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Relation of Visceral Adiposity to Circulating Natriuretic Peptides in Ambulatory Individuals

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Abstract

Natriuretic peptides have important roles in the regulation of vasomotor tone, salt homeostasis, and ventricular remodeling. Lower natriuretic peptide levels observed in obese individuals may underlie the greater cardiovascular risk associated with obesity. Thus, the aim of this study was to determine whether lower natriuretic peptide levels in obesity are attributable to differences in regional fat distribution. We investigated the relationship of plasma N-terminal pro-B-type

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natriuretic peptide (N-BNP) with regional adiposity in 1,873 community-based individuals (46% women; mean age 45 years). Subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) volumes were measured by multi-detector computed tomography. In sex-specific, multivariable analyses adjusting for age and blood pressure, log N-BNP was inversely associated with VAT in both men (β −0.11, P<0.001) and women (β −0.19, P<0.001). Log N-BNP was inversely associated with SAT in women only (β −0.14, P<0.001). In models containing both VAT and SAT, only VAT was significantly associated with log N-BNP (men, β −0.137, P<0.001; women, β −0.184, P<0.001). VAT remained associated with log N-BNP even after adjustment for body mass index and waist circumference (β −0.119, P<0.001), and in analyses restricted to non-obese individuals (β −0.114; P<0.001). Adjustment for insulin resistance attenuated the associations of N-BNP with both VAT and SAT. In conclusion, this study demonstrates that circulating N-BNP is related to variation in regional and particularly visceral adiposity. These findings suggest that excess visceral adiposity and concomitant hyperinsulinemia may contribute to the natriuretic peptide "deficiency" observed in obesity.

Keywords

adiposity; natriuretic peptides; cardiovascular risk

It is uncertain whether the link between obesity and natriuretic peptides is attributable to differences in fat mass, as most studies have used anthropometric measures to characterize obesity. One prior study noted that B-type natriuretic peptide (BNP) levels were inversely correlated with *lean* body mass, measured by DEXA.[1] Other studies have proposed that factors such as increased renal clearance of BNP[2] or confounding by clinical characteristics[3] may account for the low natriuretic peptide levels in obesity. Furthermore, it is unknown whether differences in the regional fat distribution are related to circulating natriuretic peptide levels. The two major fat compartments are subcutaneous and visceral, with the latter recognized as the more metabolically active and, hence, pathogenic fat depot.[4] Thus, we investigated the cross-sectional relations between plasma N-terminal pro-BNP (N-BNP) and visceral and subcutaneous adiposity in a large, community-based sample. Regional adiposity was assessed using multi-detector computed tomography (CT), which is capable of reliably characterizing subcutaneous and visceral adipose tissue volumes.[4]

METHODS

Beginning in 2002, Third Generation Study participants (N=4,095) of the Framingham Heart Study who had at least one parent in the Framingham Offspring Study were enrolled and underwent standard clinic examinations. A subset of 2,111 Third Generation participants also underwent multi-detector CT scans between 2002 and 2005 at their first examination.[4] Inclusion in this subset was weighted toward Framingham Heart Study participants who resided in the greater New England area.[4] Participants were eligible if they weighed <159 kg (350 pounds) and were men ≥35 years of age or women ≥40 years of age and not pregnant. Of the Third Generation participants who underwent CT scans, 1,873 (89%) had abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) volumes measured, were free of diabetes, had no history of cardiovascular disease or atrial fibrillation, had a serum creatinine ≤106 umol/L (1.2 mg/dL), and had N-BNP measured. This sample was used in analyses relating N-BNP with measures of regional adiposity for this study.

All study participants underwent a routine physical examination, with medical history, and laboratory assessment of cardiovascular disease risk factors. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Hypertension was defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or

use of antihypertensive treatment. Renal function was estimated using the estimated glomerular filtration rate (eGFR).[5] Metabolic syndrome was defined according to the 2005 American Heart Association criteria[6] as the presence of at least 3 of the following clinical risk factors: waist circumference ≥40 inches in men or ≥35 inches in women; serum triglycerides ≥150 mg/dL; HDL cholesterol <40 mg/dL in men or <50 mg/dL in women or taking medication for low HDL cholesterol; systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or taking antihypertensive medication; and, fasting glucose ≥100 mg/dL.[6] Alcohol use was defined as >14 drinks per week for men or >7 drinks per week for women. The institutional review boards of the Boston University School of Medicine and Massachusetts General Hospital approved this study protocol. All participants provided written informed consent.

