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ARTICLE

Reversal of Type 2 Diabetes Mellitus and Improvements in Cardiovascular Risk Factors After Surgical Weight Loss in Adolescents

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What's Known on This Subject

T2DM is a significant health problem with infrequent remission after standard medical management. Weight-loss surgery frequently results in remission of T2DM in adults. To date, little detailed information is available regarding the outcome of adolescents with T2DM after weight-loss surgery.

AQ: B

What This Study Adds

We describe the clinical and biochemical outcomes on the largest series of adolescents with T2DM who have undergone gastric bypass. The amelioration of clinical problems associated with T2DM is dramatic when compared to the weight loss and clinical outcomes observed during standard medical management of adolescents with T2DM.

ABSTRACT

OBJECTIVES. Type 2 diabetes mellitus is associated with obesity, dyslipidemia, and hypertension, all well-known risk factors for cardiovascular disease. Surgical weight loss has resulted in a marked reduction of these risk factors in adults. We hypothesized that gastric bypass would improve parameters of metabolic dysfunction and cardiovascular risk in adolescents with type 2 diabetes mellitus.

PATIENTS AND METHODS. Eleven adolescents who underwent Roux en Y gastric bypass at 5 centers were included. Anthropometric, hemodynamic, and biochemical measures and surgical complications were analyzed. Similar measures from 67 adolescents with type 2 diabetes mellitus who were treated medically for 1 year were also analyzed.

RESULTS. Adolescents who underwent Roux-en-Y gastric bypass were extremely obese (mean BMI of 50 ± 5.9 kg/m²) with numerous cardiovascular risk factors. After surgery there was evidence of remission of type 2 diabetes mellitus in all but 1 patient. Significant improvements in BMI (−34%), fasting blood glucose (−41%), fasting insulin concentrations (−81%), hemoglobin A1c levels (7.3%–5.6%), and insulin sensitivity were also seen. There were significant improvements in serum lipid levels and blood pressure. In comparison, adolescents with type 2 diabetes mellitus who were followed during 1 year of medical treatment demonstrated stable body weight (baseline BMI: 35 ± 7.3 kg/m²; 1-year BMI: 34.9 ± 7.2 kg/m²) and no significant change in blood pressure or in diabetic medication use. Medically managed patients had significantly improved hemoglobin A1c levels over 1 year (baseline: 7.85% ± 2.3%; 1 year: 7.1% ± 2%).

AQ: C

CONCLUSIONS. Extremely obese diabetic adolescents experience significant weight loss and remission of type 2 diabetes mellitus after Roux-en-Y gastric bypass. Improvements in insulin resistance, β-cell function, and cardiovascular risk factors support Roux-en-Y gastric bypass as an intervention that improves the health of these adolescents. Although the long-term efficacy of Roux-en-Y gastric bypass is not known, these findings suggest that Roux-en-Y gastric bypass is an effective option for the treatment of extremely obese adolescents with type 2 diabetes mellitus. *Pediatrics* 2009; 123:000

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Key Words
adolescent, type 2 diabetes mellitus, weight loss surgery, gastric bypass

Abbreviations
T2DM—type 2 diabetes mellitus
RYGB—Roux-en-Y gastric bypass
HOMA— homeostasis model assessment
HOMA2-IR—index of insulin resistance
HOMA2%S—index of insulin sensitivity
HOMA2-%B—index of β-cell function

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TYPE 2 DIABETES mellitus (T2DM) has traditionally been considered an adult disease. However, coincident with rising rates of pediatric obesity, the incidence of pediatric T2DM has dramatically increased.[1] Just 2 decades ago, T2DM was rarely seen in adolescent populations, accounting for only 3% of new cases of diabetes each year. Currently, nearly half of all new pediatric diagnoses of diabetes mellitus have features most consistent with T2DM, representing a >10-fold increase in incidence over the last 2 decades. It is widely believed that the etiology of T2DM in young people is attributable to obesity and an underlying predisposition for diabetes. Obese youth with T2DM are also at considerable risk for other comorbidities, including hypertension, dyslipidemia, obstructive sleep apnea, nonalcoholic fatty liver disease, and metabolic syndrome.

Severely obese adults with T2DM benefit from the weight reduction and increased insulin sensitivity, which follows Roux-en-Y gastric bypass (RYGB) surgery. Indeed, 85% of adults with T2DM experience remission after RYGB. The likelihood of remission of diabetes after RYGB is higher in patients with a shorter duration of diabetes.[2] To date, the clinical and metabolic outcome of bariatric surgery for adolescents with T2DM has not been described.

