Published in final edited form as:

Curr Opin Endocrinol Diabetes Obes. 2012 August ; 19(4): 255–262. doi:10.1097/MED.0b013e3283557cd5.

Insulin resistance in type 2 diabetic youth

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Abstract

Purpose of review—This review focuses on recent literature on insulin resistance in youth with type 2 diabetes mellitus (T2DM). Insulin resistance is associated with a variety of cardiometabolic problems leading to increased morbidity and mortality across the lifespan.

Recent findings—Functional pancreatic β -cell changes play a role in the transition from obesity to impaired glucose tolerance (IGT). Insulin resistance drives islet cell upregulation, manifested by elevated glucagon and c-peptide levels, early in the transition to IGT. Surrogate measurements of insulin resistance and insulin secretion exist but their accuracy compared to clamp data is imperfect. Recent large longitudinal studies provide detailed information on the progression from normoglycemia to T2DM and on the phenotype of T2DM youth. Defining prediabetes and T2DM remains a challenge in youth. Lifestyle interventions do not appear as effective in children as in adults. Metformin remains the only oral hypoglycemic agent approved for T2DM in youth.

Summary—New insights exist regarding the conversion from insulin resistance to T2DM, measurement of insulin resistance and phenotypes of insulin resistance youth, but more information is needed. Surrogate measurements of insulin resistance, additional treatment options for insulin resistance and individualization of treatment options for T2DM adolescents in particular require further investigation.

Keywords

impaired glucose tolerance; insulin resistance; pediatric; type 2 diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2DM), once exclusive to adults, is now increasingly common in pediatrics, associated with recent increases in childhood obesity [1–3]. T2DM is caused by insulin resistance, a subnormal response to insulin-mediated cellular actions, along with relative pancreatic β -cell insufficiency. Insulin resistance in children is difficult to define, but underlies the metabolic syndrome, a clustering of obesity, hyperinsulinemia, hyperglycemia, dyslipidemia and hypertension that increase risk for T2DM and

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Conflicts of interest

None declared.

cardiovascular disease (CVD) as early as midpuberty [4–6]. Further, insulin resistance is linked to multiple other comorbidities in youth including nonalcoholic fatty liver disease (NAFLD), predicted to be the leading cause of liver transplant in the next 10 years [4,7] and reduced exercise capacity, a predictor of early mortality [8]. This review will focus on recent work defining the progression from insulin resistance to T2DM in youth, the demographics and comorbidities of pediatric T2DM, and current treatment options.

ASSESSMENT OF INSULIN RESISTANCE IN CHILDREN

Accurate assessment of insulin resistance is difficult due to the dynamic relationship between glucose homeostasis and pancreatic β -cell function and the influence of factors such as diet, exercise, puberty and menstrual cycle, making precise pediatric insulin resistance data limited [9,10^{*}]. The hyper-insulinemic euglycemic clamp and related tests are the gold standard for measuring insulin resistance, and the most valid measures in individuals with abnormal β -cell function, as insulin administration bypasses the reliance on pancreatic insulin release [4,11,12^{**}]. With these techniques, we and others have demonstrated insulin resistance in obese non-diabetic adolescents, even more marked in T2DM adolescents [8,11,13]. In populations with intact β -cells, frequently sampled intravenous glucose tolerance tests (FSIVGTT) are simpler yet valid measurements of insulin resistance and insulin secretion [4]. However, clamp and IVGTT techniques are labor intensive, costly, invasive and not suitable for large-scale studies; thus, surrogate measures of insulin resistance are attempted frequently in youth. Oral glucose tolerance testing (OGTT)-derived insulin resistance indices (whole-body insulin sensitivity index; ratio of glucose and insulin areas under the curve) correlate reasonably well with clamp-derived insulin resistance in youth, although surprisingly less-so than fasting indices [12^{**},14,15^{*}]. The homeostasis model assessment of insulin resistance (HOMA-IR), a widely-used surrogate utilizing fasting insulin and glucose, is reported to be only modestly better or even inferior to fasting insulin alone in youth [4,16]. HOMA-IR changes throughout childhood, and, therefore, age-based pediatric HOMA-IR norms were recently published from a large cohort of 6100 children in Mexico [17^{**}]. Any test utilizing fasting insulin must also truly be fasting, and can only be compared to levels run in the same laboratory, due to problems with insulin assays. Furthermore, all fasting, OGTT and IVGTT methods for assessing insulin resistance become invalid once insulin secretion becomes defective [4,11]. McLaughlin *et al.* [18] reported that the fasting TG: HDL ratio correlates well with insulin suppression-based insulin resistance assessment in adults, but has not yet been validated in T2DM youth. We developed an estimate of hyperinsulinemic clamp-based insulin resistance in type 1 diabetes mellitus (T1DM) and T2DM youth [equation using waist circumference, hemoglobin A1c (HbA1c) and triglyceride data] [19]. Both latter estimates also avoid additional blood draws, as fasting lipids and HbA1c are standard components of T2DM care.

