Estimation of Serum Ferritin Levels in Patients with Acute Coronary Syndrome in Amritsar, India

Shaina Gakhar[1], Manish Chandey[2], Gurinder Mohan[3]

[1, 2, 3] Department of General Medicine, Sri Guru Ramdas University of Health and Science, Amritsar, Punjab, India.

ABSTRACT

BACKGROUND

India is leading the world in incidence, prevalence, complications and mortality due to coronary artery disease (CAD). Various risk factors for acute coronary syndrome (ACS) are diabetes, hypertension, dyslipidaemia, smoking and obesity. It has been proposed that high serum ferritin levels are associated with enhancement in myocardial ischaemic response along with decreased ischaemic threshold in the setting up of acute ischaemic conditions. In this study, we wanted to measure and compare serum ferritin levels in patients of acute coronary syndrome and healthy controls to know the association between serum ferritin levels and risk of acute coronary syndrome.

METHODS

60 patients of acute coronary syndrome admitted at Sri Guru Ram Das Hospital, Vallah Sri Amritsar were taken as cases and 60 age and sex matched healthy controls were taken. Serum ferritin levels were measured in both the cases and controls and were compared.

RESULTS

Most of the patients of ACS were in the age group of 51 - 60 years. Hypertension was the most common risk factor observed followed by diabetes mellitus (DM). Mean serum cholesterol levels were higher in cases. The most common vessel involved in ACS was left anterior descending artery (LAD). The difference in mean serum ferritin levels of cases and controls was statistically significant with higher levels in cases as compared to controls. These patients also had higher risk of developing heart failure and had a longer hospital stay.

CONCLUSIONS

The difference between serum ferritin levels in cases of ACS and controls was statistically significant. People with raised serum ferritin levels are at a greater risk of developing ACS as compared to those with normal serum ferritin levels.

KEYWORDS

Acute Coronary Syndrome, Serum Ferritin, Systolic Function, Diastolic Function, Mortality, Hospital Stay

Corresponding Author:
Dr. Manish Chandey,
10, Shastri Nagar, Near Bhabha School,
Majitha Road, Amritsar – 143001,
Punjab, India.
E-mail: chandey96098@yahoo.co.in

DOI: 10.18410/jebmh/2021/422

How to Cite This Article:
Gakhar S, Chandey M, Mohan G. Estimation of serum ferritin levels in patients with acute coronary syndrome in Amritsar, India. J Evid Based Med Healthc 2021;8(26):2260-2264. DOI: 10.18410/jebmh/2021/422

Submission 08-03-2021,
Peer Review 19-03-2021,
Acceptance 12-05-2021,
Published 28-06-2021.

BACKGROUND

India is leading the world in incidence, prevalence, complications, and mortality due to coronary artery disease.[1] Its prevalence has increased three times in the last three decades. India and other developing countries contributes to 80 % of cardiovascular related deaths worldwide.[2]

A wide range of risk factors including smoking, hypertension, obesity, and dyslipidaemia, have been established as useful predictors for occurrence of acute myocardial infarction (AMI). In addition to these classical risk factors, fatigue and insufficient sleep are also risk factors for AMI.[3] The higher incidence of cardiovascular disease is present in the elderly and it frequently presents with acute coronary syndrome. Age is an important risk factor for cardiovascular disease.[4] Some studies demonstrate that serum ferritin could be an independent factor in predicting the risk of AMI.[5] Serum ferritin is a kind of intracellular protein, which regulates the homeostasis of serum iron.[6] Serum iron is essential for oxygen metabolism, especially in the chain that generates adenosine triphosphate (ATP) through oxidative respiration in the mitochondria.[7] There is strong evidence that oxidative free radicals have a role in the development of degenerative diseases including coronary heart disease (CHD).[8] Oxidative free radicals increases the peroxidation of low-density lipoprotein (LDL), thereby increasing its uptake by macrophages with increased foam cell formation and atherosclerosis.[9]

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.[10] 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.[11] 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 studies.

