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N- terminal pro brain natriuratic peptide (nt-probnp) in apparently healthy subjects compared to metabolic syndrome subjects

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Abstract

Background and objectives: B –type natriuretic peptide is synthesized in myocardial cells to respond to increased wall stress in association with heart failure or acute myocardial ischemia. High B –type natriuretic peptide and high Nt-pro B –type natriuretic peptide levels are candidates for cardiovascular risk markers and hypertension, left ventricular hypertrophy, and albuminuria. The level and relation of Nt-pro B –type natriuretic peptide with metabolic syndrome was examined in this study.

Methods: In this case-control investigation, level of Nt-pro B –type natriuretic peptide of 80 metabolic syndrome patients diagnosed based on the International Diabetes Federation guidelines was compared to its level in 40 healthy controls. The subjects who accompanied the diabetic patients at Duhok Diabetes Center were screened for inclusion and exclusion criteria between the first March and May 2019.

Results: The concentrations of triglyceride (215.09 vs. 104.02 mg/dL), total cholesterol (179.68 vs. 162.75mg/dL), and fasting blood glucose (188.71 vs. 88.08 mg/dL) were significantly higher in metabolic syndrome patients compared to the healthy controls, respectively. Nt-pro B –type natriuretic peptide was significantly lower in patients in contrast with healthy individuals (35.00 vs. 46.00 pg/mL), respectively. However, the proBNP level was not significantly different in metabolic syndrome patients with normal and abnormal biochemical parameters.

Conclusions: This study showed a significantly lower concentration of Nt-proBNP in metabolic syndrome compared to healthy controls. However, the study did not find a significant correlation with content of metabolic syndrome.

Keywords: Metabolic syndrome; Nt-proBNP; Risk factors

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Introduction

B–type natriuretic peptide (BNP) is synthesized in myocardial cells to respond to increased wall stress in association with heart failure or acute myocardial ischemia[1]. BNP is produced initially as a 134 amino acid pre-pro-peptide. It is cleaved into proBNP that is a 108 amino acid precursor molecule stored in secretory granules in myocardial cells. When it is released, proBNP is cleaved by protease furin into BNP (which is biologically active) and N-terminal proBNP (Nt-proBNP, a 76 amino acid biologically inert protein). N-terminal pro-brain natriuretic peptide is a prohormone with a 76 amino acid N-terminal inactive protein. This protein is cleaved from the molecule to release brain natriuretic peptide (BNP)[2]. BNP and NT-proBNP are synthesized in response to ventricular stretch and ischemic injury[3]. Measurement of circulating BNP and NT-proBNP concentrations is recommended to diagnose and manage heart failure[4,5]. Determining the NT-proBNP concentrations is suggested because it is more stable form and has longer half-life[6]. Even in the absence of heart failure, elevated circulating NT-proBNP concentrations is considered a serologic marker for the assessment of cardiovascular disease[7]. High BNP and high Nt-proBNP levels currently are candidates for cardiovascular risk markers and have been shown to associate with hypertension, left ventricular hypertrophy and albuminuria[8,9]. The diagnostic and prognostic role of plasma BNP and Nt-proBNP measurements has also been confirmed various settings. Obesity is frequently accompanied by glucose intolerance, elevated blood pressure, and dyslipidemia. These traits may reflect underlying insulin resistance[10, 11]. This cluster of risk factors are called metabolic syndrome. The clinical utility of this designation is controversial, but there is widespread agreement that it describes a subgroup of individuals with a high risk of cardiovascular disease[10]. Metabolic syndrome has been shown to associate with lower plasma Nt-proBNP levels in general population[9,12]. It is hypothesized that a reduced natriuretic peptide response, called a natriuretic handicap, contributes to the increased susceptibility of obese individuals to fluid retention and hypertension[13]. However, there are few studies that examined an association between plasma Nt-proBNP levels and metabolic cardiovascular risk factors or metabolic syndrome. Metabolic syndrome is defined as

a pathological status that covers a cluster of metabolic components. The cluster includes glucose tolerance, high blood pressure, high levels of triglycerides, low levels of high-density lipoprotein-cholesterol (HDL-C), and obesity[11,14]. It has been approved that metabolic syndrome is a broad subgroup of persons that have a high risk of cardiovascular diseases[14]. There are some studies reported lower levels of Nt-proBNP in individuals with metabolic syndrome[12,15]. The aim of the present study was to investigate the levels of N-terminal pro-brain natriuretic peptide (Nt-proBNP) in metabolic syndrome cases compared to healthy controls. Besides; the relationship of Nt-proBNP with metabolic syndrome risk factors and general characteristics was examined.

