Gastric Bypass in a Low-Income, Inner-City Population: Eating Disturbances and Weight Loss

Janet D. Latner,* Scott Wetzler,† Elliot R. Goodman,‡ and Juliet Glinski†

Abstract

LATNER, JANET D., SCOTT WETZLER, ELLIOT R. GOODMAN, AND JULIET GLINSKI. Gastric bypass in a low-income, inner-city population: eating disturbances and weight loss. Obes Res. 2004;12:956-961.

Objective: To examine the prevalence of eating disturbances and psychiatric disorders among extremely obese patients before and after gastric bypass surgery and to examine the relationship between these disturbances and weight outcomes.

Research Methods and Procedures: Sixty-five women patients (ages 19 to 67) with a mean BMI of 54.1 were assessed by semistructured psychiatric interview before surgery and by telephone interview after surgery (mean followup: 16.4 months) to determine psychiatric status, eating disturbances, and weight and health-related variables.

Results: Patients lost a mean of 71% of their excess BMI, with significantly poorer weight loss outcomes among African Americans. Psychiatric disorders remained prevalent before (37%) and after (41%) surgery. In contrast, binge eating disorder dropped from 48% to 0%. Psychiatric diagnosis did not affect weight outcomes. Instead, more frequent preoperative binge eating, along with greater initial BMI, follow-up length, and postoperative exercise, predicted greater BMI loss. Postsurgical health behaviors (exercise and smoking) and nocturnal eating episodes were also linked to weight loss. Exercise frequency increased and smoking frequency tended to decrease after surgery.

Discussion: These findings indicated that eating and psychiatric disturbances did not inhibit weight loss after gastric bypass and should not contraindicate surgery. Prior binge eating, eliminated after surgery, predicted BMI loss and, thus, may have previously been a maintaining factor in the obesity of these patients. The association between health behaviors and outcome suggests possible targets for intervention to improve surgical results. Poorer outcomes among African Americans indicate that these patients should be closely monitored and supported after surgery.

Key words: bariatric surgery, eating disturbances, mental illness, health behavior, ethnicity

Introduction

Bariatric surgery is a well-established treatment for morbidly obese patients with a BMI above 40 or above 35 with comorbid conditions (1). Gastric bypass typically leads to a 60% reduction of excess weight, and vertical banded gastroplasty leads to a 40% reduction. It also improves or resolves comorbid medical problems associated with obesity in a large proportion of patients (2).

Less is known about bariatric surgery's effect on eating disturbances and psychiatric disorders. High prevalence rates of eating disturbances have been reported in patients undergoing surgery. For example, reports of prevalence rates for binge eating disorder (BED)¹ range from 17% (3) and 25% (4) to as high as 47% (5) and 48% (6). Similarly, consistent problems with night eating have been found to occur in 8% (7), 10% (8), and 33% of preoperative patients

There is evidence from prospective studies with followups ranging from 4 months (4) to 5.5 years (8) that binge eating, which occurred at least weekly in 44% to 52% of patients, ceases after surgery. However, there is evidence that other eating disturbances do persist after surgery. For example, Hsu et al. reported a decrease in prevalence but not a disappearance of frequent nocturnal eating episodes

Received for review October 8, 2003.

Accepted in final form April 19, 2004.

E-mail: ianet.latner@canterbury.ac.nz

Copyright © 2004 NAASO

^{*}Department of Psychology, University of Canterbury, Christchurch, New Zealand and Departments of †Psychiatry and Behavioral Sciences and †Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York.

Address correspondence to Janet D. Latner, Department of Psychology, University of Canterbury, Private Bag 4800, Christchurch, New Zealand.

¹ Nonstandard abbreviation: BED, binge eating disorder.

followed gastric bypass: from 33% to 11% of patients (6). Rates of night eating syndrome have been found to remain steady at 7%, whereas BED decreased from 43% to 2% after biliopancreatic diversion (7). Powers et al. reported that 2% of patients frequently engaged in self-induced vomiting after surgery; among most of the additional 31% of patients who vomited frequently after surgery, vomiting was caused by patients' deliberately overeating while knowing this would result in vomiting (8).

