Insulin Sensitivity and β-Cell Function Improve after Gastric Bypass in Severely Obese Adolescents

Thomas H. Inge, MD, PhD[1], Ronald L. Prigeon, MD[2], Deborah A. Elder, MD[1], Todd M. Jenkins, PhD[1], Robert M. Cohen, MD[3], Stavra A. Xanthakos, MD, MS[1], Stephen C. Benoit, PhD[3], Lawrence M. Dolan, MD[1], Stephen R. Daniels, MD, PhD[4], and David A. D'Alessio, MD[5,6]

Objective To test the hypothesis that insulin secretion and insulin sensitivity would be improved in adolescents after Roux-en-Y gastric bypass (RYGB).

Study design A longitudinal study of 22 adolescents and young adults without diabetes undergoing laparoscopic RYGB (mean age 17.1 ± 1.42 years; range 14.5-20.1; male/female 8/14; Non-Hispanic White/African American 17/5) was conducted. Intravenous glucose tolerance tests were done to obtain insulin sensitivity (insulin sensitivity index), insulin secretion (acute insulin response to glucose), and the disposition index as primary outcome variables. These variables were compared over the 1 year of observation using linear mixed modeling.

Results In the 1-year following surgery, body mass index fell by 38% from a mean of 61 ± 12.3 to 39 ± 8.0 kg/m^2 ($P < .01$). Over the year following surgery, fasting glucose and insulin values declined by 54% and 63%, respectively. Insulin sensitivity index increased 300% ($P < .01$), acute insulin response to glucose decreased 56% ($P < .01$), leading to a nearly 2-fold increase in the disposition index ($P < .01$). Consistent with improved β-cell function, the proinsulin to C-peptide ratio decreased by 21% ($P < .01$).

Conclusions RYGB reduced body mass index and improved both insulin sensitivity and β-cell function in severely obese teens and young adults. These findings demonstrate that RYGB is associated with marked metabolic improvements in obese young people even as significant obesity persists. *(J Pediatr 2015;167:1042-8)*.

Trial registration ClinicalTrials.gov: NCT00360373.

Severe obesity in youth is increasing in prevalence[1,2] and strongly associated with insulin resistance (IR)[3] and other comorbidities.[2] In response to IR, hypersecretion of insulin is required to maintain normal glucose tolerance.[3-6] Increasing rates of obesity and IR have been linked to the development of type 2 diabetes mellitus (T2DM) in adolescents, a condition virtually unheard of in this age group until the last 2 decades.[7,8] Thus, it seems inevitable that the increasing prevalence and severity of pediatric obesity will translate into increased IR, glucose intolerance, and diabetes in the future.

In contrast to outcomes of dietary/lifestyle interventions,[9-11] bariatric surgery causes substantial and durable weight reduction.[12] In adults, the response to surgery also includes a reduction of IR[13-15] and improvement or resolution of T2DM.[16] Longitudinal studies of adults without diabetes treated with gastric banding, Roux-en-Y gastric bypass (RYGB), or biliopancreatic diversion have demonstrated that IR improves in proportion to weight loss, and that insulin secretion is greater relative to insulin sensitivity.[13,17-19] Whereas bariatric surgery is increasingly common among middle-aged people with body mass index (BMI) >40 kg/m^2, in adolescents, these procedures have been reserved for the severely obese in whom there is sufficient concern about end-organ damage from excess body weight to justify an invasive intervention. Although prior studies have suggested improvement in IR and glucose metabolism among adolescents having bariatric surgery,[20,21] detailed metabolic analyses have not yet been reported in this age group. We hypothesized that adolescents with severe

AIR_G	Acute insulin response to glucose
BMI	Body mass index
CP	C-peptide
DI	Disposition index
IR	Insulin resistance
IV	Intravenous
IVGTT	Intravenous glucose tolerance test
PI	Proinsulin
RYGB	Roux-en-Y gastric bypass
S_I	Insulin sensitivity index
T2DM	Type 2 diabetes mellitus

From the [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [2]University of Maryland School of Medicine, and Baltimore VA Medical Center Geriatric Research, Education and Clinical Center, Baltimore, MD; [3]Department of Psychiatry, University of Cincinnati, Cincinnati, OH; [4]University of Colorado School of Medicine, Denver, CO; [5]Division of Endocrinology, Diabetes and Metabolism, Duke University Medical Center; and [6]Durham Veteran's Affairs Medical Center, Durham NC

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obesity would have improvements of insulin sensitivity and insulin secretion, the key factors governing glucose tolerance, following RYGB.

