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Metabolic Outcomes of Surgery in Youth with Type 2 Diabetes

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Abstract

Youth-onset type 2 diabetes (T2D) is a formidable threat to the health of obese adolescents because of its potential for early-onset and aggressive co-morbidities and complications. The physiology of youth-onset T2D differs from T2D in adults and is associated with a greater degree of insulin resistance, a more rapid decline in pancreatic β -cell function, and a poorer response to medications. Medical management in youth is focused on combining lifestyle intervention and pharmacological treatment, but these therapies have yet to demonstrate improvements in disease progression. Metabolic bariatric surgery (MBS) is now recommended for the treatment of T2D in adults largely because of the beneficial effects on weight, ability to improve glycemic control, and, in a large proportion of people, induce diabetes remission. MBS is now being performed in adolescents with severe obesity and T2D, with initial results also showing high rates of T2D remission. Here, we review the state of medical management of youth-onset T2D and the outcomes of MBS studies in youth with T2D published to date.

Keywords

Type 2 diabetes; Severe Obesity; Bariatric surgery; Insulin resistance

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Introduction

Youth-onset type 2 diabetes (T2D) incidence is on the rise and associated with early morbidity and mortality. This review will outline the pathophysiology and natural progression of youth-onset T2D, briefly review the evidence base for treatment of adult-onset T2D with metabolic bariatric surgery (MBS), and discuss what is known about the use of MBS for management of youth-onset T2D.

Pathophysiology and Epidemiology of Youth-onset T2D

Epidemiology of Youth-onset T2D

Youth-onset T2D has been steadily rising since the 1980s [1, 2] such that, in some ethnic and racial populations, it represents 50% or more of the incident cases of diabetes in adolescents[3]. In the U.S., youth-onset T2D is most common in Native Americans, followed by Non-Hispanic Black, Hispanic, and Asian Pacific Islander adolescents. It is also more common in girls than in boys[3, 4], a sex difference not seen in adult-onset T2D. T2D is rarely, if ever, seen prior to puberty and is confined to pubertal youth with overweight or obesity, with very rare exceptions[4, 5]. Other commonly seen features in youth with T2D are a strong family history of T2D, exposure to gestational diabetes *in utero*, physical and metabolic characteristics of insulin resistance, and significant psychosocial stressors, including low socioeconomic status. Data from the SEARCH for Diabetes in Youth Study estimates that the U.S. prevalence of youth-onset T2D was 0.46/1,000 in 2009, equating to approximately 20–22 thousand youth[3, 6]. Thus, while youth-onset T2D is on the rise, it is still a relatively rare disease. By comparison, approximately 4-fold more (1.93/1,000) youth have T1D. This is important to note in the context of MBS, as diagnostic confusion can occur in youth with clinical features of T2D (such as obesity and metabolic syndrome characteristics), resulting in missed cases of T1D. Because all patients with T1D require treatment with insulin, it is critical to test for diabetes auto-antibodies associated with T1D in all youth with diabetes[7].

Pathophysiology and Clinical Presentation

Normal glucose homeostasis requires insulin secretion by pancreatic β -cells to match changes in insulin sensitivity; if insulin sensitivity declines, there should be an increase in insulin secretion[8]. Prediabetes and T2D result from an inability to maintain β -cell insulin secretion (i.e. relative insulin deficiency) in the face of insulin resistance. While most youth with obesity have some degree of insulin resistance, only a subset will develop T2D. In fact, most of the genetic risk markers that have been identified are variants related to β -cell function [9, 10]. Other hormone abnormalities are also seen in the progression to β -cell decline, including a decrease in incretins (e.g. glucagon-like peptide-1[GLP-1])[11, 12] and an increase in glucagon secretion[11].

