



Bariatric Surgery: A Potential Treatment for Type 2 Diabetes in Youth

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Type 2 diabetes, once referred to as “adult-onset” diabetes, has now emerged as a formidable threat to the health of obese adolescents. Although there is growing evidence regarding the epidemiology of type 2 diabetes in youth and its multisystem health consequences, treatment options have lagged and progression of disease occurs even with aggressive medical therapy. Increasing interest in the application of bariatric surgery for adolescents with type 2 diabetes has evolved in part because of the evidence demonstrating improvement or remission in many adults with diabetes after surgery. Here, we review the burden of type 2 diabetes in youth including its associated complications, discuss the outcomes and complications of bariatric surgery in adolescents with diabetes, and conclude with recommendations for future research and options for refinement of the use of bariatric surgery in this patient population.

The prevalence of type 2 diabetes continues to rise among obese children and adolescents (1) but few treatments exist. Bariatric surgery has emerged as a potential treatment for obesity because it causes substantial and durable weight reduction (2,3). Recent data suggest that bariatric surgery may be effective in the treatment of type 2 diabetes. In this article, we review the burden and complications of type 2 diabetes in adolescents, discuss the outcomes and complications of bariatric surgery among youth with type 2 diabetes, and conclude with recommendations for future research and potential criteria for the use of bariatric surgery in adolescents with type 2 diabetes.

THE SCOPE OF THE PROBLEM IN YOUTH

Prior to 1992, type 2 diabetes accounted for ~4% of new diagnoses of diabetes in adolescents (4). Recent estimates suggest that now nearly half of new cases of diabetes in teens can be termed type 2 diabetes (1,5). The rise in incident type 2 diabetes among young people largely follows the rise in childhood obesity, but recent data suggest that other factors, including growth of minority ethnic populations in the U.S., exposure to maternal diabetes in utero, endocrine disruptors in the environment, and increased awareness and more common screening of children and teens, may be important (1).

The SEARCH for Diabetes in Youth (SEARCH) study, an observational investigation of the incidence and prevalence of pediatric diabetes, projects that by 2050 nearly 85,000 adolescents in the U.S. will be affected by type 2 diabetes (1). There has been a parallel rise in the 2013–2014 U.K. National Paediatric Diabetes Audit (NPDA) that includes patients up to 19 years of age, which noted 500 cases of type 2 diabetes, a marked rise in incidence from the year 2000 when the first reported cases were described in Birmingham, England (6). Similarly, data from India and

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Japan show rising incidence of type 2 diabetes among youth. In 2006–2009, nearly 50% of the youth-onset diabetes (<25 years old) was attributed to type 2 diabetes in India, and in Japan, type 2 diabetes is now diagnosed twice as often as type 1 diabetes among teens (7,8). These studies portend significant public health consequences as youth with type 2 diabetes develop comorbidities at a faster pace than those with type 1 diabetes and are at an accelerated risk for developing coronary artery disease (9).

Whereas the progression from abnormal glucose metabolism to development of type 2 diabetes in adults typically occurs over years to decades (10), the appearance of type 2 diabetes in adolescence suggests a more aggressive pathogenesis (11,12). The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study, a multicenter randomized controlled trial, carefully examined time to treatment failure in children and adolescents with new-onset type 2 diabetes. The trial defined treatment failure as an HbA_{1c} of >8% for 6 months or metabolic decompensation requiring insulin therapy (13). Rates of treatment failure were high in all three arms of the trial as 52, 39, and 47% of participants failed metformin alone, metformin plus rosiglitazone, and metformin plus lifestyle intervention, respectively, with an average time to failure of 11 months (14). Moreover, none of the treatment regimens improved or stabilized pancreatic β -cell function estimated from oral glucose tolerance tests; indeed, overall β -cell function declined by 20–35% per year in the cohort (15). Notably, for those who failed to maintain glycemic control, β -cell function was 40–50% lower at baseline than in those who did not progress to requiring insulin therapy (15). This course of diabetes progression appears to be different than what is typically seen in adults with new-onset type 2 diabetes. The A Diabetes Outcome Progression Trial (ADOPT) examined metformin monotherapy in adults with new-onset type 2 diabetes. In ADOPT, metformin monotherapy treatment failure rates were 21% (16), less than half of the 52% reported in the TODAY study. Adults also experienced a rate of decline in β -cell function of only 7–11% per year, far less than the rate of decline in adolescents. These data show that type 2 diabetes in adolescents results in a rapid

decline in β -cell function that requires more intensive medication, including a greater need for insulin. If these initial estimates on disease progression are validated, a more aggressive management approach to type 2 diabetes in youth might be warranted.

