Relation of B-Type Natriuretic Peptide Levels to Body Mass Index After Comprehensive Lifestyle Changes

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Cross-sectional studies have reported inverse associations of B-type natriuretic peptide (BNP) with the body mass index (BMI). We evaluated whether changes in the BMI are associated with changes in BNP. A nested prospective cohort study of a lifestyle intervention (low-fat, whole-foods diet, exercise, stress management, and social support) was conducted. BNP, BMI, and other biomarkers were measured at baseline and 3 months. A total of 131 subjects, 56 with coronary heart disease (CHD) and 75 at high risk, with ≥3 CHD risk factors and/or diabetes mellitus, were enrolled. At 3 months, the mean BMI had decreased (34.4 to 31.7 kg/m^2, $p < 0.001$), BNP had increased (median 18 to 28 pg/ml, $p < 0.001$), and low-density lipoprotein, C-reactive protein, apolipoprotein B (all $p < 0.002$), and angina frequency ($p = 0.017$) and severity ($p = 0.052$) had decreased. The subjects' physical limitations had decreased and their physical functioning had improved (all $p < 0.001$). The percentage of change in BNP was inversely associated with the percentage of change in insulin ($r = -0.339$, $p = 0.005$, $n = 63$ nondiabetics). It was also inversely associated with the percentage of change in BMI ($r = -0.28$, $p = 0.002$, $n = 116$), and this association remained significant ($p = 0.029$) in multiple regression analyses controlling for age, gender, CHD, diabetes mellitus, percentage of change in lifestyle index, and β-blocker use. The metabolic changes related to adipose tissue lipolysis could explain these findings. In conclusion, BNP increased in subjects experiencing weight loss while following a lifestyle intervention, and angina pectoris, physical limitations, and other CHD risk factors decreased. Therefore, in this context, increasing BNP might not indicate worsening disease or a worsening prognosis. Thus, the proposed use of BNP in monitoring disease progression should take into account changes in the BMI during the same period. **(Am J Cardiol 2010;105:1570–1576)**

Circulating B-type natriuretic peptide (BNP) levels aid in the diagnosis of acute congestive heart failure (HF) and might be useful in establishing the prognosis of patients with HF, with increased levels predictive of increased mortality.[1,2] Periodic BNP measurement has been proposed for the purpose of monitoring the response to therapy for HF and for its prognostic value.[1,3] However, BNP levels are influenced by other factors such as age, gender, diabetes, and impaired renal function.[1] In addition, an inverse association of BNP level with the body mass index (BMI) has been reported in cross-sectional studies.[4–6] Also, BMI greatly influences the sensitivity of BNP in the diagnosis of acute HF.[7] A study of 22 patients, who had undergone bariatric surgery for obesity, found that during the subsequent 6 months, the BMI had decreased significantly and the BNP and N-terminal pro BNP levels increased significantly.[8] The present report describes the changes in BNP in relation to changes in BMI in a cohort of 125 patients who underwent lifestyle changes during a 3-month period and showed improvement in other cardiac risk factors.

Methods

A prospective cohort study nested within a larger cohort participating in the health insurance administered Multisite Cardiac Lifestyle Intervention Program was conducted. The participating hospital sites included the Charleston Area Medical Center and West Virginia University Hospitals (West Virginia) and the Hamot Medical Center, Jameson Health System, and Jefferson Regional Medical Center (Pennsylvania). All the sites provided institutional review board approval, and each participant provided written in-

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Table 1
Baseline patient characteristics by coronary heart disease (CHD) status and gender

