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REVIEW

Prediabetes in Adolescents: Prevalence, Management and Diabetes Prevention Strategies

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Abstract: The ongoing obesity epidemic in children and adolescents has greatly increased the prevalence of related comorbidities. Prediabetes is defined based on levels of fasting glucose, oral glucose tolerance tests or hemoglobin A1c, that are intermediate between normal levels and thresholds that define type 2 diabetes mellitus (T2DM). As such, prediabetes represents a sign of early pathophysiology preceding T2DM development. Recent analyses of data from US adolescents estimate prediabetes to be present in 4–23% of adolescents, depending on criteria used, with other studies finding an 8% risk of progression from prediabetes to T2DM over a 3-year period. These data support the importance of intervention to avoid long-term sequelae, focusing on reducing degree of obesity and insulin resistance. Lifestyle modification, with increases in physical activity and dietary improvements, remains the first-line approach. Other interventions are based on additional long-term risks and range from metformin treatment for more moderate cases of prediabetes to bariatric surgery for adolescents with severe obesity and comorbidities. As data accumulate regarding sequelae of T2DM in adolescents, there remains a critical need for prevention of obesity and T2DM throughout childhood, and prediabetes should be a trigger for improving this risk profile.

Keywords: prediabetes, pediatrics, obesity, type 2 diabetes mellitus, insulin resistance

Plain Language Summary

Prediabetes represents blood sugar elevations that are above normal but not yet at thresholds that define type 2 diabetes. Prediabetes can be a precursor to later type 2 diabetes and represents an opportunity to improve lifestyle habits (and sometimes treat with medicines) to avoid ever getting type 2 diabetes.

Introduction

Obesity is a multifactorial disease that continues to challenge patients, healthcare providers and healthcare systems.[1] Since 1980, obesity prevalence has doubled in over 70 countries around the world—particularly rising among more developed countries.[2,3] In 2015 it is estimated that there were more than 107 million children with obesity worldwide.[2]

As a result of the ongoing obesity epidemic, diseases previously seen almost exclusively in adults are increasingly seen in children and adolescents, including prediabetes and/or type 2 diabetes mellitus (T2DM).[4] In the United States, using data from the National Health and Nutrition Examination Surveys (NHANES; 2005–2016) approximately 20% of adolescents aged 12 to 18 years have prediabetes,[5] while other researchers have estimated that the prevalence of T2DM among adolescents will quadruple by 2050.[6]

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Unfortunately, most available evidence of T2DM prevention is from adult data, and it is unclear how much can be extrapolated to pediatrics. Therefore, this review will focus on the prevalence and management options of prediabetes in adolescents. Intensive lifestyle programs are still the cornerstones of management of prediabetes in this population; however, in some cases pharmacologic intervention could be considered.

What is Prediabetes?

Definitions

According to guidelines of the American Diabetes Association (ADA),[7] prediabetes can be diagnosed by one of three laboratory values: (1) elevated fasting glucose of 100 to 125 mg/dL (5.6–6.9 mmol/L) or (2) elevated glucose at 2 hours during an oral glucose tolerance test, 140 to 199 mg/dL (7.8–11.0 mmol/L) or (3) hemoglobin A1C (HbA1C) level between 5.7% and 6.4% (39–46 mmol/mol; Table 1).

Prevalence

Using criteria from the ADA guidelines, the prevalence of prediabetes in pediatrics is high, particularly among children and adolescents with obesity, in whom the prevalence ranges from 21–40%, depending on the criterion used and the underlying population.[8,9] This prevalence of prediabetes in the setting of obesity varies by race/ethnicity, with 54% of African American adolescents, 28% of Hispanic adolescents, and 18% of whites.[10] Prediabetes is 1.7–2.4-fold higher in boys than in girls.[11] Perhaps not surprisingly, the prevalence of prediabetes has continued to rise among adolescents. For example, using the fasting glucose criterion, 1.8% of adolescents had impaired fasting glucose in 1988–1994, 7.0% in 1999–2000, and 23% in 2007–2008.[12] However, there is variability in estimates obtained using HbA1c vs fasting glucose, with 4.4% of US adolescents having prediabetes by HbA1c criteria in 1999–2014 compared to 15.0% by fasting glucose levels[13]—suggesting some criteria may be detecting abnormalities at an earlier stage in disease progression. A school-based study screening Hispanic and Native American middle-school students with multiple T2DM risk factors reported that 43% had prediabetes by definitions for impaired fasting glucose or impaired glucose tolerance.[14]

