Relationship of brain natriuretic peptide with metabolic syndrome parameters: an observational study

Beyin natriüretik peptidin metabolik sendrom parametreleri ile ilişkisi: Gözlemsel bir çalışma

Sanem Öztekin, Özlem Karakurt[1], Nuray Yazıhan[2], İlker Ünal[3]

Clinic of Internal Medicine, Nallıhan State Hospital, Ankara
[1]Clinic of Cardiology, Balıkesir State Hospital, Balıkesir
[2]Department of Pathophysiology, Faculty of Medicine, Ankara University, Ankara,
[3]Department of Biostatistics, Faculty of Medicine, Çukurova University, Adana-*Turkey*

ABSTRACT

Objective: Metabolic syndrome (MS) was independently associated with increased risk of incident heart failure and coronary artery disease. In this study, we sought to identify whether there is an association between metabolic syndrome components and left ventricular diastolic functions and brain natriuretic peptide (BNP) levels.

Methods: This study is a cross-sectional, observational study. Two hundred consecutive patients with MS were selected to form the study population. Echocardiographic parameters and BNP were determined. Mann-Whitney U test and Kruskal-Wallis test were used to compare BNP levels in categorical variables. Spearman rank correlation analysis was used to investigate the correlation between BNP level and other numerical variables. Linear regression analysis was used to find the variables affecting the BNP level.

Results: BNP level was higher in females than males [11.14 (0.12-87) vs 7.49 (0.01-99) pg/dl, p=0.04]. None of the MS parameters affects the BNP level in MS patients. MS criteria number that the patient had was not related to BNP level. Sixty seven percent of patients had left ventricular (LV) diastolic dysfunction. BNP was independent from LV diastolic function. Multiple linear regression analysis demonstrated that having diabetes mellitus increases BNP level by 7.73 unit (β=7.73, 95% CI - 2.321 - 13.149, p=0.006).

Conclusion: None of the MS parameters affects the BNP level in MS patients. Diastolic dysfunction existence did not affect the BNP level of MS patients. There is an association between diabetes mellitus and BNP, independent of left ventricle diastolic functions.

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Key words: Brain natriuretic peptide, metabolic syndrome, diastolic dysfunction, regression analysis

ÖZET

Amaç: Metabolik sendromun (MS) bağımsız olarak kalp yetmezliği ve koroner arter hastalığı ile ilişkili olduğu bilinmektedir. Bu çalışmada MS bileşenleriyle sol ventrikül (SV) diyastolik fonksiyonları ve beyin natriüretik peptit (BNP) seviyeleri arasında ilişki olup olmadığını araştırmayı planladık.

Yöntemler: Bu çalışma kesitsel ve gözlemsel bir çalışmadır. Metabolik sendromlu iki yüz hasta çalışma grubunu oluşturmak için seçildi. Ekokardiyografik belirteçler ve BNP çalışıldı. Kategorik değişkenlerdeki BNP düzeyini karşılaştırmak için Mann-Whitney U testi ve Kruskal Wallis testi kullanıldı. BNP seviyesi ile diğer sayısal değişkenler arasındaki korelasyonu araştırmak için Spearman Rank korelasyon analizi kullanıldı. BNP seviyesini etkileyen değişkenleri ve onların beta katsayılarını bulmak için lineer regresyon analizi kullanıldı.

Bulgular: Bayanlarda BNP seviyesi erkeklere göre daha yüksekti [11.14 (0.12-87) karşın 7.49 (0.01-99) pg/dl, p=0.04]. MS parametrelerinden hiçbiri MS hastalarındaki BNP seviyesini etkilememekteydi. Hastanın sahip olduğu MS kriter sayısı BNP seviyesini değiştirmedi. Hastaların yüzde altmış yedisinde SV diyastolik disfonksiyonu vardı. BNP diyastolik disfonksiyondan bağımsızdı. Tek değişken analizinden sonra p değeri 0.1'in altında çıkan değişkenlere çoklu lineer regresyon analizi uygulandı. Sonuçlara göre diyabetes mellitus (DM)'ün varlığı BNP seviyesini 7.73 birim artmasına sebep olmaktadır (β=7.73, %95GA-321 - 13.149, p=0.006).

