

## SERUM FERRITIN - A POTENTIAL THREAT AND RISK FACTOR FOR ACUTE MYOCARDIAL INFARCTION

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### ABSTRACT

*Introduction: Elevated body iron stores have been suggested to be a risk factor for the atherosclerosis and ischemic heart disease but the results of epidemiological studies that relate iron stores to risk of coronary heart disease have been inconsistent. Objectives: (1) To study the relationship of serum ferritin with acute myocardial infarction (AMI) in univariate analysis. (2) To assess the relationship of increased serum ferritin with established risk factor for AMI. Materials and Methods: Hospital based study of 30 AMI cases and 30 age and sex matched controls without having AMI in the age group of 40-80 years. Results: Median serum ferritin levels were significantly associated higher in cases (325.5µg/L) as compared to controls (65.5µg/L) (P<0.001). In univariate analysis in addition to ferritin >200µg/L (Odds Ratio=11.67, 95% Confidence Interval=3.39-40.23, P<0.001), Diabetes, Hypertension, Smoking, Alcohol, BMI, Total Cholesterol, Triglyceride, HDL, LDL, CPK, SGOT, and LDH were found to be significantly associated with AMI. Conclusion: Increased ferritin level is strongly and independently associated with AMI.*

### KEYWORDS

Acute myocardial infarction, Serum ferritin, Lipid profile, Cardiac markers

### INTRODUCTION

The association of high iron stores and coronary heart disease was first suggested by Sullivan<sup>1</sup> after that several observational and epidemiological studies have identified many new emerging potential risk factors like elevated blood levels of triglycerides, atherogenic lipoproteins fibrinogen, Homocysteine and number of genetic polymorphism are of particular interest. But apart from these there is strong evidence that oxidative free radicals have a role in the development of degenerative disease including coronary heart disease<sup>2, 3</sup>. Thus oxidized low density lipoprotein (LDL) exerts several potentially atherogenic effects<sup>4, 5, 6</sup> (1) is chemotectic for monocytes (but not neutrophils). (2) is cytotoxic to endothelial cells and (3) Rapidly taken up by macrophages

through the scavenger receptor on these cells reproducing in vitro the appearance of atherosclerotic plaque foam cells. Iron is a transition metal that can catalyze toxic redox reactions, and it has been suggested to be involved in many harmful biological processes and disease in the human body<sup>7, 8</sup>. Excessive iron has been proposed to be a potent risk factor for coronary heart disease, especially for acute myocardial infarction (AMI)<sup>1, 8-10</sup>. Supporting evidence comes from invitro lipid peroxidation and lipoprotein modification studies<sup>11-13</sup>, from cholesterol fed iron overloaded animal models<sup>14, 15</sup> and from analysis of the composition of human atherosclerotic lesions<sup>16, 17</sup>. Since serum ferritin concentrations are directly proportional to intracellular ferritin concentration, it is considered to be the best clinical measure of

body iron stores<sup>18</sup>, and the most feasible to use in epidemiologic studies<sup>19</sup>. The main objective of our study was to study the relationship of serum ferritin with acute myocardial infarction in univariate analysis and to assess the relationship of increased serum ferritin with established risk factor like smoking, alcohol intake, body mass index, hypertension, lipids, diabetes mellitus.

## MATERIAL AND METHODS

**Inclusion criteria:** 30 consecutive cases of acute myocardial infarction admitted to the intensive cardiac care unit of Bapuji hospital. Diagnosis of acute myocardial infarction was based on fulfilling two of the following criteria:

1. Chest pain of <12 hrs duration.
2. ST elevation >1mm in at least 2 consecutive leads.
3. Increased cardiac markers
4. New onset bundle branch block.

**Exclusion criteria:** Cases with high ferritin levels like hemochromatosis, liver disease, tuberculosis, chronic inflammatory disease, those on iron therapy, past h/o of acute myocardial infarction or CHD.