Characteristic	Diagnosed With CHD (n = 54)		High Risk of CHD (n = 71)	
	Men (n = 35)*	Women (n = 19)*	Men (n = 16)*	Women (n = 55)*
Age (years)	58.2 ± 7.6	59.9 ± 7.0	57.3 ± 7.8	56.1 ± 9.8
White	32/35 (91%)	19/19 (100%)	15/16 (93%)	51/55 (92%)
Previous cigarette smoker	15/35 (43%)	5/19 (26%)	8/16 (50%)	19/55 (34%)
Diabetes mellitus	8/35 (22%)	7/19 (36%)	10/16 (62%)	29/55 (52%)
Medications				
Nitrate	3/35 (8%)	1/19 (5%)	0/16 (0%)	0/55 (0%)
β Blocker	25/35 (71%)	12/19 (63%)	3/16 (18%)	12/55 (22%)
Angiotensin-converting enzyme inhibitor	16/35 (46%)	5/19 (26%)	4/16 (25%)	9/55 (16%)
Lipid-lowering medication	32/35 (91%)	16/19 (84%)	9/16 (56%)	20/55 (36%)
Antiplatelet	34/35 (97%)	16/19 (84%)	6/16 (37%)	15/55 (27%)
Body mass index (kg/m^2)	32.14 ± 6.23	32.4 ± 6.6	36.5 ± 6.8	35.4 ± 7.0
Total cholesterol (mg/dl)	157 (130–189)	171 (154–202)	167 (153–209)	191 (170–228)
Low-density lipoprotein cholesterol (mg/dl)	90 (66–110)	89 (73–106)	91 (76–126)	112 (92–139)
High-density lipoprotein cholesterol (mg/dl)	39 (33–45)	44 (38–61)	42 (39–47)	45 (37–50)
B-type natriuretic peptide (pg/ml)	30 (13–50)	27 (16–94)	15 (8–20)	16 (9–27)
Insulin (μU/L)	13 (9–24)	13 (9–26)	18 (12–33)	15 (9–24)

Data are presented as mean ± SD, n (%), or median (interquartile range).
* Because of missing data, n for individual variables ranged from 34 to 35 for men with CHD, 17 to 19 for women with CHD, 15 to 16 for high-risk men, and 53 to 55 for high-risk women.

formed consent before enrollment. The present study was registered at the Clinicaltrials.gov Website (NCT00820313).

The details on the eligibility criteria for the Multisite Cardiac Lifestyle Intervention Program and the lifestyle intervention have been previously published.[9,10] In brief, the inclusion criteria were coronary heart disease (CHD) or type 1 or type 2 diabetes or a high-risk status for CHD. The diagnosis of CHD was determined by one of the following criteria: (1) noninvasive testing demonstrating myocardial ischemia, (2) cardiac catheterization, (3) eligibility for coronary artery bypass grafting/percutaneous transluminal coronary angioplasty and seeking a clinical alternative, or (4) a history of coronary artery bypass grafting/percutaneous transluminal coronary angioplasty/stent implantation or myocardial infarction. The criteria for the high-risk category were (1) a family history of premature CHD (first-degree relative [men <55 years old and women <65 years old] with myocardial infarction or sudden cardiac death); or (2) men aged >45 years (women aged >55 years) with ≥2 of the following risk factors: current cigarette smoking (within the past 5 years), hypertension (blood pressure >140/90 mm Hg or taking antihypertensive medication), a low high-density lipoprotein cholesterol level (<35 mg/dl) or taking lipid-lowering medications, elevated lipoprotein (a) >30 mg/dl, total cholesterol >240 or taking lipid-lowering medications, low-density lipoprotein cholesterol >160 mg/dl or taking lipid-lowering medications, high-sensitivity C-reactive protein level of 3 to 10 mg/L, BMI >30 kg/m^2, and/or insulin-resistant state (metabolic syndrome X).[11] The primary exclusion criteria included (1) ischemic left main CHD, with obstruction >50%; (2) >70% proximal left anterior descending artery disease and proximal left circumflex artery disease and an ejection fraction of <50%; (3) unstable angina pectoris; (4) a history of exercise-induced ventricular tachycardia or third-degree heart block without evidence of current stability; (5) coronary artery bypass grafting or myocardial infarction within the previous 4 weeks; (6) HF with functional limitations; (7) current tobacco use; (8) uncontrolled malignant ventricular arrhythmia; and (9) impaired cognitive function (ie, dementia or delirium).

