Type 2 Diabetes in Youth: Epidemiology and Pathophysiology

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The prevalence of type 2 diabetes is significantly increased in the pediatric population, which is affected by obesity worldwide. The progression from normal glucose tolerance (NGT) to type 2 diabetes involves intermediate stages of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), also known as prediabetes. The pathophysiology underlying the development of these glucose metabolic alterations is multifactorial; however an alteration in the balance between insulin sensitivity and insulin secretion represents the most important player in the development of type 2 diabetes. Obese children and adolescents affected by IGT and type 2 diabetes are characterized by severe insulin resistance, which is associated with an increased lipid accumulation in visceral compartments, liver and muscle tissues and by reduced sensitivity of β-cell of first and second-phase insulin secretion.

The progression in obese children of insulin resistance to type 2 diabetes has been shown to be faster than in adults; in addition, type 2 diabetes is already associated with several metabolic and cardiovascular complications in this age group.

In the present review, we summarize the most recent findings concerning the prevalence of type 2 diabetes in youth and in particular we explore the pathophysiology of type 2 diabetes and the natural history of this pathology in obese children and adolescents.

Concurrent with the worldwide epidemic increase of childhood obesity, type 2 diabetes and the two prediabetic conditions, IFG and IGT, are becoming increasingly more common in obese children and adolescents (1,2). Until 10 years ago, type 2 diabetes accounted for less than 3% of all cases of new-onset diabetes in adolescents. At present 45% of cases are attributed to it (3,4).

Type 2 diabetes occurs in youth more often during the second decade of life, coinciding with the physiological occurrence of pubertal insulin resistance (1). In addition, most children who develop type 2 diabetes (>75% of cases) have a first- or second-degree relative affected by this pathology (1).

The pathogenesis of type 2 diabetes is complex, involving the interaction of genetic and environmental risk factors that strongly contribute to the development of insulin resistance in the muscle and liver as well as to β-cell failure, the two core pathophysiological defects in type 2 diabetes (5).

Early onset of type 2 diabetes seems to be associated with an increased risk of morbidity and mortality during the most productive years of life (4). Microvascular complications can be present at time of diagnosis with a progression rate that might be higher than in young people with type 1 diabetes (4). In addition, youths with type 2 diabetes are also prone to secondary obesity-related complications, including hypertension, nonalcoholic fatty liver disease, and metabolic syndrome, all of which are associated with increased cardiovascular risk (4).

Just as in adults, the pattern of development is often preceded by an intermediate state of impaired glucose tolerance (IGT) (6). This transitional state of IGT in adults is associated with a high incidence (~10%) of vascular complications (5) and importantly, a large number of studies have found that either lifestyle or pharmacological interventions may reverse it and thus prevent the development of diabetes (7).

Therefore, understanding the pathophysiology and the natural history of type 2 diabetes in youth is important in order to prevent its development and its related comorbidities in the pediatric population.

In the present review, we first describe the epidemiology of type 2 diabetes and prediabetic conditions and, in particular, we explore the current knowledge regarding the pathophysiology and the natural history of the glucose homeostasis alterations in youth.

EPIDEMIOLOGY—In the last two decades, type 2 diabetes, once thought to be a metabolic disorder exclusively of adulthood, has become increasingly more frequent in obese adolescents (3).

Although a very high prevalence of type 2 diabetes has been observed in non-Caucasian groups (African Americans, Native Americans, Hispanics), type 2 diabetes occurs in all races (1,8). In the SEARCH study (8), the incidence rate (per 100,000 person-year) of type 2 diabetes among children and adolescents varies greatly by ethnicity, with the highest rates observed among youths aged 15–19 years in minority populations. In particular, the reported incidence rate was 49.4 for Native Americans, 22.7 for Asian/Pacific Islanders, 19.4 for African Americans, 17 for Hispanics, and 5.6 for non-Hispanic whites.

