Iron, an essential element for many important cellular functions in all living organisms, can catalyze the formation of potentially toxic free radicals. Iron is a transition metal that can catalyze toxic redox reactions, and it is involved in many harmful biological reactions and diseases in human body. Excessive iron has been proposed to be a potent risk factor for CHD, especially for AMI.

Methods: The present study is a prospective nested case-control study of 55 cases of AMI and 60 controls from tertiary care centre in New Delhi.

Results: Mean iron value of cases and controls 45.22 ± 23.02 and 69.43 ± 19.06, TIBC 282.78 ± 44.25 and 320.05 ± 39.1, Ferritin 211.34 ± 126.1 and 58.05 ± 36.82.

Conclusion: In clinical medicine, ferritin predominantly utilized as a serum marker of total body iron stores. It reduces the levels of antioxidants in the plasma, increases the production of free radicals and promotes lipid peroxidation; therefore, it can be associated with progression of atherosclerosis. Thus, increased ferritin levels can be considered as the risk factor of CAD in conjunction with other risk factors.

INTRODUCTION

Coronary artery disease has spiked by 300 percent among Indians in the past three decades. Iron, an essential element for many important cellular functions in all living organisms, can catalyze the formation of potentially toxic free radicals. Iron is a transition metal that can catalyze toxic redox reactions, and it is involved in many harmful biological reactions and diseases in human body. Excessive iron has been proposed to be a potent risk factor for CHD, especially for AMI.

Atherosclerotic coronary artery disease is the leading cause of mortality and morbidity. It is the chronic progressive condition and the treatment for the same is required indefinitely. In India, CAD manifests almost a decade earlier than in western countries. 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. Risk factors CAD 1) Controllable risk factors - High blood pressure, High blood cholesterol, Smoking, obesity, Physical activity, Diabetes, Stress. 2) Uncontrollable Risk factors - Gender, Heredity, Age. 3) Emerging Risk Factors - Triglycerides, Lp (a), Fibrinogen, Homocysteine, Urine microalbumin/creatinine ratio, Hs- CRP, Impaired fasting glucose (100-125 mg/dl per ADA).

National Health and Nutrition Examination Survey (NHANES III) between 1988-1994, first time reported that there is a positive association between iron storage and risk for CAD. One of the paradoxes of life on this planet is that the molecule that sustains aerobic life, oxygen, is not only fundamentally essential for energy metabolism and respiration, but it has been implicated in many diseases and degenerative conditions. In the sequential univalent process. The linked iron induced low - inflammatory reaction may contribute to increased risk if atherosclerosis.

Iron is a transition metal that can catalyse toxic redox reactions, and it is involved in many harmful biological reactions and diseases in human body. Excessive iron has been proposed to be a potent risk factor for CHD, especially for AMI. Whether or not body iron is independent risk factor for CHD and AMI is still unanswered.

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ESIC & PGIMSR New Delhi
METHODS

The present study is a prospective nested case-control study of 55 cases of AMI and 60 controls from tertiary care centre in NewDelhi. The diagnosis of MI was based on the history of prolonged chest pain (>30 min) and it was confirmed by typical changes in ECG and elevation of CK-MB levels. Control group included 60 healthy volunteers in same age. The exclusion criteria from the study were previous MI, Cardiac disease, Endocrine/Thyroid abnormalities, chronic illness.

Procedure done: Angiography followed by angioplasty

Informed consent was taken from all patients, who participated in the study. Serum Ferritin was done by chemiluminescence.

Statistical Analysis

All the data so collected were duly recorded and was compiled; results and observations drawn and statistically analysed using Mean, Standard deviation, Annova, Unpaired Student t-test, Chi-square test and Z-test.

