Association of plasma B-type natriuretic peptide levels with obesity in a general urban Japanese population: the Suita study

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Abstract. The inverse association between plasma B-type natriuretic peptide (BNP) levels and body mass index (BMI) has been reported in Western populations. Here we analyzed the relationship between plasma BNP and obesity in a general urban Japanese population. We recruited 1,759 subjects without atrial fibrillation or history of ischemic heart disease aged 38-95 years (mean age ± standard deviation 64.5 ± 10.9 years, 56.1% women, mean BMI 22.8 ± 3.1 kg/m²) from the participants in the Suita Study between August 2002 and December 2003. In multivariable regression analyses adjusted for age, systolic blood pressure, pulse rate, serum creatinine, left ventricular hypertrophy in ECG, the inverse relationships between BNP levels and BMI (kg/m²) was found in both sexes (both p<0.001). Multivariable-adjusted mean plasma BNP levels in the group of BMI<18.5, 18.5≦BMI<22, 22≦BMI<25, and 25≦BMI were 23.4, 17.9, 14.0 and 13.0 pg/mL, respectively (trend p<0.001). The negative association of body fat (percentage and mass), skin fold thickness, or waist circumference with BNP levels was observed in both sexes (p<0.01). Among the obesity indices, body fat mass is most tightly associated with BNP. In conclusion, plasma BNP was inversely associated with obesity-related markers such as body fat mass, skinfold thickness and waist circumferences after adjusted for relevant covariates in a Japanese population.

Key words: BNP, BMI, Body fat mass, Japanese

B-TYPE natriuretic peptide (BNP) is a cardiac hormone, synthesized in, processed in and secreted from heart [1]. The secretion of BNP is stimulated in heart failure along with its severity. Plasma BNP is clinically utilized to diagnose the existence or the severity of the cardiac failure [2]. BNP levels are affected by demographic variables such as age, gender, and clinical characteristics such as hypertension [3, 4], atrial fibrillation [5], and renal function [6].

Several recent studies have suggested that obesity, as indexed elevated body mass index (BMI), also affects BNP levels, with lower circulating levels in those with higher BMI in subjects with and without heart failure [7-12]. In addition, the Dallas Heart Study revealed that BNP is closely associated with lean mass than with fat mass [8]. However, these studies were mostly conducted in Western countries, where BMI is much higher than in other parts of the world. It is not unclear whether this relationship could apply in a general Japanese population whose BMI levels are lower than in Western countries [13].

Therefore, the aim of the present study is to evaluate the association between BMI and BNP levels in a general urban Japanese population. To further elucidate the mechanisms of the relationship between obesity and BNP levels, we examine the relationship between BNP levels and various obesity related factors such as lean body mass, body fat mass, skin fold thickness, and waist circumferences.
Methods

Study Sample

The Suita Study [14-16], an epidemiological study of cerebrovascular and cardiovascular disease, was based on a random sampling of 15,200 (30–79 years of age at enrollment) Japanese residents of Suita. They were all invited, by letter, to attend regular cycles of follow-up examination (every 2 years). Subjects were recruited into the Suita Study between August 2003 and December 2004 in this study (n=2,007). Subjects with chronic atrial fibrillation at time of referral (n=40) and history of ischemic heart disease (n= 97) were excluded. After applying this exclusion, 1,759 individuals were included in this analysis. The study design was approved by the institutional review board of the National Cardiovascular Center. Informed consent was obtained from all subjects.

Routine physical examination, 12-lead surface ECG, several blood chemical variables and plasma BNP measurements were performed. A physician or nurse interviewed each patient personal history of cardiovascular disease, including angina pectoris and/or myocardial infarction. Blood pressure was measured after at least 5 minutes of rest in a sitting position. Systolic and diastolic blood pressures (SBP and DBP) were the means of two measurements by well-trained doctors (recorded at least 1 min apart) [16]. BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured in a standing position at the umbilical level by well-trained technicians [15]. Lean body mass and body fat mass were calculated by the bioelectrical impedance analyzer [17]. Brachial triceps and subscapular skin fold thickness was measured using keys calipers by trained physician epidemiologists with standard methods.