PATIENTS AND METHODS

Study Design

This study was conducted as a retrospective review of clinical data recorded during the course of treatment of adolescents with T2DM. Five academic medical centers with adolescent bariatric surgery programs participated in this study: Cincinnati Children's Hospital Medical Center, Texas Children's Hospital, University of Florida, Children's Hospital of Alabama, and University of Pittsburgh Medical Center. The data for this analysis was based on standard clinical measures collected during routine care.

Surgical Cohort

All subjects ≤21 years of age and with a preoperative diagnosis of T2DM who underwent RYGB between November 2002 and November 2004 having at least 1 year of postoperative follow-up data were included in the study (n[r] = 11). There were 7 females; 10 non-Hispanic white and 1 Hispanic. All the patients were on hypoglycemic agents preoperatively. All underwent a laparoscopic RYGB procedure. Roux limb lengths ranged from 75 cm (when BMI <50 kg/m²) to 150 cm (when BMI ≥ 50 kg/m²). Gastric pouch size was not routinely calibrated but was estimated at 30–45 mL. Perioperative (within 30 days) complications requiring readmission or reoperation were recorded.

Institutional review board approval for retrospective analysis of deidentified clinical data were obtained at each clinical center. For all patients, height, weight, and available laboratory results were obtained from the preoperative visit closest to the time of surgery and from the postoperative visit closest to the 1-year anniversary of surgery, from which BMI was calculated.

Medically Managed Comparison Group

To estimate changes in weight and health status for adolescents with T2DM undergoing routine endocrine care, relevant data were obtained from electronic medical charts from the endocrinology clinic at Cincinnati Children's Hospital Medical Center. All patients with T2DM who presented between January 2002 and April 2005 and were followed for at least 1 year were included for assessment. A variety of both oral medications and insulin preparations was used in the management of these patients over the period of observation. Medication usage was not documented in the electronic medical charts, thus information about prescribed medications was manually abstracted from the endocrinology clinic charts, which were complete and available in only 53 subjects. For analysis, baseline and 1 year status of each patient was classified according to 1 of 4 categories of therapy: (1) diet-controlled, (2) oral agent(s), (3) insulin, (4) both oral agent(s) and insulin. Outcome of medication use over the period of medical management was defined as follows: reduction = any decrease in category of therapy; unchanged = no change in category of therapy; increased = any increase in category of therapy. Changes in dosage of medications within a particular category were not considered in this analysis.

BMI and Blood Pressure Assessments

Participants' BMI was calculated as weight (kg) divided by squared height (m²). BMI values were converted to *z* scores and percentiles using age (to the nearest month)- and gender-specific median, SD, and power of the Box-Cox transformation based on national data from the Centers for Disease Control and Prevention.[3] The heart rate and blood pressure measurements were obtained by using an appropriate-sized cuff during routine clinical care of patients in both cohorts. Blood pressure percentiles were determined by using the National Heart Lung and Blood Institute guidelines and adjusted for age, gender, and height percentile,[4] with prehypertension being classified as either systolic or diastolic blood pressure between the 90th and 95th percentiles, and hypertension classified as systolic or diastolic blood pressure above the 95th percentiles.

Characterization of Glucose Metabolism and Insulin Sensitivity

The homeostasis model assessment (HOMA) was used to calculate indices of insulin resistance and insulin secretion for each patient.[5,6] The HOMA Calculator v2.2.1 (released October 23, 2007, available at www.dtu.ox.ac.uk/homa) used fasting glucose and insulin to generate the index of insulin resistance (HOMA2-IR), insulin sensitivity (HOMA2%S), and an index of ß-cell function (HOMA2-%B). An ideal, normal-weight adult <35 years of age has a HOMA-IR of 1 and HOMA-%B of 100%.[7] Normative HOMA2 data for adolescents have not, to our knowledge, been published previously. Therefore, fasting insulin and glucose data collected from a group of postpubertal, nondiabetic, lean adolescents participating in the Landmarks in the Progression to type 2 diabetes study were used to create normative reference data for comparison.

