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ОЦЕНКА ФЕНОТИПОВ ГАПТОГЛОБИНА ПРИ ОСТРОМ ИНФАРКТЕ МИОКАРДА (ОИМ) И ИХ АССОЦИАЦИЯ С НЕКОТОРЫМИ ФАКТОРАМИ РИСКА

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Резюме. Острый инфаркт миокарда (ОИМ) — одно из самых частых сердечно-сосудистых осложнений со сложным патогенезом, с вовлечением воспалительных маркеров в этиологию болезни. Целью данного исследования было исследование фенотипов гаптоглобина и их ассоциации с некоторыми факторами риска у больных с анамнезом ОИМ. Тип исследования: 120 пациентов направленных в отделение неотложной помощи госпиталя Амир Али г. Захедан (Иран) были включены в поперечно-срезовое исследование с контролем. 120 нормальных лиц были подобраны в качестве контрольной группы. Сыворотку получали из рутинных образцов крови, взятых для диагностики и применяли для определения распределения фенотипов гаптоглобина путем электрофореза. Проводили анализ различий по фенотипам среди пациентов и контрольной группы, используя тест χ^2 и программу SPSS. Обнаружена высокая частота фенотипа Hp2-2 гаптоглобина у пациентов и здорового контроля (соответственно, 62,5 и 58,3%). Значимая статистическая корреляция между высокой частотой фенотипа Hp2-2 гаптоглобина и острым инфарктом миокарда (ОИМ) не была выявлена (p = 0,484). В то же время высокая частота фенотипов Hp1-1 и Hp2-2 была ассоциирована с гиперлипидемией и гипертонией, соответственно (p = 0,01 и 0,04). Наши результаты показали высокую частоту фенотипа гаптоглобулина Hp2-2 у больных, а также здоровых лиц в популяции. Высокая частота Hp1-1 и Hp2-2 были ассоциированы у пациентов с инфарктом миокарда с гиперлипидемией и гипертензией соответственно. Таким образом, эти фенотипы у пациентов с ОИМ могут модулировать воспалительный ответ в сочетании с гиперлипидемией и гипертензией.

Ключевые слова: гаптоглобин, фенотип, острый инфаркт миокарда

EVALUATION OF HAPTOGLOBIN PHENOTYPES IN ACUTE MYOCARDIAL INFARCTION (AMI) AND THEIR ASSOCIATION WITH SOME RISK FACTORS

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Abstract. Acute myocardial infarction (AMI) is one of the most common cardiovascular complications with a complex pathogenesis where inflammatory markers are involved in disease etiology. The aim of this

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study was to investigate haptoglobin phenotypes and their association with some risk factors in patients with a history of AMI. 120 patients who were referred to the emergency department of Amir Al Momenin hospital of Zahedan city, Zahedan-Iran were recruited in a cross-sectional case control study. 120 normal individuals were also chosen as controls for this study. Serum was isolated from routine bloods taken for diagnostic tests and used to determine haptoglobin phenotype distribution by electrophoresis. Phenotype differences as percent of phenotype frequency in patient and control groups were analysed using the χ^2 test and SPSS software. A high frequency of serum Hp2-2 haptoglobin phenotype in patients and healthy control were found (62.5% and 58.3% respectively). A meaningful statistical correlation between high frequency of Hp2-2 haptoglobin phenotype and AMI was not found (p value = 0.484). Whereas high frequency of Hp1-1 and HP2-2 phenotypes was associated with hyperlipidemia and hypertension respectively (p value = 0.01 and 0.04). Our results showed that there was a high frequency of Hp2-2 haptoglobin phenotype in patients as well as healthy controls in the population studies. High frequencies of Hp1-1and Hp2-2 phenotypes were associated with AMI in patients with hyperlipidemia and hypertension respectively. Thus these phenotypes in AMI patients may modulate the inflammatory response in combination with hyperlipidemia and hypertension.

Keywords: phenotype, haptoglobin, acute myocardial infarction

Introduction

Acute myocardial infarction (AMI) is a common cardiovascular disease considered as an acute disruption of blood flow and oxygen delivery to cardiac cells and subsequently damage to the part of the heart muscle supplied by the blocked coronary arteries [23]. This disease is a significant cause of morbidity, hospitalization and mortality in most countries of the world. The incidence of AMI varies between different countries and cultures. The Middle East and parts of Eastern Europe probably have the highest cardiovascular death rates in the world and Iran possibly has a higher burden than other countries in this region [15, 27].

