"A STUDY OF SERUM FERRITIN IN ACUTE MYOCARDIAL INFARCTION : A CASE CONTROL STUDY "

By

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Dissertation submitted to BLDE(Deemed to be University), Vijayapura

In partial fulfilment of the requirements for the award of the degree of

DOCTOR OF MEDICINE

IN

GENERAL MEDICINE

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LIST OF ABBREVATIONS USED

%	-	Percentage
CAD	-	Coronary Artery Disease
CHD	-	Coronary Heart Disease
ECG	-	Electrocardiogram
AMI	-	Acute Myocardial Infarction
STEMI	-	ST Elevation Myocardial Infarction
NHANES	-	National Health And Nutrition Examination Survey
SF	-	Serum Ferritin
LCA	-	Left Coronary Artery
RCA	-	Right Coronary Artery
LCX	-	Left Circumflex Artery
LAD	-	Left Anterior Descending artery
PDA	-	Posterior Descending Artery
LBBB	-	Left Bundle Branch Block
PCI	-	Percutaneous Coronary Intervention
CRP	-	C-reactive protein
t-PA	-	Tissue Plasminogen Activator
PAI	-	Plasminogen Activator Inhibitor
ICMR	-	Indian Council of Medical Research
DNA	-	Deoxyribonucleic acid
LVH	-	Left Ventricular Hypertrophy
HsCRP	-	High-Sensitivity C-Reactive Protein
IL	-	Interleukin
VTE	-	Venous Thromboembolism

DVT	-	Deep Venous Thrombosis
PTE	-	Pulmonary Thromboembolism
IGF-1	-	Insulin like Growth Factor
CCF	-	Congestive Cardiac Failure
ACD	-	Anaemia of Chronic Disease
TNF	-	Tumor Necrosis Factor
IFN	-	Interferon
LDL	-	Low density lipoprotein
FID	-	Functional Iron Deficiency
mg	-	Milligrams
mg/dL	-	Milligrams per decilitre
min	-	Minute
ml	-	Millilitre
mmHg	-	Millimetres of mercury
mmol	-	Millimoles
PR	-	Pulse Rate
SBP	-	Systolic Blood Pressure
DBP	-	Diastolic Blood Pressure
RR	-	Respiratory Rate
Temp	-	Temperature
BMI	-	Body Mass Index
HB	-	Haemoglobin
TC	-	Total Count
ESR	-	Erythrocyte Sedimentation Rate
TCh	-	Total Cholesterol

LDL	-	Low Density Lipoprotein
HDL	-	High Density Lipoprotein
TG	-	Triglycerides
RWMA	-	Regional Wall Motion Abnormality
LVEF	-	Left Ventricular Ejection Fraction
POC	-	Point of care
VALV ABN	-	Valvular Abnormality
DD	-	Diastolic Dysfunction

ABSTRACT

AIMS AND OBJECTIVES:

1. To study the levels of serum ferritin in acute myocardial infarction.
2. Compare relationship of serum ferritin with conventional risk factors of acute myocardial infarction like diabetes mellitus, body mass index, hypertension and smoking.

MATERIAL and METHODS :

Study design: A total of 200 patients (100 cases and equal number of controls) were enrolled in a case control study to assess the levels of serum ferritin in acute myocardial infarction.

Study Site: BLDE (Deemed to be University) Shri B. M. Patil Medical college Hospital and Research Centre, Vijayapur.

Study population: Patients admitted to BLDEU'S Shri B. M. Patil Medical college Hospital and Research Centre, Vijayapur with acute myocardial infarction.

Study duration: The study was carried out from October 2015 to January 2018

RESULTS: It was observed that significantly higher number of patients in Cases Group had serum ferritin level >300µg/l as compared to Control Group (55% vs. 9%). The mean serum ferritin levels were significantly higher in Cases Group as compared to Control Group (332.5 vs. 153.8 µg/l) ($p<0.05$). The mean serum ferritin levels of males and females patients in Cases Group were significantly higher as compared to Control Group (320.3 vs. 160.1µg/l and 327.7 vs. 137.5 µg/l respectively) as per Student t-test (**$p<0.05$**). There was no significant difference of mean serum ferritin levels of males and females patients within the group ($p>0.05$). It was observed that significantly more patients in Cases Group (69%) than Control Group (34%) had concentrations above the cut-off of 200 µg/L (**$p<0.05$**). In multivariate analysis, Diabetes Mellitus (P = 0.001, OR = 7.64, 95% CI 2.37–24.58), HDL (P < 0.001, OR

= 0.86; 95% CI 0.79–0.93) and serum ferritin (>200 μg/L) (P < 0.001, OR = 5.72, 95% CI 2.16–15.17), are found to be independently associated with AMI.

Conclusion and interpretation

Higher levels of ferritin, seems to be a strong risk factor for AMI. Patients with higher ferritin level can easily be identified during routine haematological analysis along with other risk factor estimation. Regular monitoring of serum ferritin levels may help in reduction of cardiovascular morbidity and mortality.

Keywords

Acute myocardial infarction; Serum ferritin; conventional risk factors of acute myocardial infarction;

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INTRODUCTION

Cardiovascular disease is the leading cause of death worldwide. Its epidemic shows remarkable geographic variation. While the mortality associated with cardiovascular disease seems to be declining in Western Europe and North America, the burden of cardiovascular diseases in developing countries continues to rise and is expected to be a major cause of death in adults from low-income and middle-income countries worldwide. As the Indian economy grows, there is a possibility for further increase in cardiovascular disease before we see a decline similar to that being witnessed in developed countries.[1]

The incidence and prevalence of Coronary artery disease (CAD) has increased tremendously in India during the last two decades and this change is largely attributable to lifestyle changes.[2] India has reportedly shown the highest burden of Acute coronary syndromes in the world.[3]

Analysis of cross-sectional CHD epidemiological studies performed over the past 50 years reveals that this condition is increasing in both urban and rural areas. The adult prevalence has increased in urban areas from about 2% in 1960 to 6.5% in 1970, 7.0% in 1980, 9.7% in 1990 and 10.5% in 2000; while in rural areas, it increased from 2% in 1970, to 2.5% in 1980, 4% in 1990, and 4.5% in 2000. In terms of absolute numbers this translates into 30 million CHD patients in our country.[4]

There are two facets of CAD: Stable CAD and Unstable CAD which includes patients with acute coronary syndrome (Unstable angina, Non-ST elevation myocardial infarction, ST elevation myocardial infarction).[2]

Acute ST segment elevation myocardial infarction usually occurs when thrombus forms on a ruptured atheromatous plaque and occludes an epicardial coronary artery. Patient survival depends on several factors, the most important being restoration of brisk antegrade coronary flow, the time taken to achieve this, and the sustained patency of the affected artery.[5]

Diagnosis of acute myocardial infarction is based on history of acute chest pain in conjunction with ECG criteria and laboratory findings. ECG is still the most readily available and fastest method for the diagnosis of AMI.[6]

The Electrocardiogram remains a crucial tool in the identification and management of Acute myocardial infarction. A detailed analysis of patterns of ST- segment elevation may influence decisions regarding the use of reperfusion therapy.[7]

The early and accurate identification of the infarct-related artery on the Electrocardiogram can help predict the amount of myocardium at risk and guide decisions regarding the urgency of revascularization. Electrocardiographic signs of reperfusion represent an important marker of microvascular blood flow and consequent prognosis.

The electrocardiogram is also crucial for identifying new conduction abnormalities and arrhythmias that influence both short- and long-term outcome.[7]

Patients in India who have acute coronary syndromes have a higher rate of STEMI than do patients in developed countries. Since most of these patients are poor, they are less likely to get evidence-based treatments, and had greater 30-day mortality. Reduction of delays in access to hospital and provision of affordable treatments could reduce morbidity and mortality.[3]

Myocardial infarction (MI) is the most common cause of death worldwide. The major risk factors for MI are family history, diabetes mellitus, smoking, hypertension, and lipids.[8] Excess serum ferritin as a risk factor for MI is a relatively newer concept.[9] Ferritin is a large protein shell having molecular weight 450 KDa comprised 24 subunits, covering an iron core containing up to 4000 atoms of iron. Ferritin acts as the soluble storage form of iron in tissue.[10] High serum ferritin may increase the risk of MI in the presence of other risk factors that increase the formation of free radicals, thus accelerating atherogenesis through stimulation of low-density lipoprotein (LDL) oxidation.[11]

A possible association between body iron status and the risk of coronary heart disease was bolstered from a 3-year Finnish study relating increased levels of both serum levels of ferritin and dietary iron to an increased risk of MI.[12]

The association of high iron stores and coronary heart disease was first suggested by Sullivan.[13] Results of some studies have been in favor of ferritin being a risk factor for acute MI (AMI).[14]

A harmful biological effect of excessive iron loading in the human body has been recently suggested. In this regard, iron overloading especially in myocardial tissue has been proposed to be a potent risk factor for ischemic heart disease and occurring AMI.[12,13,15,16] The cardiac iron deposition results in a decrease of heart function on a certain genetic background.[17] Iron can also directly injure the myocardium. Iron can be accumulated in cells as hemosiderin, ferritin, and free iron named labile cellular iron that is the most toxic form stimulating the formation of free radicals.[18,19]

Since serum ferritin concentrations are directly proportional to intracellular ferritin concentration, it is considered the best clinical measure of body iron stores.[20] Recently, some evidences have been provided linking the increased incidence of coronary artery disease and elevated level of stored iron concentration.[12]

In these, increased estimated body iron stores have been associated with increased risk of AMI in some,[21,23] but some observations could not reveal this relationship.[24-29]

National Health and Nutrition Examination Survey (NHANES III), first time reported a significant positive association in iron storage and heart disease risk between 1988-1994. Several researchers, thereafter, have found and reported an association between iron overload, serum ferritin (SF) and acute myocardial infarction (MI).[12,13,30-31]

Free iron—a catalyst of the production of free radicals—has been implicated in ischemic myocardial damage and lipid peroxidation. Hypotheses as to how free iron may accelerate the progression of atherosclerosis or contribute to myocardial injury after an ischemic event have been generated from basic research. Direct evidence that high stored iron concentrations or high iron intakes increase the incidence of ischemic heart disease in humans, however, is limited. The strongest supporting evidence stems from a cohort study of eastern Finnish men, in whom high concentrations of serum ferritin and dietary iron were positively associated with the incidence of myocardial infarction.[12] Furthermore, serum ferritin was observed to be one of the strongest indicators of the presence and progression of carotid artery disease.[32,33] Blood donation, which depletes iron stores in the donors, was associated with reduced risk of myocardial infarction[23] and cardiovascular disease.[34] However, most subsequent studies investigating whether iron status or dietary iron intake are associated with increased risk of myocardial infarction or ischemic heart disease have not provided consistent results.[21-22,24-27,29,35-36]

Hence the present study was done at our tertiary care centre to study the levels of serum ferritin in acute myocardial infarction and Compare the relationship of serum ferritin with conventional risk factors of acute myocardial infarction like diabetes mellitus, body mass index , hypertension and smoking.

AIMS AND OBJECTIVES

1. To study the levels of serum ferritin in acute myocardial infarction.
2. Compare relationship of serum ferritin with conventional risk factors of acute myocardial infarction like diabetes mellitus, body mass index, hypertension and smoking.

REVIEW OF LITERATURE

HISTORICAL PRESPECTIVE

According to Sir William Osler, it was Seneca in 65 AD who first described heart attack. Since then heart attacks and cardiac pain have been known over the centuries but its cause-effect relationship with atherosclerosis came to be known only two centuries ago.

Leonard da Vinci (1452-1513) had actually drawn the coronary arteries and Vesalius (1543) in his “Dehumani Corporis Fabrica” had illustrated the coronary circulation, but there was no clear notion of coronary arteries as the nourishing vessels of the heart.

Drelincourt (1700) is credited with the first observation on the pathology of sclerosis of coronary arteries. Thebesius (1716) later recorded sclerosis of coronary arteries in a number of cases.

The term Angina pectoris was introduced by William Heberdon in 1768 and again in 1782, he gave an accurate clinical detail of angina pectoris and its progress from mild to fatal illness, but he knew little that chest pain of his classic description was due to Coronary artery disease.

Edward Jenner (1748-1823) published a paper on correlation between coronary artery disease and syndrome of chest pain. He demonstrated on postmortem study that narrowed coronary was the cause of Angina.

Calele Hiller Parry in his “Syncope angiosa” in 1799 gave an accurate description of the clinical picture of angina pectoris and also published autopsy findings.

In 1809, Allen Burns of Glasgow proved, by ligation of coronary artery, that the Angina phenomenon was ischaemic in origin. Kreysig (1814) and Teesta (1811) recognized the importance of coronary artery thickening in angina.

Huber in 1882 observed that in majority of cases it was atheroma in the artery, cutting off the blood supply that caused anaemic, atrophic, necrotic lesions which ultimately formed smaller or larger patches or fibrosis. Finally, in 1884, Earnest Vol Leyden accurately and clearly described pathology and clinical features of coronary thrombosis.

The Electrocardiogram, one of the most commonly used diagnostic tools in healthcare, was developed and created in the early 1900s by Willem Einthoven for which he was even awarded the Nobel Prize in Medicine in the year 1924.[37]

The first Electrocardiogram (ECG) from the intact human heart was recorded with a mercury capillary electrometer by Augustus Waller in May 1887 at St. Mary's Hospital, London. The tracings were poor and exhibited only 2 distorted deflections.

William Einthoven (1860-1927) who was professor of physiology at the University of Leiden, The Netherlands, began his studies of the ECG with the mercury capillary electrometer, and improved its distortion mathematically

so that he was finally able to register a good representation of the ECG before the beginning of the twentieth century.

Einthoven developed a system of electrocardiographic standardization that continues to be used all over the world and introduced the triaxial bipolar system with 3 limb leads and thus established uniformity of the recording process.

He also conceived the famous equilateral triangle with leads I, II, and III at its sides and the calculation of the electrical axis (in the frontal plane) depicted as a single vector with an arrow at the centre of the triangle.