Statistical Analysis

Statistical analyses were performed by using SAS v9.1 (SAS Institute Inc, Cary, NC). Paired *t* tests were used to evaluate the change in metabolic and anthropometric

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TABLE 1 **Anthropometric and Clinical Characteristics of Surgical Cohort**

Variable	Baseline						1 y						*P*	% Change
	n	Mean	Median	SD	Minimum	Maximum	*n*	Mean	Median	SD	Minimum	Maximum		
Age, y	11	17.81	18.11	2.17	14.28	21.08	11	18.96	19.04	2.05	15.53	22.11		
Weight, kg	11	149.13	142.00	23.79	113.70	183.60	11	97.81	93.70	23.79	113.70	183.60	<.001	−34.4
Weight *z*	11	3.15	3.04	0.47	2.46	3.78	11	1.99	1.95	0.63	1.10	3.20	.0001	
Weight *P*	11	99.82	99.88	0.22	99.30	99.99	11	95.83	97.44	4.16	86.45	99.93	.0047	
Height, cm	11	171.70	171.80	8.55	156.90	182.00	11	171.93	170.60	8.88	157.60	182.70	.95	0.1
Height z	11	0.64	0.41	0.97	−0.97	2.92	11	0.60	0.41	0.92	−0.88	2.72	.91	
Height *P*	11	67.61	66.06	23.00	16.65	99.82	11	66.90	65.97	23.31	18.94	99.68	.94	
BMI, kg/m²	11	50.40	48.24	5.89	43.11	63.35	11	33.07	30.23	7.01	26.27	48.22	<.0001	−34.4
BMI *z*	11	2.76	2.77	0.35	2.25	3.31	11	1.81	1.59	0.57	1.08	2.86	.0001	
BMI *P*	11	99.56	99.72	0.40	0.40	99.95	11	94.64	94.44	4.43	85.90	99.79	.0015	
BMI by category, %														
>99th percentile		91						27						
95th to 98th percentile		9						18						
85th to 94th percentile		0						55						
<85th percentile		0						0						
Ideal weight, kg	11	62.18	63.00	6.55	51.70	70.20	11	64.45	63.30	8.07	53.80	76.30		
Overweight, %	11	140.20	141.03	32.84	98.66	199.82	11	59.99	63.61	16.75	31.58	81.67	<.0001	
Excess weight, kg	11	86.95	77.90	20.90	59.00	120.60	11	33.35	20.90	20.07	14.50	69.70	<.0001	
Excess weight loss, %							11	60	64	17	32	82		
SBP, mm Hg	11	129.64	130.00	18.00	110.00	168.00	10	120.10	116.00	14.62	0.00	141.00	.20	−7.4
SPB *z*	11	1.38	1.08	1.59	−0.85	4.37	10	0.40	0.47	1.31	−2.13	2.16	.14	
SPB *P*	11	76.14	86.10	26.68	19.76	100.00	10	61.87	67.88	33.79	1.67	98.46	.29	
DBP, mm Hg	11	77.00	76.00	9.28	64.00	90.00	10	62.00	62.00	6.67	0.00	78.00	.0005	−19.5
DBP *z*	11	0.82	0.59	1.00	−0.68	2.37	10	−0.61	−0.59	0.84	−1.76	1.31	.0022	
DBP *P*	11	71.47	72.25	25.55	24.78	99.11	10	29.98	27.88	24.47	3.89	90.50	.0012	
HTN, %		45.5						20					.03	
Pre-HTN, %		9						10					.75	
Heart rate, bpm	8	91.38	91.00	9.91	76.00	106.00	10	73.70	75.00	14.50	46.00	90.00	<.01	−19.3

HTN indicates ●●●; SBP, systolic blood pressure; DBP, diabolic blood pressure; bpm, beats per minute.

measures between preoperative and 1 year postoperative measures by patient. Not all measures and values were available for each patient at both time points and the missing values varied because of differences in individual patient care. Comparisons between longitudinal changes in the surgical and medically managed groups were performed by using unpaired *t* tests.

RESULTS

Characterization of the Surgical Cohort at Baseline

The mean weight and BMI in this group at baseline were 149 kg (range: 113–184 kg) and 50 kg/m² (range: 43–63 kg/m²), respectively (Table 1). T1/AQ:D All were obese or extremely obese (BMI >99th percentile for age and gender). The group as a whole was 140% overweight (87 kg above ideal weight). Nearly half (46%) demonstrated elevated blood pressure (≥95th percentile for age, gender, and height), and an additional 9% had blood pressure readings in the prehypertensive range (90th to 94th percentile). At baseline, 10 patients were managed with oral hypoglycemic agents, and 1 was treated with insulin and oral agents. Despite medical therapy, fasting glucose and insulin, were abnormally elevated (Table 2) at baseline. T2 Insulin sensitivity, as measured by HOMA2%S was 22% at baseline. Data from the lean adolescent population provided the following reference percentiles of HOMA2%S: 5th = 34%, 50th = 75.4%, and 95th = 151%, respectively (Table 3), demonstrating that surgical patients were markedly insulin resistant at baseline. T3

Characterization of the Surgical Cohort 1 Year After Gastric Bypass

Postoperatively all patients lost weight, ranging from 33 to 99 kg. BMI values fell by 34 ± 0.1% (Table 1); however, none of the patients achieved a nonoverweight (BMI <85th percentile) status.