Methods

Participation was offered to consecutive patients who were 14-20 years of age and were preparing to undergo bariatric surgery at our institution. The decision to undergo weight loss surgery was made collaboratively by the patient, caregiver(s), and clinical staff, independent of this research protocol. Adolescents were enrolled (n = 22) who were on no medications that affect glucose metabolism, and who were without a prior diagnosis of T2DM. For subjects younger than age 18, informed written permission was obtained from a parent or legally authorized representative, and assent was obtained from the adolescent. For those 18 years and older, informed written consent was obtained directly. The study was approved by the Institutional Review Board at Cincinnati Children's Hospital Medical Center.

Subjects were assessed at baseline (within 1 month of surgery), and 2 weeks, 3 months, and 1 year postoperatively. Major comorbid conditions at baseline were abstracted from medical records. At each study visit, height was measured on a wall mounted stadiometer and weight on an electronic scale (Scale-Tronix 5200; Scale Tronix, White Plains, New York), and a frequently sampled intravenous glucose tolerance test (IVGTT) was performed.

Operative Procedure

RYGB was performed laparoscopically creating a small (20-30 mL), vertically oriented gastric pouch immediately distal to the gastroesophageal junction. This pouch was completely separated from the fundus and remainder of the stomach. The jejunum was divided 25-50 cm distal to the ligament of Treitz and a Roux limb of 75-150 cm was created, which was anastomosed to the gastric pouch using a hand-sewn technique resulting in a 1 cm gastrojejunal stoma. A jejunojejunostomy was performed in a stapled side to side fashion to complete the Roux en-Y reconstruction. Perioperative complications of subjects enrolled in this study have been previously analyzed and published.[22,23]

Frequently Sampled IVGTT

Subjects were instructed to eat their usual diet, avoid strenuous exercise, and fast (except for water) for 10 hours prior before coming to the Clinical Translational Research Center for evaluation. They were admitted to the Clinical Translational Research Center in the morning and had intravenous (IV) cannulae placed in each arm. Two basal blood samples were taken over 15 minutes, and a bolus of IV glucose (250 mg of glucose per kg of body weight) was infused over 30 seconds starting at time zero. Blood samples were drawn at 2, 3, 5, 7, 10, 12, 14, 16, and 19 minutes. At 20 minutes, insulin (0.02 units of regular insulin per kg of body weight) was administered as an IV infusion over 5 minutes, as previously described.[24] Additional blood samples were obtained at 22, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, and 240 minutes. Blood samples were placed on ice and centrifuged within 1 hour. Plasma glucose was measured immediately using an automated glucose analyzer (YSI, Yellow Springs, Ohio). The remaining plasma was stored at −20°C until assayed for insulin, proinsulin (PI), and C-peptide (CP).

Biochemical Measurements and Calculations

Insulin was measured by radioimmunoassay using a guinea pig anti-insulin serum, ^{125}I-labeled insulin as tracer and a double-antibody method of separating bound from free peptide.[25] The sensitivity of this assay was 2 pM, the intra- and interassay coefficients of variation were 5% and 7%, respectively. CP and PI were measured using commercially available radioimmunoassay (Millipore, Billerica, Massachusetts) according to the manufacturer's protocol.

