



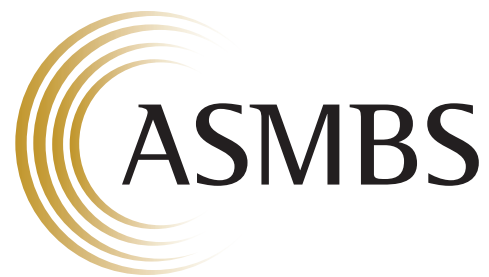
RESEARCH GRANT AWARDS

ASMBS Research Grant Award Program

The ASMBS Research Grant Award program was initiated in 2004 to encourage research in the field of Metabolic and Bariatric Surgery. The program has been primarily supported by the ASMBS Foundation, which has provided over 1 million research dollars since its inception.

The program has been managed on behalf of the society by the ASMBS Research Committee members who have worked tirelessly each year to review the many grant proposals submitted.

This booklet was compiled by the Committee Chairman Ranjan Sudan, MD and Committee Liaison Nooriel Nolan and highlights the research produced from all funded grant projects to date.



Past Award Winners:

*projects ongoing

2004

Paul R.G. Cunningham, MD

Putative Mechanisms of type 2 diabetes mellitus improvements with weight loss in a rat RYGB model

2005

Erik Wilson, MD

From fat to vessels: obesity inflammation and vascular function

Giselle Hamad, MD

The Effect of Gastric Bypass on SSRI Pharmacokinetics and Pharmacodynamics

Daniel Cottam, MD

Oncologic effects of morbid obesity on apoptic markers and tumor growth factors before and after roux-en-y gastric bypass and adjustable gastric banding

2006

Marc Bessler, MD

Effects of Obesity on Airway Inflammation and Asthma

Stanley J. Rogers, MD

Nutrient absorption in morbidly obese patients before and after gastric bypass surgery

Marzieh Salehi, MD

The role of glucagon like peptide-1 in glucose metabolism and weight loss following gastric bypass surgery

Stacy Brethauer, MD

Pelvic floor disorders in bariatric surgery patients

2007

Melissa Kalarchian, PhD

Optimizing Long-term Weight Control after Bariatric Surgery

David Sarwer, PhD

Improvements in Reproductive Status Following Bariatric Surgery

April Strader, PhD

Mechanisms underlying improved glycemia following ileal transposition

2008

Drew Rideout, MD

Adiponectin improves steatohepatitis in obese rats after roux-en-y gastric bypass

*Ronald Evans, PhD

Metabolic and cardiovascular disease risk reduction following gastric bypass surgery: the role of endothelial progenitor cells in vascular health

*Mary Elizabeth Patti, MD

Hyperinsulinemic hypoglycemia following gastric bypass: pathophysiology and molecular mechanism

2009

Daniel DeUgarte, MD

Impact of Metabolic/bariatric surgery on diet-induced childhood obesity: implication for long-term health and offspring metabolic phenotype

Michael Peters, MD

Autonomic nervous system function and novel determinants of glucose homeostasis following bariatric surgery

*Christopher Still, DO

Identification of molecular markers for NASH

2010

*William Richards, MD

Vascular endothelium changes after bariatric surgery

2011

*William Raum, MD, PhD

Treatment of low metabolic rates and low lean body mass after bariatric surgery

2012

*Stacy Brethauer, MD

Obesity-induced diabetes – searching for a cure through bariatric surgery

*Joram Mul, MD

Melanocortin receptor-4 function is critical for energy homeostasis changes following vertical sleeve gastrectomy

2013

*Kimberley Steele, MD

Neurobiologic alterations induced by bariatric surgery: the gut-brain axis and its relationship to weight loss

Update on Completed Grant Projects:

2004:



Paul R.G. Cunningham, MD

Brody School of Medicine, East Carolina University

Grant Project:

Putative mechanisms of type 2 diabetes mellitus improvements with weight loss in a rat RYGB model

Publications:

Neurohormonal pathways regulating food intake and changes after Roux-en-Y gastric bypass.
Review article *SOARD* 1 (2005) 486-495

2005:



Erik B. Wilson, MD

University of Texas Medical Center

Grant Project:

From Fat to Vessels: obesity inflammation and vascular function

Publications:

Improvements in systemic metabolism, anthropometrics, and left ventricular geometry 3 months after bariatric surgery. *SOARD* 2 (2006) 592-599

Decreased visceral adipose tissue nine months after bariatric surgery is associated with dramatic changes in metabolic gene expression. *SOARD* 3 (2007) 277-298 (Abstract)

Presentations:

Decreased visceral adipose tissue nine months after bariatric surgery is associated with dramatic changes in metabolic gene expression. Presented in Plenary Session, Emerging Medicine/Research of ASMBS 2007 Annual Meeting

Review article

Neurohormonal pathways regulating food intake and changes after Roux-en-Y gastric bypass

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John D. Halverson, M.D., F.A.C.S., Paul R. Cunningham, M.D., F.A.C.S.,
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Manuscript received October 29, 2004; revised May 24, 2005; accepted May 29, 2005

Keywords: Appetite; Hypothalamus; Ghrelin; Neuropeptide; Arcuate; Peptide YY; Bariatric surgery; Leptin; Neuropeptide Y; Adipose; Obesity; Adipokine; Adiponectin; Resistin; Diabetes; Insulin; Glucose-dependent insulinotropic polypeptide; Glucagon-like peptide-1

The major goal of obesity therapy is to reduce body weight and improve comorbidities, thereby improving the patient's quality and length of life [1]. Obesity treatment involves 2 basic principles: (1) restricting food intake by dieting and (2) increasing energy expenditure by exercise. Maintaining long-term weight loss is difficult even with the aid of approved drugs like sibutramine. Sibutramine sustains a modest 5% to 10% weight loss for up to 1 year with continued treatment; however, weight is frequently regained with cessation of pharmacotherapy [2], and long-term safety and reduction in morbidity and mortality are unclear [3].

Surgical intervention has thus far proven to be the most effective method of achieving prolonged weight loss and reverse metabolic comorbidities in morbidly obese persons (those with body mass index [BMI] ≥ 40 kg/m² or ≥ 35 kg/m² with a comorbidity) [1]. Bariatric surgery has evolved over the past 50 years and has led to the currently performed operations that achieve weight loss via restrictive mechanisms, malabsorptive mechanisms, or both [4]. Roux-en-Y gastric bypass (RYGB) combines restrictive and malabsorptive mechanisms, limiting caloric intake by limiting functional stomach volume and by excluding part of the

foregut via a Roux-en-Y gastrojejunostomy [5]. This technique introduces biliopancreatic digestive secretions into the mid-jejunum.

As shown in Figure 1, regulation of food intake is facilitated via the gut-brain-gut axis, which consists of afferent and efferent limbs within the central nervous system (CNS), enteric nervous system (ENS), and endocrine system [6]. Consequent to rearranging the gut in RYGB, nutrients pass from the gastric pouch to the mid-jejunum, bypassing the remnant of the stomach, duodenum, and proximal jejunum. This diversion alters the usual neuronal and hormonal afferent gut signals (afferent limb) to the nucleus tractus solitarius (NTS) and area postrema (AP). The NTS, AP, and dorsal motor nucleus (DMX; efferent limb) make up the dorsal vagal complex (DVC) within the medulla [7]. The NTS is the viscerosensory nucleus of the DVC and can induce satiety independently from the forebrain [8]. Higher-order sensory neurons project from the NTS to hypothalamic nuclei that regulate appetite, food intake, and energy balance [8].

In the hypothalamus, signals from the afferent limb are integrated with further feedback from the hippocampus, amygdala (memory and emotion related to food), nucleus accumbens (food reward and palatability) [9], and neurohormonal signals from gut and adipose tissue [8]. The hypothalamus transmits the sum of these hunger and satiety signals to the cortex, and feedback regulates ingestive behavior expressed as eating and drinking [8]. The CNS alters gut motility and secretion via the autonomic nervous system

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Original article

Improvements in systemic metabolism, anthropometrics, and left ventricular geometry 3 months after bariatric surgery

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Erik B. Wilson, M.D.,^e Heinrich Taegtmeier, M.D., D.Phil.^{a,*}

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Received May 9, 2006; revised August 24, 2006; accepted September 12, 2006

Abstract

Background: Several lines of evidence have suggested a link between obesity and heart failure, including chronic inflammation, increased sympathetic tone, and insulin resistance. The goal of this study was to evaluate the changes in systemic metabolism, anthropometrics, and left ventricular (LV) contraction, as well as geometry, in clinically severe obese women after bariatric surgery.

Methods: Enrollment was offered consecutively to 22 women with clinically severe obesity. Participants underwent abdominal magnetic resonance imaging to quantify the visceral adipose tissue (VAT) area and tissue Doppler imaging echocardiography to measure the LV contractile function. Fasting blood chemistries were drawn to measure inflammatory markers and to calculate insulin sensitivity. All tests were performed before surgery and 3 months postoperatively.

Results: Three months after surgery, a significant increase in insulin sensitivity (mean change \pm SEM 34.0 ± 10.4 , $P < .0001$) was present. The VAT area had significantly decreased (-66.1 ± 17.8 cm², $P = .002$) and was associated with decreases in body mass index, serum glucose concentrations, and high-sensitivity C-reactive protein levels ($r = .61$ and $P = .005$, $r = .48$ and $P = .033$, and $r = .53$ and $P = .016$, respectively). The LV mass decreased significantly (-3.8 ± 1.7 g/m^{2.7}, $P = .037$), and this decrease was associated with a decrease in glucose concentration ($r = .46$, $P = .041$). The LV systolic and diastolic contractile function were normal at baseline, and no change occurred after surgery.

Conclusion: The early phase of weight loss after bariatric surgery produces favorable changes in LV geometry, and these are associated with normalization in the glucose metabolism. © 2006 American Society for Bariatric Surgery. All rights reserved.

Keywords:

Obesity; Magnetic resonance imaging; Left ventricular hypertrophy; Echocardiograph; Insulin resistance

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DECREASED VISCERAL ADIPOSE TISSUE NINE MONTHS AFTER BARIATRIC SURGERY IS ASSOCIATED WITH DRAMATIC CHANGES IN METABOLIC GENE EXPRESSION.

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Background: The decrease in visceral adipose tissue (VAT) after bariatric surgery is associated with improved systemic glucose and free fatty acid metabolism. These alterations may have an important regulatory impact on skeletal muscle metabolism. We hypothesized that the decrease in visceral adipose tissue after bariatric

surgery alters gene expression responsible for fatty acid partitioning and glucose flux in skeletal muscle.

