages. The first stage is characterized by insulin resistance associated with a compensatory increase in insulin secretion; this stage can take several years. Patients with both IFG and IGT have insulin resistance, but the site of their predominant insulin resistance differs [28]. Those with IFG have predominantly hepatic insulin resistance, whereas those with IGT have predominantly muscle insulin resistance. In the second stage, where beta-cells fail to compensate for increased insulin resistance, hyperglycemia develops progressing from prediabetes to overt diabetes. This progressive loss of beta-cell secretion probably has a combination of genetic, environmental, and biochemical determinants. In children and adolescents, the early appearance of

prediabetes and T2DM suggests an accelerated pathophysiologic process in the young [16,29].

In a study of 117 obese children and adolescents (mean age: 12.7 years), OGTT tests were performed at baseline and after approximately 2 years out of 33 children with IGT at baseline, 45.5% reverted to normal glucose tolerance, 30.3% continued to have IGT, and 24.2% developed T2DM. Severe obesity, weight gain, IGT, and black race appeared as the best predictors of developing T2DM, whereas baseline fasting glucose, insulin level, and C-peptide level were not predictive [30]. In another study, 128 overweight/obese Hispanic children with a family history of T2DM were evaluated annually for 4 years with an OGTT (the ADA criteria for prediabetes were used). Tremendous variability was seen in the individual patterns of change in glucose status from year to year. Only 13% of participants had persistent prediabetes, whereas 47% had intermittent prediabetes, with no clear pattern over time [31].

A high rate of reversion from IGT to normal glucose tolerance was demonstrated in 128 obese white European adolescents (mean age: 13.5 years) diagnosed with IGT in 2003-2006. After a mean of 3.9 years of follow-up, 75% of these adolescents converted to normal glucose metabolism, 16% continued to have IGT, 2% developed T2DM, and 7% were lost to follow-up. Age, sex, BMI, blood pressure, and fasting glucose levels at baseline did not differ between adolescents who continued to have IGT and those who converted to normal glucose metabolism. However, 2-hour glucose levels by OGTT at baseline were significantly higher in the adolescents who continued to have IGT and were highest in adolescents who developed diabetes. These studies demonstrate that a reasonably high percentage of children and adolescents diagnosed with prediabetes revert to normal glucose tolerance [32].

Prediabetes and Type 1 Diabetes

Prediabetes was defined to identify patients at risk for T2 DM however, IFG, elevated HbA1C, and IGT also can be the first signs of T1DM. The clinical presentation of T1DM is preceded by an asymptomatic latent period, and because obese adolescents can also develop T1DM, screening of obese patients for prediabetes might identify such cases. Assessment of diabetes-associated autoantibodies might be helpful. This prediabetic period can last for months or years [20].

Potential Treatment Options and Screening for Prediabetes

The expert panel of the ADA focusing on prediabetic states acknowledged the strong association between diabetes and obesity and suggested that the first priority is maintenance of a healthy weight and prevention of obesity [20]. Although several studies have demonstrated the success of interventions to prevent obesity in children and adolescents, no studies have shown how to prevent the progression from prediabetes to diabetes in this age group. Longitudinal studies are required to document these outcomes.

Even though adoption of a healthy lifestyle is beneficial to everyone; however, the question of drug therapy in children and adolescents is much more complicated. Several short-term studies (about 6 months in duration) in normoglycemic adolescents at risk for diabetes as a result of elevated BMI, family history, and elevated fasting insulin level have shown that compared with placebo, treatment with metformin results in a progressive decline in fasting blood glucose and a reduction in fasting insulin levels [33-36]. In a meta-analysis of 4 randomized controlled trials in participants younger than 19 years who were treated with metformin for at least 2 months, a statistically significant mean

reduction in fasting insulin and BMI was seen with metformin (with and without lifestyle intervention) compared with placebo. However, because of small size and short duration of these studies none was able to document prevention of progression to diabetes [37]. Metformin treatment of 15 obese adolescents with the polycystic ovary syndrome and IGT was found to be beneficial and after 3 months 8 patients had normal glucose tolerance [38].