Table 1 American Diabetic Association Diagnostic Criteria for Normal Glucose, Prediabetes, and Diabetes

Diabetes Test	Normal	Prediabetes	Diabetes
Hemoglobin A_{1c}, % (HbA1c)	< 5.7	5.7–6.4	≥ 6.5
Fasting blood glucose, mg/dL	< 100	100–125	> 125
Oral glucose tolerance, mg/dL	< 140	140–199	≥ 200

Notes: Data from American Diabetes Association.[7]

Pathophysiology

The definition of prediabetes is based only on elevated glucose levels, leaving open whether the disorder is seen predominantly in type 1 diabetes mellitus (T1DM) or T2DM. Given that the rise in glucose levels is more rapid in T1DM compared to the more insidious progression of T2DM, there is more time for clinicians to notice glucose abnormalities related with prediabetes in T2DM.[15] As such, the majority of prediabetes in adolescents (as in adults) appears to be related to T2DM.[16] In some groups of children and adolescents, up to 45% of new diabetes cases are T2DM. The SEARCH for Diabetes in Youth Study (a surveillance study in multiple centers in the US) reported that the racial/ethnic breakdown of T2DM incidence per 100,000 adolescents aged 15–19 years was 49.4 cases among American Indians, 22.7 among African Americans, 19.4 among Asians/Pacific Islanders and 8.73 among whites.[17] There has been an increase in T2DM prevalence worldwide, including in Japan, China, Taiwan, Bangladesh and Australia.[18]

Even though T2DM has increased in the last decades, a complete understanding regarding prediabetes among adolescents is further complicated by the underlying pathophysiology behind the progression from normal glucose regulation to prediabetes to T2DM. In this sense, prediabetes shares overlapping pathophysiology with T2DM. In general the pathophysiology of T2DM includes elements of insulin resistance and inadequate insulin release to overcome this resistance. A decrease in β-cell function relative to insulin sensitivity was observed by 40% in obese youth with impaired glucose tolerance (IGT) and by 80% in children with obesity and T2DM in comparison with their peers with normal glucose tolerance (NGT).[19] These observations were obtained using hyperglycemic clamp together with the hyperinsulinemic-euglycemic clamp.

Thus, one issue exacerbating prediabetes in adolescence is puberty, which is associated with a significant increase in insulin resistance, potentially contributing to progression from prediabetes to T2DM.[20] For example, in one study of 526 adolescents with obesity and impaired

glucose tolerance followed over an average of 3 years, only 8% progressed to T2DM, with 65% converting back to normal glucose tolerance,[21] while other studies from Europe demonstrated larger percentages of adolescents who reverted to normal glucose tolerance after completion of puberty.[22] Factors that contribute to progression from a prediabetes to T2DM include the degree of underlying obesity and racial/ethnic background, with non-Hispanic black adolescents exhibiting a significantly higher risk of progressing to T2DM than seen for white adolescents.[21,23]

