Correlation between B type natriuretic peptide and metabolic risk factors

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Abstract

Introduction: It has been shown that B type natriuretic peptide (BNP) level can indicate cardiovascular disease. However, the association between BNP and metabolic risk factors is unknown. The aim of this study was to investigate the correlation between N-terminal pro-B type natriuretic peptide (NT-proBNP) and metabolic risk factors.

Material and methods: A total of 11,508 subjects were selected from those who underwent health examinations in our hospital. NT-proBNP, waist circumference, blood pressure, fasting plasma glucose and lipid profile were measured. The level of NT-proBNP was measured and classified into four stratifications (BNP ≥ 20 pg/ml, ≥ 40 pg/ml, ≥ 60 pg/ml, and ≥ 80 pg/ml) to analyze the relationship between BNP and metabolic risk factors.

Results: B type natriuretic peptide increased gradually with increasing age ($p < 0.001$). The BNP levels were significantly higher in women than in men ($p < 0.001$). Multivariate regression analysis showed a positive association between NT-proBNP levels and systolic blood pressure ($p < 0.001$), fasting plasma glucose ($p < 0.05$), and total cholesterol ($p < 0.001$ in women). The NT-proBNP levels were inversely associated with diastolic blood pressure, waist circumference, triglyceride, high-density lipoprotein, and LDL cholesterol. Logistic regression analysis demonstrated a close relationship between NT-proBNP and systolic blood pressure, fasting plasma glucose, and total cholesterol. In the BNP ≥ 60 pg/ml group, odds ratio (OR) values were 1.80, 1.56 and 1.54 (female) and 3.74, 1.59 and 1.51 (male), respectively. In the BNP ≥ 80 pg/ml group, OR values were 2.45, 1.65 and 1.84 (female) and 4.61, 1.66 and 1.75 (male), respectively.

Conclusions: NT-proBNP was independently associated with the main metabolic risk factors (systolic blood pressure, fasting plasma glucose, and total cholesterol). These findings suggest that the combined determination of NT-proBNP and the main metabolic risk factors could be important in assessing cardiovascular morbidity.

Key words: B type natriuretic peptide, metabolic risk factors, correlation.

Introduction

B type natriuretic peptide (BNP) is a neurohormone synthesized and released from the cardiac ventricles in response to increased wall tension due to blood pressure in the left ventricle which leads to ventricle dilatation [1]. Changes in N-terminal pro-B type natriuretic peptide (NT-proBNP) have been observed in many cardiovascular diseases, including chronic heart

failure and left ventricular dysfunction. NT-proBNP can describe a subgroup of individuals with a high risk of cardiovascular disease [2]. The BNP plays an important role in regulating blood pressure, blood volume, and water and salt balance. An increase in BNP levels is the final common pathway in many cardiovascular pathological states [3]. With regard to the diagnosis of cardiovascular diseases, an explanation of the processes taking place in the vascular internal membrane is of particular importance [4]. NT-proBNP has been shown to exert a variety of metabolic effects. Complex metabolic and increase the risk of cardiovascular morbidity [5] disorders are related to cardiovascular diseases. The metabolic risk factors leading to cardiovascular disease and their main consequences may induce cardiovascular damage [6]. It has been shown that lipid and fatty acid metabolism influence the natriuretic peptides and that obese individuals have reduced natriuretic peptide levels. There were, however, conflicting data on the relationship between natriuretic peptide levels and other metabolic risk factors [7]. The association between NT-proBNP and metabolic risk factors is still unclear.

The aim of the present study was to determine the correlation between NT-proBNP and metabolic risk factors and to investigate the relationship and significance of the combined determination of NT-proBNP and metabolic risk factors.

Material and methods

Subjects

This study included 11,508 subjects (6209 men and 5299 women, average age 44.56 ±0.15 years) who underwent physical examinations in Sir Run Run Shaw Hospital of the Zhejiang University School of Medicine from July 2012 to June 2013. Subjects were examined for metabolic risk factors as well as NT-proBNP levels. Participants were asked to avoid a high fat and sugar diet for three days before the examination. Those aged 20–75 years were enrolled. The subjects were divided into 6 groups: group 0, aged below 30 years; group 1, 30–39 years; group 2, 40–49 years; group 3, 50–59 years; group 4, 60–69 years; and group 5; 70 years and above. Patients diagnosed with coronary atherosclerotic heart disease, myocardial hypertrophy, cardiac enlargement and cardiac dysfunction, or pulmonary or renal insufficiency were excluded, and subjects who were receiving medication for hypertension, diabetes and hyperlipidemia were also excluded. This study was approved by the Medical Ethics Committee of the Sir Run Run Shaw Hospital.