In June 2009, an International Committee composed of experts from the American Diabetes Association, the European Association for the Study of Diabetes and the International Diabetes Federation recommended that prediabetes testing includes the Hb A1C test, fasting blood sugar test and oral glucose tolerance test [39]. According to the American Diabetes Association recommendations it would be helpful to consider monitoring patients with impaired fasting glucose or HbA1c (5.7%-6.4%) or previously Impaired Fasting Glucose (IFG) every year. Monitoring should include at least annual reassessment of FPG and/or an OGTT. For individuals where progression is suspected, annual measurements of FPG and HbA1C, with 2-hour OGTT, should all be conducted.

The AACE recommends HbA1C primarily for screening and monitoring and not for prediabetes identification. This is because the A1C test can be misleading or inaccurate in some populations [38-44].

In summary, screening for prediabetes and monitoring of glycemic abnormalities seems to be meaningful in adolescents who have a parental history of diabetes, are extremely obese, and have entered puberty; especially in adolescents of certain ethnic groups.

The Prevalence of T2DM in Children and Adolescents

The difficulties to detect T2DM in children and adolescents include a) Hyperglycemia can go undiagnosed for a long time, b) it may have no symptoms or mild symptoms, c) blood tests of variable sensitivity are needed for diagnosis d) criteria for differentiating between T1DM and T2DM in children and adolescents may be confusing. Children and adolescents with T2DM can develop ketoacidosis; while those with T1DM can be overweight; and therefore the overall prevalence of the disease may still be low. This means that scientists will have to sample a very large population of adolescents in order to find a stable estimate of prevalence [12].

T2DM appears to be an evolving as a new clinical problem within pediatric practice. Recent reports indicate an increasing prevalence of type 2 diabetes mellitus in children and adolescents around the world in all ethnicities, even if the prevalence of obesity is not increasing any more. Ethnic subgroups such as African-American, Hispanic, Asian/Pacific Islanders and American Indians pose a higher risk to develop T2DM in adolescents. The frequent mild or asymptomatic manifestation of T2DM in children and adolescents proposes that screening is important especially in high risk groups such as children and adolescents with obesity, relatives with type 2 diabetes mellitus, and clinical features of insulin resistance (hypertension, dyslipidemia, polycystic ovarian syndrome, or acanthosis nigricans) [45].

Adolescents with T2DM appear to be at a much higher risk of developing early diabetes mellitus associated complications than those with T1DM. 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 [46,47].

Treatment of choice is lifestyle intervention followed by pharmacological treatment (e.g., metformin). New drugs such as dipeptidyl peptidase inhibitors or glucagon like peptide 1 mimetics are

still under trials for treatment of youth with T2DM. Since microvascular complications of T2DM like retinopathy and nephropathy already occur in children, dilated eye examinations should be performed and screening for microalbuminuria should also be performed yearly. Angiotensin Converting Enzyme (ACE) inhibitors are the agents of choice in children with microalbuminuria. Recent reports also indicate a significant failure of the medical care system of adolescents with T2DM suggesting and recommending remodeling of current healthcare practices [45,48].

In 107 patients with clinically diagnosed T2DM (aged ≤ 20 yr at diagnosis), patients were obese (BMI -SDS): 2.6 (2.0-3.1)], and 88.0% had a family history of diabetes. Islet autoantibodies were detected in (15.0%). Autoantibody positive patients had poorer metabolic control than autoantibody negative patients. Therapies used were lifestyle only (35.5%), oral anti-diabetics (OAD) only (43.3 %), insulin + OAD (15.9%) and insulin only (5.6%). Complications including metabolic syndrome (61.7%), microalbuminuria (13.4%), and retinopathy (3.9%) were diagnosed. Patients with β -cell autoimmunity or HLA-DR genetic risk more frequently used insulin than confirmed T2DM patients (50.0 vs. 22.0%) [49].