Sonuç: MS parametrelerinden hiçbiri MS hastalarındaki BNP seviyesini etkilememekteydi. Diyastolik disfonksiyon varlığı MS hastalarındaki BNP seviyesini etkilememekteydi. Diyabetes mellitus ile BNP arasında SV diyastolik fonksiyonlarından bağımsız olarak ilişki vardı. Diyabetes mellituslu olmak BNP seviyesini artırmaktaydı. *(Anadolu Kardiyol Derg 2011; 11: 678-84)*

Anahtar kelimeler: Beyin natriüretik peptit, metabolik sendrom, diyastolik disfonksiyon, regresyon analizi

Address for Correspondence/Yazışma Adresi: Dr. Özlem Karakurt, Sağlık Bakanlığı, Balıkesir Devlet Hastanesi, Kardiyoloji Kliniği, Balıkesir-*Türkiye*
Phone: +90 266 245 90 20 E-mail: ozlemkarakurt55@yahoo.com

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Introduction

The metabolic syndrome (MS), also called insulin resistance syndrome, consists of a clustering of several metabolic and physiological risk factors, including obesity and its central distribution, impaired glucose regulation, dyslipidemia [elevated triglycerides and/or low high-density lipoprotein (HDL) cholesterol], and hypertension. MS has received great attention after being understood that it carries increased risk for development of type 2 diabetes mellitus and atherosclerotic cardiovascular disease. Studies demonstrated that MS was also associated with left ventricular hypertrophy and myocardial dysfunction (1). Voulgari et al. (2) found that MS patients have higher left ventricle myocardial performance index (Tei index) values indicating the depressed ventricle functions compared to the normal subjects. MS predicted congestive heart failure independent of interim myocardial infarction and prevalent diabetes in elderly Finns during a follow up of 20 years (3).

B-type natriuretic peptide (BNP) is a 32-amino acid polypeptide secreted by ventricular myocytes in case of increased ventricular stretch and wall tension. This peptide plays an important role in the regulation of blood pressure, blood volume, and sodium balance. After secretion, the BNP precursor is split into the biologically active peptide and the more stable N-terminal fragment (NT-proBNP). Measurement of circulating levels of BNP or NT-proBNP has been recommended in the diagnosis and prognosis of patients with symptoms of left ventricular dysfunction and for stratification of risk in patients with acute coronary syndromes (4-6). In two studies, NT-proBNP level was found to be the same in MS patients compared to the normal subjects (7, 8). On the other hand, Olsen et al. (9) demonstrated that NT-proBNP level was decreased in MS and also NT-proBNP-pulse pressure relationship was blunted in these patients.

The results of the studies are contradictive, and the relationship of BNP with MS parameters, independent of left ventricular diastolic function has not been studied before.

In this study, we sought to identify whether there is an association between metabolic syndrome components, left ventricle diastolic functions and brain natriuretic peptide (BNP).

Methods

Study design

This study is a cross-sectional, observational study.

Study population

The study was performed in Turkey Ministry of Health Ankara Dışkapı Yıldırım Beyazıt Research and Training Hospital. Participants enrolled in the study were selected among patients admitted to the internal medicine outpatient clinic from January 2008 to August 2009. Two hundred consecutive patients with MS were thus selected to form the study population.

The diagnosis of metabolic syndrome based on NCEP-ATP III (National cholesterol education program-adult treatment panel III) guidelines is made if more than three of the following risk factors are present: 1) abdominal obesity: waist circumference >102 cm in men and >88 cm in women; 2) hypertriglyceridemia: ≥150 mg/dL; 3) low levels of HDL-cholesterol: <40 mg/dL in men and <50 mg/ dL in women; 4) high blood pressure: ≥130/85 mm Hg; 5) high fasting glucose: ≥110 mg/dL (10).

Exclusion criteria were defined as the following: presence of atrial fibrillation or flutter, bundle branch block or any other intraventricular conduction delay; recent major surgical procedure in the last month; acute coronary syndromes; malignancies; pulmonary emboli; renal failure; previous myocardial infarction or coronary artery bypass graft operation, stroke, heart failure history; congenital, pericardial, or severe valvular heart disease; left ventricular (LV) ejection fraction <55%; pregnancy; thyroid disorders; concomitant inflammatory diseases such as infections and autoimmune disorders.

The study was approved by the Hospital's Ethics Committee and all patients gave informed written consent.

Anthropometric measurements

Anthropometric measurements obtained in this study included height, weight, body mass index (BMI), and waist circumference. Body mass index was computed as weight divided by height squared (kg/m^2). The waist circumference was measured at the high point of the iliac crest at normal respiration to the nearest 0.1 cm. Systolic and diastolic blood pressure were measured in the upper arm after 5 min of rest; the average of the two measurements was taken in account.