Measurement techniques

Fasting blood samples were obtained from each subject and phlebotomy was performed in a supine position, typically from 7 to 8 am. NT-proBNP levels were measured by an enzyme linked immunofluorescence method (BioMerieux Vidas 300 Shionogi, France). Samples were immediately centrifuged and measured within 1–2 h. The reference range of NT-proBNP was from 0 pg/ml to 100 pg/ml. Fasting plasma glucose levels were measured by the hexokinase method (Abbott c16000, USA). Triglyceride levels were measured by the glycerol phosphate oxidase method (Abbott c16000, USA). Cholesterol levels were measured by the cholesterol oxidase method (Abbott c16000, USA). Low-density lipoprotein cholesterol levels and high-density lipoprotein cholesterol were measured by the clearance assay method (Abbott c16000, USA). Waist circumference was measured using the WHO recommended method. Waist circumference was measured midway between the lowest rib and the iliac crest using an anthropometric tape. Blood pressure was measured using the method recommended by the China Hypertension Prevention Guidelines (2010 Edition). Blood pressure values were the means of two measurements performed on the left arm of the participant after rest for 10 min.

Assessment of metabolic risk factors

According to the uniform definition of the International Diabetes Federation (IDF) regarding metabolic syndrome in April 2005 [8] and the China Adult Dyslipidemia Prevention Guide (2007 Edition), metabolic risk factors include central obesity (waist circumference ≥ 90 cm in males or ≥ 80 cm in females), triglyceride (TG) level ≥ 1.7 mmol/l, systolic blood pressure (SBP) ≥ 130 mm Hg or diastolic blood pressure (DBP) ≥ 85 mm Hg, fasting plasma glucose (FPG) ≥ 5.6 mmol/l, high-density lipoprotein (HDL) < 1.04 mmol/l (male) or < 1.30 mmol/l (female), total cholesterol (TC) ≥ 5.18 mmol/l and low-density lipoprotein (LDL) ≥ 3.37 mmol/l.

According to the 2004 ACC expert consensus and domestic and overseas documentation, NT-proBNP levels were stratified into four groups (group 1: BNP ≥ 20 pg/ml; group 2: BNP ≥ 40 pg/ml; group 3: BNP ≥ 60 pg/ml; and group 4: BNP ≥ 80 pg/ml). The relationship between BNP by stratification and metabolic risk factors was analyzed.

Quality control

Data were collected by the coordinator, who received strict training, equipment was inspected, and random samples were obtained and retested. All biochemical indices were determined by designated staff on fixed instruments. These indices were controlled using standard quality control serum.

Table I. Characteristics of the study sample

Variables	Female (*N* = 5299)	Male (*N* = 6209)	Value of *p*
Age [years]	43.66 ±0.13	45.45 ±0.15	< 0.001
SBP [mm Hg]	116.08 ±0.19	124.83 ±0.22	< 0.001
DBP [mm Hg]	69.92 ±0.14	77.05 ±0.15	< 0.001
WC [cm]	75.72 ±0.10	87.53 ±0.11	< 0.001
FPG [mmol/l]	4.80 ±0.01	5.06 ±0.02	< 0.001
TG [mmol/l]	1.03 ±0.02	1.69 ±0.01	< 0.001
HDL-C [mmol/l]	1.40 ±0.03	1.16 ±0.04	< 0.001
TC [mmol/l]	4.62 ±0.01	4.86 ±0.02	< 0.001
LDL-C [mmol/l]	2.79 ±0.01	2.53 ±0.01	< 0.001
NT-proBNP [pg/ml]	23.13 ±0.22	14.30 ±0.33	< 0.001

Values are given as mean ± SE. SBP – systolic blood pressure, DBP – diastolic blood pressure, WC – waist circumference, FPG – fasting plasma glucose, TG – triglycerides, HDL – high-density lipoprotein, TC – total cholesterol, LDL – low-density lipoprotein, NT-proBNP – N-terminal pro-B type natriuretic peptide.