Disease symptoms include severe pain and burning sensation in the chest, palpitations, sudden shortness of breath, cold sweats, pain in left arm and shoulder area, and finally feeling of nausea and vomiting. These symptoms vary in people depending on age, gender, ethnicity, personal behavior, social, economic, spiritual, political, religious beliefs, nutritional and genetic [5].

Diagnostic criteria for AMI is at least two of the following symptoms; severe chest pain more than 20 minutes, changes in ST segment elevation of ECG, increase in cardiac markers including serum creatine phosphokinase (CK), MB creatine kinase (CKMB), cardiac troponin T (CTUT) and troponin I (CTUI) [9]. Recently molecular studies in China, indicated that a new biomarker, lymphocyte-specific protein tyrosine kinase (LCK), can be a candidate for the early diagnosis of AMI [31].

Several factors have been involved in the pathogenesis of disease, including hypertension, high cholesterol, male gender, older age, smoking, diabetes and obesity, family history, individual genetic background, environmental risk factors, lifestyle and psychological and oxidative stress [3, 10].

Recently immunological mechanism such as inflammation have been found to be involved in the development and progression of coronary artery disease.

The role of CRP as a marker of ischemic cardiovascular disease and presence of inflammatory cells and activated macrophages, B and T cells, $CD4^+CD25^+$ regulatory T (Treg) cells and Th17 cell ratio and their role in atherosclerotic plaques formation have all been proposed to be involved in the pathogenesis of cardiovascular disease [2, 17, 20, 30].

As with CRP, haptoglobin (Hp) is also considered to be an acute phase protein but its role in the pathogenesis of acute myocardial infarction has not been studied. Hence we set out to study this with an aim to use Hp as a diagnostic tool, for risk assessment and possibly as an aid in disease management [14].

Haptoglobin is an inflammatory protein that its primary function is to modulate the fate and toxicity of extra corpuscular hemoglobin [15]. Its synthesis is increased in inflammation and infection, and it is a positive acute phase protein [19, 29].

Haptoglobin has three phenotypes (Hp1-1, Hp2-1, and Hp2-2) that are associated with various diseases. Many studies have shown that patients with diabetes have the higher Hp2-2 phenotype frequency than the other phenotypes [19]. Haptoglobin phenotypes association with cancer, preeclampsia, infectious diseases, neurological disorders and preterm labor disease has also been reported [13].

Haptoglobin polymorphism has been shown to be an important determinant of clinical outcome and infarct size in AMI [24]. It is a predictor of 30-day mortality and heart failure in patients who suffer from diabetes and acute myocardial infarction [24].

An association between Hp2-2 alleles of this protein with unstable carotid plaque and major cardiovascular events has also been demonstrated [12].

In another study in 2013, it was shown that plasma Hp concentration was elevated and significantly correlated with the severity of luminal stenosis in patients with coronary artery disease (CAD) [14].

Haptoglobin phenotypes association with acute myocardial infarction and possible correlation with some risk factors has not been identified yet hence we conducted this study.

Materials and methods

The research was designed as a case-control study. Patients with acute myocardial infarction diagnosed

by cardiologists who were admitted to the emergency department of Amir Al Momenin Hospital, Zahedan, Iran, were selected. In adddition, the same number of healthy controls with no risk of heart disease were selected and their Hp phenotype frequency determined.

After obtaining informed consent from each individual based on the local ethical codes of the Zahedan University of Medical Sciences, Zahedan-Iran.

Patients notes and control interviews were used to collect epidemiological data.

5 mls of peripheral blood was taken and serum was separated and maintained in a -80^0c freezer. Serum Hp phenotype of each individual was separated with protein electrophoresis in polyacrylamide gel and identified with proprietary peroxidase coloring. The differences in the frequency of each phenotype in patients and healthy groups were evaluated by using statistical tests X^2 in SPSS version 18. Other biochemical, hematology and immunology factors were also tested.

Results

In this study, 49.1% of patients were male and 50.9% female. 47.9% of all patients had aged more than 60 years. Among of them, 0.8% aged less than thirty years, 0.8% between thirty to forty years, 10.9% between forty to fifty years, 39.5% between fifty and sixty years of age, and 47.9% above the age of 60 years old.

In all patients, 13 cases (10.8%) were Hp1-1, 75 cases (62.5%) were Hp2-2 and 32 cases (26.7%) were Hp2-1. In controls, 10 cases (8.3%) were Hp1-1, 70 cases (58.3%) were Hp2-2 and 40 cases (33.4%) were Hp2-1.