It has been hypothesized that increased iron intake or iron stores may promote atherogenesis by increasing free radical formation and oxidative stress. Oxidative stress increases the peroxidation of low-density lipoprotein thereby increasing its uptake by macrophages with increased foam cell formation and atherosclerosis.

For ACS, chest pain in the most common presentation.[12] "Anginal Equivalents" are symptoms of myocardial infarction other than angina. They include dyspnoea, nausea, epigastric discomfort and weakness. These are more common in elderly and diabetics. Older patients usually sustain adverse outcomes from ACS due to delay in recognition and atypical presentation.[13] Diagnosis of acute myocardial infarction is based on history of acute chest pain in conjunction with electrocardiogram (ECG) criteria's and laboratory findings. The electrocardiogram remains a crucial tool in the identification and management of acute myocardial infarction.

Objectives

To measure and compare serum ferritin levels in patients of acute coronary syndrome and healthy controls and study the association between serum ferritin levels and risk of acute coronary syndrome.

METHODS

The current case control study was conducted at Sri Guru Ram Das Institute of Medical Sciences and Research Vallah, Amritsar for a period from December 2018 to June 2020. In this hospital-based case control study, 60 cases of acute coronary syndrome admitted in medicine ward, SGRD Hospital and 60 healthy controls were enrolled after applying inclusion and exclusion criteria and obtaining written and informed consent.

Acute coronary syndrome refers to group of clinical symptoms compatible with acute myocardial ischaemia.
It includes

- Unstable angina.
- Non-ST elevation myocardial infarction (NSTEMI).
- ST elevation myocardial infarction (STEMI).

Unstable Angina

It is defined as angina pectoris or equivalent ischaemic discomfort with at least one of these features.

- Occurs at rest or with minimal exertion usually lasting > 10 minutes.
- It is severe and of new onset (within prior 2 weeks).
- It occurs with a crescendo pattern (distinctly more severe, prolonged or frequent than previously.

NSTEMI

- Diagnosis of NSTEMI is established if a patient with the clinical features of unstable angina develops evidence of myocardial necrosis as reflected by elevated cardiac biomarkers.

STEMI

Electrocardiogram criteria for ST elevation myocardial infarction

1. ST Elevation in at least 2 contiguous leads (in the absence of left ventricular hypertrophy and left bundle branch block)
   a. ≥ 2.5 mm in men < 40 years and ≥ 2 mm in men > 40 years in leads V2 - V3.
   b. 1.5 mm in women in leads V2 and V3
   c. 1 mm in other contiguous chest or limb leads.
2. ST depression ≥ 0.5 mm in 2 precordial leads (V1 - V3), positive T waves in V1 is suggestive of posterior MI, confirmed by ≥ 0.5 mm ST elevations in V7 - V9.
3. New onset left bundle branch block (LBBB).
4. Hyperacute T wave changes (STEMI in evolution)

Inclusion Criteria

- Recently diagnosed patients of acute coronary syndrome.

Exclusion Criteria

- Haemochromatosis
- Cirrhosis of liver
- Tuberculosis
- Those on iron therapy (Within Last three months)
- Moderate to severe anaemia
- Those on treatment for CAD
- Autoimmune diseases
- Past history of repeated blood transfusion.
- Past history of GI bleed or haemorrhoids.
- Patients on anti-inflammatory drugs or immunomodulatory drugs like steroids.

Statistical Analysis

The data has been analysed using statistical package for social sciences (SPSS) 24.0 software. Chi square test and 't' test have been used to evaluate and interpret the data. P values less than 0.05 are considered statistically significant.

RESULTS

120 subjects were studied of which 60 were patients of ACS and rest 60 were age and sex matched healthy controls. Demographic profiles were studied and compared. Most of the patients of ACS were in the age group of 51 - 60 years with mean age of 56.21 ± 11.69 years. Out of the total 60 patients of ACS, most of the patients were males 61.67 % and females constituted 38.33 % the mean haemoglobin levels in cases were 12.71 ± 1.41 g/dl.

