Weight Loss After Bariatric Surgery in Morbidly Obese Adolescents with MC4R Mutations

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Objective: To determine the frequency of Melanocortin 4 Receptor (MC4R) mutations in morbidly obese adolescents undergoing bariatric surgery and compare weight loss outcomes in patients with and without mutations.

Design and Methods: In this prospective cohort study, 135 adolescent patients evaluated for bariatric surgery were screened for MC4R mutations; 56 had 12-month postoperative data available for analysis.

Results: MC4R mutations were detected in five of the 135 patients (3.7%); four underwent restrictive bariatric surgery. For the three patients with gastric banding, percent excess weight loss (%EWL) postoperatively was 36.0% at 5 years in one, 47% at 4 years in the second, and 85% at 1 year in the third. For the patient with gastric sleeve resection, %EWL of 96% was attained at 1 year postoperatively. The four MC4R cases had a higher, although nonsignificant, %EWL compared to 52 nonmatched controls at 12 months postoperatively (48.6% vs. 23.4%; P < 0.37). When matched by age, sex, and race to 14 controls, there was no significant difference in %EWL (P < 0.31), BMI change (P < 0.27), or absolute weight loss (P < 0.20).

Conclusion: The frequency of MC4R mutations is similar to prior studies, with affected patients showing beneficial weight loss outcomes.

Introduction

Over the past 30 years, the prevalence of adolescent obesity has more than tripled, with 4% now considered morbidly obese (BMI > 99th percentile) (1,2). Bariatric surgery is widely used in the morbidly obese adult population. Increasing evidence in the adolescent literature suggests that bariatric surgery may be the most effective treatment for weight loss in this population as well (2-5). It has been estimated that between 1000 and several thousand adolescents undergo bariatric procedures each year (6,7). A recent meta-analysis found that in adolescents, roux-en-Y gastric bypass (RYGB) and laparoscopic adjustable gastric banding (LAGB) procedures were associated with permanent weight loss and resolution of concomitant metabolic conditions, including diabetes and hypertension (7). Vertical sleeve gastrectomy (VSG), originally performed as the first step in a staged weight loss procedure for severely obese adults, has also shown successful short-term weight loss in adolescence though long-term outcome data are lacking (1,8-10).

LAGB with the Lap-Band (Lap-Band System; Allergan Corp, Santa Barbara, CA) is a reversible surgical procedure in which food entry into the stomach is limited by placement of an adjustable belt-like band around the proximal portion. The band is connected to a subcutaneous port accessed percutaneously to adjust the inner diameter and the degree of gastric restriction (1,8). Sleeve gastrectomy is an irreversible procedure removing 75-80% of the stomach leaving a smaller, tubular stomach in its place (7). Both of these restrictive surgeries produce weight loss by limiting food intake and causing early satiety, as opposed to combined restrictive and malabsorptive

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procedures, such as RYGB, which restrict intake but also limit intestinal contact with digested nutrients.

Genetic factors are estimated to account for 40-70% of the obesity predisposition of an individual (11). The melanocortin 4 receptor (MC4R) is a seven transmembrane G protein coupled receptor expressed in the neurons of the paraventricular nucleus of the hypothalamus (12). Propiomelanocortin (POMC) is a key step in the anorexigenic signaling cascade of leptin with POMC-derived peptides α-MSH and β-MSH binding the MC4R in the hypothalamus. Receptor activation by melanocortins causes a decrease in appetite and an increase of energy expenditure, both leading to weight loss (13,14). MC4R mutations, the most common monogenic form of obesity, account for between 2.5% and 5.8% of morbid obesity in pediatric and adult populations (15-17).

Several mutations in MC4R have been characterized in humans. These mutations range from missense and nonsense to frameshift mutations (leading to both reduced and total loss of function) and are inherited in an autosomal dominant manner. Data on the effects of bariatric surgery in patients with monogenic obesity are limited. There are no studies that document the prevalence of MC4R mutations in adolescent patients undergoing bariatric surgery, nor are there any studies addressing long-term weight loss outcomes in adolescents with MC4R mutations postbariatric surgery. In this study, we describe five morbidly obese adolescent patients with heterozygous MC4R mutations who underwent restrictive bariatric surgery at our institution and compare their postoperative weight loss outcomes with those of control patients without mutations. We hypothesized that MC4R mutations would decrease the effectiveness of restrictive bariatric surgery with less weight loss in affected patients.