Fasting values of glucose and insulin were taken as the mean of the 2 samples drawn before the glucose bolus. Fasting insulin values of >118.2 pM were considered abnormally elevated (hyperinsulinemia). The insulin cut-point of 118.2 pM was selected as it corresponds to the 85th percentile of fasting serum insulin concentrations measured in our laboratory for a cohort of nonoverweight, nondiabetic, postpubertal adolescents (mean age 17.1 years, age range 13-20 years, 50% female, 50% Caucasian, mean BMI percentile = 53rd [BMI percentile range 7th-84.9th]) who participated in the Princeton School District Study.[26] The acute insulin response to glucose (AIR_G), expressed as pM, was computed as the average incremental insulin response above fasting levels for samples obtained from 2-10 minutes after IV glucose administration. Insulin sensitivity index (S_I), expressed as 10^{-5} $pM^{-1}\cdot min^{-1}$, was determined from the glucose and insulin values during the IVGTT using the minimal model of glucose kinetics.[27] The disposition index (DI), was computed as the product of AIR_G and S_I,[5] and expressed as $10^{-5}\cdot min^{-1}$. PI to CP ratio was computed for each subject using the mean values of fasting samples.

Statistical Analyses

Descriptive statistics for categorical variables were presented using counts and frequencies, and continuous variables were presented as means and SDs (for normally distributed data) or medians and IQR (for data that were not normally distributed). Pearson correlation coefficient was calculated to assess the relationship between baseline BMI and BMI loss at 1-year postop. Linear mixed modeling (SAS Proc Mixed, SAS Institute, Inc, Cary, North Carolina) was used to evaluate postoperative trends in BMI and IVGTT experimental outcomes. Reported percent change from baseline and associated *P* values were derived from model-based least squares means. For a subgroup of 15 subjects, paired *t* tests were used to evaluate baseline to 1 year postoperative differences in PI, CP, and PI to CP ratio.

Overall, 75% (66 of 88) of anticipated study visits were completed. Study time point completion was as follows: baseline, 100%; 2 weeks, 59%; 3 months, 73%; and 1 year, 68%. Ten of the 22 subjects completed all 4 study visits, and the remaining 12 missed at least 1 visit. These 2 subject groupings were compared and found to be similar in terms of demographics and baseline characteristics (data not shown). To address missing data, we performed multivariate imputation by chained equations using IVEware software (Survey Methodology Program, Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, Michigan) to generate 20 imputed data sets for use in the mixed modeling analyses (SAS Proc MiAnalyze, SAS Institute Inc, Cary, North Carolina). Modeling results with and without imputed data were not meaningfully different. Therefore, we elected to present findings from the latter.

Results

Of the 22 subjects included in the analysis, who were enrolled between August 2005 and March 2008, 63.6% (n = 14) were female and 77.3% (n = 17) identified as non-Hispanic, white. The mean age at surgery was 17.1 years (SD = 1.42), with a range from 14-20. Comorbidities at baseline included obstructive sleep apnea, 75%; hypertension (on medication), 28%; polycystic ovary syndrome, 25%; and dyslipidemia, 68%. Mean BMI at baseline was 61.1 ± 12.3 kg/m^2, with a range from 46.0-88.5 kg/m^2 (Table I). Complications within 30 days of operation in this cohort included 4 subjects requiring reoperation (1 for gastrointestinal leakage, 3 for small bowel obstruction), one who was readmitted for dehydration, and 3 with gastrojejunal anastomotic strictures requiring endoscopic dilation. By 1 year following RYGB, BMI declined by a mean of 38% from baseline to 39 ± 8.0 kg/m^2; $P < .01$. There was a significant trend for weight loss over 1 year to be greater in subjects with the highest starting BMI (r = −0.69; $P < .01$).

Fasting Glucose and Insulin before and after Surgery

Mean fasting glucose at baseline was 95.5 mg/dL (Table I). However 6 of the 22 (27%) subjects had impaired fasting glucose (>100 and <126 mg/dL). None had baseline fasting glucose values ≥126 mg/dL. Two weeks following surgery, fasting glucose values declined by 11% ($P < .01$), and this level was maintained through 12 months of postoperative follow-up. At all follow-up visits, fasting glucose values were below 100 mg/dL except for 1 subject who had a fasting glucose of 111 mg/dL at 3 months. Median fasting insulin values were 120.2 pM at baseline and decreased by 45% by 3 months postoperatively ($P < .01$; Table I). At baseline, 54.5% (12 of 22) were hyperinsulinemic, and 46.2% (6 of 13), 6.3% (1 of 16), and 0% (0 of 15) were hyperinsulinemic at 2 weeks, 3 months, and 12 months, respectively.