Hypertension was the most common risk factor observed followed by diabetes mellitus. Other risk factors were dyslipidaemia, smoking and obesity. Mean serum cholesterol levels were higher in cases (217.41 ± 63.22 mg/dl) as compared to controls (167.66 ± 17.74 mg/dl). Cases had lower serum high density lipoprotein (HDL) levels with the mean being 39.76 ± 8.74 mg/dl as compared to controls with mean of 52.05 ± 4.45 mg/dl.

Serum LDL levels were higher in cases (Mean LDL = 140.00 ± 64.40 mg/dl) compared to controls (Mean LDL = 98.60 ± 113.03 mg/dl). Mean body mass index (BMI) of cases was higher with values of 24.93 ± 2.84 kg/m^2 and of controls was 22.24 ± 1.56 kg/m.^{2} Most common type of acute coronary syndrome observed was STEMI (68.33 %) followed by NSTEMI (16.60 %) and 15.0 % of patients had unstable angina. The most common vessel involved was LAD (45.0 %), followed by RCA.LMCA, LAD + RCA, RCA + LCX were also involved. Most of the patients of STEMI (60.98 %) received reperfusion therapy. 36.59 % patients were thrombolysed while 24.39 % underwent primary percutaneous coronary intervention. 39.02 % were managed conservatively.

The difference in mean serum ferritin levels of cases and controls was statistically significant with higher levels in cases (370.04 ± 156.52 ng/ml) in comparison to controls (181.27 ± 92.23 ng/ml). Higher levels of mean serum ferritin levels were observed in males of cases (434.48 ± 146.20 ng/ml) as compared to females (225.82 ± 101.93 ng/ml).

A significant number of patients of ACS had systolic (85.0 %) and diastolic dysfunction (75.0 %). Type II diastolic dysfunction was most commonly observed. In all the 10 patients who had mortality, both systolic as well as diastolic dysfunction were observed. Association between type of diastolic dysfunction and mortality was statistically significant whereas between systolic dysfunction and mortality was non-significant. Of the total 51 patients with systolic dysfunction, 38 patients (63.33 %) had raised serum ferritin levels. No association was found between serum ferritin levels and systolic or diastolic dysfunction. Significant number of patients had heart failure (41.66 %), Killip class III being the most common. Of these, significant number (84.00 %) had raised serum ferritin levels.

Statistically significant association was found between Killip class of heart failure and serum ferritin levels. (P value < 0.05). Maximum patients of ACS had a hospital stay of 5 - 6 days and most of them had raised serum ferritin levels. Raised serum ferritin levels were associated with longer hospital stay in patients of ACS. (P value < 0.05). Of the total 10 mortalities observed, 9 patients had raised serum ferritin levels. But this difference was statistically not significant. Raised serum ferritin levels had no relation with mortality in ACS.

Age Groups (Years)	Cases		Controls	
	No.	% Age	No.	% Age
30 - 40	0	0.00	5	8.33
41 - 50	11	18.33	23	38.33
51 - 60	24	40.00	14	23.33
61 - 70	18	30.00	11	18.33
> 70	7	11.67	7	11.67
Total	**60**	**100.00**	**60**	**100.00**
Mean	56.21 ± 11.69		57.23 ± 10.69	

Table 1. Comparison of Age Group Distribution in Cases and Controls

P Value = 0.103

Gender	Cases		Controls	
	No.	% Age	No.	% Age
Females	23	38.33	32	53.33
Males	37	61.67	28	46.67
Total	**60**	**100.00**	**60**	**100.00**

Table 2. Sex Distribution in Cases and Controls

P Value = 0.099

Serum Ferritin Levels (ng/ml)	Cases		Control	
	No.	% Age	No.	% Age
< 100	5	8.33	12	20.00
100 - 199	4	6.67	25	41.67
200 - 299	10	16.67	18	30.00
300 - 399	10	16.67	4	6.67
400 - 499	12	20.00	0	0.00
≥ 500	19	31.67	1	1.67
Total	**60**	**100.00**	**60**	**100.00**
Mean	370.04 ± 156.52		181.27 ± 92.23	