The disposition index (product of insulin resistance and β -cell function) quantifies insulin secretion relative to insulin resistance [20]. Disposition index was recently shown to predict future T2DM in adult longitudinal studies [21,22,23^{**}]. A recent study evaluated OGTT disposition index (oDI) relative to hyperinsulinemic and hyperglycemic clamp-derived disposition index (cDI) in adolescents. oDI correlated well with cDI (overall $R^2 = 0.74$), especially among impaired glucose tolerance (IGT) ($R^2 = 0.71$), but less so in normal glucose

tolerant (NGT) and T2DM individuals ($R^2 = 0.41, 0.59$ respectively) [23^{***}]. oDI may be a reasonable estimate of insulin secretion relative to insulin resistance in adolescents in large-scale studies wherein clamps are not feasible.

PROGRESSION FROM INSULIN RESISTANCE TO TYPE 2 DIABETES MELLITUS

The progression from insulin resistance alone to IGT/impaired fasting glucose (IFG) to overt T2DM is regulated by the relationship between insulin resistance and insulin secretion [24]. Hyperglycemia develops when β -cell secretion is insufficient for the level of insulin resistance [2,25,26]. Longitudinal pediatric studies indicate that increasing insulin resistance worsens already impaired β -cells [27,28], in agreement with cross-sectional studies showing lower insulin in children who later progress to T2DM [26]. In addition, a more than 30% decline in cDI is apparent even at the upper end of 'NGT' (120–140 mg/dl) in obese youth [29^{***}], and obese youth with 1-h OGTT glucose at least 155 mg/dl had lower disposition index, even if NGT at 2 h [30^{*}]. A stepwise decline in first and second-phase insulin secretion from NGT to IGT to T2DM in obese adolescents has been documented [31,32^{***}], although overall insulin secretory capacity appears higher in youth, including higher first-phase insulin secretion in T2DM youth than T2DM adults.

Insulin secretion is dependent on β -cell mass and secretory capacity, which are governed by genetic and environmental factors [2,25,33]. Insulin resistance-induced hyperglycemia itself may cause further β -cell apoptosis [34]. Insulin resistance adults reportedly lose an average of 7% of their β -cells per year [35]. However, the tempo of conversion from IGT/IFG to T2DM appears faster in children, reported to occur over the span of only 12–21 months [2,31,36–38]. In a case report detailing the course of progression of a child to T2DM, the deterioration of β -cell function was approximately 15% per year [35]. Therefore, preventive measures should target the β -cell along with measures aimed at insulin sensitization.

However, not all obese insulin resistance youth develop T2DM. One-hundred and seventeen obese youth were followed for several years, and 45.5% of the 33 IGT individuals returned to NGT, 30.3% remained IGT and 8% progressed to T2DM. Reduction of BMI Z-score predicted a return to NGT, and severity of obesity and IGT along with African–American background predicted developing T2DM [39]. Another study in 79 whites, obese, IGT adolescents found that over a year, 66% returned to NGT, 32% remained IGT and 1% developed T2DM. Lower baseline weight, HbA1c and 2-h OGTT glucose, and reduction of weight and entering late puberty stages during follow-up predicted normalization of IGT [36]. Of another 128 white obese, IGT youth, 3–5 years later, 75% returned to NGT, 16% remained IGT, 2% developed T2DM and higher baseline 2-h glucose and weight gain over time predicted developing T2DM [40^{*}]. In a cohort of 75 NGT obese adolescents, higher baseline HbA1c and weight gain over time predicted progression to IGT [32^{***}]. In 218 obese youth after a mean of 1.7 ± 0.9 years, baseline HcA1c and 2-h glucose predicted 2-h glucose at follow-up; HbA1c more than 5.7% predicted later IGT or T2DM [41^{*}]. Therefore, youth falling in the prediabetic range, especially if white or midpubertal, frequently fail to progress to T2DM or revert to NGT in short-term follow-up.

