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Serum Ferritin and Acute Coronary Syndrome

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ABSTRACT

Iron is a vital mineral and has integral contribution in the body metabolism. Acute myocardial infarction (AMI), a severely dreaded condition of heart can be devastating for life .It expresses with symptoms of sudden, severe, and persistent pain in the back of the chest with pain radiating to the shoulder and sometimes the arm). AMI is currently a cause of mortality and morbidity with high economic costs worldwide 1 . The damage or death of myocardial cellular structure is irreversible. It is for this reason we frantically follow its course of events. Therefore, it is imperative to study the factors aggravating the disease. Important risk factors include smoking, hypertension, obesity, and dyslipidemia, which have been established as useful predictors for acute myocardial infarction 2. In addition, obesity, fatigue, insufficient sleep, is also risk factors. 3 . Studies also demonstrate that serum ferritin could be an independent factor in predicting the risk of AMI. Serum ferritin is a kind of intracellular protein, which regulates the homeostasis of iron. Serum iron is essential for oxygen metabolism, especially in the chain that generates ATPs through oxidative diseases in recent studies 5. Iron, an essential element for many important cellular functions in all living organisms, can catalyze the formation of potentially toxic free radicals. Excessive iron is sequestered by ferritin in a nontoxic and readily available form in a cell. Ferritin is composed of 24 subunits of different proportions of two functionally distinct subunits: ferritin H and L. The former is involved in ferroxidase activity necessary for iron uptake and oxidation of ferrous iron, while the latter is involved in nucleation of the iron core. The expression of ferritin is under delicate control and is regulated at both the transcriptional and posttranscriptional levels by iron, cytokines and oxidative stress. Elevated ferritin levels are associated with an increased risk of atherosclerotic coronary artery disease (CAD), the leading cause of death and illness in developed countries. Serum ferritin levels are a good indicator of iron stores in the body. In fact, epidemiological studies have suggested that elevated serum ferritin levels are associated with an increased risk of CAD and myocardial infarction (MI), though inconsistent results were obtained in some other studies. Moreover, recent proteomics and molecular biology studies have shown that ferritin levels in arteries are increased in diseased tissues, which further supports the link of ferritin to CAD/MI. Future studies will determine whether increased ferritin levels can serve as a distinct biomarker for the incidence of CAD/MI and distinguish whether increased ferritin levels are a cause of CAD or a consequence of the disease process. The objective of this paper was to perform a case control study between serum ferritin and acute myocardial infarction (AMI).

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 is an indicator for estimating 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 50 consecutive both sex patients with first AMI, suffered, admitted within 12 hours of the onset of chest pain to coronary care units (CCU) at outdoor and indoor patients at Govt. Medical College ,and Guru Nanak Dev Hospital Amritsar. A control group (n = 50) was selected without history of AMI from the same hospital. Serum ferritin was measured using ELISA assay based on straptavidin-biotin principle at the first and fifth days after admission. Age group of 30 to 70 years was included while majority were 45 to 60 years.
Results: The level of serum ferritin averaged 200 to 300 µg/dl came out in AMI cases. In the control group the ferritin level in serum came out < 100 µg/dl in came out to be significantly higher in former group (P=0.001). Serum ferritin level was also significantly high 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 AMI adjusted for initial ferritin concentration, patients' age and coronary disease risk factors (OR=5.1, P=0.017).

Keywords: Elevated serum ferritin can be a factor for predicting AMI.

INTRODUCTION

JL Sullivian (1981) was first to observe ferritin association with coronary heart disease (CHD) [1] Over the past several years, observational and epidemiological studies have identified a host of new and potential risk factors for atherothrombotic vascular diseases. Patients with AMI have elevated biomarkers of necrosis, such as cardiac troponin I or T, which are specific, sensitive and preferred markers of myocardial necrosis. 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 CHD [2, 3]. Oxidative free radicals increase the peroxidation of low-density lipoprotein (LDL), thereby increasing its uptake by macrophages with increased foam cell formation and atherosclerosis [4, 5] Iron, a dietary constituent, is a preoxidant 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) [3]. 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 [6]. Subsequently, results of the various studies showed statistically significant association of high serum ferritin and AMI [7.] However, some authors did not find any significant association of high ferritin and AMI [6].Cells of all forms of life require well-defined amounts of iron for survival, replication and expression of differentiated processes. The total iron content in the body is approximately 50 mg/kg. Majority is found in heme compounds like in hemoglobin and myoglobin. Iron is critical in converting oxygen into useable cellular energy by serving as a key component in the electron transfer chain and is also utilized as an enzymatic co-factor in numerous other reactions. Despite this the overload within the body especially myocardial tissue has been proposed has been proposed to be a potent risk factor. Iron can injure the cell myocardium directly. It can be accumulated in cells as hemosiderin, ferritin and free iron named labile cellular iron that is most toxic form stimulating the formation of free radicals. Ferritin is iron storage protein with MW 460,000 Daltons. Ferritin is intracellular product of cell smooth endoplasmic reticulum while normal ferritin