The guidelines for the lifestyle intervention included approximately 10% of daily calories from fat, 15% from protein, and 75% from complex carbohydrates. The exercise portion included a minimum of 3 hours per week of aerobic exercise, with a minimum of 30 minutes per session exercising within the prescribed target heart rates and/or perceived exertion levels, strength training activities a minimum of 2 times per week. Also, the participants were to practice stress management techniques for ≥1 hour per day. Finally, the participants were required to attend weekly group support sessions led by a licensed mental health professional twice each week.

The demographic information and medical history were obtained at baseline by interview and a review of the medical records. Clinical measurements, blood test results, and questionnaires were collected at baseline and at 3 months.[9] A fasting blood sample was drawn for laboratory analyses, which included total cholesterol, high-density lipoprotein cholesterol, triglycerides, low-density lipoprotein cholesterol, high-sensitivity C-reactive protein, fibrinogen, lipoprotein (a), homocysteine, oxidized low-density lipoprotein, insulin, BNP, and nuclear magnetic resonance Lipoprofile assays for very-low-density lipoprotein, low-density lipoprotein, and high-density lipoprotein particle concentrations and particle size. In addition, the fasting blood glucose and hemoglobin A1c levels were tested for all patients with diabetes and for a subset of patients without diabetes. Self-administered questionnaires were completed by the participants to assess their exercise and stress man-

Table 2
Lifestyle factors and coronary heart disease (CHD)-related clinical measurements and risk factors at baseline and 3 months after comprehensive lifestyle intervention

Variable	Baseline	3 Months	p Value
Fat intake (% total calories)	29.1 (21.0–35.8)	10.5 (9.0–12.1)	<0.001*
Dietary cholesterol (mg)	152 (91–250)	7 (3–11)	<0.001*
Dietary fiber (g)	22 (14–30)	34 (28–41)	<0.001*
Exercise (minutes/week)	0 (0-115)	212 (180–275)	<0.001*
Stress management† (minutes/week)	0 (0-230)	420 (0-630)	<0.001*
Group session attendance (% classes attended)	NA	100 (92–100)	NA
Body mass index (kg/m^2)	34.2 ± 6.8	31.8 ± 6.2	<0.001*
Systolic blood pressure (mm Hg)	127 ± 15	117 ± 11	<0.001*
Diastolic blood pressure (mm Hg)	77 ± 8	72 ± 7	<0.001*
Functional capacity (METS)	7.6 (5.6–10.0)	10.1 (7.8–12.5)	<0.001*
Angina frequency‡	0.0 (0.0–5.0)	0.0 (0.0–1.0)	0.017*
Angina severity‡	0.0 (0.0–2.0)	0.0 (0.0–3.0)	0.052
Total cholesterol§ (mg/dl)	180 (153–205)	161 (143–198)	<0.001*
Low-density lipoprotein§ (mg/dl)	103 (78–124)	81 (64–112)	<0.001*
High density lipoprotein§ (mg/dl)	43 (37–51)	37 (33–44)	<0.001*
Triglycerides§ (mg/dl)	129 (95–185)	125 (80–176)	0.070
B-natriuretic peptide§ (pg/ml)	18.0 (11.0–35.0)	28.0 (14.0–52.3)	<0.001*
C-reactive protein§ (mg/dl)	2.0 (0.8–5.1)	1.4 (0.6–3.6)	<0.001*
Apolipoprotein B§ (mg/dl)	87 (69–109)	84 (65–99)	0.001*
Insulin (μU/L)	14.5 (9.7–25.2)	12.0 (9.0–18.3)	<0.001*
Role physical,‡ SF-36	75 (25–100)	100 (75–100)	<0.001*
Physical functioning,‡ SF-36	80 (55–90)	90 (80–95)	<0.001*
Physical component score,‡ SF-36	47 (39–52)	52 (46–56)	<0.001*

Data are presented as mean ± SD, median (interquartile range), or median (full range).

Because of missing data, n for individual variables ranged from 120 to 122.

* Statistically significant.

† Full range reported because of low baseline values.

‡ Angina frequency: 0 (no angina symptoms) to 6 (constant angina symptoms); angina severity, 0 (mild angina pain) to 4 (severe angina pain); role physical, 0 (very physically limited) to 100 (not at all physically limited); physical functioning, 0 (very poor) to 100 (very good); physical component score, 0 (very poor) to 100 (very good); full range reported because of low baseline and 3-month values.