Methods: A cohort of 13 consecutively enrolled patients underwent abdominal MRI, to quantify VAT area, and a percutaneous muscle biopsy of the vastus lateralis to measure metabolic gene expression by quantitative reverse transcriptase polymerase chain reaction. Fasting blood samples were also obtained to measure metabolites, insulin, and adipokines. We compared studies performed before surgery and 9 months after surgery using repeated measures ANOVA.

Results: At 9 months all subjects showed a significant decrease in BMI and VAT area [Mean change (+/-SEM), p value: 12.86 kg/m² (1.7), p<0.0001 and 98.47 cm² (26.4), p=0.004, respectively]. In addition, serum insulin and leptin, as well as plasma free fatty acid concentrations decreased after 9 months of sustained weight loss [12.54 μU/mL (3.7), p=0.003, 42.77 ng/mL (7.8), p<0.0001, and 0.14 mmol/L (0.06), p=0.029, respectively]. Skeletal muscle stearoyl Co-A desaturase (SCD) and pyruvate dehydrogenase kinase-4 (PDK4) gene expression levels significantly decreased (% change in expression: -86%, p=0.007 and -87%, p=0.001, respectively).

Conclusion: 9 months after bariatric surgery decreased VAT and favorable systemic metabolic changes may contribute to improved fatty acid partitioning and glucose metabolism in skeletal muscle.

PH: S1550-7289(07)00227-4

Update on Completed Grant Projects:

2005:



Giselle Hamad, MD

University of Pittsburgh Physicians

Grant Project:

The Effect of Gastric Bypass on SSRI Pharmacokinetics and Pharmacodynamics

Publications:

The Effect of Gastric Bypass on SSRI Pharmacokinetics and Pharmacodynamics. *SOARD* 4 (2008) 312-357 (Abstract)

The effect of gastric bypass on the pharmacokinetics of serotonin reuptake inhibitors. *Am J Psych.* 2012;169(3):256-63.

Presentations:

The Effect of Gastric Bypass on SSRI Pharmacokinetics and Pharmacodynamics. Poster presentation, ASMBS 2008 Annual Meeting.

2005:



Daniel Cottam, MD

Surgical Weightloss Center of Utah

Grant Project:

Oncologic effects of morbid obesity on apoptic markers and tumor growth factors before and after roux-en-y gastric bypass and adjustable gastric banding

Publications:

Tumor growth factor expression in obesity and changes in expression with weight loss: another cause of increased virulence and incidence of cancer in obesity. *SOARD* 6 (2010) 538-541

Presentations:

Tumor growth factor expression in obesity and changes in expression with weight loss: another cause of increased virulence and incidence of cancer in obesity. Abstract presented at ASMBS 2009 Annual Meeting

P115.

**THE EFFECT OF GASTRIC BYPASS ON SSRI
PHARMACOKINETICS AND PHARMACODYNAMICS**

Giselle G. Hamad, MD¹; Gina M. Kozak, PA-C¹;
Katherine L. Wisner, MD²; James M. Perel, PhD²; ¹*Surgery,
University of Pittsburgh, Pittsburgh, PA, USA.*; ²*Western Psy-
chiatric Institute & Clinic, Pittsburgh, PA, USA.*

Background: The morbidly obese are at high risk for major depressive disorder (MDD), which is most commonly treated with serotonin-selective reuptake inhibitors (SSRI). We hypothesized that Roux-en-Y gastric bypass (RYGBP) reduces the absorption of SSRI, leading to exacerbation of depressive symptoms.

Methods: The effect of RYGBP on the pharmacokinetics and pharmacodynamics of SSRI was studied. A 48 year-old female (BMI 46) who was treated with sertraline 100 mg daily for MDD had serial blood samples drawn for sertraline levels for pharmacokinetic and pharmacodynamic studies. The pharmacokinetic parameters determined were: maximum concentration (C_{MAX}) and time to C_{MAX} (T_{MAX}). The pharmacodynamic studies consisted of the platelet membrane serotonin reuptake assay. These measures were repeated at 1 month following RYGBP. The SIGH-ADS (Structured Interview Guide for the Hamilton Depression Rating Scale—Atypical Depression Symptom Version) was used to measure depressive symptom level and to assess clinical response.

Results: The preoperative trough level of sertraline was 17.5 ng/mL. C_{MAX} was 41.6 ng/mL at T_{MAX} 300 min after dose. At 1 month postoperatively, the patient weighed 221.5 lbs (24% EWL). The 1 month trough sertraline level was 11.1 ng/mL. The 1 month C_{MAX} was 14.4 at T_{max} 240 min after dose. The patient also had exacerbation of MDD at 1 month following surgery.

Conclusion: Following RYGBP, sertraline absorption was significantly decreased compared to the pre-operative value, leading to exacerbation of depressive symptoms. Alternate formulations of sertraline may improve bioavailability. Further studies are needed to determine whether optimizing control of MDD with SSRI will improve weight loss outcomes and quality of life, thereby reducing the potential for weight regain.

PII: S1550-7289(08)00288-8

P-35

THE EFFECT OF GASTRIC BYPASS ON THE PHARMACOKINETICS OF SEROTONIN REUPTAKE INHIBITORS

Giselle G. Hamad, MD¹; Joseph C. Helsel, BA³; Gina M. Kozak, PA-S¹; Mary C. McShea, MS²; Carolyn Hughes; MsW²; Andrea L. Confer, ²Carol A. McCloskey, MD¹; Dorothy K. Sit, MD²; James M. Perel, PhD³; Katherine L. Wisner, MD, MS²; ¹Surgery, University of Pittsburgh, Pittsburgh, PA, United States; ²Psychiatry, University of Pittsburgh, Pittsburgh, PA, United States; ³Pharmacology, University of Pittsburgh, Pittsburgh, PA, United States

Background: The morbidly obese frequently present with major depressive disorder (MDD), which is most commonly treated with antidepressants classified as serotonin reuptake inhibitors (SRI), which include serotonin-selective reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI). We hypothesized that the bioavailability of SRI decreases following RYGB, leading to exacerbation of depression.

Methods: Twelve candidates for RYGB who were successfully treated with an SRI for MDD were studied prospectively. Serial blood samples for SRI plasma levels were drawn over 7 hours immediately after dose for pharmacokinetic studies (PK) preoperatively. Maximum concentration (C_{MAX}), time to C_{MAX} (T_{MAX}), and Area Under Concentration/Time curve (AUC) were determined. PK studies were repeated at one, six, and twelve months postoperatively. The Structured Interview Guide for the Hamilton Depression Rating Scale- Atypical Depression Symptom Version (SIGH-ADS) was used to measure depressive symptom levels.

Results: In eight of twelve patients, AUCs decreased from preoperative levels to 1-month postoperative levels, representing a decrease in SRI bioavailability. In six patients, the AUCs returned to baseline at six months. Four patients had an exacerbation in depressive symptoms, as measured by SIGH-ADS, which resolved by twelve months in three. Normalization of the AUC was associated with an improvement in depression scores. All subjects received greater treatment exposure.

Conclusion: Patients taking SRI antidepressants are at risk for a reduction in SRI bioavailability 1 month after RYGB; they should be monitored closely for recurrent symptomatology. Alternate SRI formulations or dose adjustment may be required to improve bioavailability. This reduction is resolved by six months postoperatively.

comes when compared to standard laparoscopic Roux-en-Y gastric bypass (LRYGB) with potential improvements in post-operative cosmesis, pain, and patient satisfaction. We present our experience with this novel approach.

Methods: A retrospective review of all patients [meeting National Institutes of Health criteria] who received single site Roux-en-Y gastric bypass (SSRYGB) was conducted. Patient demographics, peri-operative data, and outcomes were evaluated. Operative times, blood loss, complications, re-interventions, and weight loss outcomes were studied.

Results: Since August 2008, twenty patients (19 females), age 41 ± 12 years (range 27-68), with body mass index of 44 ± 6 kg/m² (range 35-53) underwent SSRYGB. Sixteen successfully completed SSRYGB. Operative times ranged 120-400 minutes (mean 205 ± 64.2), and there was a declining trend with commensurate experience. Blood loss was minimal (27.9 ± 16.5 mL), and there were no significant complications. There were no conversions to open surgery. Of the 4 conversions to standard laparoscopic surgery, 3 were due to excessive intra-abdominal adhesions and one due to mechanical failure of a flexible tip laparoscope. One patient received endoscopic re-intervention for a proximal stenosis, approximately 2 months following surgery. Excess weight loss was $50.1 \pm 21\%$ for all patients with follow-up >3 months.

Conclusion: Single site access can be safely utilized in bariatric surgery with favorable results. SSRYGB is a complex procedure, but the learning curve is favorable. Post-operative weight loss and cosmesis are excellent; and further studies are underway to evaluate SSRYGB's impact on post-operative pain.

The Effect of Gastric Bypass on the Pharmacokinetics of Serotonin Reuptake Inhibitors

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Dorothy K. Sit, M.D.

Carol A. McCloskey, M.D.

Katherine L. Wisner, M.D., M.S.

Objective: Morbidly obese patients frequently present with mood and anxiety disorders, which are often treated with serotonin reuptake inhibitors (SRIs). Having observed that patients treated with SRIs frequently relapse after Roux-en-Y gastric bypass surgery, the authors sought to assess whether SRI bioavailability is reduced postoperatively.

Method: Twelve gastric bypass candidates treated with an SRI for primary mood or anxiety disorders were studied prospectively. Timed blood samples for SRI plasma levels were drawn for pharmacokinetic studies before surgery and 1, 6, and 12 months afterward. Maximum concentration, time to maximum concentration, and area under the concentration/time curve (AUC) were determined.

Results: In eight of the 12 patients, AUC values 1 month after surgery dropped to an average of 54% (SD=18) of preoperative levels (range=36%–80%); in six of these patients, AUC values returned to baseline levels (or greater) by 6 months. Four patients had an exacerbation of depressive symptoms, which resolved by 12 months in three of them. Three of the four patients had a reduced AUC level at 1 month and either gained weight or failed to lose weight between 6 and 12 months. Normalization of the AUC was associated with improvement in symptom scores.

Conclusions: Patients taking SRIs in this study were at risk for reduced drug bioavailability 1 month after Roux-en-Y gastric bypass. The authors recommend close psychiatric monitoring after surgery.

(*Am J Psychiatry* 2012; 169:256–263)

Obesity has reached epidemic status in the United States. According to the National Health and Nutrition Examination Survey, the prevalence of obesity among American adults increased from 15% during the period 1976–1980 to 34% in 2007 and 2008 (1). Obesity severity is measured by body mass index (BMI), which is computed by dividing body weight (in kilograms) by the square of height (in meters). A BMI of 25 to 29.9 is considered to indicate overweight; a BMI of 30–34.9 is designated as obese, and a BMI ≥ 40 is designated as morbidly obese. Obesity is associated with a wide spectrum of medical comorbidities, including sleep apnea, type 2 diabetes mellitus, hypertension, cardiovascular disease, asthma, and cancers of the colon, breast, and endometrium. These conditions contribute to the substantial morbidity and mortality associated with obesity; therefore, in individuals with weight-related comorbidities, a BMI ≥ 35 is considered morbidly obese.