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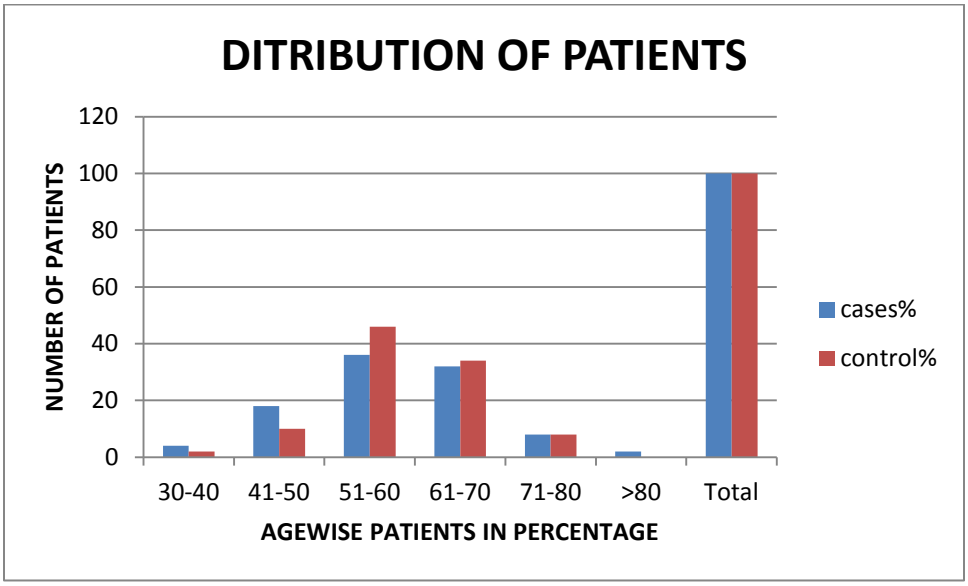
in plasma is synthesized by RER. Iron is essential for oxygen transport by hemoglobin, oxygenation of muscles by myoglobin, cellular respiration by proteins of the mitochondrial electron transport chain, DNA synthesis by ribonucleotide reductase [8].Iron also participates in several enzymatic reactions in the cytosol and other cellular compartments. The adult human body contains ~3–5 g of iron; the vast majority of it (~70%) is utilized in the erythron [9]while excess is stored in the liver. Transferrin delivers ~25–30 mg/day iron from plasma to developing erythroid cells in the bone marrow for heme biosynthesis during hemoglobinization. Transferrin also supplies lower amounts of iron (up to ~5 mg/day) to other tissues. At steady-state, transferrin contains only ~3 mg of iron, but turns over ~10 times daily to meet physiological needs. It has been postulated that free radicals so produced can be correlated with atherosclerosis.

Table: 1 Distribution according to Serum Ferritin Level

Parameter	case		Control	
Serum Ferritin µg/l	Number	Percentage	Number	Percentage
<100	0	0%	27	54%
100-199	10	20%	18	36%
200-299	21	42%	5	10%
>300	19	38%	0	0%



MATERIALS AND METHODS

The study was undertaken in Medical OPD and indoor patients of GMC and GND Hospital, Amritsar. Total 50 patients of both sexes presenting with first attack of AMI with ECG changes or raised cardiac enzymes were taken for study. It was matched with 50 healthy controls of both sexes. Study population comprised patients with ECG showing AMI or elevated enzymes concerned. Inclusion criteria was Age >18, Typical chest pain radiating to arm for <12 hours, raised cardiac enzymes as CPK MB, or Troponin T, new onset left bundle branch block. An exclusion criterion was Liver disease, Iron therapy H/O past MI or CHD, known hereditary disorder of iron metabolism like haemochromatosis. Serum Ferritin was carried out ELISA based on straptavidin-biotin principle. Lipid profile included Total cholesterol, Serum Triglycerides, HDL/LDL cholesterols. Serum bilirubin, AST, ALT was done with automated