COMPLICATIONS OF TYPE 2 DIABETES

The complications of type 2 diabetes in adults are well documented and include myocardial infarction, stroke, renal failure, neuropathy, retinopathy, and peripheral vascular disease. Nearly 70% of adult patients with type 2 diabetes succumb to death from cardiovascular disease (17). Type 2 diabetes in adults is also responsible for more cases of renal failure and peripheral vascular disease leading to amputation than any other disease (18). Although the long-term complications of adolescent-onset type 2 diabetes are not yet clear, the cardiovascular risk burden is well documented and rapidly progresses over time.

Using noninvasive markers of early atherosclerosis that predict future myocardial infarction and stroke (19), Urbina et al. found that youth with type 2 diabetes (mean age 18 years) have increased carotid intima media thickness and peripheral vascular stiffness compared with lean and obese age-, race-, and sex-matched control subjects (20,21). Greater left ventricular cardiac mass and worse diastolic function were also found in these youth (22) and were associated with higher blood pressure, BMI, longer duration of diabetes, and worse glycemic control (20–23). Others have shown that renal complications also accrue much earlier for youth with type 2 diabetes, compared with type 1 diabetes. Approximately 6% of adolescents with type 2 diabetes develop renal failure by age 20 years (within 5 years of diabetes diagnosis), and by age 29 years, 2.3% have developed end-stage renal disease (24). There is also emerging evidence that youth with type 2 diabetes have decreased cognitive function, brain volume, and white matter microstructural changes compared with obese control subjects (25,26).

In the TODAY study, the 704 participants (ages 10–17 years) with type 2 diabetes who had an average BMI of ~ 35 kg/m² demonstrated rapid progression of their cardiovascular risk

factors during treatment. The prevalence of hypertension tripled over 4 years, increasing from 11 to 34%. The prevalence of microalbuminuria increased from 6 to 17% within 3 years of study enrollment, and the prevalence of high-risk LDL (i.e., LDL >130 mg/dL or taking LDL-lowering medications) doubled from 4.5% at baseline to 11% after only 3 years (27,28). Collectively, these data suggest that youth with type 2 diabetes are at high risk to develop future cardiovascular, renal, and potentially cerebrovascular complications.

The cornerstone of medical management in obese youth with type 2 diabetes is lifestyle intervention including diet and exercise. However, the evidence shows that this approach is not successful in the majority of patients, and most patients require adjunctive pharmacological therapy with metformin and/or subcutaneous insulin (29,30). Unfortunately, metformin is often ineffective for improving glycemic control or for limiting weight gain, and insulin promotes weight gain (14). As a result, surgical weight-loss procedures are being examined as potentially attractive alternatives to treat both obesity and type 2 diabetes in adolescents.

SURGICAL TREATMENT OF OBESITY AND TYPE 2 DIABETES

There is an emerging base of scientific information providing evidence for the effectiveness of bariatric surgery to treat diabetes as well as obesity in adult patients. The Swedish Obese Subjects (SOS) trial is a controlled intervention study that has provided some of the most important data on the long-term health and mortality outcomes for severely obese adults treated with bariatric surgery or routine medical care (control subjects). The study group has reported outcomes over a period of 14–27 years and has demonstrated, for instance, a durable 25% reduction in body weight and 30% reduction in mortality over 20 years for participants who had Roux-en-Y gastric bypass (gastric bypass) (31). For participants with type 2 diabetes at baseline, the remission rate at 15 years for those who did not undergo surgery was 6.5%. For those who did undergo surgery, remission was seen in 30%. Importantly, the risk of developing microvascular complications of diabetes in the surgical

group was approximately one-half of that observed in the control group that did not have surgery (32). Several shorter-term randomized controlled trials of bariatric surgery for treatment of type 2 diabetes in adults have also demonstrated encouraging initial remission rates of nearly 50% at 3 years after gastric bypass (33,34). Although there has also been a slow and steady recurrence of diabetes in some surgical patients who initially experience remission, the rates of diabetes do not approach the levels in nonoperated control subjects (35).

