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Gastric Bypass Surgery is Associated with Reduced Inflammation and Less Depression: a Preliminary Investigation

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Background: Prior studies have documented elevated symptoms of depression among patients undergoing gastric bypass surgery, in addition to significant elevations of inflammatory markers including C-reactive protein (CRP) and interleukin-6 (IL-6). No prior study has examined the relationship of changes in depression with change in inflammation among patients undergoing gastric bypass surgery. This pilot study was designed to examine the relationship of inflammation and depression among gastric bypass patients in a 12-month longitudinal study.

Methods: 13 Caucasian women (mean age 46.9 ± 5.7 years) who were scheduled to undergo a Roux-en-Y gastric bypass (RYGBP) were recruited prior to surgery for measurement of body mass and blood markers of inflammation, as well as self-report measures of depression, quality of life, and disordered eating. 12 months later, subjects completed the same battery of physiological and psychological measures. Data were analyzed with paired *t*-tests and Pearson correlations.

Results: In addition to significant reductions in BMI (*P*<.001), participants experienced significant reductions in CRP (*P*<.001), IL-6 (*P*=.002), and depressive symptoms (*P*=.025). Reductions also were observed in binge eating (*P*=.005). Decreased depression during the 12-month follow-up was highly correlated with reduced CRP (r=.98, *P*<.001).

Conclusions: Results from this pilot study indicate that RYGBP is associated with significant reductions in inflammatory markers of cardiovascular disease risk (e.g., CRP, IL-6) and depressive symptoms, in addition to reductions in weight. Results suggested that reductions in depression were associated with the observed decreases in inflammation.

Key words: Morbid obesity, obesity surgery, Roux-en-Y gastric bypass, depression, inflammation, C-reactive protein, interleukin-6, quality of life

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Introduction

Bariatric surgery is currently one of the most common treatments for morbid obesity, and studies have indicated significant weight loss outcomes at 10 years and 14 years post-surgery.[1,2] Patients generally lose 50-60% of excess body weight within 2 years after surgery,[3,4] with an average BMI reduction of 13-16 kg/m^2. Positive postoperative outcomes also have been documented in other aspects of health (e.g., reduced cardiac risk factors)[5] and in self-reported life quality,[6] including improved marital functioning and enhanced body image.[7]

Extreme obesity has been associated with significant psychiatric co-morbidity, especially depression. Estimates of psychiatric disorder among preoperative bariatric patients range from 20 to 60%, with a 70% prevalence of lifetime history of psychiatric disorder.[7] Prevalence of depressive symptoms among surgery candidates is significantly higher than among med-

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ical patients with less extreme obesity, and depressive disorder is the most common psychiatric diagnosis among preoperative bariatric patients.[7] Depression is associated with poorer quality of life among gastric bypass patients,[8] and higher rates of depression among preoperative patients are often attributed to the psychological and social stress of living with morbid obesity. However, biological pathways may also be plausible, as reflected in recent research.

Studies indicate that depressive disorder is associated with increased activity of the hypothalamic-pituitary-adrenal (HPA) axis and with increased circulating concentrations of pro-inflammatory cytokines, including interleukin-6 (IL-6). Hypersecretion of cytokines has been observed at the onset of depressive illness.[9] Miller and colleagues[10] have postulated a directional relationship between depression and increased IL-6 via increased body weight. They found that normal-weight depressed individuals were likely to gain weight over time (due to sedentary activity), thereby promoting the release of IL-6 from adipose tissue. Higher levels of IL-6 then stimulate the release of CRP. Additionally, weight gain (increased adiposity) leads to increased levels of leptin, which also may stimulate release of IL-6. Data from Miller et al[10] indicated a pathway from depression to increased IL-6, but not from increased inflammation to depression. In support of the depression-inflammation hypothesis, Ladwig et al[11] found an association of higher CRP levels with greater symptoms of depression in a sample of obese men, but not in a non-obese comparison group.

Recent studies also indicate elevations in cytokines among obese individuals, with or without depression. Adipose tissue secretes interleukin-6 (IL-6), which can then trigger the release of C-reactive protein (CRP). In addition, adipose tissue may secrete CRP directly. Therefore, it has been suggested that obesity is associated with a chronic, low-grade inflammatory response.[12] In turn, the health risks of elevated inflammatory markers, especially CRP, include increased risk of coronary heart disease.[13]

Recent studies have found significant reductions in both BMI and CRP following gastric bypass surgery,[14] as well as enhanced regulation of leukocytes.[15] Previous studies have not evaluated the relationship of depression and inflammation among patients undergoing gastric bypass surgery. This preliminary study was designed to evaluate weight loss, depression, and inflammation among patients prior to surgery and at a 12-month follow-up.

