Plasma brain-derived neurotrophic factor in women after bariatric surgery: a pilot study

Eighteen morbidly obese women had plasma brain-derived neurotrophic factor (BDNF) measured before bariatric surgery and 3 months postoperatively. We analyzed plasma BDNF levels in all the participants then subdivided according to menopausal status and type of surgery. Brain-derived neurotrophic factor decreased significantly in all the participants and in the premenopausal group when looked at in isolation. (Fertil Steril® 2008;■:■–■. ©2008 by American Society for Reproductive Medicine.)

Key Words: Obesity, BDNF, bariatric surgery, surgical weight loss

Obesity is one of the fastest-growing health problems in the United States (1). Bariatric surgery can lead to substantial weight reduction. Both the estimated number of bariatric surgical procedures and the number of practicing bariatric surgeons have increased markedly in the United States (2).

Brain-derived neurotrophic factor (BDNF), a protein that belongs to the neurotrophin family and originally described in the nervous system, has been shown to be expressed in nonneuronal tissues like the ovaries, and to be present in plasma (3). We have demonstrated that BDNF is present in the follicular fluid of normally cycling women and in the preovulatory follicles of women undergoing assisted reproductive technology (ART), namely, in vitro fertilization (IVF) (4–7). We have also shown that the secretion of BDNF from granulosa cells is enhanced by c-AMP in a dose-dependent manner (6).

Previous studies have revealed that circulating BDNF reflects eating behavior and the development of obesity in females, with BDNF being low in anorexia and bulimia nervosa (8–11) and elevated in adult obese women (10, 12–15). This might imply that circulating BDNF level is related to the total body fat mass. It is therefore possible that the BDNF level increases in obesity to compensate for its associated pathophysiologic conditions because of its potential role in improving energy metabolism and suppressing food intake (14). Given that more reproductive-aged women are undergoing bariatric surgery (2), that BDNF may have a role in supporting granulosa cell oocyte communication within the follicle (7), that BDNF seems to mediate LH and hCG actions in promoting preovulatory oocyte meiotic maturation (16), and that there is growing research for the role of circulating BDNF and ART (16, 17), it would be insightful to assess changes in plasma BDNF after "dramatic" weight loss caused by bariatric surgery in morbidly obese women. We hypothesized that BDNF levels would drop after surgical weight loss secondary to a decrease in total body fat mass.

MATERIALS AND METHODS

Eighteen morbidly obese women who underwent bariatric surgery were enrolled in a prospective study evaluating pre- and postoperative BDNF levels. The study was approved by the institutional review boards of Maimonides Medical Center and Women and Infants Hospital, and patients signed informed consent. A phone call was placed to all the female patients scheduled for bariatric surgery over a 15-month period, and they were each asked to participate. Of >80 women called, 18 agreed to participate. Because BDNF is inversely related to menopausal status (18), we divided the patients into premenopausal and postmenopausal groups, and because BDNF might change differently according to the type of surgery, we have subdivided the participants according to either gastric bypass or gastric banding.

Patients were recruited before surgery to give a blood sample and complete a questionnaire that included information regarding demographics, medical, gynecologic, surgical, and social history and drug intake. A participant was considered menopausal if she had no menstrual periods for 12 consecutive months and her mullerian inhibiting substance level was negligible (<0.1 ng/mL). None of the patients were on hormonal medications at the time of their blood draw, and sample collection was not timed with respect to the menstrual cycle because of the poor compliance of the population studied (19), the high risk of amenorrhea associated with morbid obesity (20), and the high chance of having menstrual changes after surgical weight loss (21, 22). Samples were taken approximately 1 or 2 weeks before

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TABLE 1

Demographics and clinical profiles of the participants.

	All participants (N = 18)	Premenopausal (N = 12)	Postmenopausal (N = 6)
Age in years[a] mean (SE)	40.05 (2.46)	34.33 (1.95)	51.5 (2.37)
Type of bariatric surgery			
Gastric banding	12	7	5
Gastric bypass	6	5	1
BMI in kg/m^2[a]			
Preoperative-mean (SE)	48.21 (1.96)	48.35 (2.47)	47.95 (3.5)
Postoperative-mean (SE)	42.14 (1.88)	41.75 (2.6)	42.93 (2.48)

Note: BMI = body mass index; SE = standard error.

[a] Range for ages 25–59 years, and for body mass index of 36.4–68.2 kg/m^2 preoperatively and 30.4–58.2 kg/m^2 postoperatively.

