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Research Paper

Ferritin and Dyslipdemia: A potent threat to acute myocardial infection?

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Abstract: 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 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. One of the major risk factors of cardiovascular diseases is arteriosclerosis which is secondary to the excess of LDL cholesterol. One-third of ischemic heart diseases in the world are secondary to hypercholesterolemia, and it is estimated that hypercholesterolemia is responsible for 2.6 million (4,5%) deaths in the world
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.
Mean value of cases and controls Ferritin 211.34±126.1 and 58.05±36.82. The mean and SD of cholesterol 166.16±38.06 and 107.07±15.36, LDL 104.98±41.72 and 54.03±14.78, VLDL 24.11±13.74 and 18.13±2.26 in cases and controls respectively with $p<0.0001$ and for TG 119.78±69.83 and 92.47±8.57 , with $p< 0.007$.
In conclusion increased ferritin levels can be considered as the risk factor of CAD in conjuction with other risk factors. TG, LDL-c, VLDL-c, TG and SF levels were raised in patients of AMI and found to be statistically significant. It can be concluded that there exists a relationship in lipid profile and SF with AMI therefore dyslipidemia and raised SF levels are the features of CAD

Keywords: Coronary artery, toxic free radicals, biological reaction

Introduction:

Coronary artery disease has spiked by 300 percent among Indians in the past three decades. Indians have the highest mortality and morbidity rates from CAD as compared to any other ethnic group. Number of Indians with CAD is above 60 million of which 23 million is below the age of 40 and 10 million younger than 30. The incidence of coronary artery disease is alarmingly increasing in our country.

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Reddy and Yusuf concluded that 2.39 million people died of CAD in 1990 in India and hypothysized that the number may double by the year 2015 (Reddy and Yousuf, 1998).

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 (Singh, *et. al*., 2017). 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 (You and Wang, 2005). 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 (Sung *et. al*., 2012).

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. Wheather or not body iron is independent risk factor for CHD and AMI is still unanswered (Tuomanainen *et. al*., 1998).

"Fat Locks The Heart." Dyslipidemia is one of the modifiable CVD risk factors, but its influence on CVD rates differs at different times (ages) or with gender because of certain modifying factors. For example, our arteries age with us and the changes with age make way for atherosclerosis (Thijssen *et. al*., 2016). The fact that epidemiological investigations suggest guilt only by association is what gives a foothold for vendors of a fairy tale link between dyslipidemia and CVD to stand on. However, the science is as solid as a rock, as my ancestors from antiquity know it.

Aims and Objectives:

To estimate lipid profile and SF levels in Indian patients of AMI visiting tertiary care centre.

To find out relationship of Lipid Profile and SF levels with Acute Myocardial Infarction.

Methods:

The present study is a prospective nested case-control study of 55 cases of AMI and 60 controls age and gender matched subjects from tertiary care centre in New Delhi. 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. Subjects with neoplastic and liver disease, primary/ secondary haemochromatosis, alcohol abuse, smoking, diabetes and ESR>20 mm/hr indicating the presence of inflammation/infection, previous history of MI and other cardiac diseases that could potentially lead to elevated ferritin

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concentration were excluded from analysis.
Procedure done: Angiography followed by angioplasty
Informed consent was taken from all patients, who participated in the study. Serum Ferritin was done by chemiluminescence.
Lipid profile such as total cholesterol, HDL, Triglycerides were estimated in Vitros- 5.1 auto analyser using readymade dry chemistry slides procured from Ortho-Clinical Diagnostics, Johnson and Johnson, USA.

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.

Observations and Results:

Table 1: Number of vessels involved

No of vessels involved	Frequency	Present	Cumulative
1	30	54.55	54.55
2	19	34.55	89.09
3	6	10.91	100.0
TOTAL	55	100.0	100.0

Table 2: Risk Factors

	Frequency	Percentage
D	28	50.91%
D/H	7	12.73%
H	9	16.36%
N	11	20.00%
Total	55	100.00%

Table 3: Mean value Iron profile in number of vessels involved

	1 VESSEL	2 VESSEL	3 VESSEL	P VALUE
S.FERRITIN	195.9	201.6	319.3	<0.05

Table 4: Ferritin and odd's ratio

SERUM FERRITIN(ng/ml)	OR	P
<65	9.8	0.001
>152	22.4	<0.001

Figure 1: Graph 1 Mean Value of Ferritin in cases and controls.