It was hypothesized that participants would experience significant weight loss between a baseline assessment and a 12-month follow-up, as well as significant decreases in psychological distress and reductions in proinflammatory cytokines.

Methods

Participants

Participants were 13 Caucasian women (mean age = 46.9 ± 5.7) who completed a preoperative evaluation for gastric bypass surgery as well as a 12-month follow-up evaluation. All participants underwent the Roux-en-Y gastric bypass (RYGBP), which is the most common bariatric operation and produces the greatest weight loss. RYGBP creates a tiny gastric pouch and bypasses the initial portion of the small intestine, leading to decreased intake and reduction in the ability of the digestive tract to absorb food.

Procedures

At the time of the baseline medical evaluation and at a 12-month follow-up evaluation, measurements of body weight were recorded and blood samples were taken for evaluation of inflammatory markers, specifically IL-6 and CRP.

High sensitive C-reactive protein. Determinations were made using the CRP Elisa kit (American Laboratory Products Company, Windham Hill, NH, USA). Intra-assay coefficient variation is 5.75%, and inter-assay coefficient variation is 12.7%. Sensitivity is 0.124 ng/ml.

High sensitive interleukin-6. Determinations were made using the Quantikine HS IL-6 solid phase ELISA kit (RnD Systems, 614 McKinley Place, Minneapolis, MN). Intra-assay coefficient of variation is 7.4%, and inter-assay coefficient of variation is 7.8%. The sensitivity of the kit ranges from 0.016 to 0.110 pg/ml.

In addition, at baseline and 12-month follow-up, participants completed the following self-report measures.

Beck Depression Inventory (BDI).[16] The BDI is a 21-item questionnaire that assesses symptoms of

depression, including cognitive, behavioral and somatic symptoms. The BDI demonstrates high internal consistency with alpha coefficients ranging from .81 to .86.

Health-related quality of life was assessed with the *Medical Outcomes Study Short Form (SF-36)*.[17] The SF-36 is made up of 36 items and yields 8 subscales, including physical functioning, role functioning (physical and emotional), social functioning, bodily pain, mental health, vitality, and general health perception. The SF-36 has been widely used in prior studies of a variety of medical patient groups, with subscale reliability coefficients ≥0.80.

Binge Eating Scale[18] includes a series of 16 items made up of 3 to 4 statements describing a range of symptom severity. Questions assess aspects of eating habits such as frequency of eating when bored, and feelings of loss of control when eating. The Binge Eating Scale has good test-retest reliability (0.87).

Eating Disorder Examination-Questionnaire (EDEQ)[19] was derived from the Eating Disorders Examination Interview, and the questionnaire shows comparable reliability and validity to the interview form. The EDEQ is made up of 39 items and includes the following four scores: eating concern, weight concern, shape concern, and restraint. Respondents indicate the frequency with which they have experienced each concern over the past month. Data were analyzed via paired *t*-tests conducted on all biological markers and self-report outcomes.

Results

BMI, Inflammatory Markers, and Depression

Significant reductions in BMI were observed between baseline and 12-month follow-up (t=26.01, *P*<.001), with participants achieving an average weight loss of 54 kg, as shown in Table 1. Similarly, reductions in both IL-6 (t=5.38, *P*=.002) and CRP (t=9.52, *P*<.001) were observed. Participants reported significant decreases in symptoms of depression, with mean BDI scores decreasing from 15.8 to 6.8 (t=4.20, *P*=.025), reflecting an average reduction from mild depressive symptoms to negligible depressive symptoms.