**Controls:** 30 age, gender and haemoglobin matched control was recruited for each case irrespective of presence of risk factors (hypertension, diabetes mellitus, smoking and alcohol intake) but without having acute myocardial infarction (in the past or present) or any evidence of CHD assessed by symptoms, clinical examination and normal ECG.

All subjects were assessed by clinical examination ECG, serum- creatine kinase MB function. Height and weight were recorded. Body mass index was calculated by formula weight in kg/ height<sup>2</sup> in meter. BMI > 25 was considered as risk factor for acute myocardial infarction. Cases and controls were investigated for conventional risk factors (lipid profile, BMI, Blood sugar). Venous blood was collected and centrifuged at 3000rpm for 10 minutes and serum was used immediately for the estimation of serum ferritin by using acculite ferritin CLIA microwells test and estimation of lipid profiles and cardiac marker by enzymatic method using Roche 400 autoanalyser.

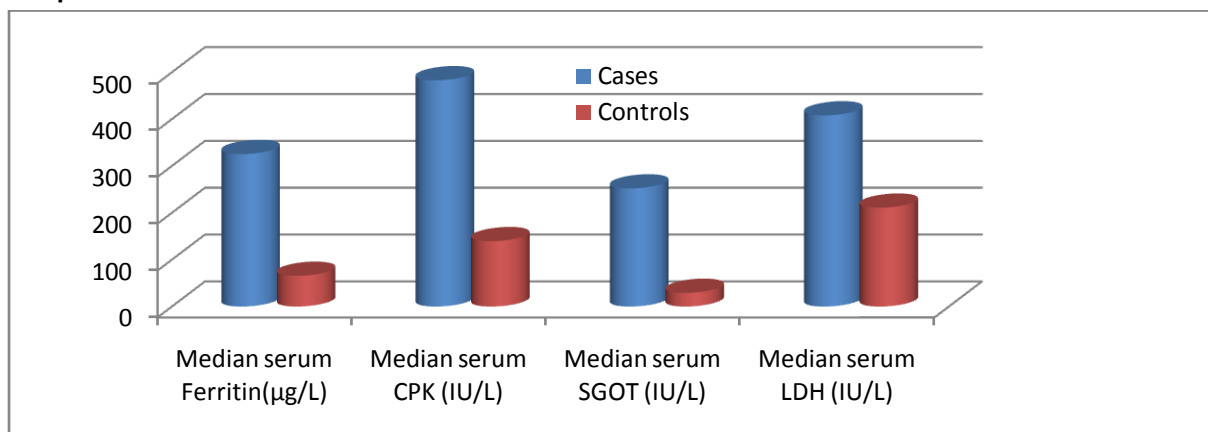
## RESULTS

A total of 30 cases and 30 controls were studied. The mean age of controls and cases was similar (56.5±8.8 years and 57.1±9.8 years) (age range 40-80 years). Males outnumbered females with a ratio of 1.5:1. Mean haemoglobin in cases and controls was similar (13.48 g% and 13.56 g %), since they were matched for haemoglobin. The median serum ferritin values were significantly higher in cases (325.5 µg/L) as compared to controls (65.5 µg/L), ( $P < 0.001$ ). Even median serum CPK, SGOT, and LDH levels are significantly increased in cases as compared to controls. (Table 1 & Figure 1).

**Table 1: Comparison of median serum ferritin and cardiac markers levels in cases and controls.**

Variables	Cases	Controls	P value
Median serum Ferritin(µg/L)	325.5	65.5	<0.001
Median serum CPK (IU/L)	483	139.5	<0.001
Median serum SGOT (IU/L)	252	29.2	<0.001
Median serum LDH (IU/L)	408	211	<0.001

**Figure 1: Bar graph showing increased median serum Ferritin, CPK, SGOT, and LDH in cases as compared to controls.**



The mean value of serum ferritin ( $\mu\text{g/L}$ ) in controls and cases were found to be  $96.3 \pm 69.5$  and  $408.7 \pm 252.8$ , respectively ( $P < 0.001$ ). There was no significant difference of mean serum ferritin levels in males and females. High serum ferritin levels ( $> 200 \mu\text{g/L}$ ) was significantly associated with AMI (OR = 11.67 (95% CI 5.37–74.5,  $P < 0.001$ ) (Table 2).