Statistical analysis

Input of descriptive data was performed by designated staff, and statistical analysis was carried out using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Quantitative data were described using mean ± SE. In order to investigate the association between NT-proBNP and the gender and age groups, we compared NT-proBNP levels using analysis of variance (ANOVA). A multiple linear regression model with step-wise selection was used to estimate the association between metabolic risk factors and NT-proBNP. Logistic regression analysis was used to determine the association between stratification of NT-proBNP and metabolic risk factors (BNP level was stratified into four groups which were analyzed and compared by logistic regression). Variables with p values < 0.05 were considered significant.

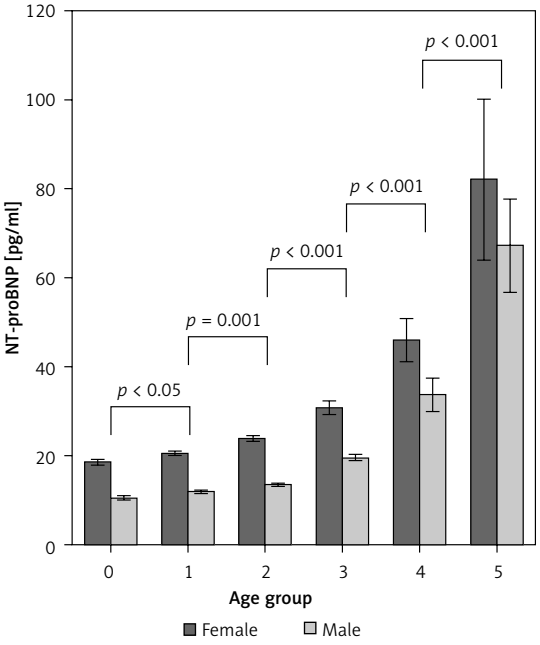

Figure 1. Gender-dependent level of BNP in different age groups

Results

Characteristics of the study sample (n = 11,508, 6209 men and 5299 women) are shown in Table I. The mean age of the female and male subjects was 43.66 years (SE 0.13 years) and 45.45 years (SE 0.15 years), respectively (p < 0.001). The mean NT-proBNP level was 23.13 pg/ml (SE, 0.22 pg/ml) in female and 14.30 pg/ml (SE, 0.33 pg/ml) in male subjects (p < 0.001). All other variables were significantly higher in men than in women (p < 0.001).

Association between NT-proBNP and different age groups

NT-proBNP increased gradually with increasing age (group 1 vs. group 0, p < 0.05, and vs. other groups, p < 0.001) (Figure 1).

Association between NT-proBNP and different gender groups

The BNP increased more significantly in women than in men (p < 0.001). In both groups, BNP increased more significantly in each age group (group 1 vs. group 0: p < 0.05, and versus other groups: p < 0.001) (Figure 2).

Multivariate regression analysis of the relationship between NT-proBNP level and metabolic risk factors

The results of multivariate regression models of the relationship between NT-proBNP level

and metabolic risk factors are shown in Table II. In these models, a positive association was observed between NT-proBNP levels and systolic blood pressure ($p < 0.001$), fasting plasma glucose ($p < 0.05$), and total cholesterol ($p < 0.05$). NT-proBNP levels were inversely associated with diastolic blood pressure, waist circumference, triglyceride, high-density lipoprotein and low-density lipoprotein ($p < 0.05$) (Table II).

Logistic regression analysis of the relationship between NT-proBNP and metabolic risk factors

Logistic regression analysis of the relationship between NT-proBNP and metabolic risk factors showed that odds ratio values of systolic blood pressure, blood glucose and total cholesterol increased gradually in the four groups (group 1: BNP ≥ 20 pg/ml; group 2: BNP ≥ 40 pg/ml; group 3: BNP ≥ 60 pg/ml; group 4: BNP ≥ 80 pg/ml). NT-proBNP and systolic blood pressure had the strongest correlation in metabolic risk factors. Odds ratio values of systolic blood pressure were 1.54, 1.80, 2.45 relatively in women, 2.72, 3.74, 4.61 relatively in men in group 2, group 3, group 4 ($p < 0.01$). Odds ratio values of blood glucose and total cholesterol increased gradually with increased BNP stratification as well ($p < 0.05$), especially in group 3, group 4. Other variables have no significantly effect in the BNP groups (Tables III, IV).