Measurement of BNP

Blood sample was collected into tubes containing EDTA. Plasma BNP was measured by validated and commercially available immunoassay kit (Shionogi, Osaka, Japan). The measurable range of the BNP assay is 4.0 to 2000 pg/mL. Average intra- and inter-assay coefficients of variation were 3.7% and 4.5%, respectively.

Statistical Analyses

Continuous data are presented as means ± standard deviations (SDs) for normally distributed variables and as medians (interquartile range) in case of skewed distribution. Categorical data are presented as numbers and percentage. Comparison of clinical characteristics between patients each BMI category were performed using Kruskal-Wallis test for continuous data and χ² test for categorical data. Variables with skewed distributions underwent logarithmic transformation to create normal distributions. The value less than the lower detection limit of the BNP assay (BNP < 4.0 pg/mL) were found 9.0% of all subjects. For analyses examining continuous BNP levels, we treated lower detection limit of the BNP assay for 4.0 pg/mL and performed multivariable linear regression with log-transformed BNP as the dependent variables. Covariates examined for inclusion in the multivariable models were age, sex, systolic blood pressure, pulse rate, serum creatinine, and left ventricular hypertrophy (LVH) in ECG. Sex-specific regression analyses were also performed. In additional models, we replaced the continuous BMI variable with BMI categories (BMI<18.5, 18.5 ≤ BMI< 22, 22 ≤ BMI < 25, and 25 kg/m² ≤ BMI). The results of the multivariable analyses were also used to examine the relations of BMI category to adjusted plasma BNP levels. Since models used log-transformed dependent variables, we exponentiated the β coefficient for BMI to characterize its multiplicative effect on absolute plasma BNP levels. Because of the skewed nature of the BNP distributions and potential violations of assumptions inherent in the least-squares model, we used multivariable logistic regression analyses to analyze correlations of normal plasma BNP levels (BNP<18.4 pg/mL). We estimated odds ratios for having normal BNP levels according to BMI category, with lowest BMI individuals as the referent group. Odds ratios were adjusted for the same covariates used in the linear models.

All data were analyzed with the JMP version 6.0 (SAS Corporation, Cary, NC, USA) statistical software package.

Results

Baseline Characteristics

The clinical characteristics of study population (mean ± SDs age 64.5 ± 10.9 years, mean BMI 22.8 ± 3.1 kg/m², 56.1% women) stratified by BMI category are listed in Table 1. Increasing BMI was associated with an increased likelihood of being men; higher systolic blood pressure, and lower BNP levels.
When BNP level was categorized by quartile (data not shown), increasing BNP levels was associated with an increased likelihood of being women and older; lower BMI, and pulse rate; an increased likelihood of having LVH; and higher systolic blood pressure.

**Association between BMI and BNP Levels**

Results of multivariable regression models are shown in Table 2. After adjustment for age, systolic blood pressure, pulse rate, serum creatinine, and LVH, BMI was inversely associated with plasma BNP levels, with 5% decrease associated with each 1 unit increase in BMI in both sexes ($p<0.001$ for both). There was also a progressive decrease in plasma BNP levels with increasing BMI category. In men, highest BMI group (BMI $\geq 25$) had 29% lower plasma BNP levels compared with lowest BMI group (BMI $<18.5$) ($p<0.001$). In women, highest BMI group (BMI $\geq 25$) had 23% lower plasma BNP levels compared with lowest BMI group (BMI $<18.5$) ($p<0.001$).

Multivariable-adjusted mean levels of plasma BNP were shown in Fig. 1 for each BMI category. For both sexes, adjusted BNP levels decreased in a stepwise fashion across categories of increasing BMI ($p<0.001$ for trend for all comparisons).