Morbid obesity has been linked to psychiatric disorders, most commonly major depressive disorder, with a reported odds ratio of 4.98 (95% confidence interval=2.07–11.99) (2). In one study, nearly two-thirds of bariatric surgery candidates received a psychiatric diagnosis, most com-

monly major depression (3). Bipolar disorder is also prevalent among candidates for bariatric surgery (4). Psychotropic medications (5) and atypical depressive symptoms such as overeating and fatigue contribute to weight gain. Persons with psychiatric disorders die decades earlier than the general population (6, 7), and the majority of premature deaths are due to cardiovascular events (8).

Roux-en-Y Gastric Bypass Surgery

Morbidly obese patients who have failed dietary or medical weight loss methods are potential candidates for bariatric surgery to achieve long-term weight reduction. In 2008, 220,000 bariatric surgeries were performed in the United States and Canada (9). The Roux-en-Y gastric bypass is one of the most common bariatric procedures. It may be performed either through an abdominal midline incision or laparoscopically, using five or six transabdominal access ports. The laparoscopic approach is associated with a more rapid recovery, lower rates of pulmonary complications and wound infections, and less postoperative pain. A gastric pouch 15–30 ml in volume is created to restrict food intake. The jejunum is then divided 40–50 cm

This article is featured in this month's AJP Audio, is the subject of a CME course (p. 341), and is an article that provides Clinical Guidance (p. 263)

Original article

Tumor growth factor expression in obesity and changes in expression with weight loss: another cause of increased virulence and incidence of cancer in obesity

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Received May 22, 2009; revised April 9, 2010; accepted April 21, 2010

Abstract

Background: Obesity is associated with increased tumorigenesis. Previously, we demonstrated that inflammation in obesity caused cancer fighting cells to display greater surface receptor levels, predisposing them to early cell death. We measured the inflammatory tumor growth factor levels to determine whether inflammation in obesity increases expression of these factors, potentially predisposing these patients to greater rates of neoplasia.

Methods: A total of 24 patients undergoing weight loss surgery had samples collected preoperatively and at 6 and 12 months after surgery. The growth factors analyzed included tumor necrosis factor (TNF)- α , granulocyte-macrophage colony-stimulating factor, interferon- γ , interleukin (IL)-1b, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, vascular endothelial growth factor, hepatocyte growth factor, TNF-receptor I (TNF-RI), TNF-RII, death receptor 5, leptin, and adiponectin. Control samples were obtained from 10 healthy, normal weight volunteers.

Results: The tumor growth factors TNF- α , TNF-RI, TNF-RII, vascular endothelial growth factor, hepatocyte growth factor, interferon- γ , IL-2, IL-5, and IL-6 all decreased significantly ($P < .05$) compared with the preoperative values. The IL-4, IL-8, leptin, death receptor 5, adiponectin, and granulocyte-macrophage colony-stimulating factor levels did not change significantly over time. The IL-1b and IL-10 levels were less than the detection limit at all points. When obese patient serum was compared with healthy volunteer pooled serum, we found that the leptin, death receptor 5, hepatocyte growth factor, vascular endothelial growth factor, TNF-RI, TNF-RII, TNF- α , IFN- γ , granulocyte-macrophage colony-stimulating factor, IL-4, IL-5, IL-6, and IL-8 levels were all 2–37 times greater than the levels in the controls at baseline. The concentrations of these same growth factors had decreased levels only 1–3.5 times greater than those of the controls at 12 months postoperatively.

Conclusion: Many inflammatory tumor growth factors are present in greater concentrations in obese individuals. This could explain the greater prevalence of neoplasia in the morbidly obese population. (Surg Obes Relat Dis 2010;6:538–541.) © 2010 American Society for Metabolic and Bariatric Surgery. All rights reserved.

Supported by an American Society for Metabolic and Bariatric Surgery grant.

Presented at the 2009 American Society for Metabolic and Bariatric Surgery meeting.

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Update on Completed Grant Projects:

2006:



Marc Bessler, MD

New York Presbyterian Hospital

Grant Project:

Effects of Obesity on Airway Inflammation and Asthma

Publications:

Exhaled nitric oxide in obese asthmatics and obese non-asthmatics. *SOARD* 5 (2009) S67-S70

Presentations:

Exhaled nitric oxide in obese asthmatics and obese non-asthmatics. Research presented in Students/Residents/Fellows Session of ASMBS 2009 Annual Meeting

2006:



Stanley Rogers, MD

UCSF Department of Surgery

Grant Project:

Nutrient absorption in morbidly obese patients before and after gastric bypass surgery

Publications:

Laparoscopic Bariatric Surgery Improves candidacy in morbidly obese patients. Abstract. *SOARD* 3 (2007) 277-298

Laparoscopic bariatric surgery improves candidacy in morbidly obese patients awaiting transplantation. *SOARD* 4 (2008) 159-165

Presentations:

Laparoscopic Bariatric Surgery Improves candidacy in morbidly obese patients. Research presented in Plenary Session, Comorbidities at ASMBS 2007 Annual Meeting

SRF-104.

EXHALED NITRIC OXIDE IN OBESE ASTHMATICS AND OBESE NON-ASTHMATICS

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Alina Johnson; Adnan Divjan; Jenny J. Choi, MD;
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Rachel L. Miller, MD; *Columbia University Medical Center,
New York, NY, USA.*

Background: Non-obese asthmatics have elevated levels of exhaled nitric oxide (eNO), a biomarker of airway inflammation. Whether obesity influences eNO levels is an open question.

Methods: Patients (n=12) with and without asthma and a BMI > 40 were recruited from the Columbia University Center for Metabolic and Weight Loss Surgery. Subjects were excluded for current smoking, > 10 pack-year smoking history, and significant comorbidities. Prior to and three months following bariatric surgery, respiratory and gastroesophageal reflux disease questionnaires were administered, allergy skin testing and pulmonary function testing conducted, and eNO measured.

Results: Mean BMI before and after surgery decreased from 47 to 41 among non-asthmatics and 48 to 45 among asthmatics. Levels of eNO ranged from 4 to 20 ppb. There were no significant differences in mean eNO among asthmatics and non-asthmatics (5.6 vs. 8.0 ppb), or before and after surgery (7.6 vs 7.8 ppb). No associations were found between eNO and allergy skin tests, BMI, ethnicity, age, or pulmonary function test parameters. However, a single correlation between eNO and forced expiratory flow rate 25-75 ($r = 0.7$, $p = 0.01$) was evident. Males had higher eNO levels than females ($p = 0.03$). Higher eNO levels were associated with lower GERD symptom scores ($r = -0.6$, $p = 0.04$).

Conclusion: In a pilot study, obese asthmatics and obese non-asthmatics had normal levels of eNO before and after bariatric surgery. Further research is needed to determine whether asthma symptoms in obese patients are due to respiratory mechanics or novel mechanisms of airway inflammation.

cation, feasibility, and complications of revision gastro-jejunostomy (G-J).

Methods: A retrospective review was conducted from 1/05 to 5/07. Patient characteristics, indication for revision of G-J, complications, and weight loss were evaluated. Patients were grouped according to operative indications: complications of prior surgery (Group A) and weight regain (Group B).

Results: 27 patients were included. There were no peri-operative mortalities. Group A had 22 patients that underwent redo G-J due to persistent strictures (10) and marginal ulcers (12). Group B had 5 patients with mean pre-operative BMI 43. After revisional surgery, group B BMI decreased to 35. Mean follow up was 12 months. Mean hospital stay was 6.2 days. Short term (1 month) complications occurred in 7 patients and included 2 post-operative admissions to ICU for respiratory distress, 1 intra-abdominal abscess, 1 retained specimen, 1 re-admission for dehydration, 1 partial SBO, and 1 abdominal wall abscess. Long term complications (>1 month) occurred in 9 patients and included 1 gastrocutaneous fistula from gastrostomy tube site. 8 patients developed severe vomiting and EGD was performed. This showed 1 marginal ulcer and 6 strictures. 4 of these 6 patients with stricture underwent successful dilation. 1 patient had a refractory stricture requiring re-operation and 1 patient had RYGB reversal for failure to thrive. Aside from these 2 reoperations, 7 of these 9 patients were asymptomatic in 9-12 months.

Conclusion: G-J revision can be performed with low mortality but complications such as stricture recurrence are common and usually amendable by EGD dilation therapy, however, some patients require reoperation.

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LAPAROSCOPIC BARIATRIC SURGERY IMPROVES CANDIDACY IN MORBIDLY OBESE PATIENTS.

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Background: Morbid obesity is a relative contraindication for kidney, liver, or lung transplantation since it is associated with higher rates of postoperative complications and reduced graft survival. **Objectives:** To evaluate the safety and efficacy of laparoscopic Roux-en-Y gastric bypass (LGBP) in patients with end stage renal disease (ESRD) and laparoscopic sleeve gastrectomy (LSG) in patients with cirrhosis or end stage lung disease (ESLD). **Methods:** Design: Retrospective review. Setting: University tertiary referral center. Patients: Eleven patients not eligible for transplantation due to morbid obesity. Outcome Measures: Operative data, postoperative complications, weight loss expressed as percentage of excess weight loss (%EWL), quality of life, and status of transplant candidacy. Demographic, clinical, peri-operative and follow-up data were prospectively collected. Quality of life measured with the Moorehead-Ardelt questionnaire.

Results: Six patients with ESRD underwent LGBP, three patients with cirrhosis and two with ESLD underwent LSG (Table 1). Complications developed in two of the eleven patients (both after LSG) and there was no mortality. The mean follow-up period after LGBP and LSG was 9 and 6 months, and mean %EWL was 46% and 34%, respectively. Quality of life was significantly improved in all patients. Three of the six patients with ESRD, two of the three patients with cirrhosis, and one patient with ESLD have now reached our institution's body mass index (BMI) limit for transplantation and are undergoing pretransplant evaluation.

Conclusion: This pilot study demonstrates that LGBP in patients with ESRD and LSG in patients with cirrhosis or ESLD appears safe and can improve their candidacy for transplantation.

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Original article

Laparoscopic bariatric surgery improves candidacy in morbidly obese patients awaiting transplantation

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Abstract

Background: To evaluate, at a university tertiary referral center, the safety and efficacy of laparoscopic Roux-en-Y gastric bypass (LRYGB) in patients with end-stage renal disease (ESRD) and laparoscopic sleeve gastrectomy (LSG) in patients with cirrhosis or end-stage lung disease (ESLD); and to determine whether these procedures help patients become better candidates for transplantation.

