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Original article

Comparative physiogenomic analyses of weight loss in response to 2 modes of bariatric surgery: demonstration with candidate neuropsychiatric and cardiometabolic genes

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Abstract

Background: Surgical weight loss response is variable, with suboptimal outcomes in some patients. We hypothesized that genetic biomarkers may be related to weight change.

Methods: We tested 330 single nucleotide polymorphisms (SNPs) in genes relevant to metabolic regulation in 161 patients whose decrease in body mass index (BMI), 1 year after laparoscopic adjustable gastric banding (LAGB) or Roux-en-Y gastric bypass (RYGB), was small (lowest quartile response) or large (highest quartile response). LAGB patients whose BMI decreased ≤ 4.7 or ≥ 10.2 units comprised groups I (n = 43) and II (n = 40), respectively. RYGB patients whose BMI decreased ≤ 13.6 or ≥ 19.8 units comprised groups III (n = 39) and IV (n = 39), respectively. Within each surgery, SNPs with large differences in reference allele frequency (z score > 2, corresponding to values displaced 2 standard deviations [SD] from the mean for all SNPs) in low versus high quartiles, were identified. We compared reference allele frequencies, within surgical procedure, using the χ^2 test (using Bonferroni correction for multiple testing).

Results: The mean percent excess weight losses (± SD) corresponding to groups I, II, III, and IV were: 16 (±12), 64 (±30), 55 (±16), and 75 (±17), respectively. SNPs with z score >2 were identified in genes involved in LAGB response, lipid metabolic regulation (*APOE*, rs439401; *APOC4*, rs2288911), neural processes (*DRD3*, rs167771; *HTR3 B*, rs3758987), and xeno- or endobiotic metabolism (*CYP3 A4,* rs12333983); and for RYGB response, in lipid transport (*SCARB1,* rs10846744), folate metabolism (*MTHFR,* rs2066470), regulation of glycolysis in immune cells (*HIF1 A,* rs1951795), vitamin K cycling (*VKORC1,* rs2359612), and xeno- or endobiotic metabolism (*CYP3 A4,* rs2242480). For LAGB response, APOE SNP frequencies were significantly different.

Conclusions: With further validation, information derived from patient DNA may be useful to predict surgical weight loss outcomes and guide selection of surgical approach. (Surg Obes Relat Dis 2015;▮:00–00.) © 2015 American Society for Metabolic and Bariatric Surgery. All rights reserved.

Keywords: Roux-en-Y gastric bypass; Laparoscopic adjustable gastric band; Genetics; SNP

Extreme obesity is associated with numerous comorbidities [1], lower quality of life [2], shortened life expectancy [3,4], and overconsumption of healthcare

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resources [5]. For many patients, bariatric surgery markedly reduces body mass, reducing or remitting debilitating co-morbidities, such as metabolic syndrome and type 2 diabetes, high blood pressure, hyperlipidemia, obstructive sleep apnea syndrome, and gastroesophageal reflux disease, and improving patient quality of life [6–9]. However, the response to surgical intervention varies across individuals and depends on the type of surgical procedure [10,11]. Courcoulas et al. [12] reported substantial interindividual variability in the trajectory of weight loss and in diabetes, blood pressure, and lipid outcomes in first 3 years after surgical intervention in the Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. Understanding the variability in surgical response is of interest because health improvement generally coincides with weight loss. If weight loss is small and health benefits are attenuated, healthcare resources may be considered misspent. Were clinicians, *before surgery*, able to predict the extent to which a beneficial response to a given surgical intervention can be expected for a given patient, those patients most likely to benefit could be targeted for surgical intervention. Such an approach would, overall, minimize the exposure of patients to unnecessary surgical procedures and optimize the allocation of healthcare resources.

Genomic factors are associated with morbid obesity [13] and contribute to the variability in weight loss in response to surgical intervention [14–21]. To date, the largest of the genetic studies of intervention have focused exclusively on or Roux-en-Y gastric bypass (RYGB) [21–24]. Still et al. [21] related differences in trajectories for weight loss to genetic markers in 4 obesity genes: the mass and obesity-associated *(FTO)*, insulin induced gene 2 *(INSIG2),* melanocortin 4 receptor *(MC4 R),* and proprotein convertase subtilisin/kexin type 1 *(PCSK1)* genes 21. Although RYGB is typically more efficacious than laparoscopic adjustable gastric banding (LAGB), a significant proportion of patients who undergo LAGB do in fact experience a large weight loss and satisfactory remission of co-morbidities [25]. LAGB is also less invasive than RYGB. Thus on several levels there are advantages to identifying the patients for whom gastric banding is therapeutic.

The aim of the present study was to investigate whether genomic markers selected from metabolic pathways can discriminate high and low weight loss response according to the surgical procedure. We utilized physiogenomics, a method of sensitivity analysis and systems engineering [26] previously applied by our group to clinical phenotypes of interest such as adverse responses to drugs [27–30] and physiologic responses to dietary intervention [31]. Here we have investigated the contributions of an array of selected single nucleotide polymorphism (SNP) markers to the variability in weight loss in patients who responded to LAGB or RYGB intervention with a small or large decrease in body mass index (BMI).

Methods

Study design and patients

Patients. One hundred sixty-one patients who underwent LAGB or RYGB at the Hartford Hospital Surgical Weight Loss Center (SWLC) between March 2005 and October 2012 participated. Patients qualified for bariatric surgery based on BMI >40 or BMI 35–40 and the presence of ≥ 1 co-morbidity from among type 2 diabetes mellitus, hypertension, hyperlipidemia, obstructive sleep apnea, and gastroesophageal reflux disease.

Design. This naturalistic, retrospective, observational study sampled real-world patients treated at SWLC. As of February 2013, the SWLC database included approximately 1800 patients with 1-year follow-up data. Response quartiles for LAGB (N = 1341) and RYGB (N = 458), respectively, were defined based on the BMI decrease at 1 year. Patients from the lower and uppermost quartiles of response to LAGB and RYGB, respectively, were recruited. Groups I and II consisted of patients who underwent LAGB and experienced decreases in BMI that were either in the lowest quartile of response (historically, ≤ 4.7 BMI units) or in highest quartile of BMI decrease (≥ 10.2 units). Group III and IV consisted of RYGB patients whose decrease in BMI was in the lowest (≤ 13.6 BMI units) or the highest quartile of BMI response (≥ 19.8 units), respectively.

Recruitment and informed consent. The study was approved by Hartford Hospital's Institutional Review Board. A research coordinator mailed letters to explain the purpose and extent of participation to qualified patients. Participation included submission to a blood sample for DNA extraction and storage and permission for researchers to access the patient's medical records. The response rate was 26%. Patients who agreed to participate signed the informed consent and enrolled.

Clinical data collection. Clinical data were retrieved from the SWLC Patient Registry. Patients self-reported heritage as Caucasian, black, Latino, Native American, or Asian. Those who did not report heritage or who reported Native American or Asian race were grouped together as Other.

Assessment of weight and weight loss. Patient body mass was measured to the nearest .25 lb. (Tanita PH-740 scale). Body mass and height were measured at the preoperative visit (baseline) and at the office visit closest to the 12-month (range: 9–18 mo) postoperative time (1 yr). BMI was calculated as (mass, kg) / (height, meters)^2. Percent excess weight lost after surgery was calculated as [(body mass, kg, 1 yr postsurgery) – (body mass, kg, presurgery) / (body mass, kg, presurgery) – (body mass, kg, corresponding to BMI 25)] $\times$ 100.