Methods

Patients

Subjects were recruited from the weight management program at Columbia University Medical Center (CUMC) or referred by private pediatricians to the Center for Adolescent Bariatric Surgery (CABS) for restrictive bariatric surgery evaluation. Eligible subjects were adolescents 14-18 years of age who had BMI > 40 or >35 kg/m² and at least one co-morbidity. The BMI guidelines used were consistent with NIH criteria for bariatric surgery in adults (18). Patients were required: (1) to be Tanner stage 4 or greater (with a bone age of at least 13.5 years for girls and 14.5 years for boys) and (2) to have a history of obesity for at least 5 years, including failed attempts at dietary and medical management of obesity. After evaluations by a pediatric surgeon, a pediatric endocrinologist, a registered dietician, a nurse practitioner/exercise specialist, and a psychologist or psychiatrist, those who demonstrated understanding and willingness to incorporate dietary and exercise changes were offered restrictive bariatric surgery. A total of 135 patients considered appropriate candidates for restrictive bariatric surgery were screened for MC4R mutations between March 2006 and March 2011. Parents and patients of 18 years old signed informed consents, and patients under 18 years old signed informed assents under CUMC Institutional Review Board approved protocols at time of entry into the CABS program and for gene studies.

Surgical methods

Patients underwent LAGB or gastric sleeve resection procedures performed at the Morgan Stanley Children’s Hospital of New York by a single pediatric surgeon (JZ). The technique for LAGB using the LAP-BAND® involves a silicone ring with an adjustable inner diameter positioned around the proximal stomach just distal to the gastroesophageal junction, creating a small proximal gastric pouch. The band is connected to a subcutaneous access port with band internal diameter adjusted by injection or withdrawal of saline. Placement of the LAP-BAND was performed laparoscopically with the patient under general anesthesia using 5 trocar sites according to the pars flaccida technique, described in detail elsewhere (19). The LAP-BAND was left empty at the end of placement to allow for possible postoperative swelling. Contrast esophagogram was performed to confirm band position and assess pouch emptying prior to discharge. Sleeve gastrectomy was performed laparoscopically as well. The sleeve resection was carried out using a multifire linear stapler with staple loads reinforced with Seamguard® (W.L. Gore & Associates, Flagstaff, AZ). Upper endoscopy was performed and demonstrated no staple line bleeding or evidence of a leak at the time of procedure. The morning after surgery a contrast upper GI series was performed to assess sleeve anatomy and to check for gastric leak before starting oral fluids.

Postoperative care

LAGB patients were instructed postoperatively to follow a standard restrictive dietary protocol including ingestion of a pureed diet in the first postoperative week, a blended diet for weeks 2-3, a soft diet for weeks 4-6, and a well-balanced low-fat diet for week 7 and beyond. Gastric sleeve patients were maintained on liquids for 2 weeks then advanced to puree for an additional 3-4 weeks. Patients were instructed to return for follow-up visits for assessment of weight changes, for nutritional advice, and for postsurgical monitoring with adjustments as indicated at weeks 2, 4, 6, and 8, then monthly for the initial 12 months, with plans for follow-up at 15, 18, and 24 months, then semiannually for 5 years (20). Nutritional supplements were prescribed as needed for documented deficiencies. Total weight loss (kg) and percentage of excess weight lost (%EWL) after surgery were calculated using Centers for Disease Control growth charts. Patient weights were plotted using Growth Analyser (Dutch Growth Research Foundation). Excess weight was defined as the weight above the 85th percentile of body mass index for age and sex (21).