Einthoven recognized the great potential importance of the ECG as a diagnostic and investigative tool and his achievements made him the founder of modern Electrocardiology.[37]

ANATOMY OF CORONARY CIRCULATION[10]

There are 2 main coronary arteries, the Left main coronary artery (LCA) and Right coronary artery (RCA). The Right and left coronary arteries encircle the epicardium like the crown encircles the head; hence, the name coronaries. They arise from the aortic bulb, which is made up of three aortic sinuses. Anatomically the three sinuses are disposed such that, one is anterior and two are posterior. The RCA arises from the anterior sinus and LCA from posterior sinus, The remaining right posterior sinus being non coronary one.

The RCA is dominant system in about 85% of individuals. It means in about 85% individuals, it supplies the posterior diaphragmatic portion of the interventricular septum and the diaphragmatic surface of the left ventricle.

RIGHT CORONARY ARTERY

The RCA originates from the right aortic sinus at a point lower than the origin of LCA. It passes down the right atrioventricular groove towards crux. The first branch of RCA is considered the conus artery. In 50% of the hearts, this vessel arises from the right coronary ostium. In the other 50% of individuals, it arises from a separate ostium in the right aortic sinus. It serves as collateral in patients with LAD obstruction.

- The second branch of RCA is the sino atrial node artery. It has been found that this artery originates from RCA in 59%, from left circumflex artery (LCX) in 38% and dual supply in the remaining 3%. When it originates from RCA, it passes obliquely backward through the upper portion of the atrial septum and the anteromedial wall of the right atrium. It sends branches to the sinus node, also to the right atrium or both atria. When it arises from LCx, it passes backwards in atrial septum to reach the sinus node area.
- The mid portion of the RCA usually gives rise to one or several medium sized acute marginal or right ventricular branches. These branches supply the anterior wall of the right ventricle and serve as a source of collateral circulation in patients with LAD obstruction.
- The important branch of RCA is the posterior descending artery (PDA) when RCA is the dominant one. The PDA usually originates at or shortly

before the crux and passes forward in the posterior interventricular groove. During its course along the groove, it gives rise to a number of small inferior septal branches, which pass upward to supply the lower portion of the interventricular septum.

- About 15% do not have RCA dominance, about half of these have LCx dominance, in the remaining half they are co-dominant. When LCx is dominant, it is large and continues down the diaphragmatic surface of the left ventricle, where it gives rise to posterior left ventricular branches and then reaches the crux and turns forward to become PDA. In these cases, the RCA is very small and terminates before reaching the crux. At or near the crux, the dominant RCA in 90% of subjects give rise to a small atrioventricular node artery, which supplies the node.

Branches

- Conus artery is the first branch, which ramifies on the lowest part of the pulmonary conus and upper part of the right ventricle and anastomoses with a similar branch of Left coronary artery. Some consider that the conus artery is of significance in coronary artery disease.
- Right anterior ventricular rami, usually two or three ramify towards apex. Right posterior ventricular rami, commonly two arise from second segment of right coronary artery and supply the diaphragmatic aspect of the right ventricle.

- As Right coronary artery approaches the crux of heart, it produces one to three posterior interventricular rami which give few branches to right ventricle and to the left ventricle.

Atrial rami of right coronary artery are divided into three main groups

Anterior group

Lateral (right or marginal) Posterior

- Anterior and lateral branches supply mainly right atrium. Posterior group supply both the right and left atrium. The artery of the SA node is an atrial branch that distributes largely to myocardium of both the atria, mainly right. It passes back between aorta and right auricular appendage and branches around base of superior vena cava.
- Ramus cristae terminalis is a large branch which transverses SA node and supplies the atria.

Septal branches: Septal branches of RCA are small, numerous and supply posterior interventricular septum, but do not reach apical septal part which is supplied by terminal septal branches of anterior interventricular artery. A large posterior septal branch of right coronary artery supplies AV node.

LEFT MAIN CORONARY ARTERY

- Left coronary artery supplies greater volume of myocardium almost all left ventricle and left atrium, most of interventricular septum.
- The main LCA arises from the left aortic sinus. The initial segment of coronary artery varies from few millimeters to few centimeters and lies between pulmonary trunk and left auricular appendage. After reaching atrioventricular sulcus, left coronary artery divides into two or three main rami and continues as anterior descending artery.
- The LAD passes down the anterior interventricular groove towards cardiac apex.

Its main branches are the septal and diagonal branches. The septal branches pass downwards into the interventricular septum and interconnect with similar septal branches of PDA, to produce a network of collateral channels. The diagonal branch of the LAD passes over the anterolateral aspects of the heart and supplies the apex. In 37% of patients, LCA has a trifurcation instead of bifurcation, in these cases ramus medianus arises between LAD and LCx, supplying free wall along lateral aspect of left ventricle. In 22% of patients, LAD is larger and longer and supplies apex

Branches

- It has two branches namely LAD and LCx. Anterior descending artery produces right and left anterior ventricular rami and also posterior and anterior rami. Right anterior ventricular rami are one or two in number and small. Left anterior ventricular rami are two to nine in number,

branch at angle from anterior descending artery, cross anterior aspect of left ventricle, larger terminal reaching the left border. One branch (diagonal artery) is often large (in 50%of cases) and it may arise separately from Left coronary trunk.

- A small left conus artery may arise from Anterior descending artery and anastomose with that of right coronary artery.
- Anterior septal rami: It passes back and down in septum to which they supply about ventral two thirds.
- Posterior septal rami: They are small and supply posterior one third septa.

CIRCUMFLEX ARTERY (LCx)

- LCx passes down the left ventricular groove, gives off obtuse marginal branches supplying free wall of left ventricle along its lateral aspect.
- Anterior and posterior rami of circumflex are small and supply left ventricle.
- Anterior ventricular branches two to three in number, run parallel to diagonal artery.
- Posterior ventricular branches- are few and supply part of left ventricle
- In addition, it gives one or two left atrial circumflex branches supplying left atrium.

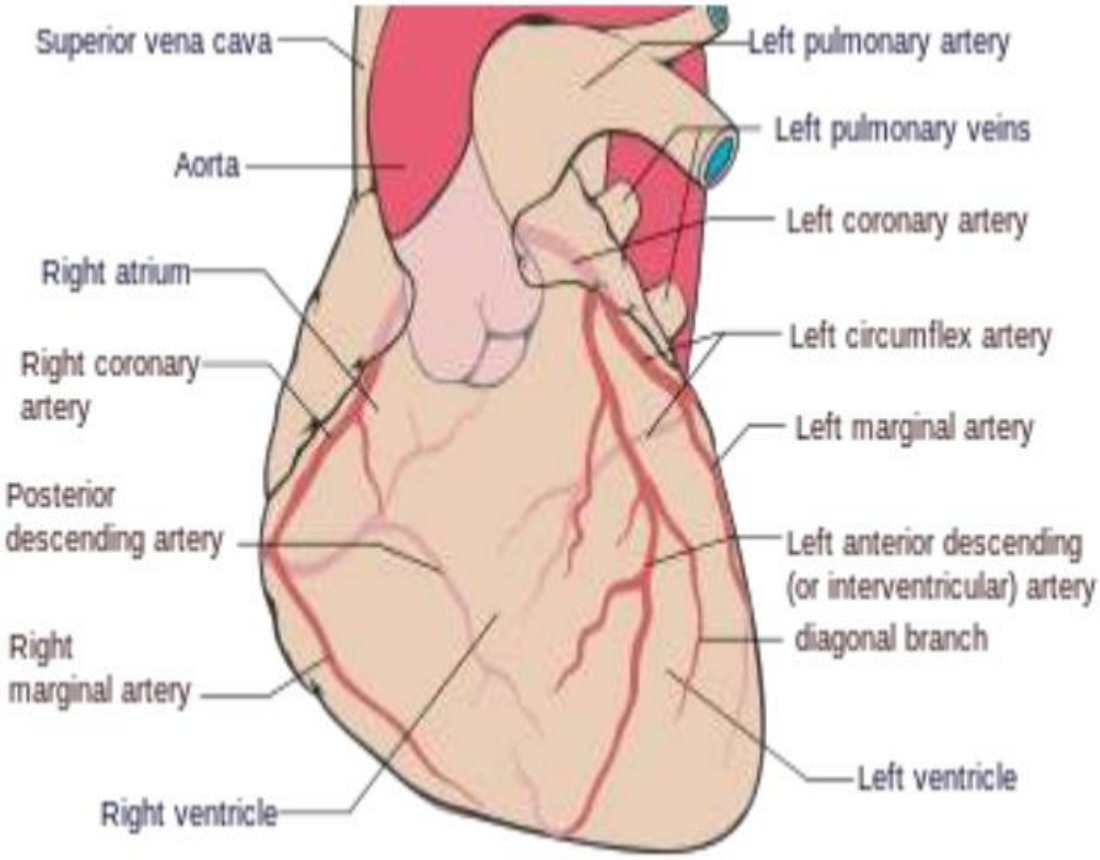


Fig 1 : CORONARY CIRCULATION

DEFINITION OF MYOCARDIAL INFARCTION

Universal Classification of Myocardial Infarction

1) Type 1: Spontaneous myocardial infarction Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, Assuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

2) Type 2: Myocardial infarction secondary to an ischemic imbalance In instances of myocardial injury with necrosis where a condition other

than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.

3) Type 3: Myocardial infarction resulting in death when biomarker values are unavailable Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.

4) Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI) Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values 5 x 99th percentile URL in patients with normal baseline values (99th percentile URL) or a rise of cTn values 20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

5) Type 4b: Myocardial infarction related to stent thrombosis Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with

a rise and/ or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

6) Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG) Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values 10 x 99th percentile URL in patients with normal baseline cTn values (99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

MYOCARDIAL INFARCTION IN YOUNG

Acute myocardial infarction (AMI) in the young, defined as myocardial infarction occurring in patients with age less than 45 years of age. Young patients with CAD are specific subset of population requiring attention. The atherosclerotic process causing ischemic heart disease begins in early life usually after the age of 20 and about 10% of patients with coronary artery disease are less than 40 years old with devastating impact to the patients and their families. There is a trend for the increased prevalence of risk factors for coronary artery disease especially smoking, lack of physical activity, social and emotional factors that will result in increased disease burden in young adults in the near future. India is undergoing a rapid health transition with rising burden of coronary heart disease (CHD). Among adults over 20 year of age, the estimated prevalence of CHD is around 3-4 percent in rural areas and 8-10 per cent in urban areas, representing a two-fold rise in rural areas

and a six-fold rise in urban areas between the years 1960 and 2000. Although uncommon entity, it constitutes an important problem for the patient and the treating physician because of the devastating effect of this disease on the more active lifestyle of young adults.

In addition, these patients have different risk factor profiles, and prognosis than older patients. A variety of other possible contributing factors that include substance abuse, coronary artery anomalies, hypercoagulable state, oral contraceptive use in young women have been implicated for the pathogenesis of myocardial infarction. The clinical presentation is also different from that of older patients. In majority of cases, a sudden myocardial infarction or unstable angina is the first manifestation of CAD. Angiographic studies also showed major differences with higher incidence of normal coronary arteries, mild luminal irregularities, and single vessel coronary artery disease.

AETIOLOGY OF CAD

Almost all myocardial infarction result from coronary atherosclerosis generally with superimposed coronary thrombosis. In over 75% of patients with myocardial infarction who come to autopsy, more than one coronary artery is severely narrowed.

One third to two third of patients with acute myocardial infarction have critical obstruction (to less than 25% of luminal area) of all 3 coronary arteries, whereas the remainder are equally divided between those having one vessel disease and those having two vessel disease, but conclusions drawn from autopsy studies of coronary arteries of patients with AMI are limited by the

selection bias (as those patients who died can be studied) and post mortem lysis of clots.

Coronary angiographic studies in surviving patients show that a higher percentage have one vessel disease. Angiographic studies performed in the earliest hours of AMI in patients presenting with ST segment elevation have revealed approximately a 90% incidence of total occlusion of infarct related vessel.[38]

There is dynamic interaction among coronary atherosclerosis, vasospasm, plaque rupture and platelet activation which leads to occlusion of a coronary artery leading to myocardial infarction – the final common pathway.[39,40]

RISK FACTORS FOR CORONARY ARTERY DISEASE (CAD)

Several conventional and non-conventional risk factors have been implicated for CAD. From an epidemiological perspective, a risk factor is a characteristic or a feature of an individual or population that is present early in life and is associated with an increased risk of developing future disease. Not all coronary events occur in individuals with multiple conventional risk factors, however, and in some individuals abnormalities of inflammation, hemostasis, and/or thrombosis appear to contribute decisively. In particular, nearly half of all MI or stroke occurs among individuals without hyperlipidemia. Conventional and non-conventional risk factors are mentioned below in table 01.

Table 1: Risk Factors for Coronary Artery Disease

Conventional risk factors	Non-conventional risk factors
Hypertension	Highly sensitive CRP
Type 2 Diabetes Mellitus	Lipoprotein (a)
Smoking	Hyperhomocysteinemia
Hyperlipidemia	Hyperfibrinogenemia
Obesity	Tissue plasminogen activator (t-PA) and plasminogen activator inhibitor (PAI- 1) imbalance

Novel risk factors for MI in young individuals are:

1. Hyperhomocysteinemia
2. Protein C deficiency
3. Protein S deficiency
4. Methylenetetrahydrofolate reductase (MTHFR) gene mutation
5. Lipoprotein a level

Age

Age is one of the most important independent risk factor for coronary artery disease. The disease tends to be more aggressive and manifests at a younger age in Indian population. The data obtained from the CREATE Registry revealed that mean age at the presentation of CAD in Indian population is 57.5±12.1 years while it was 53 years in South Asian cohort of the INTERHEART study and was lower than in the Western countries and other regions (mean age is 63 years).

McKeigue et al, Balarajan et al, Enas et al and Joshi et al found that South Asians had a lower age at presentation of first AMI and that the younger age of first AMI among the South Asian cases appears to be largely explained by the higher prevalence of risk factors in native South Asians.