Table 3. Comparison of Serum Ferritin Levels in Cases and Controls

P = 0.001

Killip Class of Heart Failure	Serum Ferritin						Total	
	Low		Normal		Raised			
	No.	% age	No.	% age	No.	% age	No.	% age
I	0	0.00	1	4.00	0	0.00	1	4.00
II	1	4.00	1	4.00	4	16.00	6	24.00
III	0	0.00	0	0.00	11	44.00	11	44.00
IV	0	0.00	1	4.00	6	24.00	7	28.00
Total	**1**	**4.00**	**3**	**12.00**	**21**	**84.00**	**25**	**100.00**

Table 4. Association between Killip Class of Heart Failure and Serum Ferritin

P = 0.051

Hospital Stay	Serum Ferritin						Total	
	Low		Normal		Raised			
	No.	% Age	No.	% Age	No.	% Age	No.	% Age
0 - 2	0	0.00	0	0.00	7	11.67	7	11.67
3 - 4	1	1.67	8	13.33	7	11.67	16	26.67
5 - 6	0	0.00	7	11.67	23	38.33	30	50.00
> 6	0	0.00	0	0.00	7	11.67	7	11.67
Total	**1**	**1.67**	**15**	**25.00**	**44**	**73.33**	**60**	**100.00**

Table 5. Association between Hospital Stay and Serum Ferritin Levels

P = 0.034

DISCUSSION

A total of 120 subjects, 60 diagnosed cases of acute coronary syndrome and 60 age and sex matched healthy controls were enrolled for the present study that aimed to study the association between serum ferritin levels and risk of acute coronary syndrome.

In the present study, most of the patients of ACS were in the age group of 51 - 60 years (40 %), Among the controls, maximum subjects belonged to the age group 41 - 50 years (38.33 %). Mean age of patients was 56.21 ± 11.69 years while those in controls was 57.23 ± 10.69 years. Out of the total 60 patients of ACS, 23 patients (38.33 %) were females and 37 (61.67 %) were males as compared to 32 (53.33 %) females and 28 (46.67 %) males in the control group. The demographic profile of our study groups was quite similar to the study conducted by Hoque et al. (2017)[14] in which maximum number of cases of ACS belonged to the age group of 50 - 59 years (38.5 %). Among cases 44 (67.7 %) were males and 21 (32.3 %) were females.

The mean haemoglobin levels in cases were 12.71 ± 1.41 g/dl whereas in controls were 12.29 ±1.48 g/dl. These were similar to the observations made by Herakall M and Biradar MS (2018),[5] where mean haemoglobin in cases and controls were 12.59 g/dl and 12.48 g/dl respectively and were statistically similar.

Out of the conventional risk factors for ACS, in the study group, hypertension (70 %) was the most common risk factor observed followed by diabetes mellitus (56.67 %). Other risk factors observed were dyslipidaemia (51.67 %), smoking (35.0 %) and obesity (15.0 %). These results were quite similar to those observed by Hoque AT et al. (2017),[14] where hypertensives constituted 72.34 % of the patients and diabetics were 60.0 %. Dyslipidemia, smoking and obesity also contributed significantly as the risk factors.

Serum lipid profiles were compared between cases and controls. Mean serum cholesterol levels in cases were 217.41 ± 63.22 mg/dl and controls were 167.66 ± 17.74 mg/dl. Cases had lower serum HDL levels with the mean being 39.76 ± 8.74 mg/dl as compared to controls with mean of 52.05 ± 4.45 mg/dl. Serum LDL levels were higher in cases (Mean LDL = 140.00 ± 64.40 mg/dl) compared to controls (Mean LDL = 98.60 ± 113.03 mg/dl). The difference was statistically significant.