Over the past decade, data demonstrating dramatic improvements in weight and cardiometabolic risk for youth undergoing a variety of bariatric weight-loss operations have also emerged (36). The results from the first large National Institutes of Health-sponsored multicenter, prospective study of bariatric surgery in adolescents and young adults were recently published (2). Participants in the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study were a mean age of 17 years at baseline prior to surgery (2). This cohort experienced a 31% reduction in weight at 1 year (similar for both gastric bypass and sleeve gastrectomy) that was only slightly regained by years 2 and 3. At year 3, the mean percent weight loss was 28% in the group that underwent gastric bypass and 26% in the group that underwent sleeve gastrectomy. Durability of weight loss has also been demonstrated in children <14 years of age after sleeve gastrectomy. At postoperative year 1, patients had an average BMI loss of 15 kg/m², with durability demonstrated by maintaining a 17 kg/m² loss by year 5 (37).

The Teen-LABS study found a 74% remission in hypertension, 66% remission of dyslipidemia, and 86% resolution of abnormal kidney function (defined by low glomerular filtration rate or proteinuria) (2). Similarly, improvements in other obesity-related comorbidities, including obstructive sleep apnea, polycystic ovarian syndrome, and fatty liver, have also been reported (38,39).

Improvements in glucose and carbohydrate metabolism after gastric bypass surgery in adolescents with and without type 2 diabetes are also being observed. Using intravenous glucose tolerance testing, measures of insulin secretion (the acute insulin response to intravenous

glucose), insulin sensitivity, and disposition index (an estimate of β -cell function corrected for prevailing insulin sensitivity) were obtained before and after laparoscopic gastric bypass in 22 youths without type 2 diabetes (40) and 2 youths with type 2 diabetes (41). At baseline, all youth presented with markedly reduced insulin sensitivity (approximately one-third that of lean adolescents) and impaired β -cell function disposition index values that were approximately one-half that reported in lean adolescents (42). In the year after gastric bypass, adolescents without diabetes demonstrated an insulin sensitivity increase of three- to fourfold, whereas the disposition index improved by twofold. Proinsulin secretion, a measure of β -cell dysfunction, also decreased significantly (40). Importantly, for the two adolescents with type 2 diabetes treated with gastric bypass, there was clear evidence that both insulin sensitivity and β -cell function improved but to a greater extent in the adolescent who had not yet required exogenous insulin at baseline. Taken together, these physiological data demonstrate that gastric bypass in adolescents not only reverses the profound insulin resistance associated with severe obesity but can also markedly improve the β -cell "fatigue" that is characteristic of individuals who are also considered to be at high risk for progression to frank type 2 diabetes.

Several other studies have reported clinical and metabolic outcomes of adolescents with type 2 diabetes after bariatric surgery. However, each included very few participants with type 2 diabetes, and the case definitions used for type 2 diabetes at baseline and the methodology used to assess response to surgery were not standardized, making inferences difficult (36). When examining only surgical outcome studies that have included 10 or more adolescent participants with type 2 diabetes and at least 1 year of follow-up data, the results have generally demonstrated excellent weight loss and diabetes remission or improvement (Table 1).

Messiah et al. (38) analyzed adolescent type 2 diabetes outcomes from the Bariatric Outcomes Longitudinal Database (BOLD), a large-scale surgical quality assurance project. In this analysis, 65 adolescents (15% of all adolescent patients) with type 2 diabetes underwent adjustable gastric banding, whereas another 67 (15% of all adolescent patients)

underwent gastric bypass. Although 1-year outcome data were missing for a high proportion of patients and the precise definition of disease response was not provided, improvement in type 2 diabetes was reported for most patients.