Measures of IV Glucose Tolerance

Measures of insulin secretion (AIR_G), insulin sensitivity (S_I), and IV glucose tolerance (k_g) before and after surgery are presented in Table I. The IV glucose dosing was based upon body weight at the time of each visit, an approach that is typical for this method. However, because of the steady weight loss after surgery, the glucose challenge was relatively smaller in the later studies as indicated by lower peak blood glucose levels during the IVGTT; lower peak insulin excursions in response to IV glucose challenge were also seen at 1 year (Figure 1). IV glucose tolerance, reflected by k_g, was normal at baseline (≥1.5%/min) and did not change significantly over the 1 year of follow-up. At baseline, mean AIR_G was 895.1 pM and did not change significantly over the first 3 months after surgery. However, by 12 months, AIR_G had decreased by 56% from baseline ($P < .01$; Table I). S_I was low in these subjects at baseline (Table I), reflecting marked IR. There was a steady improvement in S_I following surgery,

Table I. Subject characteristics and outcomes by study visit

	Baseline (N = 22)	3 mo (N = 16)	12 mo (N = 15)	*P* value*
Age at surgery, $\bar{x}(SD)$	17.1 (1.42)	16.9 (1.58)	17.2 (1.48)	NA
Female, % (n)	63.6% (14)	56.2% (9)	60.0% (9)	NA
White race, % (n)	77.3% (17)	75.0% (12)	73.3% (11)	NA
BMI (kg/m^2), $\bar{x}(SD)$	61.1 (12.27)	51.7 (10.04)†	38.9 (8.00)†,‡	<.01
Fasting glucose (mg/dL), $\bar{x}(SD)$	95.5 (8.49)	85.1 (10.09)†	83.3 (5.00)†,‡	<.01
Fasting insulin (pM), median (IQR)	120.0 (103.8, 186.0)	66.2 (48.2, 79.5)†	46.8 (35.1, 54.0)†,‡	<.01
kg (%/min), $\bar{x}(SD)$	1.51 (0.43)	1.78 (0.52)†,§	1.69 (1.09)	<.05
S_I ($\times 10^{-6}$ pM^{-1} × min^{-1}), median (IQR)	0.90 (0.42, 1.44)	1.28 (0.30, 2.80)	3.95 (2.58, 7.52)†,‡	<.01
AIR_G (pM), $\bar{x}(SD)$	895.1 (467.05)	670.6 (415.66)	397.9 (184.14)†,‡	<.01
DI (10^{-5} × min^{-1}), median (IQR)	718.5 (337.6, 1264.0)	907.4 (135.4, 1672.2)	1370.0 (925.0, 2597.6)†,‡	<.01
Fasting PI (pM),¶ $\bar{x}(SD)$	42.6 (20.95)		12.1 (3.29)	<.01**
Fasting CP (nM),¶ $\bar{x}(SD)$	0.97 (0.31)		0.38 (0.14)	<.01**
PI:CP (%),¶ $\bar{x}(SD)$	4.44% (1.91)		3.48% (1.20)	.03**

NA, not applicable.
*Overall test of time from mixed linear modeling.
†Post-hoc comparison to baseline, $P \leq .05$.
‡Post-hoc comparison to 3 months, $P \leq .05$.
§N = 12.
¶N = 15 subjects at baseline and 120-month time points.
**Paired *t* test.