Type 2 diabetes in youth is not just an American phenomenon—more cases are being reported worldwide. For example, in Japan (3) 80% of all new cases of diabetes in children and adolescents were diagnosed as type 2 diabetes. Likewise, in Taiwan (3) 54.2% of new cases were diagnosed with type 2 diabetes, with an incidence of 6.5 per 100,000. In contrast, in the U.K. the minimum incidence of type 2 diabetes in children (<17 years of

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age) was $0.53 \cdot 100{,}000^{-1} \cdot \text{year}^{-1}$ (9). In Austria, the calculated incidence of type 2 diabetes in children and adolescents (<15 years of age) was 0.25/100,000 (3). Indeed, many studies from Europe (8) indicate that type 2 diabetes is not as common as in the U.S. in these populations, accounting for only 1–2% of all diabetes mellitus cases.

In addition, although some studies (8) support the notion that type 2 diabetes has a greater prevalence in the high risk ethnic groups, type 2 diabetes accounts for 14.9% of all diabetes cases among non-Hispanic white adolescents (8). Although the lowest prevalence of type 2 diabetes, observed in Europe, could be attributed to the differences in obesity rates between U.S. and European youth, the full explanation for these discrepancies remains unclear (8).

The increased prevalence of type 2 diabetes in the obese pediatric population is paralleled by an increased prevalence of the prediabetes conditions. In particular, 25% of children and 21% adolescents with severe degree of obesity, irrespective of ethnicity, were found to have IGT (10). Similar high prevalence rates in Hispanic obese children and adolescents were subsequently reported by Goran et al. (11). Surprisingly, very high prevalence rates of IFG were reported in children from the Studies to Treat or Prevent Pediatric Type 2 Diabetes (2).

Although previous studies showed a lower prevalence of type 2 diabetes and IGT in Italian youths (0.5% and 5%, respectively) (12), a recent study conducted in Italy (13) on a large sample of overweight/obese children and adolescents reported a prevalence of glucose metabolism alterations of 12.4%. IGT was the most frequent alteration, accounting for 11.2%, with a higher prevalence in adolescents (14.8%) than in children (4.1%) (13).

PATHOPHYSIOLOGY OF TYPE 2 DIABETES

—The development of alterations in glucose metabolism results from the gradual fall in β-cell function occurring within a background of insulin resistance. The two principal components of the blood glucose regulation pathway (5) are insulin secretion and insulin sensitivity (5).

β-Cell function

Type 2 diabetes is progressive, and one main factor responsible for this is a continued decline in β-cell function (5). Several studies (5) have demonstrated that diabetes and prediabetes do not develop until the β-cell fails to compensate appropriately to the peripheral insulin resistance state. The ability of the β-cell to secrete sufficient insulin to adequately respond to the peripheral insulin resistance state depends on multiple factors, including β-cell mass (14) and secretory capacity (14), which are influenced by genetic (15) and environmental factors (15). In fact, although the progressive loss of β-cell function could be due to different metabolic derangements (insulin resistance, lipotoxicity), several studies have suggested that β-cell dysfunction depends also on a pre-existing and perhaps genetically determined risk, which is crucial for β-cell dysfunction to occur (5,15).

Cross-sectional studies. Using state-of-the-art hyperglycemic clamp in conjunction with mathematical modeling of insulin secretion, we found that obese adolescents with type 2 diabetes have a marked reduction in both first- and second-phase insulin secretion. Thus at diagnosis, just as in the adults (5), ~80% of their β-cell function is reduced or lost (16).

Furthermore, in order to assess whether the defects in β-cell function characterize all of the various prediabetic conditions seen in obese adolescents, in a cross-sectional analyses (17) we compared the β-cell function and tissue insulin sensitivity among subjects with NGT, IFG, IGT, or combined IFG/IGT. The IFG group showed an alteration in glucose sensitivity of first-phase insulin secretion (Fig. 1), while peripheral insulin sensitivity was similar between the IFG and the NGT groups. The IGT group was affected by reduction in glucose sensitivity of first-phase insulin secretion (Fig. 1) and by a more severe degree of peripheral insulin resistance. Interestingly, the IFG/IGT group was characterized by a new additional defect in glucose sensitivity of second-phase insulin secretion (Fig. 1) and by a profound insulin resistance (17).

