Prediabetes and type 2 diabetes in youth: an emerging epidemic disease?

Anna M.G. Cali and Sonia Caprio

Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut, USA

Correspondence to Sonia Caprio, MD, Yale University School of Medicine, Department of Pediatrics, 330 Cedar St, P.O. Box 208064, New Haven, CT 06520, USA
E-mail: Sonia.caprio@yale.edu

Current Opinion in Endocrinology, Diabetes & Obesity 2008, 15:123–127

Purpose of review
The prevalence of obesity in youth is increasing alarmingly among children and adolescents in the United States. The problem falls disproportionately on African-American and Hispanic children. Many of the metabolic and cardiovascular complications associated with obesity are already present during childhood and are closely linked to the concomitant insulin resistance/hyperinsulinemia and degree of obesity. Moreover, these co-morbidities persist into adulthood.

Recent findings
The progression from normal glucose tolerance to type 2 diabetes mellitus involves an intermediate stage known as prediabetes or impaired glucose regulation. Prediabetes is characterized by peripheral insulin-resistance and impaired glucose sensitivity of first-phase insulin secretion. On the other hand, in overt type 2 diabetes mellitus β-cell failure becomes fully manifested. Progression from prediabetes to type 2 diabetes mellitus in youth is characterized by marked weight gain and further reduction in insulin secretion and insulin resistance.

Summary
Reverting obesity through lifestyle modification, that involves nutrition education, behavior modification and exercise, is an important step to prevent the progression to diabetes.

Keywords
diagnosis, pre-diabetes phenotypes, type 2 diabetes, weight management program

Curr Opin Endocrinol Diabetes Obes 15:123–127.

1752-296X

Introduction

Obesity is one of the most serious and urgent public health problems in both developed and developing countries [1]. It has reached epidemic proportions in the US. Since the late 1970s, the prevalence of overweight has doubled among children 6–11 years of age and tripled among those 12–17 years of age [2]. The problem falls disproportionately on African-American and Hispanic children [3].

Many of the metabolic and cardiovascular complications associated with obesity, namely impaired glucose regulation (IGR), type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, and systemic 'low grade' inflammation, are already present during childhood and are closely linked to the concomitant insulin resistance/hyperinsulinemia [4] and degree of obesity [5]. Moreover, these comorbidities persist into adulthood [6,7]. In the recent National Health and Nutrition Examination Survey III data on the prevalence of the metabolic syndrome – defined by the coexistence of central obesity, dyslipidemia, hypertension, and prediabetes – approximately 4% of all adolescents and nearly 30% of overweight children and adolescents (BMI > 95th percentile) had the metabolic syndrome [8]. One dire prediction from the US Centers for Disease Control and Prevention estimated that, if current obesity rates continue, one in three babies born in 2000 will eventually develop T2DM [9].

In the present review, we describe epidemiological and pathophysiological studies of T2DM in youth. Particular emphasis is given to the description of studies regarding the metabolic phenotypes of prediabetes and the effectiveness of lifestyle interventions to prevent the progression to T2DM.

Epidemiology of diabetes in youth

Before 1997, virtually all diabetes in young individuals was thought to be autoimmune type 1 diabetes mellitus (T1DM). Now there is widespread recognition that T2DM can occur in childhood [10•,11••].

Diabetes is the most prevalent disease of childhood after asthma; therefore, monitoring trends in childhood diabetes is a public health imperative [12]. Parallel to the increase in prevalence and incidence of diabetes in adults, there is also an increase of diabetes in youth. T1DM is proportionately

the most common form of diabetes mellitus worldwide in youth [13]. A significant global increase in T1DM incidence of about 3% per year in the last decade has been recorded, with the most rapid increase in the youngest age groups in European populations [13]. The increasing rate of childhood obesity worldwide, however, has been associated with the rising prevalence of T2DM. Several studies have reported an increasing proportion of youth with apparent T2DM, especially among a racial/ethnic minority population [14,15]. T2DM is already more common than T1DM in Japan and Taiwan and seems to account for 7–45% of all new diabetic patients in the USA, whereas in Europe, the reported prevalence among new diabetics is still low, on the order of 0.5–1% [16,17].