Subjects and methods

In the present case-control study, the levels of Nt-proBNP of a total of 80 persons diagnosed with metabolic syndrome were compared to its levels of 40 healthy controls. The persons who accompanied the diabetic patients and attended Duhok Diabetes Center were screened for the eligibility criteria. The patients' characteristics and blood samples were collected between the first of March and May 2019. The subjects who were 18 years and older whether male or female were included in the study. Subjects with previous stroke or myocardial infarction, have an acute infection, acute myocardial infarction, pulmonary edema, chronic renal failure (serum creatinine ≥1.2 mg/dL) at the time of blood sampling or if they did not provide informed consents and those using lipid-lowering treatment were excluded from the study through medical and clinical examinations. The information which was taken from the patients and subjects were age, gender, systolic and diastolic blood pressure, body weight (kg), height (cm), waist circumference (cm). The general information was obtained from the study participates through self-reported technique. Metabolic syndrome (MetS) was diagnosed according to the guidelines of the International Diabetes Federation (IDF). The following IDF criteria were used for the diagnosis of metabolic syndrome. Persons who had central obesity along with two of the following indicators were determined as metabolic syndrome. Central obesity was determined as waist circumference (WC) according to ethnicity. The indicators were increased level of triglycerides: ≥150 mg/dL or specific therapy for the lipid abnormality; and a decreased concentration HDL-C: <40

mg/dL (males); <50 mg/dL (females) or specific therapy for this lipid abnormality. In addition, a high blood pressure: systolic blood pressure (SBP) ≥ 130 or diastolic blood pressure (DBP) ≥ 85 mm Hg or previous treatment of diagnosed hypertension; and a high fasting plasma glucose (FPG) ≥ 100 mg/dL, or previously diagnosis of Type 2 diabetes mellitus (above 5.6 mmol/L or 100 mg/dL). In this study, and central obesity was assessed through the measurement of WC examined ≥94 cm (males) and ≥80 cm (females)[16]. Fasting plasma Nt-proBNP levels were determined with an Elecsys 20.10 benchtop analyzer (Roche Diagnostics) with proBNP reagent pack (Roche Diagnostics)[17]. The analytical range was extended from 20 pg/mL to 35,000 pg/mL. The intra-assay coefficient of variation is 2.5% for a concentration of 175 pg/mL and 2% for a concentration of 1070 pg/mL; the inter-assay coefficient of variation was 3.2% and 2.7%, respectively. The descriptive purposes of the study were presented in frequency and percentage or mean and standard deviation. The concentration of biochemical parameters, including HDL, LDL, TG, TC, FGB (fasting blood glucose), and insulin were presented in mean and Sta. deviation. The concentration of Nt-proBNP was presented in median and interquartile range. The comparison of the number of male and female individuals between the MetS and healthy groups was examined in Pearson Chi-squared test. The comparison of general information and biochemical parameters between MetS and healthy groups was examined in independent t-test. The difference in the levels of Nt-proBNP between the cases and controls was examined in independent t-test. The association of the Nt-proBNP levels with patients'' characteristics was examined in linear regression model. The null hypothesis was rejected in a p-value of ≤ 0.05. The statistical calculations are performed in Statistical Package for Social Sciences 25:00 (SPSS 25:00). The ethical approval of the present protocol was obtained from the ethics committee of Kurdistan Board for Medical Specialties (KBMS). The confidentiality of the personal information of the subjects is protected throughout the study steps

Results

The study showed that the metabolic syndrome patients were older compared to the healthy controls (51.49 vs. 37.98 yrs.; p-value<0.001). Most of the MetS patients were females (75.0%; P=0.006). The MetS patients had greater WC (113.53 vs. 92.90 cm; p<0.001), higher SBP (13.98 vs. 11.44 cm Hg; p<0.001), DBP (8.87 vs. 8.00 cm Hg; p<0.001), and BMI (34.80 vs. 25.88; p<0.001), respectively, Table (1).

Table (1): Comparison of general information between patients with metabolic syndrome and apparently healthy individuals.