For logistic regression analysis, the BNP levels were considered as a categorical variable, pooling the subjects into two distinct groups: $<18.4$ pg/mL (nor-
mal) and $\geq 18.4$ pg/mL (abnormal); the same covariates were evaluated in these models as in the linear regression models described above. The adjusted odds ratios of having normal BNP levels are shown in Table 3. After multivariable adjustment, highest BMI (25 kg/m$^2$ $<\text{BMI}$) was associated with having a 2.1- to 2.3-fold increase in the odds of having normal BNP levels ($p<0.001$). Overall, for each 1 unit increase in BMI, there was a 11% to 16% greater chance of having normal BNP ($p<0.01$).

**Association between Body Composition and BNP Levels**

Results of multivariable regression models relating plasma BNP levels with various obesity related factors are shown in Table 4. Model 1 used BMI as a measure of obesity, and model 2 replaced BMI with percent of body fat. In model 3, percent body fat was replaced by body fat mass and lean body mass. Model 4 replaced BMI with skin fold thickness, and Model 5 replaced BMI with waist circumferences. After adjustment for the same covariates as in Table 2, inverse associations were confirmed between percent of body fat, body fat mass, skin fold thickness and waist circumferences and BNP levels in both sexes (all $p<0.01$). However, the inverse association with lean body mass was not significant for BNP ($p=0.188$ in men and $p=0.079$ in women).

**Discussion**

In the present study, we showed that higher BMI was significantly associated with lower plasma BNP levels in a general Japanese population. The finding is not attributable to underlying differences in cardiovascular risk factors between obese and non-obese subjects. We also showed that the inverse association between body fat mass, skin fold thickness and waist circumferences and BNP. This is the first report that analyzes the relations between BNP levels and various obesity related factors.

Several studies, including large, population-based cohorts [7, 8], have demonstrated that BMI was inversely correlated with BNP levels in patients with heart failure [9-12]. In the Dallas Heart Study [8], they focused on the body composition instead of BMI and showed an inverse association between plasma BNP and lean mass. However, these studies were conducted mostly in Western countries, where BMI is much higher than in other parts of the world.

In this study, where the average BMI levels (around 23 kg/m$^2$) was much lower in comparison with the general Western population (around 28 kg/m$^2$) [8], the association between higher BMI and lower BNP levels was observed after multivariable adjustment. Furthermore, we divided adiposity into its fat and lean mass components and found that fat mass was responsible for the association between higher BMI and lower BNP levels.

As it was already suggested, the natriuretic peptide system and adiposity are closely linked [18, 19]. Natriuretic peptide clearance receptors (NPR-C) are abundant in adipose tissue [18], and thus, it is suggested that adipocytes participate in a removal of BNP from circulation, which leads to the lower plasma BNP levels in obese patients. Furthermore, the Framingham Heart Study [7] showed that obese in-
Table 2 Multivariable linear models of plasma log BNP.

<table>
<thead>
<tr>
<th>Models</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β-coefficient (SE)</td>
<td>p value</td>
</tr>
<tr>
<td>Continuous BMI, per 1kg/m²</td>
<td>-0.022 (0.005)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI categories</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &lt; 18.5</td>
<td>Referent</td>
<td>-</td>
</tr>
<tr>
<td>18.5 ≤ BMI &lt; 22</td>
<td>-0.087 (0.033)</td>
<td>0.009</td>
</tr>
<tr>
<td>22 ≤ BMI &lt; 25</td>
<td>-0.122 (0.032)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>25 ≤ BMI</td>
<td>-0.148 (0.034)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The multiplicative effect on plasma BNP levels can be estimated by exponentiating the β-coefficient. For instance, highest BMI (BMI ≤ 25) is associated with a 29% reduction in BNP levels in men, because $10^{-0.148} = 0.71$. All models are adjusted age, systolic blood pressure, pulse rate, serum creatinine, and left ventricular hypertrophy.