The SEARCH for Diabetes in Youth Study [18••] describes a snapshot of diabetes risk for US children and teenagers in 2002–2003. The risk of diabetes before age 20 years was determined to be 24.3% per 100 000 per year overall, with higher risk (>25 per 100 000 per year) for non-Hispanic white, non-Hispanic black, and American Indian youth compared with Hispanics and Asian ethnicities, whose risk was less than the 20 per 100 000 per year. Although the majority of cases (78%) were classified as T1DM, rates of apparent T2DM increased with age and were more frequent among non-Hispanic black, Asian, and American Indian individuals. Diagnosis of T2DM was not confined to minority youth, as 15% of non-Hispanic white youth aged 10–19 years was classified as having T2DM. Furthermore, a significant fraction of American Indian and Asian youth aged 10–19 years was diagnosed with T1DM (14% and 30% respectively). More interesting, when tested for autoimmunity 66% of T1DM and 22% of T2DM patients had evidence of positive GAD65 antibody, one third of T2DM pateints were using insulin, and only 22% of T1DM patients had no endogenous insulin production. These data suggest that a substantial fraction of young patients with diabetes appears to have a mixed etiology.

Diabetes mellitus takes a huge toll on individual patients in terms of healthcare complications, such as blindness, kidney failure, cardiovascular disease, and amputations, and also exacts a huge burden on society, in terms of consumption of healthcare resources [13]. Diabetes occurring early in life has even more devastating effects on the ability of young patients to live full lives and results in substantially increased healthcare costs related to treating a lifelong, complex disease. Among children diagnosed as having diabetes (either type 1 or type 2) at age 10 years, it has been projected that on average boys will lose 18.7 life-years and 31 quality of life years (QALYs) and girls will lose 19 life-years and 32.8 QALYs. The loss of life-years and QALYs will be higher in minority groups and highest for non-Hispanics black patients [9]. Moreover, children and adolescents with T2DM may experience the microvascular and macrovascular complications of this disease at younger age than individuals who develop diabetes in adulthood. In the US, 40% of children and adolescents with T2DM were observed to have microalbuminuria (MAU) after a diabetes duration of 18 months; among Pima Indians diagnosed with diabetes during childhood, 22% had MAU. Except for retinopathy, children have no protective or delaying factors that protect them from complications [19].

Diagnosis: not always an easy task

The appearance of diabetes in children and adolescents has exacerbated the existing issues in the classification of diabetes. In most patients, classification can be made reliably on the basis of clinical presentation and course. In the slender prepubertal child, one can confidently assume a diagnosis of T1DM. In the overweight adolescent, differentiating T1DM from T2DM may be difficult; measurement of islets autoantibodies may be useful in such patients [20]. Typically 85–98% of individuals with T1DM patients at presentation are positive to specific autoantibody to insulin, to glutamic acid decarboxylase (GAD), or the tyrosine phosphatase insulin antibody (IA-2 and IA-2β). Usually presence of overweight/obesity, family history of T2DM, acanthosis nigricans, polycystic ovary syndrome, lipid disorders and hypertension occur in children with T2DM. Currently children with T2DM are usually in middle to late puberty. Fasting insulin and C-peptide are usually normal or elevated in T2DM, although not as elevated as might be expected for the degree of hyperglycemia. As the childhood populations become increasingly overweight, T2DM may be expected to occur in younger prepubertal children. The SEARCH for Diabetes in Youth Study found that the autoantibody positivity may be present in individual with a undiagnosed form of monogenic diabetes mellitus, or other causes of insulin deficiency [18••]. With a clinical diagnosis of T2DM, and similar to other smaller US studies, 21.2% of the SEARCH study participants aged 10 years or older had positive GAD antibodies, the majority of whom were overweight, of minority racial/ethnic background (68% minority), and more than half had GAD titers less than two times the cut-point used to define positivity. Similar results were recently published in a European, predominantly Caucasian, cohort of children and adolescents. Children and adolescents with T2DM were older, more overweight, and predominantly female, and 36% had at least one positive β-cell autoantibody [21].

