Serum Probnp Associated with the Severity of Coronary Artery Disease: its Limitation in Metabolic Syndrome

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Abstract

Background and Objectives: Myocardial ischemia is the leading cause of mortality and morbidity in all over the world. Previous studies demonstrated that myocardial ischemic patients subjected to coronary angiograph were more likely to have significant high serum proBNP. This study aimed to assess the level of serum proBNP levels in myocardial ischemia patients who underwent coronary angiography and to relate the proBNP levels to the severity of coronary artery disease and the components of metabolic syndrome.

Methods: A total number of 128 patients admitted to the coronary angiography unit at Diyala Teaching Hospital in Diyala were recruited in the study. Indications of coronary angiography included; acute coronary syndrome, positive treadmill test, stable coronary artery disease and percutaneous coronary intervention. The severity of coronary artery disease was assessed by detecting the significant obstructed lesions in the number of obstructed vessels. Serum proBNP levels were measured after angiography.

Results: The results showed non-significant differences in the characteristics of patients and fasting serum lipids in different categories of vessels obstructed. Significant high serum proBNP levels were observed with increasing number of vessels obstructed and weren't related to the existence metabolic syndrome components. Serum proBNP levels were significantly and inversely correlated (r =0.5, $p < 0.001$) with ejection fraction of left ventricle.

Conclusions: Serum proBNP levels in myocardial ischemia patients are related directly to the severity of coronary artery diseases and inversely to the pumping function of the heart. Metabolic factors are not involved in significant high serum proBNP levels in myocardial ischemia patients

Key word: Pro brain natriuretic peptide, coronary artery disease, metabolic syndrome.

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Introduction

The numbers of critical occlusion of coronary vessels in patients with coronary artery disease (CAD) is considered as an important prognostic factor. Current research does not reach to definite association between the numbers of occluded vessels and specific circulatory biomarkers.

Inflammatory biomarkers like tumor necrosis factor (TNF-α) and interleukin-6(IL-6) could be useful in prediction the severity of coronary artery disease as reported in one study [1] while other study failed to show an important association between inflammatory markers; high sensitive C-reactive protein (hs-CRP), IL-6, and TNF-α, and angiographic severity of CAD [2]. Patients with stable angina and/or those with CAD proved by angiography, have significant high troponin (hs-TnT) level

compared to subjects without CAD and correlated with angiographic atherosclerotic extent and burden [3]. This association was independently to the traditional cardiovascular risk factors, brain natriuric peptide (NT-pro-BNP), and CRP [4]. Rapid measuring BNP in the emergency departments is useful in evaluating the patients with acute cardiac attacks and has appeared to be a useful prognostic marker of cardiovascular event [5,6]. Some trials showed the role of BNP for predicting severity of CAD and its relation to long-term mortality. Many authors revealed the beneficial effects of NT pro BNP as a prognostic marker for predicting CAD severity based on angiography findings [7,8,9]. Furthermore, predictive role of this peptide for assessing long-term mortality of patients with CAD was demonstrated in researches by others [10, 11]. In addition, relationship between the severity of left coronary artery disease and plasma NT-pro BNP level has been suggested [12]. Peer *et al* [13] found that the predictive value of NT-proBNP for CAD severity is better than that of hs-CRP or gamma-glutamyltransferase (GGT). NT-proBNP was significantly associated with three-vessel CAD adjusted for age, sex, ventricular, renal function and classic risk factors. The aim of the study was to look for the association between circulating levels of proBNP and angiographic severity of CAD in reference to the components of metabolic syndrome.

Materials and methods

This study conducted in Department of Medicine, College of Medicine, Diyala University and The General Teaching hospital in Diyala, Iraq. The study was conducted according to the guidelines from the Declaration of Helsinki with approval from a local ethical review board. A prospective, cohort study was performed on patients with history of myocardial ischemia (ages: 36-89 years) who were referred to coronary angiography unit for assessment of vessels obstructed. Indications of coronary angiography included acute coronary syndrome, positive treadmill test, stable coronary artery disease and percutaneous coronary intervention. Severity of coronary artery disease is defined as the number of vessels obstructed: left main, anterior descending, circumference and right coronary artery. The number of significant obstructed lesions per each vessel were counted and ranged between 0 and 3. The present study did not include patients with a history of hematological, neoplastic, renal, liver, or thyroid diseases, and patients with acute or chronic infections and autoimmune disease were also excluded from the study. A total number of 128 patients (91 males and 37 females) were admitted in the study. Demographic data, medical history and treatment were collected in the hospital.

Modifiable risk factors, events or complications, and current therapy were recorded. A person who reported smoking on admission was defined as current smoker. The anthropometric measurements including weight (kg), height (m) and the calculated body mass index (kg/m^2), electrocardiogram and echocardiography were obtained. Fasting venous blood samples were obtained from participants and the sera were separated for determination lipid profile and NT- pro-BNP. The serum level of proBNP (a biomarker of heart failure) was determined in the laboratories of Specialized Center for Cardiac Surgery using the technique of Enzyme Linked Fluorescent Assay (VIDAS NT-proBNP automated test for use on the VIDAS instrument). The principle of this assay is a one step immunoassay sandwich method with a final fluorescent detection

(ELFA) and the range of measurement is 20-25000 pg/ml).