African-American children have a 4-times higher incidence of developing T2DM in comparison to their Caucasian peers.[24] In the context of the same degree of insulin sensitivity and after an intravenous glucose challenge, African-American youth have a more pronounced insulin hypersecretion in comparison with white youth.[25] First-phase and second-phase insulin concentrations were higher in African-American participants in comparison to their white controls, using hyperglycemic clamp.[26] Also, data evaluating insulin release after IV glucose administration suggest that African-American adolescents are more insulin resistant when compared with Latino adolescents, a difference which is independent of total fat mass as well as visceral fat.[27] Despite this increased insulin resistance, β-cell function was flatter in African-American compared with Latino adolescents. Hispanic children are also more insulin resistant than Caucasian children and this association is also independent of body fat content.[28] Data during pubertal maturation in Hispanic youth showed a diminished capacity of β-cells to respond to the decline in insulin sensitivity during advanced Tanner Stages, increasing the risk of progression of pediatric T2DM in this population.[29] Other race/ethnicities, including Malaysian, Korean, Taiwanese and Indian, endorse inadequate insulin secretion with even lower BMI that the African-Americans with insulin resistance. Data is even more scarce in adolescents with prediabetes of Asian descent.[30]

While long-term outcome data regarding adolescents with T2DM are limited, the available data has shown another important difference between youth and adult populations with T2DM. T2DM in youth (compared to youth with T1DM[31,32] or to adults with T2DM)[33] appears to be particularly aggressive and associated with early complications and comorbidities. The Restoring Insulin Secretion (RISE) study described ~25% lower insulin clearance in adolescents with prediabetes or recent-onset T2DM compared with adults, using the ratio of fasting C-peptide over insulin as an indirect marker of whole-body insulin clearance.[34] Hepatic insulin clearance seems to play a major role in the reduction of β-cell function in obese youth, as it could act as gatekeeper that might avoid the insulin overload to peripheral tissues and β-cells.[35] In the long-term follow up of the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) cohort, after a mean 13.3 years since T2DM diagnosis, 54% of participants had experienced diabetic kidney disease, 32% had experienced nerve disease and 51% had signs of retinal disease.[32] In addition, adolescents with T2DM experience more rapid loss of beta cell function and a higher degree of insulin resistance than seen in adults, with a higher rate of failing initial treatment, as demonstrated in the TODAY cohort.[36–38] Using NHANES data, which included 2843 adolescents aged 12–19 years, adolescents with prediabetes (compared to those without) were more likely to have multiple cardiometabolic risk factors, including obesity, high fasting triglycerides, low HDL-cholesterol, and high liver transaminase levels.[13,39]

Consequently, the concept of prediabetes is widely used to screen for T2DM risk and target preventive treatments. Furthermore significant beta cell destruction may occur before dysglycemia presents; therefore, early recognition and thus early interventions could potentially reduce the risk of potential comorbidities.

Screening for Prediabetes

Even though no studies in a pediatric population have thus far revealed if early diagnosis of prediabetes improves T2DM long-term outcome, indirect data from adult studies indicates that lifestyle interventions can delay or potentially prevent the progression to T2DM. In adult populations, lifestyle interventions decreased the percentage of patients with prediabetes who progressed over a 4-year period to T2DM from 33% to 20%.[40,41]

Since generalized screening of children and adolescents with obesity is unlikely to be cost-effective, the ADA and the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommend screening only high-risk patients.[42,43] These include asymptomatic children and adolescents with obesity after puberty onset or at ≥10 years of age (whichever occurs first) if they have one or more of the following risk factors: (1) family history of T2DM in a first- or second-degree family member; (2) an ethnicity associated with higher risk, including Native American, African American, Hispanic, Asian American, Pacific Islander; (3) history of diabetes in patient's mother

Table 2 Screening Criteria for Prediabetes and T2DM in Asymptomatic Youth with BMI ≥85th Percentile

History of Gestational Diabetes during the child's gestation
Family Hisotry of T2DM in first or second-degree family member
Race and/or ethnicity: American Indian, African American, Hispanic, Asian American and/or Pacific Islander,
Conditions associated with insulin resistance:
-Primary hypertension
-Acanthosis nigricans
-Dyslipidemia
-PCOS
-History of SGA or IUGR

Notes: Youths at puberty are at the highest risk. Screening should begin at the age of 10 years old or at the onset of puberty. Data from Hannon TS. [44]
Abbreviations: PCOS, polycystic ovary syndrome; SGA, small for gestational age; IUGR, intrauterine growth restriction.