§ p Values for biomarkers based on paired-sample *t* tests using log-transformed values.

SF-36 = Medical Outcomes Study Short Form 36-item Health Survey.

agement duration and frequency per week, psychosocial factors, and cognitive function.[9] The angina frequency and angina severity were assessed.[9,12] The participants also completed 3-day food diaries. These were entered into the software program Food Processor, version 10x (ESHA Research, Salem, Oregon) by registered dieticians for nutrient analysis.

Data analysis was conducted using the Statistical Package for Social Sciences, version 14.0 (SPSS, Chicago, Illinois). Continuous data are presented as the mean ± SD for normally distributed variables and as the median and interquartile range or range for non-normally distributed variables. For significance testing, *t* tests and the Mann-Whitney rank sum test were used. Chi-square tests were used to evaluate differences in proportions between groups. A 2-way independent analysis of variance was conducted to evaluate differences in baseline BNP levels by gender and CHD status and to evaluate the interaction of gender and CHD status. Changes from baseline were tested for significance using paired *t* tests for normally distributed variables and the Wilcoxon signed rank test for non-normal variables. A diet adherence score and a lifestyle adherence score were calculated using the same formula as previously described.[13] Higher scores indicated better adherence to the recommendations. The association between the continuous variables was evaluated using linear regression analysis. Pearson's r and associated 2-sided p values were computed. The BNP and insulin values had a non-normal distribution, and a log transformation for the baseline and 3-month values was done. Multiple linear regression analyses were conducted with the change scores for log transformed BNP values (3-month value [time 2] minus the baseline value [time 1]: log 10 [time 2/time 1]) as the dependant variable and age, gender, CHD, diabetes, percentage of change in BMI, percentage of change in lifestyle index, and β-blocker use as independent variables. The change in insulin was considered likely to be on the pathway of the association between the change in BNP and the change in BMI; therefore, a separate regression model was created with the change score log BNP as the dependant variable and the change score log insulin, β-blocker use, and insulin*β blocker as independent variables to evaluate the effect modification of this association by β-blocker use. The percentage of change in BMI was recoded as an ordinal variable with 4 categories. A 1-way analysis of variance test was done to test for differences in the percentage of change in BNP between these categories, using Bonferroni correction for multiple comparisons.

Results

A total of 131 participants (59.2% women and 43.1% with diabetes), 56 with pre-existing CHD (37.5% women and 27.3% with diabetes) and 75 at high risk of CHD with ≥3 CHD risk factors and/or diabetes (76% women and 54.7% with diabetes) were enrolled from January 2007 to March 2008. Of the 131 participants, 6 participants had withdrawn from the study by the 3-month follow-up point. The baseline patient characteristics are summarized in Table 1, and a subset of variables measured at baseline and at 3 months is summarized in Table 2.

At baseline, 6 participants had a healthy BMI of 18.5 to 24.9 kg/m^2, 27 were overweight with a BMI of 25 to 29.9 kg/m^2, and 88 were obese with a BMI of ≥30 kg/m^2. An inverse association between the baseline BNP levels and baseline BMI was observed; however, this was not statistically significant ($r = -0.111$, $p = 0.223$, $n = 123$). The BNP levels were significantly greater in both men and

