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Impact of Weight Loss Following Weight Loss Surgery on Levels of Plasma N-Terminal Pro-B-Type Natriuretic Peptide

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Abstract

Natriuretic peptides have multiple beneficial cardiovascular effects. Prior cross-sectional studies indicate that obese individuals have lower natriuretic peptide concentrations than individuals of normal weight. It is not known whether this relative natriuretic peptide deficiency is reversible with weight loss. We studied 132 obese individuals undergoing weight loss surgery with serial measurement of plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations at pre-operative, early (1–2 months) and late post-operative (6 months) time points. Twenty subjects also underwent echocardiography at baseline and 6 months after surgery. Significant weight loss was observed after surgery (median body mass index [BMI] 45.1, 41.0, and 32.9 kg/m² for the three time points respectively, ANOVA $p < 0.001$). Median NT-proBNP levels increased substantially (31.6, 66.9, and 84.9 pg/ml; $p < 0.001$). The average intra-individual increase in NT-proBNP at the two post-operative time points was 3.4 and 5.0 times the pre-operative level ($p < 0.001$ for both time points versus pre-operative). In multivariable regression models adjusting for clinical characteristics and insulin resistance, the strongest predictor of the change in NT-proBNP level 6 months after weight loss surgery was the change in weight ($p = 0.03$). Echocardiography showed a mean intra-individual reduction in LV mass index of 18% ($p < 0.001$), and mild improvements in systolic and diastolic function. In conclusion, we demonstrate that weight loss is associated with early and sustained increases in NT-proBNP concentrations, despite evidence of improved systolic and diastolic function. These findings suggest a direct, reversible relation between obesity and reduced natriuretic peptide levels.

Keywords

obesity; natriuretic peptides; surgery

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INTRODUCTION

The natriuretic peptides are secreted by the ventricles in response to increased cardiac wall stress. These molecules have a variety of actions, including natriuresis, vasodilation, and inhibition of cardiac hypertrophy and fibrosis. Individuals with obesity have lower levels of natriuretic peptides compared with lean individuals, despite having a high prevalence of conditions normally associated with elevated natriuretic peptides, such as hypertension, left ventricular (LV) hypertrophy, and increased plasma volume.¹ Accordingly, it has been suggested that obese individuals have a “natriuretic handicap”,² with a reduced natriuretic peptide response to cardiac wall stress. Because prior studies have been cross-sectional, it is unclear whether reduced plasma natriuretic peptide levels precede or follow obesity, and whether weight loss reverses the relative deficiency. Surgery has emerged as a highly effective means of achieving and maintaining significant weight loss in individuals with severe obesity. Therefore, we conducted a prospective study in individuals undergoing weight loss surgery to investigate the impact of weight loss on natriuretic peptide levels.

METHODS

Participants for this study were recruited from consecutive adult patients at the Massachusetts General Hospital Weight Center who were recommended for weight loss surgery (Roux-en-Y gastric bypass or gastric banding). Subjects were excluded if they experienced significant peri-operative complications such as myocardial infarction, persistent atrial fibrillation, sepsis, or gastrointestinal bleeding requiring blood transfusion > 2 units. Of the 161 subjects who were screened for the study and had pre- and post-operative blood draws, 17 did not undergo gastric bypass surgery, and 12 subjects withdrew consent. There was no significant difference in age or gender between the subjects who were included in the study and those that were not. This study was approved by the institutional human research committee and conducted in accordance with institutional guidelines. All participants provided written informed consent.

