ORIGINAL ARTICLE

Levels of Blood Biomarkers among Patients with Myocardial Infarction in Comparison to Control Group

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ABSTRACT

BACKGROUND: Myocardial infarction (MI) as a term for a heart attack happens due to reduced blood flow to heart myocardium and lack of oxygen supply caused by plaques in the interior walls of coronary arteries. With respect to the importance of MI etiology, we aimed to study the relationship of MI and blood examination variables.
METHODS: This study was conducted in Mazandaran Heart Center as a hospital-based case-control Comprising 894 participants including 465 cases and 429 controls, individually matched by sex and age. Considered blood markers were analyzed using routine laboratory methods and equipment.
RESULTS: Of all participants, 64.3% of the cases and 51.0% of the controls were males with a mean age of 61.2 (±13.8) in cases and 62.4 (±14.) in controls. We could not find any differences between cases and controls for total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and alkaline-phosphatase (ALP) (P>0.05). However, levels of creatine-kinase-muscle/brain (CK-MB) (P<0.0001), fasting-blood-sugar (FBS) (P<0.0001), aspartate-aminotransferase (AST) (P<0.0001), alanine-transferase (ALT) (P<0.0001) and erythrocyte sedimentation rate (ESR) (P=0.001) were significantly higher in cases compared to the controls (P<0.05). Multivariable analyses revealed that the risk of MI was associated with high levels of AST (adjusted OR=24.3, 95%CI=3.5±165.6, P=0.001) and LDL (adjusted OR=7.4, 95%CI=1.0±51.8, P=0.001).
CONCLUSION: Our investigation indicated that the levels of CK-MB, FBS, AST, ALT and ESR were significantly higher in patients with MI. Besides, our findings showed that the risk of MI in cases with high levels of AST and LDL was about 24 and 7 times more than the control group respectively.
KEYWORDS: Cardiovascular Stroke, Heart Attack, Biochemical Markers, Serum Marker, Laboratory Markers

INTRODUCTION

Myocardial infarction (MI) is defined as the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia (1). MI happens due to reduced blood flow to heart myocardium and lack of oxygen supply caused by plaques in the interior walls of coronary arteries (2). It is a major cause of death and disability worldwide (3). Over 15% of mortalities worldwide happens due to MI each year (4). According to the global burden of disease report 2017, cardiovascular diseases are the leading cause of death in Iran with 196.32 in 100/000 people (5). There are approximately 3.6 million patients with cardiovascular disease in Iran, and MI is responsible for 46% deaths due to cardiovascular diseases (6).

In the clinical aspect, there is quite a number of enzymes, hormones, biological substances and other biomarkers derived from blood or urine that can be used in diagnosis (7). Since only myocardium contains a considerable amount of creatine kinase-muscle/brain (CK-MB), measuring CK-MB isoenzyme is a good indicator of MI (8). CK-MB appears 4 to 6 hours after the onset of chest pain, and it consists nearly 30% of CK in the myocardium (9). Plasma lipoproteins are risk factors for cardiovascular (CV) events after MI. High levels of low-density lipoprotein (LDL) is associated with increased risk of CV and high levels of high-density lipoprotein (HDL) associated with decreased risk of CV. Decreased LDL and variable HDL levels have been reported after MI and increased risk of in-hospital mortality was associated with lower LDL levels (10).

Nonspecific tests which indicate inflammation can be used to diagnose various diseases. The inflammatory response following MI causes an increased erythrocyte sedimentation rate (ESR) (11). ESR is also a significant predictor of heart failure and might be useful for the diagnostic criterion for coronary heart disease (12). High levels of blood sugar can increase the risk of death and poor outcome in patients with MI, and it is associated with increased risk of in-hospital mortality in these patients (13). Fasting hyperglycemia in early MI could be a marker for high-risk individuals (14). Liver markers can also

predict the outcome of patients after acute myocardial infarction. Increased serum level of alanine transferase (ALT) and aspartate aminotransferase (AST) are associated with a higher risk of CV events. ALT and AST can be elevated due to cardiac failure, and AST can be significantly correlated with death (15). Serum alkaline phosphatase (ALP) is also a good prognostic factor in MI patients (16).