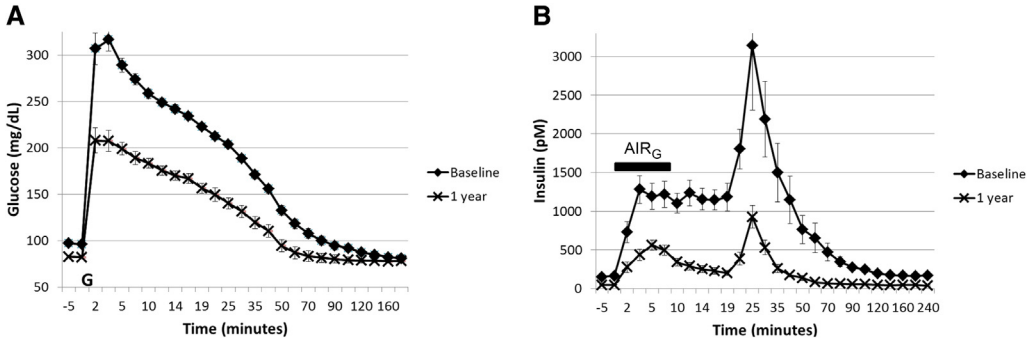

Figure 1. **A**, Mean ±SD glucose during IVGTT (n = 15). "G," glucose bolus administration at time zero. **B**, Mean ± SD insulin values during IVGTT. "AIR_G," acute insulin response to IV glucose. To enhance the sensitivity of the analysis, an intravenous insulin challenge was administered at 20 minutes, leading to a spike in insulin concentrations.

increasing >4-fold from baseline by 12 months ($P < .01$; Table I). Insulin secretion corrected for insulin sensitivity (DI) increased nearly 2-fold from baseline over 1 year ($P < .01$; Table I and Figure 2). Similar trends were found when the metabolic data were analyzed separately for only those subjects (n = 10) who completed all 4 visits (Table II). Correlations were sought for predictors of change in insulin secretion and sensitivity at 1 year, including age at baseline, BMI at baseline, and BMI change. No significant relationships were found in this analysis.

PI to CP Ratios

As another marker of β-cell function before and after surgery, the precursor-product relationship of fasting PI and CP was compared at baseline and 1 year. Consistent with the decrease in fasting insulinemia and AIR_G, PI, and CP also fell over this period (Table I). However, there was a proportionally greater fall in PI levels compared with CP, as demonstrated by the 21% decline in the PI:CP (14.1%-11.1%) over 1 year ($P < .01$).

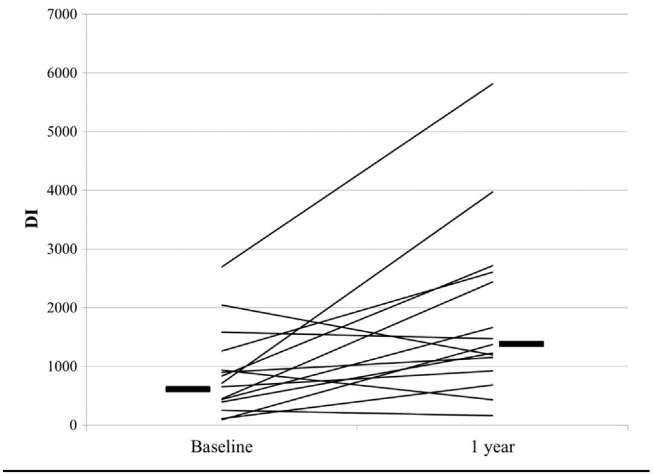

Figure 2. Disposition index for 15 individuals with baseline and 1 year data. Median values of 718 and 1370 for baseline and 1 year are plotted as the heavy lines ($P = 0.01$).

Discussion

The goal of this study was to evaluate the effects of RYGB on glucose metabolism in severely obese adolescents. The main findings were that severely obese adolescents presented for surgery with profound IR at baseline but had significant improvement in this measurement and in insulin secretion, over time. The improved insulin secretion relative to insulin sensitivity, and increased efficiency of PI processing that we observed suggests that β-cell function had improved by 12 months postoperatively. Thus, in severely obese adolescents, RYGB is associated with changes in both insulin secretion and sensitivity, effects that are apparent despite persistent obesity. These findings provide support for protection of key organ systems involved in glucose regulation by surgical weight loss.

RYGB is an effective treatment for severe obesity and for T2DM in adults.[16] However, no studies have yet reported the effects of this procedure on key aspects of glucose metabolism in adolescents and young adults. This study was designed to address fundamental questions about the metabolic responses to surgery in adolescents, who are relatively heavier than adults undergoing RYGB. This was certainly the case in our cohort with a mean BMI >60 kg/m^2 preoperatively. We used the frequently sampled IVGTT because it is a relatively simple and well-validated means of determining insulin secretion and sensitivity in a single test.[5,28] Correction of insulin secretion for insulin sensitivity was originally validated using IVGTTs,[5,26] and this type of analysis has become common in studies of adults with bariatric surgery to account for improvements in IR.[13,17-19] Moreover, techniques that use oral ingestion of carbohydrate are difficult to interpret after RYGB because the changes in gastrointestinal anatomy, speed of enteral transit and significantly altered plasma glucose dynamics as compared to the preoperative state or as