Sequencing

Patients had 5 ml of whole blood drawn for genetic analysis. Genomic DNA was isolated from peripheral leukocytes by cell lysis followed by DNA extraction and precipitation. Each subject’s DNA was amplified by polymerase chain reaction for the coding regions and splice sites (primers and conditions available upon request) and sequenced by dideoxysequencing with the BigDye terminator kit using an ABI 377 sequencer (Applied Biosystems). Sequence was analyzed using Sequencer software. In addition, each electropherogram was visually reviewed to identify any heterozygous DNA variants not detected by the automated sequencing software. Variants classified as mutations have been previously reported as mutations or resulted in frameshift mutations and were absent from the 1000 genomes database (http://www.1000genomes.org/) and EVS database (http://evs.gs.washington.edu/EVS/). Mutations were confirmed with bidirectional sequencing.

Statistical analysis

Subjects were divided based on the presence of MC4R mutations. The data are summarized with means ± standard deviations or
counts and percentages, whereas comparisons between subgroups are presented as means ± standard errors. The comparison of %EWL, absolute weight loss, and percent total weight loss at 12 months between MC4R mutation carriers (cases; n = 4) and the cohort of 52 patients without MC4R mutations (nonmatched controls) at 12 months postoperatively was performed using an independent, two-tailed t test. Each of the four cases were then matched (without replacement) with between two and five controls of the same race, sex and age within 2 years. The within-matched pair differences between MC4R cases and controls were tested with Analysis of Variance.

Results

Identification of MC4R mutations

One hundred thirty five patients evaluated for restrictive bariatric surgery were screened for MC4R mutations. The mean ±SD of age and BMI prior to surgery was 16.5 ± 1.2 years and 54.4 ± 8.6 kg/m², respectively. Mutations in MC4R were detected in five of the 135 patients (3.7%) and included the heterozygous MC4R mutations: p.Cys271Arg, p.Asp146His, p.Phe202Leu, p.Ser139Cysfs*22, and p.Leu250Trpfs*34 (Table 1). Case 1 has functional studies that demonstrate loss of function. Case 2 is reported in the literature as a mutation but has one functional study demonstrating wild type activity, although this particular assay does not fully assess the function and all prediction algorithms suggest it is a pathogenic change (references in Table 1). Cases 3 and 4 are frameshift mutations resulting in premature termination and are strongly predicted to result in loss of function. Case 5 has another amino acid substitution at the same position that is a proven mutation, but our substitution has not been observed. All prediction algorithms predict the Asp146His variant to be pathogenic, and this allele is not observed in databases of normal individuals.

Weight loss after bariatric surgery

Four of the five MC4R mutation carriers underwent restrictive bariatric surgery (Figure 1). Of the 135 patients screened, 117 patients underwent bariatric surgery with LAGB performed in 113 patients. The remainder of patients (three controls, one MC4R carrier) underwent GSR. Thirty-one patients (26.5%) missed the 12 month visit, but returned to clinic for continued postoperative care at subsequent visits. Thirty of the 117 patients who underwent bariatric surgery (25.6%), missed the 12 month postoperative visit and were lost to follow-up. Fifty-six patients of the original cohort had 12 month postoperative data available for analysis.

The mean age of the 56 subjects analyzed was 16.5 ± 1.2 years with mean BMI 54.4 ± 8.6 kg/m². Twenty-four patients (43%) were male. Patients were of diverse racial background (36% were Caucasian, 45% were Hispanic, 14% were African-American, and 5% were of mixed ethnicity). The mean %EWL of the entire cohort at 12 months equaled 25.0 ± 24.9%, ranging from 95.2% of excess weight lost to 17.7% of excess weight gained.

The four MC4R mutation carriers were found to have a higher %EWL compared to the cohort of 52 nonmatched controls at 12 months postoperatively (48.6% vs. 23.4%), although the difference in weight loss between the two groups did not reach statistical significance (P < 0.37). For the three patients with LAGB, %EWL postoperatively was 36.0% at 5 years in one, 47% at 4 years in the...
second, and 85% at 1 year in the third. For the patient with gastric sleeve resection, %EWL of 96% was attained at 1 year. Of note, sex differences were observed with regards to weight loss at 12 months postoperatively among the entire cohort (Figure 2), but the slightly increased weight loss in females compared to males (26.6 ± 4.6% vs. 19.1 ± 3.6%) was not statistically significant (P < 0.23).

