Original Article:

Association of high serum pro-BNP levels with severity of coronary artery disease and its limitations

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Abstract

Myocardial ischemia is the leading cause of mortality and morbidity all over the world. Previous studies demonstrated that myocardial ischemic patients subjected to coronary angiograph were more likely to have significant high serum proBNP. The study aims 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. 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 occluded lesions in the number of occluded vessels. Serum proBNP levels were measured after angiography. The results show non-significant differences in the characteristics of patients and fasting serum lipids in different categories of vessels occluded. Significant high serum proBNP levels were observed with increasing number of vessels occluded and were not seen to be related to the components of metabolic syndrome. Serum proBNP levels were significantly and inversely correlated ($r = 0.5$, $p < 0.001$) with ejection fraction of left ventricle.

Key words: Pro brain natriuretic peptide, Coronary artery disease, Cardio metabolic risk factor.

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Introduction

The number 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 predicting the severity of coronary artery disease (1), while others have 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) levels as compared to subjects without CAD and correlated with angiographic atherosclerotic extent and burden (3). This association was independent 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 events and has appeared to be a useful prognostic marker of cardiovascular event (5, 6). Several studies have shown serum BNP level's usefulness as a prognostic marker in predicting CAD severity. 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-glutamyl transferase (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.

Methods

This study was 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. It was a prospective, cohort study and included all the patients with history of myocardial ischemia (age: 36-89 years) who were referred to coronary angiography unit for assessment of vessels occluded. 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 occluded: left main, anterior descending, circumference and right coronary artery. The numbers of significant occluded lesions per vessel were counted (range 0-3). All patients with history of hematological, neoplastic, renal, liver, or thyroid diseases, and patients with infections and autoimmune diseases were excluded from the study. A total number of 128 patients (91 males and 37 females) were recruited in the study. Demographic data, medical treatment and history were obtained from the hospital record. 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; weight (kg), height (m), 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 determining 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. National Cholesterol Education Program (NCEP) criteria were used to define metabolic syndrome (14).

Statistical analysis

Data is expressed as Mean ± 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 baseline characteristics of the study population. Patients with angiograph findings were more likely to have a history of hypertension, diabetes mellitus, and high rate of smoking compared with patients who did not have occluded vessels. Body mass index and blood pressure levels in patients with occluded vessels were inconsistently different from patients without angiographic findings. Fasting serum lipids of patients with angiograph findings related to occluded vessels did not significantly differ from patients without occluded vessels (Table 2). The most common of the vessels occluded was anterior descending artery followed by circumference and right coronary arteries (Table 3).

Serum proBNP levels were significantly high among patients who had one, three and four vessels involved. The levels were not high in two vessel disease. (Table 4). Ejection fraction (%) progressively declined with multivesicular involvement; 66.0±7.13 (no vessels occluded); 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 the best fit line equation estimated 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 population according to the severity of coronary artery disease (number of vessels occluded).

Characteristics	Number of vessels occluded				
	0	1	2	3	4
Gender					
Male	7	32	26	21	5
Female	8	11	7	11	0
Age (year)	56.46 ± 8.65	54.88 ± 9.66	57.03 ± 8.40	61.78 ± 8.85	60.80 ± 7.79
Smoking	5	17	13	12	2
Hypertension	12	28	17	23	1
Diabetes mellitus	4	18	16	20	3
Body mass index (kg/m^2)	25.06 ± 3.87	24.64 ± 2.66	24.83 ± 3.20	23.60 ± 3.23	26.54 ± 1.59
Blood pressure (mmHg)	146.7 ± 25.96	141.0 ± 22.95	140.42 ± 23.87	144.1 ± 23.85	126.4 ± 8.76
Systolic Diastolic (mmHg)	87.2 ± 12.11	87.34 ± 10.99	86.03 ± 11.15	87.19 ± 12.06	80.4 ± 6.066

The results are expressed as mean ± SD

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

Characteristics	Number of vessels occluded				
	0 (n=15)	1 (n=43)	2 (n=33)	3 (n=32)	4 (n=5)
Cholesterol	3.74 ± 1.13	4.16 ± 0.85	3.91 ± 0.79	3.96 ± 1.13	4.20 ± 0.90
Triglycerides	1.66 ± 0.51	1.90 ± 0.56	1.76 ± 0.55	1.81 ± 0.52	2.06 ± 0.74
High density lipoprotein	1.51 ± 0.43	1.46 ± 0.42	1.49 ± 0.34	1.38 ± 0.34	1.60 ± 0.71
Low density lipoprotein	1.90 ± 1.23	2.31 ± 1.02	2.06 ± 0.98	2.22 ± 1.30	2.18 ± 1.13
Very low density lipoprotein	0.33 ± 0.12	0.38 ± 0.11	0.32 ± 0.11	0.36 ± 0.10	0.41 ± 0.14
Triglycerides/high density Lipoprotein ratio	1.22 ± 0.66	1.48 ± 0.75	1.26 ± 0.56	1.42 ± 0.59	1.62 ± 1.16

The results are expressed as mean ± SD

Table 3: Distributions according to significant angiographic findings with respect to the number of vessels occluded.