In conclusion serology cannot completely distinguish between the two main forms of diabetes.

Pathophysiology of prediabetes and type 2 diabetes melitus in youth

In adults, T2DM develops over a long period. Most, if not all, patients initially have impaired glucose tolerance (IGT), which is an intermediate stage in the natural history of T2DM [22] and is highly predictive of cardiovascular disease [23] as well as diabetes. With appropriate changes in lifestyle or pharmacologic interventions, progression from IGT to frank diabetes can be delayed or prevented [24,25]. Thus, great emphasis has recently been placed on the early detection of IGT in adults. Prior to our project, little was known about IGT in pediatrics.

Pre-diabetes phenotypes in youth: are they really different?

Studies from our group have reported the prevalence of IGT in a multiethnic clinic-based population of 55 obese children and 112 obese adolescents. Irrespective of ethnicity, IGT was detected in 25% of the obese children and 21% of the obese adolescents, and silent type 2 diabetes was identified in 4% of the obese adolescents [26]. In the most recent data from our multiethnic clinic-based cohort of 761 obese nondiabetic youth, the prevalence of impaired fasting glucose (IFG) is 10%, whereas for IGT it is 15% (personal data). Of note, only a small number of subjects meet both criteria, showing that these categories overlap only to a very limited extent in children, as already reported in adults [27•]. This would suggest that different abnormalities characterize these different phenotypes.

Does obesity really matter?

The rapid tempo at whichT2DM develops in obese children raises a question regarding the potential impact of obesity *per se* in the underlying pathophysiology of the disease. Obesity is the major cause of peripheral insulin resistance in childhood and is tightly related to the development of altered glucose metabolism.

Potential candidates that can link obesity and altered glucose metabolism include elevated free fatty acid, fat-derived inflammatory cytokines, and low adiponectin levels, which might all mediate accelerated β-cell failure.

In a previous longitudinal study, we followed 102 obese children and adolescents from a pediatric weight management clinic (71 with normal and 31 with impaired glucose tolerance) by repeating the oral glucose tolerance testing after 18–24 months [28]. Six of the subjects with normal glucose tolerance became impaired. Ten subjects (32.3%) with IGT developed type 2 diabetes, 10 (32.3%) converted to normal glucose tolerance and 11 remained impaired (36.4%). Transition from normal to impaired glucose tolerance and from impaired glucose tolerance to diabetes was associated with significant increases in weight, whilst conversion from impaired to normal glucose tolerance was associated with the least amount of weight gain. We concluded that an increased degree of obesity and continuous weight gain will have an independent effect on levels of glycemia, independent of changes in insulin sensitivity or β-cell demand [29]. Our data also illustrate the importance of variations in weight gain on changes in glucose tolerance in childhood obesity. Most of the children grew in height and gained weight on a track consistent with their prior growth patterns resulting in stable BMI z-scores or relative adiposity. The children who progressed from normal glucose tolerance (NGT) to IGT, however, had the largest increase in body weight and an increase in relative adiposity. Even more exciting is the observation that IGT subjects who converted back to NGT had minimal increases in body weight and a reduction in BMI z-score [28].

Beta-cell function: early defect in prediabetes status?