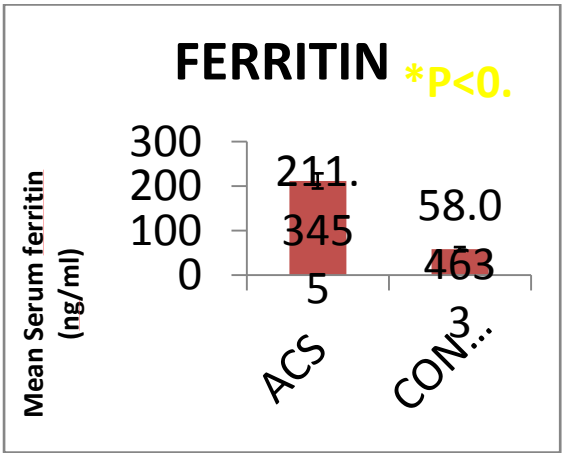

Figure 2: Mean Ferritin value

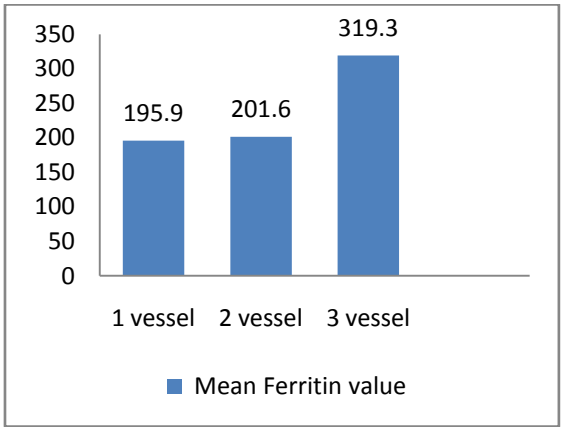

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Figure 3: Ferritin, Lipid profile cases and controls

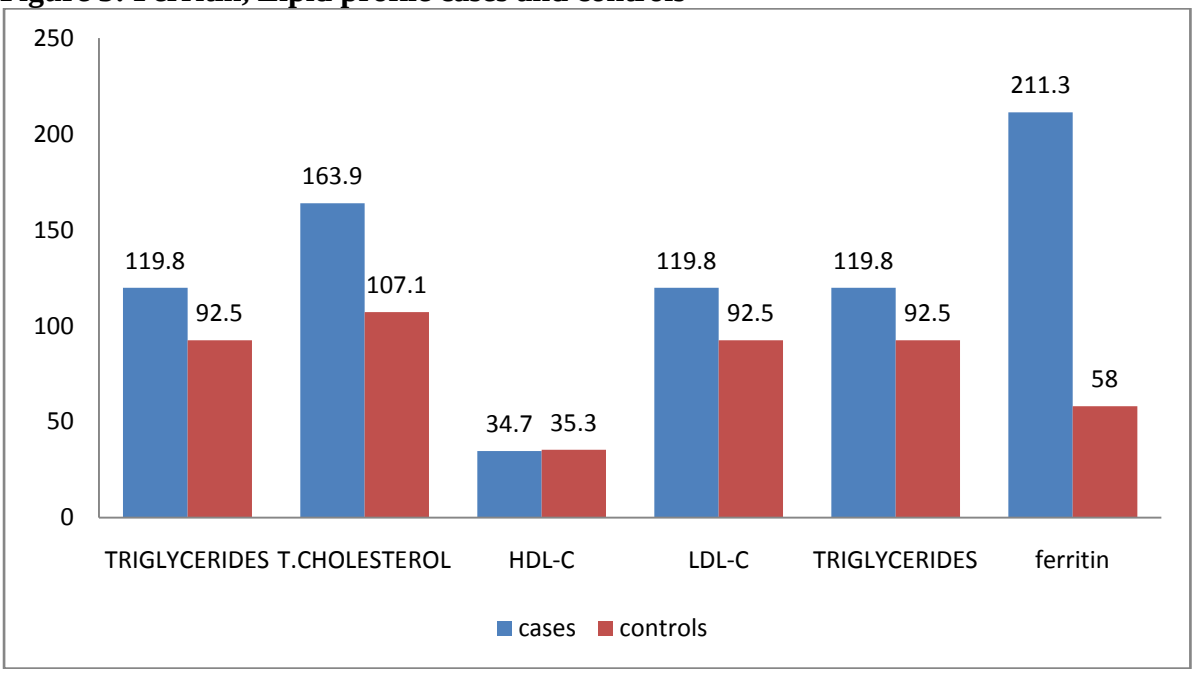

Figure 4: Mean and SD Parameters

	Case	Control	P value
	55	60	
FERTN	211.34 ± 126.1	58.05 ± 36.82	<0.0001
CPK	431.14 ± 188.05	125.35 ± 32.01	<0.0001
CKMB	52.91 ± 48.88	10.88 ± 5.4	<0.0001
LDH	1126.6 ± 938.78	163 ± 25.48	<0.0001
AST	245.2 ± 436.64	30.2 ± 13.3	<0.0001
RBS	189.2 ± 80.55	109.75 ± 18.47	<0.0001

	Case	Control	P value
ua	5.96 ± 1	3.99 ± 1.36	<0.0001
chol	166.16 ± 38.06	107.07 ± 15.36	<0.0001
hdl	38.53 ± 11.45	34.92 ± 5.47	0.031
ldl	104.98 ± 41.72	54.03 ± 14.78	<0.0001
vldl	24.11 ± 13.74	18.13 ± 2.26	0.001
tg	119.78 ± 69.83	92.47 ± 8.57	0.007