Methods: A retrospective review was performed of selected patients with end-stage organ failure who were not eligible for transplantation because of morbid obesity who underwent LRYGB or LSG. The prospectively collected data included demographics, operative details, complications, percentage of excess weight loss, postoperative laboratory data, and status of transplant candidacy.

Results: Of the 15 patients, 7 with ESRD underwent LRYGB and 6 with cirrhosis and 2 with ESLD underwent LSG. Complications developed in 2 patients (both with cirrhosis); no patient died. The mean follow-up was 12.4 months, and the mean percentage of excess weight loss at ≥ 9 months was 61% (ESRD), 33% (cirrhosis), and 61.5% (ESLD). Obesity-associated co-morbidities improved or resolved in all patients. Serum albumin and other nutritional parameters at ≥ 9 months after surgery were similar to the preoperative levels in all 3 groups. At the most recent follow-up visit, 14 (93%) of 15 patients had reached our institution's body mass index limit for transplantation and were awaiting transplantation; 1 patient with ESLD underwent successful lung transplant.

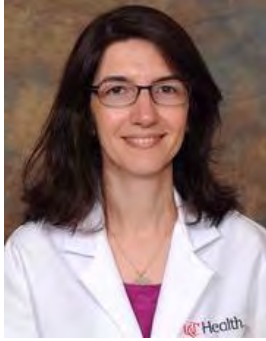
Conclusion: The results of this pilot study have provided preliminary evidence that LRYGB in patients with ESRD and LSG in patients with cirrhosis or ESLD is safe, well-tolerated, and improves their candidacy for transplantation. (Surg Obes Relat Dis 2008;4:159–165.) © 2008 American Society for Metabolic and Bariatric Surgery. All rights reserved.

Keywords:

Laparoscopic bariatric surgery; Obesity; Transplantation; End-stage renal disease; Cirrhosis; End-stage lung disease; Laparoscopic gastric bypass; Laparoscopic sleeve gastrectomy

Update on Completed Grant Projects:

2006:



Marzieh Salehi, MD

University of Cincinnati College of Medicine, Dept of Medicine, Division of Endocrinology

Grant Project:

The role of glucagon like peptide-1 in glucose metabolism and weight loss following gastric bypass surgery

Publications:

Gastric Bypass surgery enhances glucagon-like peptide 1-stimulated postprandial insulin secretion in humans. *Diabetes* 60(9): 2308-14, 2011

Presentations:

Patients with hypoglycemia following Roux-en-Y gastric bypass surgery have enhanced incretin secretion mediated by GLP-1 action. Endocrine Society Annual Meeting 2008

The role of GLP-1 in hypoglycemic syndrome. Joslin Diabetes Center International Symposium 2008

Insulin secretion mediated by GLP-1 action is enhanced following Roux-en-Y gastric bypass surgery. American Diabetes Association Scientific Session 2009

Bariatric Surgery: Mechanisms of surgery-based therapy for obesity and diabetes, more than rearranging the plumbing. Symposium: Obesity and its complications. Endocrine Society Annual Meeting 2012.

Bariatric Surgeries & Diabetes Resolution. The Ohio ACP Chapter Scientific Meeting 2012

Altered glucose metabolism after bariatric surgeries: what every surgeon should know. The Ohio ASMBS Chapter 2013

2006:



Stacy Brethauer, MD

Cleveland Clinic Bariatric and Metabolic Institute

Grant Project:

Pelvic floor disorders in bariatric surgery patients

Publications:

Obesity is associated with increased prevalence and severity of pelvic floor disorders. *SOARD* 4 (2008) 312-357

Psychosocial correlates of pelvic floor disorders in women seeking bariatric surgery. *SOARD* 8 (2012) 792-796

Presentations:

Obesity is associated with increased prevalence and severity of pelvic floor disorders. Poster Session ASMBS 2008 Annual Meeting.

Comprehensive evaluation of the effect of bariatric surgery on pelvic floor disorders. Abstract submitted and accepted for oral presentation at ASMBS 2013 Annual Meeting/Obesity Week.

Gastric Bypass Surgery Enhances Glucagon-Like Peptide 1–Stimulated Postprandial Insulin Secretion in Humans

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OBJECTIVE—Gastric bypass (GB) surgery is associated with postprandial hyperinsulinemia, and this effect is accentuated in postsurgical patients who develop recurrent hypoglycemia. Plasma levels of the incretin glucagon-like peptide 1 (GLP-1) are dramatically increased after GB, suggesting that its action contributes to alteration in postprandial glucose regulation. The aim of this study was to establish the role of GLP-1 on insulin secretion in patients with GB.

RESEARCH DESIGN AND METHODS—Twelve asymptomatic individuals with previous GB (Asym-GB), 10 matched healthy nonoperated control subjects, and 12 patients with recurrent hypoglycemia after GB (Hypo-GB) had pre- and postprandial hormone levels and insulin secretion rates (ISR) measured during a hyperglycemic clamp with either GLP-1 receptor blockade with exendin-(9–39) or saline.

RESULTS—Blocking the action of GLP-1 suppressed postprandial ISR to a larger extent in Asym-GB individuals versus control subjects (33 ± 4 vs. $16 \pm 5\%$, $P = 0.04$). In Hypo-GB patients, GLP-1 accounted for $43 \pm 4\%$ of postprandial ISR, which was not significantly higher than that in Asym-GB subjects ($P = 0.20$). Glucagon was suppressed similarly by hyperglycemia in all groups but rose significantly after the meal in surgical individuals but remained suppressed in nonsurgical subjects. GLP-1 receptor blockade increased postprandial glucagon in both surgical groups.

CONCLUSIONS—Increased GLP-1–stimulated insulin secretion contributes significantly to hyperinsulinism in GB subjects. However, the exaggerated effect of GLP-1 on postprandial insulin secretion in surgical subjects is not significantly different in those with and without recurrent hypoglycemia. *Diabetes* 60:2308–2314, 2011

Surgery to induce weight loss has become increasingly common (1) as obesity has become pandemic (2). Roux-en-Y gastric bypass (GB), which is associated with substantial and durable weight loss (3), has been reported to cause near complete remission of diabetes within days—before any significant weight loss (4,5). The mechanisms for these metabolic

benefits independent of weight loss are still unknown, but it is clear that the insulin response to meal ingestion is exaggerated after surgery (6). Postprandial insulin secretion is augmented by the actions of hormones released from the gastrointestinal (GI) tract, primarily glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) (7), and GB subjects have elevated plasma concentrations of GLP-1 (6,8–13). These findings are the basis for a popular but as yet unproven hypothesis that increased GLP-1 secretion is responsible for the improvement in glucose regulation following GB.

Moreover, in recent years there have been increasing reports of severe hyperinsulinemic hypoglycemia occurring in patients several years after GB (14,15). Affected individuals have exaggerated insulin and GLP-1 responses to meal consumption compared with asymptomatic individuals with GB (16). These observations raise the question as to whether an amplified GLP-1 effect, either from higher plasma levels or increased sensitivity to the peptide, accounts for the syndrome of post-GB hypoglycemia.

In the current study, exendin-(9–39) (Ex-9), a specific GLP-1 receptor (GLP-1r) antagonist (17), was used to test the hypothesis that GB-associated hyperinsulinemia is mediated by increased GLP-1 action and to determine whether enhanced GLP-1 action accounts for greater β -cell stimulation in subjects with postsurgical hypoglycemia.

RESEARCH DESIGN AND METHODS

Twelve asymptomatic subjects with previous GB (Asym-GB) and 10 control subjects with normal glucose tolerance and no prior GI surgery were recruited. Twelve patients with recurrent hypoglycemia following GB (Hypo-GB) based on their clinical symptomatology also participated. The hypoglycemic group was defined by recurrent events that included the presence of Whipple's triad (capillary blood glucose level <2.8 mmol/L associated with hypoglycemic symptoms that resolved with carbohydrate ingestion) (18). Ten of the Hypo-GB subjects had clinically severe hypoglycemia marked by a progression from adrenergic symptoms of hypoglycemia to neuroglycopenic symptoms (cognitive dysfunction, loss of consciousness, and/or seizure) over the period of 1–2 years before they were studied. None of the Asym-GB subjects reported any hypoglycemic symptoms after surgery, whereas Hypo-GB subjects develop postprandial hypoglycemic symptoms (adrenergic symptoms) 2–5 years after their surgery. Three subjects each from the Asym-GB and Hypo-GB groups had a history of type 2 diabetes with no known complications that was controlled with diet or oral antidiabetic medications preoperatively and resolved completely after surgery.

The three groups had similar BMI, age, and sex distribution, and had stable body weight for at least a month before study. Asym-GB and Hypo-GB subjects had similar total weight loss and time since surgery, even though Hypo-GB subjects had a larger weight loss in the 1st year after surgery ($P = 0.01$) and consequently larger weight gain prior to their recruitment compared with Asym-GB subjects (Table 1).

The studies were approved by the institutional review board of the University of Cincinnati, and all participants provided written informed consent prior to the studies.

Peptides. Synthetic exendin-(9–39) (Ex-9) (C S Bio, Menlo Park, CA) was greater than 95% pure, sterile and free of pyrogens. Lyophilized Ex-9 was dissolved in 0.25% human serum albumin and dispensed by the Research Pharmacy at Cincinnati Children's Hospital. The use of synthetic Ex-9 is approved under the U.S. Food and Drug Administration IND 65837.

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See accompanying commentary, p. 2203.

P35.

OBESITY IS ASSOCIATED WITH INCREASED PREVALENCE AND SEVERITY OF PELVIC FLOOR DISORDERS

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Background: Although an association between obesity and urinary incontinence (UI) has been reported, the association between obesity and pelvic organ prolapse (POP) and anal/ fecal incontinence (AI/FI) is less clear. The aim of this study was to determine the prevalence of pelvic floor disorders (PFD) in obese women seeking bariatric surgery compared with normal weight subjects. **Methods:** From 9/06 to 9/07, obese women (BMI > 35) seeking bariatric surgery completed the validated Sandvik incontinence severity index and Rockwood fecal incontinence severity index and questions regarding POP. Women with BMI < 30 from general screening gynecology clinics also completed the questionnaires. Demographic variables and other clinical parameters were also obtained.

Results: 220 obese women (mean BMI of 50 kg/m²) and 120 normal weight controls (mean BMI 24 kg/m²) were screened. The presence of any PFD was 72% and 35%, respectively (P < 0.0001). Stress UI was the most common disorder (60% v. 27%, P<0.0001) followed by urge UI (52% v. 23%, P<0.0001), AI/FI (23% v. 7%, P<0.0004) and POP (5% v. 4%, NS). Moderate or severe UI symptoms were more common among obese patients than controls (55% v. 26%, P=0.002). Obese patients had a higher fecal incontinence severity index compared with controls (mean score 21 +/- 11 versus 14 +/- 11), but this was not statistically significant. Obesity remained a risk factor for UI and AI/FI after adjusting for baseline demographic differences between groups with an adjusted odds ratio (OR) of 7.8 (95% confidence interval (CI) 3.0 - 21.6) and 2.9 (95% CI 1 - 9), respectively.

