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Relation between the Serum Ferritin Level and the Risk for Acute Myocardial Infarction

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ABSTRACT

Background: Increased estimated body iron stores have been suggested to be associated with increased risk of acute myocardial infarction (AMI). However, the question of whether serum ferritin level as an indicator for estimating body iron is an independent risk factor for cardiac events is still questioned. In this study, we assessed whether serum ferritin was associated with the incidence of AMI.

Methods: The study population consisted of 100 consecutive male patients with first AMI, including 50 suffered from ST Elevation Myocardial Infarction (STEMI) and 50 with non-ST Elevation Myocardial Infarction (NSTEMI) diagnosis, admitted within 12 hours of the onset of chest pain to coronary care units (CCU) at Ekbatan hospital in Hamadan, Iran in 2014. A control group (n = 50) was selected among men without history of AMI from the same hospital. Serum ferritin was measured using ELISA assay at the first and fifth days after admission.

Results: The first and fifth day serum ferritin concentrations averaged 56.75 and 112.5 µg/dl in STEMI group, 36.5 and 87.25 µg/dl in NSTEMI group, and 22.5 and 42.0 µg/dl in control group that was significantly higher in former group (P=0.001). Serum ferritin level was also significantly higher in AMI group compare to control group (P=0.001). Multivariable logistic regression model showed that the elevated level of serum ferritin could predict occurrence of STEMI adjusted for initial ferritin concentration, patients' age and coronary disease risk factors (OR=5.1, P=0.017).

Conclusions: Elevated serum ferritin can be a factor for predicting AMI especially STEMI.

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Introduction

A harmful biological effect of excessive iron loading in the human body has been recently suggested. In this regard, iron overloading especially in myocardial tissue has been proposed to be a potent risk factor for ischemic heart disease and occurring acute myocardial infarction [1-4]. The cardiac iron deposition results in a decrease of heart function on a certain genetic background [5]. Iron can also directly injure the myocardium. Iron can be accumulated in cells as hemosiderin, ferritin, and free iron named labile cellular iron that is the most toxic form stimulating the formation of free radicals [6-7].

Since serum ferritin concentrations are directly proportional to intracellular ferritin concentration, it is considered the best clinical measure of body iron stores[8]. Recently, some evidences have been provided linking the increased incidence of coronary artery disease and elevated level of stored iron concentration[9]. In these, increased estimated body iron stores have been associated with increased risk of coronary heart disease (CHD) death or acute myocardial infarction (AMI) in some[10-12], but some observations could not reveal this relationship[13-18]. It seems that the observed discrepancy may be largely a result of the vast biological and measurement variability in methods used in assessing the body iron stores and, to some extent, study outcomes. In total, the question of whether body iron or its indicator as serum ferritin level is an independent risk factor for acute myocardial infarction is still questioned. In the present study, we assessed whether serum ferritin was associated with the incidence of myocardial infarction.

Methods

In this comparative cross-sectional study, the study population consisted of 100 consecutive patients with first acute myocardial infarction, 50 suffered from ST elevation myocardial infarction (STEMI) and 50 with non-ST elevation myocardial infarction (NSTEMI) diagnosis admitted within 12 hours of the onset of chest pain to coronary care units (CCU) at Ekbatan hospital in the city of Hamadan, Iran in 2014. Patients had the following criteria: a) typical chest pain lasting ≥20 min; b) increase in serum creatine kinase (CK) level (values exceeding 200 U/l in male subjects and 150 U/l in female subjects were considered to be raised), or troponin I enzyme (values exceeding the 99th percentile of the values obtained from a reference group) according to the American College of Cardiology and the European Society of Cardiology (ACC/ESC) guideline;[19] and c) ST-segment