Anatomical coronary artery	Number of vessels occluded					Total (%)
	0	1	2	3	4	
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 levels and number of occluded vessels in patients with and without metabolic syndrome.

	Number of vessels occluded				
	0	**1**	**2**	**3**	**4**
MetS (+ve)	< 20 (n=3)	19.5 ± 21.3 (n=14)	29.0 ± 34.7 (n=9)	26.1 ± 21.3 (n=9)	504 (n=1)
MetS (-ve)	17.5 ± 19.8 (n=12)	38.2 ± 46.6 (n=29)	21.3 ± 20.4 (n=24)	40.8 ± 32.7 (n=23)	1182.3 ± 88 (n=4)
Total	14.6 ± 18.2 (n=15)	32.7 ± 40.9** (n=43) T=2.39	23.2 ± 24.6 (n=33)	36.7 ± 30.9*** (n=32) T=3.07	91.6 ± 72.5* (n=5) T=2.38

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

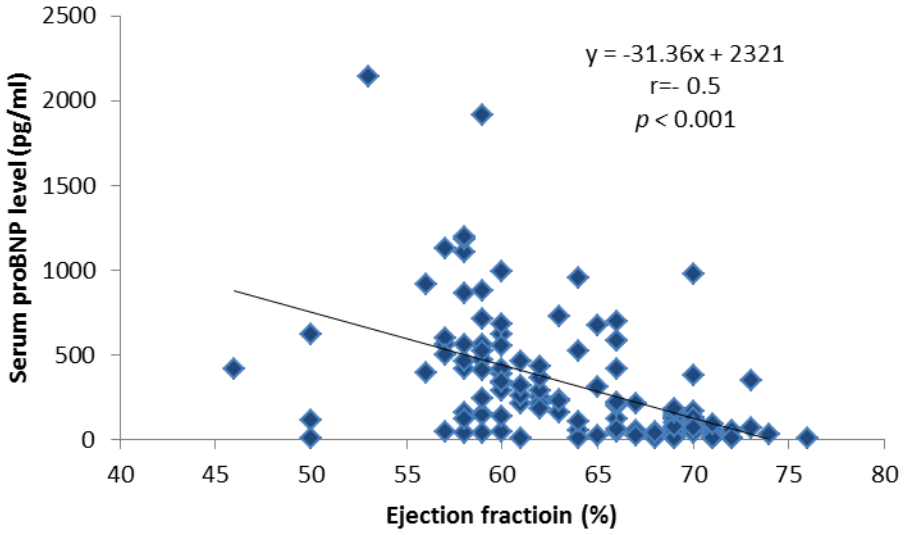

Figure 1: Correlation between serum proBNP levels (pg/ml) and ejection fraction of patients subjected to coronary angiogram.

Discussion

The study demonstrates that high serum proBNP levels are associated with positive angiography findings and the increment is not related to the components of metabolic syndrome. The study also demonstrates that the ejection fraction tend to decline with disease severity. 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 of the severity of coronary artery disease. 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 bypass graft surgery. Moreover, recent study points at the

association of high NT-proBNP level with significant coronary lesions in patients with acute coronary syndrome subjected to angiography. It also considers that NT-proBNP is superior to cardiac troponins in prediction of long-term mortality (16). Also, the plasma level of pro-BNP is a strong predictor of no-reflow phenomenon that followed primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction (17). In a study of patients with stable CAD, the level of NT-proBNP was 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 is positively correlated with pulse pressure. On the other hand, 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 are in agreement with the above mentioned studies. The significant negative correlation between ejection fraction and proBNP levels may be indicative of impending heart failure or ventricular dysfunction in these patients. It concludes that the serum proBNP levels in myocardial ischemia patients are directly related to the severity of coronary artery diseases however inversely related to the pumping function of the heart. Metabolic factors are not associated with high serum proBNP levels in myocardial ischemia patients.

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