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the patients underwent the bariatric surgical procedure; postoperative samples were taken a mean (±SE) of 87 ± 7 days (3 months) after the operation. Blood was drawn into 7-mL Vacutainer tubes containing 0.5 mL of 3.8% sodium citrate. We preferred to analyze plasma rather than serum BDNF concentration to avoid possible interindividual variations connected with physiologic and/or pathologic alterations of platelets count (platelets are known to be one of the major human BDNF storage sites) (23). The blood samples were processed by centrifuge after collection, and then all samples were frozen at −80°C until they were analyzed for plasma BDNF levels. There were no differences in the pre- and postoperative sample collection processes.

Brain-derived neurotrophic factor levels were determined in duplicate using the commercially available BDNF Emax immunoassay system (Promega Corp., Madison, WI). The ELISAs were performed according to the manufacturer's protocol and as previously described (6). The BDNF assay lower limit of sensitivity was 16 pg/mL and intrassay coeffcients of variation were <15%.

Data are expressed as mean ± SE. The Wilcoxon signed ranked test was used to compare pre- to postoperative BDNF levels. Differences in pre- and postoperative levels of BDNF were compared using the Mann-Whitney rank sum test. The correlations between BDNF, age, and body mass index (BMI) were calculated using Spearman rank correlation coefficients. Exact probabilities were computed because of the small sample size. Computations were done using the SPSS Exact Statistic module. A value of $P<.05$ was considered statistically significant.

RESULTS

Clinical and demographic characteristics of the participants are shown in Table 1. There were 12 premenopausal women and 6 postmenopausal women in this cohort. Plasma mean BDNF concentrations decreased by 38% after surgery (7,708.0 ± 1,145.3 pg/mL preoperatively to 4,146.3 ± 705.4 pg/mL postoperatively, P=.009) in all the participants, whereas BMI dropped by 12.6%. Plasma BDNF decreased by 54% in the premenopausal group (7,988.1 ± 1,551.4 pg/mL preoperatively to 3,616.5 ± 813.2 pg/mL postoperatively, P=.026), whereas BMI dropped by 13.6%, and plasma BDNF decreased by 17% in the postmenopausal group, although that drop was not significant (7,147.6 ± 1,641.5 pg/mL preoperatively to 5,205.8 ± 1,352.2 pg/mL postoperatively, P=.148), whereas BMI dropped by 10.4%.

Twelve patients had undergone gastric banding procedures and six had gastric bypass. Because patients who had bypass (preoperative BMI = 50 ± 4.0 and postoperative BMI = 40 ± 4.0; P=.0001) lost significantly more weight than those with a banding procedure (preoperative BMI = 47 ± 2.3 and postoperative BMI = 43 ± 2.1; P=.0001; 20% and 8.5% drop in BMI in the bypass and the banding group, respectively), we also performed the analysis according to the surgery type. Although BDNF decreased in both banding (from 7,893 ± 1,507 pg/mL preoperative to 4,831 ± 978 pg/mL postoperative; P=.09) and bypass groups (from 7,337 ± 1,837 pg/mL preoperative to 2,777 ± 552 pg/mL postoperative; P=.06), because of the small sample sizes these changes were not significant. The drop in BDNF was greater in the bypass (62% drop) than the banding group (39% drop) but once again because of the small sample size the difference did not achieve statistical significance (P=.49) (Table 2). When Spearman correlation was performed, there was no correlation between the amount of weight loss and the drop in BDNF and no correlation between age and BDNF.

DISCUSSION

We measured plasma BDNF in a cohort of morbidly obese women who underwent surgical weight loss and have

TABLE 2

Summary of plasma BDNF levels.

	Preoperative BDNF levels (pg/mL)	Postoperative BDNF levels (pg/mL)
All participants (N = 18)	7708.0 ± 1145.3	4146.3 ± 705.4[a]
Premenopausal group (N = 12)	7988.1 ± 1551.4	3616.5 ± 813.2[a]
Postmenopausal group (N = 6)	7147.6 ± 1641.5	5205.8 ± 1352.2
Banding group (N = 12)	7893 ± 1507	4831 ± 978
Bypass group (N = 6)	7337 ± 1837	2777 ± 552

Note: Data are expressed as mean ± SE.
[a] $P < .05$.

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shown a drop in the BDNF levels. Studies on animal models have revealed that endogenous BDNF levels significantly drop in the dorsal vagal complex (DVC) and in the ventromedial hypothalamus (VMH) in the starvation state (24). Bariohay et al. (24) revealed that within the DVC, BDNF protein content decreased by 40% after 48 h fasting. Blood BDNF levels were not measured in those two studies, but because BDNF crosses the blood–brain barrier, and because blood BDNF has been reported to reflect central BDNF levels in animal models (25), we hypothesize that the postbariatric surgery period, considered a relative starvation state, could be an explanation for the low plasma BDNF levels we found in this study. A tempting hypothesis for this drop in BDNF postbariatric surgery is that it relates to changes in leptin. The postbariatric surgery period is considered a low leptin state, and a strong positive correlation has been shown between leptin and BDNF, and BDNF may constitute a common downstream effector of leptin through the melanocortin 4 receptor (MC4R) (22). In fact, infusion of leptin centrally induced an increase in BDNF content within the DVC (22). The role of leptin in the association between surgical weight loss and BDNF needs to be explored.

