Association of Amino-terminal Pro-brain Natriuretic Peptide with Metabolic Syndrome

Wen-Yi Li¹, Fu-Chun Chiu¹, Yu-Fen Chien³, Jou-Wei Lin² and Juey-Jen Hwang²

Abstract

Objective This study evaluated the relationship between individual components in metabolic syndrome (MetS) and amino-terminal pro-brain natriuretic peptide (NT-proBNP).

Methods A screening program for MetS in 2008 in Taiwan excluded subjects aged <30 years and pregnant women. Fasting glucose, insulin level, high-sensitivity C-reactive protein (hsCRP), and NT-proBNP were assessed. A propensity-score matching process was used to select subjects with and without MetS comparable in age, gender, body height, and serum creatinine levels. A multiple regression model was used to determine the association between individual components of MetS and NT-proBNP. Finally 270 subjects with MetS and another 270 matched subjects without MetS aged ≥30 years were included.

Results The subjects with MetS had higher uric acid and hsCRP, but not NT-proBNP. Multiple regression model showed that log (NT-proBNP) was positively associated with systolic blood pressure ($\beta=0.002$ per mmHg, $p=0.013$), but negatively associated with body mass index ($\beta=-0.017$ per kg/m², $p=0.018$), triglyceride ($\beta=-0.00048$ per mg/dL, $p=0.020$) and insulin level ($\beta=-0.005$ per mU/L, $p=0.005$). Log (NT-proBNP) was neutral to waist circumference, fasting glucose, high-density lipoprotein cholesterol, and diastolic blood pressure.

Conclusion MetS was not associated with serum NT-proBNP concentrations due to the contradictory effects of each component.

Key words: metabolic cardiovascular syndrome, amino-terminal pro-brain natriuretic peptide, propensity score


Introduction

Brain natriuretic peptide (BNP), synthesized mainly in the ventricles, plays a key role in the regulation of body fluid and blood pressure (1). Amino-terminal pro-brain natriuretic peptide (NT-proBNP) is more stable than BNP (2). Both NT-proBNP and BNP are sensitive indicators of left ventricular dysfunction (3) and useful predictors of future outcome in patients with heart failure (4). Although a higher BNP level was found in heart failure patients, the state of a reduced natriuretic peptide level exists in obese individuals with heart failure (5, 6). Many studies found obesity or adipose tissue itself has an inverse correlation with natriuretic peptide level (7, 8). Metabolic syndrome (MetS), which is closely related to abdominal adiposity, has been proven to be related to increased incidence of cardiovascular morbidity and mortality (9, 10). It is of interest to determine the correlation between MetS and natriuretic peptide level.

Wang et al demonstrated that both BNP and N-terminal pro-atrial natriuretic peptide (NT-proANP) are significantly decreased in patients with MetS (11). Plasma natriuretic peptide levels were inversely associated with all components of the MetS except for elevated blood pressure. In contrast with those findings, Sezen et al showed that NT-proBNP levels do not show a significant decrease in MetS (12).

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However, it remains uncertain whether or not levels of NT-proBNP are associated with MetS. Multiple factors, such as age, sex, renal function, and total cholesterol could influence the BNP metabolism, and there was no well-matched study to reduce these biases. So we conducted a propensity score matching study to investigate the relationship between the natriuretic peptide level and MetS.

**Materials and Methods**

**Setting**

An on-site screening program for MetS and diabetes was held in late November 2008 in Yun-Lin, Taiwan. The exclusion criteria were age <30 years and pregnant women. People with a history of heart failure or renal disease were also excluded. Each subject who visited the hospital underwent a simple physical examination; body height (to the nearest 0.5 cm), body weight (to the nearest 0.1 kg), waist circumference (to the nearest 0.1 cm), and hip circumference (to the nearest 0.1 cm). Body mass index (BMI) was calculated as the ratio between body weight (kg) and the square of body height (m²). Subjects were seated and asked to refrain from talking for 10 minutes. Blood pressure and heart rate were checked 3 times, with at least a 1-minute interval between two consecutive readings, using an automatic blood pressure monitor (Model MX3, OMRON Corporation, Tokyo, Japan). The average of the second and third readings was used for the analysis. The institutional review board approved this study, and informed consent was obtained from each participant.

Data on demographic variables and anthropometric measurements were obtained. Fasting blood was drawn and a series of biochemical tests were performed, including glucose, insulin level, lipid profiles, and high-sensitivity C-reactive protein (hsCRP). NT-proBNP was measured on a Roche Elecsys 2010 analyzer (in pg/mL). As the minimal threshold of NT-proBNP detection is 5 pg/mL in our laboratory, the subjects with NT-proBNP levels under the detection limit were treated as 5 pg/mL. Measures of insulin resistance were determined using the homeostasis model assessment (HOMA)-2 with the use of a HOMA calculator (www.dtu.ox.ac.uk).