elevation ≥0.2 mV in ≥2 contiguous precordial leads (for the diagnosis of anterior wall MI) or in leads V_1–V_3 (for the diagnosis of anteroseptal wall MI) as well as ≥0.1 mV in II, III, and aVF leads (for the diagnosis of inferior wall MI) on the admission ECG in the absence of left ventricular hypertrophy or left bundle branch block (LBBB) (for diagnosis of ST-segment elevation myocardial infarction) or transient ST-segment depression>=1 mm or T wave inversion in 2 or more contiguous precordial leads without evidences of pathological Q wave (for diagnosis of non ST-segment elevation myocardial infarction)[20].The main exclusion criteria were: non-diagnostic ECG, previous myocardial infarction or ST elevation in the background of LBBB or pacemakers rhythms or aneurysms arising from previous infarction, concurrent diseases including renal, hepatic, or hematological disorders (anemia, polycythemia, myeloproliferative disorder s), history of cancer in the past or present, recent infection or autoimmune disease, severe bleeding that required a blood transfusion, or patient dissatisfaction for blood sampling. Informed consent was taken from all patients. This study was also approved by Ethics Committee of the Hamden University of Medical Sciences.

A control group was also selected 50 men aged 35 to 75 years without any evidences of myocardial infarction that referred to cardiology clinic of hospital to any reason for examining and visiting. Demographic characteristics and clinical criteria of these patients were extracted from hospital- recorded files as well as face-to-face interviewing on admission and entered into a computerized database form. The patients were also given self-administered questionnaires about their demographics and medical history included general characteristics, coronary artery disease risk factors: current smoking history (patients regularly smoke a tobacco product/products one or more times per day or have smoked in the 30 days prior to admission) [21], hypercholesterolemia (total cholesterol ≥5.0 mmol/l, HDL-cholesterol <1.0 mmol/l in men, or <1.1 mmol/l in women, and triglycerides ≥2.0 mmol/l)[22], family history of CAD (first-degree relatives before the age of 55 in men and 65 years in women) [23], hypertension (systolic blood pressure ≥140 mmHg and/or diastolic ≥90 mmHg and/or on antihypertensive treatment) [24], and diabetes mellitus (symptoms of diabetes plus at least one of the following: plasma glucose concentration ≥11.1 mmol/l, fasting plasma glucose ≥7.0mmol/l, and 2-hpp ≥11.1 mmol/l)[25]. When it was impossible to speak to the patient or when the information provided by the patient was deemed unreliable by the interviewer, the participant was not included into the study. These men were relatively similar to AMI (including STEMI and NSTEMI) group in terms of Demographic characteristics and coronary risk factors (Table 1). Participants also underwent a clinical examination that included measurement of fasting glucose, body composition, systolic and diastolic blood pressure, as well as serum lipids. Weight and standing height was expressed as body Mass Index (weight in kilograms divided by height in meters squared). Blood pressure was recorded using an automatic oscillometric blood pressure recorder after at least 5 min of rest in a chair and arm supported at heart level. Systolic blood pressure was measured at the point where the first of two or more sounds was heard (phase 1), and diastolic blood pressure with the disappearance of sounds (phase 5). For biochemical analysis, blood samples of 5 ml were drawn after 12 h overnight fasting for measuring lipid profile, and fasting blood sugar. Serum ferritin was measured using an ELISA assay by a special kit at the first and fifth days after admission in both cases and control groups.

Table 1: The status of traditional risk factors and laboratory biomarkers in STEMI, NSTEMI and control groups

Characteristics	STEMI group, n (%)	Non-STEMI group, n (%)	Control group, n (%)
Age (yr), mean (SD)	53.5 (8.4)	55.6 (9.0)	52 (7.2)
ESR (ml/hr), mean (SD)	6 (4.0)	7 (5.0)	10 (6.0)
CRP (mg/ml), mean (SD)	37 (20.0)	5 (4.0)	2 (1.0)
WBC count, mean (SD)	11314 (1700)	8200 (1500)	7800 (2100)
Diabetes mellitus, n (%)	10 (20)	10 (20)	10(20)
Hypertension, n (%)	11 (22)	18 (36)	10(20)
Current Smoking, n (%)	37(70)	31 (62)	30 (60)
Hyperlipidemia, n (%)	10 (20)	2 (4)	5 (10)

Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Categorical variables were compared using chi-square test or Fisher's exact test when more than 20% of cells with expected count of less than 5 were observed. Quantitative variables were also compared using *t test, Mann-Whitney U test, one-way ANOA test, or Kruskal Wallis test*. The changes in ferritin level within 5 days after initial assessment was examined by the paired *t test or Wilcoxon test.* The multivariable logistic regression model was used to examine the difference in serum ferritin level changes. Multivariate-adjusted Odds ratios and 95% confidence intervals were also calculated. Statistical significance was determined as a p value of ≤ 0.05. All the statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) and SAS version 9.1 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

The average age of the subjects in STEMI (53.5±8.4 years), in NSTEMI (55.6±9.0 years) and in control ones (52±7.2 years) were comparable across the groups. As shown in table 1 comparing prevalence of traditional risk factors for heart diseases between STEMI, NSTEMI and control groups, hyperlipidemia was more prevalent in STEMI group, while other risk factors including diabetes mellitus, current smoking, were similar in three groups. Regarding serum levels of chemical biomarkers, the STEMI group had significantly higher level of WBC count and CRP compared to the other groups, but no discrepancy was observed in serum ESR index between the these groups.

The serum ferritin concentrations ranged from 7 to 716µg/dl and averaged 56.75, and 112.25µg/dl in STEMI group in first and fifth day respectively, ranged from 15 to 161 µg/dl and averaged 36.5, and 87.25 µg/dl in NSTEMI

group in first and fifth day respectively, and ranged from 13 to 120 µg/dl and averaged, 22.5, and 42.0 µg/dl in control group in first and fifth day, respectively, that was significantly higher in former group. In this regard, the medium level of ferritin in STEMI, NSTEMI, and control groups were 159, 146, and 32.5 µg/dl, respectively that was significantly higher in those who suffered STEMI than in other study subgroups (*P*= 0.001) (Table 2).

Table 2: The changes in serum ferritin level in ST elevation myocardial infarction (STEMI), Non ST elevation myocardial infarction (NSTEMI), overall myocardial infarction (MI) and control group in the first and fifth days

Ferritin (µg/dl)	Control group	STEMI		NSTEMI		AMI	
	Mean	Mean	*P* value	Mean	*P* value	Mean	*P* value
1st day	22.50	56.75	0.001	36.50	0.20	46.62	0.001
5th day	42.00	112.5	0.001	87.25	0.07	99.75	0.001

Serum ferritin level was significantly higher in AMI groups (including NSTEMI and STEMI) compared to control group in first and fifth day measurements (*P*=0.001). Serum ferritin level was 46.62 µg/dl and 99.75 µg/dl in first and fifth day, respectively in former group and 22.5 µg/dl and 42 µg/dl in first and fifth day in latter group, respectively. (Table 2)

With respect to correlation between changes in ferritin level and chemical parameters, in STEMI group, the level of last ferritin was positively correlated with CRP level (r=0.44, *P*<0.001), but not with other biomarkers. In NSTEMI group, none of the biomarkers was correlated with serum ferritin concentration.

Multivariable logistic regression model (table 3) showed that the elevated level of serum ferritin could predict occurrence of STEMI adjusted for initial ferritin concentration, patients' age and coronary disease risk factors (OR=5.1, 95% CI: 1.3, 20.1, *P*=0.017). Furthermore, considering different ferritin level in five day after initial assessment, the highest of ferritin level was associated with the significant increase in the risk for STEMI compared with the lowest adjusted for age (OR=3.9, 95% CI: 1.1, 13.5, *P*=0.033) and also adjusted for all general coronary risk factors (OR=5.1, 95% CI: 1.3, 20.0, *P*=0.027).

