Prediabetes in children and adolescents: A ticking bomb!

Gupta A et al. Prediabetes in children

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Abstract
Prediabetes in children and adolescents is on the rise which has drawn significant attention over the past decade. It is an early warning sign of the underlying pathophysiological changes which in due course of time might compound into type II diabetes mellitus. The incidence of prediabetes in adolescents ranges from 4%-23% which is alarmingly high and requires active intervention from the system. We have discussed early identification of high-risk patients, prompt screening and active intervention to manage this growing problem.

Key Words: Prediabetes; Children; Adolescents; Glucose metabolism; Complications


Core Tip: Prediabetes is an early warning sign of an underlying pathophysiological change in glucose metabolism which in the due course of time might advance to type II diabetes mellitus. There has been a recent global upsurge in prediabetes in children and adolescents. Notwithstanding, there is still a dearth of sufficient literature regarding this very pertinent issue. Prediabetes status must be identified at the earliest to prevent further medical complications. American Diabetes Association and the International Society for Paediatric and Adolescent Diabetes recommend the screening of high-risk children for developing prediabetes. At present, the possible
ways of managing this crisis are the prevention of childhood obesity, early identification and screening of high-risk patients, and active intervention.
INTRODUCTION

Prediabetes in children and adolescents is on the rise which has drawn significant attention over the past decade. It is an early warning sign of the underlying pathophysiological changes which in due course of time might compound into type II diabetes mellitus (T2DM). The incidence of prediabetes in adolescents in the United States ranges from 4%-23% which is alarmingly high and requires active intervention from the system[1]. Studies have found that there is a likelihood that 8% of prediabetic adolescents will develop T2DM over the next three years[1]. Juvenile onset or the youth-onset T2DM has been found to have a more aggressive course with early organ system involvement[2]. Therefore, it becomes the need of the hour to have a proper understanding of the disease process with the goal aimed at prevention, early diagnosis and management of the disease.

In the present era, it becomes imperative to discuss the role of childhood obesity in outgrowing the number of prediabetics in this cohort. Obesity is a multifactorial disorder which directly or indirectly affects most organ systems. From 1980 till the next three decades, the number of obese patients has nearly doubled in 70 countries worldwide, of which the majority of the countries belong to developed nations[3,4]. As per the survey done in 2015, there are more than 107 million obese children worldwide which cannot be ignored in any healthcare system. Obesity has been linked with insulin-resistance which lays the fertile ground for dysglycaemia leading to prediabetes, diabetes and other cardiovascular sequelae[5]. National Health and Nutrition Examination Surveys (2005–2016) done in United States reported that the incidence of T2DM in adolescents aged 12 to 18 years is likely to quadruple by the year 2050[6]. A recent systematic review and meta-analysis pooled in the data from 48 studies and found that the overall prevalence of prediabetes in adolescents is 8.84%[6].

While we deliberate on prediabetics in children and adolescents, there is still a dearth of sufficient literature regarding this very pertinent global issue. This patient cohort is majorly diagnosed and managed primarily on the lines of the adult population[1]. The criteria for prediabetes (in children and adolescents) are the same as that for adults i.e. fasting blood glucose between 100-125 mg/dL or post-prandial (after 2 h of glucose) between 140-199 mg/dL or glycosylated haemoglobin between 5.7%-6.4%[7]. Based on
the American Diabetes Association (ADA), the prevalence of prediabetes in obese children ranges from 21%–40% which varies with race, sex and ethnicity. As there are various criteria for diagnosing prediabetes, the prevalence varies owing to differences in their sensitivity\textsuperscript{[8,9]}.

It is essential to understand the basic pathophysiology of prediabetes, not only to prevent future generations from this growing epidemic but also to help in the successful management of those who have been diagnosed with it. Prediabetes is diagnosed based on blood glucose levels and therefore it’s difficult to predict future outcome as T1DM or T2DM. The pathophysiology of prediabetes and T2DM is very similar which includes insulin resistance, impaired insulin secretion and damaged beta cells\textsuperscript{[10]}. Even puberty has been linked with insulin resistance which can be synergistically with factors leading to T2DM\textsuperscript{[11]}.