Blood sampling protocol

Peripheral venous blood samples were obtained following an overnight fasting period. The serum was separated from the cells by centrifugation at 3000 rpm for 10 min and stored at -78°C until measurement of BNP and other parameters. Blood glucose, lipid parameters, liver function tests, Hb A1C were measured by automated analyzers (P800 Roche Hitachi and Olympus AU 5200, Olympus corp., USA). Low density lipoprotein (LDL) cholesterol was calculated using Friedewald formula [LDL= total cholesterol-high density lipoprotein (HDL)+ triglyceride (TG)/5]. Complete blood count was completed by automated analyzer (ROCHE Sysmex SE 9000, Roche Diagnostics Corp. Indianapolis, US).

Plasma insulin levels were measured using a commercial human insulin Enzyme Linked Immunosorbent Assay (ELISA) kit (Linco Research, MO, USA) following the protocol suggested by the manufacturer.

Serum BNP level was measured using Phoneix Pharmaceuticals Human BNP (Germany) ELISA kit and reference range was 0 to 100 pg/dl.

Echocardiography measurements

All patients underwent two-dimensional transthoracic and Doppler echocardiographic studies in the left lateral decubitis

position from multiple windows. A GE Vivid 3 (Israel) echocardiograph with a 2-5 MHz transducer was used. A Doppler velocity range was selected as -20 to 20 cm/s. The LV volumes and ejection fraction were obtained by the modified biplane Simpson's method. Left atrial, LV end-diastolic and end-systolic dimensions, interventricular septal and end-diastolic LV posterior wall thicknesses were measured from the parasternal long-axis view. From the apical four-chamber view, mitral inflow pulsed-wave velocities during early (E) and late (A) filling were measured and then the tissue Doppler investigation (TDI) cursor was placed on the lateral wall of the left ventricle, 1 cm apical to the mitral annulus. From TDI of the LV lateral annulus: systolic velocity (Sa), early diastolic velocity (Ea), and late diastolic velocity (Aa) were recorded. LV diastolic function was graded as: grade 1 if the mitral E/A ratio is <0.8, deceleration time (DT) is >200 ms, isovolumic relaxation time (IVRT) is ≥100 ms, annular Ea is <8 cm/s, and the E/Ea ratio is <8; grade 2 if the the mitral E/A ratio is 0.8 to 1.5 (pseudonormal) and decreases by ≥50% during the Valsalva maneuver, the E/Ea (average) ratio is 9 to 12, and Ea is <8 cm/s; grade 3 if the E/A ratio ≥2, DT <160 ms, IVRT ≤ 60 ms, and average E/Ea ratio >13 (or septal E/Ea ≥15 and lateral E/Ea >12) (11).

Statistical analysis

Data were analyzed with the software SPSS version 19.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Categorical variables were expressed as numbers (n) and percentages (%), whereas continuous variables were reported as mean and standard deviation and as median and minimum-maximum where appropriate. Mann-Whitney U test and Kruskal-Wallis test were used to compare BNP levels between groups. Spearman Rank correlation analysis was used to investigate the correlation between BNP level and other numerical variables. Linear regression analysis was used to find the variables affecting the BNP level. A p value of <0.05 was considered significant.

Results

Basal characteristics

The demographic, clinical and laboratory characteristics of the patients are shown in Table 1. Forty-nine male (24.4%) and 151 female (75.6%) patients were enrolled in the study. Among them 10 patients (5%) were healthy, 59 patients (29.4%) were overweight, 121 patients (60.2%) were obese and 10 patients (5%) were morbidly obese. 80.6% of patients were non-smokers. One hundred and fifty eight patients (79.1%) were hypertensive. 142 patients (71.1%) fasting plasma glucose were over 110 mg/dl. Thirty patients (14.9%) had impaired fasting plasma glucose (110≤FPG<126 mg/dl). Twenty-eight patients (13.9%) had glucose intolerance (140≤ postprandial plasma glucose <200 mg/dl). Fifty eight percent of patients were diabetic. One hundred and sixty patients (80.1%) waist circumference were above the upper limit. One hundred and fifty five patients (77.6%) HDL-cholesterol were low, 159 patients (79.6%) TG values were high (Table 1). On the echocardiographic examination mean LV ejection fraction was 68±3.4%.