Diabetes results from the combination of insulin resistance and impaired β-cell function. The mechanisms by which obesity relates to diabetes risk are not clear. The majority of, if not all, children and adolescents with T2DM or IGT have a significant degree of insulin resistance, which may be caused by obesity, sedentary lifestyle, ethnicity, pubertal stage of development, and family history of diabetes. Early in the pathogenesis of glucose intolerance, insulin-producing β-cells are able to compensate for the insulin resistance by increasing insulin secretion. This compensatory hyperinsulinemia maintains glucose homeostasis in the face of insulin resistance. The failure in pancreatic β-cells, resulting in insufficient insulin secretion, underlies the transition from insulin resistance to prediabetes and clinical diabetes.

Loss or reduced first phase insulin secretion is one of the most sensitive indicators of a decline in β-cell function. Earlier studies from our group showed that the IGT phenotype in obese adolescents is a prediabetic state with marked peripheral insulin resistance [30] and impaired first phase secretion [31]. More recently we published a cross-sectional analysis of β-cell function and tissue insulin sensitivity in a multiethnic cohort of obese adolescents with a wide range of disturbance in glucose metabolism, using state-of-art techniques. We compared the sensitivity of the β-cell to glucose between subjects with NGT, IFG, IGT or combined IFG/IGT [32]. Interestingly IFG, in obese adolescents, is linked primarily to alterations in glucose sensitivity of first phase insulin secretion and liver insulin sensitivity. The IGT group is affected by a more severe degree of peripheral insulin resistance and reduction in glucose sensitivity of first phase insulin secretion. IFG/IGT is hallmarked by a profound insulin resistance and by a new additional defect in glucose sensitivity of seconnd phase insulin secretion. This defect was previously described by us to be present only in childhood T2DM [31]. In that

study, however, our comparator of prediabetic state was formed from children with isolated IGT, not by children with IFG/IGT. Hence, one wonders whether IFG/IGT should not be considered just as diabetes, but the answer to this question can be found only in longitudinal studies.

Can weight management programs prevent the progression to type 2 diabetes mellitus in youth?

Impaired glucose tolerance has been demonstrated to be reversible in adults who undertook significant lifestyle modifications resulting in a reduction in body weight. While lifestyle programs can have positive clinical outcomes in adults [24], few studies have reported successful interventions in children and adolescents. Our data suggest that, even in the absence of frank weight loss, IGT may be able to be reversed in obese children by lifestyle interventions that are successful in maintaining a stable body weight during a period of active growth [28]. Treatment modalities for children present a unique challenge as nutrition education, physical activity, and behavior modification must be presented to both the parent or caregiver and child, with the parent or caregiver being the major agent change in the family [33,34]. (Comprehensive family-based programs that have reported positive long-term outcomes had limited participation by minority youth.) The Yale Bright Bodies Weight Management is a family-based, intensive lifestyle intervention that has been specially tailored for the needs of the inner-city minority children. In a nonrandomized pilot study, we showed that this intervention could achieve a sustained decrease in BMI for 2 years [35]. In particular, adolescents who were educated about better food choices of moderate portion sizes were more successful long-term than teenagers who were given a structured meal plan. In a more recent randomized clinical trial [36••], we further evaluated the efficacy of the weight management program in comparison to routine care provided by our pediatric obesity clinic. When viewed in isolation, the impact of the Bright Bodies program on body weight, BMI, and body composition was highly favorable: essentially no weight gain over 12 months, a 4% reduction in body fat, and a modest fall in BMI. When viewed in comparison with the increases in all these parameters in the control group, the benefits of the program are even more impressive. Improvements from the Bright Bodies program achieved during the first 6 months of intensive follow-up were sustained during the second 6-month maintenance phase and the gap between the two groups widened due to continued excessive weight gain in the control group. Moreover the benefits of the Bright Bodies program extended beyond changes in anthropometrics. As a surrogate of insulin resistance, we also measured changes in the homeostasis model assessment of insulin resistance (HOMA-IR) in the two groups. In agreement with changes in anthropometric parameters, HOMA-IR increased in the control group and decreased in the Bright Bodies group, so that differences in changes in HOMA-IR at 6 and 12 months were substantial. We have shown that a family-based program that uses nutrition education, behavior modification, and supervised exercise can lower BMI, improve body composition, and increase insulin sensitivity. The success of the Bright Bodies program undoubtedly relates, in part, to the frequent contacts between families and the professional staff. Future work for our group includes cost–benefit analyses.