Medical history and medications were verified by chart review. Subjects were considered to have a history of coronary artery disease based upon a history of myocardial infarction, stable angina, or unstable angina documented in physician notes or a positive stress test or cardiac catheterization. The presence of heart failure, arrhythmia, and asthma was determined from physician notes. Similarly, subjects were considered to have obstructive sleep apnea (OSA) if this diagnosis was present in physician notes or if there was a documented positive sleep study. Subjects were evaluated at routinely scheduled clinic visits before surgery, and at early post-operative (1–2 months) and late post-operative (6 months) time points. These visits included a physical examination with calculation of body mass index (BMI) and measurement of blood pressure in the seated position. Phlebotomy was performed on fasting subjects for assessment of N-terminal pro-B-type natriuretic peptide (NT-proBNP), blood urea nitrogen, creatinine, glucose, insulin, erythrocyte sedimentation rate, and lipids. Insulin resistance was estimated by the homeostasis model assessment.³ Creatinine clearance was estimated using the method of Salazar and Corcoran for individuals with obesity.⁴

Blood samples were drawn in tubes containing EDTA and centrifuged within 30 minutes. Plasma was frozen at –80°C until measurement of NT-proBNP using a commercially available automated immunoassay⁵. The lower limit of detection of this assay was 5 pg/ml; samples below the limit were assigned a value of 5 pg/ml.

Subjects enrolled in the main study between March 2006 and April 2007 were invited to participate in the echocardiographic substudy if they did not have any of the following: prior

myocardial infarction, coronary artery disease, congestive heart failure or abnormal LV ejection fraction, valvular disease, hypertrophic cardiomyopathy, chronic obstructive lung disease, persistent or permanent atrial fibrillation, chronic renal insufficiency, or poorly-controlled hypertension (systolic blood pressure ≥ 170 mmHg or diastolic blood pressure ≥ 100 mmHg). Thirty patients agreed to participate in the substudy. Of these, 10 were excluded from analysis, 7 due to incomplete data and 3 others due to poor image quality. A significantly higher proportion of substudy subjects were male, compared with those not in the substudy. The two groups were otherwise similar (data not shown).

Participants underwent echocardiography before and 6 months after surgery. Echocardiograms were performed by a single investigator (ACT) and interpreted by the investigators (ACT, MSC) in a blinded fashion, with the pre- and post-operative echocardiograms randomly ordered. Heart rate and blood pressure were measured. Two-dimensional and pulse-wave and tissue Doppler imaging were performed in standard views using a commercial system (Vivid 7, GE Vingmed, Milwaukee, WI). Images were recorded digitally and off-line analysis was performed using commercial software (EchoPAC, GE Health). Measurements were averaged over 3 cardiac cycles. LV volumes were calculated using the biplane Simpson's method to determine LV ejection fraction.⁶ LV mass was estimated using the area-length method and indexed to height in meters.⁷ Early transmitral diastolic velocity (E) and early diastolic tissue Doppler velocity (Ea) at the lateral mitral annulus were measured.

Data were tested for normality using the Kolmogorov-Smirnov test. Normally-distributed variables were compared at different time points using the paired t-test or analysis of variance. The Wilcoxon paired signed ranks test or the Mann-Whitney U test was used when the assumption of normality was not met. Categorical variables were compared using the chi-square test. Statistical tests of interaction were performed to evaluate possible interactions of NT-proBNP levels with sex or type of surgery.

Multivariable linear regression models were fitted to examine predictors of change in NT-proBNP, including age, sex, change in creatinine clearance, HOMA-IR, anti-hypertensive and anti-diabetic medication use, and weight. Anti-hypertensive and anti-diabetic medication use were treated as dichotomous variables. Statistical analyses were performed using PASW Statistics version 17.0 (SPSS Inc., Chicago IL) and SAS version 9.1.3 (SAS Institute, Cary, North Carolina).

RESULTS

Tables 1 and 2 display the characteristics of the study sample at baseline and after surgery. There were no significant differences in baseline characteristics between patients who underwent Roux-en-Y gastric bypass surgery and those who underwent adjustable gastric banding (data not shown). None of the subjects were excluded for peri-operative complications.

The mean weight loss at the early and late post-operative time points was 14 ± 6 kg and 36 ± 12 kg (10% and 27% of baseline weight), respectively. As expected, after surgery, significant improvements were noted in blood pressure, insulin sensitivity, and lipid profiles, with corresponding decreases in medications (Table 2).