Ascertainment of metabolic syndrome is considered from the laboratory measures, if a person satisfied 3 out of 5 National Cholesterol Education Program (NCEP) criteria for metabolic syndrome (14), s/he was deemed to have metabolic syndrome. The NCEP criteria included:

1. Central obesity waist circumference > 102 cm (male) or 88 cm (female)
2. Fasting blood glucose > 110 mg/dl (6.1 mmol/L) or having diabetes
3. Systolic blood pressure ≥ 130 mm Hg Diastolic blood pressure ≥ 85 mmHg
4. Triglyceride ≥ 150 mg/dL(1.69 mmol/L)
5. High density lipoprotein cholesterol < 40 mg/dL(1.04 mmol/L in male)< 50 mg/dL (1.29 mmol/L in female).

Statistical Analysis

Data are expressed as means ± SD. Unpaired Student's t-test was used to evaluate differences in normally distributed continuous variables between the two groups. Correlation analysis between variables of the study was made by means of rho correlation coefficient r for continuous variables. For all tests, a 2-tailed $p<0.05$ was considered statistically significant. All calculations were made using SPSS statistical software for Windows (version 10.0).

Results

Table 1 shows the characteristics of the study. Patients presented angiograph findings were more likely to have history of hypertension, diabetes mellitus, and high rate of smoking compared with patients who haven't obstructed vessels. Body mass index and blood pressure levels in patients with obstructed vessels were inconsistently differed from patients without angiographic findings.Fasting serum lipids of patients presented with angiograph findings related to obstructed vessels did not significantly differ from patients without obstructed vessels (Table 2). The most common site of vessels obstructed was anterior descending artery followed by circumference and right coronary arteries (Table 3).

Serum proBNP levels were increased in patients with positive angiograph findings related to vessels obstructed to reach significant level in any number of vessels obstructed except two vessels obstructed (Table 4). Further analysis revealed that the serum proBNP levels were non-significantly, less in patients without metabolic syndrome components compared with patients who have metabolic syndrome components (Table 4). Ejection fraction (%) was progressively declined with increased vessels obstructed; 66.0±7.13 (no vessels obstructed); 64.37±5.9 (one vessel); 64.3±5.9 (two vessels); 63.31±4.58 (three vessels); and 57.6±2.792 (four vessels).Significant negative correlation between serum proBNP and ejection fraction was observed and it was estimated from the best fit line equation that for each 74.01 pg/ml increment of serum proBNP the ejection fraction declined by 1% (Figure 1).

Table (1): Characteristics of the study according to the severity of coronary artery disease (number of vessels obstructed).

Characteristics	number of vessels obstructed				
	0	1	2	3	4
Gender (M:F)	7:8	32:11	26:7	21:11	5:0
Age (year)	56.46±8.65	54.88±9.66	57.03±8.40	61.78±8.85	60.8±7.79
Smoking	5	17	13	12	2
History of:					
Hypertension	12	28	17	23	1
Diabetes mellitus	4	18	16	20	3
Body mass index (kg/m^2)	25.066±3.874	24.648±2.663	24.833±3.203	23.603±3.231	26.54±1.594
Blood pressure (mmHg)	146.7±25.96	141.0±22.95	140.42±23.87	144.1±23.85	126.4±8.76
Systolic	87.2±12.11	87.34±10.99	86.03±11.15	87.19±12.06	80.4±6.066
Diastolic					

The results expressed as mean ± SD

Table (2): Fasting serum lipids (mmol) according to the severity of coronary artery disease (number of vessels obstructed)**.**

Characteristics	number of vessels obstructed				
	0 (n=15)	1 (n=43)	2 (n=33)	3 (n=32)	4 (n=5)
Cholesterol	3.746±1.135	4.165±0.857	3.912±0.796	3.965±1.131	4.2±0.902
Triglycerides	1.666±0.514	1.909±0.564	1.762±0.556	1.818±0.526	2.06±0.746
High density lipoprotein	1.513±0.438	1.465±0.428	1.490±0.346	1.381±0.349	1.6±0.717
Low density lipoprotein	1.9±1.233	2.318±1.028	2.068±0.983	2.220±1.307	2.188±1.139
Very low density lipoprotein	0.333±0.122	0.381±0.112	0.352±0.111	0.363±0.105	0.412±0.149
Triglycerides/high density lipoprotein ratio	1.220±0.66	1.486±0.754	1.262±0.562	1.428±0.598	1.620±1.164

The results expressed as mean ± SD

Table (3): Distribution of cases according to the presence of significant angiographic findings that related to vessels obstructed in respect to the number and anatomical vessels obstructed.