Conclusion

The epidemic of pediatric obesity and T2DM is having a huge impact on the physical and social well being of today's children and adolescents, in particular among racial/ethnic minority populations. The progression from NGT to T2DM involves an intermediate stage known as impaired glucose tolerance. These young patients are characteristically obese, with severe insulin resistance and impaired first phase insulin secretion. Progression from IGT to T2DM in youth is characterized by marked weight gain and further reduction in insulin secretion and insulin resistance. Reverting obesity through lifestyle modification, that involves nutrition education, behavior modification and exercise, is an important step to prevent the progression to diabetes.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 196–197).

1 Strauss RS, Pollack HA. Epidemic increase in childhood overweight, 1986–1998. JAMA 2001; 286:2845–2848.

2 Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. JAMA 2002; 288:1723–1727.

3 Hedley AA, Ogden CL, Flegal KM, *et al.* Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. JAMA 2004; 291: 2847–2850.

4 Kaufman FR. Type 2 diabetes in children and youth. Endocrinol Metab Clin North Am 2005; 34:659–676.

5 Weiss R, Dziura J, Burgert TS, *et al.* Obesity and the metabolic syndrome in children and adolescents. N Engl J Med 2004; 350:2362–2374.

6 Dietz WH. Health consequences of obesity in youth: childhood predictors of adult disease. Pediatrics 1998; 101 (3 Pt 2):518–525.

7 Berenson GS, Srinivasan SR, Bao W, *et al.* Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med 1998; 338:1650–1656.

8 Cook S, Weitzman M, Auinger P, *et al.* Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988–1994. Arch Pediatr Adolesc Med 2003; 157:821–827.

9 Narayan KM, Boyle JP, Thompson TJ, *et al.* Lifetime risk for diabetes mellitus in the United States. JAMA 2003; 290:1884–1890.

10 • Lipscombe LL, Hux JE. Trends in diabetes prevalence, incidence, and mortality in Ontario, Canada 1995-2005: a population-based study. Lancet 2007; 369:750–756.

A population-based study showed a steady increase in the prevalence of diabetes in a non-US population.

11 Haines L, Wan KC, Lynn R, *et al.* Rising incidence of type 2 diabetes in •• children in the U.K. Diabetes Care 2007; 30:1097–1101.
An interesting report from the UK shows a similar pattern of increased obesity and T2DM also in the European population.

12 Lipton RB. Incidence of diabetes in children and youth–tracking a moving target. JAMA 2007; 297:2760–2762.

13 DIAMOND Project Group (2006) Incidence and trends of childhood type 1 diabetes worldwide 1990–1999. Diabet Med 2006; 23: 857–866.

14 Dabelea D, Pettitt DJ, Jones KL, Arslanian SA. Type 2 diabetes mellitus in minority children and adolescents. An emerging problem. Endocrinol Metab Clin North Am 1999; 28:709–729.

15 Pinhas-Hamiel O, Dolan LM, Zeitler P, *et al.* Increased incidence of noninsulin-dependent diabetes mellitus among adolescents. J Pediatr 1996; 128 (5 Pt 1): 608–615.

16 Gungor N, Hannon T, Libman I, *et al.* Type 2 diabetes mellitus in youth: the complete picture to date. Pediatr Clin North Am 2005; 52:1579–1609.

17 Singh R, Shaw J, Zimmet P. Epidemiology of childhood type 2 diabetes in the developing world. Pediatr Diabetes 2004; 5:154–168; Review.