All subjects had NT-proBNP levels at all 3 time points. Levels of NT-proBNP were significantly higher at both post-operative time points compared with baseline (Figure 1). The average intra-individual increase in NT-proBNP compared to baseline was 3.4-fold at 1–2 months, and 5.0-fold at 6 months ($p < 0.001$ for both). Figure 2 illustrates the relation

between the weight lost and the increase in NT-proBNP at the late post-operative time point, compared to pre-operative values.

At baseline, 14 subjects had NT-proBNP levels at or below the detection threshold of 5 pg/ml. Among these, median NT-proBNP increased to 30.3 [IQR 13.3–52.9] and 42.3 [IQR 27.0–79.8] pg/ml at the two post-operative time points, with average intra-individual increases compared to baseline of >8.4-fold and >11.7-fold ($p<0.001$ for both). Two of 14 (14%) individuals continued to have NT-proBNP levels at or below 5 pg/ml at the first post-operative time point, but both had detectable levels by the late post-operative time point.

Men had lower median NT-proBNP levels compared with women (20.5 [IQR 8.3–41.0] vs. 33.9 [IQR 16.9–67.3] pg/ml, $p=0.03$) at baseline. This difference could not be attributed solely to their difference in BMI, as both sex and BMI were independent predictors of baseline NT-proBNP concentrations. Average intra-individual increases in NT-proBNP compared to baseline were similar between men and women at both post-operative time points (3.9 vs. 3.5-fold at 1–2 months, and 6.5 vs. 5.8-fold at 6 months; p for sex interaction >0.10). Men had higher BMI at all time points compared with women, but the percent change in BMI was similar between the two groups at the two post-operative time points (–11% vs. –10% at 1–2 months, $p=0.31$; –28% vs. –26% at 6 months, $p=0.10$).

The 7 patients who underwent adjustable gastric banding had similar BMI and NT-proBNP levels at baseline compared to those who underwent gastric bypass. At 6 months, the banded patients lost significantly less weight (16% vs. 27%, $p=0.02$). These patients tended to have smaller intra-individual increases in NT-proBNP over baseline values at the early (2.3 vs. 3.7-fold, for banding versus gastric bypass) and late post-operative time points (2.1 vs. 5.1-fold).

In multivariable linear regression models, the increase in NT-proBNP remained significant after adjusting for age, sex, change in blood pressure, change in HOMA-IR, and use of anti-hypertensive (including diuretics) and anti-diabetic medications. Only the change in weight predicted the magnitude of change in NT-proBNP at 6 months ($p=0.03$). This finding persisted when subjects with coronary artery disease ($n=6$) and heart failure ($n=1$) were excluded. For each standard deviation increment in the amount of weight lost, NT-proBNP levels increased by 40 pg/mL. The findings were unchanged by adjustment for changes in creatinine clearance.

Participants in the echocardiographic substudy had similar baseline values and intra-individual increases in NT-proBNP after surgery compared with those observed in the total cohort (for substudy subjects, 2.6- and 4.5-fold increase at the two post-operative timepoints, $p<0.001$ compared with baseline). Concomitantly, there was an 18% reduction in LV mass index and a 15% reduction in E/Ea ratio ($p<0.001$ and $p=0.001$, respectively). The LV ejection fraction was unchanged (data not shown).

DISCUSSION

We found that weight loss in individuals with marked obesity was associated with early and sustained increases in NT-proBNP concentrations. The increase in NT-proBNP was not attributable to the development of clinical conditions that typically upregulate NT-proBNP secretion, such as elevated blood pressure, cardiac hypertrophy, increased LV filling pressures, or ventricular dysfunction. Indeed, improvements in cardiac function were noted, consistent with prior reports of cardiac changes after weight loss.^{8–14} Our findings support the hypothesis that obesity directly promotes reduced natriuretic peptide levels, a condition that is reversed with weight loss.