The four MC4R mutation carriers were matched by age, sex, and race to 14 controls (Table 2). The two female cases were matched to six female controls (age 16.3 ± 0.3 vs. 16.4 ± 1.4 years, initial weight 125.8 ± 6.2 vs. 128.7 ± 4.9 kg, initial BMI 44.9 ± 3.1 vs. 44.6 ± 1.6 kg/m², respectively); two male cases were matched to eight male controls (age 16.6 ± 1.1 vs. 16.3 ± 1.1 years, initial weight 178.4 ± 36.2 vs. 141.0 ± 7.1 kg, initial BMI 54.7 ± 7.8 vs. 46.0 ± 1.9 kg/m², respectively). There were no statistically significant between pair differences in %EWL (P < 0.31; females 0.10, males 0.60), BMI change (P < 0.27; females 0.13; males 0.79), or absolute weight loss (P < 0.20; females 0.08; males 0.92) when comparing cases and controls at 12 months postoperatively (Table 3).

Discussion
To our knowledge, this study is the first to report the prevalence of MC4R mutations in a cohort of morbidly obese adolescent patients presenting for bariatric surgery. It is also the first to document successful weight loss after restrictive bariatric surgery procedures in patients with MC4R mutations suggesting that patients with these mutations are able to lose as much weight as patients without MC4R mutations. The overall pattern of results of the pair-matched analysis supports the findings from the general analysis. MC4R mutation carriers did not lose less weight than controls as...
had been hypothesized, although the difference in weight loss between the two groups did not reach statistical significance. Thus, carriers of MC4R mutations are expected to respond to bariatric surgery similarly to non-carriers, suggesting that the favorable effects of surgery on body weight are not mediated by MC4R activity variations.

Studies in animals and humans show a direct link between MC4R mutations and obesity. Rats with MC4R defects have decreased energy expenditure, hyperphagia, and early onset obesity (22). Humans have similar symptoms in addition to hyperinsulinemia, increased fat mass, increased linear growth, and elevated bone mineral density (23-25). MC4R agonists given to rats lead to decreased food intake and reduced body weight (26) and increased thermogenesis in brown adipose tissue (27,28).

Data on the effects of bariatric surgery in patients with monogenic forms of obesity are extremely limited with little known regarding long term weight outcomes in adults or adolescents. It has been suggested that aberrant satiety signaling by the melanocortins could place individuals with MC4R mutations at higher risk for bariatric surgery failure, in particular after LAGB (29). In a previous study of 300 adult gastric banding patients by Potoczna et al., MC4R mutation carriers (6.3%) were found to have poorer outcomes with less weight loss and five-fold more gastric complications than noncarriers (30). Of note, the study by Potoczna et al. included a large number of patients with binge eating disorders, which have been independently implicated in poorer outcomes postsurgery, possibly confounding the results of the study. A recent study focusing on adult patients with complications following banding requiring re-operation could not confirm this association between higher complication rates and MC4R mutation status following LAGB (29).

Aslan et al. published a case report of unsuccessful weight loss with postoperative weight gain following LAGB in an 18.7 year old with compound heterozygosity and complete functional loss of both alleles of the MC4R (31). Although mutations in MC4R have been reported to be associated with up to 5.8% of the cases of severe obesity, less than ten patients have been described in the literature with homozygous or compound heterozygous MC4R mutations. The presence of two mutations may make bariatric surgery ineffective in affected individuals.

In contrast to the above findings, studies in adults with heterozygous MC4R mutations demonstrate sustained weight loss in response to gastric bypass. Aslan et al. was the first to document weight loss after RYGB in adults with heterozygous MC4R mutations (32). They screened 92 patients finding 4.3% with MC4R mutations and noted similar weight loss between those with and without MC4R mutations at 12 months postoperatively.