Studies evaluating tissue-specific insulin resistance and secretion in obese adolescents across the spectrum of glucose tolerance showed increased peripheral insulin resistance in IGT and combined IFG/IGT, whereas hepatic insulin resistance was increased in IGT, IFG, IFG/IGT and T2DM [27,42,43]. Hyperglycemia may also be related to increased hepatic glucose output. Basal glucagon and c-peptide were elevated in obese IGT youth, and in follow-up (approximately 2.7 years) of the 16 NGT adolescents, eight (two men, six women) converted to IGT [44[■]]. This subgroup had increased hyperinsulinemic euglycemic clamp-derived insulin resistance, and fasting glucagon. Thus, it appears that islet cell upregulation, manifesting as elevated glucagon and c-peptide secretion, appears early in the course of IGT [44[■]].

PREVALENCE AND DIAGNOSIS OF PEDIATRIC TYPE 2 DIABETES MELLITUS

Thirty years ago, pediatric diabetes was almost exclusively T1DM, but today 8–45% of new pediatric cases are T2DM, especially in nonwhite populations [45[■],46,47]. The pediatric T2DM incidence is currently 8.5 of 100 000, reflecting increased rates of pediatric obesity [3,48]. Similar rates are reported in other countries, with a 0.3% prevalence in Serbia [49[■]], and incidence rates of eight of 100 000 in Japan [50]. In 2010, approximately 17% of US children were obese, up to 50% of obese children in the recent National Health and Nutrition Examination Study had insulin resistance and 10–25% of obese children reportedly have glucose abnormalities [3,26,51]. However, after years of steady increase, the US obesity prevalence stayed constant for the last 2 years [3].

The diagnosis of early T2DM remains problematic in children. In 2010, adult diagnostic criteria for T2DM was changed to a HbA1c of more than 6.5% [52]. It remains unclear whether the same cutoffs should apply to youth, and whether mild elevations during the increased insulin resistance of puberty will persist [41[■],52,53[■],54,55[■]]. Both fasting and OGTT-based measures can be problematic for early diagnosis [17[■],26,56[■],57[■],58,59], HbA1c and OGTT values are poorly correlated [41[■]], repeated OGTT's have poor reproducibility in youth [60] and HbA1c can vary substantially depending on method, making diagnosis of prediabetes and early T2DM difficult. One recent proposal was to conduct OGTTs in children with a HbA1c more than 5.5% [61], whereas others recently proposed an algorithm including glucose, triglycerides and BMI; HbA1c did not add to the predictive value of this method [62[■]]. Developing a better algorithm for T2DM screening in children is clearly needed, as well as long-term data on the factors in youth that best predict future diabetes-related complications.

The differentiation between T1DM and T2DM is also increasingly difficult in the face of rising obesity rates in all youth [63[■]]. A recent small retrospective study found that half of obese children presenting in diabetic ketoacidosis were able to be weaned off insulin, and thus likely had T2DM, whereas the other half more likely had T1DM [64[■]]. Furthermore, many features of T1DM (autoimmunity) and T2DM (insulin resistance and obesity) overlap in adolescents [34]. In the SEARCH for Diabetes in Youth study, over 2000 newly diagnosed diabetes mellitus patients less than 20 years of age were categorized into four groups based on autoimmunity (positive titers for either GAD-65 or IA-2 antibodies) or

estimated insulin resistance [19]. Of this cohort, 15.9% was classified as nonautoimmune + insulin resistance, of which 76.4% had a clinical diagnosis of T2DM. However, 19.5% of the cohort had both evidence of autoimmunity and insulin resistance [65]. In the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study, 9.8% of adolescents clinically diagnosed as T2DM had evidence of autoimmunity [66]. Individuals with positive antibodies were more likely to be male (51.7%), white (40.7%) and have lower BMI Z-scores, C-peptide, HbA1c, triglycerides, HDL cholesterol and blood pressure [66]. This is consistent with previous studies reporting that 10–75% of patients clinically diagnosed with T2DM have evidence of islet-cell autoimmunity [13,37], and we and others have shown that even normal weight-youth with T1DM are more insulin resistant than controls [67]. Therefore, providers cannot assume obese youth have T2DM, and insulin resistance is also likely to be important to T1DM.