or Gestational Diabetes Mellitus (GDM) during the child's gestation; and/or (4) conditions or signs associated with insulin resistance, including hypertension, dyslipidemia, acanthosis nigricans, polycystic ovarian syndrome (PCOS), and small-for-gestational age status at birth (Table 2).[44] The ADA recommendations advise that this screening should be repeated at least every 2–3 years–sooner if BMI is increasing; they recommend screening by measuring HbA1C and FPG or by performing an oral glucose tolerance test (OGTT). To be considered diagnostic, abnormal results have to be confirmed either using the same test on a different day or assessing a different test.[42]

Management

Given the distinctive characteristics of prediabetes and T2DM in adolescents, pediatric studies are vital. Most of the studies regarding T2DM prevention in pediatric populations include intensive lifestyle programs as their main intervention with only short term evaluations (6 months or less).[4] However, other studies have evaluated the effect of medications, emphasizing important physiological considerations that may ultimately be shown to prevent or delay diagnosis of T2DM.

Lifestyle Modifications

In pediatrics, intensive lifestyle programs are the cornerstones in the management of prediabetes. An approach combining dietary and physical activity changes is intervention most likely to be effective.[45,46] This is many explained by the fact increased energy outflow might lead to a compensatory surge in food consumption,[47] while isolated caloric restraint would be expected to decrease of the basal metabolic rate.[46,48]

Physical activity has a beneficial effect not only associated through producing weight loss but also on increasing insulin sensitivity independently from the amount of fat tissue.[49] The Endocrine Society Clinical Practice Guidelines suggest at least 30 minutes of moderate to vigorous physical activity each day with an objective of 60 minutes daily.[50] Low aerobic and resistance exercises combined together is recommended as this appears to improve insulin sensitivity.[46,51] Savoye et al[52] published the results of a 6-month program named "Bright Bodies Healthy Lifestyle" which entailed a randomized control trial of pubertal adolescents with prediabetes diagnosed via 2-hour OGTT glucose levels. These investigators reported that compared to controls, this intensive lifestyle intervention resulted in greater reductions in 2-hour glucose, as well as increased insulin sensitivity.[12] A meta-analysis that evaluated exercise intervention efficacy in obese adolescents showed 40% improvement in OGTT and 1.02 unit improvement in the homeostasis model of insulin resistance (HOMA-IR), an estimate of insulin resistance based on fasting glucose and insulin. This meta-analysis included 15 trials with a total of 556 participants; however, most interventions were short-term (6–36 weeks).[53] A recent trial published its results from the first 6 months of a 24-month multidisciplinary intervention approach that included a balanced diet and circuit training among 242 children and adolescents aged 6 to 17 years with obesity.[54] The preliminary data showed improvement in BMI z-score (−0.14) in the exercise group and reduction in adiponectin and waist circumference, however they could find a significant decrease in HOMA-IR. Interestingly they performed a sensitivity analysis based on puberty stage and found significant reduction in HOMA-IR when considering pubertal participants only.[54]

Also, a meta-analysis which included 24 studies that assessed the effects of physical activity on fasting insulin showed positive effects in improving fasting insulin as a marker of pediatric insulin resistance, with the greater effects seem among those with higher BMI z-scores.[55] Different training interventions such as resistance, aerobic and circuit training were used between studies, as well as non-traditional games to encourage an increase in levels of physical activity. However, the investigators did not find a difference between aerobic and resistance training approaches, suggesting that the most significant factor of an exercise program designed to have an impact on fasting

insulin and insulin resistance in children and adolescents is not related to a specific type of exercise but just that the children are encouraged to be active somehow.[55]

Furthermore, other health behaviors like food intake and sleeping routines can affect insulin sensitivity. For example, getting less sleep (less than 9 h/day) and having sleep apnea are associated to insulin resistance.[56]