Reports conflict on whether the above-mentioned eating disturbances affect weight outcome after surgery. Kalarchian et al. (4) and Powers et al. (8) have found no weight loss differences between patients with and without presurgical binge eating and associated eating pathology. However, weight regain is more likely among those patients whose eating disturbances have persisted at the time of follow-up (9). Hsu and colleagues have reported that the presence of presurgical eating disturbances is most likely to predict weight outcome after 2 years postsurgery, once weight regain begins (6). The high prevalence rates of eating disturbances in patients presenting for bariatric surgery warrant further investigation to determine whether these disturbances adversely affect outcome.

Research on the relationship between psychiatric disorders and postsurgical outcome is limited. Improvements in psychological functioning after surgery have been reported (10). For example, there is evidence of reductions in anxiety, depression, and negative perception of body shape at 6-month postoperative follow-up (11). Psychological factors have been found not to predict weight loss or drop-out from treatment in the 3 years after surgery (12). It has been suggested that psychopathology seldom contraindicates surgery, because even patients with severe emotional disturbances can have successful outcomes (10,13).

However, the prevalence of psychiatric disorders in the populations studied has been low to normal (e.g., 12), and more research is needed to determine the potential effects of psychological disturbances on postsurgical outcomes. In addition, although the overwhelming majority of patients in previous studies have been white [e.g., 93% (14) and 73% (8)], there is limited evidence that African Americans show poorer weight loss results and are at higher risk of dropping out of follow-up care (14). Research is needed to identify factors associated with these poor outcomes among minorities (14); the present study sought to examine factors that might be associated with outcomes among an ethnically diverse, inner-city population.

A previous report of preoperative patients at Montefiore Medical Center, Albert Einstein College of Medicine, has documented an unusually high rate of current preoperative psychiatric disorders, with 50% of patients diagnosed with a disorder, 23% taking psychotropic medication, and 22% and 17% with reported histories of sexual and physical abuse, respectively (13). Therefore, an additional sample of patients from this population was evaluated to assess their eating disturbances, psychiatric status, and surgery outcomes and to examine the relationships among these vari-

Research Methods and Procedures

Patients

Participants were recruited from a list of 150 patients who had undergone gastric bypass for severe obesity performed by one of the authors (E.R.G.) at Montefiore Medical Center, Albert Einstein College of Medicine, at least 6 months before follow-up. Only women patients were recruited because over 90% of the patients in this cohort were women. Six telephone call attempts were made to each potential participant, and directory assistance was sought if a person was no longer present at the number available for them. Sixty-five patients (43%) were contacted and administered telephone interviews at follow-up; two additional patients refused participation, and an additional two had died due to medical complications.

Measures

The preoperative psychological evaluation included a semistructured psychiatric clinical interview. Postoperative follow-up interviews were conducted by telephone and included a detailed assessment of weight- and health-related variables. Patients were assessed for psychiatric disorders using the Prime-MD (15), a screening tool validated for use in medical settings to detect mood and anxiety disorders, substance abuse, and somatoform disorders. To assess preand postsurgical eating concerns, patients were administered an abridged version of the Eating Disorder Examination (16) that included its diagnostic items, along with supplemental questions regarding BED (17) and nocturnal eating. The Eating Disorder Examination has been well supported in tests of its reliability (18) and concurrent validity (19). Patients also rated their satisfaction with the results of the surgery on a five-point Likert scale ranging from "not at all satisfied" to "extremely satisfied."

Statistical Analysis

The amount of excess BMI lost by patients was defined as: [(BMI lost] ÷ [initial BMI - 25)]. Paired sample Student's t tests assessed postsurgical changes in healthrelated variables, eating disturbances, and psychiatric disturbances. Pearson correlation coefficients were computed to assess the association between weight outcome (excess BMI lost and total BMI lost) and health variables, including medical conditions and health behaviors, and between weight outcome and disordered eating behaviors. Independent sample Student's t tests compared the weight outcome of patients with and without psychiatric disturbances and with and without eating disturbances. ANOVA and independent sample Student's *t* tests were used to explore differences in outcome among ethnic groups. Step-wise regression analysis determined predictors of BMI lost.

Results

Sample

Patients' mean age was 39.5 years at the time of surgery, with 39% unemployed, 18% receiving disability assistance, and 12% receiving public assistance. Fifty-eight percent were single, 23% were married or cohabitating, and 19% were divorced, separated, or widowed. Thirty percent were African American, 30% were Hispanic, and 40% were white.