Table 3: Multivariate regression analysis for determining value of serum ferritin level for predicting STEMI

Characteristics	Odds Ratio (95% CI)	*P* value
Baseline Ferritin level (µg/dl)	5.19 (1.34, 20.12)	0.017
Age (yr)	0.99 (0.95, 1.05)	0.942
Smoking	1.87 (0.71, 4.94)	0.204
Hypertension (mmHg)	0.35 (0.11, 1.08)	0.068
Diabetes mellitus (mg/dl)	0.94 (0.27, 3.29)	0.928
Hyperlipidemia (mg/dl)	7.99 (1.41, 45.23)	0.019

Discussion

In the present study of Iranian male adults, elevated serum ferritin concentrations was associated with increased risk of STEMI. Having scrutinized the findings in this study, patients with myocardial infarction regardless of presence or absence of ST elevation have had higher concentration of ferritin level in the first and fifth day after AMI. Of note, ferritin concentration was significantly higher in STMI groups.

Previous evidences of an association between AMI and elevated serum ferritin concentrations came from some human studies. Men with serum ferritin concentrations >200 µg/L had 2.2-fold higher risk of AMI than did men with low serum concentrations after adjustment for other risk factors[26]. Similarly, serum ferritin >200 µg/L has been introduced as a major predictor for occurrence of AMI that the higher rate of this blood marker led to 5-fold increased risk of MI [27].

In spite of these evidences, some other studies could not present supportive reasons for this association. Frey and Krider did not support the hypothesis that high serum ferritin levels could be associated with myocardial infarct [28].Also, based on Sempos et al. observations, the results did not demonstrate the hypothesis that positive body iron stores, as measured by serum ferritin, were associated with an increased risk of cardiovascular disorders and related mortality [28].this inconsistent findings may be due to different study design, different following-up time and ignoring some potential confounders in the multivariable regression modeling affecting the relation between serum ferritin level and risk of AMI.

A variety of underlying reasons has been proposed to explain association between increased ferritin level and occurrence of AMI. First considering the key role of stress on triggering AMI, it was shown that peripheral blood monocytes derived from healthy individuals incubated with hydrocortisone, showed a significant enhancement of their ferritin content, a finding suggesting that these cells activated by steroids during stress could be a source of the increased serum ferritin level leading AMI [29]. In addition, along with our findings with regard to significant association between serum ferritin level and some general coronary disease risk factors such as diabetes, cigarette smoking and hypertension, synergistic inter-correlation between some underlying risk factors for MI and ferritin level have been suggested. In this regard, the effects of iron stores on atherogenesis were more pronounced in smokers[30] ,and synergistic effects between serum ferritin and serum cholesterol or LDL cholesterol have been reported as discussed above [31-32].These findings indicate that high serum ferritin may increase the risk of ischemic heart disease in the presence of other risk factors that increase the formation of free radicals, thus accelerating atherogenesis via stimulation of LDL oxidation[3,34] .In fact, oxidation of LDL-cholesterol by serum ferritin may play a role in the inflammatory reaction and for the increased high-sensitive C-reactive protein[35]. Regarding association between diabetes and serum ferritin concentration, ferritin was significantly higher in diabetic male patients in comparison with non-diabetic male patients[36].Besides environmental risk profile, the role of some underlying genetic factors has been examined regarding relation between serum ferritin and coronary heart diseases. Compared with the mutant genotype of tagSNP rs9366637, subjects with wild allele had higher risk of coronary artery disease[37]. Despite some identified genetic and pathophysiological mechanisms for the role of serum iron and ferritin levels to predict occurrence of AMI, the underlying mechanism remained to be elucidated in further studies.

Findings in this study confirmed the role of iron store in body in both atherosclerosis process and severity of

presentation in vulnerable patients with AMI. Given the fact that iron supply is mainly provided by dietary regimen, limitation of diet containing high level of iron may be paramount important.

Though the differences we observed in ferritin concentrations between AMI group and control group were statistically significant, we were unable to measure all potential confounders, such as fever and inflammation that may affect ferritin level in acute phase.

Conclusions

Increased serum level of ferritin is independently associated with AMI especially STEMI, which may be due to probable synergistic effects of serum ferritin regulation pathways and underlying risk factors for AMI.

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Conflict of interest statement

The authors have no conflict of interest to declare.

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