Regarding dietary intake, the ideal dietary management is still being debated. The chief approach for nutritional approaches in children and adolescents, recommended by the American Academy of Pediatrics, the American Heart Association and the World Health Organization (WHO), is an increase in vegetable and fruit consumption, a decrease in intake of saturated fat, and a complete removal of sugar-sweetened beverages.[57,58] Several studies confirmed that the consumption of food with a higher fiber content was associated with greater insulin sensitivity.[59,60] A diet with higher fiber intake offers several beneficial effects, such as increased satiety, slower absorption of carbohydrates and the addition of low-energy food to the diet.[61] Low glycemic index foods reduce blood glucose and insulin postprandial peaks, stimulate fat oxidation and increase satiety, however their effect on insulin resistance is still unclear.[62]

These lifestyle recommendations are sometimes challenging to accomplish, especially for adolescents. Thus, the prevention or treatment of childhood obesity as a means of preventing prediabetes should start as early as possible. As therapeutic methods often only show modest effects, prevention should be the primary objective. The WHO commission advocates individual and community-based prevention strategies to battle the obesity epidemic.[63] Multiple guidelines have emphasized crucial roles for government, society, and healthcare system policy approaches to take action against childhood obesity.[64]

Metformin

Metformin, a biguanide derivative, is an oral antihyperglycemic drug that works by inhibiting hepatic glucose production, augmenting peripheral glucose uptake and blocking glucose absorption in the small intestine.[65] Metformin has also shown an improvement on lipid levels and displays potentially cardio-protective benefits in patients with obesity (see Figure 1).

There is still some controversy regarding the benefit of metformin to improve hyperglycemia or its effects on delaying the onset of T2DM in individuals with prediabetes.[65] Several clinical trials in populations with prediabetes—including adolescents and adults—have suggested that metformin can delay or even halt the progression from prediabetes to T2DM.[34,66] Improvements in BMI, fasting serum glucose, fasting insulin, HOMA-IR and lipid levels have been seen in pediatric randomized, controlled trials which include patients on metformin for treatment of obesity associated with insulin resistance. In short-term periods, some of these studies have confirmed that metformin combined with standard lifestyle interventions could reduce body weight and improve insulin sensitivity in children and adolescents with obesity. The majority of investigations have focused on metformin's

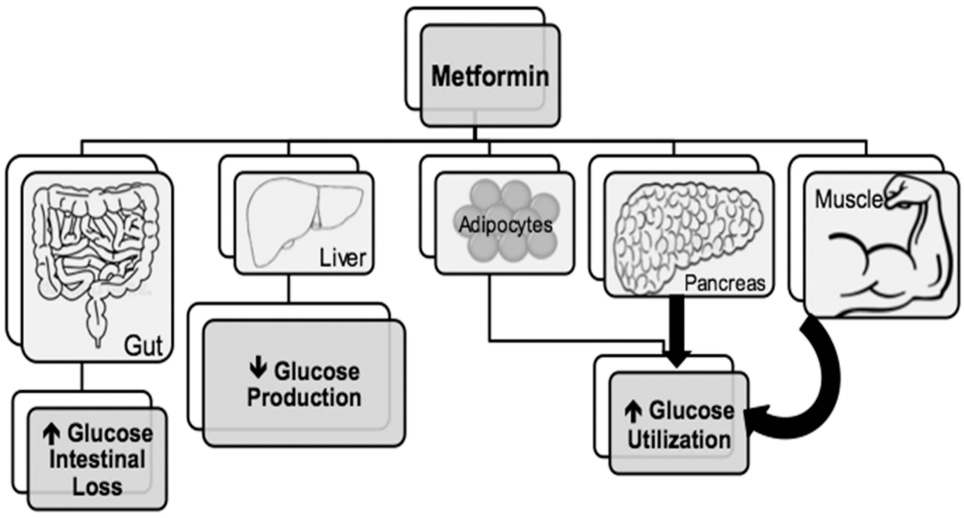

Figure 1 Main mechanisms of action of metformin in different end-organs. Metformin induces a reduction of hepatic glucose output and an increase in intestinal glucose loss, as well as favorable influences on glucose utilization in beta cells, adipocytes and muscle tissue.