RESULTS AND OBSERVATION

![Graph 1 Sex Distribution](image)

**Table 2 Type of MI**

<table>
<thead>
<tr>
<th>MI</th>
<th>Frequency</th>
<th>Present</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMWI</td>
<td>37</td>
<td>67.27</td>
<td>67.27</td>
</tr>
<tr>
<td>IWMI</td>
<td>12</td>
<td>21.82</td>
<td>89.09</td>
</tr>
<tr>
<td>LWMI</td>
<td>5</td>
<td>9.09</td>
<td>98.18</td>
</tr>
<tr>
<td>PWMI</td>
<td>1</td>
<td>1.82</td>
<td>100.0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>55</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**Table 3 Number of Vessels Involved**

<table>
<thead>
<tr>
<th>No of vessels involved</th>
<th>Frequency</th>
<th>Present</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>54.55</td>
<td>54.55</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>34.55</td>
<td>89.09</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>10.91</td>
<td>100.0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>55</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**Table 4 Mean Value Iron Profile in Number of Vessels Involved**

<table>
<thead>
<tr>
<th></th>
<th>1 VESSEL</th>
<th>2 VESSEL</th>
<th>3 VESSEL</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.FERRITIN</td>
<td>195.9</td>
<td>201.6</td>
<td>319.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SERUM IRON</td>
<td>48.3</td>
<td>40.1</td>
<td>45.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SERUM TIBC</td>
<td>267.3</td>
<td>271.7</td>
<td>278.1</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Table 5 Tertiles of Serum Ferritin**

<table>
<thead>
<tr>
<th>Serum ferritin</th>
<th>ACS</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65</td>
<td>3</td>
<td>37(61.6%)</td>
</tr>
<tr>
<td>65-152</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>&gt;152</td>
<td>36</td>
<td>2(70.9%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>55</td>
<td>60</td>
</tr>
</tbody>
</table>

**Graph 2 Mean Value of Ferritin in Cases and Controls**

**Graph 3 Mean Value of IRON, TIBC, Ferritin in Cases and Controls**

**Graph 4 Mean Ferritin Value and Number of Vessels Involved**

**Graph 5 Mean Ferritin value**

**Table 6 Ferritin and Odd’s Ratio**

<table>
<thead>
<tr>
<th>SERUM FERRITIN(ng/ml)</th>
<th>OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65</td>
<td>9.8</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt;152</td>
<td>22.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

DISCUSSION

One of the paradoxes of life on this planet is that the molecule that sustains aerobic life, oxygen, is not only fundamentally essential for energy metabolism and respiration, but it has been implicated in many diseases and degenerative conditions.

In the sequential univalent process by which O$_2$ undergoes reduction, several reactive intermediates are formed, such as superoxide (O$_2^-$), hydrogen peroxide (H$_2$O$_2$), and the extremely reactive hydroxyl radical (.OH); collectively termed as the reactive oxygen species (ROS).

\[O_2 + e^- \rightarrow O_2^- + e^- \rightarrow H_2O_2 + e^- \rightarrow OH + e^- \rightarrow H_2O\]

Fe$^{3+}$ + •O$_2$ $\rightarrow$ Fe$^{2+}$ + O$_2$ The second step is the Fenton reaction:

Fe$^{2+}$ + H$_2$O$_2$ $\rightarrow$ Fe$^{3+}$ + OH$^- +$ •OH

Net reaction:

O$_2^-$ + H$_2$O$_2$ $\rightarrow$ •OH + OH$^- +$ O$_2$
The reaction is named after Fritz Haber and his student Joseph Joshua Weiss.

The Haber-Weiss reaction and Fenton chemistry use iron in generating free radicals that oxidize low-density lipoprotein (LDL).

Microhemorrhage into atherosclerotic plaque with macrophage-mediated phagocytosis and degradation of aged red blood cells leads to accumulation of reoxid-active iron.

Oxidized LDL binds the macrophage scavenger-receptor, leading to unregulated uptake, foam cell formation, and accelerated atherogenesis.

**FENTON CHEMISTRY**

\[
Fe^{3+} + \cdot O_2^- \rightarrow Fe^{2+} + O_2
\]

\[
Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \cdot OH
\]

**HABER-WEISS REACTION**

\[
O_2^- + H_2O_2 \rightarrow OH^- + OH^- + O_2
\]

**LDL PEROXIDATION**

\[
OH^- + LDL \rightarrow H_2O + LDL-\cdot O
\]

Two main forms of iron in the body are: transferrin and ferritin.