Characteristics	Study Groups No. (%)		p-value
	Metabolic (n=80)	Healthy (n=40)	
Gender			0.006
Male	20 (25.0)	20 (50.0)	
Female	60 (75.0)	20 (50.0)	
	Study Groups Mean (SD)		
Age	51.49 ± 8.79	37.98 ± 10.24	<0.001
Waist Circumference	113.53 ± 9.07	92.90 ± 6.65	<0.001
SBP	13.98 ± 1.64	11.44 ± 0.51	<0.001
DBP	8.87± 0.94	8.00 ± 0.00	<0.001
BMI	34.80 ± 4.18	25.88 ± 3.45	<0.001

The concentrations of TG (215.09 vs. 104.02 mg/dL; p<0.001), TC (179.68 vs. 162.75mg/dL; p=0.013), and FBG (188.71 vs. 88.08 mg/dL; <0.001) compared to the healthy controls, respectively. There was no statically significant difference in the LDL (104.65 vs. 98.03 mg/dL; p=0.193) and insulin concentrations (20.94 vs. 18.38 mU/mL; p=0.214) between the MetS patients and healthy controls, respectively. The concentration of Nt-proBNP was significantly lower in MetS patients in contrast with healthy individuals (35.00 vs. 46.00 pg/mL; p=0.003), respectively,Table (2).

Table (2): Comparison of biochemical parameters between patients with metabolic syndrome and apparently healthy individuals

Biochemical Parameters	Group		p-Value
	Metabolic (n=80)	Healthy (n=40)	
HDL (mg/dl)	41.28 ± 13.21	47.43 ± 12.24	0.014
LDL (mg/dl)	104.65 ± 31.81	98.03 ± 21.65	0.193
TG (mg/dl)	215.09 ± 110.74	104.02 ± 32.68	<0.001
TC (mg/dl)	179.68 ± 37.71	162.75 ± 32.53	0.013

FBG	188.71 ± 54.99	88.08 ± 5.13	<0.001
Insulin	20.94 ± 13.93	18.38 ± 7.72	0.214
Nt-proBNP (pg/mL)	35.00 ± 31.0	46.00 ± 45.5	0.003

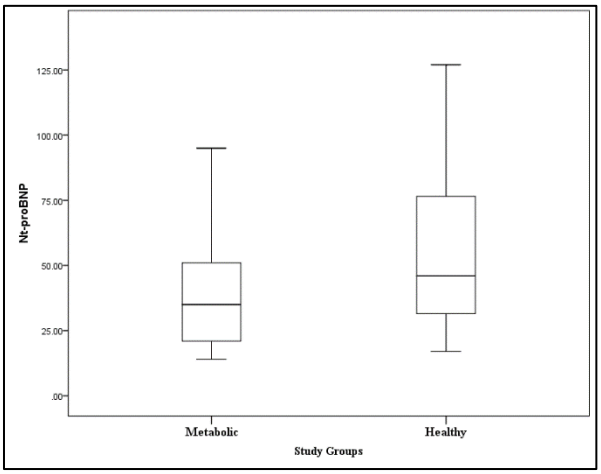

Figure (1): Comparison of Nt-proBNP levels between patients with metabolic syndrome and apparently healthy individuals

The study found that metabolic syndrome patients with normal HDL had significantly higher level of Nt-proBNP compared to those who had abnormal HDL; 38.40 vs. 29.70 pg/mL; P=0.012. The study did not show a significant difference in Nt-proBNP level in metabolic syndrome patients with other normal and abnormal biochemical parameters,Table(3).

Table (3): Comparison of Nt-proBNP between metabolic syndrome patients with normal and abnormal biochemical parameters

Patients' characteristics	**Nt-proBNP**		**p-value**
	Mean	**Stand. Deviation**	
Gender			
Male	31.13	11.51	0.161
Female	36.42	18.02	
TG			
Normal	35.48	15.93	0.778
Abnormal	36.64	18.70	
HDL			
Normal	38.40	16.90	0.012
Abnormal	29.70	11.55	
SBP			
Normal	35.00	20.52	0.564

Abnormal	32.58	12.37	
DBP Normal Abnormal	 31.12 36.00	 12.08 17.65	 0.199
BMI Overweight Obese	37.75 35.83	3.59 18.27	0.504
All patients had abnormal FBG WC. Independent t-test was performed for statistical analysis.			