Table 1. Mean (± SD) for BMI, markers of inflammation, and depression at baseline and at 12-month follow-up

Variable	Baseline	12 months
Weight (kg)	139.8 (21.5)	84.2 (21.2)***
Body mass index (kg/m^2)	51.3 (6.3)	32.0 (5.8)***
C-reactive protein (mg/l)	0.87 (0.20)	0.13 (0.07)***
Interleukin-6 (pg/ml)	5.41 (1.91)	2.24 (0.86)**
Beck Depression Inventory	15.8 (1.3)	6.8 (4.6)*

*P<.05; **P<.01; ***P<.001

Quality of Life

As shown in Table 2, participants indicated improvements in multiple dimensions of quality of life. Significant increases were observed on four subscales of the SF-36, including Physical Functioning (t=5.69, *P*=.01), Role Functioning-physical (t=6.79, *P*=.007), Vitality (t=7.00, *P*=.02), and Bodily pain (t=4.32, *P*=.049). Changes on the other four sub-

Table 2. Mean scores (± SD) for quality of life and disordered eating at baseline and at 12-month follow-up

Variable	Baseline	12 months
SF-36: Physical functioning	39.6 (17.7)	79.0 (15.6) *
SF-36: Role functioning -Physical	15 (22.4)	90 (22.4) **
SF-36: Role functioning -Emotional	46.7 (50.0)	100 (0)
SF-36: Social functioning	53.1 (29.5)	81.3 (21.7)
SF-36: Bodily pain	39.6 (17.7)	83.5 (19.5) *
SF-36: Mental health	62.4 (15.9)	72.8 (18.2)
SF-36: Vitality	22.5 (14.4)	71 (8.2) *
SF-36: General health	57.6 (29.0)	72.6 (17.0)
Binge eating scale	19.8 (4.3)	4.5 (2.6) **
EDEQ: Eating concern	1.9 (0.8)	0.5 (0.3) *
EDEQ: Weight concern	4.4 (0.9)	1.4 (0.8) *
EDEQ: Shape concern	4.9 (0.5)	2.1 (0.4) *
EDEQ: Restraint	2.6 (1.1)	2.9 (1.4)

Note: SF-36=Medical outcomes short form 36, higher *t*-scores indicate better functioning; EDEQ=Eating disorder examination questionnaire, lower scores indicate less eating concerns; Binge eating scale, lower scores indicate less binge eating. *P<.05; **P<.01

scales of the SF-36 were not statistically significant.

Disordered Eating

Participants indicated significant reductions in binge eating (t=14.00, *P*=.005), as well as reductions on three of the four subscales of the EDE-Q, including eating concern (t=4.01, *P*=.028), weight concern (t=5.25, *P*=.034), and shape concern (t=8.47, *P*=.014), as shown in Table 2. There was no change on the restraint subscale.

Depression, Inflammation, and Weight Loss

Correlations were conducted between change in depression and change in markers of inflammation. There was a significant correlation between decreased depression and decreased CRP (r=.98; *P*<.001), but the magnitude of the relationship between reduced depression and reduced IL-6 was much smaller (r=.46, n.s.). Weight loss, as measured by BMI change, was correlated with decreased IL-6 (r=.87; *P*=.05), as well as decreased CRP (r=.79) and reduced depression (r=.82), although the latter correlations were not statistically significant due to the small sample size.

Discussion

This study indicates that RYGBP is associated with a number of biological and psychosocial changes, in addition to weight loss. In particular, both IL-6 and CRP were reduced in this sample at the 12-month follow-up, reflecting improvements in risk factors associated with cardiovascular disease. These improvements in biological markers of function appeared to be associated with improvements in self-reported quality of life and reductions in disordered eating behavior. Furthermore, the sample experienced reduced symptoms of depression that were associated with reductions in inflammatory markers. Thus, the data suggest that weight loss following RYGBP is associated with numerous changes both in physical function and psychological functioning 1 year after surgery. The association observed between reduced depression and decreased CRP provides further evidence for the close relationship of inflammatory indicators with psychological mood state following RYGBP.

Although the results of the study are promising, they must be interpreted with caution for several reasons. First, the sample size was very small and restricted to Caucasian women. Therefore, the results may not be generalizable to men or to individuals from ethnic minority groups. Second, the study was observational and did not include a randomized control group. Although it would be ideal to conduct a study with a randomized no-treatment or delayed treatment control group, such a study may not be practical. Often, morbidly obese individuals seeking surgery are extremely motivated to proceed with surgery and may not be willing to participate in a randomized study in which they might be compelled to delay treatment.

Future studies evaluating biological factors and psychological functioning among patients undergoing RYGBP would be an important extension of this study and would help to identify relevant health outcomes of the procedure. In addition, studies examining the biological and psychological concomitants of RYGBP will help identify mechanisms by which the surgery may influence health outcomes. These data suggest that obesity, depression, and inflammatory factors appear to be interrelated and that reduction in weight via RYGBP contributes to significant reductions in depression and inflammation, as well as enhanced quality of life and less disordered eating.

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