Weight Variables

The mean length of follow-up was 16.4 months. Patients' mean BMI decreased from 54.1 (10.2 SD) presurgery to 34.1 (8.5 SD) postsurgery. Patients lost an average of 71% of their excess BMI. Eighty percent of patients lost over 50% of their excess BMI. However, African-American patients lost only 62% relative to white patients' loss of 80% [t(35) = 2.07, p < 0.05]. Hispanic patients lost 69% and were not significantly different from the other groups. There was also a trend for African-American patients' final BMI to be higher (36.7) than that of white patients' [31.9; t(35) = 1.70, p < 0.10] despite similar initial BMIs (54.1 and 53.4, respectively).

Health Variables

Patients' mean number of medical problems decreased from 2.5 to 1.0 [t(62) = 8.3, p < 0.001; varying degrees of freedom indicate numbers of patients for whom data were available]. Pre- and postsurgical number of medical conditions were correlated [r(62) = 0.608, p < 0.001]. A greater number of postsurgical medical conditions was significantly correlated with higher postsurgical BMI [r(62) = 0.285, p < 0.05], further distance from weight loss goal [r(51) = -0.288, p < 0.05], and lower percentage excess BMI lost [r(62) = -0.260, p < 0.05].

As shown in Figure 1, significant improvements in health behaviors occurred from pre- to postsurgery: Exercise frequency (≥ 20 minutes of physical activity) increased from 0.7 to 2.8 episodes per week [t(54) = 5.48, p < 0.001]. Similarly, there was a marginally significant drop in number of cigarettes smoked per day, from 3.7 presurgery to 2.5 postsurgery [t(54) = 1.86, p = 0.068]. Postsurgical exercise frequency was positively correlated with proximity to goal weight [t(54) = 0.345, t(54) = 0.02] and negatively correlated with number of current medical problems [t(51) = -0.284, t(51) = -0.284, t(52) = -0.306]. Smoking frequency presurgery was negatively correlated with proximity to goal weight [t(52) = -0.306, t(52) = -0.306]. Postsurgical exercise frequency was also positively correlated with satisfaction with the results of the

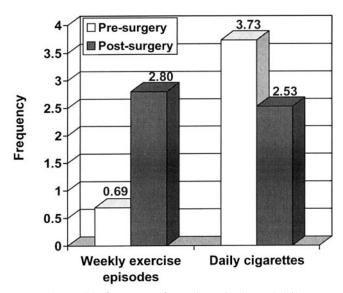


Figure 1: Weekly frequency of exercise episodes and daily number of cigarettes smoked by patients before and after gastric bypass.

surgery [r(51) = 0.319, p < 0.02], whereas postsurgical smoking was negatively correlated with satisfaction [r(51) = -0.294, p < 0.05], controlling for BMI loss. ANOVA revealed differences among ethnic groups in postsurgical smoking frequency (F(3,55) = 6.13, p < 0.05). Post hoc comparisons (least significant difference) showed that Hispanics (p < 0.01) and African Americans (p < 0.05) both smoked less frequently than whites.

Psychiatric Disturbances

Before surgery, 37% of patients were diagnosed with a psychiatric disorder: 23% depressive disorders, 8% anxiety disorders, and 6% comorbid depressive and anxiety disorders. This was comparable with the 41% of patients after surgery who met criteria for a psychiatric diagnosis: 12% depressive disorders, 13% anxiety disorders, 6% comorbid depressive and anxiety disorders, and 10% somatoform disorders. Twenty-seven percent were receiving psychotropic medications both before and after surgery. Twelve percent reported a history of physical abuse, and 12% reported a history of sexual abuse. There were no significant differences between those with and those without a psychiatric diagnosis before or after surgery (or between those with and those without a history of abuse) in initial BMI, BMI lost, percentage excess BMI lost, or eating disturbances.

