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Original article

Serum ferritin—a novel risk factor in acute myocardial infarction

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KEYWORDS

Acute myocardial infarction (AMI)
conventional risk factors
coronary heart disease (CHD)
Serum ferritin

ABSTRACT

Background: A possible association between body iron status and risk of coronary heart disease (CHD) has been found to be controversial from the data obtained from various studies.
Objectives: To study the relationship of serum ferritin with acute myocardial infarction (AMI) in univariate and multivariate analysis and to assess the relationship of high serum ferritin with established conventional risk factors.
Methods: Hospital based case-control study of 75 cases of AMI, and 75 age and equal number of age, and gender-matched controls without having AMI in the age group of 30–70 years.
Results: Median serum ferritin levels were significantly higher in cases (220 μg/L) than controls (155 μg/L) ($P \leq 0.0001$. In univariate analysis in addition to ferritin >200 μg/L (odds ratio [OR] 6.71, 95% confidence interval [CI]=3.22–12.89, $P<0.05$), diabetes (OR=7.68, 95% CI=2.95–19.13, $P<0.05$), hypertension (HTN) (OR=2.36, 95% CI=1.02–5.14, $P<0.05$) high-density lipoprotein (HDL) <35 mg/dL (OR=11.9, 95% CI=2.66–52.57, $P<0.05$) and smoking (OR=2.17, 95% CI=1.12–3.87, $P<0.05$) were found to be significantly associated with AMI. After controlling for all conventional risk factors, in multiple logistic regression analysis, high ferritin was significantly associated with AMI. (adjusted OR=5.72, 95% CI=2.16–15.17, $P<0.001$). Serum ferritin was significantly higher in diabetics than non-diabetics ($P<0.01$).
Conclusion: High serum ferritin is strongly and independently associated with AMI.

Introduction

Over the past several years, observational and epidemiological studies have identified a host of new and potential risk factors for atherothrombotic vascular diseases. In this growing list of new and emerging risk factors, the entities like elevated blood levels of homocysteine, fibrinogen, inflammation and infection, atherogenic lipoprotein, elevated triglyceride, and number of genetic polymorphism are of particular interest. Apart from these, there is strong evidence that oxidative free radicals have a role in the development of degenerative diseases including coronary heart disease (CHD).[1,2] Oxidative free radicals increases the peroxidation of low-density lipoprotein (LDL), thereby increasing its uptake by macrophages with increased foam cell formation and atherosclerosis.[3,4] Iron, a dietary constituent, is a pre-oxidant and a high concentration of blood ferritin, which measures stored iron, is a potential novel risk factor for CHD. Free iron which acts as a catalyst for the production of free radicals has been implicated in lipid peroxidation and atherosclerosis leading to myocardial infarction (MI).[2] Serum ferritin concentrations are directly proportional to intracellular ferritin concentration and considered to be the best clinical measure of body iron stores and most feasible to use in epidemiological studies.[5]

The role of ferritin in pathogenesis of coronary artery diseases (CAD) like acute MI (AMI), has generated considerable interest in recent times. There is a plethora of articles reporting the relationship between serum ferritin and AMI but with conflicting and contradictory results. Sullivan JL (1981) was the first to observe that high level of stored iron is a risk factor for heart disease.[6] Subsequently, results of the various studies showed statistically significant association of high serum ferritin and AMI.[7–9] However, some authors did not find any significant association of high ferritin and AMI.[10–13] The main objective of our study was to compare the ferritin levels in cases and controls, in order to assess the relationship of serum ferritin with AMI, in both univariate and also in multivariate analysis, after controlling for established

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conventional risk factors (like diabetes mellitus [DM], HTN, lipids, body mass index [BMI], smoking, and alcohol intake).

Materials and methods

Inclusion and exclusion criteria

In this hospital based case-control study, 75 consecutive cases of AMI admitted to the Coronary Care Unit of Indira Gandhi Government Medical College, Nagpur, were enrolled. The diagnosis of AMI was based on fulfilling any two of the following criteria.[14] (1) Chest pain of <12 hours duration, (2) ST elevation >1 mm in at least two consecutive leads, (3) increased cardiac markers (creatine phosphokinase-MB (CPK-MB) two times the upper limit of normal), and (4) presumably new onset bundle-branch block. Cases with high ferritin levels like haemochromatosis, liver disease, tuberculosis, chronic inflammatory diseases, those on iron therapy and those having past history of AMI or CHD were excluded from the study.