All the serum iron in the human body is bound to proteins except when it is increased. Free or excess iron has an ability to accept and donate electrons by exchanging between ferrous and ferric forms. This exchanging may generate reactive oxygen species (ROS) such as hydroxyl radical through Fenton and Haber-Weiss reactions, causing oxidative stress and oxidation of organic bio-molecules. Iron overload would elevate the risk of CAD by promoting the lipid peroxidation, which is being measured by malondialdehyde (MDA).

This relationship between body iron and CAD was first observed by Jerome Sullivan, in 1981, indicating that body iron overload was positively associated with CAD risk.

Several researchers, thereafter, have found and reported an association between iron overload, serum ferritin (SF) and acute myocardial infarction.

According to iron hypothesis by Sullivan, the iron overload produces the free radicals, which modify the low density lipoprotein cholesterol (LDL) into oxidized LDL (ox-LDL). This ox-LDL is important in the pathogenesis of atherosclerosis and dysfunction of vascular endothelium. Ferritin can act as a catalyst in the production of oxygen free radicals and lipid peroxidation and play a role in the formation of oxidized LDL. Oxidation of LDL causes the accumulation of lipids in endothelial and smooth cells, and prevents macrophages from leaving the arterial wall. Thus, these effects promote the atherosclerosis lesion.

Haidari et al. in 2001 conducted a study on 400 CAD patients. This study concluded that high stored iron concentration, as assessed by serum ferritin, is a strong and independent risk factor for premature CAD in the male Iranian population. The results were also showed serum iron and transferrin saturation significantly high, whereas total iron binding capacity was found to be significantly low in coronary heart disease patients as compared to the control subject.

Iron (Fe) and Atherosclerosis Study (FeAST) Trial: The findings of Ralph et al (2010) support a biologic rationale for measurement of serial ferritin levels in patients with atherosclerosis. Because iron-induced oxidative stress contributes to inflammatory responses, determination of optimal iron marker levels to be maintained by calibrated phlebotomy is a clinically relevant concept for future outcome studies in ischemic heart disease. Blood donation, which depletes iron stores in the donors, was associated with reduced risk of myocardial infarction and cardiovascular disease.

Kraml P et al (2004) conducted a case-control study, which enrolled 216 subjects (76 patients of cardio vascular disease and 140 healthy controls). They observed that the plasma ferritin levels were found to be significantly increased while anti-oxLDL antibodies, nitrites/nitrates, tocopherol and HDL levels were significantly decreased in patients, as compared to healthy controls. Study supports the hypothesis that high ferritin levels contribute to oxidative stress and thus elevate the risk for development of cardiovascular disease.

On the other hand, Bozzini’s angiography based study could not support a role for biochemical or genetic markers of iron stores as predictors of the risk of CAD or its thrombotic complications. 17-year follow-up study done by Knuiman et al., in Australia, did not show any evidence in relation to ferritin level as a risk factor for cardiovascular disease.

Iron concentrations were low in the first five to seven days in the patients with acute myocardial infarction; the lowest being in the first two days. Of the 20 patients with myocardial infarction two-thirds showed abnormally low values for serum iron on the first day. The lowest serum iron level was observed on the third day, when all patients except one had serum iron below the normal range.

**CONCLUSION OF THE STUDY**

The hypothesis that body iron stores are associated with risk of CAD has been generated in extensive debate in the literature. In clinical medicine, ferritin predominantly utilized as a serum marker of total body iron stores. It reduces the levels of antioxidants in the plasma, increases the production of free radicals and promotes lipid peroxidation; therefore, it can be associated with progression of atherosclerosis and increase in the risk of cardiovascular events in the body. Thus, increased ferritin levels can be considered as the risk factor of CAD in conjunction with other risk factors.

**References**


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