Treatment with RYGB was associated with a dramatic effect on the metabolic profile in this adolescent diabetic cohort. Oral hypoglycemic agents were discontinued in 10 patients who had previously used them for glycemic control. One patient, who received insulin and oral diabetic medication before surgery, showed metabolic improvement but remained diabetic (HbA1c before and after surgery was 10.5% and 7.6%, respectively). This patient required a significantly lower dose of insulin postoperatively (238 U/d preoperatively; 88 U/d postoperatively) without additional oral therapy.

Despite discontinuation or reduction of T2DM medications in the surgical group, major improvements in glycemic control were observed (Table 2; Figure 1). F1 Mean preoperative fasting glucose in the previously diabetic patients was 144 ± 57 mg/dL, whereas postoperatively the mean 85 ± 16 mg/dL for 8 patients with data available. Postoperatively, no one had levels in the dia-

TABLE 2 Biochemical Characteristics of Surgical Cohort

Variable	Baseline						1 y						*P*	% Change[a]
	n	Mean	Median	SD	Minimum	Maximum	*n*	Mean	Median	SD	Minimum	Maximum		
Glucose, mg/dL	10	143.80	118.5	56.88	87	241	8	84.50	86.5	15.70	53	110	.0282	−41
Insulin, μIU/mL	7	44.43	36	18.24	20.1	66.7	7	8.66	8.1	3.20	3.7	13	.0056	−81
HbA1c %	8	7.33	6.35	2.07	5.5	10.5	5	5.58	5.2	1.32	4.2	7.6	.0410	−2
HOMA2%B	7	164.90	176.5	81.60	40.5	267.1	7	112.10	96.9	48.80	68.8	213.6	.0839	−32
HOMA2%S	7	22.90	23.5	11.30	13.3	45.5	7	124.81	110.8	64.31	69	247.3	.0068	445
HOMA2-IR	7	5.20	4.3	2.00	2.2	7.5	7	0.96	0.9025	0.38	0.404	1.4493	.0016	−82
Triglyceride, mg/dL	8	213.38	207	73.18	115	319	6	83.00	70.5	47.89	34	166	.0038	−61
Cholesterol, mg/dL	8	202.13	191.5	38.46	162	273	6	143.00	142	24.49	114	176	.0163	−29
HDL, mg/d	8	38.88	37	12.71	19	56	6	44.17	39.5	9.95	35	60	.2269	14
LDL, mg/dL	8	119.50	115.5	28.68	88	177	6	82.33	78.5	20.25	60	115	.0307	−31
ALT, U/L	9	61.6	56.0	32.8	22.0	124.0	9	30.0	26.0	16.0	14.0	61.0	.0	−51
AST, U/L	9	44.7	42.0	16.2	22.0	72.0	9	28.1	28.0	8.8	11.0	44.0	.0	−37

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

[a] The % change represents a quotient of baseline versus 1-year mean values.

TABLE 3 Lean Control Reference Data for HOMA2 Parameters

Variable	*n*	Mean	Median	SD	Minimum	Maximum	5th Percentile	95th Percentile
Age, y	199	17.11	17.36	1.85	13.41	20.87		
BMI *z*	199	0.53	0.57	0.22	0.07	0.85		
Glucose, mg/dL	199	80.39	79.40	6.78	70.00	99.80	71.20	93.90
Insulin, μIU/mL	199	14.37	12.35	9.17	3.90	75.20	6.10	26.90
HOMA2%B	199	160.17	153.70	59.16	67.20	584.40	88.70	239.50
HOMA2%S	199	82.03	75.40	37.30	13.00	232.80	34.30	151.00
HOMA2-IR	199	1.54	1.33	0.94	0.43	7.69	0.70	2.90

These HOMA2 values were calculated based on glucose and insulin measurements in lean, healthy adolescents who participated in the Landmarks in the Progression to Type 2 Diabetes study in Cincinnati, Ohio.