**Table 2: Association of acute myocardial infarction with high serum ferritin and high serum cardiac markers.**

Variable	Cases	Controls	Total	P value
Serum ferritin $\geq 200 \mu\text{g/L}$	25	9	34	$X^2 -17.37$ O.R -11.67 C. I -5.37-74.5 $P < 0.001$
Serum ferritin $< 200 \mu\text{g/L}$	5	21	26	
Serum CPK $\geq 195 \text{ IU/L}$	22	5	27	$X^2 -19.46$ O.R -13.75 C. I -3.92-48.3 $P < 0.001$
Serum CPK $< 195 \text{ IU/L}$	8	25	33	
Serum SGOT $\geq 37 \text{ IU/L}$	25	11	36	$X^2 -13.61$ O.R -8.64 C. I -2.57-29.07 $P < 0.001$
Serum SGOT $< 37 \text{ IU/L}$	5	19	24	
Serum LDH $\geq 300 \text{ IU/L}$	22	7	29	$X^2 -15.01$ O.R -9.036 C. I -2.8-29.1 $P < 0.001$
Serum LDH $< 300 \text{ IU/L}$	8	23	31	

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

**TABLE-3: Comparison of conventional risk factors for myocardial infarction in cases and controls (Univariate Analysis)**

Variable	Cases	Controls	P value
Diabetes mellitus Present Absent	19 11	8 22	$X^2$ -8.148 O.R -4.75 C. I -1.58-14.25 P < 0.005
Hypertension Present Absent	18 12	6 24	$X^2$ -10 O.R -6 C. I -2.08-17.29 P < 0.005
Serum cholesterol ≥200mg/dl <200 mg/dl	17 13	5 25	$X^2$ -10.33 O.R -6.54 C. I -1.97-21.74 P < 0.005
Serum triglyceride ≥160 mg/dl <160 mg/dl	20 10	6 24	$X^2$ -13.3 O.R -8 C. I -2.45-25.9 P < 0.001
Serum LDL ≥150 mg/dl <150 mg/dl	18 12	5 25	$X^2$ -11.6 O.R -7.5 C. I -2.24-25.1 P < 0.001
Serum HDL <35 mg/dl ≥35 mg/dl	17 13	7 23	$X^2$ -6.94 O.R -4.297 C. I -1.41- 13.1 P < 0.01
BMI ≥25Kg/m <sup>2</sup> <25 Kg/m <sup>2</sup>	24 6	5 25	$X^2$ -24.1 O.R -20 C. I -5.38- 74.29 P < 0.001
Alcohol intake Present Absent	15 15	5 25	$X^2$ -10.33 O.R -6.54 C. I -1.97-21.74 P < 0.005
Smoking Present Absent	24 6	7 23	$X^2$ - 19.29 O.R -13.14 C. I -3.84-45.01 P < 0.001