Data from the INTERHEART Study reveals that first MI attack occurred in 4.4% of Asian women and 9.7% of men at age less than 40 years, which is 2 to 3.5 fold higher than in the West European population and is third highest of all the regions studied worldwide. Asians in general and Indians in particular are at increased risk of MI at a younger age (<40 years), irrespective of whether they have migrated to other countries or are resident Asians. Thus myocardial infarction in young individual is emerging fast in south Asian countries, particularly in India. Hence need for comprehensive study for clinical features & risk factors associated with them.

Sex

Decades of observational studies have verified excess coronary risk in men compared with premenopausal women. After menopause, however, coronary risk accelerates in women. At least part of the apparent protection against CHD in premenopausal women derives from their relatively higher HDL levels compared with those of men. After menopause, HDL values fall in concert with increased coronary risk.

In the INTERHEART study and its South Asian cohort, 76% of overall study population and 85% of south Asian cohort patients were males amongst patients with STEMI. Also, in CREATE Registry76.4% study population were males.

Smoking

Smoking is an independent important risk factor for coronary artery disease. Ischemic heart disease causes 35 to 40 % of all smoking related deaths, with an additional 8% attributable to second hand smoke exposure in developed contraries. Various toxins have different roles in atherogenesis. Carbon monoxide causes direct toxic effect on endothelial cells due to local hypoxia and associated with increased production of thromboxane A2 due to platelet dysfunction. Whereas nicotine causes sudden adrenaline rush which leads to tachycardia and vasopressor effect leading to endothelial injury. The dyslipidemia and smoking have synergistic role in the development of atherosclerosis.

In Framingham study, 60% of the patients with CAD were tobacco smokers. Tobacco smoking is major independent risk factor for CAD. Tobacco smoking interacts with other risk factors synergistically and increases the risk of CAD. These risk factors are Diabetes Mellitus, Hypertension & low level of HDL-C. In India, 15.4 to 40.8% population in various parts of country consume tobacco in various forms i.e. in the form of cigarette, bidi, hukka, chilam, pipe etc. The recent study of I.C.M.R. (Indian Council of Medical Research) showed that prevalence of CAD in attribution to tobacco use is significantly increased in India.

Even among non-smokers, inhaled smoke, whether from passive exposure or from cigar or pipe consumption, increases coronary risk. Passive smoking exposure can cause endothelial dysfunction in the coronary circulation as well as increased bronchial responsiveness and concomitant pulmonary dysfunction.

Because of adverse synergy with oral contraceptives, young female smokers who take oral contraceptives have particularly elevated risks of premature coronary disease and stroke. Smoking is also hazardous for women with diabetes.

Smoking has adverse haemostatic and inflammatory effects, including increased levels of CRP, soluble intercellular adhesion molecule-1 (ICAM-1), fibrinogen, and homocysteine.[41] Compared with non-smokers, smokers have an increased prevalence of coronary spasm and reduced thresholds for ventricular arrhythmia.

Smoking affects atherothrombosis by accelerating atherosclerotic progression; long-term smoking may enhance oxidation of low-density lipoprotein (LDL) cholesterol and impair endothelium-dependent coronary artery vasodilation. This latter effect has been linked to dysfunctional endothelial nitric oxide biosynthesis following chronic as well as acute cigarette consumption.

Accruing evidence has suggested that insulin resistance represents an additional mechanistic link between smoking and premature atherosclerosis.

Cessation of cigarette consumption overwhelmingly remains the single most important intervention in preventive cardiology. In a major overview, smoking cessation was found to reduce coronary heart disease mortality by 36 percent as compared with mortality in subjects who continued smoking, an effect that did not vary by age, gender, or country of origin.

Hypertension

High blood pressure often confers silent cardiovascular risk, and its prevalence is steadily increasing.

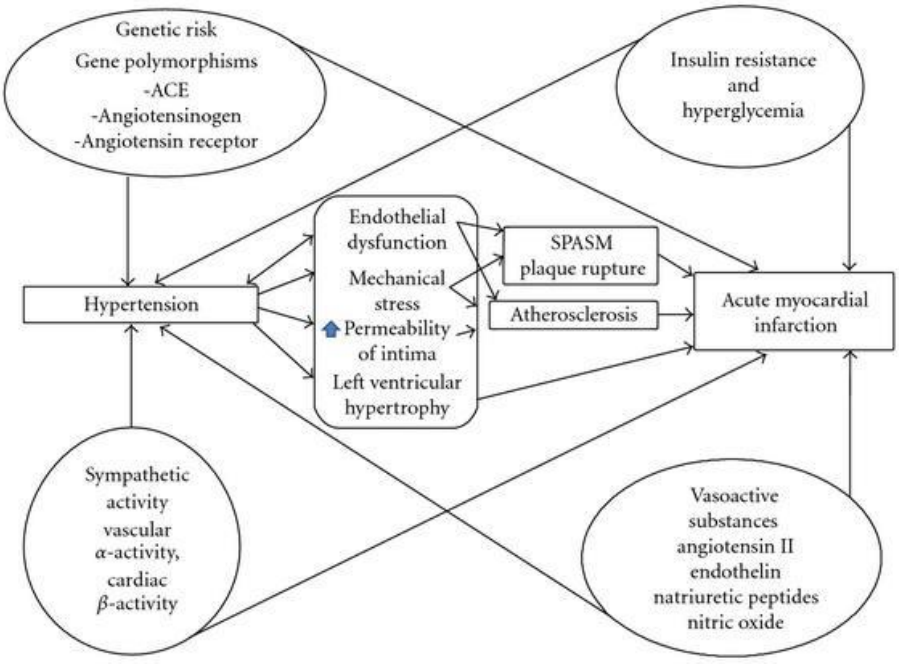
The prevalence of hypertension reported in CREATE Registry was 37.7%. The prevalence of hypertension in south Asian cohort of INTERHEART study was 17.8%.

Pulse pressure, generally reflecting vascular wall stiffness, also predicts first and recurrent myocardial infarction. Pulse pressure appears to predict cardiovascular events independently; particularly heart failure.

These data stress the importance of arterial compliance and stiffness in atherogenesis as well as in the development of left ventricular hypertrophy (LVH).

In an analysis of 354 randomized trials, regimens of multiple drugs given at low doses were estimated capable of reducing systolic blood pressure (SBP) by 20 mmHg and diastolic blood pressure (DBP) by 11 mmHg, effects that could result in stroke reductions of 63 percent and coronary heart disease risk reductions of 46 percent. Patients with obesity, the metabolic syndrome, and frank diabetes represent high-risk groups. For all these patients, target blood pressure should be in the “optimal” range of lower than 120/80 mmHg.

Fig 2: Pathophysiological Factors that Link Hypertension and Acute Myocardial Infarction



The clinical course of STEMI can be affected by several complications related to hypertension, including (1) renal failure, due both to contrast induced nephropathy and acute heart failure, (2) cardiogenic shock, (3) major and minor bleedings causing a new anaemic state, and (4) acute glucose imbalance.

Diabetes Mellitus

There is a consensus in the literature about an increased prevalence of coronary plaques in diabetic hearts, with such plaques bearing a higher propensity for rupture. In the event of a plaque rupture, the increased thrombogenesis and platelet dysfunction present in diabetes worsen the clinical consequences of plaque rupture. In a postmortem study of coronary atherectomy specimens from diabetic and non-diabetic patients, Moreno et al. noted a larger lipid content and increased macrophage infiltration and thrombosis in the atheromas of diabetic patients. Multiple mechanisms appear to be involved, including endothelial dysfunction, hypercoagulability, and platelet dysfunction, with hyperglycemia being the common trigger. Shechter et al. were able to demonstrate the role of glucose as an independent predictor of platelet dependent thrombosis. Furthermore, insulin has been found to increase serum concentrations of Plasminogen Activator Inhibitor type I (PAI-1) which has been shown to correlate with impaired fibrinolysis.

Diabetic patients are also known to have worse outcomes after an acute coronary syndrome when compared with the general population. Diabetes was an independent mortality risk factor in patients receiving thrombolytic therapy for ST elevation MI in both the GUSTO-I and GISSI-2

trials. Data from a meta-analysis of 19 trials comparing primary PCI and fibrinolysis in ST elevation MI showed that diabetic patients had a higher mortality reduction with PCI but continued to have worse outcomes than nondiabetics.

Native Indians living in India now constitute the largest population of diabetics in the world. CREATE Registry reported that prevalence of diabetes is 30.4% in acute coronary events, while the INTERHEART study reported it to be 10.5% in a similarly aged population from South Asian countries.

Dyslipidemia

Abnormalities in plasma lipoproteins and derangements in lipid metabolism rank among the most firmly established and best understood risk factors for atherosclerosis. Current ATP III guidelines recommend lipid screening in all adults >20 years of age. The screen should include a fasting lipid profile (total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol) repeated every 5 years.

In the INTERHEART study 56.15% of subjects from the south Asian region were dyslipidemic. However, no significant difference was found in the prevalence of dyslipidemia between men and women suggesting that dyslipidemia is equally prevalent in both genders. Various studies have shown 35 to 40% CVD related mortality reduction with HMG Co-A reductase inhibitors (statins) indirectly suggesting the benefit of correcting dyslipidemia.

LDL cholesterol: Knowledge of the LDL receptor pathway plus emerging understanding of the vascular biology of atherosclerosis provides

biological plausibility for the involvement of LDL in atherogenesis. The human mutations in the LDL receptor produce hypercholesterolemia on a monogenic basis that causes accelerated atherosclerosis as early as the first decade of life in individuals with homozygous familial hypercholesterolemia. Finally, intervention in large clinical trials to lower LDL cholesterol levels by various pathways (e.g., bile acid–binding resins, intestinal bypass surgery, HMG-CoA reductase inhibitors) have shown a reduction in cardiovascular events. Thus, LDL cholesterol fulfils the criteria of modified Koch's postulates as one causative agent in atherosclerosis.

As is the case with LDL cholesterol, abundant prospective cohort studies have demonstrated a strong inverse relationship between HDL cholesterol and vascular risk. In general, each increase of HDL cholesterol by 1 mg/dl is associated with a 2 to 3 percent decrease in risk of total cardiovascular disease.

The process of reverse cholesterol transport may explain in part the apparent protective role of HDL against coronary death. According to this concept, HDL could ferry cholesterol from the vessel wall, augmenting peripheral catabolism of cholesterol.

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) has recommended treatment of hypercholesterolemia. Target levels depend on overall risk of cardiovascular death or nonfatal MI. Patients with CAD or atherosclerosis of other vascular beds (carotids or peripheral vascular disease), adults with diabetes, and those patients with an estimated 10-year risk of developing CAD of greater than 20 percent fall into a high-risk

category and merit aggressive treatment including medications along with lifestyle modifications, exercise, and diet to achieve a primary target of an LDL cholesterol level less than 2.6 mmol/liter (100 mg/dL). In subjects with triglycerides greater than 200 mg/dL, ATP III presents a secondary target of a non-HDL cholesterol level less than 3.4 mmol/liter (130 mg/dL). Many of these individuals have the metabolic syndrome.

Obesity

Obesity is becoming a global epidemic. Over the last three decades, the age-adjusted prevalence of overweight and obesity has increased both in children and adults. It has been shown that individuals with metabolic syndrome, which includes obesity, are at increased risk for CHD. The root causes of metabolic syndrome are overweight/obesity, physical inactivity, and genetic factors. Furthermore obesity is associated with multiple comorbidities such as cardiovascular disease, type 2 diabetes, hypertension, certain cancers, and sleep apnoea.

The relationship of obesity with atherosclerosis and CHD in the past was uncertain, but it is now confirmed to be a major risk factor for CHD. Previous studies suggested that obesity was not an important contributor to coronary atherosclerosis. The Framingham Heart Study showed that the relation between body weight and risk of CHD was mediated largely through other risk factors, such as hypertension, total cholesterol, high-density lipoprotein cholesterol, and diabetes . The INTERHEART study of 27,000 participants showed abdominal obesity as an independent risk factor, but it

failed to demonstrate body mass index (BMI) as an independent risk factor for CHD.

Obese individuals have a pro-inflammatory state that may predispose them to acute coronary syndrome. Surplus adipose tissue secretes increased amounts of several cytokines that underlie the pro-inflammatory state. Plasminogen activator inhibitor-1 (PAI-1), mainly produced by the endothelium, is also released in increased amounts by the adipose tissue, which in turn favours a prothrombotic state.

Physical inactivity

Physical exercise reduces myocardial oxygen demand and increases exercise capacity, both of which correlate with lower levels of coronary risk.

The cardio-protective effects of exercise include reduced adiposity and diabetes incidence, lowered blood pressure, and improvement of dyslipidemia, as well as vascular inflammation. Exercise also enhances endothelial dysfunction, insulin sensitivity, and endogenous fibrinolysis. It is thus not surprising that prospective epidemiological studies almost universally demonstrate strong graded associations between levels of physical activity and reduced rates of cardiovascular morbidity and all-cause mortality.

Mental Stress, Depression, and Cardiovascular Risk

Both depression and mental stress predispose to increased vascular risk. The adrenergic stimulation of mental stress can augment myocardial oxygen requirements and aggravate myocardial ischemia. Mental stress can cause coronary vasoconstriction, particularly in atherosclerotic coronary

arteries, and hence can influence myocardial oxygen supply as well. Studies have further linked mental stress to platelet and endothelial dysfunction, the metabolic syndrome, and the induction of ventricular arrhythmias.

Novel Atherosclerotic Risk Factors

In one analysis of more than 120,000 patients with coronary heart disease, 15 percent of the women and 19 percent of the men had no evidence of hyperlipidemia, hypertension, diabetes, or smoking and more than 50 percent had only one of these general risk factors. Thus, because of the considerable need to improve vascular risk detection, much research over the past 10 or 15 years has focused on the identification and evaluation of novel atherosclerotic risk factors. Table 02 shows data describing the relative efficacy of several variables measured at baseline in two large cohorts of initially healthy middle-aged men and women.