METABOLIC PHENOTYPE OF CHILDREN WITH TYPE 2 DIABETES MELLITUS

The metabolic syndrome is implicated in the development of T2DM and CVD in youth [1,4–6]. The TODAY study, the largest and most ethnically diverse pediatric T2DM study to-date, recently published baseline data on 704 T2DM youth [45^{*}]. The majority were obese (average BMI Z-score 2.2), 72% were minorities (41% Hispanic, 31% non-Hispanic Black) and 41.5% reported a household annual income of less than US\$ 25 000. Sixty-five percent were female and had developed T2DM at a younger age. Twenty-five percent of individuals had baseline hypertension, 80% low HDL cholesterol, 10% hypertriglyceridemia, 13% microalbuminuria and 3.3% liver enzymes 1.5–2.5 times the upper limit of normal [68^{**}]. Further, the insulinogenic index and disposition index decreased with increasing HbA1c, whereas insulin resistance did not change, suggesting that insulin secretion defects predominantly determine glycemic control [68^{**}]. TODAY findings are consistent with previous reports of higher rates of baseline comorbidities and more rapid progression to end-organ damage such as microalbuminuria and macroalbuminuria in T2DM vs. T1DM youth [38,42]. Other studies confirm the female predominance in pediatric T2DM, and that T2DM youth are more obese and more sedentary than T2DM adults [37,69,70].

In adolescents, as in adults, insulin resistance is related to excess BMI and abnormal fat partitioning [1,2]. A recent study in Japanese children showed that all with T2DM had insulin resistance (OGTT-derived); insulin resistance correlated with the degree of obesity [71^{*}]. Increased visceral, hepatic and intramyocellular lipid is also associated with insulin resistance in youth with prediabetes and T2DM [8,63^{*},72–74]. NAFLD may be an important marker of multiorgan insulin resistance as hyperinsulinemic euglycemic clamps demonstrate both hepatic and peripheral insulin resistance in youth with NAFLD [75]. The severity of NAFLD appears related to the degree of insulin resistance and to impairments in β -cell function in obese youth [27]. Although it is unclear whether hepatic steatosis precedes insulin resistance or vice versa, NAFLD is a strong risk factor for developing IGT, IFG and T2DM [2,8,74], and T2DM youth have three times the liver fat of BMI-matched nondiabetic controls [76^{**}]. Because not all obese youth develop T2DM, these studies suggest that early storage of fat in the liver, viscera and muscle increases risk for developing T2DM.

T2DM adolescents also have increased markers of inflammation (CRP and IL-6) and decreased adiponectin and cardiovascular function (cardiac hypertrophy, increased aortic pulse wave velocity, decreased peak forearm vascular reactivity) [8,38,42], all of which may relate to insulin resistance. For example, T2DM adolescents have significantly decreased cardiopulmonary function vs. BMI and activity-matched controls, and hyperinsulinemic euglycemic clamp-derived insulin resistance (not T2DM duration or HbA1c) strongly predicted VO₂ peak ($r = 0.84$, $P < 0.0001$) [8]. Similarly, T2DM women were reported to have decreased exercise capacity, blunted stroke volume and a lower maximal heart rate at submaximal exercise, unrelated to T2DM duration or HbA1c [77]. Recently, sleep-disordered breathing was also correlated with evidence of insulin resistance via OGTT and fasting indices in adolescents [78].

TREATMENT OPTIONS FOR YOUTH WITH TYPE 2 DIABETES MELLITUS

Treatment guidelines in T2DM youth are not well established and often based on adult recommendations. As with adults, lifestyle modifications including multidisciplinary dietary change, physical activity and psychosocial support are often the first approach [63[•],73,79–81]. Specific dietary changes associated with improved insulin resistance include high whole-grain or dietary fiber intake and possibly low glycemic load [4]. One randomized controlled trial showed that T2DM adolescents undergoing a weight management program improved HOMA-IR, percentage body fat, and BMI Z-score at 24 months [81]. Exercise, as with adults, has been shown in a few studies to improve fasting insulin levels and body composition independent of weight loss [4,78,82–84]. However, the optimal form of exercise, training regimen or level of intensity for youth is yet unclear [4]. A recent study found that parenting skills training alone, despite no specific guidance on diet or exercise, significantly improved the offspring's BMI, indicating that pediatric obesity is a complex family problem [85[•]]. The National Institutes of Health (NIH) TODAY trial, discussed above, is a large multi-center, randomized control trial comparing metformin vs. metformin–rosiglitazone vs. metformin with lifestyle changes in 699 youth with T2DM, concluded in late 2011 [42]. The addition of an intensive lifestyle component (focusing on weight loss through diet and exercise) to metformin had no statistically significant additional benefit on maintaining glycemic control compared to metformin alone in these youth [86^{••}]. BMI was significantly more positively impacted in the lifestyle group at 6 months, although this effect was no longer significant at 24 months and neither BMI at baseline nor BMI over time was a determinant of failure of glycemic control [86^{••}]. Thus, there is little evidence to-date suggesting that individual lifestyle modifications improve glycemic control in youth with T2DM [78], arguing for the need for societal public-policy level approaches.