Another retrospective cohort study from five adolescent centers reported 1-year outcomes of 11 adolescents with type 2 diabetes undergoing gastric bypass (43). At 1-year follow-up, a 33% decrease in BMI was observed. Remission of type 2 diabetes (fasting glucose <126 mg/dL without medications for type 2 diabetes) was observed for 8 of the 9 evaluable subjects (89% remission), whereas 2 of 11 (18%) had insufficient data for characterization of diabetes status. Importantly, improvements in cardiovascular risks were also noted in this study, and estimates of disease status obtained from a nonsurgically treated cohort were also provided.

The Teen-LABS study enrolled 23 adolescents with type 2 diabetes who underwent gastric bypass (14% of all gastric bypass participants) (2). Of these, there were insufficient data available to classify a diabetes treatment response in five participants at 3 years. In the remaining 18 participants, remission of type 2 diabetes (HbA_{1c} <6.5% without medications) was observed in 17 (94% remission [95% CI 84–100]). Additionally, no incident cases of type 2 diabetes were observed over 3 years in the 153 subjects who did not have type 2 diabetes at baseline. An additional six patients with type 2 diabetes in the Teen-LABS study underwent vertical sleeve gastrectomy. Sufficient data from two of these six were available at 3 years to assess diabetes response, and both were in remission at that time. The statistically modeled results, taking into account all available data on these patients undergoing vertical sleeve gastrectomy between baseline and 3 years, produced a modeled remission rate of 68% for this group.

Three-year outcomes of vertical sleeve gastrectomy for 52 adolescents with type 2 diabetes were also recently published (39). In this analysis, all 52 patients were represented in the 3-year outcome. Remission of type 2 diabetes (fasting glucose <126 mg/dL, HbA_{1c} <6.5%, and without medications for type 2 diabetes) was observed in 46 of 52 patients (88%), and glucose improvement (decrease in glucose or HbA_{1c} and

Table 1—Outcome of adolescents and young adults with type 2 diabetes after bariatric surgery

Author	<i>n</i> (b)	<i>n</i> (f)	Age (years)	Operation	BMI (b)	Follow-up	Outcome	Comments
Messiah et al. (38)	65		18.5 (11–19)*	AGB	46 kg/m ² *	1 year	59% improvement	Diabetes outcomes reported as part of larger AGB series (<i>n</i> = 436). Data from 65% of all AGB patients in the larger series were missing at 1 year. Specific loss to follow-up and definitions for change in diabetes status (or improvement) was not provided.
Messiah et al. (38)	67		18.5 (11–19)*	RYGB	51 kg/m ² *	1 year	79% improvement	Diabetes outcomes reported as part of larger RYGB series (<i>n</i> = 454). Data from 76% of all RYGB patients in the larger series were missing at 1 year. Specific loss to follow-up and definitions for change in diabetes status (or improvement) was not provided.
Inge et al. (43)	11	9	17.8 (14–21)	RYGB	50 kg/m ²	1 year	88% remission	Analysis contains only those with diabetes. BMI decreased by 33% over 1 year. Remission defined as HbA _{1c} <6.5% (or FBG <126 mg/dL) and off of diabetes medications. Nine of 11 patients had sufficient biochemical and medication use data at 1 year to score remission.
Inge et al. (2)	23	18	17 (13–19)*	RYGB	54 kg/m ² *	3 years	94% remission†	Diabetes outcomes reported as part of larger series. Remission defined as HbA _{1c} <6.5% (or FBG <126 mg/dL) and off of medications.
Inge et al. (2)	6	2	17 (13–19)*	VSG	50 kg/m ² *	3 years	68% remission	Diabetes outcomes reported as part of larger series. Remission defined as HbA _{1c} <6.5% (or FBG <126 mg/dL) and off of medications.
Alqahtani et al. (39)	52	52	14.4 (4.9–21)*	VSG	48 kg/m ² *	3 years	89% remission	Diabetes outcomes reported as part of larger series. Remission defined as HbA _{1c} <6.5% (or FBG <126 mg/dL) and off of medications.
Alqahtani et al. (37)	11	11	11.2	VSG	45 kg/m ²	5 years	100% remission	Diabetes outcomes reported as part of larger series. Remission defined as HbA _{1c} <6.5% (or FBG <126 mg/dL) and off of medications.