Table 2. Clinical Epidemiology of Proposed Plasma-Based Biomarkers for Prediction of Future Cardiovascular Events

Biomarker	Prospective Studies Convincing?	Standardized Commercial Assay?	Additive to Lipid Screening?	Additive to Framingham Risk Score?
Inflammation				
HsCRP	++++	+++	+++	+++
sICAM-1	++	±	+	-

Biomarker	Prospective Studies Convincing?	Standardized Commercial Assay?	Additive to Lipid Screening?	Additive to Framingham Risk Score?
SAA	++	-	+	-
IL-6/IL-18	++	-	+	-
Myeloperoxidase	+	-	±	-
sCD40L	+	-	-	-
Altered thrombosis				
t-PA/PAI-1	++	±	-	-
Fibrinogen	+++	±	++	-
Homocysteine	++++	+++	±	-
D-dimer	++	+	-	-
Oxidative stress-oxidized LDL	±	-	-	-
Altered lipids				
Lipoprotein(a)	+++	±	±	-

Biomarker	Prospective Studies Convincing?	Standardized Commercial Assay?	Additive to Lipid Screening?	Additive to Framingham Risk Score?
LDL particle size	++	±	±	-

HsCRP = high-sensitivity C-reactive protein; IL = interleukin; LDL = low-density lipoprotein; PAI-1 = plasminogen activator inhibitor-1; sICAM-1 = intercellular adhesion molecule-1; SAA = serum amyloid A; sCD40L = soluble CD40 ligand; t-PA = tissue plasminogen activator. Plus signs indicate increasing strength of evidence

High-Sensitivity C-Reactive Protein (hsCRP)

Inflammation characterizes all phases of atherothrombosis and provides a critical pathophysiological link between plaque formation and acute rupture, leading to occlusion and infarction.

Primary pro inflammatory cytokines released during atherothrombosis result in the expression of messenger cytokines such as interleukin-6, which can travel from local sites of inflammation to the liver, where a change in the program of protein synthesis characteristic of the acute phase response is thereby triggered. The acute-phase reactant, CRP, a simple downstream marker of inflammation, has now emerged as a major cardiovascular risk factor.

More than simply a marker of inflammation, CRP may influence directly vascular vulnerability through several mechanisms, including enhanced expression of local adhesion molecules, increased expression of

endothelial PAI-1, reduced endothelial nitric oxide bioactivity, and altered LDL uptake by macrophages, and co-localization with complement within atherosclerotic lesions.

hsCRP adds prognostic information at all levels of LDL cholesterol and at all levels of risk, as determined by the Framingham Risk Score.

In other major studies from the United States and Europe, hsCRP levels predicted subsequent risk better than LDL cholesterol level.

American Heart Association and the Centres for Disease Control and Prevention issued guidelines in 2003 for the use of hsCRP in clinical practice. Briefly, hsCRP levels less than 1, 1 to 3, and higher than 3 mg/liter should be interpreted as lower, moderate, and higher relative vascular risk, respectively, when considered along with traditional markers of risk.

Levels of hsCRP greater than 3 mg/liter also predict recurrent coronary events, thrombotic complications after angioplasty, poor outcome in the setting of unstable angina, and vascular complications after bypass surgery.

Additionally, hsCRP has prognostic usefulness in cases of acute ischemia, even without troponin level elevation, suggesting that an enhanced inflammatory response at the time of hospital admission can determine subsequent plaque rupture. These findings help explain why individuals with elevated hsCRP levels are also more likely to benefit from aggressive interventions compared with those with low hsCRP levels.

Elevated levels of hsCRP predict not only cardiovascular events but also the onset of type 2 diabetes mellitus. Perhaps because hsCRP levels correlate with several components of the metabolic syndrome, including those not easily measured in clinical practice such as insulin sensitivity, endothelial dysfunction, and hypo fibrinolysis. Thus, hsCRP assessment also adds prognostic information at all levels of the metabolic syndrome.

Statins lower hsCRP levels in a manner largely unrelated to the magnitude of LDL cholesterol reduction, data from primary and secondary prevention trials have indicated that the relative benefit of statin therapy in terms of event reduction may be greater in the presence of elevated hsCRP levels.

In the PROVE IT-TIMI 22 clinical trial conducted in patients with acute coronary syndromes treated with statin therapy, achieving levels of hsCRP less than 2 mg/liter was as important for long-term event-free survival as was achieving levels of LDL cholesterol less than 70 mg/dl; in fact, the best long-term outcomes were found in those who achieved both these goals. This new concept of “dual goals” for statin therapy, which includes both CRP and LDL level reduction, has been corroborated in the A-to-Z clinical trial as well as in studies using intravascular ultrasound to monitor disease progression. In this latter setting, only those with CRP reduction had coronary regression with statin therapy, whereas those who achieved both CRP and LDL level reduction had the greatest regression overall.

Other Markers of Inflammation

Although hsCRP is by far the best-characterized and most reliable inflammatory biomarker for clinical use, several other markers of inflammation have shown promise in terms of predicting vascular risk. These include cytokines such as interleukin-6, soluble forms of certain cell adhesion molecules such as intercellular adhesion molecule (sICAM-1), P-selectin, or the mediator CD40 ligand, as well as markers of leukocyte activation such as myeloperoxidase. Other inflammatory markers associated with lipid oxidation such as lipoprotein-associated phospholipase A_2 and pregnancy-associated plasma protein A have also shown promise.

HPERHOMOCYSTEINEMIA

Patients with rare inherited defects of methionine metabolism can develop severe hyperhomocysteinemia (plasma levels higher than 100µmol/liter) and have markedly elevated risk of premature atherothrombosis as well as venous thromboembolism.

Mechanisms suggested to account for these effects include endothelial dysfunction, accelerated oxidation of LDL cholesterol, impairment of flow-mediated endothelium-derived relaxing factor with subsequent reduction in arterial vasodilation, platelet activation, and oxidative stress.

Nygard O et al have shown a strong graded relation between increasing homocysteine level and overall mortality in individuals with angiographically demonstrable CAD.

However with regard to clinical trials of homocysteine reduction, several major studies have been completed and none have shown substantive benefit. In the Heart Outcomes Prevention Evaluation (HOPE-2) trial of 5522 patients with vascular disease or diabetes, 5 years of therapy with folate, vitamin B_6, and vitamin B_{12} resulted in no benefit compared with placebo for total vascular events (HR, 0.95; 95 percent CI, 0.84 to 1.07), cardiovascular mortality (HR, 0.96; 95 percent CI, 0.81 to 1.13), or any of several pre specified secondary endpoints.

Despite reduced enthusiasm and lack of evidence that homocysteine reduction lowers risk, there remain a few specific patient populations for whom homocysteine evaluation may prove appropriate, including those lacking traditional risk factors, with renal failure, or with markedly premature atherosclerosis or a family history of myocardial infarction and stroke at a young age.

1. Fibrinogen and Fibrin D-Dimer

Plasma fibrinogen influences platelet aggregation and blood viscosity, interacts with plasminogen binding and in combination with thrombin, mediates the final step in clot formation and the response to vascular injury. In addition, fibrinogen associates positively with age, obesity, smoking, diabetes, and LDL cholesterol level, and inversely with HDL cholesterol level, alcohol use, physical activity, and exercise level. Given these relationships, it is not surprising that fibrinogen was among the first “novel” risk factors evaluated, like CRP, it is an acute-phase reactant and increases during inflammatory responses.

In one analysis, the age- and gender-adjusted hazard ratio per 1 g/liter increase in fibrinogen was 2.4 for coronary heart disease and 2.1 for stroke. Interestingly; these effects were largely unaffected in those studies in which further adjustment for hsCRP was possible. In more recent studies, hsCRP and fibrinogen levels appeared to be additive in their ability to predict risk, although the absolute effect of hsCRP appeared to be larger. Other studies have suggested that the predictive usefulness of fibrinogen is highest in those with other concomitant elevations of lipoprotein (a) or homocysteine.

Following MI, D-dimer levels also predict recurrent events and, like CRP, D-dimer predicts poor outcome in troponin-negative ischemia.

2. Lipoprotein(a) {Lp(a)}

The close homology between Lp(a) and plasminogen has raised the possibility that this lipoprotein may inhibit endogenous fibrinolysis by competing with plasminogen binding on the endothelium.

More recent studies have suggested that Lp(a) binds and inactivates tissue factor pathway inhibitor and may upregulate the expression of plasminogen activator inhibitor, further linking lipoproteins and thrombosis.

Lp(a) also co-localizes within atherosclerotic lesions and may have local actions through oxidized phospholipids pathways. Thus, several mechanisms may contribute to a role of Lp(a) in atherothrombosis.

However, whether the assessment of Lp(a) truly adds prognostic information to overall risk in primary prevention remains uncertain because, in most studies, Lp(a) has been predictive only for those already known to be at

high risk because of the presence of other risk factors, in particular elevated levels of LDL cholesterol. Data from the Italian Longitudinal Study on Aging, the Prospective Cardiovascular Munster study, the Bruneck Heart Study, and the PRIME study have suggested that a high serum lipoprotein(a) level is an important risk factor, primarily in individuals with type 2 diabetes or overt hyperlipidemia. Other investigators have found that Lp(a) signifies elevated risk in limited situations such as the presence of hyperfibrinogenemia or elevated homocysteine levels, or in the elderly, with multiple other risk factors.

Markers of Fibrinolytic Function

Plasma levels of Plasminogen activator inhibitor (PAI)-1 peak in the morning, whereas concentrations of t-PA demonstrate a less prominent circadian variation. On this basis, a relative hypo fibrinolytic state may prevail in the morning that, along with increased platelet reactivity, may contribute to the increased risk of myocardial infarction seen during this period.

Visceral obesity yields enhanced PAI-1 production from adipocytes, and thus impaired fibrinolysis may help explain how weight gain and obesity influence atherothrombosis. Individuals with the insulin resistance syndrome commonly have impaired fibrinolysis and, in the setting of metabolic syndrome. PAI-1 as well as CRP levels predict adverse vascular outcomes in addition to the onset of type 2 diabetes.

Protein C & Protein S deficiency and MI in young

Protein C is a vitamin K-dependent protein, synthesized in the liver, that inactivates coagulation factors Va and VIIIa, which are required to

thrombin generation and factor X activation. This process is strongly supported by protein S activity as cofactor. Moreover Protein C has established anti-inflammatory activity and seems to harbour cytoprotective properties on endothelial cells. It is estimated that congenital protein C deficiency is present in 2 to 5% of patients with thromboembolism. Prevalence of clinically symptomatic deficiencies of protein C in the general population lies between 1:16,000 and 1:36,000 while that of symptomatic protein S deficiency is 1:20,000. Both protein C and S deficiencies are associated with increased risk of developing deep venous thrombosis (risk ratio 8.1 for protein S deficiency and 7.3 for protein C deficiency) and higher risk of recurrent thrombosis, with typically young age of onset and family cluster occurrence. The few available reports of families with combined protein C and S deficiency suggest that both genes segregate independently as an autosomal dominant trait. Although venous system is typically involved (deep veins, pulmonary artery, jugular vein), arterial thrombosis has been reported. Aorta, mesenteric and cerebral arteries can be affected. Patients with C protein deficiency are at potential risk of warfarin induced skin necrosis, and for that we preferred LMWE and dabigatran to vitamin K antagonist.

Hereditary Thrombophilia

Thrombophilia or hypercoagulable state is a clinical condition characterized by a tendency to develop venous and (less frequently) arterial thrombosis. Thrombosis is defined as the obstructive clot formation within a vessel. Since the first observation of Virchow, three major pathogenic causes of thrombosis have been identified: changes in the vessel wall, in the blood

flow and in the blood composition. Although all these mechanisms may contribute to thrombosis, arterial events are mainly determined by changes in the vessel wall, in particular atherosclerosis, while stasis and pro thrombotic blood abnormalities play a major role in venous thrombosis.

Hereditary thrombophilia is a genetically determined increased risk of thrombosis; acquired or secondary thrombophilia is a physiologic or pathologic condition that predisposes affected persons to thromboembolic diseases. Hereditary thrombophilia should be suspected in persons with a family history of thrombosis, especially if the thrombotic events occurred in young patients or when trigger factors are absent or minimal. A congenital or acquired hypercoagulable state should also be suspected in the case of idiopathic recurrent venous thromboembolism (VTE) or in thrombosis involving atypical locations, like upper extremities, visceral veins (hepatic, portal, mesenteric) or cerebral veins. The most common inherited defects include activated protein C resistance caused by the factor V Leiden mutation, the prothrombin gene G20210A mutation and hyperhomocysteinemia. Less common disorders include deficiencies of anti-thrombin, protein C, protein S, plasminogen and dysfibrinogenemias. These thrombophilic defects either enhancing pro coagulant reactions or inhibiting natural anticoagulant mechanisms, promote hypercoagulability. Prevalence of hereditary thrombophilia mentioned in Table 03.

Table 3: hereditary thrombophilia Prevalence

Hereditary thrombophilia	Prevalence (%)
Antithrombin deficiency	1.1
Protein C deficiency	0.5-4
Protein S deficiency	1.3
Factor V Leiden mutation	12-40
Prothrombin gene G20210A mutation	6-18
MTHFR mutation	1.4-15
Factor XII deficiency	2-3
Dysfibrinogenemias, Plasminogen deficiency C	Unknown

Hereditary thrombophilia usually associated with venous thrombosis, but may be associated with arterial occlusion too. In patient with known thromboembolic disorder like deep venous thrombosis (DVT)/ pulmonary thromboembolism (PTE), suffered from MI, then hereditary thrombophilia should be suspected and he should be evaluated for these genetic mutations.

Antiphospholipid syndrome (Hughes' syndrome)

Arterial and venous thrombosis is a prominent feature of this syndrome together with antiphospholipid antibodies and miscarriages of pregnancy. Antiphospholipid antibodies are associated with autoimmune diseases such as systemic lupus erythematosus, but when they occur in isolation, this is known as primary antiphospholipid syndrome. The main antiphospholipid antibodies implicated in thrombosis and atherosclerosis are the anticardiolipin antibody, the lupus anticoagulant, and IgG antibodies against plasma phospholipid-binding proteins such as β2-glycoprotein I and prothrombin.