Table 3 Influence of BMI on odds of having normal plasma BNP levels (< 18.4 pg/mL).

<table>
<thead>
<tr>
<th>BMI categories</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>BMI &lt; 18.5</td>
<td>1.00 (referent)</td>
<td>-</td>
</tr>
<tr>
<td>18.5 ≤ BMI &lt; 22</td>
<td>1.66 (1.10-2.56)</td>
<td>0.019</td>
</tr>
<tr>
<td>22 ≤ BMI &lt; 25</td>
<td>2.08 (1.38-3.19)</td>
<td>0.001</td>
</tr>
<tr>
<td>25 ≤ BMI</td>
<td>2.25 (1.47-3.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (continuous), per 1kg/m²</td>
<td>1.11 (1.04-1.18)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Multivariable logistic regression models for low BNP levels are adjusted for age, systolic blood pressure, pulse rate, serum creatinine, and left ventricular hypertrophy.

Table 4 Multivariable associations between obesity related factors and BNP.

<table>
<thead>
<tr>
<th>Models</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β-coefficient (SE)</td>
<td>p value</td>
</tr>
<tr>
<td>Model 1</td>
<td>BMI</td>
<td>-0.002 (0.005)</td>
</tr>
<tr>
<td>Model 2</td>
<td>Percent of body fat</td>
<td>-0.012 (0.003)</td>
</tr>
<tr>
<td>Model 3</td>
<td>Body fat mass</td>
<td>-0.014 (0.003)</td>
</tr>
<tr>
<td>Lean body mass</td>
<td>0.004 (0.003)</td>
<td>0.188</td>
</tr>
<tr>
<td>Model 4</td>
<td>Skinfold thickness</td>
<td>-0.007 (0.002)</td>
</tr>
<tr>
<td>Model 5</td>
<td>Waist circumference</td>
<td>-0.006 (0.002)</td>
</tr>
</tbody>
</table>

The multiplicative effect on plasma BNP levels can be estimated by exponentiating the β-coefficient. All models are adjusted for age, systolic blood pressure, pulse rate, serum creatinine, and left ventricular hypertrophy.
individuals had higher odds of having low plasma N-terminal proANP. In the Dallas Heart Study [8], the association between higher BMI and lower NT-proBNP was observed. Since both N-terminal proANP and N-terminal proBNP are not cleared by clearance receptors, the findings of reduced N-terminal proANP levels and N-terminal proBNP levels in obese individuals indicate the mechanism other than the adipocyte clearance of the peptides exists. Recent investigations have raised the possibility that the relation between fat and BNP is bidirectional. Adipocytes also express natriuretic peptide receptor-A (NPR-A), which mediate the biologic effects of ANP and BNP [18]. Investigators have demonstrated activation of NPR-A on adipocytes induces lipolysis [19]. Thus, low BNP levels may lead to reduced lipolysis, additionally perpetuating the obese state.

Several limitations of our study deserve comment. First, since our study was cross-sectional study, we cannot demonstrate the cause-effect relation between low plasma BNP and obesity related factors. Second, plasma BNP levels are under the calculable levels of the assay detection limits in 9.0% of all subjects. Misclassification of BNP levels above and below the detection limit would be expected to cause a conservative bias. To overcome the potential bias, we also used logistic regression analyses to account for the left censoring of the BNP distribution. Finally, we cannot exclude the possibility that obese individuals might have had better cardiac function. However, since many previous studies suggest that obesity has been consistently associated with left ventricular hypertrophy [20, 21], dilatation [22] and the increase in the risk of overt heart failure [23], the possibility is highly unlikely.

In conclusion, higher BMI was associated with lower BNP levels in a general Japanese population, even after adjusted for relevant factors. Body fat mass was responsible for this relationship. Further studies will be needed to explore the underlying mechanism.

Acknowledgement

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References