Screening for T2DM in Adolescents

The Canadian Diabetic Association recommends that screening for T2DM should be performed every 2 years using an fasting plasma glucose test (FPG test) in children and adolescents with any of the following [50]:

1. ≥ 3 risk factors in non-pubertal or ≥ 2 risk factors in pubertal children
2. Obesity (BMI ≥ 95 th percentile for age and gender)
3. Member of a high-risk ethnic group (e.g. Aboriginal, African, Asian, Hispanic or South Asian descent)
4. Family history of T2DM and/or exposure to hyperglycemia in utero
5. Signs or symptoms of insulin resistance (including acanthosis nigricans, hypertension, dyslipidemia, Non-Alcoholic Fatty Liver Disease (NAFLD) (ALT: 3 times upper limit of normal or fatty liver on ultrasound) and features of polycystic ovary disease (PCOS).

The ADA recommends a screening in overweight children and adolescents at onset of puberty in high risk patients (BMI > 90 percentile + one of the followings; family history of T2DM, Asian, American Indian, Africa-Americans or Hispanic race, acanthosis nigricans, hypertension, dyslipidemia or polycystic ovarian syndrome). Testing is recommended every 2 years starting at the age of 10 years or at onset of puberty if it occurs in a younger age by fasting glucose or OGTT [48].

Screening in those high- risk groups demonstrated T2DM in around 1% of obese Caucasian children in Germany and in 4% of screened obese adolescents in particular ethnic groups in the United States [51,52].

Conclusion

Prediabetic states are prevalent among children and adolescents. Moreover, the prevalence of prediabetes has increased markedly over recent decades. Screening for prediabetes and monitoring of glycemic abnormalities seems to be meaningful in adolescents who have a parental history of diabetes, are extremely obese, especially in

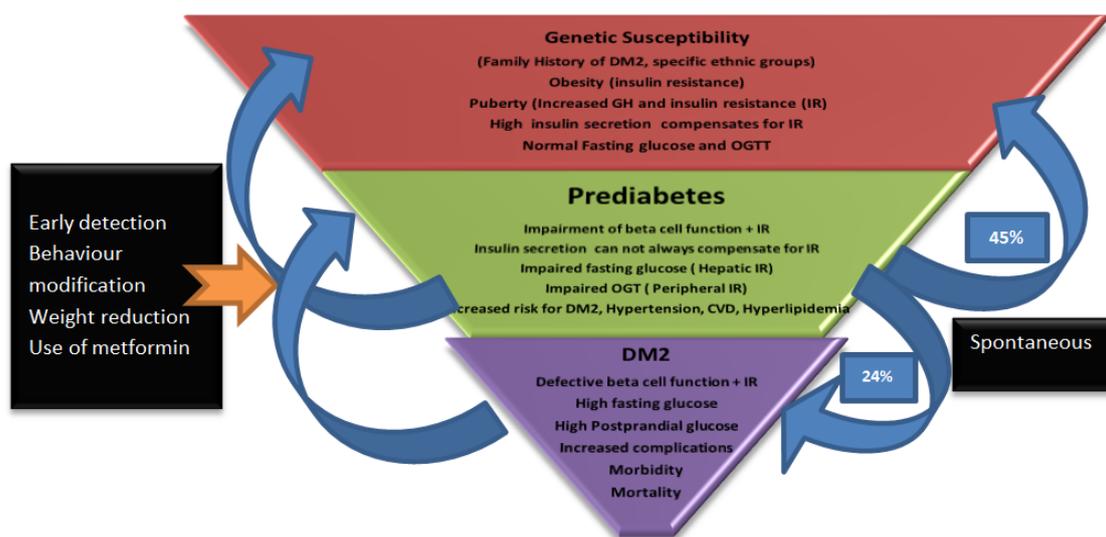


Figure 1: Sequence of type 2 diabetes mellitus development in adolescents and its reversibility.

adolescents of certain ethnic groups and affected by special systemic diseases with potential insult to the beta cells. Recent reports indicate an increasing prevalence of T2DM prevalence in adolescents all over the world possibly due to increasing obesity. Obese adolescents with clinical signs of insulin resistance (acanthosis nigricans, dyslipidemia, hypertension, PCOS) or family history of T2DM and those with certain ethnicity have higher risk to develop T2DM. It seems appropriate to screen those children and adolescents above the age of 10 years for T2DM. Early detection, prevention and treatment of prediabetes and T2DM should become one of the targets of public health intervention programs. Physicians should make the public aware of both adolescent obesity epidemic and its serious consequences including prediabetes and T2DM (Figure 1).

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