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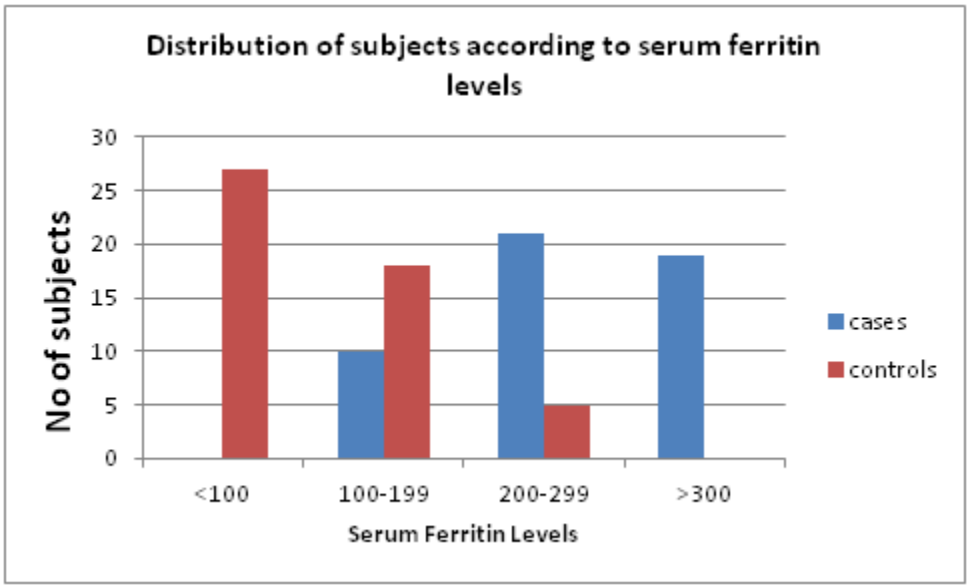
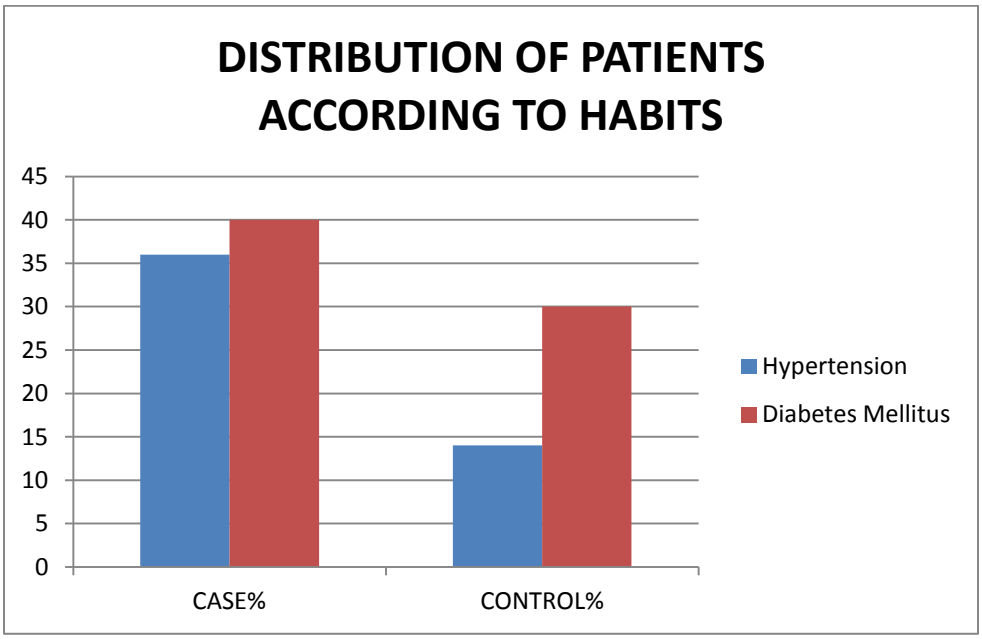
ERBA XL, serum by diazo method. FBS, PPF done by GOD/POD method.



AIMS AND OBJECTIVES

1. To study correlation of serum ferritin with acute myocardial infarction.
2. To compare and contrast mean ferritin levels between patients of acute myocardial infarction and controls.