A recent study by Hatoum et al also documented sustained weight loss in patients heterozygous for hypomorphic MC4R alleles after RYGB (31). Of 972 patients sequenced preoperatively, 62 (6.4%) had at least one heterozygous mutation. Patients heterozygous for MC4R mutations exhibited the same magnitude and distribution of postoperative weight loss as patients without MC4R mutations. Hatoum et al. also studied male age- and litter mate-matched MC4R knockout (MC4R−/−), heterozygous (MC4R+/−), and wild type mice. They reported MC4R−/− mice having substantially less weight loss after surgery than wild-type animals, with MC4R+/− mice remaining fully responsive to gastric bypass. The authors concluded that two normal copies of the MC4R gene are necessary for normal weight regulation, but a single normal copy of the MC4R gene may be sufficient to regulate the weight loss effects of RYGB (33).

Mul et al. analyzed the effect of VSG on body weight, food intake, and glucose sensitivity of wild-type and MC4R-deficient MC4R(+/−) and MC4R(−/−) rats compared with sham-operated controls. Results showed reduced body weight and fat mass and improved glucose metabolism postoperatively independent of MC4R activity. In 46 adult human subjects who underwent VSG and were screened for MC4R mutations, BMI, body weight, and HbA1c levels 12 months postoperatively were unaffected by the genetic variations in the coding sequence in five subjects suggesting that the beneficial effect of VSG on body weight and glucose metabolism were not mediated by MC4R activity alterations (34).

In our study, one male MC4R mutation carrier (case 1) lost a similar percent excess body weight (EBW; 15.3%) to the male noncarrier cohort (17.7%) at 1 year postoperatively. It appeared that female MC4R mutation carriers lost more EBW (84.4 and 95.2%, respectively) at 12 months compared to the group of female nonmatched control patients (26.6%) and the male cohort (17.7%). However, five additional females in the non-matched control cohort also lost greater than 70% of their EBW. In addition, although one male carrier (case 3) gained 0.6% EBW, four nonmatched control patients also had a net weight gain at 12 months postoperatively and nine patients lost less than 10% of their EBW. By 48 months postoperatively, case 3 had lost 30.7 kg from baseline with total %EWL of 46.7%.

The limitations of our study include the small sample size of MC4R mutation carriers limiting the ability to draw definitive conclusions due to the lack of power. The intermittent follow-up of our four MC4R mutation carriers made it difficult to compare weight loss at different time points. A visit frequency of five total visits during the first 12 months postoperatively was anticipated. The actual visits of the four MC4R carriers averaged 3.8 visits versus 4.0 in the 52-patient control group. Possible explanations for the insufficient weight loss and weight gain in our patient population at 12 months postoperatively have been discussed in a previous paper published by our group (20). These include lack of social support, failure to change eating habits, and failure to incorporate recommended exercise. Degree of adherence to follow-up appointments could have further contributed to disappointing outcomes in certain patients. Patients were encouraged by their surgeon, dietician, and endocrinologist to attend all recommended postoperative appointments and received telephone reminders in order to maximize care and weight loss outcomes. Despite these limitations, our experience indicates that restrictive bariatric surgery with LAGB or sleeve gastrectomy may result in significant long term weight loss for patients with heterozygous MC4R mutations comparable to a cohort of patients without mutations.

In conclusion, the frequency of MC4R mutations in our morbidly obese adolescent patient population who underwent bariatric surgery appears to be similar to other studies. Studies in the adult literature indicate sustained weight loss in patients with heterozygous MC4R mutations following RYGB and VSG, with poor outcomes...
suggested for patients homozygous for loss-of-function mutations. Our study is the first to document weight loss after bariatric surgery in adolescent patients with heterozygous \textit{MC4R} mutations and provide preliminary information on outcomes of mutation carriers after restrictive bariatric surgery. These findings support considering patients heterozygous for \textit{MC4R} mutations as appropriate candidates for restrictive, in addition to malabsorptive, bariatric surgery procedures. 