Youth-onset T2D is rare prior to puberty. Data from both the Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) and SEARCH studies show a mean age of onset of 14 years, typically occurring during mid- to late-puberty[4, 5]. This is likely in part related to the transient insulin resistance seen in all youth during puberty[13–15], which is

exaggerated in youth with obesity[16, 17]. This results in a critical window of increased risk for those with a predisposition to T2D, such that they are unable to maintain β -cell function and develop diabetes. This risk is highest in youth with predisposing factors described above; in addition, youth with a history of atypical antipsychotic treatment are at greater risk for developing T2D[18].

It is important to note that, while pediatric patients with T2D do progress through a phase of prediabetes in the progression to T2D, youth with prediabetes do not progress to T2D as consistently as adults do. Studies suggest that a significant proportion of youth with a diagnosis of prediabetes, based on the adult American Diabetes Association (ADA) standards, will revert to normoglycemia in a second test[19–21]. Retrospective clinical data suggest that risk progression is highest with an HbA1c of $\geq 6\%$, particularly if there is ongoing weight gain [22]. For this reason, and because little is known about the impact of pubertal insulin resistance on glycemia in normal weight youth, prediabetes is challenging to define in youth; however, current ADA recommendations are to use the same laboratory criteria as for adults [23].

The presentation of youth-onset T2D ranges from asymptomatic detection during routine screening for obesity-associated comorbidities, to mild symptomatic presentation (polyuria, polydipsia, unexplained weight loss), to diabetic ketoacidosis (5–11%) or hyperosmolar state [24, 25]. The ADA criteria for diagnosing T2D require repeat confirmatory testing for asymptomatic patients, with laboratory criteria defined as: a fasting glucose ≥ 126 mg/dL, 2-hour glucose ≥ 140 mg/dL during oral glucose tolerance testing, or an HbA1c of $\geq 6.5\%$ [23].

Treatment of Prediabetes and Diabetes in Youth

The majority of what is known about long-term medical management of youth-onset T2D comes from the TODAY study, a randomized control trial of ethnically diverse youth (n=699) who were aged 10–17 years and had a BMI $\geq 85^{\text{th}}$ percentile at enrollment [26]. These youth were randomized to receive metformin monotherapy, metformin + intensive lifestyle intervention, or metformin + rosiglitazone, with a primary outcome of loss of glycemic control (HbA1c $\geq 8\%$ for at least 6 months or failure to wean from temporary insulin started after metabolic decompensation) [27]. Loss of glycemic control was seen in almost half of participants (45.6%), after a median treatment duration of 11.5 months [26]. Failure rates were significantly lower in the metformin + rosiglitazone group (38.6%) than in the metformin monotherapy group (51.7%, $p=0.006$). There were some significant sex and racial/ethnic differences in response to treatment: rosiglitazone was associated with significantly less glycemic failure in girls than boys and metformin was particularly ineffective in non-Hispanic Blacks. Loss of glycemic control was most strongly associated with ongoing β -cell failure, as opposed to decline in insulin sensitivity [28]. Notably, at the time of randomization, the median duration of T2D was 7.8 months and average HbA1c was 5.9% on treatment with metformin monotherapy [5]. Thus, almost half of youth with T2D had rapid progression of their disease, despite initial good control on metformin alone [29]. This is significantly different from the natural history of T2D in adults. By comparison, in the A Diabetes Outcome and Progression Trial (ADOPT), the glycemic failure rate of

metformin monotherapy was only 20% in adults at the end of 5 years of follow up [30]. Similarly, the failure rate of metformin and rosiglitazone from the U.S. Department of Defense Database was <20% [31]. Unfortunately, evidence-based treatment to prevent this rapid progression is limited. Until the recent approval of liraglutide for use in pediatric T2D [32], the only two FDA-approved medications in youth were insulin and metformin. Treatment with insulin has been associated with weight gain, which could contribute to worsening of insulin resistance and comorbid conditions such as hypertension and musculoskeletal problems. Furthermore, in TODAY, the addition of insulin after glycemic failure was not associated with any further improvement in glycemic control [33]. Clinical trials are currently underway to study other agents in youth-onset diabetes, including other GLP-1 agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, and sodium glucose transporter 2 (SGLT2) inhibitors.