**Determination of metabolic syndrome status**

The MetS status was defined as the presence of at least three of the following criteria in Adult Treatment Panel (ATP) III with modification of Asian criteria: 1) waist >90 cm in men or >80 cm in women, 2) fasting serum triglyceride >150 mg/dL, 3) high-density lipoprotein cholesterol (HDL-C) <40 mg/dL in men and <50 mg/dL in women, 4) systolic blood pressure (SBP) >130 mmHg or diastolic blood pressure (DBP) >85 mmHg, and 5) fasting glucose >100 mg/dL.

**Statistical analysis**

We used the SPSS software, version 13.0 (SPSS, Chicago, IL, USA) for statistical analyses. A two-tailed p value of less than 0.05 was considered to be statistically significant. Continuous variables were described by the mean ± standard deviation (SD). Student’s two-tailed t-test was applied to compare continuous variables, and the chi-square test was used for categorical data.

Propensity scores were used primarily to reduce bias and increase validity in a non-randomized observational study (13). In this study, the propensity score was the conditional probability for metabolic syndrome, as a binary dependent variable, under a set of measurements. Age, sex, body height, and serum creatinine levels were added into a non-parsimonious multivariate logistic regression model to predict the possibility of metabolic syndrome. The predicted probability derived from the logistic equation was used as the propensity score for each individual. Subjects with metabolic syndrome and without metabolic syndrome were pooled and sorted according to their propensity score in ascending order. The selection process began from the first two cases with the lowest propensity score. If one was metabolic syndrome and the other was not metabolic syndrome, both were selected as a matched pair. If this was not the case, then four cases were included. If there were two metabolic syndromes and two non-metabolic syndrome cases, the four were selected as two matched pairs. In the same way, subjects with metabolic syndrome and subjects without metabolic syndrome were matched by their propensity score in 1:1, 2:2, 3:3 or 4:4 blocks. A subject who did not have a suitable match within the acceptable rank range was excluded from further analysis, and the matching process moved down the sort list until all possible matched pairs were included. The selected patients formed well-matched 1:1 pairs in both groups (14). Hotelling’s T-test was used to compare the multivariate results (NT-proBNP, hsCRP and uric acid) between the two matched groups. NT-proBNP and hsCRP were logarithmically transformed to meet the normality assumption. A multiple regression model was used to find the association between individual component of MetS and NT-proBNP.

**Results**

There were 270 subjects with MetS and another 270 matched subjects without MetS aged 30 years and above in the analysis. As shown in Table 1, the two groups had comparable baseline characteristics in gender, age, body height, serum creatinine, and low-density lipoprotein cholesterol (LDL-C). The subjects with MetS had higher levels of aspartate aminotransferase (AST) (mean difference 0.04 μkat/L, p=0.030), alanine aminotransferase (ALT) (mean difference 0.14 μkat/L, p<0.0001), uric acid (mean difference 36.3 μmol/L, p<0.0001), insulin levels (mean difference 21.97 pmol/L, p=0.005) and HOMA2-IR (mean difference
Table 1. Demographic Data of Study Subjects. These Subjects were Matched by Age, Sex, Height, Serum Creatinine.

<table>
<thead>
<tr>
<th></th>
<th>MetS (n=270)</th>
<th>Non-MetS (n=270)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>52±11</td>
<td>52±11</td>
<td>0.656</td>
</tr>
<tr>
<td>BH (cm)</td>
<td>161.8±12.1</td>
<td>162.2±8.5</td>
<td>0.683</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.19±3.51</td>
<td>24.10±3.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>89.7±9.8</td>
<td>80.4±10.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.90±1.42</td>
<td>5.25±1.23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>T-CHO (mmol/L)</td>
<td>5.39±1.03</td>
<td>5.36±0.99</td>
<td>0.739</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>2.12±1.46</td>
<td>1.24±0.85</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.15±0.24</td>
<td>1.39±0.30</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>3.56±0.92</td>
<td>3.43±0.96</td>
<td>0.112</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>96.36±16.80</td>
<td>96.36±15.03</td>
<td>0.888</td>
</tr>
<tr>
<td>AST (μkat/L)</td>
<td>0.48±0.22</td>
<td>0.44±0.21</td>
<td>0.030</td>
</tr>
<tr>
<td>ALT (μkat/L)</td>
<td>0.61±0.43</td>
<td>0.47±0.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>141.1±35.6</td>
<td>127.5±16.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>91.5±9.8</td>
<td>83.9±10.1</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

AST, aspartate aminotransferase; ALT, alanine aminotransferase; BH, body height; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; LDL-C, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure; T-CHO, total cholesterol;