The relationship between insulin sensitivity and secretion is described by a hyperbolic function, which implies that a feedback loop governs the interaction between the β-cells and the peripheral

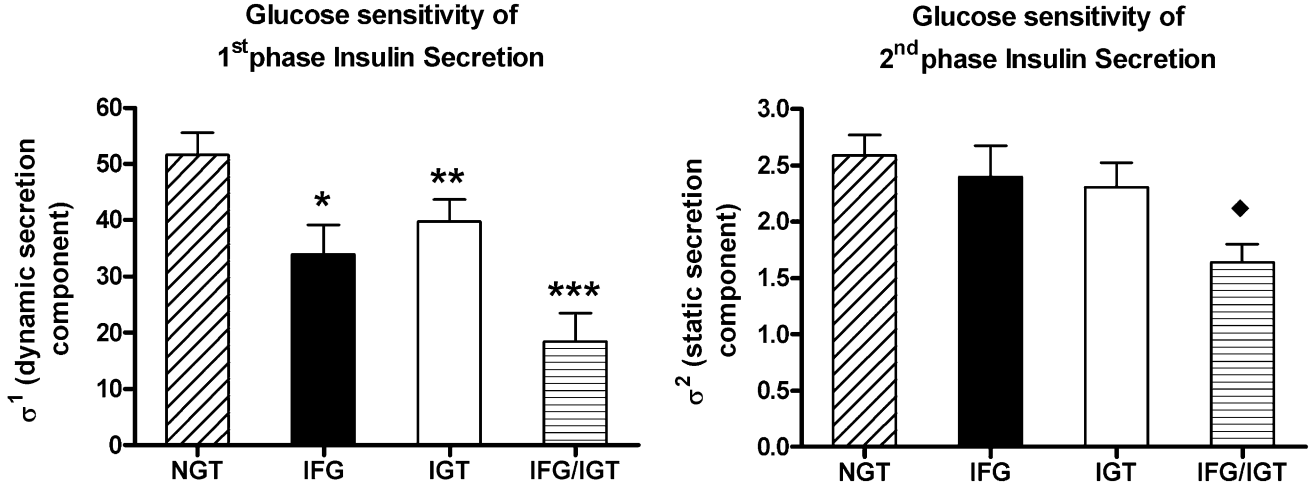

Figure 1—*Glucose sensitivity of first-phase (σ^1, dynamic secretion component) and second-phase (σ^2, static secretion component) insulin secretion among NGT, IFG, IGT, and IFG/IGT obese adolescents.* (*P = *0.004 IFG vs. NGT;* **P = *0.04 IGT vs. NGT;* ***P = *0.0001 IFG/IGT vs. NGT;* ◆P = *0.02 IGT vs. NGT).*

tissue (18). Thus, when insulin sensitivity decreases, insulin secretion increases for glucose tolerance to remain normal. This equilibrium is quantitatively described by the "disposition index" (DI), which is the product of insulin sensitivity and β-cell function and therefore can be considered an index of β-cell function weighted by insulin sensitivity (18). Studies conducted in adult populations (19) have demonstrated that the DI is not only a measure for identifying subjects with poor β-cell function but also a strong predictor for the development of type 2 diabetes. In fact, as we will further discuss, we have previously demonstrated in a longitudinal study (20) that obese children who progress to IGT manifest lower DI values than those who do not experience a worsening of glucose tolerance.