Since clinical symptoms are not reliable enough in the diagnosis of MI and electrocardiography (ECG) can show uncertain patterns, serum biochemical markers can be helpful in confirming and diagnosis of MI (17). With respect to the importance of MI etiology using blood biomarkers, we aimed to investigate the relationship between MI and blood biomarkers in Mazandaran Heart Center.

MATERIALS AND METHODS

Study design: In this hospital-based case-control study, data were obtained from all patients admitted to the Mazandaran Heart Center in Sari city for the period of three months during students' internship in this center. This tertiary center is the largest heart center in the north of Iran, and most of the patients referred to this center are Mazandaranis. The study was conducted from September 2018 to December 2018 (according to the Persian solar calendar).

Study population: Hospitalized patients diagnosed with MI based on diagnostic criteria of the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) guidelines (18) entered into our study as cases. Sex- and age-matched (± 1 years) seemingly healthy people, without a history of MI and negative troponin test participated in our study as controls. All of the participants were from the same geographic background (Mazandaranis). A consent letter was obtained from all participants, and no one refused to participate in the study. Exclusion criteria were as follows: 1) age under 18 years, 2) history of malignancy, 3) pregnant women, 4) insufficient medical record, and 5) participation refusal.

Laboratory measurements: After at least eight hours overnight fasting, blood samples were drawn from all participants. Serum levels of CK-MB, fasting blood sugar (FBS), total cholesterol (TC),

LDL, HDL, AST, ALT, and ALP were determined using the automatic biochemistry analyzer (Hitachi 912, Fameco, Japan). Troponin levels were analyzed using MINI VIDAS® immunoanalyzer (bioMérieux, France). According to Westergren method, whole blood of the patients was mixed with sodium citrate in a standardized calibrated tube, which are allowed to sit for 60 minutes in the LENA ESR analyzer to measure the sedimentation level.

Statistical analysis: The Statistical Package for the Social Sciences 16.0 (SPSS Inc., Chicago, Illinois, USA) was used for data analysis. A descriptive analysis of categorical variables was performed using frequencies and percentages. Variables comparisons were calculated using *chi*-square or Fisher exact tests, as appropriate. CK-MB>190, FBS>115, TC>200, LDL>160, HDL<40, AST>35, ALT>40, ALP>306 and ESR>20 were considered as abnormal levels. Comparisons of cases and controls regarding study variables were performed using the unpaired *t*-test or ANOVA for normally distributed parameters. In order to evaluate the interactive effects of study variables on MI

occurrence, we used logistic regression model to calculate the odds ratio (OR) with 95% confidence interval (95% CI). A *P*-value less than 0.05 was considered statistically significant.

This study was approved in the Ethical Review Committee of the Mazandaran University of Medical Science (MAZUMS) with ethical code IR.MAZUMS.REC.1398.469. The Student Research Committee of the MAZUMS sent a request to the Mazandaran Heart Center for collaboration. To comply with ethical standards, the consent form was filled out with all participants and their medical records were used confidentiality, exclusively for the research purpose.

RESULTS

In total, 894 subjects: 465 cases including 299 (64.3%) males and 166(35.7%) females and 429 controls including 219(51.0%) males and 210 (49.0%) females, which matched by sex and age participated in the investigation. The characteristics of the cases and controls are presented in Table 1.

Table 1: Demographical and laboratory characteristics of the cases and controls

Variable	Case (*n*=465)	Control (*n*=429)	*P*-value
Sex, male *n* (%)	299 (64.3)	219 (51.0)	matched
Age, years[*]	61.2 ±13.8	62.4 ±14.1	matched
CK-MB, IU/L[*]	108.3 ± 155.6	42.0 ± 88.9	<0.0001
FBS, mg/dL[*]	131.4 ± 78.4	101.5 ± 44.2	<0.0001
TC, mg/dL[*]	174.5 ± 49.7	178.8 ± 101.6	0.340
LDL, mg/dL[*]	150.6 ± 768.8	99.2 ± 42.7	0.103
HDL, mg/dL[*]	36.6 ± 12.1	36.6 ± 13.0	0.754
ESR, mm/h[*]	47.0 ± 48.7	28.5 ± 27.3	0.001