Anatomical coronary artery	**Number of vessels obstructed**					
	0	1	2	3	4	Total (%)
Left main	0	0	0	5	5	10 (7.8)
Left anterior descending	0	30	28	32	5	95 (74.2)
Left circumference	0	8	19	30	5	62 (48.4)
Right	0	5	19	29	5	58 (45.3)

Table (4): Serum ProBNP level in patients with angiograph obstructed vessels in reference to the presence components of metabolic syndrome**.**

	Number of vessels obstructed				
	0	1	2	3	4
MetS (+ve)	< 20 (n=3)	190.5±219.3 (n=14)	297.0±348.7 (n=9)	261.1±213.3 (n=9)	504 (n=1)
MetS (-ve)	174.5±197.83 (n=12)	389.2 ±462.6 (n=29)	213.3±202.4 (n=24)	403.8±326.7 (n=23)	1182.3±882 (n=4)
Total	141.6 ±188.2 (n=15)	324.7±407.9** (n=43) T=2.391	236.2±247.6 (n=33)	363.7±302.9*** (n=32) T=3.07	914.6±723.5* (n=5) T=2.386

The results are expressed as mean ± SD;*$p < 0.05$, **$p < 0.02$, ***$p < 0.01$ in comparison without vessels obstructed.

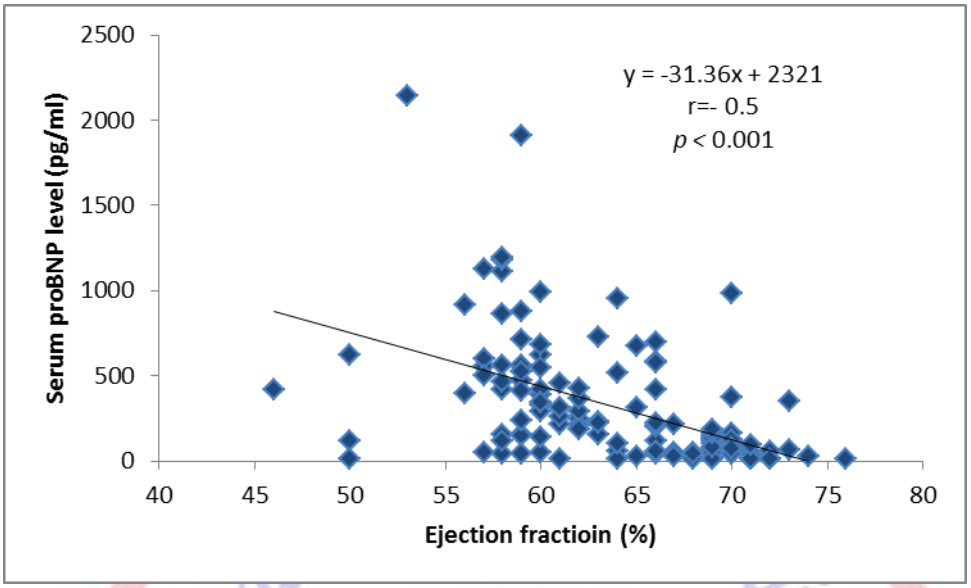

Figure (1): Correlation between serum proBNP level (pg/ml) and ejection fraction of patients subjected to coronary angiogram.

Discussion

The results of this study demonstrate that high serum proBNP level is associated with positive angiography findings and the increment in pro-BNP level is not related to the signs of metabolic syndrome. The study also the study demonstrated that the ejection fraction tended to decline as the obstructed vessels number increased. It is well known that serum NT-proBNP level is considered as a good diagnostic and prognostic biomarker for heart failure. The results in this study add a new application for estimation of proBNP as a marker for assessment the severity of coronary artery disease. The results of Chen *et al* [15] referred to use the plasma level of NT-proBNP for predicting intensive care unit stay and hospitalization in patients subjected to coronary artery by-pass graft surgery. Moreover, recent study points to the association of NT-proBNP level with the presence of significant coronary lesions in patients with acute coronary syndrome subjected to angiography and considered that NT-proBNP is superior to cardiac troponins in prediction of long-term mortality [16]. The plasma level of pro-BNP is also a strong predictor of no-reflow phenomenon that followed primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction [17]. In one study carried on patients with stable CAD, the level of NT-proBNP found to be a useful predictor of the outcomes in high risk patients [18].The non significant high serum pro-BNP level in patients with metabolic syndrome compared with those without metabolic syndrome suggesting that this marker is valuable in detecting the people at risk. Olsen *et al* [19] reported that metabolic syndrome was associated with lower Nt-proBNP levels but it positively correlated with pulse pressure i.e. NT-proBNP is linked with only one component of metabolic syndrome. On the other hands Sung *et al* [20] reported a significant negative correlation between body mass index, the other component of metabolic syndrome, and plasma NT-ProBNP. Therefore the results reported in this study are in agreement with the above mentioned studies. The significant negative correlation between ejection fraction and proBNP level indicated the patients were in impending heart failure or ventricular dysfunction. It concludes that

serum proBNP levels in myocardial ischemia patients are related directly to the severity of coronary artery diseases and inversely to the pumping function of the heart. Metabolic factors are not involved in significant high serum proBNP levels in myocardial ischemia patients.

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