Table II. Complete case subject characteristics and outcomes by study visit

	Baseline (N = 10)	2 wk (N = 10)	3 mo (N = 10)	12 mo (N = 10)	*P* value*
Age at surgery, $\bar{x}(SD)$	17.6 (1.24)				NA
Female, % (n)	50.0% (5)				NA
White race, % (n)	70.0% (7)				NA
BMI (kg/m^2), $\bar{x}(SD)$	65.3 (12.36)	60.9 (11.83)	51.9 (10.50)	39.6 (9.46)†,‡,§	<.01
Fasting glucose (mg/dL), $\bar{x}(SD)$	95.6 (11.08)	85.5 (6.04)	86.1 (12.31)	82.6 (6.02)†	.02
Fasting insulin (pM), median (IQR)	115.2 (90.6, 208.8)	108.2 (78.0, 137.1)	62.4 (39.3, 81.0)†	40.2 (35.1, 50.7)†,‡	<.01
Kg (%/min), median (IQR)¶	1.69 (1.41, 1.87)	1.60 (1.55, 2.43)	1.63 (1.53, 1.95)	1.31 (1.18, 1.57)	.56
S_I ($\times 10^{-6}$ pM^{-1} $\times$ min^{-1}), median (IQR)	0.94 (0.50, 1.34)	1.57 (0.52, 2.02)	1.80 (0.93, 3.06)	4.22 (2.58, 7.52)‡,§	.03
AIR_G (pM), median (IQR)	1102.7 (485.9, 1427.5)	763.3 (513.5, 1276.5)	637.5 (497.2, 681.5)	347.0 (229.7, 529.3)†,‡	<.01
DI (10^{-5} $\times$ min^{-1}), median (IQR)	834.3 (651.1, 1580.6)	1160.7 (668.9, 1663.6)	1141.9 (158.1, 1672.6)	1285.8 (925.0, 2597.6)	.53
Fasting PI (pM), $\bar{x}(SD)$	38.3 (21.80)			11.3 (3.12)	<.01**
Fasting CP (nM), $\bar{x}(SD)$	0.88 (0.20)			0.34 (0.10)	<.01**
PI:CP (%), $\bar{x}(SD)$	4.29% (1.89)			3.56% (1.25)	.13**

*Overall test of time from mixed linear modeling.
†Post-hoc comparison to baseline, $P \leq .05$.
‡Post-hoc comparison to 2 weeks, $P \leq .05$.
§Post-hoc comparison to 3 months, $P \leq .05$.
¶N = 9.
**Paired *t* test.

compared to unoperated controls.[29,30] Despite our efforts to minimize subject burden for the evaluations of glucose tolerance, many subjects were unable to complete all 4 tests. However, we were able to complete 66 of 88 (75%) expected study visits with a majority of subjects studied at baseline also having evaluation at 1 year.

We observed profound IR in our adolescent subjects at baseline and steady improvements in insulin sensitivity over 1 year of follow-up. The >4-fold increase in S_I between baseline and 12 months is comparable with what has been described in adults after surgery[13-15] and is far greater than changes in IR that have been measured in obese adolescents treated with dietary[30] or pharmacologic[31] interventions. However, we also noted metabolic changes that preceded the majority of weight loss. For instance, in the subjects who were studied 2 weeks following the operation, both fasting glucose and insulin had decreased significantly with only a 7% decrease in BMI (Table II). Similar findings of rapid metabolic improvement have been noted in adults after surgery.[32] Importantly, the marked increase in S_I and reduction of hyperinsulinemia occurred despite starting BMIs that were much greater in our cohort than most studies of adults undergoing bariatric surgery, and despite persistent obesity in most of our subjects postoperatively. These results support the view that surgical treatment with RYGB has profound and beneficial metabolic effects that extend across the spectrums of age and obesity.