CK-MB: creatine kinase-muscle/brain; FBS: Fasting Blood Sugar; TC: Total Cholesterol; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; AST: Aspartate Aminotransferase; ALT: Alanine transaminase; ALP: Alkaline phosphatase; ESR: Erythrocyte Sedimentation Rate. ∗mean ± SD

The mean age of cases was 61.2 years (±13.8) while the mean age of controls was 62.4 years (±14.1). There were no differences between cases and controls regarding TC, LDL, HDL, and ALP.
As a cardiac marker, CK-MB levels were higher in MI patients in comparison to the control group (*P*<0.0001). The mean amount of FBS was significantly higher in cases than in controls

(*P*<0.0001). Regarding liver enzymes, although levels of ALP was not different between the two groups, levels of both AST (*P*<0.0001) and ALT (*P*<0.0001) were significantly higher in cases than controls. Moreover, level of ESR was meaningfully higher in cases (*P*=0.001).

Multivariable analyses revealed that the increase in risk for MI was associated with high

levels of AST (adjusted OR=24.3, 95%CI=3.5±165.6, *P*=0.001) and LDL (adjusted OR=7.4, 95%CI=1.0±51.8, *P*=0.001). However, no significant relationships were observed for other parameters. Risk estimates were present in Table 2.

Table 2: Associations between considered variables and risk of Myocardial infarction

Variable	OR* (95%CI)	*P*-value
Sex	0.050 (0.008-0.308)	0.001
Age	0.980 (0.934-1.028)	0.415
CK-MB	0.209 (0.003-15.391)	0.475
FBS	2.365 (0.511-10.948)	0.271
TC	0.566 (0.107-2.990)	0.503
LDL	7.481 (1.080-51.806)	0. 042
HDL	3.629 (0. 757-17.396)	0.107
AST	24.366 (3.583-165.697)	0.001
ALT	0.791 (0.063-9.879)	0.856
ALP	1.857 (0.376-9.166)	0.447
ESR	0.263 (0.043-1.616)	0.149

CK-MB: creatine kinase-muscle/brain; FBS: Fasting Blood Sugar; TC: Total Cholesterol; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; AST: Aspartate Aminotransferase; ALT: Alanine transaminase; ALP: Alkaline phosphatase; ESR: Erythrocyte Sedimentation Rate.
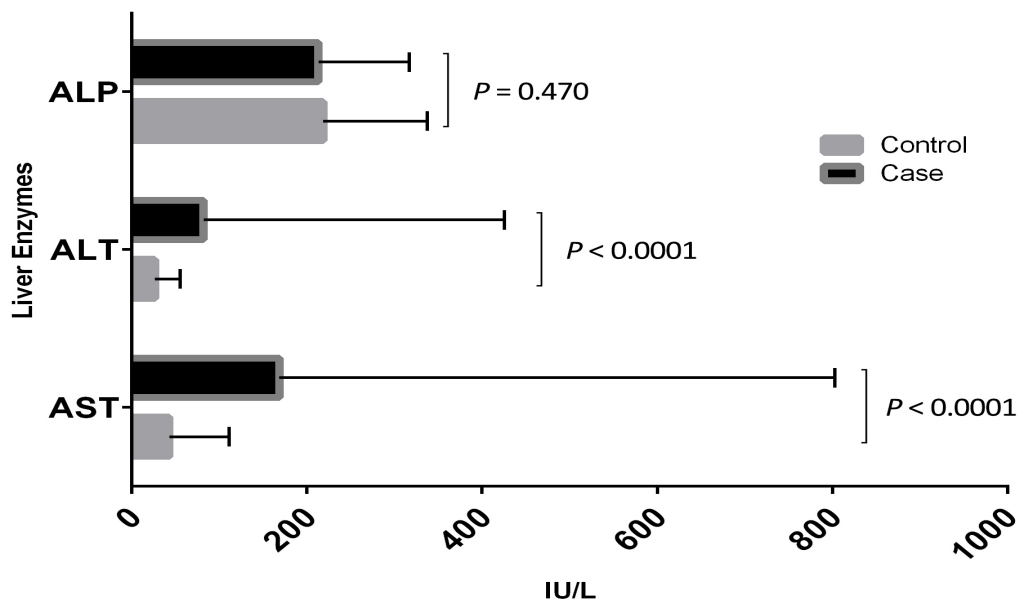*Adjusted by age and sex