AGB, adjustable gastric band; BMI (b), BMI at baseline; FBG, fasting blood glucose; *n* (b), number in sample at baseline; *n* (f), number in sample at final time point; RYGB, Roux-en-Y gastric bypass; VSG, vertical sleeve gastrectomy. *Data derived from the larger series in the analysis and is not specific to the diabetes subpopulation. †Remission data were modeled, taking into account the influence of missing data.

decreased type 2 diabetes medication use) was observed in the remaining 6 patients (12%). A 100% remission rate was seen when the same study group studied 11 youth <14 years of age (37).

Studies of adults using comparable definitions of diabetes response have estimated remission rates of ~40–70% at 3 years. Thus, the type 2 diabetes remission rates of 68–100% in adolescents with type 2 diabetes undergoing gastric bypass and vertical sleeve gastrectomy appear to indicate similar if not greater metabolic effectiveness of surgery when used in adolescents compared with similar operations in adults with type 2 diabetes. There are

several testable hypotheses that might explain why adolescents may have better treatment responses compared with adults, including the age at surgery, shorter duration of obesity or type 2 diabetes, severity of disease (i.e., HbA_{1c} level and intensity of diabetes therapy) at presentation, and differences in physical activity after weight loss.

POTENTIAL COMPLICATIONS OF WEIGHT-LOSS SURGERY IN YOUTH

Although the remission rates of type 2 diabetes in youth after bariatric surgery appear high, there are clear risks from surgery, including surgical and

nutritional complications that need to be carefully considered. In 2013, surgical outcomes from a single children's hospital that included 77 consecutive gastric bypass procedures in obese adolescents were reported (44). Intraoperative complications were seen in 3% of youth, perioperative complications (defined as a complication within 30 days) were seen in 22%, and 13% had a complication between 31 and 90 days. The most common postoperative complications included gastrojejunal anastomotic stricture (17%), reoperation (13%), leak (7%), and dehydration (7%) (44). Multicenter prospective complication data over 3 years

were reported in the Teen-LABS study in 161 patients undergoing gastric bypass and 67 patients undergoing vertical sleeve gastrectomy (2). Over 3 years, 30 adolescents (13% of all participants or 14% of gastric bypass and 10% of vertical sleeve gastrectomy participants) required 47 additional intra-abdominal procedures, most commonly cholecystectomy. Serious complications such as anastomotic leakage were infrequently observed after each type of procedure. Upper endoscopic procedures (including stricture dilations) were experienced by 15 and 7% of gastric bypass and vertical sleeve gastrectomy participants, respectively.

Nutritional deficiencies, commonly seen as vitamin B₁₂, thiamine, and vitamin D deficiency, are also a potential significant short- and long-term complication of adolescent bariatric surgery (2). The Teen-LABS study showed 37% of patients were vitamin D deficient at baseline and 43% of gastric bypass and vertical sleeve gastrectomy patients remained deficient at 3 years. Vitamin B₁₂ deficiency increased from 1% at baseline to 8% at 3 years ($P = 0.005$). Additionally, low ferritin levels were seen in 57% 3 years after surgery compared with 5% of patients at baseline ($P < 0.001$) (2). A comprehensive meta-analysis describing surgical and nutritional complications after all bariatric procedures in obese children and adolescents has been published (45).

Type 2 diabetes relapse is another potential complication after bariatric surgery. Retrospective data in adults suggest that up to one-third of adults experience relapse within 5 years of initial remission (35). Diabetes relapse in adults is associated with weight regain, longer duration of diabetes, and insulin use prior to surgery (35,46). Relapse rates in children and adolescents are yet to be published.

Thus, when considering surgical weight-loss procedures as a potential treatment of type 2 diabetes, the risks of surgery need to be thoroughly considered. Discussions that inform patients and families about potential surgical and nutritional complications as well as potential for diabetes relapse are enormously important.