Youth-onset T2D is also associated with early complications. In TODAY, cardiovascular risk worsened as the study progressed, with increasing incident hypertension, dyslipidemia, and inflammation [34, 35]. TODAY also found evidence of endothelial dysfunction [36], vascular stiffness [37] and cardiac structure and functional defects [38]. Several TODAY participants have also had cardiovascular events before the age of 30 in ongoing follow-up (presented at ADA Annual Meeting, 2019). Both TODAY and SEARCH found a relatively high prevalence (10–20%) of retinopathy [39, 40], nephropathy [34], and neuropathy [41]. Youth-onset T2D was also associated with high rates of obstructive sleep apnea and non-alcoholic fatty liver disease [42]. In TODAY, those girls who became pregnant experienced significantly higher rates of stillbirth, spontaneous abortions, prematurity, and congenital anomalies as compared with the general adolescent population [43]. Finally, both TODAY [44] and SEARCH [45] showed significant mental health comorbidity associated with a diagnosis of T2D, including depression and disordered eating.

Given the rapid progression of β -cell failure and early-onset comorbidities in TODAY, the pediatric arm of the Restoring Insulin Secretion (RISE) study was designed to determine whether early treatment with metformin alone (for 12 months) or insulin (for 3 months) followed by metformin (for 9 months) in youth with impaired glucose tolerance or recently-diagnosed T2D (n=91) would help preserve β -cell function. In this study, pediatric participants had ongoing β -cell failure during the treatment phase, regardless of treatment arm, which worsened after treatment withdrawal [46]. These results were different from the parallel adult RISE study, in which adult participants demonstrated preservation of β -cell function while on treatment [47]. Due to the similarity in enrollment criteria for youth and adults in the RISE study, a direct head-to-head comparison could be made in terms of insulin sensitivity, which was more than 2 times lower, insulin secretion, which was more than twice as high, and insulin clearance which was approximately 50% lower in youth than in adults at baseline [48].

Metabolic Bariatric Surgery for Treatment of T2D: Adult Evidence

The poor responses to medical treatment observed in youth-onset T2D demands alternative approaches to improve glycemic control, slow the progression of pancreatic β -cell decline, and reduce long term co-morbidities. MBS is now recommended for the treatment of T2D in

adults largely based on data showing the ability to induce substantial weight loss, lead to remission of T2D, and reduce co-morbidities [49, 50]. A consensus statement endorsed by 48 medical and surgical organizations now recommends MBS in adults with T2D who have class III obesity (BMI ≥ 40 kg/m²) or class II obesity (BMI 35–39.9 kg/m²) and inadequate glycemic control [51]. Clinical practice guidelines specify that MBS should also be considered for adults with T2D and BMI 30–34.9 kg/m² if hyperglycemia is inadequately controlled despite optimal treatment with either oral or injectable medications [51].

Some of the most robust data examining T2D outcomes after MBS have come from the multi-center adult Swedish Obese Subjects (SOS) study, a prospective, controlled observational study comparing MBS to conventional medical treatment. At baseline, 343 of 2,010 surgical patients and 260 of 2,037 control patients had T2D. At two years, T2D remission rates were 72.3% (95% CI, 66.9%–77.2%) in the MBS group vs. 16.4% (95% CI, 11.7%–22.2%) in the controls. At 15 years, T2D remission rates remained higher in the MBS group than controls (30.4% vs. 6.5% with an odds ratio of 6.3 [95% CI, 2.1–18.9], $p < 0.001$) [52]. The SOS study also demonstrated reduction in the incidence of T2D in those without T2D at baseline (28.4 per 1,000 in the MBS group compared to 6.8 cases per 1,000 patients in the control arm over 15 years) [53]. Importantly, the risk of microvascular complications from T2D in the MBS group was one-half of that observed in the control group [54]. The anti-diabetic effect of MBS appears long lasting and has been documented with 16 years of follow-up [55], although the incidence of reoperation for conversion from less effective operations to more modern and more effective procedures is not well described. While some MBS patients experienced a slow and steady recurrence of T2D, the rates of T2D were still less than in non-operated controls [56].