Before planning for any intervention against prediabetes, prediabetes status must be screened at the earliest to prevent further medical complications. In a survey of the adult population, it was found that active intervention in the form of lifestyle modification over a period of 4 years decreased the disease progression to T2DM from 33% to 20%\textsuperscript{[12,13]}. However, it is not practically feasible to screen all obese children for prediabetes and therefore ADA and the International Society for Paediatric and Adolescent Diabetes recommend the screening of children who are at high risk of developing prediabetes\textsuperscript{[14,15]}. These include children with a history of gestational diabetes to mother, those with a history of T2DM in 1\textsuperscript{st} or 2\textsuperscript{nd}-degree relatives, race and ethnic groups with high prevalence rates, and medical conditions which are known to be associated with insulin resistance (e.g. primary hypertension, dyslipidaemia etc.)\textsuperscript{[16]}.

Efficient and timed management of prediabetes plays a pivotal role in the prevention of T2DM. These include: (1) Lifestyle modification in the form of increased physical activity and dietary control play very crucial in successfully treating prediabetes\textsuperscript{[17,18]}. Physical activity has been found to have a role in increasing insulin sensitivity and the Endocrine Society Clinical Practice Guidelines recommend a minimum of 30 min of moderate to vigorous physical activity while aiming at 60 min per day\textsuperscript{[19]}. In a meta-analysis including 15 trials, it was found that physical activity
brought a 40% improvement in oral glucose tolerance test results while increasing insulin sensitivity[20]. In another study performed on children and adolescents (6-17 years), physical activity decreased adiponectin and waist circumference[21]. They also observed increased insulin sensitivity in the pubertal age group[21]. Regarding dietary intake, the American Academy of Pediatrics and World Health Organization (WHO) recommend increased intake of fruits and vegetables, decreased intake of saturated fat and avoiding sugar-containing beverages[22,23]. The role of roughage has been extensively studied wherein it has been shown to increase insulin sensitivity[24]. WHO advocates preventing obesity via individual and community-based programs[25]; (2) Metformin, an oral hypoglycaemic agent (OHA) acts by decreasing glucose absorption, preventing gluconeogenesis and increasing peripheral uptake of glucose[26]. It has been found to delay or stop the progression of prediabetes to T2DM. In a meta-analysis, it was observed that metformin resulted in decreased body mass index (-1.3 kg/m²) with one-fourth of trials showing an improved insulin sensitivity with the drug[27,28]. However, the Paediatric Obesity Clinical Guidelines from The Endocrine Society and ADA recommend the use of metformin in addition to lifestyle modification in high-risk patients[29]; (3) Glucagon-like peptide analogs are a class of OHA which act by increasing glucose-dependent insulin secretion while suppressing glucagon secretion and decreasing gastric emptying[30]. Liraglutide is approved for the treatment of obesity in children above 12 years of age. In 2019, the Food and Drug Administration approved its use for the treatment of T2DM in children above 10 years of age although it lacks sufficient data regarding its role in the management of prediabetes[31]; (4) Other drugs like sibutramine and orlistat have been shown to improve insulin sensitivity in children although their use in this patient cohort is still controversial. Also, there is some evidence to support the role of peroxisome-activated receptor gamma agonists in increasing insulin sensitivity in children[32]; and (5) Bariatric surgery helps in controlling obesity which is an important factor responsible for insulin resistance leading to prediabetes and T2DM. In the Teen-Longitudinal Assessment of Bariatric Surgery study, 20 adolescents had T2DM while 17 had prediabetes at the time of bariatric surgery. These patients were followed for a period
of 3 years. They showed a remission rate of 76% for prediabetes and 95% for T2DM respectively[33].

Despite the above-mentioned modalities of treatment, the focus should be on the timely diagnosis of the problem. Childhood obesity is a very important factor which aids in the development of prediabetes. Despite realising the problem, the data based on the paediatric population is very limited. The majority of the criteria and treatment protocols are based on the adult population. Although the aforementioned interventions have shown moderate improvement, there is still no generalised consensus on the line of management. Monitoring the improvement with these interventions requires the development of new biochemical markers such as a single-point insulin sensitivity estimator or new score systems such as metabolic syndrome severity score[34]. These tools should be developed and validated on the paediatric population to help in the medical management of this grave problem. Owing to different prevalence rates in different races and ethnicities, research is required concerning race/ethnicity-specific management protocol[35]. Also, the role of gut microbiome in future treatment of prediabetes or T2DM cannot be overlooked. Prevention of childhood obesity, early identification of high-risk patients, prompt screening and active intervention are the only ways of managing this growing problem.

CONCLUSION

To conclude, prevention of childhood obesity, early identification of high-risk patients, prompt screening and active intervention are the only ways of managing this growing problem.
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