effects on weight loss, while its effect on insulin resistance has been a less common outcome for these studies.[65] Furthermore, some of the studies have differing views on whether metformin could improve insulin resistance in obese children and adolescents.[67–71]

A recent meta-analysis of 15 randomized controlled trials assessing treatment of children and/or adolescents with obesity and insulin resistance with metformin 1000 mg to 2000 mg daily for 6 months found that more than half of the studies reported a greater drop in BMI with metformin compared to controls (average decrease of −1.3 kg/m^2), and about one fourth of the trials reported significant decreases in HOMA-IR following metformin treatment (average reduction compared to control of −0.6).[70,72] Additionally, low-dose metformin (850 mg/day) in pediatric patients with obesity and risk indicators for metabolic syndrome was effective, well tolerated, and showed improvements in body composition and inflammation markers, which could potentially translate to long-term health benefits.[65,73]

On the other hand, metformin did not have the same degree of success in T2DM treatment in youth in comparison to the data seen in adults. This was shown in the previously-mentioned TODAY study, a randomized controlled trial of 669 participants from aged 12–17 years of age with recently-diagnosed T2DM (mean 7.8 months).[38] This cohort experienced a high rate of treatment failure by 5 years with metformin monotherapy, which was more prevalent in pediatric (51.7%) versus adult (21%) T2DM, despite good medication adherence (80%). Interestingly, the addition of rosiglitazone, was superior to metformin alone; however, the addition of an intensive lifestyle intervention was not more effective than metformin alone. This study reinforced the idea of premature and rapid deterioration of beta cell function in T2DM in childhood and adolescence compared with adults with newly-diagnosed T2DM. This emphasizes the need for aggressive prevention and eventually combination treatment or insulin therapy early after diagnoses, frequently within a few years.[38]

In conclusion, metformin seems to have a positive effect on insulin sensitivity; however, 2017 Pediatric Obesity Clinical Guidelines from The Endocrine Society and ADA recommendations suggest that it should be introduced only in certain patients. Treatment with metformin should be considered in addition to lifestyle intervention in high risk adolescents.[4] These high-risk characteristics include a strong family history of T2DM, a BMI greater than 35 kg/m^2, and glycemic criteria for prediabetes (IGT, IFT, and HbA1C > 5.7%).[50,74] Even so, the long-term benefits of metformin, including diabetes prevention, in children will insulin resistance require further analysis.

Glucagon-Like Peptide (GLP-1) Analogs

Glucagon-like peptide (GLP-1) is part of the family of incretin hormones, which are released after nutrient intake with the capacity to increase insulin secretory responses during periods associated with hyperglycemia.[75] It is proposed that there are several mechanisms leading to decreases in blood glucose: (a) actions related to glucose-dependent insulin release, (b) suppression of over-secretion of glucagon (except in the setting of hypoglycemia), and (c) slowing of gastric emptying, which has been associated with clear effects on post-prandial blood glucose excursions.[76] A large part of the effect of pharmacological doses of GLP-1 appeared to be related to acute reductions in appetite, increased satiety, and reduced caloric intake.[75]

Recently, one of the GLP-1 agonists, liraglutide, was approved for obesity management in children older than 12 years. Liraglutide is a GLP-1 receptor agonist (GLP-1RA) that has 97% homology to endogenous GLP-1 and can be provided as a once-daily subcutaneous injection.[77] This approval was based on results published last year demonstrating that liraglutide 3.0 mg once daily (along with lifestyle modifications) has an impact on BMI and body weight among adolescents with obesity and difficulty managing their weight with lifestyle modifications alone. Nevertheless, after the 12-week run-in period, there were no substantial differences in blood pressure, lipid abnormalities, fasting glucose levels, or HbA1c.[78]