Eating Disturbances

The mean frequency of binge eating [objective bulimic episodes (16), the consumption of a large amount of food accompanied by a loss of control over eating] fell from 2.92

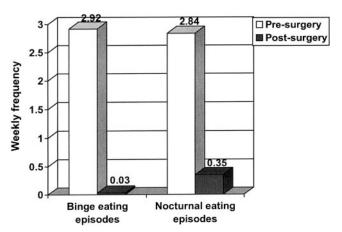


Figure 2: Weekly frequency of episodes of binge eating and episodes of nocturnal eating in patients before and after gastric bypass.

weekly episodes before surgery to 0.03 after surgery [t(57) = -5.33, p < 0.001; Figure 2]. Before surgery, 48% of patients met criteria for BED, compared with 0% after surgery. One additional patient met criteria for bulimia nervosa before surgery and did not meet these criteria after surgery. Twenty percent also engaged in objective overeating episodes before surgery (consumption of a large amount of food without a loss of control over eating) at an average frequency of 3.4 episodes per week, compared with 0% after surgery. More frequent presurgical binge eating was associated with greater importance of shape in patients' self-evaluation after surgery [r(49) = 0.282, p < 0.05]. Patients' mean number of nocturnal eating episodes per week fell from 2.84 presurgery to 0.35 postsurgery [t(55) = -4.32, p < 0.001]. Presurgical nocturnal eating frequency was positively correlated with binge eating frequency [r(55) = 0.242, p < 0.01]. Before surgery, 55% had episodes of nocturnal eating at least twice per week for the previous 3 months, compared with 2% after surgery. Selfinduced vomiting occurred in 7% of patients before surgery and 5% of patients after surgery, at a mean rate of 5.9 and 0.8 episodes per month, respectively. Involuntary vomiting after surgery occurred in 60% of patients at an average of 4.7 episodes per month. There were no differences in disturbed eating behaviors between patients with and without psychiatric disorders before or after surgery.

There were no differences between responders (those who lost at least 50% excess BMI lost) and nonresponders in presurgical binge eating, vomiting, or nocturnal eating frequency. Similarly, there were no differences in initial BMI, BMI lost, or percentage excess BMI lost between patients with and without presurgical BED. Finally, neither presurgical binge eating nor nocturnal eating episode frequency was correlated with initial BMI, BMI lost, or excess BMI lost. Marginally greater satisfaction with the surgery

was reported by those who met criteria for BED than by those who did not [t(44) = 1.8, p < 0.10]. However, more frequent postsurgical nocturnal eating episode frequency was associated with greater postsurgical BMI [r(59) = 0.308, p < 0.02] and with less satisfaction [r(51) = -0.365, p < 0.01].

Greater weight and shape concerns after surgery were correlated with less satisfaction with the outcome of the procedure [r(51) = -0.280, p < 0.05] for importance of weight; r(51) = -0.350, p < 0.02 for importance of shape]. However, there was no association between shape and weight concern and any weight loss outcome measure, and there was no relationship between satisfaction and any weight loss measure. Importance of weight also correlated with postsurgery exercise frequency [r(51) = 0.284, p < 0.05], and importance of shape was associated with more frequent exercise before surgery [r(51) = 0.411, p < 0.005].

Patients' mean daily energy intake was estimated by 24-hour recall as 794 kcal. White patients reported significantly greater intake (886 kcal) than African-American patients [684 kcal; t(35) = 2.20, p < 0.05].

Regression analysis revealed that BMI lost was associated with four significant predictors [$R^2=0.57$, F(4,49)=14.77, p<0.001]: initial BMI ($\beta=0.71$, p<0.01), time since surgery ($\beta=0.33$, p<0.01), postsurgical exercise ($\beta=0.29$, p<0.01), and presurgical binge eating ($\beta=0.26$, p<0.01). Similar significant results emerged for these four independent variables when percentage excess BMI lost [$R^2=0.44$, F(4,49)=8.92, p<0.001] and proximity to goal weight [$R^2=0.54$, F(4,49)=12.22, p<0.001] were used as the dependent variable in the regression equation; in these analyses, however, initial BMI was a significant negative (rather than positive) predictor.

Discussion

This study examined eating and psychiatric disturbances and outcome of gastric bypass surgery in a sample that differed from previous studies in a number of ways. Previous samples have been primarily white, well-educated, and with high rates of employment and marriage (e.g., 90% and 66%, respectively) (3). In the current sample, 60% were from African-American or Hispanic backgrounds. The majority of patients were unmarried, and many were unemployed or receiving government assistance. They also had a somewhat higher initial BMI (54.1) than in previous studies [e.g., 44.9 (5) and 48.4 (3)].

Although large losses of BMI and excess BMI were found in the group as a whole, poorer weight outcomes were found among African-American patients compared with white patients, with 62% vs. 80% excess BMI lost and final BMIs of 36.7 vs. 31.9, respectively. This occurred despite significantly less frequent smoking among African-American and Hispanic patients and also despite lower reported

daily caloric intake among African Americans compared with whites. There were also no ethnic group differences in exercise frequency that might explain this result, and there were no differences in binge eating or other eating disturbances.

