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

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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

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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.