One age (±5 years), gender and haemoglobin-matched control was recruited for each case, irrespective of presence of risk factors (HTN, DM, smoking and alcohol intake) but without having AMI (in the past or present) or any evidence of CHD (assessed by symptoms, clinical examination and normal electrocardiogram [ECG]). Controls were selected randomly from subjects attending out patient department of hospital for minor ailments or routine medical check-up, subjects accompanying patients or amongst office working staff from various departments of this institution without having any evidence of AMI/CHD. The other exclusion criteria were same for controls as that for cases.

All the subjects were assessed by clinical examination ECG, serum creatine kinase-MB fraction (CK-MB). Height and weight were recorded. Body mass index was calculated by formula, weight in kg/height^2 in m. Body mass index >25 was considered as a risk factor for AMI.

Cases and controls were investigated for conventional risk factors (BMI, blood sugar, lipid profile). History of smoking and alcohol consumption was noted in details. Estimation of lipids was done by enzymatic method using autoanalyser while glucose oxidase and peroxidase (GOD-POD) method was used for measurement of blood sugar. Serum ferritin was done in all the subjects and was estimated by using Genix ferritin enzyme-linked immunosorbent assay (ELISA) test which is based on a solid phase ELISA using ELISA reader.[15] Since serum ferritin is a sensitive marker of body iron store, estimation of serum iron and total iron binding capacity (TIBC) was not considered in the present study.

Data analysis

Statistical analysis included the usual descriptive and univariate analysis. Discrete (categorical) variables were compared by χ^2-test and for continuous variable, Students *t*-test was used. Since, the distribution of serum ferritin values in cases was slightly skewed, and the assumption of normality was not met, we used the non-parametric test (Mann–Whitney test) to compare the median values of ferritin in cases and controls. Unadjusted odds ratio with 95% CI were calculated and *P* values were computed. All *P* values were two-tailed and values <0.05 were considered statistically significant.

To determine the independent association of serum ferritin with AMI, multivariate analysis was carried out by performing multiple logistic regression analysis, with AMI as a dichotomous independent outcome variable and serum ferritin and other conventional risk factors as dependent predictor variables and adjusted odds ratio (ORs) and 95% CIs were computed using Minitab statistical package Minitab II on personal computer.

The study was approved by Medical Ethic Committee of the Institution and written informed consent was obtained from all participants.

Results

A total of 75 cases and an equal number of controls were studied. The mean age of controls and cases was similar (50.6±7.8 years and 51.16±8.0 years) respectively (age range 30–70 years). Males outnumbered females with a ratio of 2.4:1. Mean haemoglobin in cases and controls was similar (13.29 g% and 13.39 g%, respectively), since they were matched for haemoglobin.

The median serum ferritin values were significantly higher in cases (220 μg/L) as compared to controls (155 μg/L). ($P<0.0001$) (Table 1). The mean value of serum ferritin (μg/L) in controls and cases were found to be 155.65±79.76 and 324.4±256.8, respectively ($P<0.001$). The distribution of serum ferritin for cases and control subjects indicated a shift towards higher concentration in patients with AMI (Figure 1). Correspondingly, more patients with AMI (62.66%) than control subjects (20%) had concentrations above the cut-off of

Table 1
Comparison of median serum ferritin levels in cases and controls (by non-parametric Mann–Whitney test).

	Cases ($n=75$)	Controls ($n=75$)	*P* value
Median serum ferritin (μg/L)	220	155	<0.0001*

*Statistically significant.

Table 2
Association of acute myocardial infarction with high serum ferritin.

Serum ferritin	Cases (%) ($n=75$)	Controls (%) ($n=75$)	Total (%) ($n=150$)	*P* value
≥200 μg/L	47 (62.66)	15 (20)	62 (41.33)	$P<0.05$*
<200 μg/L	28 (37.33)	60 (80)	88 (58.66)	χ^2 41.21
				OR 6.71
				95% CI
				=3.22–12.89

*Statistically significant. CI: confidence interval, OR: odds ratio.