Longitudinal studies. In order to assess the evolution of the β-cell, we followed longitudinally a group of obese adolescents with NGT and repeated the serial oral glucose tolerance test over a period of ~3 years (20). Of note, we found that those adolescents who progressed to IGT had a lower β-cell function at baseline than those nonprogressors (Fig. 2*A*), as indicated by the glucose β-cell responsitivity (Φ_d), measured by the oral minimal model (21). Furthermore, the development of IGT was characterized by progressive decline in the DI (Fig. 2*B*). Thus, those who progressed to IGT had relatively worse β-cell function at baseline, suggesting that an early defect in β-cell function may underlie the development of IGT and possibly type 2 diabetes in obese youth (20).

These data suggest the presence of a preexisting β-cell dysfunction risk in obese adolescents with NGT. Early identification of markers of β-cell dysfunction in obese adolescents with NGT might be critical for the prevention of diabetes in youth.

Insulin resistance

Although the pathophysiological mechanism of type 2 diabetes is not completely understood, it is clear that insulin resistance plays an important role in its development. Evidence of this comes from cross-sectional and longitudinal studies demonstrating that insulin resistance occurs 10–20 years before the onset of the disease and that it is the best predictor of whether or not an individual will later become diabetic (22).

In addition, insulin resistance, by placing an increased demand on the β-cell to hypersecrete insulin, influences the progressive β-cell failure of type 2 diabetes (5). The precise mechanism(s) by which insulin resistance leads to β-cell failure remain(s) unknown, however a possible hypothesis is that the cause of insulin resistance is also directly responsible for the β-cell failure (i.e., lipotoxicity) (5,14).

Obesity is the most important cause in the development of insulin resistance and it has been demonstrated that the critical determinant of insulin sensitivity is not the degree of obesity per se but the distribution of fat partitioning (6). In a previous study by our group (6), we have demonstrated that obese adolescents with IGT were more insulin resistant than those with NGT despite the similar degree of adiposity. The phenotype of subjects with IGT was characterized by increased intramyocellular lipid content (IMCL) and by increased visceral and decreased subcutaneous fat deposition. Indeed, IMCL and visceral lipid were positively related to the 2-h plasma glucose and inversely related to the glucose disposal and nonoxidative glucose metabolism (6).

The role of IMCL in modulating insulin sensitivity has been well established in both adults (23) and children (6,24). Petersen et al. (23) showed an increase of IMCL in offspring of patients with type 2 diabetes and an inverse correlation between insulin resistance and IMCL. In a previous studies by our group (6,24) we observed an association between IMCL and insulin resistance in children with prediabetes (6) and a strong inverse correlation between IMCL and adiponectin (24) in obese children and adolescents.

In addition to an increase in IMCL, there is ample evidence indicating that visceral fat accumulation is associated with an impaired insulin action in the obese pediatric population. Although controversy remains regarding the contribution of visceral and subcutaneous fat to the development of insulin resistance