Cardiac complications include myocardial infarctions and a high prevalence of valvular abnormalities of varying severity. It is postulated that the valvular damage is secondary to repeated thrombosis on normal valves that heal by scarring and valve distortion. There is an association between the presence of antiphospholipid antibodies in patients with intermittent claudication and young adults who survive a myocardial infarction. The mechanism for thrombosis in this syndrome is complex and not well understood. A mild thrombocytopenia is a common finding in antiphospholipid antibody syndrome, though this does not seem to correlate with thrombosis. However, there is in vitro evidence that the anticardiolipin antibody increases platelet adhesiveness. It is possible that the antiphospholipid antibodies predisposesto premature atherosclerosis compounding the risk for infarction with this syndrome.

IMPACT OF AGE (YOUNG VS OLD) IN RISK FACTORS, CLINICAL PRESENTATION, TREATMENT AND OUTCOME OF ACS

Although coronary heart disease (CHD) primarily occurs in patients over the age of 40, younger men and women can be affected. Most studies have used an age cut-off of 40 to 45 years to define "young" patients with CHD .The prevalence of CHD in younger subjects is difficult to accurately establish since coronary atherosclerosis is frequently a silent process. However, about 4 percent of patients with MI are ≤40 years of age. In the Framingham Heart Study of 5127 subjects, the incidence of an MI over a 10 year follow-up was 12.9/1000 in men 30 to 34 years old and 5.2/1000 in women 35 to 44 years old. In contrast, the incidence was eight to nine times greater in men and women aged 55 to 64 years.

According to the National Commission on Macroeconomics and Health (NCMH), there would be around 62 million patients with CAD by 2015 in India, and of these, 23 million would be patients who were younger than 40 years of age.

In one study, it was found that in both the age groups, males were more likely to have AMI than females, the ratio being higher in the younger group (7.8:1) than the older group (2.6:1).

A similar trend in young individuals with AMI was seen in the research done by Siwach SB et al in Haryana, India, where the male to female ratio was 20:1.

Some research papers have reported that elderly AMI patients were most likely to be females compared to young AMI patients.

Although CHD is an uncommon entity in young patients at present, it constitutes an important problem for the patient and the treating physician because of the devastating effect of this disease on the more active lifestyle of young patients. In addition, these patients have different risk factor profiles, clinical presentations, and prognoses than older patients. All of these factors should be taken into consideration when treating young patients with CHD and/or MI.

CORONARY RISK FACTORS —Young patients with MI usually have multiple risk factors for CHD. In some studies, for example as many as 90 to 97 percent patients have one or more traditional risk factors for atherosclerosis. The prevalence of each of these risk factors is also different from that in older patients.

1. **Cigarette smoking**

Cigarette smoking is the most common risk factor, and the most important modifiable risk factor, in young patients. It has been reported in 73 to 90 percent of young patients with MI, compared to 24 to 56 percent in patients older than 45 years of age. Reported prevalence of smoking in young versus old patients with CHD were 70% vs. 22% by Nesligul et al. Another study done by Warrenet al, found 73% of young patients surviving myocardial infarction were smoker.

Another study by chen et al reported 73 % vs 46 % smoking in young adult versus old patients with CHD.

2. **Family history**

A family history of premature CHD is also more common in younger patients. As an example, in one study of 2643 patients, a family history of premature CHD was more common in young patients (less than 45 years) than in middle aged or elderly patients (41 versus 28 and 12 percent, respectively).

A similar difference was noted in the larger Coronary Artery Surgical Study (CASS) (57 versus 43 percent in younger [≤45 years] and older patients, respectively).

3. **Lipid abnormalities**

Hypercholesterolemia is common in young patients with CHD, but its prevalence is similar to that in older patients. However, when compared to older patients, young patients have lower mean serum high density lipoprotein (HDL) concentrations (35 versus 43 mg/dL [0.9 versus 1.1 mmol/LL]) and higher serum triglycerides (239 versus 186 mg/dL) [2.7 versus 2.1 mmol/L].

Hypertriglyceridemia was, in one series, the most common lipid abnormality in young patients with MI. It may be associated with glucose intolerance and a predominance of small atherogenic LDL particles, both of which predispose to atherosclerosis.

In one study dyslipidemia in terms of hypercholesterolemia, hypertriglyceridemia, low HDL and high LDL were found in both young and old groups of CHD patients. While statistically not significant, numerically younger patients were found to have lower HDL levels (44% in male and 67% in female). This result is supported by other studies done by Nesligul et al and Wolfe et al who found dyslipidemia was present in 23% young patients with CHD compared to 17% in older CHD group.

4. **Diabetes and hypertension**

Diabetes mellitus and hypertension are less common in young patients with CHD than in older patients. Young patients commonly have subtle problems with glucose metabolism.

In one study of 108 patients without a history of diabetes mellitus who had an MI before the age of 45, 65 percent had decreased oral glucose tolerance and a hyperinsulinemic response to oral glucose challenge.

In study by Siddique et al 34% of older CHD patients compared to 4% of younger patients were diabetics. Nesligul et al in his study found the prevalence of diabetes to be 23% versus 7.5% in older and younger CHD group respectively. Another study carried out by Wolfe et al also revealed the prevalence to be 26% and 3% in older and younger CHD patients respectively. Thus it implies that diabetes is less likely to have role in pathogenesis of CHD in young patients.

In same study by Siddique et al, Hypertension was more prevalent in older CHD patients(72%) when compared to younger CHD patients (38%)

and the ratio was nearly 2:1. It is much higher than the study done by Nesligul et al [19] in which the prevalence was found to be 47% and 22% in older and younger CHD patients respectively. This difference was not significant in the study done by Chen (38% vs. 25%). Similarly its was found to be 48% in older CHD patients compared to 28% in younger CHD group in the study done by Wolfe et al.

5. **Other factors**:

A variety of other possible contributing factors have been identified in young patients with MI. These include Defective fibrinolytic function, mainly due to elevated plasma plasminogen activator inhibitor-1 (PAI-1) activity. Oral contraceptive use in young women, particularly in combination with smoking. Insulin-like growth factor-I (IGF-I). In one study of young patients who had an MI, serum IGF-I concentrations were directly related to progression of coronary artery disease as assessed by angiography at two and five years after the infarction. Several studies have proposed increased homocysteine level as independent risk factor for young IHD. In study done by Eftychiou C et al it was found that higher levels of homocysteine are associated with acute MI and multi-vessel disease in Cypriot patients under the age of 50.

CLINICAL PRESENTATION

1. **Symptoms**:

The clinical presentation of CHD in young men and women is different from that in older patients. A higher proportion of young patients do not experience angina, and, in the majority of cases, a sudden MI or unstable angina that progresses rapidly to infarction if left untreated is the first manifestation of CHD.

As an example, one study of 200 patients with CHD documented by angiography found that patients ≤45 years of age had a lower incidence of stable angina than patients ≥60 years of age (24 versus 51 percent) and a higher incidence of acute coronary syndromes (76 versus 49 percent).

In one study More than 90% of younger patients presented with chest pain whereas less than 80% of elderly patients presented with chest pain ($p<0.002$). There were significantly more elderly patients presenting with atypical features like shortness of breath or syncope ($p<0.005$).

In similar study Bayer studied a series of 777 unselected elderly hospitalized patients with AMI, Chest pain was less frequently reported with increasing age. Syncope, stroke and acute confusion became more common and were often the sole presenting symptom as found in many other studies.

A study comparing clinical presentation of AMI in elderly with young showed that although chest pain was common mode of presentation in both age group it was less frequent in elderly (66.3% Vs 88.9%).atypical

presentation was seen more common in elderly with shortness of breath as commonest mode of atypical presentation (20.8 % Vs 5.4% , $p < 0.001$).

In another study of 85 patients, less than 40 years old referred for cardiac catheterization and angiography . The first manifestation of CHD was angina in 14 percent and acute MI in 69 percent, two-thirds of whom denied chest pain prior to the infarct. Among those who do have chest pain, the first episodes often occur only in the week prior to MI.

2. **Complications**:

Cardiovascular complications like CCF, atrial fibrillation, cardiogenic shock are less common in younger as compared to old age with ACS which suggests either pre-existing heart disease or decline in cardiac reserve in elder population.

Aging is also associated with decline in heart rate variability which is marker of increased risk of sudden death after MI.

It was also noted that VPCs and A V blocks were less common in younger with MI as compared with old patients.

Cardiac rupture post MI is more common in elderly.

3. **Angiographic findings**

In one study the young age group patient with MI had a higher incidence of normal coronary arteries, mild luminal irregularities, and single vessel coronary artery disease. In one study single or zero vessel disease was seen in 63 % young, 40% middle aged and 23 % elderly patients while

triple vessel disease was noted in 17% young, 27 % middle aged and 33 % elderly patients.

The largest study of angiographic findings in young patients with CHD is from a sub study of the CASS trial, which compared results of coronary angiography in 500 young men and women with a history of an MI to those in 8266 older patients. Normal coronary arteries were more common in the young patients (18 versus 3 percent). Young women had a higher frequency of angiographically normal coronary arteries than young men. Non obstructive coronary disease (≤70 percent stenosis) was more common in younger patients (9 versus 4 percent). Single vessel coronary disease was more common (38 versus 24 percent) and three vessel disease was less common (14 versus 39 percent) in the younger patients as compared with old.

In some series have shown a predilection for involvement of the left anterior descending arterial system in young patients.

In one study in India coronary arteriography profile in 125 young patients (below 40 years) with clinical evidence of ischemic heart disease (IHD) (Group I) and compared it with 125 older patients with IHD (more than 40 years) (Group II) studied during the same period. Left anterior descending coronary artery was the most frequently involved vessel in both the groups, 102/125 (81.6%) in young and 120/125 (96%) in old group (P less than 0.001). The incidence of left main coronary artery involvement was 5/125 (4%) in young and 15/125 (12%) in old Group (P less than 0.05) and coronary artery calcification was 17/125 (13.7%) in young and 72/125 (57.6%) in old Group (P less than 0.001). Triple vessel disease was the most common form

of involvement, 56/125 (44.8%) in Group I and 65/125 (52.8%) in Group II (P = NS). The incidence of diffuse disease was 35/125 (28%) in young's vs 39/125 (31.2%) in old Group (P = NS).Thus left main and left anterior descending coronary artery disease and coronary calcification were more common in the older age group. These findings suggest that in young Indian patients with IHD, multivessel and extensive coronary artery involvement in frequently seen. This pattern of involvement has many features resembling the disease pattern in their older counterparts.

In another study which studied 50 young IHD patient (below 40yrs) and 50 old patients(above 40yrs) it was found that 68% of patients of older group and 38% of younger group had stenosis in left anterior descending artery (p = 0.003). The involvement of left circumflex and right coronary artery in older age group were higher (56% and 66% respectively) than those in younger group (36% and 40% respectively) (p = 0.045 and p = 0.009).

In another report, young patients with an MI were more likely than older patients to have complex coronary lesions (59 versus 36 percent); this may explain the higher likelihood of presenting with an acute coronary syndrome coronary atherosclerosis.

PHYSIOLOGY OF IRON ABSORPTION

Erythropoiesis is a part of the larger process of hematopoiesis. In the normal adult human, the daily turnover of red blood cells (RBCs) exceeds 1011 cells. In periods of increased RBC loss caused by hemolysis or hemorrhage, the production of RBCs increases rapidly and markedly.

However, an overproduction of RBCs (i.e. rebound polycythemia) does not occur even after the most severe loss of RBCs. Thus, erythropoiesis is a finely regulated yet rapidly responsive process that maintains the normal number of circulating RBCs within a narrow range.[42]

The commitment of multipotent hemopoietic stem cells to erythroid progenitors is driven by several growth factors, such as stem cell factor, thrombopoietin, and interleukin (IL)-3.[43] The most immature stage of committed erythroid progenitors is the burst-forming unit-erythroid, which differentiates into colony-forming unit-erythroid (CFU-E) in approximately 7 d, with declining proliferative potential as the progenitors approach CFU-Es. Each CFU-E develops a single cluster of 8-64 mature erythroblasts within 7 d, after several differentiation stages (pro-erythroblast, basophilic erythroblast, polychromatic erythroblast, and orthochromatic erythroblast). Orthochromatic erythroblasts do not divide but they enucleate, and form nascent RBCs, called reticulocytes, which are release into the bloodstream. After 1 d of circulation in the peripheral blood, reticulocytes mature into RBCs.[44] The normal proliferation and differentiation of erythroid progenitor cells require several essential nutrients, such as iron, folate, and vitamin B12, the interaction with the stromal cells in the bone marrow, and stimulation by erythropoietin (EPO).[44]

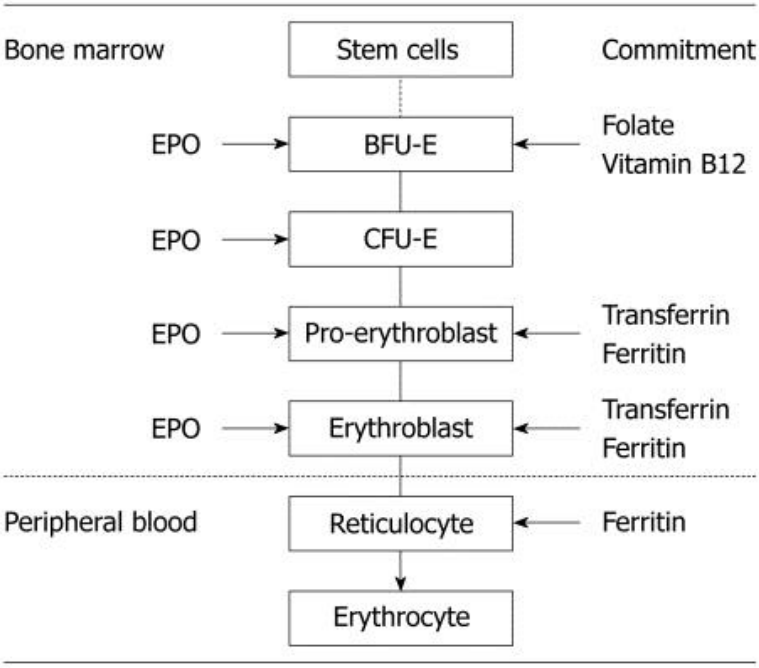


Fig 3 :STAGES OF HUMAN ERYTHROPOIESIS

Major stages of human erythropoiesis showing the point of commitment, the period of EPO dependence and the requirements for essential nutrients. BFU-E: Burst-forming unit-erythroid; CFU-E: Colony-forming unit-erythroid; EPO: Erythropoietin.