Even though the FDA approved liraglutide in 2019 for management of T2DM in children greater than 10 years of age, there is a lack of data of its use in pediatric patients with prediabetes. Clinical trials on wider populations are needed to determine its role in the treatment of insulin resistance in children. In addition, the high cost of liraglutide treatment for obesity and the ultimate regain of weight following cessation make it a questionable approach for long-term weight management among adolescents, who would require a lifetime of treatment to sustain the 4 kg drop in body weight.[78]

Other Medications

Drugs used for weight loss such as sibutramine and orlistat have also been shown to improve insulin sensitivity in children and adolescents, although their use in this age group is still controversial and continues to require careful thought prior to use. There are also some data that

peroxisome proliferator-activated receptor (PPAR) gamma agonists could improve insulin sensitivity in adolescents.[38]

Regarding sibutramine, it was evaluated in a randomized, double-blind, placebo-controlled trial which included 82 adolescents from ages of 13 to 17 years, which showed more weight lost on sibutramine in comparison to behavioral therapy and placebo.[79] After 12 months of follow-up the researchers also reported an improvement in HOMA-IR.[79] Orlistat was evaluated on 20 adolescents with comorbidities associated with obesity and after 6 months of treatment, participants exhibited improvements in BMI, total and LDL cholesterol, OGTT-derived insulin sensitivity and HOMA-IReffects which were greatest among white participants. Nonetheless, the main issue with orlistat is the fact that its tolerability is often very poor due to high rate of flatulence and stool incontinence.[80]

Another study evaluated the use of rosiglitazone in 21 adolescents with obesity with impaired glucose tolerance. More teenagers in the rosiglitazone group returned to normal glucose tolerance vs placebo (58% vs 44%), associated with an increase in insulin sensitivity (by hyperinsulinemic-euglycemic clamp) and beta cell function, as measured by OGTT.[81]

Bariatric Surgery

In many cases, achieving or maintaining weight loss can be challenging, particularly in young populations; therefore, recent guidelines recommend weight loss surgery as an effective therapy for severe obesity disease in adolescents.[82] Importantly, bariatric surgery results in overall sustained improvements in BMI, while medications only reduce BMI while the patient is taking them. Indications for weight loss surgery include BMI of greater than 35 kg/m^2 with major comorbidities of obesity including T2DM, severe sleep abnormalities (moderate to extreme sleep apnea), pseudotumor cerebri, debilitating orthopedic problems, and non-alcoholic steatohepatitis (NASH).[50] Adolescents are also candidates for bariatric surgery if they have a BMI of ≥40 kg/m^2 with mild obesity complications such as hypertension, lipid abnormalities, orthopedic problems, mild or moderate sleep apnea, and extreme psychological distress due to their obesity.[83]

Along with the reduction on size of gastric size that both procedures entailed, both the roux-and-y gastric by-pass (RYGB) and vertical sleeve gastrectomy (VSG) result in a decrease in appetite and thus improvement in insulin resistance. Both approaches reduce ghrelin concentrations and decrease its orexigenic (appetite increasing) effects and at the same time increase the anorexigenic incretins such as glucagon-like peptide 1 and peptide YY,[84,85] as a means of curtailing appetite and increasing insulin sensitivity.

A prospective, multisite observational study which included 5 academic centers, entitled The Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study, demonstrated 61% excess weight loss at 1 year and 62% excess weight loss at 2 years after bariatric surgery.[86] Positive effects of RYGB on glucose homeostasis parameters were showed in a study including 22 adolescents with extreme obesity, who were able to achieve a drop in their BMI from 61 to 39 kg/m^2 equivalent to a decrease of 38% of their BMI.[87] Encouraging effects of bariatric surgery include reversal of T2DM, a discontinuation of most of diabetes medications,[88] improvements in glucose homeostasis in populations without diabetes,[89] and enhanced insulin sensitivity and secretion.[90]

The Teen-LABS study also reported that that 39% of enrolled patients had more than 4 major obesity-associated comorbidities at baseline. At the time of surgery 20 teens had T2DM and after 3 years of follow-up, 95% showed remission of T2DM, 76% remission of prediabetes (which had been noted in 13 of 17 patients), 74% showed normalization of blood pressure (noted in 56 of 76 with initial hypertension), and a 66% normalization of their lipid profiles (seen in 84 of 128 patients).[91]