T2D remission rates were also examined in the STAMPEDE randomized clinical trial, wherein adults with uncontrolled T2D were randomized to intensive medical therapy (IMT) alone, IMT plus Roux-en-Y gastric bypass (RYGB) or IMT plus vertical sleeve gastrectomy (VSG) [49, 50]. Remission of T2D at years one and three in those undergoing MBS were ~40% (42% RYGB; 37% VSG) and 31% (38% RYGB; 24% VSG), respectively; compared to 12% and 5% for the medical group [49, 57]. At 5-years of follow-up, remission rates for RYGB and VSG were 29% and 23%, respectively and 5% for patients treated with IMT alone [49]. T2D remission after MBS is likely the result of improved insulin sensitivity, an augmented incretin response, and overall improvements in pancreatic β -cell responsiveness to glucose [55, 58, 59].

The effects of MBS on T2D remission in adolescents has been less studied but initial results mirror findings in adults where both weight loss and remission of diabetes have been observed [60–64]. In adolescents, MBS is considered for adolescents who meet clinical criteria for T2D and severe obesity (defined as an absolute BMI ≥ 35 kg/m² or a BMI $\geq 120\%$ of the 95th percentile for age and sex) [65].

Teen-LABS is one of the largest and longest observational studies of pediatric patients undergoing MBS with 3 and 5 years of follow-up data published. Participants in the Teen-LABS study were enrolled at a mean age of 17 years [66]. At one year, this cohort experienced a 31% reduction in weight (similar for both RYGB and VSG) with minimal

weight regain by years 2 and 3. Of the 242 obese adolescents who underwent MBS, 29 had T2D[66]. A 95% (95% CI 85–100%) T2D remission rate occurred at 3 years with no incident T2D cases in the youth without T2D at baseline [60]. Similarly, 19 participants had prediabetes at baseline with a 76% (95% CI 56–97) remission rate observed at 3 years [60]. Recently, these T2D remission rates in Teen-LABS were compared to LABS, a related but independent study of adults who underwent MBS. Among those who underwent RYGB, adolescents were more likely than adults to have remission of T2D (86 vs. 53%, risk ratio 1.27, 95%CI 1.21–1.88) at 5 years [67]. Other pediatric studies have reported improved glycemic control and T2D remission after MBS but each included few participants with T2D, and the case definitions used for T2D at baseline and the methodology used to assess response to surgery were not standardized, making inferences difficult [63, 66, 68–70].

Adult studies estimate remission rates of T2D to be approximately 40–70%. Thus, the T2D remission rates of 88–95% in adolescents with T2D undergoing MBS appear to be similar if not greater than adults [60, 63, 64, 67, 71]. The SOS study showed that shorter T2D duration at baseline was associated with higher T2D remission rates in MBS patients after 2, 10, and 15 years of follow-up [54]. In contrast, older age, higher baseline HbA1c, and treatment with insulin or other diabetes medications at baseline were associated with decreased likelihood of T2D remission over a 5-year period in another cohort [72]. Thus, MBS at a younger age, earlier in the disease, or before insulin dependence may improve T2D remission rates and explain the better treatment responses in adolescents vs. adults.

While direct comparisons of MBS to medical therapy in youth has yet to occur, a retrospective comparison of outcomes from youth studied in the TODAY clinical trial were compared to youth from Teen-LABS [71]. Despite a higher starting BMI, over 2 years HbA1c fell from 6.8% on medication to 5.5% off medication in Teen-LABS, but increased from 6.2% to 7.8% on medication in TODAY. T2D-related comorbidities including hypertension decreased from 45% at baseline to 20% at 2 years in the MBS group vs. a near doubling in TODAY from 22 to 41%[71]. Similarly, dyslipidemia decreased from 72% to 24% in Teen-LABS with no appreciable change in TODAY [71] and the proportion of youth in Teen-LABS with elevated urinary albumin excretion decreased from 26% to 5% over 2 years with no change in TODAY [73].