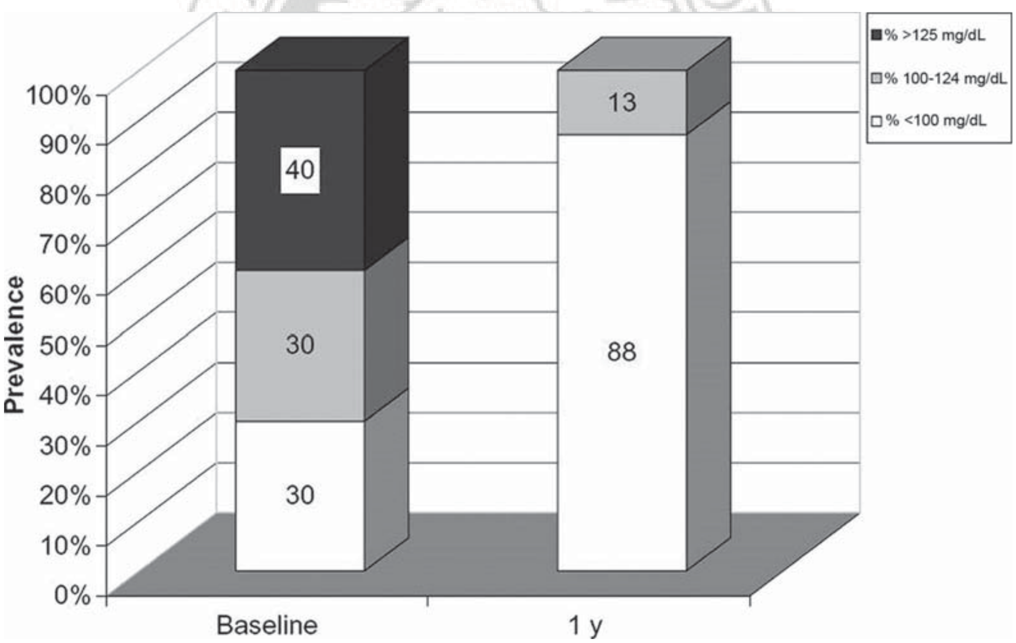

FIGURE 1
Change in prevalence of abnormal glucose homeostasis in the surgical cohort. Baseline (Preop) data were compared with data at 1 year after RYGB (Postop).

betic range (>125 mg/dL), although the single patient still on insulin therapy postoperatively did not have a fasting glucose value included in this data set. Overall, the mean fasting glucose fell by 41% after surgery. HbA1c values were available for 5 surgical patients at 1 year and in 4 of these 5, the value was < 6.2%. The mean HbA1c value at 1 year was 5.6 ± 1.3%, an average decrease of 1.7% (range: −0.7 to −6.1%). The mean

TABLE 4 Medically Managed Cohort

Variable	Baseline						1 y						*P*	% Change
	n	Mean	Median	SD	Minimum	Maximum	*n*	Mean	Median	SD	Minimum	Maximum		
Age, y	67	15.45	15.00	1.83	13	21	67	16.4	16.055	1.84	13.8	22.1		
Weight, kg	67	101.94	97.00	28.59	41	179	67	102	93.4	27.6	57.5	172	.7927	−0.3
Weight z	67	2.37	2.48	1.16	−4	4.3	67	2.26	2.3373	0.95	−0.5	4.35	.1210	
Weight *P*	67	95.41	99.34	13.61	0	100	67	94.6	99.029	11.6	30.7	100	.2324	
Height, cm,	67	168.53	166.87	10.75	140	196	67	170	168	10.8	141	198	.0124	0.8
Height z	67	0.62	0.70	1.41	−4.9	4.23	67	0.53	0.6272	1.24	−3.3	3.9	.2012	
Height *P*	67	66.09	75.70	31.37	0	100	67	63.3	73.473	31.1	0.05	100	.0001	
BMI, kg/m^2	67	35.40	34.40	7.32	21	52.5	67	34.9	34.106	7.22	21.7	53.9	.1371	−1.6
BMI z	67	2.16	2.26	0.62	−0.3	3.1	67	2.06	2.1677	0.68	−0.3	3.06	.0033	
BMI *P*	67	96.12	98.82	8.96	39	99.9	67	95.1	98.491	10.1	38.7	99.9	.0111	
BMI by category, %														
>99th percentile		0.43						42						
95th to 98th percentile		0.42						40						
85th to 94th percentile		0.07						6						
<85th percentile		0.07						12						
SBP, mm Hg	67	117.91	120.00	13.76	88	152	67	119	120	12.3	96	146	.4324	1.0
SPB *z*	67	0.44	0.38	1.19	−2.4	3.25	67	0.46	0.5382	1.1	−1.6	2.44	.8578	
SPB *P*	67	61.42	64.90	31.23	0.7	99.9	67	61.9	70.478	31	5.1	99.3	.9052	
DBP, mm Hg	67	72.90	72.00	10.28	42	90	67	72.1	70	9.69	40	96	.6032	−1.1
DBP z	67	0.59	0.53	0.90	−2.2	2.29	67	0.47	0.4335	0.85	−2.3	2.76	.3672	
DBP *P*	67	67.96	70.33	25.21	1.5	98.9	67	64.3	66.766	23.9	0.96	99.7	.3462	
Pre-HTN, %	67	0.25					67	13					.0077	
HTN, %	67	0.18					67	21					.5930	
HbA1C		7.84	7.20	2.27	4.5	14.9	67	7.07	6.4	1.95	4.8	14	.0047	−0.8