RESULTS

The possibility that high serum ferritin has a role in AMI was first postulated in 1985. [9] Later, few studies supported the association of high ferritin and acute myocardial infarction, including: (1) Elevated ferritin concentration as a marker of high levels of stored iron, which is a strong risk factor related to acute myocardial infarction. Men with high serum ferritin, not less than 200ug/compared with lower serum ferritin. [2] (2) A study reported an association between reduced stored serum iron through blood donation and the risk of myocardial infarction; however, a study did not support it. [2] (3) Increased serum levels of ferritin as an independent predictor of the

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occurrence of acute myocardial infarction, especially ST-elevation acute myocardial infarction. [5] Our paper is case-control studies on serum ferritin related to acute myocardial infarction and provides insight into its associated risks. In this paper, there is a significantly positive association between serum ferritin and acute myocardial infarction. There is a distinction of serum ferritin in the body between the premenstrual and menstrual stage for the same female participant. In general, the levels of serum ferritin are higher in men than women. The method used to measure the phase of acute myocardial infarction and the corresponding therapeutic measures were different; the followed levels of serum ferritin were not standardized. From all studies included, except for the study by Claeys et al. [8], the level of LDL-cholesterol in controls was greater than in the cases in the studies by Yiping [9] and lqbal et al. [11], respectively, the others were the opposite. In the study by Salonen et al. [2], the increased serum ferritin accelerated the oxidative metabolism of LDL-cholesterol and induced the process of atherosclerosis, indirectly. [4] Therefore, the levels of LDL-cholesterol found in all participants of the studies included were a potential factor, which played a role in increased heterogeneity. In the stage of health examination, high levels of serum ferritin, combined with other physical symptoms, could be an indicator of the risk of acute myocardial infarction. A total of 100 subjects were included in the study, among which 100 were cases and another 50 were age and sex matched controls. Age group of 30 to 70 years was included while majority were 45 to 60 years. Similar group of control subjects was included. There is evidence of serum ferritin and risk of AMI.There is contradictory view by some studies. There can be lipid peroxidation, foam cells, cytotoxic endothelial injuries, and smooth muscle cell proliferation. One author highlighted carotid atherosclerosis and iron store levels in the body. Blood donation reduces the incidence of MI. There was almost equal incidence in both the sexes. Alcohol was less dangerous than smoking. Serum ferritin increase justified smoking as Iron Hypothesis. Small coronary arteries were most affected. Despite all these genetic factors were also significantly involved.

Table: 2 Serum Ferritin level according to various Age groups

Age Group	N	Serum Ferritin		f Value	p value
	2	Mean	SD		
30-40	9	231.5	0.71	3.111	0.017
41-50	18	187.87	23.87		
51-60	16	276.43	108.98		
61-70	4	312.67	68.65		
71-80	1	321.87	89.90		
>80	2	312.92	0		

DISCUSSION

In the present venture 100 patients of AMI were taken. Serum ferritin level of these was taken. There was no substantial difference for sex in this global relation. Study has positively potentiated the correlation between positive correlation between body iron stores and AMI. Since the myocardial tissue has been damaged irreversibly, innate immune system is potentiated. This has been conceded by various authors in their study. Iron overload leads to increased lipid peroxidation and foam cell formation. But here the oxidized lipoproteins were found to be chemotactic to blood monocytes. This leads to endothelial injury and give rise to proliferation of smooth muscle cells leading to repair of the infarct tissue. Native LDL lacks all these factors which are