High rates of eating disturbances were evident before surgery, as were moderately high rates of psychiatric disorders before and after surgery. Consistent with previous literature (12), psychiatric conditions had little relationship with surgical outcome. This finding suggests that comorbid psychiatric illnesses should not disqualify patients from surgical treatment, although it should be noted that the majority of affected patients were receiving ongoing treatment for these conditions, in the forms of psychotropic medication and psychotherapy. The prevalence of psychiatric disorders was also unaffected by surgery.

In contrast, eating disturbances dropped dramatically after surgery, with the prevalence of BED falling from 48% to 0%. After surgery, frequent nocturnal eating episodes, which occurred in 55% of patients before surgery, persisted in 9% of patients, and frequency of these episodes was associated with greater final BMI and less satisfaction with surgery. Although it is not possible to determine the causal direction of these findings, they are consistent with previous research showing that remaining postsurgical eating disturbances are associated with poorer weight outcome (9,14).

However, eating disturbances before surgery were not associated with poorer outcome. On the contrary, there was a trend toward greater satisfaction with the outcome of surgery among former binge eaters. In addition, predictors of BMI lost and excess BMI lost included initial BMI, length of follow-up, postsurgical exercise, and presurgical binge eating. Unexpectedly, binge eating emerged as a positive, rather than a negative, predictor of outcome. It may be that among binge eaters in this sample, frequent binge eating constituted one factor that contributed to their extreme obesity, so that when binge eating ceased after surgery, they lost more weight in proportion to how much they formerly binged. These patients may, in turn, have felt greater satisfaction, due not only to their weight loss, but also to their dramatic reduction in binge eating. The lack of an association between binge eating frequency and presurgical BMI is also surprising given previous findings of increased prevalence of binge eating in heavier patients (20), as well as previous findings of greater body weight in binge eaters presenting for surgery (5).

The presence of involuntary vomiting after surgery in the majority of patients may help to explain the drop in patients' binge eating frequency. Patients indicated that this vomiting followed the intake of larger than usual amounts of food or of particular food types (e.g., often those high in sugar). It is possible that when failed attempts to overeat are followed by vomiting, this unpleasant experience reduces the likelihood of future overeating and, in turn, may force patients to attend to and obey their satiety cues. In addition, physiological changes in hunger and satiety after surgery, as suggested by gastric bypass patients' severely impaired 24-hour release of ghrelin, a hormone that increases food intake (21), undoubtedly play a role in eliminating binge eating.

In addition to the typical striking improvements in medical conditions, patients showed improvements in important health behaviors including exercise and smoking frequency. These behaviors appeared to be closely linked to outcome. Postsurgical exercise frequency predicted BMI lost and excess BMI lost. It was also associated with proximity to goal weight and was inversely correlated with patients' number of medical problems. Presurgical smoking frequency was inversely correlated with proximity to goal weight. After surgery, satisfaction with its results was positively correlated with exercise frequency but negatively correlated with smoking frequency. Patients with greater shape and weight concerns exercised more frequently both before and after surgery, suggesting that although shape and weight concerns were also associated with less satisfaction with surgery, they may have prompted healthy behavior, as well.

A limitation of the present study is the retrospective assessment of eating disturbances. However, it has been suggested that a reason for the lower prevalence rates reported in studies using prospective assessment is that patients are reluctant to disclose eating problems for fear of not being covered by health insurance (3) or failing to qualify as a suitable candidate for the surgery (13). Future research could specifically examine this potential underreporting of binge eating by comparing prospective and retrospective reports. Researchers and clinicians should then determine ways to more accurately assess binge eating before surgery, for example, through the use of self-monitoring along with interview data. Another limitation of the present study was the absence of men in this group, as well as the reliance on self-report for the collection of follow-up weight and medical information. Although use of psychotropic medications may influence phase of recovery (and determination of a patient's eligibility to undergo bariatric surgery), it does not reduce the likelihood of psychiatric diagnosis. In addition, the postoperative interviews were conducted by telephone even though these measures have been validated in face-to-face contexts. Finally, the length of follow-up in the present study did not allow us to determine whether eating disturbances re-emerged several years after surgery. Hsu et al. (6) have reported that presurgical eating disturbances do predict weight regain, but only beginning 2 years after surgery. Future research should employ longer follow-up periods to clarify how eating disturbances may influence longer term weight regain and whether these disturbances might return several years after surgery.