Plasma samples were obtained in the morning after an overnight fast and frozen at −70°C. Plasma N-BNP was determined using a commercially available immunoassay (Elecsys proBNP, Roche Diagnostics, Indianapolis, Indiana) on an Elecsys 1010 analyzer according to established methods.[7] The mean inter-assay coefficient of variation was 2.7%. Serum insulin was measured by a radioimmunoassay (Linco Human Insulin ELISA Kit, Linco Research, St. Charles, Missouri) that had minimal cross-reactivity with other insulin-related molecules and an intra-assay coefficient of variation of 2.7%. The homeostasis model assessment of insulin resistance (HOMA-IR) was estimated using fasting insulin and glucose values, where HOMA-IR = (fasting insulin [uU/mL] * fasting blood glucose [mmol/L])/22.5. Individuals with HOMA-IR in the top quartile were considered to have insulin resistance.[8] Free testosterone was calculated using the law of mass action equation[9] and using measures of serum total testosterone concentrations, quantified by liquid chromatography-tandem mass spectrometry assay.

Imaging was performed with an 8-slice multi-detector CT scanner (Lightspeed Ultra, General Electric, Milwaukee, WI) using a standard protocol that has been reported previously.[4] Briefly, 25 contiguous 5-mm-thick slices were acquired above the level of S1. The abdominal muscular wall separating visceral from subcutaneous fat compartments was manually traced on acquired images and volumetric assessments of SAT and VAT were made. Intra- and inter-reader reproducibility were high, with interclass correlations of 0.997 for SAT and 0.992 for VAT.[4]

The regression dependent variable, N-BNP, was logarithmically transformed due to its skewed distribution. Correlations between BMI, SAT, and VAT were assessed in the study sample using unadjusted Spearmen correlation analyses.

Multivariable linear regression was performed in the total sample to examine the age- and sex-adjusted association of N-BNP (dependent variable) with adiposity measures (SAT and VAT). In multivariable models further adjusting for systolic blood pressure and antihypertensive treatment, which are clinical variables known to be associated with N-BNP,[10] we used multiplicative interaction terms to test for effect modification by sex or age on the relation of adiposity measures with plasma N-BNP. Sex-specific analyses were performed in instances when a positive sex interaction was noted. Further adjustment for BMI as well as waist circumference was included in analyses of VAT but not in analyses of SAT. Adjustment for BMI or waist circumference in analyses of SAT is generally avoided due to known collinearity between anthropometric measures (BMI and waist circumference) and subcutaneous adiposity.[4]

In secondary analyses, we assessed the relation of plasma N-BNP with adiposity measures while additionally accounting for eGFR, metabolic traits[11] that included metabolic syndrome and HOMA-IR ≥75th percentile, and circulating androgens (total testosterone, and

free testosterone).[12] In multivariable models, we also included additional covariates known to correlate with CT measures of adiposity: hormone replacement therapy (in women) and alcohol use.[13] Finally, we repeated all analyses using generalized estimating equations linear regression to account for correlations among related individuals (siblings) in the study sample (SAS PROC GENMOD).[14]

All analyses were performed using SAS version 9.1.3 (SAS institute, Cary, NC), and a 2-tailed P-value of <0.05 was considered significant.

RESULTS

The characteristics of the study sample are shown in Table 1. The mean age was 45 years, and 46% of participants were women. Overall, 25% of participants were obese (BMI ≥30 kg/m^2) and 39% were overweight (BMI ≥25 kg/m^2 and <30 kg/m^2). Spearman correlation coefficients for the relations of BMI to SAT and VAT were 0.81 and 0.77, respectively. Correlation coefficients between SAT and VAT were 0.60 in men and 0.78 in women.