Overall, 43.8% of patients had 3 components, 31.8% of 4 components, 24.4% of 5 components of MS. Increased waist circumference was the most common observed MS criteria in our patients.

BNP values in MS subgroups

Mean BNP level was 7.73 (0.01-99) pg/dl. There were no differences (p=0.94) in BNP levels between MS groups with 3, 4 and 5 criteria (Table 2).

Relationship between BNP values and MS parameters

BNP level was higher in females than males (p=0.04). There was no any difference in the BNP level between patients with or without hypertension (p=0.66). BNP levels were the same between patients with normal or increased TG level (p=0.77) and with normal or increased waist circumference (p=0.31). Similarly, there were no differences between BMI subgroups (p=0.86).

There was no any difference (p>0.05) in BNP levels between subgroups with normal and impaired fasting, postprandial blood glucose level. BNP level was same between diabetic and non

Table 1. Basal characteristics of patients

Variables	Descriptive statistics
Age, years	54.32±8.48
Female, n (%)	148 (77.1)
Male, n (%)	44 (22.9)
BMI, kg/m^2	32.0±4.49
Smoking, n (%)	37 (19.3)
Hypertension, n (%)	152 (79.2)
Fasting plasma glucose, mg/dl	145.18 (64-380)
Mean postprandial blood glucose, mg/dl	203.1±105.5
Waist circumference, cm	103.5±9.84
HDL cholesterol, mg/dl	44.63±12.15
TG, mg/dl	224.33 (40-1729)
Systolic blood pressure, mmHg	132.06±19.6
Diastolic blood pressure, mmHg	79.4±11.8

Data are presented as number (percentage), mean±SD and median (range) values
BMI - body mass index, HDL - high density lipoprotein, TG - triglyceride

Table 2. BNP values in MS subgroups

MS criteria number patient has	BNP, pg/dl
3 criteria positive	7.99 (0.01-87)
4 criteria positive	7.14 (0.01-99)
5 criteria positive	9.40 (0.02-89)
p*	0.94

Data are presented as median (minimum-maximum) values
*Kruskal-Wallis test
BNP - brain natriuretic peptide, MS - metabolic syndrome

diabetic patients (p=0.08). In patients with normal HOMA index (<2.5) and no insulin resistance BNP level was 7.63 (0.02-99), whereas in patients with insulin resistance, with increased HOMA index (>2.5) it was 11.19 (0.01-83) pg/dl (p=0.22) (Table 3).

Univariate analysis showed that gender affects the BNP level. Multiple linear regression analysis was used for the variables that have p value below 0.1. Results are summarized in Table 4. According to the results presence of diabetes mellitus increases BNP level by 7.73 units (β=7.73, 95% CI 2.321-13.149, p=0.006).

BNP values according to diastolic dysfunction grades in MS patients

Of 200 patients, 63% of patients had grade 1, 4%-grade 2 LV diastolic dysfunction and 32.3% of patients had normal diastolic function. Diastolic dysfunction incidence was the same between patients who have 3 and 4 and 5 components of MS. Presence of diabetes mellitus did not change diastolic dysfunction grade of patients.

BNP level was independent from LV diastolic function. In patients with normal LV diastolic function BNP level was 7.59 (0.01-87) pg/dl, in grade 1 diastolic dysfunction 7.70 (0.02-99) pg/dl and in grade 2 diastolic dysfunction 12.10 (5.10-22) pg/dl (p=0.57) (Table 5).

Discussion

We demonstrated that none of the MS parameters affects the BNP level. Only in multiple linear regression analysis diabetes mellitus presence was found to be related to increased BNP level. Interestingly female gender was associated to increased BNP level. In our study, diastolic dysfunction prevalence was 2 fold of the previous reports (67.7% of the all MS patients). LV diastolic function grade did not affect BNP level. As a result, in MS patients diastolic dysfunction may be much more common than the expected and BNP cannot be used as a diagnostic marker of diastolic function and BNP level is independent of MS parameters.

Effect of MS on cardiovascular system has been demonstrated in many studies. In a population of 65 years and older age, age- and race-adjusted hazard ratios (HRs) for coronary heart disease (CHD) and congestive heart failure (CHF) were 1.30, 1.40 for women and 1.35, 1.51 for men, respectively (12). In 20-year follow-up study of 1032 Finns, MS by all four criteria was significantly associated with a 1.45-1.74-fold risk for incident CHF after the adjustment for confounding factors. When subjects with interim myocardial infarction during the follow-up and with prevalent diabetes were excluded, the MS was significantly associated with a 1.37-1.87-fold risk for incident CHF after the adjustment for confounding factors (3).