SBP indicates systolic blood pressure; DBP, diabolic blood pressure; HTN, ●●●.

postoperative fasting insulin level in the surgically treated patients was 8.7± 3μU/mL, an 81% decrease. For 7 patients with paired insulin and glucose measurements before and 1 year after operation, HOMA%B fell by 32%, and HOMA2%S normalized to 124% (equivalent to the 85th percentile, based on the lean adolescent reference population).

Clinically important changes in blood pressure were seen postoperatively (Table 1). Although not reaching statistical significance, mean systolic blood pressure declined after surgery (129.6 ± 18 vs 120 ± 16 mm Hg; *P* = .2). Mean diastolic blood pressure was significantly lower after RYGB (77 ± 9 vs 62 ± 7 mm Hg, *P* = .0005). Importantly, only 20% of patients had either systolic or diastolic hypertension after surgery compared with 46% before surgery. In addition, heart rates significantly decreased by 19% by 1 year after gastric bypass.

For 8 patients in whom lipid values were available, there were marked improvements in dyslipidemia after surgery (Table 2). Triglyceride values decreased by 61% (213 ± 73 vs 83 ± 48 mg/dL; *P* = .004), whereas total cholesterol decreased by 29% (202 ± 38 vs 143 ± 24 mg/dL; *P* = .02), and LDL cholesterol decreased by 31% (119 ± 29 vs 82 ± 20 mg/dL; *P* = .03). Although an improvement was also seen in HDL values, this finding did not reach statistical significance in this small group. Finally, significant reductions in hepatic transaminases were also recorded in 9 patients, suggestive of improvement in fatty liver disease (Table 2).

There were no intraoperative complications noted. Perioperatively (within 30 days of surgery), 1 patient required a 1-day readmission for dehydration. One patient conceived at 11 months after operation and experienced an 11-kg weight gain during pregnancy. There was no evidence of gestational diabetes in this patient who was monitored closely, and a healthy 3.2-kg infant girl was delivered transvaginally without obstetrical complications.

Comparison to a Medically Managed Group

To put the surgical outcomes data into context, the clinical outcome of 67 adolescents with T2DM managed medically for 1 year was retrospectively reviewed. As shown in Table 4, the mean age of this comparison T4
group was 15.5 years and similar to the surgical cohort, 40% were males. Both obesity and extreme obesity were commonly found with 82% having a BMI for age/gender ≥95 percentile. The mean BMI for this cohort was 35 kg/m². Similar to our operative cohort, this group was also skeletally mature and therefore no change in height (<1%) occurred over the 1-year interval. BMI decreased by 1.6% (*P* = .14) over 1 year of medical management, with no major changes in the weight class distribution. Indeed, 85% were obese or extremely obese at 1 year. Comparison of the baseline BMI values in the surgical compared with the medically managed group demonstrated significantly higher values in the surgical group (50 ± 6 kg/m² vs 35 ± 7 kg/m², *P* < .001) and significantly greater reduction in BMI in the surgical compared with medically managed group over 1 year of observation (*P* < .001).

Mean HbA1c was 7.8 ± 2.3% at the start of follow-up and 7.1 ± 2% after 1 year (*P* = .005; Table 4). The prevalence of elevated blood pressure in this medically

TABLE 5 **Medication Use in the Medically Managed Cohort**

Baseline	*n*	1 y	*n*	%
Diet-controlled	4	Reduced	0	0
		Unchanged	2	50
		Increased	2	50
Oral agent only	23	Reduced	1	4
		Unchanged	17	74
		Increased	5	22
Insulin only	12	Reduced	4	33
		Unchanged	5	42
		Increased	3	25
Insulin + oral agent	14	Reduced	7	50
		Unchanged	7	50
		Increased	0	0
Total	53	Reduced	12	22.6
		Unchanged	31	58.5
		Increased	10	18.9

Medication use data for only 53 of 67 subjects in the medically managed cohort was available at the time of this analysis. "Reduced" refers to a decrease in category of diabetes treatment (eg, those on an oral agent become diet controlled, those on insulin become oral or diet controlled, or those on insulin + oral have reduction in treatment to insulin only or to oral only or to dietary control). "Unchanged" refers to no change in category of treatment. "Increased" refers to escalation in diabetes therapy. The % column refers to the proportion of subjects in each category who reduced, did not change, or increased in category of diabetes therapy over the 1-year period of observation.

managed diabetic cohort was 20% and did not change over time, whereas the prevalence of blood pressures in the prehypertensive range did significantly decrease from 25% prevalence at baseline to 13% at 1 year (Table 4).