Table 2. Multiple Regression Model for Log(NT-proBNP)

<table>
<thead>
<tr>
<th>Factor</th>
<th>β</th>
<th>95% CI</th>
<th>p value</th>
<th>β</th>
<th>95% CI</th>
<th>p value</th>
<th>β</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>-0.017</td>
<td>-0.031 to -0.003</td>
<td>0.018</td>
<td>-0.020</td>
<td>-0.038 to -0.001</td>
<td>0.040</td>
<td>-0.022</td>
<td>-0.043 to -0.001</td>
<td>0.043</td>
</tr>
<tr>
<td>Waist</td>
<td>-0.00035</td>
<td>-0.00509 to -0.0044</td>
<td>0.886</td>
<td>0.002</td>
<td>0.005 to 0.008</td>
<td>0.599</td>
<td>-0.005</td>
<td>-0.012 to -0.001</td>
<td>0.120</td>
</tr>
<tr>
<td>SBP</td>
<td>0.002</td>
<td>0.000 to 0.004</td>
<td>0.013</td>
<td>0.001</td>
<td>0.001 to 0.002</td>
<td>0.451</td>
<td>0.013</td>
<td>0.008 to 0.018</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP</td>
<td>-0.002</td>
<td>-0.006 to -0.003</td>
<td>0.429</td>
<td>-0.002</td>
<td>-0.008 to -0.005</td>
<td>0.604</td>
<td>-0.015</td>
<td>-0.023 to -0.007</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.00002</td>
<td>0.00173 to 0.00178</td>
<td>0.978</td>
<td>-0.001</td>
<td>-0.003 to -0.002</td>
<td>0.650</td>
<td>-0.001</td>
<td>-0.003 to -0.002</td>
<td>0.638</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.002</td>
<td>0.001 to 0.006</td>
<td>0.200</td>
<td>0.010</td>
<td>0.003 to 0.016</td>
<td>0.003</td>
<td>-0.002</td>
<td>-0.007 to 0.003</td>
<td>0.360</td>
</tr>
<tr>
<td>TG</td>
<td>-0.00048</td>
<td>-0.00089 to -0.00008</td>
<td>0.020</td>
<td>0.0043</td>
<td>-0.00004 to -0.00008</td>
<td>0.096</td>
<td>-0.00076</td>
<td>-0.00149 to -0.00002</td>
<td>0.044</td>
</tr>
<tr>
<td>Insulin</td>
<td>-0.005</td>
<td>-0.008 to -0.001</td>
<td>0.005</td>
<td>-0.004</td>
<td>-0.008 to -0.001</td>
<td>0.104</td>
<td>-0.005</td>
<td>-0.010 to 0.000</td>
<td>0.601</td>
</tr>
</tbody>
</table>

BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglyceride

The logarithmic transformation of hsCRP (mean difference 0.179, p<0.0001) was also higher in the subjects with MetS. But log(NT-proBNP) was not significantly different between the two groups (mean difference -0.023, p=0.63).

Multiple regression model showed that there was a positive association between systolic blood pressure (β=0.002 per mmHg, p=0.013) and log(NT-proBNP). In turn, BMI (β=0.017 per kg/m², p=0.018), triglyceride (β=-0.00048 per mg/dL, p=0.020) and insulin (β=-0.005 per mU/L, p=0.005) were negatively associated with log(NT-proBNP). There was no association between log(NT-proBNP) and waist circumference (p=0.886), diastolic blood pressure (p=0.429), fasting glucose (p=0.978), or HDL-C (p=0.200) (Table 2). In subjects with MetS, NT-proBNP was only positively correlated with HDL-C (β=0.010 per mg/dL, p=0.003) and negatively correlated with BMI (β=-0.020 per kg/m², p=0.040). Log(NT-proBNP) was neutral to waist circumference, fasting glucose, triglyceride, insulin, systolic and diastolic blood pressures (Table 2).

Discussion

This propensity score matched analysis showed that NT-proBNP was positively associated with SBP, but negatively associated with BMI, triglyceride and insulin. NT-proBNP was not related to waist circumference, fasting glucose, diastolic blood pressure and HDL-C. Serum NT-proBNP level, due to contradictory effects of each component, was not statistically different in those with and without MetS.
Comparison with prior studies

Wang and colleagues analyzed the association of plasma levels of BNP and N-terminal pro-atrial natriuretic peptide with metabolic risk factors in 3333 Framingham study participants without heart failure (11). BNP was positively associated with SBP and HDL-C, and negatively associated with BMI, DBP, total cholesterol, fasting glucose and insulin resistance. Olsen et al reported similar findings in a large-scale Danish investigation (15). Sezen et al (12) found that NT-proBNP levels did not have a significant increase in MetS patients as compared with similar age and sex individuals. Those results were compatible with ours. However, our study demonstrated that MetS as a whole was not associated with serum NT-proBNP level after adjusting for age, gender, body height, and serum creatinine. A meticulous matching process has rarely been used in previous studies. The relationship between MetS and NT-proBNP was clarified through the fine balance of potential covariates.