Discussion

B type natriuretic peptide is a peptide hormone produced mainly by ventricular myocytes and is a natural antagonist in the sympathetic nervous system and renin–angiotensin-aldosterone system (RASS) [9]. Research has shown that an increased level of BNP is the final common pathway

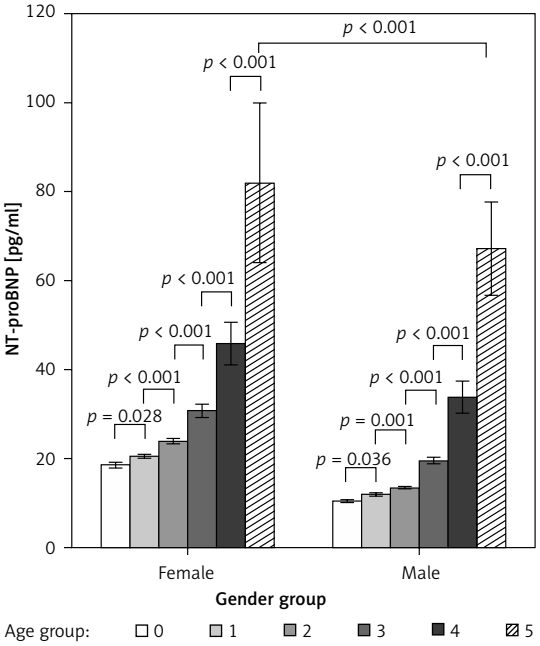

Figure 2. Age-dependent level of BNP in different age and gender groups

in many types of cardiovascular pathology. The BNP level increases with ischemia, cardiovascular fibrosis and coronary endothelial dysfunction, and indicates the predictive value of BNP in cardiovascular diseases [10]. Research has shown that metabolic risk factors and age are closely related to cardiovascular diseases [11].

This study used correlation analysis to determine the association between NT-proBNP and metabolic risk factors. NT-proBNP increased gradually with increasing age. The BNP levels were significantly higher in women than in men. The results of multivariate regression analysis showed a positive relationship between NT-proBNP and metabolic risk factors such as systolic blood pres-

Table II. Multivariate regression analysis of the relationship between BNP and metabolic risk factors

Variables	Total			Male			Female		
	β	Value of *p*	95% CI	β	Value of *p*	95% CI	β	Value of *p*	95% CI
Age [years]	0.22	< 0.001	4.31–5.13	0.24	< 0.001	3.91–4.80	0.24	< 0.001	4.96–6.54
SBP [mm Hg]	0.24	< 0.001	0.28–0.36	0.26	< 0.001	0.27–0.36	0.20	< 0.001	0.24–0.37
DBP [mm Hg]	–0.19	< 0.001	–0.40–0.29	–0.17	< 0.001	–0.33–0.21	–0.16	< 0.001	–0.45—0.26
WC [cm]	–0.10	< 0.001	–0.26–0.16	–0.02	0.124	–0.11–0.01	0.01	0.684	–0.08–0.12
FPG [mmol/l]	0.03	< 0.001	0.17–1.20	0.04	0.003	0.26–1.24	0.02	0.049	0.19–1.43
TG [mmol/l]	–0.07	< 0.001	–1.80–0.65	–0.03	0.275	–0.90–0.26	–0.09	< 0.001	–4.23–1.52
HDL [mmol/l]	0.03	0.082	–0.23–3.58	0.06	0.001	1.60–6.00	–0.08	< 0.001	–9.45–2.80
TC [mmol/l]	0.04	0.097	–0.18–2.14	–0.034	0.31	–1.90–0.60	0.13	0.001	1.34–5.55
LDL [mmol/l]	–0.10	< 0.001	–4.13–1.65	–0.050	0.091	–2.51–0.20	–0.14	< 0.001	–6.84–2.42

The abbreviations are the same as in the Table I. CI indicates confidence interval.

Table III. Logistic regression analysis of the relationship between NT-proBNP and metabolic risk factors in women

Variables	Group 1		Group 2		Group 3		Group 4	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
SBP [mm Hg]	1.33*	1.12–1.57	1.54**	1.23–1.92	1.80**	1.30–2.49	2.45**	1.58–3.80
DBP [mm Hg]	1.08	0.86–1.35	0.99	0.74–1.32	1.11	0.73–1.68	0.89	0.50–1.59
WC [cm]	1.10	0.96–1.26	1.13	0.94–1.36	1.14	0.87–1.51	1.06	0.71–1.59
FPG [mmol/l]	1.00	0.78–1.28	1.17*	0.85–1.62	1.56*	0.94–2.67	1.65*	0.79–2.99
TG [mmol/l]	0.73	0.59–0.90	0.82	0.62–1.10	0.98	0.65–1.46	0.92	0.52–1.63
HDL [mmol/l]	1.02	0.90–1.15	0.97	0.82–1.16	1.21	0.93–1.59	1.25	0.85–1.84
TC [mmol/l]	1.03	0.85–1.25	1.08	0.83–1.41	1.54*	0.83–2.53	1.84*	1.09–3.12
LDL [mmol/l]	0.81	0.66–1.00	0.72	0.54–0.96	0.63	0.40–0.97	0.43	0.23–0.79