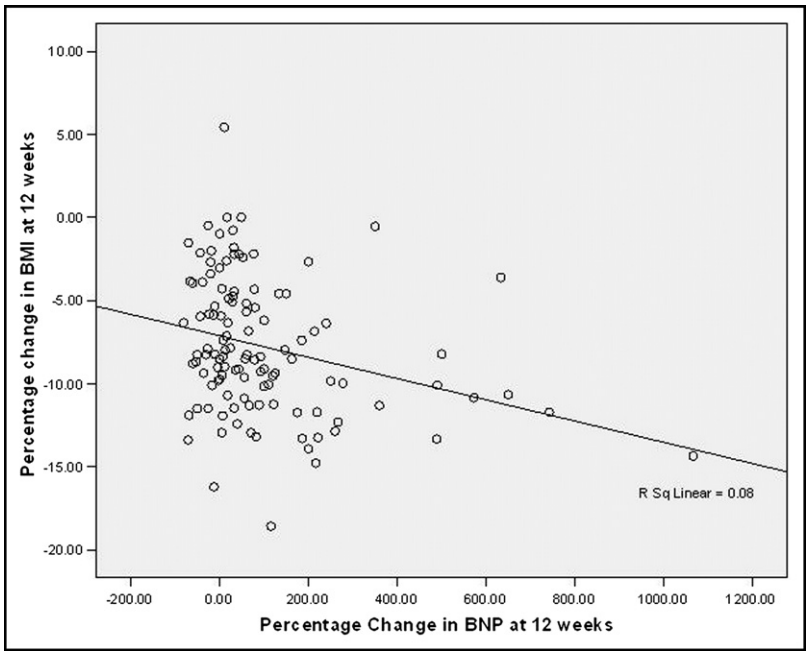

Figure 1. Scatterplot demonstrating inverse association between percentage of change in BMI at 12 weeks and percentage of change in BNP levels at 12 weeks. Pearson's r for this association = −0.283 (p = 0.002, n = 116).

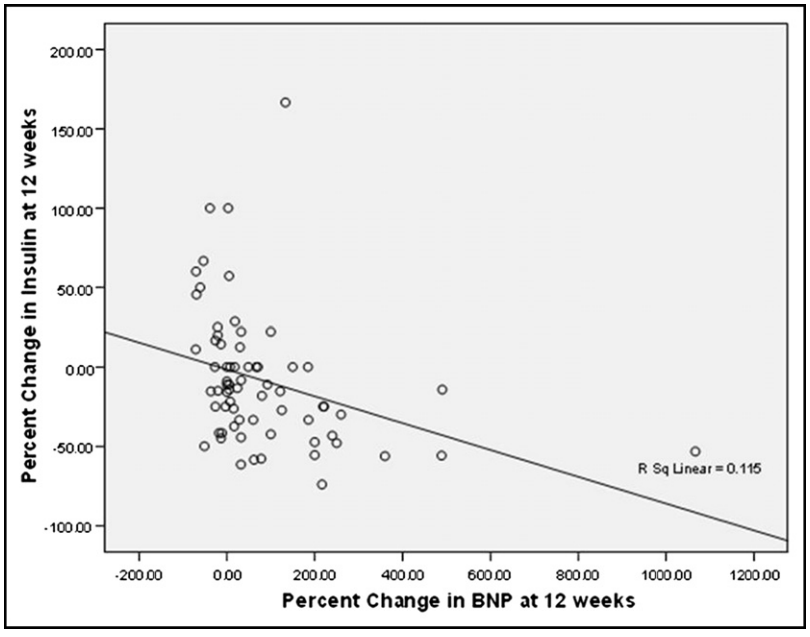

Figure 2. Scatterplot demonstrating inverse association between percentage of change in insulin levels at 12 weeks and percentage of change in BNP levels at 12 weeks. Pearson's r for this association = −0.339 (p = 0.005, n = 68; patients with diabetes were excluded).

women with CHD than in those in the high-risk group ($p < 0.001$). The BNP levels did not differ significantly ($p = 0.328$) between men and women, and the interaction of gender and CHD status was not significant ($p = 0.714$). The baseline BNP levels were higher in patients taking β-blocker medication in both the CHD group (median 39 vs 16 pg/ml, $p = 0.001$) and the high-risk group (median 19 vs 15 pg/ml, $p = 0.062$). At baseline, no significant association between BNP and insulin ($r = -0.045$, $p = 0.621$, $n = 122$), BNP and fasting blood glucose ($r = -0.062$, $p = 0.528$, $n = 106$), or BNP and hemoglobin A1c ($r = 0.076$, $p = 0.545$, $n = 65$) was found. As expected, a strong positive association was seen between the baseline insulin and fasting blood glucose ($r = 0.423$, $p < 0.001$, $n = 105$), and baseline insulin and hemoglobin A1c ($r = 0.386$, $p = 0.002$, $n = 65$).