### TABLE 2 Clinical data from patients heterozygous for \textit{MC4R} mutations and 14 matched controls

| Pair  | \textit{MC4R} mutation | Sex | Age (yrs) | Ethnicity | BMI (kg/m\(^2\)) | DLD | HTN | IFG | IGT | OSA | PCOS |
|-------|------------------------|-----|-----------|-----------|------------------|-----|-----|-----|-----|-----|------|
| Pair 1 | p.Cys271Arg            | M   | 15.92     | AA        | 62.6             | -   | +   | -   | -   | -   | -    |
| Control |                        | M   | 16.22     | AA        | 47.10            | +   | -   | +   | -   | +   | -    |
| Control |                        | M   | 16.44     | AA        | 46.80            | -   | -   | -   | -   | -   | -    |
| Control |                        | M   | 16.55     | AA        | 50.30            | -   | -   | -   | -   | -   | -    |
| Pair 2 | p.Phe202Leu            | M   | 17.42     | AA        | 49.4             | +   | +   | -   | -   | -   | -    |
| Control |                        | M   | 14.56     | AA        | 47.20            | +   | -   | -   | -   | +   | -    |
| Control |                        | M   | 15.14     | AA        | 44.90            | +   | -   | -   | -   | -   | -    |
| Control |                        | M   | 16.01     | AA        | 48.30            | +   | -   | +   | +   | -   | -    |
| Control |                        | M   | 17.76     | AA        | 35.30            | +   | +   | +   | +   | -   | -    |
| Control |                        | M   | 17.87     | AA        | 47.80            | +   | -   | -   | -   | +   | -    |
| Pair 3 | p.Ser139Cysfs*22       | F   | 16.08     | AA        | 41.9             | -   | -   | -   | -   | -   | -    |
| Control |                        | F   | 16.21     | AA        | 45.60            | -   | -   | -   | -   | -   | -    |
| Control |                        | F   | 17.64     | AA        | 42.30            | -   | -   | -   | -   | -   | -    |
| Pair 4 | p.Leu250Trpfs*34       | F   | 16.50     | AA        | 48.0             | +   | -   | -   | +   | +   | +    |
| Control |                        | F   | 14.15     | AA        | 41.50            | +   | -   | -   | -   | -   | -    |
| Control |                        | F   | 15.5      | AA        | 47.00            | +   | -   | -   | -   | -   | -    |
| Control |                        | F   | 17.35     | AA        | 46.30            | +   | -   | -   | -   | -   | -    |
| Control |                        | F   | 17.49     | AA        | 44.80            | +   | -   | -   | -   | -   | -    |
| Case 5 | p.Asp146His            | F   | 17.08     | AA        | 44.4             | +   | -   | -   | -   | -   | -    |

**AA,** African-American; \(C,{\text{ }}\) Caucasian; \(DLD,{\text{ }}\) dyslipidemia; \(H,{\text{ }}\) Hispanic; \(HTN,{\text{ }}\) hypertension; \(IFG,{\text{ }}\) impaired fasting glucose; \(IGT,{\text{ }}\) impaired glucose tolerance; \(OSA,{\text{ }}\) obstructive sleep apnea; \(PCOS,{\text{ }}\) polycystic ovarian syndrome; + presence of comorbidity, - absence of comorbidity.