Prevention of Obesity

Given the solid association between obesity and T2DM, many authors emphasize weight reduction or healthy weight maintenance throughout childhood and teenage years as the ultimate means of preventing T2DM. Table 3 summarizes the main recommendations to prevent obesity.[50] Overall, the development and execution of obesity prevention policies should 1) address factors contributing to obesity, 2) target obstacles to lifestyle change at personal, environmental and socioeconomic levels, and 3) actively include different levels of parties in government, schools and healthcare centers.

Conclusion

Prediabetes represents an important warning sign for risk of T2DM associated with childhood obesity—itself an ongoing complex health issue with risk for additional chronic illnesses. Given that the diagnostic criteria and management for prediabetes has been largely determined

Table 3 Summary of Obesity Prevention Strategies According to 2017 Pediatric Obesity Clinical Guidelines from the Endocrine Society

Recommendations for Obesity Prevention
Clinicians' promotion and participation in the ongoing education of healthy nutrition and physical activity of children and adolescents, parents, and communities Encourage schools to provide adequate education about healthy eating
Discuss healthy eating behaviors such as: a.Reduce as much as possible the intake of calorie-dense, nutrient-poor foods (eg, sugar-sweetened beverages, sports drinks, fruit drinks, most "fast foods" or those with added sugar, high-fructose corn syrup, high-fat or high-sodium processed foods, and calorie-dense snacks) b.Encourage whole fruits rather than fruit juices
Vigorous physical activity at least for 20 minutes, optimally for 60 minutes, with a minimum of 5 days per week
Try to reduce screen time, balancing unavoidable technology-related screen use with increased opportunities for physical activity
Clinicians' obesity prevention efforts should involve the entire family rather than just the individual patient.
Encourage participation in school-based programs and community commitment to prevent pediatric obesity.

Notes: Data from Styne DM, Arslanian SA, Connor EL, et al.[50]

based on adult data, there is a shortage of long-term data in pediatric populations.

Clinical trials exploring prediabetes treatment in children and adolescents thus far remain small, compared with those in adults, and provide only short-term outcomes. Pediatric populations so far have experienced only modest improvements in insulin sensitivity when receiving interventions such as intensive lifestyle modification, metformin or other insulin sensitizers, and weight loss medications, and it is likely that most of these results originate from weight loss or weight stabilizing benefits of these practices in the short term.[12] Even though there is no consensus, some providers are more inclined to start treatment with metformin on patients with persistent HbA1c of 6.0% to 6.4%, and/or those with impaired fasting glucose or glucose intolerance.

In addition to the need to further delineate the role of medication in addressing prediabetes, additional gaps in current knowledge include the best way to track improvement over time. Recent studies have discussed the further need of new markers of insulin resistance that do not rely on insulin pulsatility, like single-point insulin sensitivity estimator (SPISE) based on BMI, triglycerides and high-density lipoprotein (HDL) cholesterol.[92] A metabolic syndrome severity score accurately tracked reduction in the risk for future T2DM and CVD among adults in the Diabetes Prevention Program[93,94] and was linked to future risk for T2DM and CVD among adolescents.[95–98] Still additional studies are required to assess the validity of these surrogate markers during long-term treatment of adolescents with prediabetes. Another area for further investigation includes potential mechanisms behind the racial/ethnic disparities, to asses if specific target treatment could work better in certain racial/ethnic groups. Finally, early research has led to questions regarding whether altering the intestinal microbiome may be a future treatment for prediabetes or T2DM.[99]

Furthermore, still the only current universally-accepted management for prediabetes is intensive lifestyle modifications with a combination of increased physical activity, and healthy improved nutrition—an approach that usually requires a high amount of counselling and clinic support. Prevention of obesity in the first place needs to be a focus for all pediatric healthcare providers.

Disclosure

The authors report no conflicts of interest.

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