



Research Article

The Relation Between Homocysteine Levels in Patients With Acute Coronary Syndrome and GRACE Score

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Abstract

Objectives: In this study we investigated the correlation between homocysteine levels in patients with acute coronary syndrome and GRACE score.

Methods: The study included 191 cases -140 patients with non-ST MI and 51 patients with ST elevation MI in our hospital Coronary Intensive Care Unit between December 2008 and March 2010.

The reference range for homocysteine was between 5-15 Mmol/L for male and female adults. The patients were classified into three risk groups as low, intermediate and high on the basis of the criteria identified in GRACE risk score: age, heart rate, systolic blood pressure, serum creatine level, Killip classification, cardiac arrest on admission, increased cardiac enzymes and ST segment depression. The relation between homocysteine levels in patients with acute coronary syndrome and GRACE risk score was evaluated.

Results: In the patients with non-ST MI, a statistically-moderate positive correlation was observed between homocysteine levels and GRACE risk score ($p < 0.05$). However, in the patients with ST elevation MI, no correlation was found between homocysteine levels and GRACE risk score ($p > 0.05$). Overall, despite the low figures, a meaningful positive relation was observed between homocysteine level and GRACE risk score considering both patient groups.

Conclusion: Homocysteine is an independent risk factor other than the well-established classical risk factors for cardiovascular diseases. Therefore, we believe that routine plasma homocysteine levels should be controlled for evaluating the risk factors for atherosclerotic coronary artery disease.

Keywords: Coronary syndrome; homocysteine; grace score.

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Acute coronary syndrome is one of the leading causes of mortality and morbidity in adults. It is claimed that there were 6.3 million deaths due to this syndrome, which made up 28.9% of the total deaths worldwide. By 2020, the percentage is expected to rise to 36.3%.^[1] In TEKHARF (Turkish Adults Coronary Risk Factors Study) performed by Turkish Society of Cardiology, it was found that overall

annual death rate from coronary heart disease was 5.2 per 1.000 person (3.2 in females). Causes of total mortality rates reflects that the highest rate happens to be coronary heart disease with 42.5%.^[2]

Measures have been considered to prevent cardiovascular diseases, and the risk factors have been determined. Fram-

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ingham Heart Study^[3] has played a central role in identifying the common risk factors for heart disease, which are age, smoking, genetics, hypertension, hyperlipidemia, and diabetes mellitus. However, these traditional factors alone do not fully explain the prevalence of coronary artery disease and the development of premature coronary artery disease. Notably, nearly half of the patients with acute myocardial infarction or unstable angina do not have classical risk factors.^[4] Currently, new atherosclerotic risk factors, such as elevated homocysteine levels are in consideration. Homocysteine is a sulfur-containing amino acid and it is produced during the metabolism of methionine. Hyperhomocysteinemia may occur from various nutritional and genetic factors. Elevated plasma homocysteine level is an independent risk factor for peripheral vascular disease, cerebrovascular disease, and as well as coronary heart disease.^[5] It is known that homocysteine inhibits the proliferation of endothelial cells and many in vitro studies presented that adding homocysteine to cell cultures caused endothelial cell damage.^[6]

Patients with acute coronary syndrome represent a heterogeneous population. Significant differences exist in the early and late complications and prognosis. Estimating an early risk score is highly important in order to develop strategies for prevention. A good prognosis may be achieved through preventive measures and suitable treatments, considering myocardial infarction leads to a need of coronary intensive care and lethal outcomes. Therefore, calculating a risk score plays the key role in the decision pathway for assessment and management.

In this study, we aimed to evaluate the correlation between the homocysteine levels in patients with acute coronary syndrome and GRACE risk score.

Methods

This study includes 191 cases -140 patients with non-ST MI and 51 patients with ST elevation MI in our hospital Coronary Intensive Care Unit between December 2008 and March 2010. All of the patients were informed about the study and their informed consent was obtained.