IRON HOMEOSTASIS

For a 70-kg male individual, total body iron is about 3.5 g (50 mg/kg). Most of the iron in the body is distributed within RBC hemoglobin (65%; 2300). Approximately 10% is present in muscle fibers (in myoglobin) and other tissues (in enzymes and cytochromes) (350 mg). The remaining body iron is stored in the liver (200 mg), macrophages of the reticuloendothelial system (RES; 500 mg), and bone marrow (150 mg). In premenopausal women, total body iron (especially the stored fraction, 250-300 mg) is lower than in men. The normal diet contains 15-20 mg of iron, and the body absorbs 1-2 mg/d of dietary iron. This is balanced with losses via sloughed intestinal

mucosal cells, menstruation and other blood losses. Therefore, internal turnover of iron is essential to meet the bone marrow requirements for erythropoiesis (20-30 mg/d).[45,46]

On the other hand, the body has no effective means of excreting iron and thus the regulation of absorption of dietary iron from the duodenum plays a critical role in iron homeostasis in the body. This is extremely important as iron is essential for cellular metabolism and aerobic respiration, whilst cellular iron overload leads to toxicity and cell death via free radical formation and lipid peroxidation, thus, iron homeostasis requires tight regulation.[47]

Table 4 : Main proteins involved in iron homeostasis in mammals

Protein name (alternative name)	**Acronyms**	**Function**	**Localization**
Divalent metal transporter 1 (divalent cation transporter 1, NRAMP 1 and 2)	DMT1	Traffics divalent metal ions such as iron, zinc, copper and cobalt across the membrane by a proton coupled mechanism	Enterocyte (apical membrane)
	DCT1		Erythroblast (siderosome)
	NRAMP1*		Macrophage (plasma membrane, phagocytic vesicles*)
	NRAMP2		
			Hepatocyte
			Kidney cells
Ferrireductase	Dcytb	Reduction of Fe^{3+} to Fe^{2+}	Enterocyte (apical membrane)
	STEAP3*		Erythroblast (siderosome*)

Protein name (alternative name)	**Acronyms**	**Function**	**Localization**
Heme carrier protein 1	HCP1	Putative transporter that traffics heme across the membrane by an unknown mechanism	Enterocyte (apical membrane)
			Hepatocyte
			Kidney cells
Heme oxygenase		An enzyme that disassembles heme to liberate iron	Enterocyte (microsomal fraction)
			Macrophages
Ferroportin 1 (Iron regulatory protein 1)	FPN 1	Transmembrane Fe^{2+} transporter (exporter)	Enterocyte (basolateral membrane)
	Ireg1		Macrophages
	MTP1		Hepatocytes
Hephaestin	Hp	Membrane-bound multicopper ferroxidase, similar to plasma ceruloplasmin, which oxidizes Fe^{2+} to Fe^{3+} to load it onto transferrin	Enterocyte (basolateral)
		Maintenance of cell-surface localization of ferroportin	Macrophage
			Hepatocyte?
Transferrin	Tf	Plasma Fe^{3+} binding protein	Plasma
		Ligand for transferrin receptors 1 and 2	
Transferrin receptor 1	TfR1	Cellular uptake of transferrin bound iron	Ubiquitously expressed

Protein name (alternative name)	Acronyms	Function	Localization
Transferrin receptor 2	TfR2	Sensor for diferric transferrin; regulates hepcidin expression; may participate in a signaling complex with HFE	Enterocyte
			Hepatocyte
			Erythroblast
Mitoferrin	SLC25A37	Mitochondrial iron importer that plays a critical role in supplying iron to ferrochelatase for insertion in protoporphyrin IX to form heme	Erythroblast (mitochondria)
Ferritin	Ft	Iron storage protein (H and L chains)	Enterocyte
		Ferroxidase activity (H chain)	Erythroblast
			Macrophage
			Hepatocyte
			Myocytes and cardiomyocytes
Hemosiderin		Iron storage protein; breakdown product of ferritin that occurs when iron levels are high	Macrophage (lysosomes)
			Hepatocytes (lysosomes)
Heme exporters	LFLVCR*	ATP-independent heme export at the cell membrane* ATP-dependent heme export at the cell membrane** and mitochondrial membrane***	Erythroblast*
	Bcrp/Abcg2**		Ubiquitously expressed**,***
	Abcb6***		
HFE	HFE	Regulates hepcidin expression, mechanism uncertain; may participate in a signaling complex with	Enterocyte
			Macrophage

Protein name (alternative name)	Acronyms	Function	Localization
		TfR2; interacts with TfR1 & β-2-microglobulin	Hepatocyte
Hemojuvelin	HFE2	Acts as a BMP co-receptor to stimulate hepcidin transcription	Hepatocytes
Lipocalin 2		Mediates a siderophore-like iron uptake pathway. Its an innate immune response to bacterial infection by sequestrating iron, but its physiologic role in iron absorption is not fully worked out	Enterocytes (apical membrane)
			Macrophages
			Adipocyte
Hepcidin	HEP	Iron regulatory hormones, binds ferroportin to cause its internalization and degradation	Hepatocytes
	HAMP		Adipocytes (low secretion)
	LEAP1		Enterocytes?
Erythropoietin	EPO	Upregulates the expression ferroportin in macrophages, TfR1 in erythroblasts, and DMT1 and hephaestin in enterocytes	Kidney (interstitial peritubular cells)
		Downregulates hepcidin expression in hepatocytes and DMT1 expression in macrophages	Hepatocytes (low secretion)

BMP: Bone morphogenetic protein.

Iron absorption

Nearly all absorption of dietary iron occurs in the duodenum. Several steps are involved, including the reduction of iron to a ferrous state, apical uptake, intracellular storage or transcellular trafficking, and basolateral release. Dietary iron is found in heme (10%) and non-heme (ionic, 90%) forms and their absorption occurs at the apical surface of duodenal enterocytes via different mechanisms. Dietary non-heme iron primarily exists in an oxidized (Fe^{3+}) form that is not bioavailable, and must first be reduced to the Fe^{2+} form by a ferrireductase enzyme, before it is transported across the intestinal epithelium by a transporter called divalent metal transporter 1 (DMT-1), which also transports other metal ions such as zinc, copper and cobalt by a proton-coupled mechanism. There is also a siderophore-like iron uptake pathway mediated by lipocalin-2 (that seems to exert an innate immune response to bacterial infection by sequestrating iron) but its physiological role is not fully worked out.

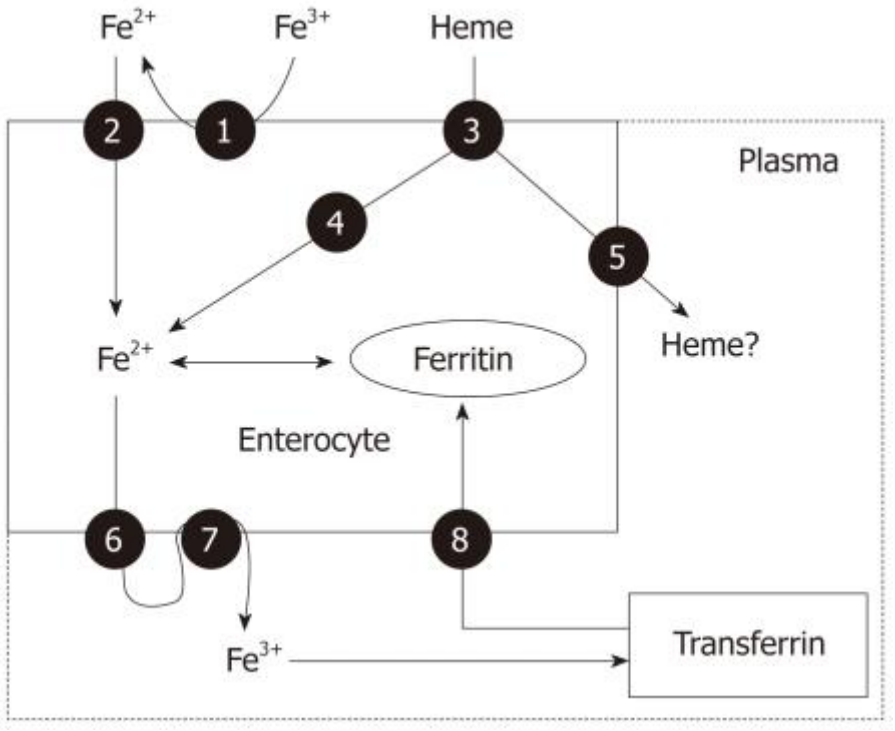


Fig. 4 :MAIN PATHWAYS OF IRON ABSORPTION BY ENTEROCYTES IN MAMMALS

Main pathways of iron absorption by enterocytes in mammals. 1: Ferrireductase; 2: Divalent metal transporter 1 (DMT-1); 3: Heme protein carrier 1 (HPC1); 4: Heme oxygenase; 5: Heme exporter; 6: Ferroportin (Ireg-1); 7: Hephaestin; 8: Transferrin receptor-1 (TfR1)

The absorption of non-heme can be diminished by co-administration of tetracyclines, proton pump inhibitors and antacid medication, phytates (high-fiber diets), calcium, and phenolic compounds (coffee and tea). In addition, infection with Helicobacter pylori (H pylori) produces gastric atrophy that, even in the absence of significant bleeding, can lead to profound iron-deficiency anemia (IDA). As expected, this anemia is poorly responsive to oral iron therapy, but can be corrected by eradication of H pylori infection.[48]

Heme iron is absorbed into enterocytes by a putative, not totally identified heme carrier protein 1, which is a membrane protein found in the proximal intestine, where heme absorption is greatest.[49] Once internalized in the enterocytes, it is likely that most dietary heme iron is released as ferrous iron by heme oxygenase to enter a common pathway with dietary non-heme iron before it leaves the enterocytes. However, it remains uncertain whether some heme might traverse the cells intact, leaving the enterocytes through the action of the recently characterized heme exporters, Bcrp/Abcg2 and feline leukemia virus C receptor (FLVCR). If this does occur, the subsequent disposition of plasma heme is unknown. In addition, it is not yet known whether heme carrier protein 1 has physiological roles in tissues other than the intestine. The protein is also expressed in the kidneys and liver, which suggests that it may act at those sites. It might, for example, scavenge free heme or mediate cellular uptake of heme from its circulating carrier protein, hemopexin.[50]

Once inside the intestinal epithelial cell, iron may either remains in the cell for use or storage (this iron is never absorbed into the body; rather, it is lost when enterocytes senesce and are sloughed into the gut lumen) or exported across the basolateral membrane of the enterocyte into the circulation (absorbed iron). Ferroportin 1 is the only putative iron exporter identified to date. Ferrous iron once exported across the basal membrane by ferroportin 1, is then oxidized by a multi-copper oxidase protein called hephaestin (an enzymatic protein similar to plasma ceruloplasmin) before being bound by plasma transferrin. Ferroportin 1 is also the putative iron exporter in macrophages and hepatocytes.

The absorption of iron is dependent on the body's iron stores, hypoxia and rate of erythropoiesis. Two models have been proposed to explain how the absorption of iron is regulated: the crypt programming model and the hepcidin model.

The crypt programming model: This model proposes that enterocytes in the crypts of the duodenum take up iron from the plasma. The intracellular iron level of the crypt cells corresponds to the body's iron stores, which in turn determines the amount of iron absorbed from the gut lumen, as these crypt cells migrate upwards to become absorptive cells at the brush border. The crypt cells express both transferrin receptor 1 (TfR1) and TfR2, which mediate the cellular uptake of transferrin-bound iron from plasma.

TfR1 is expressed ubiquitously and transferrin mediated iron uptake is thought to occur in most cell types. HFE, an MHC-class 1-like molecule that interacts with β2-microglobulin and forms a complex with TfR1, is highly expressed in crypt cells. Its role in the regulation of TfR1-mediated transferrin-bound iron uptake remains unclear, but it seems to enhance transferrin-bound iron uptake from the plasma into crypt cells via TfR1, and may also inhibit the release of iron from the cell via ferroportin 1. In contrast, TfR2 is restricted to hepatocytes, duodenal crypt cells and erythroid cells, which suggests a more specialized role in iron metabolism. The intracellular iron concentration controls the interaction of cytosolic iron regulatory proteins (IRPs) 1 and 2 with iron regulatory elements (IREs; which act as iron sensors in mammalian cells and regulate translation or stability of mRNA-encoding proteins) in the 3' and 5' regions of different mRNA molecules. In the absence of iron, IRP1 binds to

IREs of TfR1, DMT-1, and ferroportin 1 mRNA, the transcript is stabilized, translation proceeds, and the proteins are synthesized. Thus, a high IRP binding activity reflects low body iron stores and results in upregulation of these proteins in the duodenum and increased dietary iron absorption. When IRPs bind to IRE of ferritin mRNA, translation of the transcript is blocked and synthesis is halted. Thus, ferritin levels are regulated reciprocally - being increased in iron-replete states and decreased in iron-deplete states.[44]

The hepcidin model: Liver hepcidin is a 25-amino-acid cysteine-rich peptide with antimicrobial properties, which is regulated by a number of factors such as liver iron levels, inflammation, hypoxia and anemia. The hepcidin model proposes that hepcidin is secreted into the blood and interacts with villous enterocytes to regulate the rate of iron absorption, by controlling the expression of ferroportin 1 at their basolateral membranes. The binding of hepcidin to ferroportin 1 results in internalization of ferroportin 1 and loss of its function. Ferroportin 1 molecules present in macrophages and liver are also targets for hepcidin. Thus, it is hypothesized that when hepcidin levels are increased in iron overload (by the uptake of transferrin bound iron via TfR1/HFE and TfR2) or inflammation (via IL-6), iron release from intestinal crypt cells, liver and macrophages is reduced. In contrast, when hepcidin levels are reduced, as in iron deficiency (ID), anemia or hypoxia, it is likely that ferroportin 1 expression and iron release from intestinal cells, liver and cells of reticuloendothelial system is increased.[51] In contrast, a mutation in the ferroportin 1 gene is responsible for type IV hemochromatosis.