## DISCUSSION

Epidemiological studies have found a positive relationship between body iron stores and coronary artery diseases<sup>9, 20</sup>. Subsequently, evidence of an association of elevated serum ferritin and increased risk of AMI came from various authors<sup>10, 21</sup>, which is similar to our findings. However results of some other studies did not show significant correlation between high ferritin and risk of AMI<sup>22, 23</sup>. The main possibility that iron over load leads to increased lipid peroxidation and foam cell formation but apart from this the chemical properties of oxidized lipoproteins were found to be chemotactic to blood monocytes, facilitate the entry of lipoproteins by a cytotoxic endothelial injury, and give rise to smooth muscle cell proliferation<sup>4,24,25</sup>. Native low density lipoprotein in contrasts lacks all these atherogenic potentials<sup>4, 25</sup>. One study yielded a strong relation between sonographically assessed carotid atherosclerosis and prominent iron stores in both genders particularly when associated with hypercholesterolemia<sup>26</sup>. Lipid peroxidation therefore may constitute an initiating and crucial step in the development of fatty streaks and plaques. Blood donation has also been reported to be associated with decreased risk of cardiovascular events<sup>27</sup>. High ferritin levels have been associated with established conventional risk factors like diabetes mellitus and hypertension by various authors<sup>28,29</sup>. Reduced extraction of hepatic with increasing iron stores leading to peripheral hyper insulinemia was the proposed mechanism for diabetes mellitus<sup>30</sup> and pronounced metabolic alteration is the proposed mechanism for high ferritin hypertensive<sup>29</sup>. Significant association of LDL cholesterol and ferritin was also reported previously<sup>21,31</sup>. High ferritin levels have been observed in smokers. Cigarette smoke mediated iron mobilisation from ferritin and represents

specific pro-oxidant mechanism related to smoking<sup>32, 33</sup>.

## CONCLUSION

Our present findings suggest that there is strong and independent relationship of high serum ferritin with acute myocardial infarction and serum ferritin was significantly high in diabetics and smokers.

## STUDY LIMITATIONS

Sample size in the present study was small. Large prospective studies in Indian population are needed to support the results of present study.

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## REFERENCES

1. Sullivan JL. Iron and sex difference in heart disease risk. *Lancet* 1981; 1:1293-4.
2. Aviram M. Modified forms of low density lipoproteins and atherosclerosis. *Atherosclerosis* 1993; 98:1-9.
3. Oliver MF. Antioxidant nutrients, atherosclerosis and coronary heart disease. *Br Heart J* 1995; 73:299-301.
4. Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL. Beyond cholesterol: modifications of low density lipoprotein that increase its atherogenicity. *N Engl J Med.* 1989; 320:915-924.
5. Esterbauer H, Dieber-Rotheneder M, Waeg G, Striegl G, Jurgens G: Biochemical, structural, and functional properties of oxidized low-density lipoprotein. *Chem Res Toxicol* 1990; 3:77-92.
6. Montgomery RR, Nathan CF, Cohn ZA: Effects of reagent and cell-generated hydrogen peroxide on the properties of low density lipoprotein. *Pmc Natl Acad Sci USA* 1986; 83:6631-6635.
7. Gutteridge JM, Halliwell B. Iron toxicity and oxygen radicals. *Baillieres Clin Haematol.* 1989; 2:195-256.