Exclusion criteria were as follows: diseases or conditions which might influence homocysteine levels such as hypothyroidism or hyperthyroidism, renal failure, rheumatoid arthritis, Behçet disease, malignancy, vegetarianism, B12 deficiency, folic acid deficiency, chronic alcohol use; use of anticonvulsants, oral contraceptives, hormonal therapy, vitamin intake, acetylcysteine, penicillamine, methotrexate, L-dopa, cholestyramine, nitric oxide anesthesia.

Demographic data and medical history was recorded for each patient, and GRACE risk score were calculated. Ad-

ditionally, homocysteine levels were determined. Demographic characteristics were a) gender b) risk factors as diabetes, hyperlipidemia, hypertension, smoking c) medical history as myocardial infarction (MI), myocardial revascularization (Percutaneous coronary intervention [PCI], Coronary Artery Bypass Grafting [CABG]), Streptokinase [SKZ], peripheral arterial disease, transient ischemic attack, stroke d) drugs used by the patient before admission such as platelet inhibitors, aspirin, beta blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), statins e) cardiac markers; blood CK-MB, Troponin-I levels. In addition to risk factors, blood glucose, urea, creatinine, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, FT3, FT4, TSH, folic acid, vitamin B12 and homocysteine levels of each patient were measured after overnight fasting.

Homocysteine Measurement: Homocysteine level was measured by immulite 2000 device, using chemiluminescence method and competitive immunoassay principle. The kit was obtained from DPC Company for the measurement. The reference range for homocysteine was between 5-15 Mmol/L for male and female adults.

The GRACE risk score was calculated by the eight different baseline variables as age, heart rate, systolic blood pressure, serum creatinine level, cardiac arrest at admission, ST-segment deviation on ECG, elevated c Tn and congestive heart failure (Killip class).^[11] According to the GRACE risk score, patients were classified into three risk groups for in-hospital mortality as low risk (<108), intermediate risk (109-140) and high risk (>140). The relation between homocysteine level and GRACE risk score was evaluated.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) were used as programs. For evaluating the data of our study, student t test was used to compare descriptive statistical methods (average, standard deviation, frequency) as well as quantitative data. Chi-square test was used to compare qualitative data. Level of significance was set at $p < 0.05$.

Results

The study included 191 cases -140 patients with non-ST MI and 51 patients with ST elevation MI in our hospital Coronary Intensive Care Unit between December 2008 and March 2010. The mean age was 61.1 ± 13.97 . One hundred and twenty seven patients were male and 64 patients were female. There was no statistically significant differences between the ages of the groups. Mean age of patients with

non-ST MI was 62.14 ± 14.48 and mean age of patients with ST elevation was 58.29 ± 12.16 .

There were statistically significant differences between the gender distributions of the groups. The number of male patients were higher in patients with ST-elevation. The rate of patients with diabetes and hypertension were higher in patients with non-ST MI. In patients with ST elevation MI, the number of smokers were higher (Table 1).

The number of patients with a history of MI and CABG was higher in patients with non-ST MI. There was no differences between history of myocardial revascularization as PCI and streptokinase/tissue plasminogen activator (tPA) in both groups. There was no difference between history of peripheral artery disease (PAD) and cerebrovascular event (CVE) in both groups (Table 2).

The level of homocysteine between the groups did not show any statistically significant difference ($p > 0.05$). An evaluation based on two subgroups considering homocysteine levels did not show any significant difference either. It was found at 38.6% in patients with non-ST MI and 41.2% patients with ST elevation MI. A significant difference was not observed between the averages of groups according to GRACE risk scores ($p > 0.05$). An evaluation based on three

subgroups secondary to GRACE risk scores did not show any significant difference ($p > 0.05$). 36.4% of patients with non-ST MI group was in low risk category, 30% in intermediate risk category and 33.6% in high risk category. 39.2% of patients with ST elevation MI was recorded in low risk category, 37.3% in intermediate risk category and 23.5% in high risk category (Table 3).