In the medically managed group, 8% to 9% of patients were managed with dietary changes alone, whereas >90% were managed with single or combination medical therapy (Table 5). Over the year, no changes in category of treatment were seen for the majority (58.5%) of patients. Overall, 19% of subjects experienced an increase, and 23% experienced a decrease in category of therapy.

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DISCUSSION

Extreme obesity (≥99th percentile of BMI for age) may affect 2% and 6% of all children and adolescents. Youth are increasingly developing health complications of obesity[8,9] and also increased morbidity and later mortality compared with nonobese youth.[10–15] Given the increasing prevalence of childhood obesity, some have suggested that T2DM could develop in as many as 33% to 50% of all Americans born in the year 2000.[16]

We previously found a 10-fold increase in the incidence of adolescent T2DM in Cincinnati from 1982 and 1994.[1] Up to 25% of obese children and adolescents have impaired glucose tolerance,[17,18] and 4% to 6% are at risk of T2DM. In addition, many obese children have insulin resistance, which may contribute to a number of serious sequelae of obesity including T2DM, metabolic syndrome, polycystic ovary syndrome,[19,20] steatohepatitis,[21] and even sleep apnea.[22] Fifty percent of severely obese adolescents (mean BMI = 41 kg/m²) satisfied criteria for metabolic syndrome.[23] Thus, effective treatment options for adolescent obesity, insulin resistance, and diabetes are critically needed.

The pathogenesis of T2DM involves a reduction in insulin sensitivity and a progressive decrease in the acute insulin response of β-cells to glucose levels, both of which seem to worsen over time.[24–28] Obese individuals who are insulin resistant but do not have T2DM are able to maintain normal glucose levels by increasing their acute insulin response proportionally to the degree of insulin resistance. T2DM develops when β-cells are unable to compensate for increased insulin demands.[29]

There is clear evidence from adult studies dating back to the early 1990s that bariatric surgery results in remission of established T2DM.[30,31] Dixon et al[32] demonstrated 73% remission of T2DM in subjects treated for 2 years with an adjustable gastric band compared with 13% remission in patients assigned randomly to medical and dietary management of their T2DM. Observational studies have also demonstrated that surgical weight loss likely prevents T2DM in populations at high risk.[2,31,33,34] Improvements in glycemic control occur early in the postsurgical recovery phase, within days to weeks after surgery, even before major weight loss is achieved. Insulin sensitivity and β cell function also improve significantly after surgical weight loss.[35–39] To our knowledge, there are no other antidiabetic therapies that result in more effective and long-term glycemic control than that seen with bariatric surgery.

No previous studies have examined the response of adolescents with T2DM to surgical weight reduction. We postulated, based on the experience in adults, that adolescents with T2DM would derive both metabolic and weight-loss benefits from RYGB. Postoperatively, it is interesting to note that the surgical cohort remained markedly obese with a mean BMI quite similar to that of the medically managed group (33 ± 7 vs 35 ± 7 kg/m²). However, biochemical and medication use data strongly support the hypothesis RYGB can result in remission of diabetes and dramatic improvement in metabolic health, despite remaining markedly obese. Conversely, although glycemic control modestly improved in the medically managed comparison group, this group experienced no major changes in weight, medication usage, or blood pressure.

In addition to improved glycemic control in this cohort of diabetic youth undergoing RYGB, we note that the patients experienced significant and important improvements in measures of fatty liver disease, blood pressure, serum triglycerides, and total cholesterol. These observations are consistent with the experience in adult diabetics undergoing bariatric surgery.[2,31,34] These data further suggest that adolescent diabetics who undergo surgical weight loss may experience a reduction in risk of cardiovascular events and obesity-related liver disease later in life. Although numerous well-designed studies have demonstrated a significant survival benefit for adults who undergo weight-loss surgery,[40–44] and specifically a reduction in cardiovascular mortality,[43] more research will be required to assess these longer term end points for adolescents undergoing bariatric surgery.