Mean BMI of cases was 24.93 ± 2.84 kg/m^2 and of controls was 22.24 ± 1.56 kg/m.^{2} The statistically significant difference pointed to obesity, as being an important risk factor for ACS. In a similar study conducted by Herakall M and Biradar MS (2018),[5] the mean serum cholesterol levels in cases and controls were 242.8 ± 32.63 mg/dl and 189.4 ±13.01 mg/dl respectively. Mean body mass index in cases and controls was 27.1 ± 3.77 kg/m^2 and 24.9 ± 3.73 kg/m^2 respectively in the same study.

In our study, 41.66 % of the patients of ACS had heart failure, Killip class III being the most common. In a study by Moradi M et al. (2015),[15] 33.42 % patients showed signs of left ventricular failure in ACS. The most common vessel involved in ACS was LAD (45.0 %), followed by right coronary artery (RCA) (23.33 %). Left main coronary artery (LMCA) was involved in 6.67 % of patients. LAD+RCA were involved in 5.0 % patients and 8.33 % patients had involvement of RCA+LCX. Similar observations were seen in the study by Bonaca MP et al. (2012)[16] that LAD was the most commonly involved vessel followed by RCA and LCX

In the present study, the mean serum ferritin levels in cases were 370.04 ± 156.52 ng/ml while in controls were 181.27 ± 92.23 ng/ml. In cases of ACS, 19 patients (31.67 %) had serum ferritin levels of $\geq$ 500 ng/ml. In controls, only 1 patient (1.67 %) had serum ferritin levels of $\geq$ 500 ng/ml. The difference was statistically significant (P value > 0.05). Odds ratio was 1.6. People with raised serum ferritin levels are at 60 % greater risk of developing ACS as compared to those with normal serum ferritin levels. These results were quite comparable to the study by Herakall M et al. (2018) where it was observed that significantly higher number of patients in cases group had serum ferritin level > 300 µg/l as compared to control group. The mean serum ferritin levels were significantly higher in cases group as compared to control group (332.5 vs. 153.8 µg/l) (P < 0.05).

In the present study, out of the total 51 patients with systolic dysfunction, 38 patients (63.33 %) had raised serum ferritin whereas 12 patients (20.00 %) had normal levels. Serum ferritin levels were observed in patients of diastolic dysfunction. 34 patients (75.56 %) had raised serum ferritin levels. But the difference was found to be statistically non-significant. The results were comparable to the study by Dominguez-Rodriguez A et al. (2012)[17] that also showed no association between serum ferritin levels and left ventricular dysfunction.

Out of the total 25 patients of heart failure in this study, 21 patients (84.00 %) had raised serum ferritin levels. In the patients with raised serum ferritin levels, 11 patients (44.00 %) had Killip class III heart failure (most common). Statistically significant association was found between Killip class of heart failure and serum ferritin levels. Also, maximum number of patients (50.00 %) had a hospital stay of 5 - 6 days. 7 patients had a hospital stay of > 6 days. All these 7 patients had raised serum ferritin levels. Raised serum ferritin levels were associated with longer hospital stay in patients of ACS.

These observations were in comparison to the study by Silvestre OM et al. (2017)[18] which showed that disorders of iron metabolism were associated with increased risk of heart failure in patient of acute coronary syndrome. In patients who suffered from heart failure, 52.35 % patients had hyperferritinaemia. The mean hospital stay of these patients was 9.5 ± 3.7 days and patients with higher serum ferritin levels had a longer hospital stay.

CONCLUSIONS

Serum ferritin levels were compared between cases and controls. The difference between serum ferritin levels in cases of ACS and controls was statistically significant with a P value of 0.001. The Odds ratio was 1.6. Hence, we come to an inference that people with raised serum ferritin levels are at 60 % greater risk of developing ACS as compared to those with normal serum ferritin levels and these patients have higher risk of developing heart failure and have a longer hospital stay.

Limitations

First, ferritin was the only marker of iron status investigated. Its serum level can also be elevated in inflammatory conditions and in certain liver diseases. To minimize this limitation, C-reactive protein, an inflammatory marker, was included in the model for analysis. Second, some patients presented late to emergency, after 24 hours of symptoms onset. Those patients could not be included in the study as the serum ferritin levels were expected to rise in them as acute phase reactants.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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