Conclusion: Prevalence of PFD including stress and urge UI and AI/FI and severity of UI is higher in obese women seeking bariatric surgery than in normal weight women.

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Original article

Obesity is associated with increased prevalence and severity of pelvic floor disorders in women considering bariatric surgery

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Abstract

Background: Although an association between obesity and urinary incontinence (UI) has been reported, the association between obesity and other PFDs is less clear. The aim of this study was to determine the prevalence of pelvic floor disorders (PFDs), including stress urinary incontinence (SUI), urge urinary incontinence (UUI), pelvic organ prolapse (POP), and anal incontinence (AI), in obese women contemplating bariatric surgery compared with nonobese subjects at a tertiary care referral hospital.

Methods: From September 2006 to December 2007, obese women contemplating bariatric surgery and nonobese women from general gynecology clinic completed a validated screening questionnaire for PFDs, the Sandvik urinary incontinence severity index, and the Rockwood fecal incontinence severity index.

Results: A total of 217 obese (mean body mass index of 50 ± 10 kg/m²) and 210 nonobese controls (mean body mass index 23 ± 3 kg/m²) were screened. The presence of any PFD occurred in 159 patients (75%) in the obese group compared with 89 nonobese patients (44%; $P < .0001$). More obese patients experienced SUI, UUI, and AI, but not POP. Obese patients also had more severe UI and AI. Obesity remained a significant risk factor for UI and AI, even after adjusting for baseline differences in demographics and medical conditions, with an adjusted odds ratio of 4.1 (95% confidence interval 2.3–7.8) and 2.1 (95% confidence interval 1.1–4.1), respectively.

Conclusion: The prevalence of PFDs, including SUI, UUI, and all forms of AI, was greater in the obese and morbidly obese women contemplating bariatric surgery. Obesity was also associated with an increased severity of UI and AI. Obesity appears to confer a fourfold and twofold increased risk of UI and AI, respectively. (Surg Obes Relat Dis 2009;5:411–415.) © 2009 American Society for Metabolic and Bariatric Surgery. All rights reserved.

Keywords:

Obesity; Pelvic floor disorders; Prolapse; Urinary incontinence; Anal incontinence

Integrated health article

Psychosocial correlates of pelvic floor disorders in women seeking bariatric surgery

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Kathleen Ashton, Ph.D.^{a,b}, Leslie Heinberg, Ph.D.^{a,b}

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Received October 13, 2011; accepted January 30, 2012

Abstract

Background: Women who struggle with obesity are at a significant risk for pelvic floor disorders (PFDs), defined as urinary incontinence, pelvic organ prolapse, and/or fecal incontinence. The association between PFDs and reduced quality of life has been demonstrated; however, the psychosocial correlates of PFDs in women undergoing bariatric surgery have yet to be examined. The present study explored the potential psychosocial correlates of PFD. The setting was an academic medical center.

Methods: Data were analyzed from 421 female patients evaluated for bariatric surgery. Based upon a screening questionnaire, participants were dichotomized as women with PFDs ($n = 121$) and women without PFDs ($n = 300$). Patients completed the “Minnesota Multiphasic Personality Inventory, 2nd ed., Restructured Form (MMPI-2-RF),” and medical records were reviewed for demographic data, body mass index, substance abuse/dependence history, history of physical and/or sexual abuse, psychiatric medication usage, and psychiatric diagnoses. MMPI-2-RF scales measuring depression, anxiety, somatic symptoms, and social support were examined.

Results: Women with PFDs were significantly older ($F_{1,420} = 3.87, P < .05$) and more likely to evidence a history of substance abuse/dependence (chi-square = 4.53, $P < .05$) and depression (chi-square = 4.31, $P < .05$) than women without PFDs. There also was a trend for previous inpatient hospitalization (chi-square = 2.93, $P < .09$), outpatient behavioral health treatment (chi-square = 2.89, $P < .09$), and psychotropic medication usage (chi-square = 3.32, $P < .07$). No differences were found in the objective psychological testing.

Conclusion: Women with PFDs may be more psychiatrically vulnerable than other bariatric surgery candidates. Additional research on the association among PFDs, substance abuse, and depression is warranted. Future research should consider whether this potential relationship changes postoperative bariatric surgery. (Surg Obes Relat Dis 2012;8:792–796.) © 2012 American Society for Metabolic and Bariatric Surgery. All rights reserved.

Keywords:

Bariatric surgery; Pelvic floor disorders; Pelvic floor dysfunction; Depression; Substance abuse; Dependence

Update on Completed Grant Projects:

2007:



Melissa Kalarchian, PhD

Western Psychiatric Institute & Clinic, Pittsburgh School of Medicine

Grant Project:

Optimizing Long-term Weight Control after Bariatric Surgery

Publications:

Optimizing long-term weight control after bariatric surgery: A pilot study. *SOARD* 8 (2012) 710-716

Physical activity and physical function in individuals post-bariatric Surgery. *Obes Surg.* 2011; 21(8)1243-1249. Pub Med PMID: 21153567.

Presentations:

Optimizing long-term weight control after bariatric surgery. Masters Course in Behavioral Health, ASMBS 2008 Annual Meeting

Subsequent applications:

The Obesity Society (TOS) Research Grant: *Use of Nutrisystem to Facilitate Dietary Adherence after Bariatric Surgery* (2012-2013): ongoing randomized, controlled pilot study (n = 40) to evaluate the use of Nutrisystem® to facilitate dietary adherence and maximize weight loss after gastric bypass.

PCORI. Promoting Behavioral Self-Management After Adjustable Gastric Banding. To be reviewed in 7/2013.

Career Impact:

Promotion to Associate Professor at University of Pittsburgh School of Medicine 10/2008

2007:



David Sarwer, MD

University of Pennsylvania, Dept of Weight & Eating Disorders

Grant Project:

Improvements in Reproductive Status Following Bariatric Surgery

Publications:

Manuscripts currently under review:

Sexual Functioning and sex hormones in persons with extreme obesity and seeking surgical and nonsurgical weight loss *SOARD* 11 (2013)

Presentations:

Examination of Reproductive and Psychosocial Functioning: A comparative study of women seeking bariatric surgery and behavioral weight loss – ASMBS 2010 Annual Meeting

Results on the relationship between reproductive biomarkers, adipokines, and measures of adiposity -- Annual meeting of the American Society for Reproductive Medicine October 2010.

Changes in Reproductive and Psychosocial Functioning in Obese Women Following Bariatric Surgery or Surgery or Lifestyle Modification – ASMBS 2012 Annual Meeting

Original article

Optimizing long-term weight control after bariatric surgery: a pilot study

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Received January 4, 2011; accepted April 7, 2011

Abstract

Background: Although bariatric surgery is associated with significant overall weight loss, many patients experience suboptimal outcomes. Our objective was to document the preliminary efficacy of a behavioral intervention for bariatric surgery patients with relatively poor long-term weight loss and to explore the factors related to outcome at an academic medical center in the United States.

Methods: Patients with a body mass index (BMI) ≥ 30 kg/m² who had undergone bariatric surgery ≥ 3 years before study entry and had $< 50\%$ excess weight loss were enrolled. The participants were randomly assigned to a 6-month behavioral intervention or wait list control group. The assessments were conducted at baseline (before intervention) and 6 months (after intervention) and 12 months (6-mo follow-up).

Results: On average, the participants ($n = 36$) had undergone surgery 6.6 years before study entry. The average age was 52.5 ± 7.1 years, and the BMI was 43.1 ± 6.2 kg/m²; most participants were women (75%) and white (88.9%). The intervention patients had a greater percentage of excess weight loss than did the wait list control group at 6 ($6.6\% \pm 3.4\%$ versus $1.6\% \pm 3.1\%$) and 12 ($5.8\% \pm 3.5\%$ versus $.9\% \pm 3.2\%$) months. However, the differences were not significant and the results varied. The intervention patients with more depressive symptoms ($P = .005$) and less weight regain before study entry ($P = .05$) experienced a greater percentage of excess weight loss.

Conclusion: Behavioral intervention holds promise in optimizing long-term weight control after bariatric surgery. More research is needed on when to initiate the intervention and to identify which patients will benefit from this type of approach. (Surg Obes Relat Dis 2012;8:710–716.) © 2012 American Society for Metabolic and Bariatric Surgery. All rights reserved.

Keywords:

Bariatric surgery; Gastric bypass; Weight loss; Long-term follow-up; Lifestyle intervention; Behavioral weight control

Physical Activity and Physical Function in Individuals Post-bariatric Surgery

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Abstract

Background A better understanding of the physical activity behavior of individuals who undergo bariatric surgery will enable the development of effective post-surgical exercise guidelines and interventions to enhance weight loss outcomes. This study characterized the physical activity profile and physical function of 40 subjects 2–5 years post-bariatric surgery and examined the association between physical activity, physical function, and weight loss after surgery.

Methods Moderate-to-vigorous intensity physical activity (MVPA) was assessed with the BodyMedia SenseWear[®] Pro (SWPro) armband, and physical function (PF) was measured using the physical function subscale of the 36-Item Short Form Health Survey instrument (SF-36_{PF}). Height and weight were measured.

Results Percent of excess weight loss (%EWL) was associated with MVPA ($r=0.44$, $p<0.01$) and PF ($r=0.38$, $p<0.02$); MVPA was not associated with PF ($r=0.24$, $p=0.14$). Regression analysis demonstrated that MVPA was associated with %EWL ($\beta=0.38$, $t=2.43$, $p<0.02$). Subjects who participated in ≥ 150 min/week of MVPA had a greater

%EWL (68.2 ± 19 , $p<0.01$) than those who participated in <150 min/week (52.5 ± 17.4).

Conclusions Results suggest that subjects are capable of performing most mobility activities. However, the lack of an association between PF and MVPA suggests that a higher level of PF does not necessarily correspond to a higher level of MVPA participation. Thus, the barriers to adoption of a more physically active lifestyle may not be fully explained by the subjects' physical limitations. Further understanding of this relationship is needed for the development of post-surgical weight loss guidelines and interventions.

Keywords Physical activity · Physical function · Bariatric surgery · Obesity

Introduction

Severe obesity (defined as having a body mass index (BMI) ≥ 40 kg/m²) is reaching epidemic proportions and increasing at an exponential rate [1]. This increased prevalence is one of the many factors that has resulted in an increased growth in bariatric surgery, with the most commonly performed procedure being laparoscopic Roux-en-Y gastric bypass surgery (RYGB) [2].