*The abbreviations are the same as in the Table I. *p < 0.05: metabolic risk factors have an influence on NT-proBNP. **p < 0.01: metabolic risk factors have a significant influence on NT-proBNP.*

Table IV. Logistic regression analysis of the relationship between NT-proBNP and metabolic risk factors in men

Variables	Group 1		Group 2		Group 3		Group 4	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
SBP [mm Hg]	1.77*	1.48–2.12	2.72**	2.01–3.67	3.74**	2.45–5.73	4.61**	2.64–8.02
DBP [mm Hg)]	0.82	0.67–1.01	0.62	0.46–0.89	0.49	0.30–0.82	0.38	0.19–0.75
WC [cm]	0.97	0.83–1.15	0.98	0.73–1.31	0.97	0.63–1.48	1.01	0.58–1.75
FPG [mmol/l]	1.27*	0.88–1.85	1.50*	1.22–1.84	1.59*	0.89–2.94	1.66*	0.88–3.14
TG [mmol/l]	0.57	0.47–0.69	0.41	0.28–0.59	0.40	0.24–0.69	0.35	0.17–0.71
HDL [mmol/l]	0.92	0.77–1.09	0.96	0.71–1.30	0.76	0.48–1.22	0.77	0.42–1.42
TC [mmol/l]	0.95	0.76–1.19	0.92	0.60–1.40	1.51*	0.79–2.83	1.75*	0.83–3.67
LDL [mmol/l]	0.78	0.62–0.97	0.66	0.44–1.00	0.41	0.22–0.76	0.31	0.14–0.71

*The abbreviations are the same as in the Table I. *p < 0.05: metabolic risk factors have an influence on NT-proBNP. **p < 0.01: metabolic risk factors have a significant influence on NT-proBNP.*

sure, fasting plasma glucose and total cholesterol. NT-proBNP levels were inversely associated with diastolic blood pressure, waist circumference, triglyceride, high-density lipoprotein and low-density lipoprotein. Logistic regression analysis suggested that the main factors affecting NT-proBNP were systolic blood pressure, fasting plasma glucose and total cholesterol. The influence was enhanced by increased NT-proBNP levels. These findings show that NT-proBNP may be related to the main metabolic risk factors, and are consistent mostly with the study by Bao *et al.* [12]. However, Bao's study only included a small sample and an older average age group. A relationship was found between several metabolic risk factors such as diastolic blood pressure, fasting plasma glucose, lipid profile, etc. and low circulating natriuretic peptide levels. Meanwhile an inverse relationship between plasma NT-proBNP levels and fasting plasma glucose and total cholesterol was found in some studies. Unlike Bao's study, a positive relationship between NT-proBNP and these metabolic risk factors was found in our study. There were some advantages in our study, including a very large sample size and younger average age groups (lower than 45 years old). Crucially, the relationship between BNP by stratification and metabolic risk factors was analyzed in our study. The effect of NT-proBNP on systolic blood pressure, fasting plasma glucose and total cholesterol was greater in the BNP ≥ 60 pg/ml group. The groups with lower NT-proBNP were analyzed by stratification and may have significance for assessing cardiovascular metabolic disorders.

The mechanism involved in the association between NT-proBNP and metabolic risk factors may be related to the following:

1. The relationship between NT-proBNP and both age and sex

NT-proBNP increased gradually with increasing age. It was likely that (1) cardiac diastolic func-

tion decreased with increasing age. (2) Excretion of BNP in the kidney decreased gradually with increasing age [13]. In this study, the decrease in NT-proBNP was lower in men than in women. Presumably among those with central obesity, waist circumference was significantly higher in men than in women (87.53 ±0.11 vs. 75.72 ±0.10, $p < 0.001$). It was reported that obesity is associated with lower levels of BNP expression [14]. The level of NT-proBNP might also be related to sex hormone levels.