OPTIMAL TIMING OF SURGICAL INTERVENTION FOR TYPE 2 DIABETES IN YOUTH

For adults, the 2011 International Diabetes Federation statement recommends weight-loss surgery should be prioritized

for patients with type 2 diabetes who have a BMI >40 kg/m². Surgery is also indicated for patients with BMI 35–40 kg/m² and poorly controlled diabetes (HbA_{1c} $>7.5\%$) despite fully optimized conventional therapy. The statement also advises consideration of surgery for patients with BMI 30–35 kg/m² if target HbA_{1c} ($<7.5\%$) is not achieved and if other obesity comorbidities are present (47). In adolescents, indications for use of weight-loss surgery in patients with type 2 diabetes have been somewhat less stringent. Surgery has been recommended for those who meet clinical criteria for type 2 diabetes and severe obesity (defined as an absolute BMI ≥ 35 kg/m² or a BMI $\geq 120\%$ of the 95th percentile for age and sex) (48). Although this is a reasonable starting point, individually tailored treatment recommendations (or timing of treatment) taking into account biological factors may be preferable from the standpoint of optimizing the risk-benefit ratio in the future. For example, Khanna et al. (49) recently reported the effect of diabetes duration on outcomes after bariatric surgery in adults. They showed that adults with <5 years duration of type 2 diabetes had better glycemic control, greater insulin secretory capacity, and greater disposition index 2 years after surgery compared with adults with >10 years duration of diabetes independent of weight loss and postprandial incretin response (49). Additionally, Panunzi et al. (50) combined data from the SOS trial and two randomized controlled studies and found shorter diabetes duration, lower fasting glucose before surgery, and that type of surgery (gastric diversion vs. gastric stapling or banding) independently predicted higher rates of diabetes remission. Furthermore, baseline HbA_{1c} and waist circumference predict improved glycemic control postsurgery (50). Taken in conjunction with the TODAY study findings showing that changes in β -cell function (as measured by oral disposition index) after the diagnosis of diabetes in adolescents can predict those with more rapid disease progression, it seems that a better treatment paradigm, informed by both clinical and biological factors, may be useful. Thus, among severely obese adolescents, duration of diabetes, tempo of diabetes therapy escalation, glycemic control, and/or assessment of the rate of β -cell decline during the initial 6 months

after diagnosis should be examined as key factors that drive decisions for use of surgical treatment in youth with type 2 diabetes. This approach would potentially preserve β -cell function, leading to more improved glycemic responses and disease remission and ultimately lower relapse rates.

FUTURE RESEARCH

Although documenting the metabolic and clinical responsiveness of type 2 diabetes in adolescents undergoing surgery is an important preliminary step, future research should also include well-designed, prospective, controlled studies with sufficient sample sizes to definitively assess both the benefits and risks of surgery in this special patient population. Furthermore, study design should incorporate a biologically based treatment algorithm with end points including glycemic response rates early (1–2 years) and late (5+ years) after surgery, estimates of relapse of diabetes, and mechanistic studies aimed at elucidating β -cell functional responses before and after surgery. The inclusion of a well-matched nonsurgical group undergoing medical and behavioral weight management would provide estimates of the extent to which surgery can protect against the progression to end organ damage, including renal (micro- and macroalbuminuria, estimated glomerular filtration rate), vascular (atherosclerosis), nonalcoholic steatohepatitis, retinopathy, and cognitive impairment. Finally, objective measurement of the risks of surgical intervention, including reoperations, nutritional deficiencies, hypoglycemic events, and other adverse outcomes, should be collected. With high-quality data from sufficiently powered studies, the role of surgery in the treatment paradigm for adolescent type 2 diabetes will be better delineated.

CONCLUSIONS

Accumulating evidence suggests that type 2 diabetes in adolescents progresses rapidly and is more aggressive than type 2 diabetes in adults. Type 2 diabetes in youth results in early multi-system target organ damage over time, likely the combined result of hyperglycemia, hypertension, and dyslipidemia among other risk factors. Data from clinical studies demonstrate substantial

improvement in insulin resistance and β -cell function in severely obese youth without diabetes after gastric bypass, and several observational studies also demonstrate high rates of type 2 diabetes remission in youth. These observations support the recommendations for bariatric surgical management of appropriately selected severely obese adolescents with type 2 diabetes (3,48). Decisions regarding optimal timing of surgery for the maximal impact on type 2 diabetes should aim to preserve β -cell secretory function.

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