8. Halliwell B, Gutteridge JM. Role of free radicals and catalytic metal ions in human disease: an overview. *Methods Enzymol.* 1990; 186:1–85.
9. Salonen JT, Nyyssonen K, Korpela H, Tuomilehto J, Seppanen R, Salonen R. High stored iron levels are associated with excess risk of myocardial infarction in Eastern Finnish men. *Circulation* 1992; 86:803-11.
10. Salonen JT, Nyyssonen K, Salonen R. Body iron stored and the risk of coronary heart disease. *NEJM* 1994; 331:1159–60.
11. Salonen JT, Yla-Herttuala S, Yamamoto R, et al. Autoantibody against oxidized LDL and progression of carotid atherosclerosis. *Lancet* 1992; 339:883-7.
12. Balla G, Jacob HS, Eaton JW, Belcher JD, Vercellotti GM. Hemin: a possible physiological mediator of low density lipoprotein oxidation and endothelial injury. *Arterioscler Thromb.* 1991; 11:1700–1711.
13. Witztum JL. The oxidation hypothesis of atherosclerosis. *Lancet.* 1994; 344:793–795.
14. Weiner MA, Paige SB, Bailey SR. Antioxidant therapy decreases atherosclerotic plaque burden in an iron loaded animal model. *Eur Heart J.* 1994; 425(suppl 15):2241. Abstract.
15. Araujo JA, Romano EL, Brito BE, Parthe V, Romano M, Bracho M, Montano RF, Cardier J. Iron overload augments the development of atherosclerotic lesions in rabbits. *Arterioscler Thromb Vasc Biol.* 1995; 15:1172–1180.
16. Smith C, Mitchinson MJ, Aruoma OI, Halliwell B. Stimulation of lipid peroxidation and hydroxyl-radical generation by the contents of human atherosclerotic lesions. *Biochem J.* 1992; 286:901–905.
17. Swain J, Gutteridge JM. Prooxidant iron and copper, with ferroxidase and xanthine oxidase activities in human atherosclerotic material. *FEBS Lett.* 1995; 368:513–515.
18. Cook JD, Lipschitz DA, Miles LEM, Finch CM. Serum ferritin as a measure of iron stores in normal subjects. *Am J Clin Nutr* 1974; 27:681-7.
19. Beaton GH, Corey PN, Steele C. Conceptual and methodological issues regarding the epidemiology of iron deficiency and their implications for studies of the functional consequences of iron deficiency. *Am J Clin Nutr* 1989; 50:575-85.
20. Solymoss BC, Marcil M, Gilfix BM. The place of ferritin among risk factors associated with coronary artery disease. *Coron Artery Dis* 1994; 5:231–5.
21. Delphine W, Silvia CR, Biswas S, Uthappa S, Shetty P. Ferritin—a potent threat for acute myocardial infarction. *J Assoc Physicians (India)* 2003; 51:947–50.
22. Reunanen A, Takkunen H, Knekt P, Seppanen R, Aromaa A. Body iron stores, dietary iron intake and coronary heart disease mortality. *J Intern Med* 1995; 238:223–30.
23. Gupta R, Rastogi S, Nagar R, Kastia S, Kaul V. Dietary and serum iron, body iron stores and coronary heart disease. *J Assoc Physicians (India)* 2000; 48:489–92.
24. Boulanger CM, Tanner FC, Bea ML, Hahn AWA, Werner A, Luscher TF. Oxidized low density lipoproteins induce mRNA expression and release of endothelin from human and porcine endothelium. *Ore Res.* 1992; 70:1191-1197.
25. Quinn MT, Parthasarathy S, Fong LG, Steinberg D. Oxidatively modified low density lipoproteins: a potential role in recruitment and retention of monocyte/ macrophages during atherogenesis. *Proc Natl Acad Sci USA.* 1987; 84:2995-2998.
26. S Kiechl, F Aichner, et al. Body iron stores and the risk of carotid atherosclerosis. Prospective results from the Bruneck study.
27. Meyer DG, Strickland D, Maloeley PA, Seburg JJ, Wilson JE, McManus BF. Possible association of a reduction in cardiovascular events with blood donation. *Heart* 1997; 78:188-93.
28. Haidari M, Javadi E, Sanati A. Association of increased ferritin with premature coronary stenosis in men. *Physiol Genomics* 2003; 13:25–30.
29. Piperno A, Trombini P, Gelosa M. Increased serum ferritin is common in men with essential hypertension. *J Hypertension* 2002; 20:1513–8.
30. Niedery C, Berger M, Stremmet W. Hyperinsulinemia in non cirrhotic haemochromatosis impaired hepatic insulin degradation. *Diabetologica* 1984; 26:441–4.
31. Karml P, Potockova J, Koprivova H, et al. Ferritin oxidative stress and coronary atherosclerosis. *Vintr Lek* 2004; 50:183–5.
32. Lapenna D, De Givia S, Mezzette A. Cigarette smoke, ferritin, lipid peroxidation. *Am J Respir Crit Care Med* 1995; 151:431–519.
33. Grobusch KK, Koster JF, Grobbee DE. Serum ferritin and risk of myocardial infarction in the elderly; Rotterdam study. *Am J Clin Nutr* 1999; 69:1231–6.



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