Following surgical therapy, the mean β-cell secretory compensation for IR (DI) increased 2-fold in our subjects, potentially reducing their risk for progression to T2DM. This pattern of change in AIR_G, insulin sensitivity, and DI has been observed in adults undergoing RYGB,[13] but when examined specifically, restitution of β-cell function to this degree has not been described following other interventions for weight loss in pediatric groups.[30,33,34] It is also important to consider that AIR_G may have been artificially reduced in our study because of the relatively decreased glucose challenge that resulted from adjustment of the IV bolus based on body weight (Figure 1). However, even with this limitation, potentially blunting the improvement of insulin secretion, the median DI nearly doubled, representing a significant improvement in β-cell function.

Hyperproinsulinemia has been used previously as an index of beta cell dysfunction[35,36] because it increases as β-cell function declines and is useful for prediction of progression to T2DM.[36,37] Our findings that levels of PI, indexed for CP, decreased postoperatively are consistent with the findings of improved DI in our postsurgical subjects. To put these findings into perspective, fasting PI, CP, and PI:CP are available from obese (n = 12, BMI 35.9 $\pm$ 6.6 kg/m^2) adolescents without diabetes (aged 14.9 $\pm$ 1.7 years) previously studied at our center.[25] In these subjects, mean $\pm$ SD values of PI, CP, and PI/CP were 24.4 $\pm$ 16.2 pM, 0.86 $\pm$ 0.43 nM and 3.00 $\pm$ 1.99%, respectively. Thus, the PI:CP in our bariatric cohort 1 year after RYGB approached that of comparably obese adolescents without RYGB.

β-cell function, summarized as DI, has been reported from a number of studies of adults without diabetes after RYGB. In most, the response has been less than the doubling in DI that we report here,[14,15,18,32,38,39] but in others DI increased comparably with our cohort.[13,19,40] Without a direct comparison between adult and adolescent subjects, it is not possible to determine whether abnormalities related to glucose tolerance may be more amenable to improvement in younger persons undergoing surgical weight loss. Other bariatric surgical outcome studies have linked chronicity or severity of disease with likelihood of response. For instance, remission of T2DM is known to be inversely related to age at time of surgery and to duration of T2DM.[41,42] To determine whether younger patients have relatively greater benefits from surgery would require studies with direct comparisons across the spectrum of age.

The relatively small sample size of this study considerably limits any inferences about sex, race, or ethnicity-specific outcomes. In addition, lack of age- and sex-matched lean and

obese control subjects limits the ability to infer the true degree of normalization of metabolic variables at 1 year. Another distinct limitation of this study was the missing data because of missed visits and other technical problems with IV access. When only those with complete data were examined (**Table II**), the sample with 12-month outcome data was decreased from 15-10; even with this reduction in sample size most of the physiologic changes described in **Table I** were still significant, with the exception of Kg, DI, and PI:CP outcomes at 12 months. Irrespective of the fact that the *P* value for DI increased with a lower sample size at 12 months, we believe that beta cell function demonstrated biologically significant improvement between baseline and 1 year based on the robust changes in the key variables used to calculate DI, namely, S_I and AIR_G. Finally, we cannot determine whether the improvements in carbohydrate metabolism at 1 year represent transient changes in these participants; longer term study with greater numbers of subjects would be necessary to clarify the extent to which RYGB improves or restores β-cell function in the long term, especially given the persistent excess body weight.

In summary, severely obese adolescents undergoing RYGB had steady and substantial loss of body weight over 1 year. This was associated with early reduction in fasting glucose and insulin levels followed by improved insulin sensitivity, and by a significant enhancement of β-cell function by 1 year. Although these beneficial changes in glucose metabolism likely portend a reduced risk for T2DM, it will require trials of longer duration with nonsurgical controls to prove this. However, our findings support the hypothesis that severely obese, insulin-resistant adolescents have considerable pancreatic endocrine "reserve" that can be activated with surgical intervention, shifting their metabolic health and potentially limiting the end-organ damage of IR and glucose intolerance. ■

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Reprint requests: Thomas H. Inge, MD, PhD, Division of Pediatric Surgery, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, MLC 2023, Cincinnati, OH 45229-3039. E-mail: thomas.inge@cchmc.org

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Appendix

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