Studies evaluating pharmaceutical options for adolescent T2DM are also limited. Metformin, the only oral hypoglycemic agent approved for T2DM in children more than 10 years, likely works by decreasing insulin resistance and hepatic glucose production [63[•]]. In a randomized, double-blind, placebo-controlled study, 82 T2DM adolescents were treated with metformin or placebo for 16 weeks. Metformin significantly improved fasting plasma glucose and mean HbA1c vs. placebo (7.5 vs. 8.6%) [87]. In another pediatric T2DM study, glimepiride, an insulin secretagogue, and metformin had equivalent effects at 12 and 24 weeks on HbA1c, but metformin's lowering of fasting glucose was superior [88].

Furthermore, glimepiride was associated with hypoglycemia and weight gain [42,88]. Therefore, metformin and insulin are the current first and second-line drugs, respectively, in T2DM youth [63⁸,89,90⁹]. In the TODAY trial, rosiglitazone, a thiazolidinedione that alters lipid deposition and insulin resistance, and metformin was significantly more effective in maintaining glycemic control when compared to metformin alone, despite more weight gain in the rosiglitazone group [86¹⁰]. The rate of treatment failure with metformin alone was higher in the TODAY cohort than in similar adult cohorts [86¹⁰]. Thus, the pathophysiology of T2DM in adolescents may differ from adults and metformin monotherapy may be inadequate for the majority of youth with T2DM within a few years, but rosiglitazone use has now been restricted due to new concerns about potential side-effects in adults. Studies of glucagon-like peptide-1 agonists in T2DM youth are also currently underway, as is a new NIH multicenter β -cell preservation trial in youth and adults with early T2DM.

Currently, there are no medications approved to treat isolated insulin resistance in nondiabetic youth. However, rosiglitazone was recently evaluated in a 4-month randomized, double-blind, placebo-controlled study of 21 obese adolescents with IGT. Within the rosiglitazone group, 58% of individuals converted to NGT (vs. 44% in the placebo group, $P = 0.53$). Restoration of NGT was associated with a significant increase in insulin sensitivity ($P < 0.04$) and a doubling in the disposition index ($P < 0.04$) [91¹¹] suggesting rosiglitazone may improve insulin resistance and β -cell function. Weight increased 1.8 kg in the rosiglitazone group, but there were no significant changes in BMI, BMI Z-score or other adverse events [91¹¹], but current concerns about negative outcomes in adults with thiazolidinediones has currently limited their use in pediatrics. Metformin has also been shown to improve insulin resistance, and decreased liver inflammation in obese nondiabetic youth [74].

CONCLUSION

Pediatric obesity, insulin resistance and T2DM are increasing. Prediabetes is difficult to define in children, and does not always predict future T2DM. When progression occurs, it appears more rapid than in adults, and related to increasing weight gain, insulin resistance and decreased pancreatic function. T2DM youth tend to be non-white, of lower socioeconomic status, have concerning cardiometabolic abnormalities and appear to require multiple medications to control glycemia earlier in their course than adults. A modeling study predicted adolescent-onset T2DM will decrease lifespan by 15 years, with significant complications occurring by the fourth decade of life [92¹²]. Therefore, the limited options to assess and treat insulin resistance in youth require expansion and societal change to prevent the forecasted poor outcomes.

Acknowledgments

K.J.N. is supported by ADA 7-11-CD-08, JDRF 11-2010-343, and NIH/NIDDK 1R56DK088971-01. M.C.G. is supported by a fellowship training grant, T32 DK063687, awarded to Dr Georgeanna Klingensmith.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 329–330).

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KEY POINTS

- Obesity and T2DM are now critical problems in pediatrics requiring public policy changes to adequately address them.
- Insulin resistance plays a pivotal role in the development of T2DM in children, but is difficult to assess clinically.
- Children with type 1 diabetes mellitus (T1DM) can be obese, and it is important to distinguish between the two types of diabetes with antibody testing.
- Metformin and insulin remain the only currently approved drugs for treatment of T2DM in children.