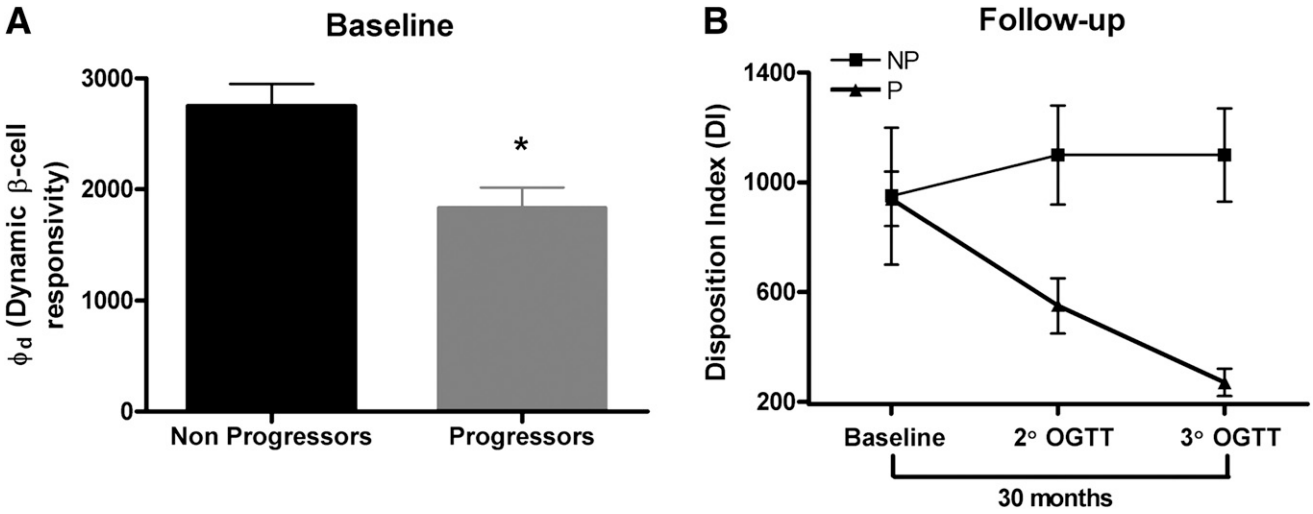

Figure 2—A: *Baseline values of the dynamic β-cell responsivity (Φ_d) in subjects who maintained NGT (nonprogressors [NP]) and in subjects who developed IGT (progressors [P])* (P = *0.04*). B: *Changes of the DI values according to changes in glucose tolerance over the course of approximately 30 months. Subjects who developed IGT (progressors) experienced a progressive decline of overall β-cell function, as assessed by the DI. OGTT, oral glucose tolerance test.* **P = 0.04.*

(25), a previous study by Cruz et al. (26) showed a direct impact of visceral fat accumulation on insulin sensitivity and secretion, independent of total body adiposity, in obese children with a family history of type 2 diabetes. Indeed, by stratifying a multiethnic cohort of obese adolescents into tertiles based on the proportion of visceral fat in the abdomen (visceral/subcutaneous fat ratio), we observed a significant increase in 2-h glucose and insulin resistance (homeostasis model assessment) and decrease in insulin sensitivity (Matsuda index) in obese adolescents with high proportion of visceral fat and relatively low abdominal subcutaneous fat (25).

These findings suggest that adolescents at risk for developing alterations in glucose metabolism are not necessarily the most severely obese, but are characterized by an unfavorable lipid partitioning profile.

Despite the demonstrated relationship between IMCL, visceral fat, and metabolic dysfunction, the ectopic fat deposition in the liver is emerging as the most important marker of insulin resistance and glucose dysregulation in adults (27) as well as in obese pediatric population (28).

Although it remains unclear whether hepatic steatosis is a consequence or a cause of derangements in insulin sensitivity, the presence of steatosis is an important marker of multiorgan insulin resistance (29); moreover, insulin resistance is directly related to percent liver fat (29).

Previously, we reported that rising alanine transaminase levels in obese children and adolescents were associated with deterioration in insulin sensitivity and glucose tolerance (30). Furthermore, abnormal alanine transaminase levels were found in children with type 2 diabetes (31).

In order to understand the potential role of fatty liver in the onset of type 2 diabetes in obese youth, we have recently assessed whether the severity of hepatic steatosis affects the presence of glucose metabolism dysregulation in a multiethnic cohort of obese adolescents (28). Independent of obesity, the severity of fatty liver was associated with the presence of prediabetes conditions (IGT and IFG/IGT) and hepatic steatosis, independently, predicted prediabetes in obese adolescents. In addition, paralleling the severity of hepatic steatosis, there was a significant decrease in insulin sensitivity and impairment of β-cell function (assessed by using the DI) (Fig. 3) (28).

These findings suggest that the intrahepatic fat accumulation is a strong risk factor for type 2 diabetes, and its early identification is critical to prevent the development of metabolic complications in youth.