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atherogenic. One study put forth sonographically assessed carotid atherosclerosis and prominent iron stores in both genders when associated with hypercholesterolemia.Lipid peroxidation thus puts forth thus starts the crucial step in which fatty streaks and plaques were formed. Blood donation is found to be equally responsible with deceased risk of ominous injury. In our study majority of patients were past 50 or even 60 years of life while very small 2% were above 80 years of life. Control group were >50 years age group.58 ± 9.41.The serum ferritin association levels in different age groups was found to be statistically significant ($p<0.05$).In this study >34% patients were hypertensive, while >38% patients were diabetic. Hypertension and smoking were two precipitating factors. But these were found not found to be significant ($p>0.05$). While consistent studies in India have found smoking and alcohol to be significant. But alcoholism was found to be important risk factor when compared to serum ferritin levels ($p>0.05$). Exposure to smoking activates a number of factors predisposing to atherosclerosis including thrombosis, insulin resistance, and dyslipidemia. There is found abnormal vascular growth and angiogenesis as well as loss of endothelial homeostatic and regenerative functions. Smoke contains over 4000 different chemicals among these polycyclic hydrocarbons damaging endothelial tissue. Nicotine includes the release of catecholamines leading to tachycardia and hypertension. These cause platelet aggregation and progression of atherosclerosis. As far as lipid profile is concerned serum levels of cholesterol, LDL, Triglycerides are high in cases while reverse is true in controls.HDL values were higher in controls comparatively. The mean value of serum ferritin was found to be >321.76 ug/l among cases as compared to controls having 106.98ug/l.Difference was significant as p value was <o.0001. Association of serum ferritin was found to be statistically significant in our study which is in agreement to studies done by Holay et al, Salonen et al,moroz et al and Delphine et al in them serum ferritin level was found to be >200ug/l. This depicts the correlation between serum ferritin and AMI called 'Iron hypothesis which states that iron is detrimental to CVS. Free iron forms oxygen derived reactive species. These free radicals cause lipid peroxidation, endothelial activation and proliferation which cause in turn atherogenesis. These also cause atherosclerosis of coronary arteries leading on to atherosclerosis that in turn explains serum ferritin as risk factor to AMI when increased. Some findings indicate serum ferritin may be accompanied by other risk factors like smoking, Diabetes, hypertension which increases the formation of free radicals thus causing atherosclerosis by lipid peroxidation. Genetic factors were also indicated like mutant genotype of tagSNP rs9366637, subjects with wild allele had higher CAD. Despite all the possible causes explained here, increased level of serum ferritin seems to be diagnostic importance. Despite some identified genetic and pathophysiological mechanism for the role of serum iron and ferritin levels to predict AMI, underlying mechanism remained to be elucidated in other studies.

Table: 3 MASTER CHARTS FOR VARIOUS CO-MORBID CONDITIONS

Co-Morbid conditions	Serum Ferritin		t value	p value
	Mean	SD		
Alcoholics	312.7	312.87	1.765	0.9875
	243.67	87.90		
Hypertensive	276.98	63.89	18.98	0.879
	287.98	98.98		
Diabetics	298.90	343.87	1.765	1.870
	287.90	85.98		

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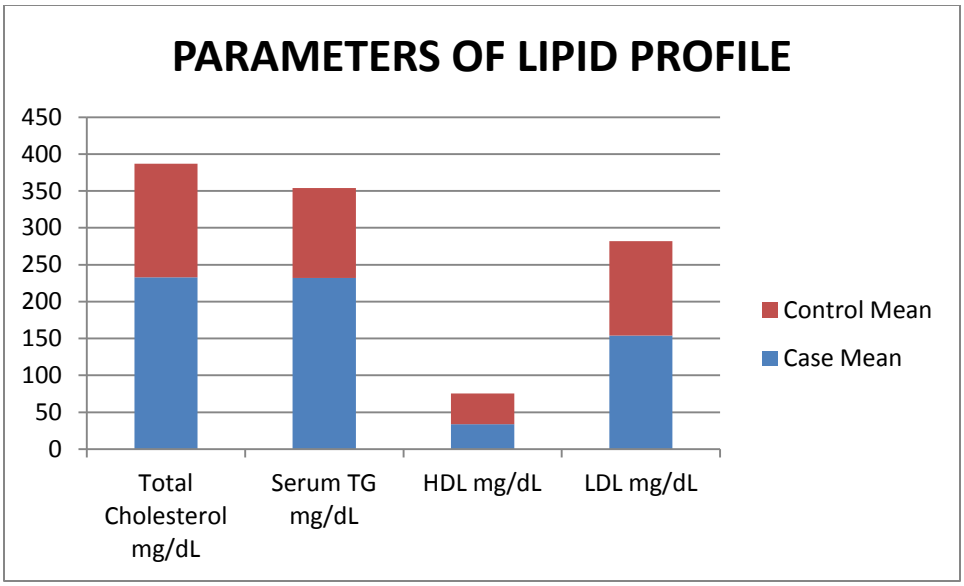

CONCLUSION

As per study serum ferritin has absolute relation with AMI. The level of serum ferritin can be estimated during the routine hematological investigations along with risk factors like estimation of diabetes and hypertension. Higher levels of serum ferritin, seems to be strong risk factor for AMI..Patients with higher serum levels can be identified. Monitoring of ferritin at specific intervals can reduce the cardiovascular morbidity and mortality. Though there are various other causes like genetic and pathophysiological mechanisms that can predict AMI, the underlying mechanism remains to be elucidated in ensuing studies. Therefore, screening for iron status and supplementation of antioxidants may be beneficial in the management of AMI.

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