Obesity and natriuretic peptides

As already noted, the natriuretic peptide system and adiposity are closely linked (7, 8). Natriuretic peptide clearance receptors are abundant in adipose tissue (16), suggesting that adipocytes participate in the removal of natriuretic peptides from the circulation. Thus, the clearance of natriuretic peptide is increased in obese patients, and a state of reduced natriuretic peptide concentration could occur. In addition, natriuretic peptides have potent lipolytic effects in isolated human fat cells and in adipocytes in vivo through cyclic guanosine monophosphate (cGMP)-mediated phosphorylation (17). Therefore, a reduced natriuretic peptide signaling could promote lipid accumulation in adipose tissue and skeletal muscle (18), and perpetuate the obese state. The present study found that NT-proBNP was negatively associated with BMI (p=0.018), the same as the inverse relationship of NT-proBNP and obesity observed in a previous study (15). Usually, BMI and waist circumference are highly correlated (r=0.583, p<0.001 in both; r=0.480, p<0.001 in the MetS subjects, and r=0.505 p<0.001, in the non-MetS subjects). Even so, the model showed that BMI, rather than waist circumference, is the factor that is correlated with NT-proBNP. This is also compatible with the findings in other studies. This might imply that the abdominal adiposity does not represent the amount of whole body adipose tissue.

Lipid and natriuretic peptides

In previous large-scale investigations, plasma NT-proBNP was inversely associated with serum total cholesterol and triglyceride, but positively associated with HDL-C (11). In a Japanese study, plasma BNP did not correlate with total cholesterol and HDL-C (19). Our matched study showed that NT-proBNP was neutral to HDL-C. However, NT-proBNP was positively correlated with HDL-C in the MetS group. The causal relationship between natriuretic peptide and cholesterol or triglyceride is unclear and might not be direct. A reduced natriuretic peptide signaling could promote lipid accumulation in adipose tissue and skeletal muscle (18), and lead to developing visceral adiposity, which is associated with dyslipidemia.

Blood pressure and natriuretic peptides

Plasma natriuretic peptide levels were inversely related to all components of MetS except for elevated blood pressure and HDL-C in Wang’s study (11). Contrary to other metabolic factors, elevated SBP was associated with higher BNP levels in the present study. Natriuretic peptides have diuretic, natriuretic and vasodilatory properties. The observation that BNP levels relate differently to blood pressure than to other metabolic syndrome components might just reflect the hemodynamic influence of blood pressure on natriuretic peptide synthesis. But it also implies that blood pressure may share different pathophysiological determinants from other metabolic factors (20). Our previous structural equation model studies demonstrated that obesity had a strong influence on hypertension without the intermediation of inflammation or insulin resistance (21).

Insulin and natriuretic peptides

The relationship of fasting glucose to BNP is inconsistent. Olsen et al (15) found a negative association between fasting glucose and NT-proBNP. This was not observed by Sezen et al (12), or by the present study. However, the insulin level was consistently and inversely related to NT-proBNP level in the study of Olsen et al and in ours.

We also examined CRP and uric acid in both groups. An elevated level of uric acid might be linked to inflammation (22) and increased cytokine production (23). Uric acid was an endogenous danger signal mediating immune response upon cell injury (24). CRP and the uric acid were higher in the subjects with MetS and were also negatively associated with NT-proBNP. Combined with the inverse correlation of triglyceride/decreased HDL-C and NT-proBNP level, we found that the metabolic factors and inflammation factors have similar effect to NT-proBNP. These relationships could reflect the previous statement of a sequential effect from obesity to inflammation, insulin, and dyslipidemia (20, 21, 25). Because of the independent pathway of obesity to vasopressive factor and to metabolic/inflammatory factors, and these two factors have the opposite effects on NT-proBNP level, it may help to explain the inconsistent relationships between NT-proBNP level and MetS.

There were some limitations in this study. First, this study was cross-sectional, so we could not establish a temporal relationship between NT-proBNP and metabolic factors. Second, our cohort was predominantly composed of middle-aged Asian subjects. The results might not be generalized to younger individuals and other races.

In conclusion, the results demonstrated that blood pressure, lipid, and insulin resistance had different impacts on serum NT-proBNP levels. MetS as a whole, due to the contradictory effects of each component, was not associated
with NT-proBNP. Clinically, we should take these metabolic factors, inflammatory markers, and blood pressure components into consideration when interpreting natriuretic peptide levels for diagnostic or prognostic purposes.

The authors state that they have no Conflict of Interest (COI).

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