There is evidence to support both models and it is possible that both control mechanisms may contribute to the regulation of iron absorption. In this regard, there is emerging evidence that hepcidin may act directly on mature villous enterocytes rather than crypt enterocytes. There are several situations (e.g. acute phase response) when iron absorption can be modulated more rapidly (within hours) than can be accounted for via the mechanism that involves the programming and maturation of crypt enterocytes (lag time of days).

Iron distribution

Iron released into the circulation binds to transferrin and is transported to sites of use and storage. Transferrin has two binding sites, binding one iron atom each (thus three forms can be found in plasma: apo-transferrin which contains no iron, monoferric-transferrin and diferric-transferrin). About 30%-40% of these sites are occupied under normal physiological conditions. Thus, transferrin-bound iron is about 4 mg, but this is the most import dynamic iron pool.[52] Transferrin-bound iron enters target cells - mainly erythroid cells, but also immune and hepatic cells- through a process of receptor-mediated endocytosis. As diferric-transferrin has a much higher affinity for TfR than does monoferric-transferrin, it binds to the TfR at the plasma membrane, and patches of cell-surface membrane that carry receptor-ligand complexes invaginate to form clathrin-coated endosomes (siderosomes). After clathrin is removed, the siderosomes become acidified through an ATP-dependent proton influx, which leads to conformational changes in transferrin and TFR1, and promotes iron release of Fe3+ from transferrin. Fe3+ is then reduced to

Fe2+ by a ferrireductase and transported to the cytoplasm through the DMT-1, whereas the TfR is recycled to the cell membrane and transferrin shed back to the circulation[53] (Figure5). Production of hemoglobin by the erythron accounts for most iron use. High-level expression of TfR1 in erythroid precursors ensures the uptake of iron into this compartment. To make heme, iron must again cross an ion-impermeable membrane to enter the mitochondria. The mitochondrial iron importer was recently identified as mitoferrin (also known as SLC25A37), a transmembrane protein that plays a crucial role in supplying iron to ferrochelatase for insertion into protoporphyrin IX to form heme.[53] Recently, different human heme exporters have been identified in erythroblasts, and their activity seems to be essential for erythropoiesis, by transferring heme from the mitochondria to citosol (Abcb6) and removing the excess of heme from the erythroid cells (FLVCR, Bcrp/Abcg2).

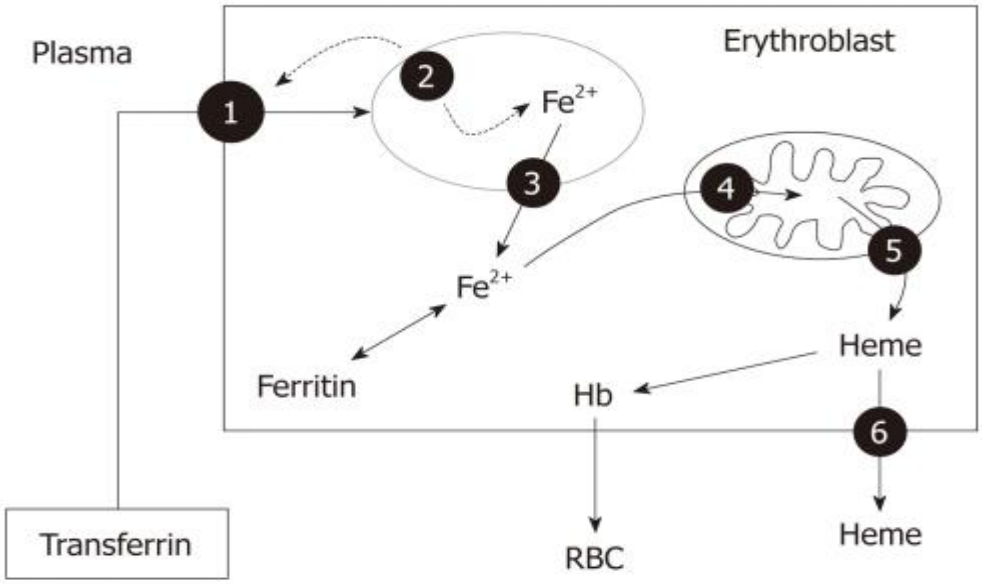


Fig 5 : MAIN PATHWAYS OF IRON UTILIZATION BY ERYTHROBLASTS IN MAMMALS

Main pathways of iron utilization by erythroblasts in mammals. 1: TfR1; 2: Diferric-transferrin-TfR1 complex; 3: Natural resistance macrophage protein (NRAMP-1); 4: Mitoferrin; 5: Mitochondrial heme exporter (Abcb6); 6: Heme exporter (FLVCR, Bcrp/Abcg2)

In the erythroid precursors, the expression of TfR1, DMT-1 and ferritin are regulated reciprocally through IRP1 and IRP2, which act on the IRE present in their RNA. Thus, when increased iron uptake is needed, the expression of TfR1 and DMT-1 is increased, whereas the synthesis of ferritin is halted[3]. In addition, there is evidence that EPO activates IRP-1, leading to upregulation of TfR1 expression in the erythroid precursors, which is maintained along with the differentiation process, and DMT-1 and hephaestin gene expression in the duodenum.[54] To date, three patients have been reported with DMT-1 mutations that cause microcytic hypochromic anemia, as a result of decreased erythroid iron utilization, but lead to increased liver iron storage.[55]

A truncated form of the TfR can be detected in human serum. The serum concentration of this soluble form of TfR (sTfR; normal median concentration: 1.2-3.0 mg/L, depending on the assessment kit used) is proportional to the total amount of surface TfR. Increased sTfR concentrations indicate ID even during the anemia of chronic disease (ACD), as well as increased erythropoietic activity without ID, whereas lower sTfR concentrations may reflect decreased numbers of erythroid progenitors.[56]

Iron storage

Hemoglobin iron has substantial turnover, as senescent erythrocytes undergo phagocytosis by RES macrophages. Within the phagocytic vesicles, heme is metabolized by heme oxygenase and the released iron is exported to the cytoplasm through the action of natural resistance-associated macrophage protein-1, a transport protein similar to DMT-1. Macrophages can also obtain iron from bacteria and apoptotic cells, from plasma through the action of DMT-1 and TfR1, and from other sources. Within the cell, iron can be stored in two forms: in the cytosol as ferritin and, after breakdown of ferritin within the lysosomes, as hemosiderin. Hemosiderin represents a very small fraction of normal body iron stores, mostly in macrophages, but increases dramatically in iron overload. Iron export from macrophages to transferrin is accomplished primarily by ferroportin 1, the same iron-export protein expressed in duodenal enterocytes, and hephaestin. The amount of iron required for daily production of 300 billion RBCs (20-30 mg) is provided mostly by recycling iron by macrophages[4]. Importantly, iron storage at the macrophages is safe, as it does not lead to oxidative damage. EPO reduces iron retention in macrophages by decreasing DMT-1 and increasing ferroportin 1 expression.[57]

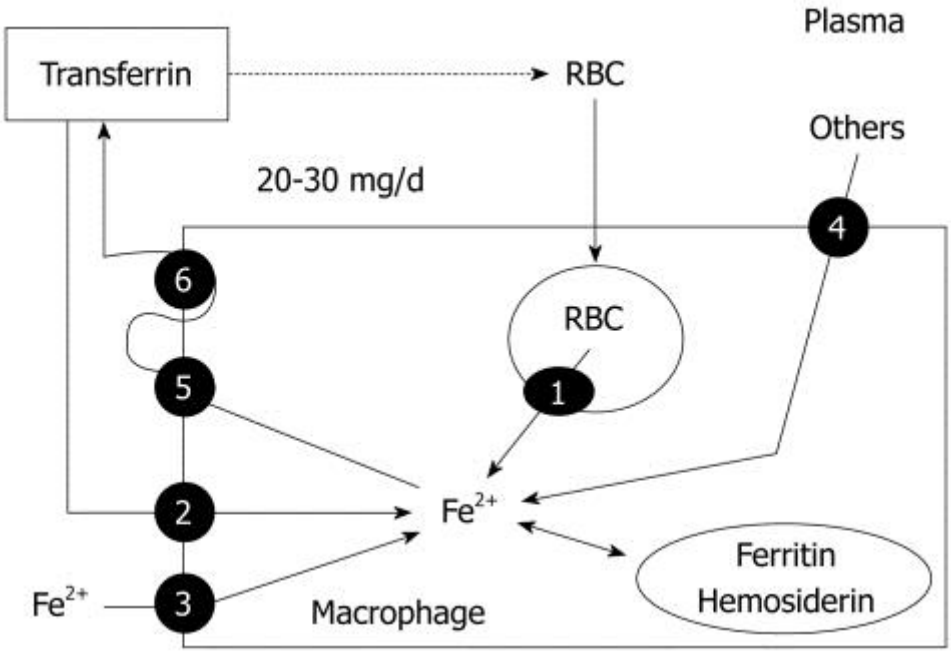


Fig. 6 : MAIN PATHWAYS OF IRON STORAGE AND EXPORTATION BY MACROPHAGES IN MAMMALS

Main pathways of iron storage and exportation by macrophages in mammals. 1: NRAMP-1; 2: TfR1; 3: DMT-1; 4: Others: others: bacteria, lactoferrin, hemoglobin-haptoglobin, heme-hemopexin; 5: Ferroportin (Ireg-1); 6: Hephaestin.

The liver is the other main storage organ for iron. In iron overload, free radical formation and generation of lipid peroxidation products may result in progressive tissue injury and eventually cirrhosis or hepatocellular carcinoma.[58] Iron is sequestrated in hepatocytes predominantly in the form of ferritin or hemosiderin. The uptake of transferrin-bound iron by the liver from plasma is mediated by TfR1 and TfR2. In iron overload, TfR1 is downregulated in hepatocytes. TfR2 is expressed highly in human liver and is likely to play an important role in liver iron loading in iron overload states. Unlike TfR1, TfR2 lacks an IRE and thus is not regulated reciprocally in

response to the level of plasma iron. Instead, TfR2 protein expression is regulated by transferrin saturation (TSAT), and is upregulated in iron overload. In normal and iron-loaded conditions, expression of TfR2 exceeds that of TfR1, which suggests that TfR2 plays an important role in hepatic iron loading in hemochromatosis. In fact, a mutation in TfR2 is responsible for type 3 hemochromatosis.[55]

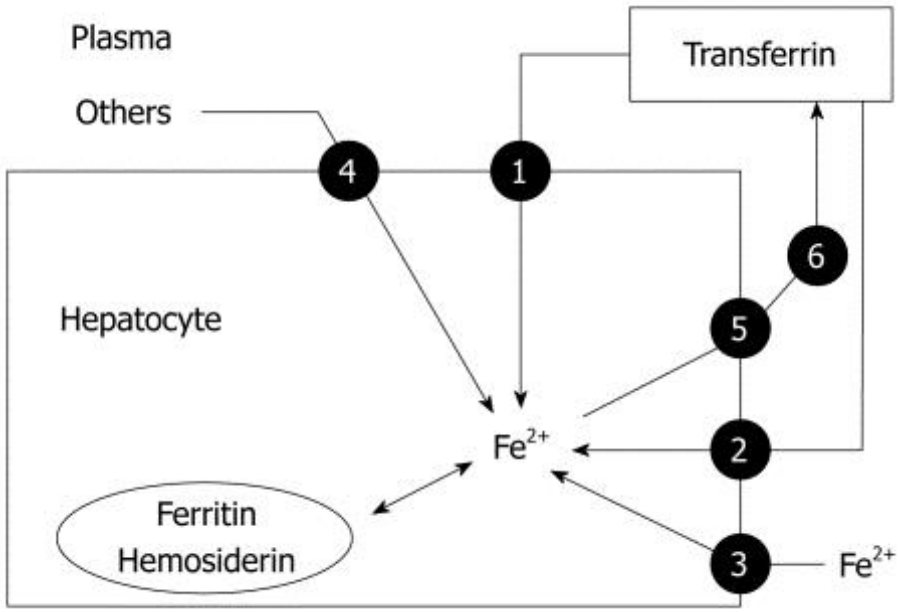


Fig 7 : MAIN PATHWAYS OF IRON STORAGE AND EXPORTATION BY HEPATOCYTES IN MAMMALS

Main pathways of iron storage and exportation by hepatocytes in mammals. 1: TfR1; 2: TfR2; 3: DMT-1; 4: Others: hemoglobin, heme, ferritin; 5: Ferroportin (Ireg-1); 6: Ceruloplasmin.

As transferrin becomes saturated in iron overload states, excess iron is also found as non-transferrin-bound iron is transported across the hepatocyte membrane via a carrier-mediated process consistent with DMT-1. The hepatocytes may also store iron from ferritin, hemoglobin-haptoglobin

complexes, and heme-hemopexin complexes. In contrast, once again, ferroportin 1 is likely to be the only protein that mediates the transport of iron out of hepatocytes, which is then oxidized by ceruloplasmin and bound to transferrin.

Iron storage within cardiomyocytes is also of outstanding interest, as cardiac failure is the leading cause of death among patients with untreated hereditary hemochromatosis or transfusion-associated hemosiderosis. In cardiac cells, excess iron may result in oxidative stress and alteration of myocardial function because of DNA damage by hydrogen peroxide through the Fenton reaction.