### TABLE 3 Matched pair analysis results \((n = 18)\)

|        | Females | Males |
|--------|---------|-------|
|        | MC4R Cases \((n = 2)\) | Controls \((n = 6)\) | \(P\)-value within pair | MC4R Cases \((n = 2)\) | Controls \((n = 8)\) | \(P\)-value within pair |
| Age    | 16.3 ± 0.3 | 16.4 ± 1.4 | 0.69          | 16.6 ± 1.1 | 16.3 ± 1.1 | 0.69          |
| Wt at baseline (kg) | 125.8 ± 6.2 | 128.7 ± 4.9 | 0.98          | 178.4 ± 36.2 | 141.0 ± 7.1 | 0.36          |
| BMI at baseline | 44.9 ± 3.1 | 44.6 ± 1.6 | 0.86          | 54.7 ± 7.8 | 46.0 ± 1.9 | 0.35          |
| Wt at 12months (kg) | 75.7 ± 11.1 | 107.2 ± 6.8 | 0.27          | 168.6 ± 10.5 | 133.6 ± 5.4 | 0.28          |
| % Wt loss | 39.6 ± 13.0 | 14.7 ± 5.9 | 0.09          | 4.6 ± 2.5 | 6.0 ± 1.3 | 0.79          |
| Wt loss (kg) | 50.1 ± 15.4 | 18.4 ± 7.6 | 0.08          | 9.9 ± 4.0 | 8.8 ± 2.1 | 0.92          |
| EBW (kg) | 55.4 ± 5.5 | 58.2 ± 3.4 | 0.86          | 99.0 ± 11.8 | 67.6 ± 6.1 | 0.38          |
| % EWL | 89.8 ± 21.8 | 35.2 ± 13.3 | 0.10          | 7.3 ± 4.4 | 12.4 ± 2.3 | 0.60          |
| BMI at 12months (kg/m\(^2\)) | 27.1 ± 5.0 | 37.5 ± 3.1 | 0.12          | 51.8 ± 2.3 | 42.7 ± 1.2 | 0.24          |
| BMI change (kg/m\(^2\)) | −17.9 ± 3.9 | −7.0 ± 2.4 | 0.13          | −2.9 ± 1.3 | −3.7 ± 0.7 | 0.79          |

Means ± SEM; \(P\)-value for average within matched-pair difference by ANOVA.
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References