Blood BDNF levels of normal-weight patients have been compared with those of obese patients, although the results have not been uniform. Monteleone et al. (10) found that BDNF levels were significantly higher in obese women (mean BMI of 37) than in normal BMI patients. However, El-Gharbawy et al. (13) reported that serum BDNF was lower in extremely overweight children and adolescents (mean BMI of 36) than those of normal weight. Further, although Suwa et al. (14) showed a positive correlation between serum BDNF levels and BMI in female patients (mean BMI of 26), Lommatzsch et al. (15) showed a negative correlation between plasma BDNF levels and weight in adult patients (median BMI of 24). A study by Bullo et al. (12), including morbidly obese patients, showed that BDNF seems to be more related to lipid profile than to BMI in female patients (morbidly obese group with mean BMI of 47). In our cohort of morbidly obese women, we have shown that there is a greater drop in BDNF in the bypass group compared with the banding group, with the bypass group having lost significantly more weight than the banding group. We have also found that there is a nearly significant correlation between the amount of weight loss and the drop in BDNF in the banding group. However, lipid data were not available for these patients.

Most of studies on the relationship between BDNF and age have found that BDNF decreases with age. Lommatzsch et al. (15) showed a negative correlation between plasma BDNF level and age in 140 healthy adults (age range 20–60 years old). Begliuomini et al. (18) showed that plasma BDNF is significantly lower in postmenopausal women compared with fertile women, and found that in the postmenopausal group BDNF is negatively correlated with age. Ziegenhorn et al. (26) showed a negative correlation between serum BDNF and age in a large elderly cohort (age >70 years old). Additionally, studies on animal models revealed a decrease in BDNF levels with aging in the hippocampus and hypothalamus (27). In our cohort of morbidly obese women, plasma BDNF levels at baseline were lower in the postmenopausal group compared with the premenopausal group (although it did not reach statistical significance, most likely because of the small number of participants) but we did not find any correlation between BDNF and age either pre- or postoperatively. The absence of statistically significant correlations in the present study may partly result from the small sample size. However, the small sample size would not result in low correlation coefficients if indeed there were strong correlations in the population. Another possible explanation to the fact that BDNF dropped significantly in the premenopausal group but not in the postmenopausal group is that more patients had bypass surgery in the first group (five out of seven) than in the second group (one out of five), and ultimately lost more weight.

BDNF has been shown to be important in the development of mouse oocyte into preimplantation embryos because it promotes the nuclear and cytoplasmic maturation of the oocyte (28). A recent study determining follicular-fluid BDNF levels in women undergoing ART for different etiologies of infertility revealed that patients with a history of endometriosis had significantly lower levels of BDNF, that patients with diminished ovarian reserve had lower levels of BDNF (not statistically significant) and that women with PCOS and unexplained infertility had no changes in BDNF levels when compared with the control group (male factor infertility) (29). The investigators postulated that the low levels of follicular-fluid BDNF in endometriosis patients might be associated with the poor oocyte quality and poor fertility status associated with endometriosis. Another study demonstrated that LH and hCG in vitro enhanced BDNF secretion by cumulus cells, and that human follicular-fluid BDNF levels are significantly higher in ART cycles (with hCG administration) than in natural cycles (without hCG administration) (16). Little is known regarding ovarian BDNF levels and IVF success.

In conclusion, plasma BDNF significantly dropped in bariatric surgery patients after rapid weight loss, both when all participants were combined and when the premenopausal group was looked at in isolation. Although there was also a drop in BDNF in the postmenopausal patients and separately in the banding and the bypass groups, because of small subset sizes, the differences did not reach significance at traditional levels. The decline in levels of BDNF was greater in those who had bypass surgery rather than banding. This suggests that changes in circulating BDNF in obesity, and after surgical weight loss are likely secondary to an altered energy balance. One hypothesis could be that in obesity, increased levels of plasma BDNF may represent an adaptive mechanism to counteract the condition of positive energy imbalance by stimulating energy expenditure and decreasing food ingestion (10); similarly, a BDNF reduction after surgical weight loss might promote food intake in an attempt to counterbalance the negative energy balance. The mechanism of action for BDNF in the regulation of food intake has yet to be established.

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