One of the surgical patients in this study did not experience resolution of diabetes. In this case, BMI decreased by 30% (BMI change from 51 to 35.5 kg/m²;

50-kg weight loss), and he required substantially less insulin for superior glycemic control. The reason for this persistent requirement for medication is not clear but a strong family history was present in this case as the patient has a younger sibling and mother with T2DM. Follow-up at 3 years after surgery revealed that the BMI was further reduced to 23 kg/m^2 and yet he remained on medication for glucose control. This case is interesting when viewed in light of the adult experience with surgical treatment of T2DM. Although significant improvements in carbohydrate metabolism occur after surgical weight loss in adults, studies also demonstrate that in response to a glucose challenge there is only incomplete normalization of parameters of insulin secretion and insulin resistance.[35,36,38,45,46] A plausible explanation for lack of complete correction is that over time, diabetics experience progressive β cell dysfunction that may not be recoverable even after bariatric surgery. Indeed, data suggest that the frequency of remission of T2DM is inversely related to age at time of surgery, to duration of diabetes, and severity of disease (diet-controlled insulin dependent).[2,30,39] Thus, a greater benefit may be derived by reducing insulin resistance earlier in the course of T2DM to prevent β cell fatigue, perhaps before the requirement of insulin therapy.

This study has several important limitations. First, the limitations imposed by the retrospective review of data collected during routine clinical care of patients at multiple institutions without the benefit of common patient management protocols are numerous. Specifically, analysis of change in metabolic status suffered from missing data, particularly laboratory data at 1 year in the surgical cohort. In addition, HbA1c, an important marker for disease status, was only available in 5 of the 11 patients at the 1-year time point. Second, there was no standardization of laboratory assays for the biochemical variables reported in this study. However, in the design of this retrospective study, we did define the acceptable timeframes and uniformly applied data definitions. Third, it was not possible to match cohorts on even a small number of characteristics because of the small numbers of patients available. For instance, there were only 8 medically managed diabetics with BMI within the range of the surgical cohort (43–63 kg/m^2). However both the Centers for Disease Control and Prevention and NHLB analysis programs used to calculate BMI and blood pressure percentiles control for age, gender, and height. Finally, we are reporting data on a small number of surgical patients over a relatively short follow-up period and therefore this experience could differ when a larger population of adolescents is studied longitudinally. A prospective collection of surgical outcome data are now underway at several institutions to verify these results (the Teen-LABS study; www.cchmc.org/teen-LABS).

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Despite these limitations, the study also has several strengths. We have for the first time, to our knowledge, detailed the clinical and metabolic changes that might be expected for adolescents with T2DM who undergo RYGB. We also demonstrate that a small group of adolescents with T2DM can undergo a major operation safely. These data may prove useful for clinical decision-making and designing prospective studies. For example, reporting the variability in weight loss and change in blood pressure and laboratory parameters to be expected in both surgical and nonsurgical cohorts should allow future investigators to more accurately predict sample sizes needed to verify and extend these findings. The lack of any major medical or surgical complications suggests that the risk/benefit ratio for RYGB in adolescents with T2DM is favorable. This is not unexpected, because these adolescents have likely not yet developed the cardiovascular pathology that is seen in obese diabetic adults. Indeed, recent analyses suggest that both perioperative morbidity and mortality risks may be lower for adolescents compared with adults undergoing bariatric surgery.[47,48]

A final strength of this report is the important comparison data derived from a group of markedly obese medically managed adolescents with T2DM. This "natural history" data from a relatively large adolescent diabetic cohort is informative and is rarely found in the literature. The findings demonstrate that weight reduction is not typically achieved by adolescent diabetics, even under optimal conditions. In addition, the magnitude of the improvement in T2DM disease status, as measured by HbA1c and medication usage, may well be superior with surgery.

CONCLUSIONS

Our observations provide evidence that bariatric surgery reverses or significantly improves T2DM in adolescents over a 1-year period, further supporting the role of surgery outlined in recent treatment recommendations.[49] In addition, we document significant improvement in major cardiovascular risk factors. Thus, in selected cases, surgical weight loss seems to provide an effective method to reverse adverse health outcomes, at least for the short-term. However, the long-term safety and efficacy of bariatric surgery in adolescents remains to be firmly established. If the concept of metabolic memory demonstrated in the EDIC study[50,51] applies, we hypothesize that earlier rather than later surgical intervention in selected subjects (severely obese diabetics refractory to medical therapy or at high risk for morbidities associated with T2DM) may be an effective method for providing tight control of hyperglycemia, and thus preventing adverse health outcomes in the long-term. However, to properly test this hypothesis, larger cohorts who are prospectively studied for longer periods of time will be needed.

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AUTHOR QUERIES

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AQA—AUTHOR: Center for Epidemiology and Biostatistics at Cincinnati Children's Hospital was deleted because no authors were attached to it. Please verify, or edit as necessary.

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