200 μg/L. There was no significant difference of mean serum ferritin levels in males and females. High serum ferritin levels (>200 μg/L) was significantly associated with AMI (OR=6.71 (95% CI 3.2–12.89, $P<0.05$) (Table 2).

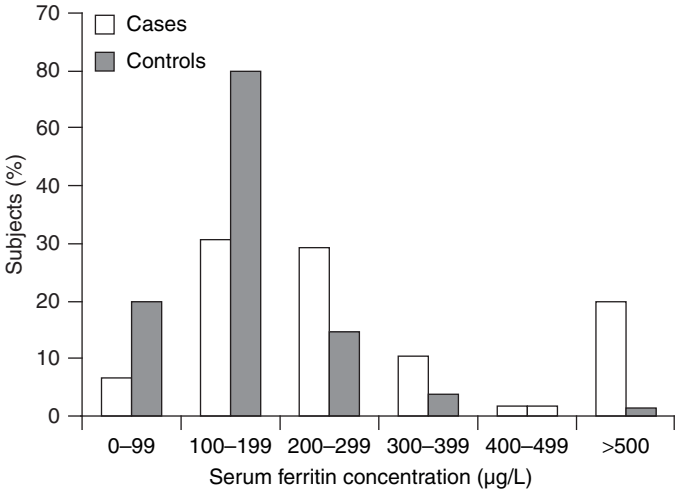

Figure 1 Percentage of control and cases in comparison with serum ferritin concentration.

In univariate analysis, DM, hypertension, serum cholesterol, high-density lipoprotein (HDL) <35 and smoking were found to be significantly associated with AMI (Table 3).

In multivariate analysis, high serum ferritin (>200 μg/L) ($P<0.001$, OR=5.72, 95% CI 2.16–15.17), DM ($P=0.001$, OR=7.64, 95% CI 2.37–24.58), low HDL (<35 mg%) ($P<0.001$, OR=0.86; 95% CI 0.79–0.93) are found to be independently associated with AMI (Table 4). When ferritin, cholesterol, BMI and HDL were taken as continuous variables, then also mean serum ferritin ($P=0.001$) was found to be significantly associated with AMI.

We also assessed the relationship of serum ferritin with other risk factors. Mean serum ferritin was significantly higher in diabetics (346±275.19) than non-diabetics (206.31±169.04) ($P=0.01$). There was no statistically significant relationship of ferritin with HTN, serum cholesterol, HDL, BMI, smoking and alcohol.

Discussion

We found serum ferritin to be significantly higher in cases of AMI as compared to controls. Epidemiological studies have

Table 3
Comparison of conventional risk factors for myocardial infarction in cases and controls (univariate analysis).

Variable	Cases (%) ($n=75$)	Controls (%) ($n=75$)	P value
Mean age (±SD) yr range	51.16+8.002 (37–69)	50.6+7.806 (33–64)	$t=0.43$ P=NS
Diabetes mellitus*			
Present	30 (40)	6 (8)	$\chi^2=21.05$
Absent	45 (60)	69 (92)	OR=7.68; 95% CI=2.95–19.13; $P<0.05$*
Hypertension*			
Present	20 (26.66)	10 (13.33)	$\chi^2=25.35$
Absent	55 (73.33)	65 (86.66)	OR=2.36 95% CI=1.02–5.14; $P<0.05$*
Mean serum cholesterol (±SD)*	182.77±49.8	160.29±43.5	$t=2.94$
mg/dL range	2 (105–330)	3 (100–300)	$P<0.001$
Serum cholesterol mg%			
>200	24 (32)	14 (18.66)	$\chi^2=3.52$
<200	51 (68)	61 (81.33)	OR=2.05 95% CI=0.96–4.08; $P>0.05$
Mean HDL (±SD) mg/dL range*	39.76±5.96 31–55	44.49±5.63 33–64	$t=05$ $P<0.001$
HDL*			
<35	18 (24)	2 (2.66)	$\chi^2=3.42$
≥35	57 (76)	73 (97.33)	OR=11.92 95% CI=2.66–52.57; $P<0.05$
Mean BMI (+SD)	23.78±3.01	22.97±3.20	$t=1.60$; P=NS
BMI			
≥25	26 (34.66)	16 (21.33)	$\chi^2=3.30$
<25	49 (65.33)	59 (78.66)	OR=1.9595% 95% CI=0.94–3.78; $P>0.05$
Smoking*			
Present	39 (52)	25 (66.66)	$\chi^2=6.10$
Absent	36 (48)	50 (66.66)	OR=2.17 95% CI=1.12–3.87; $P<0.05$
Alcohol intake			
Present	32 (42.66)	22 (29.33)	$\chi^2=5.2$
Absent	43 (57.33)	53 (70.66)	OR=1.79 95% CI=0.91–3.26; $P>0.05$