There is evidence to support the effectiveness of weight loss and reduction of co-morbidities associated with RYGB in the short term, but there are limited data on long-term weight loss with RYGB [3–6]. Individuals typically lose 65–80% of their excess body weight following RYGB. The peak of this weight loss is usually between 12 and 18 months and generally levels off by 2 years [7]. Despite the fact that most people lose a significant amount of weight, preliminary studies are suggesting that an ample amount of patients have weight regain and have the return

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Surgery for Obesity and Related Diseases ■ (2013) 00–00

SURGERY FOR OBESITY
AND RELATED DISEASES

Original article

Sexual functioning and sex hormones in persons with extreme obesity and seeking surgical and nonsurgical weight loss

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Abstract

Background: Many individuals with obesity are motivated to lose weight to improve weight-related co-morbidities or psychosocial functioning, including sexual functioning. Few studies have documented rates of sexual dysfunction in persons with obesity. This study investigated sexual functioning, sex hormones, and relevant psychosocial constructs in individuals with obesity who sought surgical and nonsurgical weight loss.

Methods: One hundred forty-one bariatric surgery patients (median BMI [25th percentile, 75th percentile] 44.6 [41.4, 50.1]) and 109 individuals (BMI = 40.0 [38.0, 44.0]) who sought nonsurgical weight loss participated. Sexual functioning was assessed by the Female Sexual Function Index (FSFI) and the International Index of Erectile Function (IIEF). Hormones were assessed by blood assay. Quality of life, body image, depressive symptoms, and marital adjustment were assessed by validated questionnaires.

Results: Fifty-one percent of women presenting for bariatric surgery reported a sexual dysfunction; 36% of men presenting for bariatric surgery reported erectile dysfunction (ED). This is in contrast to 41% of women who sought nonsurgical weight loss and reported a sexual dysfunction and 20% of men who sought nonsurgical weight loss and reported ED. These differences were not statistically significant. Sexual dysfunction was strongly associated with psychosocial distress in women; these relationships were less strong and less consistent among men. Sexual dysfunction was unrelated to sex hormones, except for sex hormone binding globulin (SHGB) in women.

Conclusions: Women and men who present for bariatric surgery, compared with individuals who sought nonsurgical weight loss, were not significantly more likely to experience a sexual dysfunction. There were few differences in reproductive hormones and psychosocial constructs between candidates for bariatric surgery and individuals interested in nonsurgical weight loss. (Surg Obes Relat Dis 2013;■:00–00.) © 2013 Published by Elsevier Inc. on behalf of American Society for Metabolic and Bariatric Surgery.

Keywords : Sexual functioning; Quality of life; Obesity

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Many individuals with obesity are motivated to lose weight to improve weight-related medical co-morbidities. Others may be just as motivated to improve psychosocial functioning. One often overlooked area is sexual functioning. Problems with sexual functioning are highly prevalent in the general population, 34% of women and 31% have

Update on Completed Grant Projects:

2007:



April Strader, MD

Southern Illinois University

Grant Project:

Mechanisms Underlying Improved glycemia following ileal transposition

Publications:

Ileal interposition improves glucose tolerance in low dose streptozotocin-treated diabetic and euglycemic rats. (2009) *Obesity Surgery*; 19(1):96-104. (IF-2.934)

Presentations:

Ileal interposition alters intestinal gene expression and increases pancreatic islet number in rats – 2010 ASMBS Annual Meeting

Diabetes Resolution following obesity surgery: role of the lower intestine – Univ of Wisconsin-Milwaukee 2010

Role of the lower intestine in the resolution of type-2 diabetes following obesity surgery – Penn State Medical School Hershey 2009.

Role of the lower intestine in diabetes resolution following obesity surgery – Eli Lilly 2008

Ileal interposition improves glucose tolerance in low-dose streptozotocin-treated diabetic and euglycemic rats –The Obesity Society Annual Meeting 2008

Invited Expert Faculty Panalist – 1st World Congress on Interventional Diabetology 2008

Career Impact: Received an ARAA Challenge Grant from NIH 2009; Promotion to Associate Professor in Department of Physiology at SIU School of Medicine followed

2008:



Drew Rideout, MD

University of South Florida

Grant Project:

Adiponectin improves steatohepatitis in obese rats after roux-en-y gastric bypass

Publications:

Downregulation of Adiponectin/AdipoR2 is Associated with Steatohepatitis in Obese Mice. *J Gastrointest Surg.* 2009;13(11):2043-9

Does LKB1 mediate activation of hepatic AMP-protein kinase (AMPK) and Sirtuin1 (SIRT1) after Roux-en-Y Gastric Bypass in obese rats? *J Gastrointest Surg.* 2010 Feb;14(2):221-8

Involvement of Adiponectin-SIRT1-AMPK Signaling in the Protective Action of Rosiglitazone against Alcoholic Fatty Liver in Mice. *Am J Physiol Gastrointest Liver Physiol.* 2010 Mar;298(3):G364-74

RYGB Alters TNF-alpha but not Adiponectin Signaling in the Immediate Postoperative Period in Obese Rats. *SOARD* 5 (2009) S1-S23

Diet-induced obesity associated with steatosis, oxidative stress, and inflammation in liver. *SOARD* 8 (2012) 73-83

Presentations:

11 presentations at national surgical conferences including annual meetings for the: 2008 & 2009 American College of Surgeons, 2009 Academic Surgical Congress (AAS/SUS), 2008 & 2009 Digestive Disease Week (SSAT), 2009 & 2010 ASMBS, and 2009 American Academy of Pediatrics.

Ileal Interposition Improves Glucose Tolerance in Low Dose Streptozotocin-treated Diabetic and Euglycemic Rats

April D. Strader · Trine Ryberg Clausen ·
Sean Z. Goodin · Donna Wendt

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Abstract

Background The surgical treatment for obesity promotes massive weight loss and early improvement in co-morbid conditions such as type-2 diabetes. Because surgically mediated glycemic improvements are immediate, the mechanisms involved appear to be weight loss independent. Ileal interposition has been used to gain understanding of the relative role that the lower intestine plays in mediating metabolic improvement. Here, we report that ileal interposition is sufficient for improving glucose tolerance in a low-dose streptozotocin-treated diabetic rat model as well as in normal rats with no effect on body weight.

Methods Male Long–Evans rats were treated with streptozotocin (35 mg/kg) or left untreated and then received sham or ileal interposition. Body weight was measured as well as glucose and insulin tolerance. Plasma insulin and gut hormones were measured during the glucose tolerance test.

Results Streptozotocin treatment resulted in hyperglycemia within 48 h after treatment. Diabetic rats with ileal interposition showed improvement in glucose tolerance as early as 4 weeks after surgery compared to sham ($p < 0.05$). By 11 weeks after surgery glucose and insulin tolerance was markedly improved in interposed-diabetic compared to sham-diabetic rats ($p < 0.05$). Normal non-diabetic rats showed improved glucose tolerance after ileal interposition

compared to sham ($p < 0.05$). Insulin secretion was increased in interposed rats following glucose administration ($p < 0.05$). The ileal-derived hormones glucagon like peptide-1 (GLP-1), peptide YY (PYY), and glucagon were all significantly elevated in the ileal interposed rats ($p < 0.01$). Gastric inhibitory polypeptide (GIP) was unchanged. In neither study did body weight between the surgical groups differ at any time point.

Conclusions Ileal interposition effectively improves glucose tolerance in streptozotocin-diabetic and euglycemic rats. Enhanced insulin secretion can explain the lowered glucose concentrations in euglycemic rats following ileal interposition. Ileal interposition is associated with dramatically elevated ileal hormones, GLP-1, PYY, and glucagon ($p < 0.01$) with no change in the duodenal hormone GIP.

Keywords Ileal transposition · Bariatric surgery · Glucagon like peptide-1 · Peptide YY · Glucagon · Insulin · Glucose tolerance

Introduction

Obesity surgery is currently the most effective treatment for morbid obesity. Weight loss is typically massive and co-morbid conditions show dramatic amelioration following surgery. Specifically, patients demonstrate immediate and long-standing improvement or resolution of type 2 diabetes following specific surgical procedures that appears to be independent of weight loss. Gastric bypass and biliopancreatic diversion result in 84% and 99% resolution of type 2 diabetes respectively [1]. Restrictive procedures such as gastric banding also result in improvement in type 2 diabetes; however, with a later appearance, that is likely a consequence of weight loss.

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PL-301

ILEAL INTERPOSITION ALTERS INTESTINAL GENE EXPRESSION AND INCREASES PANCREATIC ISLET NUMBER IN RATS

April Strader, PhD; Donna Wendt; Sean Goodin, BS, BA; Physiology, Southern Illinois University School of Medicine, Carbondale, IL

Background: Ileal interposition is a novel metabolic procedure that improves glucose homeostasis in a variety of diabetic rat models. An important role of the ileum as a potential mechanism for the metabolic improvements after surgery may be an altered ability to reabsorb bile and possibly glucose. In addition, long-term ileal stimulation resulting in abundant GLP-1 secretion may result in improved pancreatic function. In the present study we examined

gastrointestinal genes related to glucose, lipid and bile transport and quantified pancreatic islet number and diameter in rats with either sham or ileal interposition.

Methods: Portions of duodenum, jejunum, ileum (interposed and intact), colon, remnant ileum and pancreata were harvested from rats following sham or interposition surgery. Using QPCR, genes involved in bile salt transport, lipid and glucose transport, and satiety were examined in all segments. Pancreata were sectioned and stained and every islet diameter was quantified in at least 3 separate sections per rat.

Results: Interposition resulted in an elevation of circulating bile salts, a decrease in cholesterol and an improvement in glucose tolerance ($p < 0.05$). Gene expression within the ileum and other segments of intestine for GLUT2 and APO-AIV in rats with interposition increased. Interestingly, the apical bile salt transporter (ABST) was significantly reduced following interposition. In addition, preproglucagon and peptide-YY were highly elevated in both the interposed ileum and remnant ileum following interposition ($p < 0.05$). Lastly, rats with interposition showed increased numbers of islets with a diameter of 50-150 microns ($p < 0.05$).

Conclusion: Ileal interposition results in gastrointestinal and pancreatic changes that favor improved lipid and glucose homeostasis.

Downregulation of Adiponectin/AdipoR2 is Associated with Steatohepatitis in Obese Mice

Yanhua Peng, Drew Rideout, Steven Rakita, Mini Sajan, Robert Farese, Min You, Michel M. Murr

ABSTRACT

Background

Recent evidence suggests that obesity is associated with hypo-adiponectinemia and chronic inflammation. Adiponectin regulates fat storage, energy expenditure, and inflammation. We propose that high fat diet induces steatohepatitis, reduces serum adiponectin, and liver adiponectin receptors.