As evaluating all of the patients with both non-ST MI and ST MI, a modestly significant relationship was noted between the level of homocysteine and GRACE risk score ($p < 0.05$). In patients with non-ST MI, a modestly significant relationship was observed between homocysteine and GRACE risk score ($p < 0.05$), whereas there was not any significant relationship between homocysteine and GRACE risk score in patients with ST MI ($p > 0.05$) (Table 3 and Fig. 1).

Table 1. Distribution of risk factors in both groups

	Non ST MI (n=140) Avg±SD	ST Elevation MI (n=51) Avg±SD	Total Avg±SD	^b p
Diabetes	44 (%31.4)	8 (%15.7)	52 (%27.2)	0.031*
Hyperlipidemia	80 (%57.1)	32 (%62.7)	112 (%58.6)	0.487
Hypertansion	82 (%58.6)	16 (%31.4)	98 (%51.3)	0.001**
Smoking	80 (%57.1)	40 (%78.4)	120 (%62.8)	0.007**

^bchi-square test; * $p < 0.05$; ** $p < 0.01$.

Table 2. Distributions of CVD-related history in both groups

	Non ST MI (n=140) Avg±SD n (%)	ST Elevation MI (n=51) Avg±SD n (%)	Total Avg±SD n (%)	p
MI	27 (19.3)	2 (3.9)	29 (15.2)	0.009**
Myocardial revascularization				
PCI	14 (10)	2 (3.9)	29 (15.2)	0.180
CABG	12 (8.6)	0	12 (6.3)	0.031*
SKZ/TPA	1 (0.7)	0	1 (0.5)	1.000
PAD	1 (0.7)	1(2)	2 (1)	0.464
CVE	16 (11.4)	3 (5.9)	19 (9.9)	0.257

PCI: Percutaneous Coronary Intervention. CABG: Coronary Artery Bypass Grafting. SKZ/ TPA: Streptokinase/ Tissue Plasminogen Activator. PAD: Peripheral Artery Disease. CVE: Cerebrovascular Event. ^bchi-square test; * $p < 0.05$; ** $p < 0.01$.

Table 3. The level of homocysteine and Grace risk scores of patients in the both groups

	Non ST MI (n=140) Avg±SD	ST Elevation MI (n=51) Avg±SD	Total Avg±SD	^b p
H-SYS (µmol/L)	15.12±9.06	14.40±6.82	14.92±8.51	0.606
GRACE risk score	124.29±39.57	134.12±33.48	126.91±38.21	0.116
	n (%)	n (%)	n (%)	^b p
H-SYS (µmol/L)				
Normal	86 (61.4)	30 (58.8)	116 (60.7)	0.744
Abnormal	54 (38.6)	21 (41.2)	75 (39.3)	
GRACE risk score				
Low risk	51 (36.4)	20 (39.2)	71 (37.2)	
Intermediate risk	42 (30)	19 (37.3)	61 (31.9)	0.384
High risk	47 (33.6)	12 (23.5)	59 (30.9)	

^aStudent t test; ^bchi-square test.

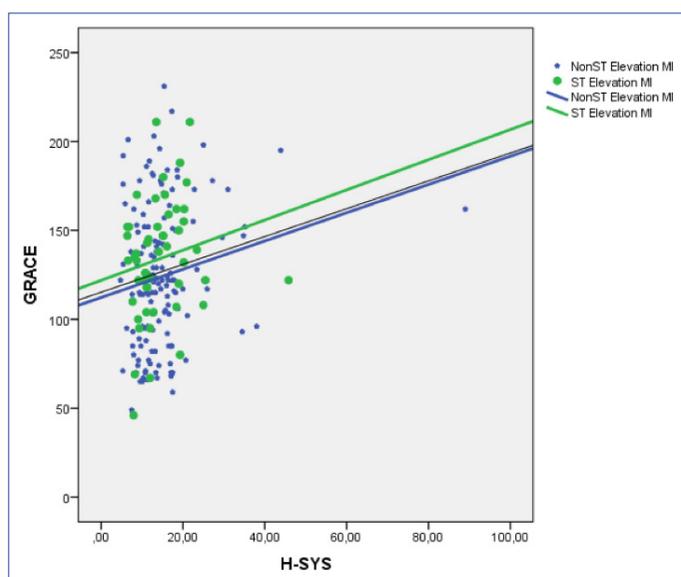


Figure 1. Homocysteine and grace risk score relation.