The 3-month data showed a significant reduction in the mean BMI (34.2 to 31.7 kg/m^2, $p < 0.001$; Table 2).

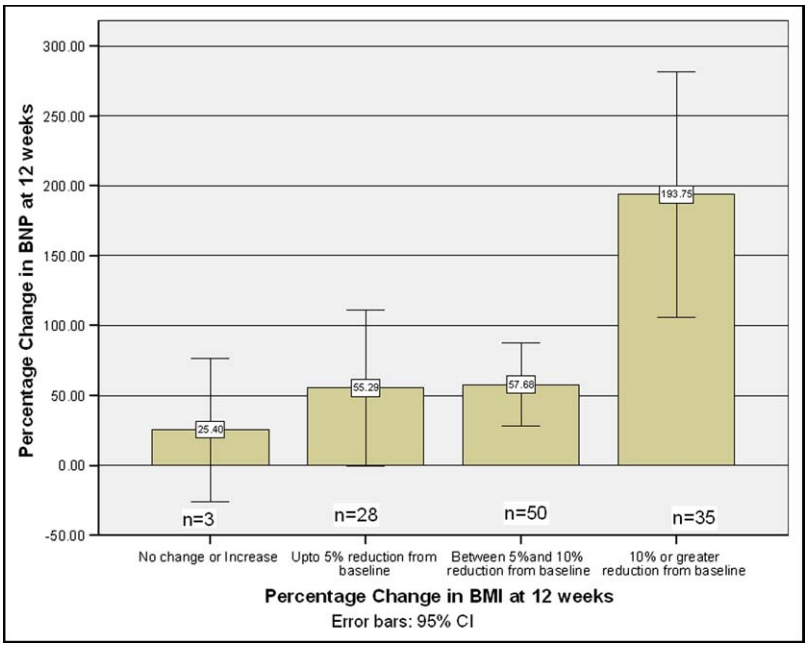

Figure 3. For 4 ordinal BMI categories, mean percentage of change in BNP in group 1 (decrease in BMI >10%, n = 35), group 2 (5% to 10% decrease in BMI, n = 50), group 3 (≤5% reduction in BMI, n = 28), and group 4 (no change or an increase in BMI, n = 3) was 193.7%, 57.6%, 55.2%, and 25.4%, respectively [F(3,27.74) = 5.284, p = 0.007, p for linear trend = 0.001, group 1 versus group 2, p 0 003; and group 1 vs group 3, p = 0.012].

The bivariate association between the percentage of change in BMI and the percentage of change in the lifestyle index score was r = −0.152 (p = 0.109, n = 112). BNP increased from a median of 18 to 28 pg/ml (p <0.001). On the bivariate analyses, the percentage of change in BNP was significantly associated with the percentage of change in lifestyle index score (r = 0.361, p <0.001, n = 111), with the percentage of change in the diet score (r = 0.264, p = 0.005, n = 112) and with the change in exercise score (3-month value minus baseline value, r = 0.269, p = 0.003, n = 118) but not with the change in the stress management score (3-month value minus baseline value, r = 0.061, p = 0.513, n = 118).

The percentage of change in BNP was inversely associated with the percentage of change in BMI (r = −0.28, p = 0.002, n = 116; Figure 1). This association did not change after exclusion of the outlier value of 1,066, −53.33 (r = −0.242, p = 0.009, n = 115). This association remained significant (p = 0.029) on multiple regression analyses controlling for age, gender, CHD, diabetes, percentage of change in lifestyle index, and β-blocker use. An inverse association was found between the percentage of change in BNP and the percentage of change in insulin (r = −0.339, p = 0.005, n = 68; Figure 2). This association did not differ significantly by β-blocker use, with a nonsignificant interaction term for β-blocker*percentage of change in insulin. Patients with diabetes were excluded from this analysis, because of the expected influence of exogenous insulin and oral hypoglycemic agents on the measured insulin levels. For the 4 ordinal BMI categories, significant differences in the mean percentage of change in BNP were seen among groups (Figure 3). At 3 months, the bivariate correlation between BNP and BMI was r = −0.060 (p = 0.514, n = 119).