Discussion

The current study found that the level of Nt-proBNP in patients with metabolic syndrome is significantly lower compared to healthy controls. However, the study did not find a significant correlation with risk factors of metabolic syndrome. A study conducted to examine the relation of Nt-proBNP with metabolic and hemodynamic cardiovascular (CV) risk factors in a general population included 2070 patients without previous stroke or myocardial infarction who did not receive the CV, antidiabetic, or lipid-lowering treatments. They found that the higher Nt-proBNP concentration is associated with female gender, older age, higher clinic pulse pressure, lower serum total cholesterol, lower LVEF (Left ventricular ejection fraction), lower serum insulin, lower plasma glucose, lower serum triglyceride, lower body mass index; lower heart rate, higher UACR (urine albumin/creatinine ratio) and higher LV (left ventricular) mass index. In addition, they showed that metabolic syndrome is correlated to lower concentration of Nt-proBNP (35 pg/mL versus 48 pg/mL; $p<0.001$). The positive relationship was found between pulse pressure and Nt-proBNP to the right meaning the level of Nt-proBNP increases with an increasing pulse pressure[12]. The present study did not find a statistically significant difference of Nt-proBNP concentration between the patients with different BMIs. The inverse association between serum brain natriuretic peptide (BNP) and BMI has been reported in some investigations[8,12,18]. It is hypothesized that there is a potential link between obesity and hypertension wing to lower natriuretic peptides of pulse pressure[8]. Accordingly, it impairs the regulation of blood pressure. This kind of link was not find in the present study. It seems that the link between pulse pressure and Nt-proBNP is positive among

patients with metabolic syndrome. Individuals with metabolic syndrome have higher pulse pressure for a given level of Nt-proBNP. Some other investigations have shown hyperinsulinemic [19] or obese individuals [20] are more sensitive to sodium load due to decreased impact of atrial natriuretic peptide [21, 22] and partly owing to an increased clearance in adipose tissue[13]. The present study did not find the significant difference in the Nt-proBNP level in patients with normal or abnormal biochemical parameters except for HDL. BNP or Nt-proBNP may change metabolic status through lipolytic and lipomobilizing effects since it has been approved for atrial natriuretic peptide[23]. Therefore, it could have a role in reduction of incidence of overweight and obesity[24]. The present study did not find the significant correlation of Nt-proBNP with age. In contrast, other studies have shown that Nt-proBNP is increased with age and is significantly higher in women[12,15]. This difference possibly could be due to undetermined cardiovascular disease (CVD) with high Nt-proBNP. It is possible that we have missed some cases with CVD in metabolic syndrome patients. Also, there was no a balance of male and female subjects between metabolic syndrome and control subjects in the current study. Another study examined the relations between Nt-proBNP and components of metabolic syndrome in forty-four hypertensive patients. They found that plasma Nt-proBNP level is significantly lower in hypertensive patients with metabolic syndrome. In addition, they found that there is a converse association relation between plasma Nt-proBNP levels and albumin, TG, insulin, insulin resistance and pancreatic b-cell function (HOMA-b-homeostasis model assessmentof pancreatic b-cellfunction). However, these kinds of relations were not found in the present study. The HOMA-IR (homeostasis model assessment of insulin resistance) was found to be the independent predictor of Nt-proBNP levels in hypertensive patients[26]. A recent study that compared the different biochemical parameters between metabolic syndrome patients and healthy controls showed that the HOMA-IR is the only predictor of metabolic syndrome[27]. The lower levels of plasma BNP have been confirmed to associate with development of insulin resistance in healthy individuals[9]. Some experimental studies have shown that intensive lifestyles could raise Nt-proBNP levels in obese diabetic patients.[28] Importantly, the low baseline Nt-proBNP levels could have a role to predict the

incidence of diabetes[29]. Further research is needed to clarify the role of Nt-proBNP levels in the development of metabolic syndrome and diabetes mellitus. The findings reported in this study must be interpreted with caution, since the case-control study may not reflect the causal pathway. In addition, the patients were selected from one clinical setting that may not be representative of other subjects across the country.

Conclusions

The present study showed a lower concentration of Nt-proBNP in metabolic syndrome compared to healthy controls. However, the study did not find a significant correlation with content of metabolic syndrome.

Conflict of interests

The authors recorded no conflict of interests.

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