Methods

A 4-week-old C57BL male mice were fed high fat diet ($n = 8$) or regular chow (control; $n = 6$) for 7 weeks. Body weight, liver weight, and serum adiponectin were measured. Liver sections were stained with hematoxylin and eosin and oil red for fat content. Liver homogenates were used for protein (immunoblotting) and mRNA (reverse transcription PCR) of Toll-like receptor 4 (TLR4), tumor necrosis factor alpha (TNF- α), interleukin (IL)-6, sterol regulatory element-binding proteins (SREBP)-1c, and adiponectin receptors (AdipoR1/AdipoR2) in addition to nuclear phosphorlated p65NF- κ B. Gels were quantified using densitometry; t test was used, and $p < 0.05$ was significant.

Results

High fat diet increased body (50%) and liver weight (33%), as well as hepatocyte fat content and ballooning. Mice fed high fat diet exhibited reduced serum adiponectin and liver AdipoR2. High fat diet increased hepatic levels of SREBP-1c, TLR4, TNF- α , and IL-6 protein and mRNA and increased activation of p65NF- κ B.

Conclusions

Diet-induced liver steatosis is associated with increased lipogenesis, upregulation of pro-inflammatory cytokines, and transcription factors as well as downregulation of AdipoR2. Reduction in serum adiponectin suggests that adiponectin signaling may be the crosslink between high fat diet, hepatic inflammation, and nonalcoholic fatty liver disease.

Presented as an oral presentation in the SSAT Annual Meeting in San Diego, CA, May 2008.

This work was support by the VA Merit Award (MM), NIH R01 AA013623-06, AA015951-03 (MY), NIH R01 DK065969-05, and VA Merit Award (RF).

Does LKB1 Mediate Activation of Hepatic AMP-Protein Kinase (AMPK) and Sirtuin1 (SIRT1) After Roux-en-Y Gastric Bypass in Obese Rats?

Yanhua Peng, Drew A. Rideout, Steven S. Rakita, William R. Gower Jr, Min You, Michel M. Murr

ABSTRACT

Introduction

Roux-en-Y gastric bypass (RYGB) improves steatosis and reduces liver triglycerides in obese rats. Sirtuin1 (SIRT1) and AMP-activated protein kinase (AMPK) are key metabolic regulators that reduce lipogenesis and increase fatty acid oxidation. LKB1 phosphorylates AMPK and may activate SIRT1. We hypothesize that RYGB in obese rats is associated with an upregulation of the LKB1-AMPK-SIRT1 signaling pathway.

Methods

Obese Sprague-Dawley male rats underwent RYGB or sham. Liver tissue was obtained at 9 weeks postoperatively. Protein levels of SIRT1, LKB1, p-LKB1, AMPK α , p-AMPK α , and p-protein kinase C- ζ (PKC- ζ) were determined. Protein associations of LKB1 with each of SIRT1, AMPK α , and PKC- ζ were determined by co-immunoprecipitation. Data are mean \pm SD; for *t* test, $p < 0.05$ was significant.

Results

RYGB increased protein levels of hepatic AMPK α , p-AMPK α , and SIRT1 (all $p < 0.001$ vs. sham); p-LKB1 but not LKB1 increased after RYGB ($p < 0.001$ vs. sham). Physical interactions of LKB1-AMPK and LKB1-SIRT1 increased after RYGB ($p < 0.001$ vs. sham). Although PKC- ζ mRNA and p-PKC- ζ did not change, interactions between LKB1 and PKC- ζ increased after RYGB ($p < 0.001$ vs. sham).

Conclusion

RYGB increases hepatic levels of SIRT1, AMPK, and p-AMPK as well as increasing interactions of LKB1 with AMPK or SIRT1. p-PKC- ζ may play an intermediary role in the interaction between AMPK and SIRT. These findings demonstrate key signaling changes in powerful metabolic regulators that may account for the resolution of steatosis after RYGB.

Presented at the Plenary Session of the 2009 SSAT Meeting in Chicago, IL.

USF Internal Grant (YP); ASMBS Research Grant (DR, MM); NIH: AA-015951 and AA-013623 (MY).

Involvement of adiponectin-SIRT1-AMPK signaling in the protective action of rosiglitazone against alcoholic fatty liver in mice

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Departments of Molecular Pharmacology and Physiology, University of South Florida Health Sciences Center, Tampa, Florida

Submitted 5 November 2009; accepted in final form 7 December 2009

ABSTRACT

The development of alcoholic fatty liver is associated with reduced adipocyte-derived adiponectin levels, decreased hepatic adiponectin receptors, and deranged hepatic adiponectin signaling in animals. Peroxisomal proliferator-activated receptor- γ (PPAR- γ) plays a key role in the regulation of adiponectin in adipose tissue. The aim of the present study was to test the ability of rosiglitazone, a known PPAR- γ agonist, to reverse the inhibitory effects of ethanol on adiponectin expression and its hepatic signaling, and to attenuate alcoholic liver steatosis in mice. Mice were fed modified Lieber-DeCarli ethanol-containing liquid diets for 4 wk or pair-fed control diets. Four groups of mice were given a dose of either 3 or 10 mg·kg body wt⁻¹·day⁻¹ of rosiglitazone with or without ethanol in their diets for the last 2 wk of the feeding study. Coadministration of rosiglitazone and ethanol increased the expression and circulating levels of adiponectin and enhanced the expression of hepatic adiponectin receptors (AdipoRs) in mice. These increases correlated closely with the activation of a hepatic sirtuin 1 (SIRT1)-AMP-activated kinase (AMPK) signaling system. In concordance with stimulated SIRT1-AMPK signaling, rosiglitazone administration enhanced expression of fatty acid oxidation enzymes, normalized lipin 1 expression, and blocked elevated expression of genes encoding lipogenic enzymes which, in turn, led to increased fatty acid oxidation, reduced lipogenesis, and alleviation of steatosis in the livers of ethanol-fed mice. Enhanced hepatic adiponectin-SIRT1-AMPK signaling contributes, at least in part, to the protective action of rosiglitazone against alcoholic fatty liver in mice.

PL-306.

RYGB ALTERS TNF-ALPHA BUT NOT ADIPONECTIN SIGNALING IN THE IMMEDIATE POSTOPERATIVE PERIOD

Drew A. Rideout, MD¹; Yanhua Peng, PhD¹;
Steven S. Rakita, MD³; William R. Gower, PhD³;
Min You, PhD²; Michel M. Murr, MD¹; ¹Department of Surgery, University of South Florida, Tampa, FL, USA; ²Department of Molecular Pharmacology & Physiology, University of South Florida, Tampa, FL, USA; ³James A. Haley Veterans Affairs Medical Center, Tampa, FL, USA.

Background: Adiponectin has anti-inflammatory effects and is reported to increase with weight loss. Tumor necrosis factor alpha (TNF-alpha) is an important pro-inflammatory cytokine. We demonstrated that Roux-en-Y gastric bypass (RYGB) in rats induces weight loss, improves steatosis, and decreases serum leptin with no increase in adiponectin shortly after RYGB. Therefore, we hypothesize that after RYGB, mRNA levels of adipose adiponectin and the corresponding hepatic adiponectin receptor 2 (AdipoR2) do not increase, but that TNF-alpha mRNA levels may instead be altered. **Methods:** Obese Sprague-Dawley male rats underwent RYGB (n=5) or sham (n=4) and were sacrificed at 9 weeks post-operatively. Adipose and liver mRNA from final tissue samples were quantified by semi-quantitative differential - polymerase chain reaction (PCR) or real-time PCR. Data are mean±SD; for t-test, p<0.05 was significant.

Results: After RYGB, adipose tissue adiponectin mRNA levels were not changed (1159±293 vs. 1440±246; p=0.22 vs. sham). Additionally, hepatic AdipoR2 levels were not significantly altered (0.9±0.3 vs. 1.3±0.2; p=0.057 vs. sham). However, TNF-alpha mRNA levels decreased in adipose tissue (0.99±0.4 vs. 1.81±0.4; p=0.044 vs. sham) while remaining unchanged in the liver (1.56±0.63 vs. 1.58±0.54; p=0.96 vs. sham).

Conclusion: Surgically-induced weight loss in a rat model of RYGB does not increase adiponectin signaling in the immediate postoperative period but is associated with decreased pro-inflammatory signaling in adipose tissue. During this period leptin and pro-inflammatory signaling may play a more important role than adiponectin. Longer follow-up is necessary to determine if up-regulation of adiponectin plays a role in weight loss and improvement of steatosis after RYGB.

Original article

Diet-induced obesity associated with steatosis, oxidative stress, and inflammation in liver

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Received June 04, 2010; accepted July 01, 2011

Abstract

Background: Obesity induces steatosis and increases oxidative stress, as well as chronic inflammation in the liver. The balance between lipogenesis and lipolysis is disrupted in obese animals. At a cellular level, the changes in metabolic sensors and energy regulators are poorly understood. We hypothesized that diet-induced steatosis increases oxidative stress, inflammation, and changes the metabolic regulators to promote energy storage in mice. The setting was a university-affiliated basic science research laboratory.

Methods: Four-week-old C57BL mice were fed a high-fat diet ($n = 8$) or regular chow ($n = 8$) for 7 weeks. The liver sections were stained for fat content and immunofluorescence. Liver homogenates were used for protein analysis by immunoblotting and mRNA analysis by reverse transcriptase-polymerase chain reaction. The gels were quantified using densitometry $P \leq .05$ was considered significant.

Results: The high-fat diet upregulated protein kinase-C atypical isoforms ζ and λ and decreased glucose tolerance and the interaction of insulin receptor substrate 2 with phosphoinositide kinase-3. The high-fat diet increased the transcriptional factors liver X receptor (4321 ± 98 versus 2981 ± 80) and carbohydrate response element-binding protein (5132 ± 135 versus 3076 ± 91), the lipogenesis genes fatty acid binding protein 5, stearyl-co-enzyme A desaturase-1, and acetyl-co-enzyme A carboxylase protein, and fatty acid synthesis. The high-fat diet decreased 5'-adenosine monophosphate-activated protein kinase (2561 ± 78 versus 1765 ± 65), glucokinase-3 β (2.214 ± 34 versus 3356 ± 86), and SIRT1 (2015 ± 76 versus 3567 ± 104) and increased tumor necrosis factor- α (3415 ± 112 versus 2042 ± 65), nuclear factor kappa B (5123 ± 201 versus 2562 ± 103), cyclooxygenase-2 (4230 ± 113 versus 2473 ± 98), nicotinamide-adenine dinucleotide phosphate oxidase (3501 ± 106 versus 1600 ± 69) and reactive oxygen species production (all $P < .001$, obese mice versus lean mice).