The inverse relation between BMI and circulating natriuretic peptide levels has been observed in cross-sectional studies in diverse populations, including healthy individuals and patients with heart failure.^{15–19} Prior studies have attempted to examine the influence of weight loss on natriuretic peptide levels, with conflicting findings.^{20–24} Chainani-Wu et al observed an increase in BNP levels during a lifestyle intervention resulting in weight loss.²⁵ Two other studies of non-surgical weight loss reported little change²⁰ or a decrease in BNP,²¹ but the weight loss in these studies was relatively modest. A retrospective study of obese individuals found that a history of gastric bypass surgery predicted higher natriuretic peptide levels.²² Two small longitudinal studies have investigated natriuretic peptide levels in surgically treated patients. van Kimmenade et al. reported that NT-proBNP increased among 22 patients at 3 and 6 months after weight loss surgery,²³ while Hanusch-Enserer et al. observed a *decrease* at 12 months in 34 patients who had undergone gastric banding.²⁴ In the latter study, NT-proBNP levels were higher at baseline in obese patients than in normal controls, and the decrease in mean BMI was modest. Thus, the discordant results may be due to differences in the study populations, or in the magnitude and temporal patterns of weight loss.

Obesity-associated renal hyperfiltration resolves following weight loss surgery.²⁶ A decrease in creatinine clearance could lead to an increase in natriuretic peptide levels post-operatively. While there was a minor decrease in estimated creatinine clearance between the early and late post-operative time points in our study, the increase in NT-proBNP was detectable prior to any change in creatinine clearance and of substantially larger magnitude. Furthermore, the change in NT-proBNP remained highly significant in analyses adjusting for changes in creatinine clearance.

The mechanisms underlying the relative natriuretic peptide deficiency in obesity are not known. Because natriuretic peptide clearance receptors (NPR-C) are found on adipocytes, and because both elevated NPR-C expression and increased secretion of neutral endopeptidases have been demonstrated in patients with obesity,^{2,27} increased peripheral clearance of natriuretic peptides in obesity has been postulated. However, NT-proBNP is not cleared by either NPR-C or neutral endopeptidases. Thus, the fact that both mature B-type natriuretic peptide and NT-proBNP are reduced implies an effect at the level of natriuretic peptide synthesis or release. This is supported by an animal model of obesity in which reduced ventricular expression of natriuretic peptides has been observed.²⁸

Strengths of the present study include the large sample size for a surgical weight loss study, the large magnitude of weight loss achieved, the prospective study design, careful assessment of potential confounders and the use of multiple time points. Several limitations of this study deserve mention. Echocardiography was performed on a small subset of participants. The purpose of the substudy was to exclude marked deterioration in ventricular function that would account for the observed increase in natriuretic peptide levels. If anything, we observed improvements in LV mass and diastolic function, consistent with prior reports.^{8–14} This supports the hypothesis that changes in natriuretic peptide levels were not secondary to underlying cardiac changes, but attributable to the weight loss itself. Previous studies suggest that weight loss surgery reduces the apnea hypopnea index in individuals with OSA.²⁹ Because we did not obtain polysomnographic data before and after surgery, we cannot ascertain whether or not there was an improvement in OSA with weight loss in this study. However, we would expect that resolution of or improvement in OSA would lead to reduced right ventricular wall stress, which would lower rather than raise NT-proBNP levels. Weight loss surgery results in the loss of both lean and fat mass,³⁰ although the majority of weight loss is attributable to loss of fat mass. It has been suggested that natriuretic peptide levels may be more strongly associated with lean mass than fat mass.¹⁹ We cannot exclude the possibility that changes in lean mass contributed to the observed

changes in natriuretic peptide levels. Follow-up data were available only up to 6 months, when subjects may not have reached the point of maximal weight loss. Additionally, a proportion of subjects in this study were taking medications which may impact natriuretic peptide levels,²⁷ but adjustment for anti-hypertensive medication use did not alter the results.

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Figure 1.

Plasma NT-proBNP levels after weight loss surgery.

* $p < 0.05$ compared with baseline NT-proBNP

† $p < 0.05$ compared to early post-operative NT-proBNP

Early post-operative time point = 1–2 months

Late post-operative time point = 6 months

Figure 2. Percent weight loss vs. fold increase in NT-proBNP at the late post-operative time point (6 months) compared to baseline.