2. Relationship between NT-proBNP and blood pressure

The heart pressure of patients with metabolic abnormalities increases as systolic pressure rises, causing changes in ventricular volume and increased ventricular wall stiffness, leading to increases in ventricular muscle subjected to stretch or wall pressure and increased concentrations of BNP [15]. Diastolic blood pressure may reflect the influence of pulse pressure, as increased pulse pressure (reduced arterial compliance) is likely to be accompanied by lower diastolic blood pressure [16]. It is possible that mild diastolic dysfunction leads to low diastolic blood pressure in abnormal metabolism [17].

3. Relationship between NT-proBNP and fasting plasma glucose

Hyperglycemia increases target organ injury in patients with essential hypertension, and increases the occurrence and development of the disease [18]. In addition, hyperglycemia activates endothelial cells, macrophages and polymorphonuclear leukocytes to release endothelin 1 (ET 1) and ET 1 immune-like activator. Increased NT-proBNP levels suggest damage to cardiac function in patients with hyperglycemia [19]. Dawn *et al.* [20] recently confirmed that patients with diabetes and high levels of BNP were more prone to strokes.

4. Relationship between NT-proBNP and obesity and lipid abnormalities

Logistic regression analysis suggested that there was little association or even a negative association between NT-proBNP level and waist circumference, triglycerides, low-density lipoprotein and high-density lipoprotein. The mechanism involved in this process may be as follows: (1) Increased waist circumference indicates central obesity [21]. Lower BNP level in obese subjects may be attributed to increased removal of natriuretic peptide from the circulation by adipocytes through abundant natriuretic peptide clearance receptors in the adipose tissue of obese people. The clearance receptor of BNP (natriuretic peptide receptor C) is often highly expressed in the adipose tissue of obese persons, which leads to reduced levels of BNP in patients with obesity [22]. Wang examined BNP levels in 3389 volunteers, and the concentrations of BNP in obese persons were significantly lower than those in normal weight subjects ($p < 0.001$) [23]. (2) Lipid abnormalities are risk factors for cardiovascular disease, and cause atherosclerosis, an increase in heart load and tend to escalate BNP secretion. It has been reported that BNP can dissolve fat tissues [24]. In addition, dyslipidemia may cause vascular endothelial cell injury, leading to an increase in neutral endopeptidase release, thus increasing the degradation of BNP [25]. Fat has little effect on BNP concentration, and can even have a negative effect, possibly because abnormal blood lipid escalates NT-proBNP secretion. A negative correlation was found between both triglycerides and low-density lipoprotein and BNP in this study. However, it was also found that total cholesterol was positively correlated with NT-proBNP. An effect on cholesterol, especially in those with high values of NT-proBNP (BNP ≥ 60 pg/ml), was observed. Cholesterol is one of the most important risk factors for atherosclerosis [26]. With an increase in total cholesterol level in acute coronary events, the risk of atherosclerosis onset is increased [27], and it is speculated that high total cholesterol may result in hardening of the coronary arteries, an increasing cause of myocardial ischemia, leading to increased NT-proBNP [28]. However, due to the effect of cardiovascular diseases, such as atherosclerosis resulting from high blood lipid, on NT-proBNP concentration, a higher concentration of NT-proBNP (≥ 60 pg/ml) has a more significant influence than lower concentrations of NT-proBNP (≥ 40 pg/ml) on cholesterol.

There are certain limitations related to our study. Firstly, this cross-sectional study was performed in subjects undergoing physical examinations, so the sample chosen may not be totally representative. Secondly, some parameters were not examined. There are reports suggesting that monitoring a combination of BNP, serum uric acid and eGFR may be useful in the management of patients with congestive heart failure.

In conclusion, this study showed that there is a relationship between the level of NT-proBNP and metabolic risk factors. NT-proBNP level is mainly related to systolic blood pressure, plasma glucose and total cholesterol. The combined determination of the main metabolic risk factors and NT-proBNP enables further evaluation of cardiovascular diseases. Also, an NT-proBNP concentration of 60 pg/ml or greater could be an indicator of early cardiovascular metabolic disorder. Prospective studies are needed to investigate the relationships between NT-proBNP levels and parameters such as serum uric acid, eGFR, fatty liver and early atherosclerosis. The impact of lower natriuretic peptide levels and metabolic risk factors on early cardiovascular morbidity and late cardiovascular events should also be investigated.

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Conflict of interest

The authors declare no conflict of interest.

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