18 Dabelea D, Bell RA, D'Agostino RB Jr, *et al.* Writing Group for the SEARCH •• for Diabetes in Youth Study Group. Incidence of diabetes in youth in the United States. [Erratum in JAMA 2007 Aug 8;298(6):627.] JAMA 2007; 297:2716–2724.
This describes the most up-to-date study showing an increased incidence of epidemic proportion of diabetes, particularly in the US population.

19 Pavkov ME, Bennett PH, Nelson RG, *et al.* Effect of youth-onset type 2 diabetes mellitus on incidence of end-stage renal disease and mortality in young and middle-aged Pima Indians. JAMA 2006; 296:421–426.

20 Silverstein J, Klingensmith G, Copeland K, *et al.* Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. Diabetes Care 2005; 28:186–212.

21 Reinehr T, Schober E, Wiegand S, *et al.,* DPV-Wiss Study Group. Beta-cell autoantibodies in children with type 2 diabetes mellitus: subgroup or misclassification? Arch Dis Child 2006; 91:473–477.

22 Polonsky KS, Sturis J, Bell GI. Seminars in Medicine of the Beth Israel Hospital, Boston. Noninsulin-dependent diabetes mellitus: a genetically programmed failure of the beta cell to compensate for insulin resistance. N Engl J Med 1996; 334:777–783.

23 Edelstein SL, Knowler WC, Collins VR, *et al.* Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. Diabetes 1997; 46:701–710.

24 Knowler WC, Barrett-Connor E, Walker EA, *et al.* Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346:393–403.

25 Tuomilehto J, Salminen V, Uusitupa M, *et al.,* Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001; 344:1343–1350.

26 Sinha R, Fisch G, Teague B, *et al.* Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. N Engl J Med 2002; 346:802–810.

27 Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of beta-cell • dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. Diabetes Care 2006; 29:1130–1139.
This is an interesting review on the possible different mechanisms underlying the different prediabetic phenotypes in adults.

28 Weiss R, Taksali SE, Tamborlane WV, *et al.* Predictors of changes in glucose tolerance status in obese youth. Diabetes Care 2005; 28:902–909.

29 Caprio S, Hyman LD, Limb C, *et al.* Central adiposity and its metabolic correlates in obese adolescent girls. Am J Physiol Endocrinol Metab 1995; 269 (1 Pt 1):E118–E126.

30 Weiss R, Dufour S, Shulman GI, Caprio S, *et al.* Prediabetes in obese youth: a syndrome of impaired glucose tolerance, severe insulin resistance, and altered myocellular and abdominal fat partitioning. Lancet 2003; 362: 951–957.

31 Weiss R, Caprio S, Trombetta M, *et al.* Beta-cell function across the spectrum of glucose tolerance in obese youth. Diabetes 2005; 54:1735–1743.

32 Cali AMG, Bonadonna RC, Trombetta M, *et al.* Metabolic abnormalities underlying different prediabetes phenotypes in obese adolescent. (in press).

33 Epstein LH, McCurley J, Wing RR, Valoski A. Five-year follow-up of family-based behavioral treatments for childhood obesity. J Consult Clin Psychol 1990; 58:661–664.

34 Wrotniak BH, Epstein LH, Paluch RA, Roemmich JN. The relationship between parent and child self-reported adherence and weight loss. Obes Res 2005; 13:1089–1096.

35 Savoye M, Berry D, Dziura J, *et al.* Anthropometric and psychosocial changes in obese adolescents enrolled in a Weight Management Program. J Am Diet Assoc 2005; 105:364–370.

36 Savoye M, Shaw M, Dziura J, Caprio S, *et al.* Effects of a weight management •• program on body composition and metabolic parameters in overweight children: a randomized controlled trial. JAMA 2007; 297:2697–2704.
A randomized-controlled trial highlighted the importance of a family-based weight management program along with lifestyle changes in the prevention of prediabetes and T2DM in obese children and adolescent.