In age- and sex-adjusted analyses, log N-BNP was inversely associated with SAT (β −0.074 change in log N-BNP per standard deviation [SD] increment in SAT, P<0.001) as well as VAT (β −0.124, P<0.001). In multivariable analyses adjusting for age, sex, systolic blood pressure, and antihypertensive treatment, there was no significant interaction of age with either VAT or SAT (P>0.10). However, there was evidence of a sex interaction for the association of log N-BNP with SAT (P=0.02) but not VAT (P=0.10). Therefore, analyses of SAT were performed in men and women separately (Table 2). In these sex-specific analyses, the multivariable-adjusted association of higher SAT with lower log N-BNP was significant in women but not men (Table 2); a 1 SD increment in SAT was associated with a 13% lower N-BNP level in women.

In multivariable analyses, log N-BNP was inversely associated with VAT in the total sample; thus, a 1 SD increment in VAT was associated with a 13% lower N-BNP level in both sexes. In sex-specific multivariable analyses, higher VAT was significantly associated with lower N-BNP in both men and women (Table 2). Further, in models containing both SAT and VAT, N-BNP was significantly associated with VAT but not SAT (Table 2).

In analyses adjusting for either BMI or waist circumference, VAT remained significantly associated with N-BNP (Table 3). The multivariable-adjusted relation of lower N-BNP with higher VAT, but not SAT, remained significant in models that included the metabolic syndrome (Table 3). However, when adjusting instead for HOMA-IR, the inverse association between BNP and VAT was attenuated (Table 3).

To examine the effects of adiposity and body size separately, we repeated multivariable analyses of adiposity measures in individuals without obesity (BMI <30 kg/m^2). In non-obese individuals (N=1405), the multivariable-adjusted association of log N-BNP with VAT was statistically significant (−0.114 change in log N-BNP per SD increment in VAT, P<0.001). Results for VAT were similar when analyses were repeated in individuals who were overweight or obese (N=1192) (β −0.130, P<0.001).

The results were also similar in multivariable models that included adjustment for eGFR, postmenopausal status, hormone replacement therapy, total testosterone, free testosterone, and alcohol use, and in models using generalized estimating equations (data not shown).

DISCUSSION

The principal findings of the present study are 3-fold. First, circulating N-BNP concentrations are inversely related to abdominal adipose tissue mass. Second, circulating N-BNP is more strongly related to visceral adiposity than subcutaneous adiposity. Third, the association between plasma N-BNP and VAT is attenuated by adjustment for HOMA-IR, suggesting that hyperinsulinemia could be a mediator of the link between visceral adiposity and lower natriuretic peptide levels. Taken together, these findings offer novel insights into possible mechanisms underlying the relation of obesity with natriuretic peptides and, in turn, cardiovascular risk.

The natriuretic peptides play an important role in the regulation of vascular tone, sodium balance, and cardiovascular remodeling. Although it is well recognized that obese individuals have lower circulating natriuretic peptide levels,[1] the mechanisms underlying this relationship have been unclear. Obese individuals have both higher fat mass and higher lean body mass. A report from the Dallas Heart Study found that lean body mass, as measured by DEXA, was more strongly associated with N-BNP than fat mass.[1] Although DEXA scans do not distinguish subcutaneous from visceral adipose tissue, the majority of fat mass assessed by DEXA is thought to comprise of SAT.[4] Accordingly, we found that the association of N-BNP with SAT was attenuated in multivariable models, particularly in men. In contrast to our findings with SAT, we observed a robust inverse association of N-BNP with VAT, even in analyses restricted to non-obese individuals.

In a smaller study of individuals with advanced type II diabetes, visceral fat mass was also observed to be associated with lower N-BNP.[15] However, the role of fat depots on natriuretic peptide levels in ambulatory adults has not been investigated previously. The results of our analysis in a large community-based sample suggest that the distribution of adiposity contributes to variation in natriuretic peptide levels, with fat in the visceral compartment being a stronger correlate than subcutaneous fat.