Discussion

This is the first report on the changes in BNP in relation to the changes in BMI after 3 months of following a comprehensive lifestyle intervention. Our baseline findings are consistent with other reports showing an inverse association of BMI with BNP level.[4–6] Possible explanations previously suggested have included a decrease in the secretion of BNP[14] or an increase in the clearance of BNP from the bloodstream with an increasing BMI. The clearance of BNP is by binding to the cell surface clearance receptor natriuretic peptide receptor-C (NPR-C) and by enzymatic degradation by neutral endopepdidase.[15] Both are present on adipocytes;[16,17] therefore, it has been postulated that the increase in adipose tissue in obesity might result in increased clearance of BNP.[17]

Adipose tissue lipolysis is strongly regulated by insulin (antilipolytic) and catecholamines (lipolytic). More recently, it has been found that natriuretic peptides, including BNP, have lipolytic activity.[18] At 3 months, we found an inverse association in the percentage of change in BNP with the percentage of change in BMI and the percentage of change in insulin. The increase in adipose tissue lipolysis in response to the ongoing lifestyle changes at 3 months might explain both the increase in BNP and the associated decrease in insulin. The study participants, on average, reduced their caloric intake by 382 cal/day and increased their exercise levels by 152 min/week from baseline and demonstrated a mean reduction in weight of 7.6 kg at 3 months. A dramatic reduction in the NPR-C receptors in rats has been demonstrated after a period of fasting.[19] Also, it was found that the lipolytic effects of BNP are enhanced after a low-calorie diet in a study of obese women.[20] Decreased expression of NPR-C with a reduction in caloric intake, together

with the overall reduction in NPR-C receptors owing to a decrease in adipose tissue mass, might explain the observed increase in BNP in our study. In addition, although the baseline BNP levels correlated inversely with the baseline BMI and the changes in BNP correlated inversely with the changes in BMI, the cross-sectional correlation between the BNP levels at 12 weeks and BMI at 12 weeks was weak. This also supports the hypothesis that at the 12-week measurement in this cohort, the BNP levels were influenced by ongoing metabolic changes initiated by the comprehensive lifestyle intervention.

The BNP levels can be transiently elevated for several hours after exercise in both healthy subjects and patients with CHD.[21,22] In our study, the percentage of change in BNP was significantly associated with the change in exercise score, even after controlling for the percentage of change in BMI. Because the participants in the present study had had a fasting blood sample taken, it is unlikely that they had exercised much in the hours before the blood sampling. However, this information was not collected; therefore, it was not possible to quantify the contribution of this transient elevation to the observed increase in BNP in the present study.

Evaluating BNP changes by β-blocker use in the present study provided an opportunity to assess the postulated compensatory increase in natriuretic peptides[23] as an alternative pathway for lipolysis in patients taking β-blocker medications (owing to blockade of catecholamine-induced lipolysis by adipose tissue β-adrenergic blockage by these medications). β-Blocker medications can result in an increase in BNP levels,[24] and patients with CHD who are taking β blockers have shown a greater exercise-associated increases in atrial natriuretic peptide and BNP.[25] In our study, at baseline, the BNP levels were greater in the patients taking β blockers in both the CHD group and the high-risk group. However, the changes in BNP at 3 months did not differ significantly by β-blocker use. A limitation of the present study was that relevant factors, including N-terminal pro BNP, testosterone, and others, were not measured, because we have reported on incidental findings from a study that was not designed to investigate the underlying mechanisms.

However, the findings are of clinical significance, because the observed changes in BMI and BNP occurred in a cohort that experienced an improvement in the symptoms of heart disease as measured by the frequency and severity of angina, a decrease in physical limitations, and an increase in physical functioning. They also experienced an increase in functional capacity and a reduction in the levels of biomarkers of heart disease, such as low-density lipoprotein cholesterol, C-reactive protein, and apolipoprotein B, suggesting that, in this context, increasing BNP levels might not indicate worsening disease or a worsening prognosis. Thus, the proposed use of BNP to monitor disease progression should take into account the changes in BMI during the same period.

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