Figure 1: Differences between cases and controls regarding liver enzymes

DISCUSSION

Our investigation indicated that levels of CK-MB, FBS, AST, ALT, and ESR were significantly higher in patients with MI. Besides, our findings showed that the risk of MI in cases with high levels of AST and LDL was about 24 and 7 times more than the control group respectively.

Our findings showed that CK-MB levels were significantly higher in cases with MI, and many other studies reported the good performance of this biomarker in detection of MI (19,20). In contrast, it is also reported that the weak sensitivity and specificity for CK-MB in this regard and its accuracy is still controversial, especially after resuscitation (21). However, it seems that it can be a useful marker along with other diagnostic approaches for MI detection.

Regarding FBS, our results were in the same line with the study of Abbasi *et al.*, which considered the high levels of FBS as one of the MI risk factors (22). It is remarkable that the study of Ishihara *et al.* showed that hyperglycemia is associated with MI and that it can deteriorate the prognosis in both diabetic and non-diabetic individuals (23). It is also reported that hyperglycemia is associated with the development of kidney injury and left ventricular dysfunction (because of the no-reflow phenomenon) in patients with MI (24, 25). Hyperglycemia can affect MI through several ways such as induction of electrophysiological alterations following arrhythmias, ischemic preconditioning, coagulation alteration, which likely to increase thrombosis activation, inflammatory amplification, and inducing endothelial dysfunction (26).

Among liver enzymes, levels of AST and ALT were elevated in MI patients significantly in comparison to the control group, which was also reported in the study of Lofthus *et al.* (27). About ALP, although we did not find any relationships with MI, Nunes *et al.* found that high levels of ALP can act as a diagnostic factor for decreased survival rate and renal function in male diabetic patients with MI (28).

Besides, our check results showed that the probability of MI in individuals with high levels of AST is nearly 17 times more than the control group. This enzyme was one of the first cardiac biomarkers used in the year 1954, and because of weak specificity for the matter, it is no longer used as a gold standard. Thereafter, total creatine kinase level and lactate dehydrogenase were used as a diagnostic factor for MI by the years 1959 and 1960 respectively (29,30). Eventually, the World Health Organization (WHO) suggested using these three factors for MI diagnosis by the year 1979, which was altered by the immunoassay's development in 1980 (31,32).

Regarding lipids profile, our findings showed that cases with high levels of LDL are at risk of MI 7 times more than the control group, which is in the same line with previous studies (33,34). However other members of lipids, although we could not find any relationships, previous studies indicated a relationship between low levels of HDL (35) and high levels of triglycerides (36) and risk of MI. However, facts regarding HDL are still controversial (37).

Our investigation indicated that high levels of ESR could be related to poor prognosis of MI, which was previously reported in several studies similarly (38,39). Therefore, it seems that ESR can be considered as a prognostic factor for monitoring of patients with MI to prevent the heart acute attacks (40).

As a strength of the study, to our knowledge, there is no investigation regarding the association of blood biomarkers with MI in this extent, at least in Iran. However, due to the retrospective nature of the study as a limitation, it is recommended that a comprehensive longitudinal cohort study be designed in order to examine the accurate role of these markers in MI.

In conclusion, we found that levels of CK-MB, FBS, AST, ALT, and ESR were significantly higher in patients with MI compared to the control group. Besides, our results indicated that individuals with high levels of AST were at risk of MI about 24 times more than the control group. Moreover, this risk was also 7 times higher in cases with high levels of LDL. Hence, clinicians may consider these factors as a valuable diagnostic or prognostic factor for patients with MI to prevent the next attacks and for a healthy population to prevent the first attack. Nevertheless, more comprehensive studies in different regions need to be done to avoid the geographical and race biases, which may affect the matter.

ACKNOWLEDGMENTS

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