Further research is needed to continue to clarify the relationships between surgical outcome and eating and psychiatric disturbances in men and women from diverse backgrounds. In light of previous research showing poorer outcomes among African-American patients (14), the present findings suggest that these patients should be carefully monitored and supported after surgery. More research is needed to understand and improve the postsurgical outcomes of these patients.

Acknowledgment

There was no outside funding/support for this study.

References

- 1. National Heart, Lung, and Blood Institute. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. Bethesda, MD: 1998.
- 2. Brolin RE, Kenler HA, Gorman JH, Cody RP. Long-limb gastric bypass in the super-obese: a prospective randomized study. Ann Surg. 1992;215:387-95.
- 3. de Zwaan M, Mitchell JE, Howell LM, et al. Two measures of health-related quality of life in morbid obesity. Obes Res. 2002;10:1143-51.
- 4. Kalarchian MA, Wilson GT, Brolin RE, Bradley L. Effects of bariatric surgery on binge eating and related psychopathology. Eat Weight Disord. 1999;4:1-5.
- 5. Adami GF, Gandolfo P, Bauer B, Scopinaro N. Binge eating in massively obese patients undergoing bariatric surgery. Int J Eat Disord. 1995;17:45-50.
- 6. Hsu LKG, Sullivan SP, Benotti PN. Eating disturbances and outcome of gastric bypass surgery: a pilot study. Int J Eat Disord. 1997;21:385-90.
- 7. Adami GF, Meneghelli A, Scopinaro N. Night eating and binge eating disorder in obese patients. Int J Eat Disord. 1999;25:335-8.
- 8. Powers PS, Perez A, Boyd F, Rosemurgy A. Eating pathology before and after bariatric surgery: a prospective study. Int J Eat Disord. 1999;25:293-300.

- 9. Hsu LKG, Betancourt S, Sullivan SP. Eating disturbances before and after vertical banded gastroplasty: a pilot study. Int J Eat Disord. 1996;19:23-34.
- 10. Stunkard AJ, Stinnett JL, Smoller JW. Psychological and social aspects of the surgical treatment of obesity. Am J Psychol. 1986;143:417-29.
- 11. Kincey J, Neve H, Soulsby C, Taylor TV. Psychological state and weight loss after gastroplasty for major obesity: some outcomes and inter-relationships. Psychol Health Med. 1996;1:113-18.
- 12. Schrader G, Stafanovic S, Gibbs A, Elmslie R, Higgins B, Slavotinek A. Do psychosocial factors predict weight loss following gastric surgery for obesity? Austr N Z J Psychiatry. 1990;24:496-99.
- 13. Glinski J, Wetzler S, Goodman E. The psychology of gastric bypass surgery. Obes Surg. 2001;11:581-88.
- 14. Kalarchian MA, Marcus MD, Wilson GT, Labouvie EW, Brolin RE, LaMarca LB. Binge eating among gastric bypass patients at long-term follow-up. Obes Surg. 2002;12:270-75.
- 15. Spitzer RL, Williams JB, Kroenke K, et al. Utility of a new procedure for diagnosing mental disorders in primary care: the Prime-MD study. JAMA. 1994;272:1749-56.
- 16. Fairburn CG, Cooper Z. The Eating Disorder Examination. In: Fairburn CG, Wilson GT, eds. Binge Eating: Nature, Assessment, and Treatment. 12th ed. New York: Guilford Press; 1993, pp. 317-32.
- 17. American Psychiatric Association. The Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: 1994.
- 18. Wilson GT, Smith D. Assessment of bulimia nervosa and evaluation of the Eating Disorder Examination. Int J Eat Dis. 1989;8:173-80.
- 19. Rosen J, Vara L, Wendt S, Leitenberg H. Validity studies of the Eating Disorders Examination. Int J Eat Disord. 1990;9:
- 20. Telch CF, Agras WS, Rossiter EM. Binge eating increases with increasing adiposity. Int J Eat Disord. 1988;7:115–19.
- 21. Cummings DE, Weigle DS, Frayo RS, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N Engl J Med. 2002;346:1623-30.