In the Cardiovascular Health Study presence of MS and elevated inflammation markers were independently associated with increased CHF risk (hazard ratios: 1.32, for MS; 1.53 for CRP; 1.37 for IL-6) (13). After adjusting for other confounders, participants with MS were twice as likely to have LV hypertrophy as participants without MS. The association of LV hypertrophy with MS remained strong (OR=1.67) when hypertension was added to the model (14).

Metabolic syndrome was also found to be associated with increased LV dimension, mass, relative wall thickness, left atrial diameter, a higher prevalence of LV hypertrophy, with lower ejection fraction, mid wall shortening and mitral E/A ratio after controlling for confounders (15). In another study, it was demonstrated that TDI-derived septal E wave velocity and global E

Table 3. BNP values and MS parameters

Variables	Subgroups	BNP, pg/dl	p*
Hypertension	Hypertensives	7.70 (0.01-99)	0.66
	Non hypertensives	9.70 (0.01-87)	
Diabetes mellitus	Diabetics	9.70 (0.01-99)	0.08
	Non diabetics	7.17 (0.20-92)	
Waist circumference, cm	Normal	8.92 (0.01-99)	0.31
	Increased	7.63 (0.01-92)	
Triglyceride, mg/dl	Normal	8.01 (0.01-87)	0.77
	Increased	7.73 (0.01-99)	
Gender	Female	11.14 (0.12-87)	0.04
	Male	7.49 (0.01-99)	
BMI, kg/m^2	Healthy	7.77 (0.32-83)	0.86
	Overweight	8.41 (0.01-99)	
	Grade 1 and 2 obese	7.63 (0.01-92)	
	Morbid obese	4.74 (0.20-48.27)	
HOMA index	Normal	7.63 (0.02-99)	0.22
	Increased	11.19 (0.01-83)	

Data are presented as median (minimum-maximum) values
*Mann-Whitney and Kruskal-Wallis tests
BMI - body mass index, BNP - brain natriuretic peptide, HOMA - homeostatic model assessment, MS - metabolic syndrome

Table 4. Multiple linear regression analysis of association of BNP level with MS variables

Variable	Beta coefficient	95% Confidence interval	p
Diabetes mellitus presence	7.73	2.321-13.149	0.006

*Multiple linear regression analysis was used for the variables that have p value below 0.1
BNP - brain natriuretic peptide, MS - metabolic syndrome

Table 5. BNP values according to diastolic dysfunction grades in MS patients

LV diastolic function grade	BNP, pg/dl
Normal LV diastolic function	7.59 (0.01-87)
Grade 1 diastolic dysfunction	7.70 (0.02-99)
Grade 2 diastolic dysfunction	12.10 (5.10-22)
p*	0.57

Data are presented as median (minimum-maximum) values
*Kruskal-Wallis test
BNP - brain natriuretic peptide, LV - left ventricle, MS - metabolic syndrome

wave velocity were significantly lower in both the MS and pre-metabolic syndrome than in the absent group (16). These findings suggest that there is a progressive impairment in LV relaxation as the number of MS criteria increase. Turhan et al. (17) demonstrated that deceleration time, isovolumic relaxation time and isovolumic contraction time were significantly higher and ejection time and E/A ratio were significantly lower in metabolic syndrome group compared with control group. The myocardial performance index an index of global ventricular function was found to be significantly higher in patients with MS compared with control subjects (17).

Metabolic syndrome is an important predictor of subclinical myocardial dysfunction in patients without overt cardiovascular disease. Number of the features of the MS was associated with the degree of myocardial dysfunction (1, 18). Azevedo et al. (15) supported these findings demonstrating that after adjusting for systolic blood pressure, as the MS components number increase left ventricle mass, posterior wall and interventricular septum thickness, left atrial diameter, heart failure and diastolic dysfunction incidence increases too. Butler et al. (19) reported that MS was independently associated with 1.5-2 fold increased risk of incident heart failure. As we expect there is an increased diastolic dysfunction prevalence in MS patients and diastolic dysfunction prevalence is reported to be 35% in patients with MS, this accounts for approximately 4 fold increased risk compared to the normal participants carrying 7-9% diastolic dysfunction risk (16). Metabolic syndrome with high waist circumference, low HDL, high blood pressure, elevated CRP or IL-6 were associated with incident CHF. Participants with both MS and an elevated inflammation marker had a lower time free from CHF compared with participants with neither or either of MS or an inflammation marker (13).