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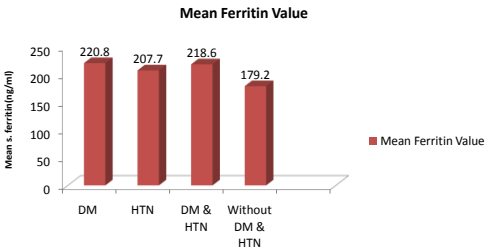
Figure 5: Mean value of Ferritin and comorbidit



Lipids alone, do not in isolation result in CVD. They need the endothelium to be injured first before they seize the moment. Therefore, the initial lesion is endothelial dysfunction brought on by hemodynamic or shearing consequence. Other factors involved in endothelial dysfunction include tobacco use, especially smoking, hyperglycemia, hyperuricemia, vasculitides, alcohol abuse, obesity, and stress among others. These set up inflammation in the intima (Okeahialam, 1919). Dyslipidemia and lipid oxidation are thought to be important determinants of atherosclerosis that leads to CVD (Mendis *et. al*., 2011). LDL-C is considered to be a major risk factor in the incidence of ischaemic strokes, atherothrombotic process and cardiovascular death (Berman and Blankstein, 2019). This is supported by numerous trials including two recent clinical outcome trials of proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors that increase the expression of the LDL-C receptor on hepatocytes as well as LDL-C clearance by the liver (Ridker, 2014). Elevated levels of TG were found to increase the risk of CVD among men more than women, though the role of TG in the pathogenesis of CVD and atheroma formation is still not clear (Nordestgaard and Varbo).

A study by Wallace *et al*. and Wilson *et al*. has demonstrated a direct relationship between serum LDL-C and CVD incidence (Wilson et. al., 1998, Varbo and Nordestgaard, 2018). It has also been shown that an increased level of TC (hypercholesterolemia), particularly LDL-C promotes the atherosclerosis process, leading to the deposition of cholesterol and fatty acids in the artery wall, whilst HDL-C is usually considered to be protective and returns cholesterol to the liver (Glasser *et. al*., 2016).

Our study is in accordandance with Shipra *et. al*., TC, LDL-c, VLDL-c, TG and SF levels were raised in patients of AMI and found to be statistically significant; while HDL-c levels were reduced in such patients and is also statistically significant (Shipral *et. al*., 2014).

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 O2 undergoes reduction, several reactive intermediates are formed, such as superoxide (O2 –), hydrogen peroxide (H2O2), and the extremely reactive hydroxyl radical (.OH): collectively termed as the *reactive oxygen species (ROS).*

$O2 + e- \rightarrow O2^{-} + e- \rightarrow H2O2 + e- \rightarrow .OH + e- \rightarrow H2O$

$Fe^{3+} + \bullet O_2^{-} \rightarrow Fe^{2+} + O_2$ The second step is the Fenton reaction:

$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{-} + \bullet OH$

Net reaction:

$O_2^{-} + H_2O_2 \rightarrow \bullet OH + OH^{-} + O_2$

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 redox-active iron. Oxidized LDL binds

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

FENTON CHEMISTRY

$Fe^{3+} + \bullet O_2^- \rightarrow Fe^{2+} + O_2$

$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \bullet OH$

HABER –WEISS REACTION

$O_2^- + H_2O_2 \rightarrow \bullet OH + OH^- + O_2$

LDL PEROXIDATION

$OH^{\cdot} + LDL \rightarrow H_2O + LDL\text{-}OX$

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) (Yesilbursa *et. al*., 2001)

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 [risk17].

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 (Sullivan 1981), The iron overload produces the free radicals, which modify the low density lipoproptein 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 catalyzer in the production of oxygen free radicals and lipid peroxidation and play a role in the formation of oxidized LDL (Liao *et. al*., 2012). 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 leisions (Meyers, 2000).

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 (Haidari *et. al*., 2001).

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 Ralph *et. al*., 2010). Blood donation, which depletes iron stores in the donors, was associated with reduced risk of myocardial infarction and cardiovascular disease (Ralph et. al., 2010, Tuomainen et. al., 1997).

Kraml *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 ferritn 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 contributes to oxidative stress and thus elevate the risk for development of cardiovascular disease.

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The mean and SD of ferritin and uric acid in the study group significantly increased , which suggest that there is underlying inflammation.

Conclusion:

TG, LDL-c, VLDL-c, TG and SF levels were raised in patients of AMI and found to be statistically significant; while HDL-c levels were reduced in such patients and is also statistically significant. It can be concluded that there exists a relationship in lipid profile and SF with AMI therefore dyslipidemia and raised SF levels are the features of CAD . So do not be deceived. Dyslipidemia in the right ambient would cause CVD via atherosclerosis. Even if one takes care of the modifiable risk factors, age and genetics which are non-modifiable would still put the individual in the presence of dyslipidaemia at risk for atherosclerotic CVD. Therefore, if any study excludes the right ambient, you may not see this adverse consequences. 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 atherosclesosis 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 conjuction with other risk factors.

Limitation of the study:

The study group was too small, Larger study group might be useful in proving the above hypothesis in better way.

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