Our findings are consistent with a growing body of evidence linking the natriuretic peptides and insulin resistance. We and others have previously observed an association of the metabolic syndrome with low natriuretic peptide levels.[11,16] Interestingly, the association of N-BNP with visceral adiposity in the present study was attenuated by adjustment for HOMA-IR but not by adjustment for metabolic syndrome. These results support the hypothesis that metabolic syndrome, as a clinical entity, does not completely capture the metabolic abnormality associated with elevated HOMA-IR.[17,18] It is possible that insulin resistance is more closely related than metabolic syndrome to pathways that promote cardiovascular risk, via mechanisms that have yet to be unidentified. Visceral adiposity is a well-known correlate of hyperinsulinemia, and hyperinsulinemia has been shown in some physiologic studies to suppress natriuretic peptide secretion and activity.[19,20] Thus, one model is that visceral adiposity leads to hyperinsulinemia, which suppresses circulating N-BNP. However, other experimental studies have investigated results of acute insulin administration and found either increased[21] or no significant change[22] in natriuretic peptides. The physiologic effects of acute and chronic hyperinsulinemia on natriuretic peptide secretion and activity remain an important area for future study.

There is accumulating evidence that the natriuretic peptides themselves have effects on glucose and insulin related pathways, including the ability to facilitate glucose transport via cyclic-GMP[23,24] and stimulate lipolysis.[25] Experimental models suggest that natriuretic peptides increase expression of PGC-1α,[26] a transcriptional coactivator that plays a central role in maintaining glucose, lipid, and energy homeostasis.[27] In fact, a recent study in mice showed that over-expression of BNP led to upregulation of PGC-1α and less accumulation

of abdominal adiposity on a high fat diet;[26] this finding appeared more pronounced for visceral than subcutaneous adiposity. In addition, a recent meta-analysis of genetic data indicated that BNP promoter variants associated with higher BNP concentrations were also related to lower risk of type 2 diabetes.[28] Together, these data suggest a complex, possibly bi-directional interplay between low natriuretic peptides, visceral adiposity, and insulin resistance.

Several limitations of this study merit consideration. The use of cross-sectional data precludes inference of a causal relation between regional adiposity and low natriuretic peptide levels. Further research is needed to elucidate possible underlying biological mechanisms. The results of our study may not be generalizable to all racial/ethnic groups or age groups, because our sample was primarily white and young to middle-aged. Furthermore, adiposity measures were limited to those who weighed <350 pounds. Since we did not subdivide subcutaneous fat into superficial and deep compartments, we cannot comment on the relative importance of these compartments with respect to variation in N-BNP. HOMA-IR is a surrogate measure of insulin resistance. It is less precise than measures obtained from the hyperinsulinemic euglycemic glucose clamp technique or the insulin suppression test. Nonetheless, it is regarded as a reasonably reliable surrogate in individuals without severely impaired pancreatic beta-cell function and it is practical for epidemiological studies.[29] Notwithstanding the above limitations, the present study had several strengths. Our community-based sample was not selected on the basis of adiposity-related traits, cardiovascular disease risk factors, or natriuretic peptide levels. For assessing regional adiposity, we used a highly reproducible volumetric method of measuring SAT and VAT,[30] which accounts for the heterogeneity of fat distribution throughout the abdomen. Finally, our large sample size provided adequate power for performing multivariable analyses and comparing strengths of association.

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Table 1

Sample Characteristics

Variable	Whole Sample (N=1,873)	Men (N=1,007)	Women (N=866)
Clinical and Anthropometric Measures			
Age (years)	44.8 ± 6.1	43.7 ± 6.2	46.1 ± 5.6
Body mass index (kg/m^2)	27.3 ± 5.2	28.0 ± 4.4	26.4 ± 5.8
Waist circumference (inches)	37.3 ± 5.5	39.0 ± 4.6	35.4 ± 5.9
Systolic blood pressure (mm Hg)	119 ± 14	121 ± 13	116 ± 16
Diastolic blood pressure (mm Hg)	77 ± 9	79 ± 9	74 ± 9
Hypertension	20%	23%	16%
Smoker	14%	15%	14%
Postmenopausal*	9%	…	18%
Hormone replacement therapy*	5%	…	10%
Alcohol use†	15%	16%	14%
Metabolic syndrome	24%	29%	17%
Biochemical Measures			
NT-proBNP‡ (pg/mL)	27.7 (13.3, 52.5)	16.6 (8.4, 30.3)	46.5 (27.3, 78.0)
HOMA-IR‡	1.0 (0.7, 1.5)	1.1 (0.8, 1.7)	0.9 (0.7, 1.3)
Computed Tomography Measures			
Subcutaneous adipose tissue (cm^3)	2761 ± 1404	2571 ± 1240	2982 ± 1545
Visceral adipose tissue (cm^3)	1565 ± 898	1958 ± 864	1109 ± 699