Hp2-2 phenotype was found at a higher frequency in the cases than in the control group. Hp1-1 and Hp2-1 were higher in control group, but there was no statistically significant difference between the two groups (p value = 0.484) (Figure 1 and Table 1).

In addition, there was no statistical difference between the 2 groups with regards to demographic factors such as sex, occupation, marital status, place of residence and level of education (p = 0.352). In addition, comparison of all three Hp phenotypes was differ as Hp2-2 frequency was calculated high (p = 0.001).

The result of a second analysis showed in patients, Hp1-1 frequency were significant associated with hyper lipidemia and Hp-2-2 frequency with hypertension (p value = 0.001) and (p value = 0.004) respectively. Figure 2 shows electrophoretic pattern of different Hp phenotypes in patients. Based on size of each phenotype, Hp 2-1 and Hp 2-2 because of different polymerization of subunit Hp2 are varied (Hp2-1 has 86-3000 KD and Hp2-2 has 170-900 KD) whereas Hp 1-1 phenotype has one Hp1 subunit is non polymerized and has 86 KD as shown in figure of gel (Figure 2).
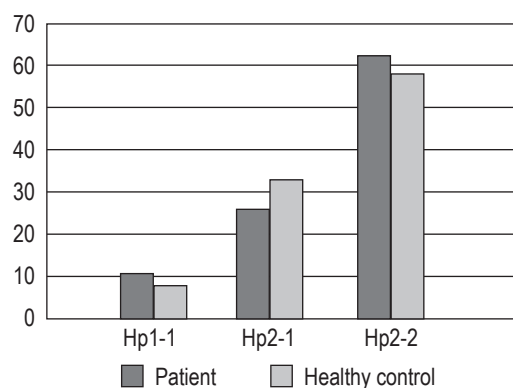

Figure 1. Comparison of different Hp phenotypes distributions in patients and healthy controls

TABLE 1. COMPARISON OF PHENOTYPES DISTRIBUTION BETWEEN PATIENTS AND HEALTHY GROUPS

Hp Phenotype \ Group	Patients	Control	Total	p value
Hp1-1	13 10.8%	10 8.3%	23 9.6%	
Hp2-1	32 26.7%	40 33.4%	72 30.0%	0.484
Hp2-2	75 62.5%	70 58.3%	145 60.4%	
Total	120 100%	120 100%	240 100%	

Discussion

In this study serum Hp phenotype distribution of 120 patients with AMI were evaluated. There was no significant difference between male and female risk factors for AMI. These results are consistent with some studies [1, 8, 23] but differ from the findings reported by Mohammad et al. that the risk factors profile in men is different from that in women [3].

Additionally, in keeping with other studies [11, 25], this study found that individuals over 60 years of age had the highest risk of AMI. Therefore these findings place further emphasis on the fact that it is essential to predict and prevent this disease in patients over sixty years of age [28, 32].

We assumed that inflammation underlies the development and progression of AMI disease and as discussed Hp is an inflammatory marker. Some evidence suggests that the Hp phenotype is associated with the development of cardiovascular events and has a role in induction of AMI pathogenicity [9]. The inflammation mechanisms underlies the development and progression of AMI linking with Hp phenotype frequency have been listed by some researchers. An early study in 1997, examined Hp polymorphism in Korean patients with cardiovascular disease. The results indicated that Hp polymorphism, at least in the Korean population, does not predispose to the occurrence of cardiovascular disease [9] and Hp may
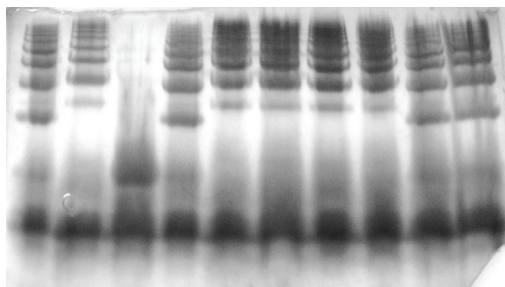
Figure 2. Electrophoretic pattern of different Hp phenotypes in patients

a global marker of inflammation and is not specific for cardiovascular disease.

Furthermore, a study with the aim of the relationship between Hp type and prevalence of coronary heart disease in a cross-sectional study from a large community-based cohort, the results showed interaction between Hp type and diabetes in the prevalence of coronary heart disease (CHD) [16]. On the other hand study of Hp polymorphism in patients who suffered from diabetes and acute myocardial infarctions showed that this polymorphism was a predictor of 30-day mortality and heart failure [24]. Since these studies, associations between two alleles of this protein with unstable carotid plaques and major cardiovascular events have been reported [12]. While some studies report association of elevated plasma Hp concentrations with the severity of luminal stenosis in patients with coronary artery disease (CAD) whereas Hp phenotype was not associated with CAD disease [14].