NATURAL HISTORY OF TYPE 2 DIABETES—The transition from prediabetes to type 2 diabetes in adults is usually a gradual phenomenon that occurs over 5–10 years (32). Therefore, the early presentation of type 2 diabetes in youth raises the possibility of an accelerated process in pediatric age compared with adults, thus shortening the transition time between IGT and type 2 diabetes. In fact, an interesting report by Gungor and Arslanian (33) suggested that despite a relatively robust initial insulin secretion, the deterioration in β-cell function in youth with type 2 diabetes is more accelerated (~15% per year) than that observed in adults.

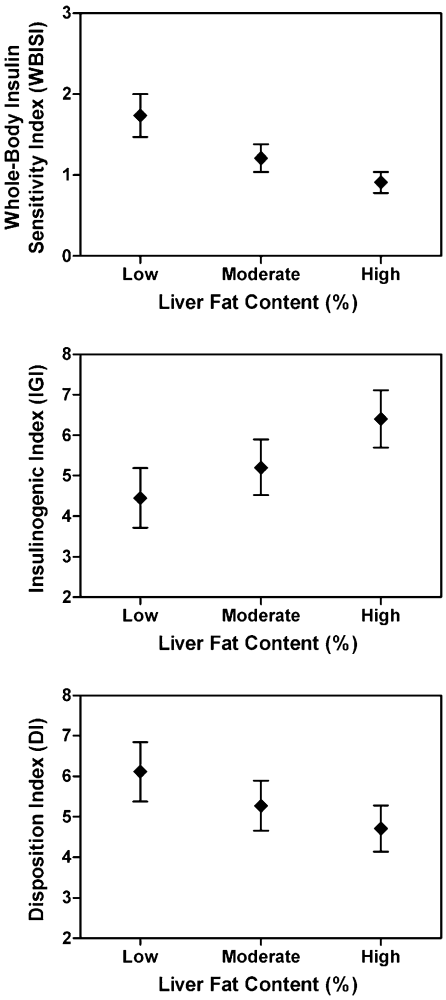

Figure 3—*Liver fat content and impairment of insulin sensitivity and β-cell function in obese children and adolescents. The whole-body insulin sensitivity index (WBISI) decreased* (P = *0.007) across low (median 0.7%), moderate (median 4.5%), and high (median 28.8%) liver fat content (%) tertiles. The insulinogenic index (IGI) tended to be higher* (P = *0.05) and the DI tended to be lower* (P = *0.05) in the high tertile compared with the low tertile.*

To study the natural history of IGT in youth, we have longitudinally followed 117 obese children and adolescents (84 with NGT and 33 with IGT) (32). Those with IGT displayed a mixed picture: 45.5% converted to NGT, 30.3% remained IGT, and 8% progressed to diabetes. It should be noted that the tempo of progression was remarkably fast—only 21 months. The factors associated with the transition of glucose category were marked weight gain, profound insulin resistance at baseline, and reduced first-phase insulin secretion at baseline (32). These data illustrate the importance of variations in weight gain on changes in glucose tolerance in childhood obesity. The children who progressed from NGT to IGT had the largest increase in body weight, and the IGT subjects who converted back to NGT had minimal increases in body weight and a reduction in BMI *Z*-score (32), which underlines that cessation of weight gain, and not necessarily weight loss, may suffice to prevent further deterioration in the glucose tolerance.

The observed rapid progression of the glucose homeostasis alterations in pediatric age underlines the importance of focusing the attention on the earliest stages of the disease before the onset of any alterations in glucose tolerance. In addition, the rapid tempo of the development of type 2 diabetes, which is driven by the rapid failure of β-cell function, would suggest a rather more aggressive course in the development of the disease than what is usually seen in adulthood. This would suggest that early intervention, even before the prediabetic conditions are established, should be implemented to prevent further decline in β-cell function.

CONCLUSIONS—The growing number of obese children and adolescents affected by type 2 diabetes and the rapid development of glucose homeostasis dysregulation in this age group explain why type 2 diabetes is becoming one of the most important public health problems.

Therefore, identifying obese children at risk for type 2 diabetes is of primary importance in order to interrupt its progression and the diabetes-related cardiovascular complications in this age group.

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