1. Xanthakos SA. Bariatric surgery for extreme adolescent obesity: Indications, outcomes, and physiologic effects on the gut-brain axis. Pathophysiology 2008;15:135-146.
2. O’Brien PE, Sawyer SM, Laurie C, et al. Laparoscopic adjustable gastric banding in severely obese adolescents: A randomized trial. JAMA 2010;303:519-526.
3. Dolan K, Creighton L, Hopkins G, Fielding G. Laparoscopic gastric banding in morbidly obese adolescents. Obes Surg 2003;13:101-104.
4. Dillard BE, 3rd, Gorodner V, Galvani C, et al. Initial experience with the adjustable gastric band in morbidly obese US adolescents and recommendations for further investigation. J Pediatr Gastroenterol Nutr 2007;45:240-246.
5. Nadler EP, Youn HA, Ren CJ, Fielding GA. An update on 73 US obese pediatric patients treated with laparoscopic adjustable gastric banding: comorbidity resolution and compliance data. J Pediatr Surg 2008;43:141-146.
6. Ingelfinger JR. Bariatric surgery in adolescents. N Engl J Med 2011;365:1365-1367.
7. Treadwell JR, Sun F, Schoelles K. Systematic review and meta-analysis of bariatric surgery for pediatric obesity. Ann Surg 2008;248:763-776.
8. Kendrick ML, Dakin GF. Surgical approaches to obesity. Mayo Clin Proc 2006;81:SI3-S24.
9. Alqahtani AR, Antonisamy B, Alamri E, Elahmedi M, Zimmerman VA. Laparoscopic sleeve gastrectomy in 108 obese children and adolescents aged 5 to 21 years. Ann Surg 2012;256:266-273.
10. Hsia DS, Fallon SC, Brandt ML. Adolescent bariatric surgery. Arch Pediatr Adolesc Med 2012;166:757-766.
11. Ranadive SA, Vaise C. Lessons from extreme human obesity: Monogenic disorders. Endocrinol Metab Clin North Am 2008;37:733-751, x.
12. Mountjoy KG, Mortrud MT, Low MJ, Simerly RB, Cone RD. Localization of the melanocortin-4 receptor (MC4-R) in neuroendocrine and autonomic control circuits in the brain. Mol Endocrinol 1994;8:1298-1308.
13. Takahashi H, Teranishi Y, Nakanishi S, Numa S. Isolation and structural organization of the human corticotropin—beta-lipotropin precursor gene. FEBS Lett 1981;135:97-102.
14. Ellacott KL, Cone RD. The central melanocortin system and the integration of short- and long-term regulators of energy homeostasis. Recent Prog Horm Res 2004;59:395-408.
15. Lubrano-Berthelier C, Dubern B, Lacorte JM, et al. Melanocortin 4 receptor mutations in a large cohort of severely obese adults: Prevalence, functional classification, genotype-phenotype relationship, and lack of association with binge eating. J Clin Endocrinol Metab 2006;91:1811-1818.
16. Calton MA, Ersoy BA, Zhang S, et al. Association of functionally significant Melanocortin-4 but not Melanocortin-3 receptor mutations with severe adult obesity in a large North American case-control study. Hum Mol Genet 2009;18:1140-1147.
17. Farooqi IS, Keogh JM, Yeo GS, Lank EJ, Cheetham T, O’Rahilly S. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. N Engl J Med 2003;348:1085-1095.
18. NIH conference. Gastrointestinal surgery for severe obesity. Consensus Development Conference Panel. Ann Intern Med 1991;115:956-961.
19. Ren CJ, Fielding GA. Laparoscopic adjustable gastric banding: Surgical technique. J Laparoendosc Adv Surg Tech A 2003;13:257-263.
20. Conroy R, Lee EJ, Jean A, et al. Effect of laparoscopic adjustable gastric banding on metabolic syndrome and its risk factors in morbidly obese adolescents. J Obes 2011;2011:906384.
21. Kuczmerski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. Adv Data 2000;1-27.
22. Huszar D, Lynch CA, Fairchild-Huntress V, Dunmore JF, Fang Q, Berkemeier LR, et al. Targeted disruption of the melanocortin-4 receptor results in obesity in mice. Cell 1997;88:131-141.
23. Lubrano-Berthelier C, Cazavos M, Dubern B, et al. Molecular genetics of human obesity-associated MC4R mutations. Ann N Y Acad Sci 2003;994:49-57.
24. Chung WK. An overview of mongenic and syndromic obesities in humans. Pediatr Blood Cancer 2012;58:122-128.
25. Mancio M, Dallapiccola B. Genetics of pediatric obesity. Pediatrics 2012;130:123-133.
26. Benoit SC, Schwartz MW, Lachey JL, et al. A novel selective melanocortin-4 receptor agonist reduces food intake in rats and mice without producing aversive consequences. J Neurosci 2000;20:3442-3448.
27. Yasuda T, Masaki T, Kakuma T, Yoshimatsu H. Hypothalamic melanocortin system regulates sympathetic nerve activity in brown adipose tissue. Exp Biol Med (Maywood) 2004;229:235-239.
28. Vaughan CH, Shrestha YB, Bartness TJ. Characterization of a novel melanocortin receptor-containing node in the SNS outflow circuitry to brown adipose tissue involved in thermogenesis. Brain Res 2011;1411:17-27.
29. Peterli R, Peters T, von Flue M, Hoch M, Eberle AN. Melanocortin-4 receptor gene complications after gastric banding. Obes Surg 2006;16:189-195.
30. Potoczna N, Bramson R, Kral JG, et al. Gene variants and binge eating as predictors of comorbidity and outcome of treatment in severe obesity. J Gastrointest Surg 2004;8:971-981; discussion 981-972.
31. Aslan IR, Ranadive SA, Ersoy BA, Rogers SJ, Lustig RH, Vaise C. Bariatric surgery in a patient with complete MC4R deficiency. Int J Obes (Lond) 2011;35:457-461.
32. Aslan IR, Campos GM, Calton MA, Evans DS, Merriman RB, Vaise C. Weight loss after Roux-en-Y gastric bypass in obese patients heterozygous for MC4R mutations. Obes Surg 2011;21:930-934.
33. Hatoum II, Stylopoulos N, Vanhoose AM, et al. Melanocortin-4 receptor signaling is required for weight loss after gastric bypass surgery. J Clin Endocrinol Metab 2012;97:E1023-E1031.
34. Mul JD, Begg DP, Alsters SI, et al. Effect of vertical sleeve gastrectomy in melanocortin receptor 4-deficient rats. Am J Physiol Endocrinol Metab 2012;303:E103-E110.
35. Stutzmann F, Tan K, Vatin V, et al. Prevalence of melanocortin-4 receptor deficiency in Europeans and their age-dependent penetrance in multigenerational pedigrees. Diabetes 2008;57:2511-2518.