Conclusion: A high-fat diet impairs glucose tolerance and hepatic insulin signaling, upregulates transcriptional and translational activities that promote lipogenesis, cytokine production, proinflammatory signaling, and oxidative stress, and downregulates lipolysis. Understanding the complex cellular signals triggered by obesity might have profound clinical implications. (Surg Obes Relat Dis 2012;8:73–83.) Published by Elsevier Inc. on behalf of American Society for Metabolic and Bariatric Surgery.

Keywords: Fatty acid; Obesity; Diabetes; Metabolism; Energy regulation

Supported by Veterans Affairs Merit grant (to M. Murr) and American Society for Metabolic and Bariatric Surgery research grant (to D. Rideout and M. Murr).

Presented at the plenary session of the American Society for Metabolic and Bariatric Surgery Annual Meeting, Las Vegas, Nevada, June 2010.

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Update on Completed Grant Projects:

2009:



Daniel DeUgarte, MD

David Geffen School of Medicine UCLA

Grant Project:

Impact of Metabolic/bariatric surgery on diet-induced childhood obesity: implication for long-term health and offspring metabolic phenotype

Publications:

Metabolic Effects of sleeve gastrectomy in a female rat model of diet-induced obesity. *SOARD* 7 (2011) 372-416

Risk factors for morbidity and mortality in pediatric patients with peritoneal dialysis catheters. *Journal of Pediatric Surgery* 2013 48(1):197-202

Presentations:

Impact of sleeve gastrectomy on markers of bone metabolism in a female rat model of diet-induced obesity. Plenary session. ASMBS, Orlando, FL. Jun 16, 2011

The role of bariatric surgery in Adolescent Obesity. UCLA Pediatric Gastroenterology Lecture. Lost Angeles, CA. September 9, 2011.

2009:



Michael B. Peters, MD

Christiana Institute for Advanced Surgery, PA

Grant Project:

Autonomic nervous system function and novel determinants of glucose homeostasis following bariatric surgery

Publications:

Effects of surgically induced weight loss by roux-en-Y gastric bypass on cardiovascular autonomic nerve function. *SOARD* 9 (2013) 221-228

Presentations:

Effect of osteocalcin on short-term glucose homeostasis before and after surgery-induced weight loss – ASMBS 2011 Annual Meeting Poster Session

SCIENTIFIC RESEARCH

P-81

METABOLIC EFFECTS OF SLEEVE GASTRECTOMY IN A FEMALE RAT MODEL OF DIET-INDUCED OBESITY

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Catherine E. Lewis, MD¹; Daniel A. DeUgarte, MD¹; ¹Surgery,
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Background: Sleeve gastrectomy is an attractive weight loss procedure for reproductive-age female patients as it avoids the malabsorption associated with intestinal bypass. Previous rodent studies utilizing males cannot be used to evaluate the metabolic, reproductive, and transgenerational impact of sleeve gastrectomy on reproductive-age women. We sought to evaluate the impact of sleeve gastrectomy on young female rats with diet-induced obesity.

Methods: Sprague-Dawley female rats (n= 35) were fed a 60% high-fat diet. At 12 weeks of age, animals underwent either sleeve gastrectomy or sham surgery. Animals were sacrificed four weeks after surgery. A chemistry panel was performed and serum adipokines were assayed using Multiplex and ELISA. Homeostasis model assessment score (HOMA) was calculated. Liver histology was graded for steatohepatitis. Two-sample t-test was used to compare groups.

Results: Sleeve gastrectomy was associated with significant weight loss ($5 \pm 6\%$ vs. $-4 \pm 6\%$, $p < 0.001$), lower leptin (1.3 ± 1.2 vs. 3.5 ± 2.3 ng/ml, $p < 0.01$), and higher adiponectin (432 ± 185 vs. 174 ± 140 ng/ml, $p < 0.01$) when compared to sham animals. There were no significant differences in ghrelin, GIP, GLP-1, PYY, cholesterol, aminotransferases, grade of steatohepatitis, and HOMA score.

Conclusion: Sleeve gastrectomy resulted in weight loss and improvement in leptin and adiponectin profiles in young female rats. Interestingly, there was no difference in ghrelin levels. We hypothesize that this may be in part due to the large aglandular forestomach present in rats. Furthermore, we did not observe evidence of insulin resistance or steatohepatitis in this model. As the majority of bariatric surgery patients are female, further studies should be undertaken in this population.



Risk factors for morbidity and mortality in pediatric patients with peritoneal dialysis catheters[☆]

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Received 30 September 2012; accepted 13 October 2012

Key words:

Peritoneal dialysis;
Pediatric;
Omentectomy;
Laparoscopy;
Gastrostomy;
Reoperation

Abstract

Purpose: As peritoneal dialysis (PD) is the preferred long-term dialysis modality in the pediatric population, we sought to identify risk factors for mortality and reoperation.

Methods: A retrospective review of patients undergoing PD catheter insertions at a single center from 1994–2009 was performed. The following variables were evaluated: age (<1 year), comorbidities, omentectomy, concomitant gastrostomy, and laparoscopic technique. Multivariable Cox regressions analyses were used to evaluate patient survival and reoperation-free survival of PD catheters.

Results: 207 patients with a median age of 10 years underwent PD insertion. Mortality was 7% with a median follow up of 72 months. Reoperation for malfunction and infection was required in 49% of patients with a median PD catheter survival of 11 months. Reoperation for hernias occurred in 14% of patients. Multivariate Cox regressions analyses identified age <1 year, lack of omentectomy, concomitant gastrostomy, and prematurity as variables significantly associated with higher rates of mortality or reoperation.

Conclusions: In this large study of pediatric patients undergoing PD, higher complication rates were noted in infants less than one year of age. Concomitant gastrostomy was associated with a higher rate of reoperation for infection. Failure to perform omentectomy was associated with a higher rate of catheter failure.

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Peritoneal dialysis (PD) is currently the therapy of choice to bridge pediatric patients with end-stage renal disease to transplant. Although catheter quality and surgical technique have improved, the reported incidence of complications remains high in infants less than one year of age [1,2].

Successful insertion of the PD catheter remains challenging in this age group due to the large catheter size relative to the infant's thin and fragile abdominal wall [3]. In addition, rapid changes in body mass and length within the first four years of life, along with increases in intraperitoneal pressure promote the risk of hernia and leakage [3]. Exit site infections and peritonitis remain the most common causes of treatment failure in children ages one to seven with 25% of younger patients experiencing complications within the first six months following surgery [4]. In addition to the risk of infection, poor catheter survival has been documented in the pediatric population [5].

[☆] The research was presented at the 2012 American Pediatric Surgical Association meeting on May 23, 2012 in San Antonio, Texas.

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Original article

Effects of surgically induced weight loss by Roux-en-Y gastric bypass on cardiovascular autonomic nerve function

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Isaias Irgau, M.D.^d, Gail M. Wynn, M.D.^d

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Received July 27, 2011; accepted November 14, 2011

Abstract

Background: Obesity is associated with autonomic imbalance. With respect to cardiovascular autonomic dysfunction, this is characterized by reduced heart rate variability (HRV). Our objective was to determine the effect of surgically induced weight loss on cardiovascular autonomic nerve fiber function in subjects with severe obesity and examine whether an association with reduced insulin resistance exists. The setting was a hospital and private practice in the United States.

Methods: A total of 32 morbidly obese patients (body mass index $51 \pm 11 \text{ kg/m}^2$) underwent laparoscopic Roux-en-Y gastric bypass. Measures of HRV (e.g., power spectral analysis, RR variation during deep breathing) were used to evaluate autonomic function before and 6 months after surgery. The homeostasis model assessment of insulin resistance index (HOMA-IR) was used to assess insulin resistance.

Results: At 6 months after bariatric surgery, the patients had lost 58% excess body mass index with improvement in the HOMA-IR (3.0 ± 1.4 versus $1.1 \pm .7$; $P < .001$). Measures of RR variation during deep breathing and total spectral power, low frequency (LF) power (influenced by sympathetic and parasympathetic activity), and high frequency (HF) power (parasympathetic activity) increased with weight loss. The LF/HF ratio was lower (1.5 ± 1.5 versus $.9 \pm .7$, $P < .05$) with a reduction in weight. Spectral analysis of HRV combined with spectral analysis of respiratory activity generated the respiration frequency area (RFA) and low frequency area. The RFA was increased, and the LFA/RFA ratio was reduced with weight loss. HOMA-IR and HRV did not correlate.

Conclusion: Surgically induced weight loss has a favorable effect on autonomic function, but it does not appear to be directly attributable to reduced insulin resistance. (*Surg Obes Relat Dis* 2013; 9:221–228.) © 2013 American Society for Metabolic and Bariatric Surgery. All rights reserved.

Keywords:

RR variation; Heart rate variability; Bariatric surgery; Roux-en-Y gastric bypass

Funded by a grant from the American Society of Metabolic and Bariatric Surgery.

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Variability in beat-to-beat heart rate intervals is a function of sympathetic and parasympathetic nerve fibers [1]. In normal healthy individuals, there is a high degree of beat-to-beat variability that fluctuates with respiration. A reduction in heart rate variability (HRV) is the earliest indicator of cardiovascular autonomic nerve fiber dysfunction [2]. Analysis of HRV (i.e., measures of parasympathetic and sympathetic nerve fiber activity) provides information of autonomic function, with enhanced activity of the sympa-

Update on Completed Grant Projects:

2010:



William Richards, MD

Vascular endothelium changes after bariatric Surgery

Presentation:

Bariatric surgery improves the numbers of late outgrowth endothelial progenitor cells -- Abstract submitted and accepted for oral presentation at ASMBS 2013 Annual Meeting/Obesity Week.

Projects Currently in Process:



Ronald K. Evans, PhD

Metabolic and Cardiovascular disease risk reduction following gastric bypass surgery: The role of endothelial progenitor cells in vascular health



Mary-Elizabeth Patti, MD

Hyperinsulinemic hypoglycemia following gastric bypass: Pathophysiology and molecular mechanism



Christopher Still, MD

Identification of molecular markers for NASH



Aurora Pryor, MD

Early intervention in patients with predicted poor long-term outcome following laparoscopic Roux-en-Y gastric bypass: a prospective randomized study

Update on Completed Grant Projects:



William Raum, MD, PhD

Treatment of low metabolic rates and low lean body mass after bariatric surgery



Stacy Brethauer, MD

Obesity-induced diabetes – searching for a cure through bariatric surgery



Joram Mul, MD

Melanocortin receptor-4 function is critical for energy homeostasis changes following vertical sleeve gastrectomy

Newly Awarded: 2013



Kimberley Steele, MD

Neurobiologic alterations induced by bariatric surgery: The gut-brain axis and its relationship to weight loss

THANK YOU

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