HOMA-IR, homeostasis model assessment of insulin resistance; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Data are presented as mean ± SD (for continuous variables that are normally distributed) or percentages (for categorical variables) for all individuals with available data.

*Data are from women only (n=866).

†Defined as >14 drinks per week (men) or >7 drinks per week (women).

‡Median (interquartile range) presented for continuous variables that are not normally distributed.

Table 2

Multivariable-Adjusted Relations of Adiposity Measures with Log N-terminal Pro-B-Type Natriuretic Peptide

	Model including SAT		Model including VAT		Model including both SAT and VAT	
Independent Variables	**β (SE)***	**P-value**	**β (SE)**	**P-value**	**β (SE)**	**P-value**
Total Sample: ***adjusting for age, sex, SBP, and anti-hypertensive treatment***						
SAT	N/A†		—		N/A†	
VAT	—		−0.143 (0.021)	<0.001	−0.152 (0.028)	<0.001
Men Only: ***adjusting for age, SBP, and anti-hypertensive treatment***						
SAT	−0.032 (0.028)	0.25	—		0.043 (0.034)	0.20
VAT	—		−0.111 (0.029)	<0.001	−0.137 (0.036)	<0.001
Women Only: ***adjusting for age, SBP, and anti-hypertensive treatment***						
SAT	−0.141 (0.029)	<0.001	—		−0.009 (0.043)	0.83
VAT	—		−0.191 (0.030)	<0.001	−0.184 (0.044)	<0.001

SAT, subcutaneous adipose tissue; SBP, systolic blood pressure; VAT, visceral adipose tissue.

*Values represent change in log N-BNP (dependent variable) per standard deviation (SD) increase in the value of the independent continuous variables shown. For example, 1 SD increase in VAT was associated with an $e^{-0.143} = 0.87$ change in N-BNP in the total sample.

†Only sex-specific analyses were performed for SAT, given the presence of a significance sex interaction with SAT on variation in log N-BNP.

Table 3

Multivariable-Adjusted Relations of Adiposity Measures with Log N-terminal Pro-B-Type Natriuretic Peptide After Adjustment for Selected Metabolic Traits

Independent Variables	Model including SAT		Model including VAT	
	β (SE)*	P-value	β (SE)	P-value
Adjusting for age, sex, SBP, anti-hypertensive treatment, and BMI				
SAT†	N/A		—	N/A
VAT	—		−0.105 (0.031)	0.0008
Adjusting for age, sex, SBP, anti-hypertensive treatment, and waist circumference				
SAT	N/A		—	N/A
VAT	—		−0.130 (0.033)	<0.0001
Adjusting for age, sex, SBP, anti-hypertensive treatment, and metabolic syndrome				
SAT	−0.036 (0.023)	0.11	—	N/A
Adjusting for age, sex, SBP, anti-hypertensive treatment, BMI, and metabolic syndrome				
VAT	—		−0.073 (0.033)	0.028
Adjusting for age, sex, SBP, anti-hypertensive treatment, and HOMA-IR				
SAT	−0.012 (0.023)	0.59	—	N/A
Adjusting for age, sex, SBP, anti-hypertensive treatment, BMI, and HOMA-IR				
VAT	—		−0.057 (0.033)	0.081

BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; SAT, subcutaneous adipose tissue; SBP, systolic blood pressure; VAT, visceral adipose tissue.

*Values represent change in log N-BNP (dependent variable) per standard deviation (SD) increase in the value of the independent continuous variables shown.

†Models including SAT are not adjusted for BMI or waist circumference due to high collinearity between these variables.