*Statistically significant. BMI: body mass index, CI: confidence interval, HDL: high-density lipoprotein, NS: non-significant, OR: odds ratio, SD: standard deviation.

Table 4
Multiple logistic regression showing association of various risk factors with myocardial infarction (serum ferritin, serum cholesterol, body mass index, were taken as categorical variables).

Risk factors	Adjusted OR	95% CI	*Z* value	*P* value
High serum ferritin (>200 μg/L)*	5.72	2.16–15.17	3.5	0.000*
Hypertension	0.91	0.27–3.08	–0.15	0.877
DM*	7.64	2.37–24.58	3.14	0.001*
Hypercholesterolemia (>200 mg/dL)	1.01	0.98–1.04	0.76	0.446
BMI >25	0.99	0.86–1.15	–0.10	0.921
Smoking	2.04	0.72–5.81	1.33	0.183
Alcohol	1.07	0.38–3.01	0.12	0.905
TG (>150 mg/dL)	0.88	0.73–1.06	–1.30	0.193
HDL (<35 mg/dL)*	0.86	0.79–0.93	–3.50	0.000*
LDL (>130 mg/dL)	0.99	0.96–1.03	–0.36	0.719
VLDL (>40 mg/dL)	1.97	0.77–5.03	1.42	0.157

*Statistically significant. BMI: body mass index, CI: confidence interval, DM: diabetes mellitus, HDL: high-density lipoprotein, LDL: low-density lipoprotein, OR: odds ratio, TG: transaction gateway, VLDL: very low-density lipoprotein.

found a positive relationship between body iron stores and CAD.[16,17] Subsequently, evidence of an association of elevated serum ferritin and increased risk of AMI came from various authors[9,18,19] which is similar to our findings. However, the results of some other studies did not show significant correlation between high ferritin and risk of AMI.[10,11,13] High ferritin was observed as a strong indicator of presence of carotid artery atherosclerosis (assessed sonographically). Iron induced lipid peroxidation, involved in the early steps of the human atherogenesis which was the proposed underlying pathogenic mechanism.[20] Blood donation has also been reported to be associated with decreased risk of cardiovascular (CV) events.[21] High ferritin levels have been associated with established conventional risk factors like DM and HTN by various authors.[22–24] Reduced extraction of hepatic with increasing iron stores leading to peripheral hyperinsulinaemia was the proposed mechanism for DM[25] and pronounced metabolic alteration is the proposed mechanism for high ferritin in hypertensives.[24] Significant association of LDL cholesterol and ferritin was also reported previously.[9,26] Presence of iron accelerates oxidation of polyunsaturated fatty acids in LDL and it is the possible explanation given by authors. High ferritin levels have been observed in smokers. Cigarette smoke mediated iron mobilisation from ferritin and it represents specific pro-oxidant mechanism related to smoking.[27,28]

Thus, our study found a strong and independent relationship of high serum ferritin with AMI, and serum ferritin was significantly high in diabetics.

Study limitations

Sample size in the present study was small but adequate to show the association of high serum ferritin with AMI. Since, the case-control studies are retrospective studies, they have their own limitations in assessing the causal relationship of risk factors with AMI. Larger prospective studies in Indian population are needed to support the results of the present study.

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