Discussion

Acute coronary syndrome (ACS) is a condition characterized by symptoms and clinical findings of acute myocardial ischemia. The common classical factors that leads to the development of coronary artery disease (CAD) can only explain till a certain degree the pathogenesis, prevalence, and changes in severity.^[7] Recent studies have highlighted new risk factors that play a pivotal role in the physiopathology of CAD. Several studies have shown that homocysteine is one of the new risk factors for CAD. Homocysteine is regarded as an independent risk factor other than the classical risk factors for cardiovascular diseases.^[8-10]

Patients with acute coronary syndrome constitute a heterogeneous population with different early and late complications and prognosis. Calculating a risk score on the early phase of the progression is important in order to develop preventive strategies. GRACE risk score is a model which is preferred in routine clinical practice.^[11]

An increase by 5 Mmol/L in homocysteine level, increases CAD risk 1.8 and 1.6 times in male and female patients, respectively. A study performed by Tokgözoğlu and her colleagues found that homocysteine levels over 15 Mmol/L increased the risk for CAD by 2.1.^[12]

In NHANES III (The Third National Health and Nutrition Examination Survey), Ganji and his colleagues found that men had a 1.9 Mmol/L higher homocysteine level than women. However, no significant difference was detected in both genders in our study.

Homocysteine levels in patients with classical risk factors of CAD were significantly higher in those who were smokers. In the studies performed by Nygard and Bergmak,

there was a meaningful relationship between the number of cigarettes smoked per day and elevated homocysteine levels.^[13-15] Kato and his colleagues stated that women who smoked more than 20 cigarettes per day had 18% higher homocysteine levels.^[16] Nevertheless, in our study, there was no statistically significance between smoking and homocysteine levels.

It has been often suggested that there is a direct relation between homocysteine levels and age.^[13, 17] In the Framingham study, it was stated that patients over the age of 65 had 23% higher homocysteine levels than the patients younger than 45.^[18] There are two different explanations for the elevated homocysteine levels. The first explanation is the age-related decline in renal function, and the second one is the age-related decline in cystathionine β -synthase and other enzymes in homocysteine metabolism.^[19, 20] Age-related serum folate and vitamin B12 deficiency may also cause high homocysteine levels.^[21, 22] In our study the patients with ST elevation MI had a meaningful correlation between homocysteine levels and age.

In SHEP (Systolic Hypertension in the Elderly Program), a positive correlation was observed between homocysteine levels and systolic blood pressure measuring. In this study, homocysteine level was an independent risk factor for atherosclerosis in normotensive patients, whereas it could not be regarded as a risk factor in hypertensive patients.^[23]

In the patients with non-ST MI group, a statistically moderate positive correlation was seen between homocysteine and GRACE risk score in our study ($p < 0.05$). However, in the patients with ST elevation MI, such a correlation was found ($p > 0.05$). Overall, despite the low figures, a meaningful positive relation was observed between homocysteine levels and GRACE risk score considering both the patient groups. In a study which was published in the journal of Turkish Society of Cardiology in 2009, no significant relationship was found between homocysteine levels in non-ST MI patients and TIMI score as well as GRACE risk scores.^[24]

Many studies have shown that an elevated homocysteine level is an independent risk factor for CAD other than the classical risk factors.^[8-10] Therefore, we believe that routine plasma homocysteine levels should be controlled as evaluating risk factors for atherosclerotic coronary artery disease.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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