Many of the MS components cause CHF independently. For example in the Framingham study, diabetes mellitus was found to be associated with increased heart failure development risk (20). In the HERS (Heart and Estrogen/progestin Replacement Study), diabetes was the strongest independent risk factor for development of HF, with an adjusted hazard ratio of 3.1. In a cohort of type 2 DM patients it has been demonstrated that each 1% increase in HbA1C was associated with 8% increased risk of HF hospitalization or HF death even after adjusting for other risk factors (21).

Changes in diabetic myocardium may be explained in three main categories. Firstly, insulin may function as a growth factor in the myocardium, a notion supported by experimental observations of increased myocardial mass and decreased cardiac output in rats with sustained hyperinsulinemia (22, 23). Secondly, hyperinsulinemia activates the sympathetic nervous system, which is a presumed causal factor for HF (24, 25). Thirdly, insulin resistance has recently been shown to increase the trophic effects of angiotensin II on cellular hypertrophy and collagen production in patients with hypertension, which leads to myocardial hypertrophy and fibrosis, both key substrates for HF (26). Fourthly, advanced glycosylation end-products are produced at a greatly accelerated pace in insulin-resistant people, which leads to increased collagen cross linking and myocardial stiffness (27).

All these factors contribute to myocyte hypertrophy, perivascular fibrosis, increased collagen deposition, deposition of advanced glycation end products and biochemically decreased glucose utilization, increased fatty acid utilization, increased inflammation markers, renin- angiotensin- aldosterone system activation, increased sympathetic activation and epinephrine, and oxidative stress (26, 28-34). Metabolic syndrome has numerous plausible direct myocardial effects, which are related to insulin resistance and accompanying hyperinsulinemia.

All these biochemical and histological changes contribute to the heart failure of MS and diabetes. Another component of MS: increased BMI is associated with CHF independently. Per unit increase in BMI results in 5-7% percent increase in risk of heart failure after adjustment for other risk factors (35). In another study, obesity was associated with 2.8-fold increased risk of heart failure compared to the people who have normal BMI (36).

BNP measurement carries great value in HF, risk stratification of acute coronary syndromes, pulmonary thromboembolism. When evaluating the general population, in a comparison of individuals in the top third of baseline levels of either natriuretic peptide with those in the bottom third of the population separate cardiovascular disease (CVD) outcomes, the adjusted relative risk (RR) for CHD was 2.03 or 2.25, the corresponding RR for stroke was 1.93 or 1.64. Overall, there was an almost 3-fold increase in risk of CVD in people in the top third of baseline natriuretic peptide values compared with those in the bottom third, even after reported adjustment for several conventional risk factors (37, 38). There are conflicting results about the value of BNP measurement at MS patients. Wang et al. (38) demonstrated recently an inverse relationship between serum BNP and body mass index. Olsen et al. (9) demonstrated that serum NT-proBNP was lower in subjects with dyslipidemia, hyperinsulinemia, and high body mass index but not in subjects with wide waist or hyperglycemia. Serum NT-proBNP was lower in patients with the metabolic syndrome attributable to inverse relationships between serum NT-proBNP and body mass index, serum insulin, cholesterol, and triglyceride independently of age and gender (9). On the other hand Sezen et al. (7) and Li et al. (8) reported that NT-proBNP levels were similar in subjects with MS and control subjects. There was not a graded association between increasing number of components of the metabolic syndrome and NT-proBNP. Significant correlations were found between NT-proBNP, and age, LDL-cholesterol, HDL cholesterol, and LV mass index. By multiple linear regression analysis, age and LDL-cholesterol were identified as independent predictors of NT-proBNP.

Study limitations

Relatively small number of the patients is the most important limitation of the study.

Conclusion

None of the MS parameters affects the BNP level. Only in multiple linear regression analysis diabetes mellitus presence was found to be related to increased BNP level. Interestingly female gender was associated to increased BNP level. In our study, diastolic dysfunction prevalence was 2- fold of the previous reports (67.7% of the all MS patients). LV diastolic function grade did not affect BNP level. As a result, in MS patients diastolic dysfunction may be much more common than the expected and BNP cannot be used as a diagnostic marker of diastolic function and BNP level is independent of MS parameters.

Conflict of interest: None declared.

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