While these initial results suggests a beneficial effect of MBS on glycemia and T2D related co-morbidities in youth, it is important to note that most results in youth to date have evaluated RYGB, which is no longer the preferred MBS in adolescents sue to higher rates of complications with RYGB [74]. VSG now accounts for more than 80% of MBS procedures in the US [74], but only a limited number of youth with T2D to date have been prospectively evaluated after VSG [60] and no studies have prospectively compared VSG to medical management. Thus, the superiority of VSG compared to medical therapy has not been established nor have the mechanisms underlying changes in glycemic control in response to VSG in youth with T2D been explored.

NIH funded new trial in 2019: Surgical or Medical Treatment for Pediatric T2D (ST₂OMP)

These gaps in the literature led to the authors of this review to propose of a prospective, open labelled clinical trial, Surgical or Medical Treatment for Pediatric T2D, ST₂OMP (Figure).

ST₂OMP will compare VSG to advanced medical therapy (AMT) for the treatment of adolescent-onset T2D. Funded by the National Institutes of Health, ST₂OMP investigators will recruit 90 post-pubertal adolescents with a BMI ≥ 35 kg/m² at two large pediatric centers in the US, Cincinnati Children's Hospital Medical Center and Children's Hospital Colorado. A BMI of ≥ 35 kg/m² will be required for inclusion because it follows the current best-practice clinical guidelines to consider MBS in adolescents [65], is low enough to allow for BMI-comparable surgical and medical study groups at enrollment, and it ensures all participants will have the potential option of surgery, as insurance companies will not presently cover MBS at a BMI <35 kg/m².

AMT in ST₂OMP is defined as use of lifestyle intervention and multi-drug therapy for T2D and its related co-morbidities aimed at aggressive lowering of HbA1c to $<6.5\%$. Given the previous results of the TODAY clinical trial and the RISE study demonstrating metformin alone or basal insulin followed by metformin are insufficient to achieve or maintain glycemic control and prevent β cell function, ST₂OMP was designed to use combination therapy including newer medications such as glucagon-like peptide (GLP-1) agonists and sodium-glucose transport-2 (SGLT-2) inhibitors with the goal to attempt to achieve HbA1c levels similar to those achieved after MBS.

The primary outcome of ST₂OMP is glycemic control at one year. Secondary endpoints include the effects of VSG vs. AMT on T2D-related co-morbidities including kidney function, fatty liver disease, dyslipidemia and hypertension as well as pancreatic β -cell function at one and two years. Mechanisms underlying the impact of MBS will also be explored. ST₂OMP will begin enrollment in October of 2019.

In conclusion, treatment with metformin and basal insulin do not result in achievement of glycemic control, reduction in youth-onset T2D related co-morbidities, or slow the progression of pancreatic β -cell decline. GLP-1 agonists have been shown to lower glycemic control in youth, but the ability to induce substantial weight loss or slow pancreatic β -cell decline have not yet been demonstrated [32]. Newer pharmacological therapy such as DPP-4 inhibitors and SGLT-2 inhibitors are currently being studied. Currently, MBS is the only treatment that results in significant weight loss and remission of T2D in adults, with ongoing data collection on VSG in youth-onset T2D. Direct comparisons to aggressive medical therapy are needed and are also currently underway.

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Figure: Design of Surgical or Medical Treatment for Pediatric T2D (ST₂OMP) Trial

The ST₂OMP trial, led by the authors of this review article, aims to directly compare vertical sleeve gastrectomy and advanced medical therapy for control of T2D in adolescents. The primary endpoint will be the proportion of participants in each group with hemoglobin A1c values less than 6.5% at 1 year. Secondary endpoints will be mechanistic in nature, including differences in β cell function, insulin sensitivity, and other metabolic and cardiovascular abnormalities at baseline, one, and two years after enrollment.

HTN, hypertension; DKD, diabetic kidney disease; NAFLD, non-alcoholic fatty liver disease