Table 1

Baseline clinical characteristics of the study population

Characteristic	Baseline (n=132)
Age (years)	46.1±11.3
Female	85 (64%)
African-American	9 (7%)
Hispanic	7 (5%)
Asian-American	1 (0.7%)
Bariatric Procedure	
• Open Roux-en-Y	11(8%)
• Laparoscopic Roux-en-Y	114(86%)
• Adjustable gastric banding	7 (5%)
Hypertension	94 (71%)
Diabetes mellitus	56 (42%)
Coronary artery disease [†]	6 (4.5%)
Heart failure [‡]	1 (0.7%)
Arrhythmia [‡]	3 (2%)
Asthma [‡]	25 (19%)
Obstructive sleep apnea [§]	86 (65%)
Smoker	
• Current	7 (5%)
• Former	57 (43%)
• Never	68 (52%)

[†]History of myocardial infarction, stable angina, or unstable angina documented in physician notes or a positive stress test or cardiac catheterization.

[‡]Determined from physician notes.

[§]Diagnosis present in physician notes or documented positive sleep study.

Table 2

Clinical and serological characteristics of the study population before and after weight loss surgery

Variable	Pre-Op	Early Post-Op	Late Post-Op	p value (Early vs. Pre-Op)	p value (Late vs. Early)
Weight (kg)	129 [115–151]	116 [37–47]	95 [83–111]	<0.001	<0.001
Body mass index (kg/m ²)	45 [42–52]	41 [37–47]	33 [30–38]	<0.001	<0.001
Beta-blocker	25%	29%	22%	0.49	0.20
Angiotensin converting enzyme inhibitor or angiotensin receptor blocker	41%	20%	20%	<0.001	0.99
Diuretic	30%	6%	6%	<0.001	0.99
Calcium channel blocker	9%	5%	5%	0.23	0.78
Insulin	9%	4%	0.8%	0.08	0.10
Oral anti-diabetic medications	32%	8%	8%	<0.001	0.82
Statin or other anti-lipid medication	35%	25%	21%	0.08	0.47
Heart rate (bpm)	80 [74–84]	72 [66–79]	72 [66–76]	<0.001 [†]	0.005 [†]
Systolic blood pressure (mm Hg)	124 [118–135]	116 [109–124]	118 [108–126]	<0.001 [‡]	0.48 [‡]
Diastolic blood pressure (mm Hg)	80 [74–84]	76 [70–80]	75 [70–80]	<0.001 [‡]	0.17 [‡]
Blood urea nitrogen (mg/dl)	15 [11–18]	10 [8–13]	12 [10–15]	<0.001	<0.001
Creatinine clearance (ml/min)	127 [105–148]	126 [104–154]	114 [96–138]	0.099	<0.001
Fasting insulin (uIU/ml)	16.0 [11.0–25.0]	9.7 [6.8–14]	5.0 [3.0–8.0]	<0.001 [§]	<0.001 [§]
Fasting glucose (mg/ml)	101 [90–133]	93 [87–102]	88 [83–94]	<0.001	<0.001
Homeostasis model assessment of insulin resistance	4.2 [2.5–7.4]	2.3 [1.6–3.7]	1.0 [0.7–1.8]	<0.001 [§]	<0.001 [§]
Erythrocyte sedimentation rate (mm/hr)	24 [15–41]	21 [13–30]	15 [10–24]	0.002	<0.001
Total cholesterol (mg/dl)	190 [162–208]	154 [130–173]	156 [141–179]	<0.001	0.001
Low-density lipoprotein (mg/dl)	103 [89–123]	83 [65–103]	83 [68–97]	<0.001	0.45
High-density lipoprotein (mg/dl)	49 [42–56]	39 [34–48]	52 [44–61]	<0.001	<0.001
Triglycerides	133 [99–197]	123 [93–149]	92 [76–129]	<0.001	0.002

Values for continuous variables represent median [25th percentile, 75th percentile]

[†] n=93;[‡] n=104;

§ n=54;
// n=80

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