Our results showed that the Hp2-2 serum Hp phenotype was observed in 75 cases of AMI (62.5%) and 70 healthy controls (58.3%). Statistical comparisons of these phenotype, showed no significant difference between the two groups (p value = 0.484). Therefore, the risk of AMI cannot be attributed to these Hp phenotypes and a Hp-dependent mechanisms is not supported by these results. The reason for this is not clearly understood but it may correlate to different biological properties of these three phenotypes.

In addition comparison of Hp phenotypes with each other was differ as Hp2-2 frequency was calculated high (p value = 0.001). Thus due to the presence of clinical symptoms of AMI disease in patients, this association is clinically may meaningful but the exact mechanism of this is unclear and may related to differences in the biological role of this type of phenotypes or serum concentration of Hp. Our results in this aspect, is slightly consistent with Chin-Wei Lee et al. [14] in which they showed there is no association with Hp phenotype and CAD disease.

As far as we are aware, this is the first study to examine Hp phenotype in patients with AMI and until now other researchers have not reported phenotype associations. Further studies need to be performed to understand phenotype association better. Study of the genotype and measurement of the amount of this protein through doing ELISA and molecular tests such as PCR could be very interesting.

On the other hand no statistical correlation between hematologic factors such as cell blood count (CBC + differ) and all hemoglobulin (Hb) indices with the frequency of phenotypes Hp, was found (P value = 0.673). There is no any similar report has been introduced yet and only some researchers have noted the role of these factors in combination with Hp genotypes [25] family history [27], anti to pro-inflammatory cytokine ratios [4] and hematological factors [18], plays a role in coronary heart disease in predisposing to the disease

In addition, based on the result of some other predisposing factors such as hyperlipidemia and hypertension in association with Hp phenotype, the results of this study showed Hp1-1 and Hp2-2 Haptoglobin phenotypes frequencies have been significantly associated with hyperlipidemia and hypertension manifestations respectively (p value = 0.01 and 0.04).

Hong S.H. et al. investigated the relationship between Hp polymorphism and plasma lipid levels and found that the distribution of Hp phenotypes did not show any significant differences between the healthy controls and the patients with cardiovascular disease. But Hp phenotypes were associated with levels of high-density lipoprotein cholesterol in the hypertensive group [9]. Since that study, there have been several reports have demonstrated the role of cardiovascular events in pathogenicity of AMI. The impact of cardiometabolic risk factors on major cardiovascular events such as diabetes, metabolic syndrome (MetS) and hypertension in patients with familial combined hyperlipidemia and arterial hypertension, have been reported by some investigators [6, 7, 22] in which they showed these factors have been involved in the pathogenesis of AMI disease. These factors also in combination to other factors involved in the pathogenesis of AMI disease are supposed to be more a product of environmental factors than inherited aspects and are independent of the synthesis and expression Hp which the reason in many cases is unknown that require further investigate. Despite of fact, individual differences among patients with various aspects of gene especially Hp genotypes plays a role in coronary heart disease [21] as our study did not examine this association in a particular place in the gene set. So far, this also needs to be examined in further to examine the potential diagnostic and monitoring significance of such a link. So far, this also needs to be examined in further.

Conclusions

In conclusion, although we initially found high frequency of Hp2-2 haptoglobin phenotype in AMI patients but this was not statistically significant confirmed the association of certain types of Hp-dependent mechanism and all three phenotypes have been equally implicated in the pathogenesis of the AMI disease.

In secondary analyses we found a different pattern of Hp type with some risk factors as high frequency of Hp1-1and and HP2-2 phenotypes has been associated

with hyperlipidemia and hypertension respectively. This needs to be investigated more preferably using data and samples from ongoing longitudinal epidemiologic studies with repeated measurements of other risk factors in Hp phenotype association of AMI diseases.

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Authors' contributions

All authors have had equally participated in the design of the study, performed the laboratory work, and drafted the manuscript. They also performed statistical analyses, the protein identification, made substantial contributions to acquisition of the samples and the clinical data. It is also declare that all authors were involved in revising the manuscript critically, and all authors read and approved the final manuscript. All authors declared there were no conflicting interest.

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