EFFECTS OF INFLAMMATION ON IRON HOMEOSTASIS AND ERYTHROPOIESIS

Anemia is a frequent complication of chronic inflammatory diseases (e.g. cancer, rheumatoid arthritis, inflammatory bowel diseases, and congestive heart failure), as well as sepsis and chronic renal failure. In addition to blood loss, hemolysis, hepatic or endocrine disorders, nutritional deficiencies, bone marrow infiltration (cancer cells), or vitamin consumption (bacteria), this anemia may be the result of activation of the immune system by the underlying process, and certain immune and inflammatory cytokines including tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and IL-1, 6, 8 and 10.[59,60]

As for chronic inflammatory diseases (and sepsis), these inflammatory mediators lead to anemia through several of the following pathophysiological mechanisms: (1) decreased RBC half-life because of dyserythropoiesis, RBC

damage and increased erythrophagocytosis (TNF-α); (2) EPO responses are inadequate for the degree of anemia in most, but not all (e.g. systemic-onset of juvenile chronic arthritis) (IL-1 and TNF-α)[20]; (3) impaired responsiveness of erythroid cells to EPO (IFN-γ, IL-1, and TNF-α); (4) inhibited proliferation and differentiation of erythroid cells (IFN-γ, IL-1, TNF-α, and α-1-antitrypsin); and (5) pathological iron homeostasis caused by increased DMT-1 (IFN-γ) and TfR (IL-10) expression in macrophages, reduced ferroportin 1 expression (IFN-γ and IL-6-induced high hepcidin levels) in enterocytes (inhibition of iron absorption) and macrophages (inhibition of iron recirculation), and increased ferritin synthesis (TNF-α, IL-1, IL-6, IL-10) (increased iron storage). All these lead to hypoferremia through iron diversion to the RES [functional iron deficiency (FID) that is characterized by low serum iron and decreased TSAT], iron-restricted erythropoiesis, and mild-to-moderate anemia.

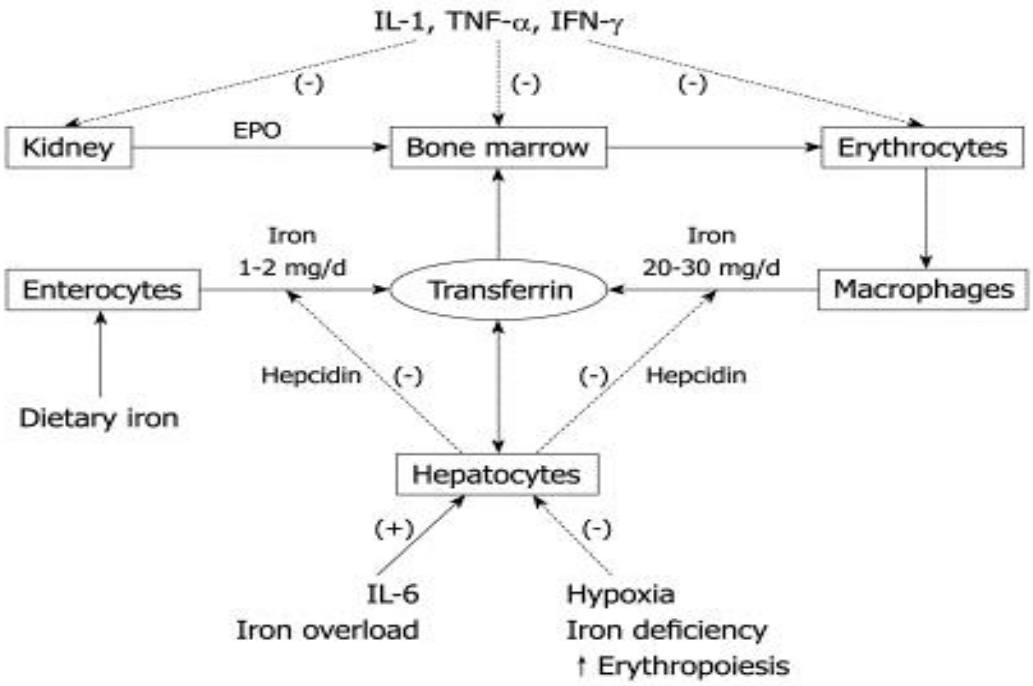


Fig 8 : EFFECTS OF INFLAMMATION ON ERYTHROPOIESIS AND IRON HOMEOSTASIS IN MAMMALS

Effects of inflammation on erythropoiesis and iron homeostasis in mammals. (-): Negative effect; (+): Positive effect.

Thus, the immunological pathophysiology of ACD includes disturbances of iron homeostasis, impaired proliferation of erythroid progenitor cells, and a blunted EPO response to anemia. However, the pathophysiology of acute inflammation-related anemia (e.g. trauma or surgery) is somewhat different. In this setting, inflammatory responses are mediated mainly by IL-6 and IL-8 (with transient contribution of TNF-α and IL-1 in some visceral surgery, such as gastrointestinal or cardiac procedures), whereas IFN-γ plasma levels are undetectable or within the normal range.[61-64] Therefore, in most of these conditions, the two major mechanisms that lead to anemia are perioperative or traumatic blood loss and blunted erythropoiesis caused by decreased iron availability (caused by IL-6-induced high hepcidin levels), whereas EPO levels are normal or near-to-normal.[65] Finally, with persisting decreased iron absorption and/or chronic blood loss, ACD may evolve to ACD with true ID (ACD + ID).

On the other hand, it must be borne in mind that iron is not only required for erythropoiesis and oxidative metabolism. Cellular immune responses are also dependent on the presence of iron, and specific defects in cell-mediated immunity have been described in detail, even in mild ID, including the impaired proliferation and function of lymphocytes and natural killer cells, and a depressed neutrophil respiratory burst.[66,67] Thus, ID or FID may lead not only to a blunted erythropoiesis and chronic fatigue, but also to an inappropriate immune response. For this reason, systemic inflammatory

response episodes last longer in critically ill patients with FID, and result in prolonged stay in the intensive care unit and increased morbidity.[68] On the other hand, the effectiveness of the administration of iron sucrose, alone or in combination with EPO, has been assessed in a population of anemic, critically ill patients. Compared to those in the control group who only received folic acid, patients treated with iron sucrose experienced an amelioration of systemic inflammatory response [decreased C-reactive protein (CRP) levels]. These beneficial effects were not as evident in patients who received iron sucrose plus recombinant human EPO (rHuEPO), probably because of the persistence of FID caused by rHuEPO-enhanced erythropoietic activity.

LABORATORY ASSESMENT OF IRON STATUS

Under physiological conditions, there is a balance between iron absorption, iron transport and iron storage in the human body. However, ID and IDA are common conditions among medical, surgical and critically ill patients, and result from the interplay of three distinct risk factors: increased iron requirements [e.g. growth or use of erythropoiesis-stimulating agents (ESAs), pregnancy and post-bleeding recovery], limited external supply (e.g. malnutrition, malabsorption caused by inflammatory bowel disease, use of gastric antiacid agents, infection with H pylori, even in the absence of significant bleeding), and increased blood loss (e.g. chronic gastrointestinal bleeding).[69] ID can be either absolute or functional. In absolute ID, iron stores are depleted; in FID, iron stores, although replete, cannot be mobilized as fast as necessary from the macrophages of the RES to the bone marrow. As

stated above, FID occurs in anemia of inflammatory diseases because iron is trapped in the RES.[70]

Thus, laboratory tests for investigating ID fall into two categories: measurements providing evidence of iron depletion in the body, and measurements reflecting iron-deficient RBC production[30]. The appropriate combination of these laboratory tests will help to establish a correct diagnosis of anemia and ID status.

Iron is an essential micronutrient, as it is required for an adequate erythropoietic function, oxidative metabolism and cellular immune response. Although the absorption of dietary iron (1-2 mg/d) is regulated tightly, it is just balanced with losses. Therefore, internal turnover of iron is essential to meet the requirements for erythropoiesis (20-30 mg/d). Hepcidin, which is primarily made in hepatocytes in response to liver iron levels, inflammation, hypoxia and anemia, is the main iron regulatory hormone for iron absorption and recirculation. Increased iron requirements, limited external supply, and increased blood loss may lead to ID and IDA. During inflammation, the excess of hepcidin decreases iron absorption and prevents iron recycling, which results in hypoferremia and iron-restricted erythropoiesis, despite normal iron stores, and finally, in ACD, which can later evolve to ACD + ID. An appropriate combination of laboratory tests that provides evidence of iron depletion or reflects iron-deficient RBC production will help to establish a correct diagnosis of ID status and anemia.[71]

Body Iron Stores and Coronary Heart Disease

Over the past 20 years, the hypothesis that body iron stores are associated with risk of coronary heart disease (CHD) has generated extensive debate.[13,72-74] This debate has intensified in the last 4 years after reports from three studies that carriers of the recently discovered HFE C282Y mutation commonly seen in hereditary hemochromatosis have significantly increased risk of CHD.[75-79] Clinical trial has recently been proposed as the ultimate resolution to assess protective effects of iron depletion against CHD among C282Y heterozygotes. In this issue of Clinical Chemistry, Bozzini et al.[80] show that neither a biochemical marker (serum ferritin) nor a genetic marker (C282Y carrier status) of body iron stores was significantly associated with angiographically documented coronary atherosclerosis.

Do increased body iron stores increase risk of CHD? Are individuals who are heterozygotes for the common C282Y mutation at especially high risk of CHD? Can iron depletion reduce the risk? These questions have important implications given the common practice of fortification of food and supplements with iron in industrialized countries and the high frequency of HFE C282Y carriers (~9% of them are of northern European descent).[81] Moreover, the “Oxidative Stress Theory” suggests that iron, as a potent catalytic agent, could promote formation of highly reactive oxygen species and lipid peroxidation, a crucial step in atherosclerosis (4). Thus, evaluation of the iron hypothesis for CHD will lead to advances in our understanding of its pathogenesis. To date, conflicting results have been reported from

epidemiologic studies[82,83,84] conducted in different countries and populations using different biochemical and genetic markers of body iron stores.

Among biochemical markers of iron stores, serum ferritin is generally considered the best measure that can be readily assessed in epidemiologic studies. Nine of the 11 cross-sectional or case-control studies [including the study of Bozzini et al.][80] reported no association between serum ferritin and CHD or atherosclerosis, with the exception of the Italian Bruneck Study [32] and a study of young Iranian male CHD patients.[85] All of these studies evaluated serum ferritin among patients with CHD, but ferritin, an acute-phase protein, can be increased by myocardial damage and inflammation.[86] A positive association could therefore be biased by post-myocardial infarction damage and inflammation. Chronic inflammation (as measured by fibrinogen, C-reactive protein, albumin, leukocytes, and erythrocyte sedimentation rate) has consistently been found to be associated with increased CHD risk.[87] In the present Italian study of Bozzini et al. serum C-reactive protein, but not ferritin, was significantly higher among CHD patients than the CHD-free controls, although the two markers were significantly correlated with each other. On the other hand, the lack of an association with serum ferritin in a case-control study could also reflect bias by factors related to treatment, such as aspirin, or behavioral changes, such as a healthy diet or increase in exercise.

Prospective cohort studies measure biomarkers using blood samples collected before the disease is diagnosed. Because CHD patients are prospectively ascertained and CHD-free controls arise from the same cohort, many potential biases can be avoided. Eight prospective cohort studies have

reported results for the relationship of serum ferritin with risk of CHD or atherosclerosis; only two found a significant positive association.[33] The first positive finding was based on the Finnish Kuopio Ischemic Heart Disease Risk Factor Study (KIHD)[12,16] in men, which reported a twofold increased risk of CHD (a total of 83 incident cases) among men with serum ferritin >200 µg/L. The other was based on the Italian Bruneck Study[33] and found a positive association between serum ferritin and ultrasound measures of progression of carotid atherosclerosis over a 5-year follow-up period. The Bruneck Study presented results on the basis of a combined sample of men and women that is hard to interpret given the large gender difference in ferritin concentrations. Transferrin saturation percentage is the most widely used indicator for screening iron overload. However, none of the five cohort studies assessing transferrin saturation reported increased risk of CHD.[82]

In addition to assessing the effect of iron overload, several recent studies have specifically addressed the hypothesis that “iron depletion” is associated with lower risk of CHD. In a recent prospective analysis of the second National Health and Nutrition Examination Study, Sempos et al.[83] observed either no association (in Caucasian men) or a possible nonsignificant increased risk (in Caucasian women) of cardiovascular or CHD death among individuals with low ferritin concentrations. In the current study, the observed higher prevalence of iron depletion in CHD-free vs CHD women was mainly explained by age and other CHD risk factors. In addition to the use of biomarkers, the comparison of blood donors with nondonors appears to provide a good test of the iron-depletion hypothesis because of the marked contrast in body iron stores of regular donors compared with those of

nondonors. However, of three published studies on blood donation,[34,88] only the Finnish KIHD study found a significant inverse relation with CHD.

Hereditary hemochromatosis causes progressive accumulation of iron in most tissues and has been used as a “human model” to evaluate the effect of marked iron overload on CHD. Autopsy or mortality studies have consistently shown that atherosclerosis, CHD, stroke, and peripheral artery disease are neither prominent clinical features nor frequent causes of death in clinically diagnosed hemochromatosis patients. Because most of these studies included patients with severe iron overload, individuals with moderate iron overload were not represented.

The recent discovery of the HFE gene mutation provides a new opportunity to address the iron hypothesis. Of the two common mutations of the HFE (C282Y and H63D), C282Y carrier status has recently been associated with significantly increased risk of CHD incidence or cardiovascular mortality in three cohort studies. The first study was from a subgroup of the original Finnish KIHD cohort. Eight (11.8%) of 68 individuals diagnosed with acute myocardial infarction and 77 (6.7%) of 1150 non-CHD participants were carriers of C282Y. The crude relative risk of myocardial infarction was 2.0 [95% confidence interval (CI), 0.9–4.1), and the adjusted relative risk was 2.3 (95% CI, 1.1–4.8). In a cohort of 12 239 Dutch postmenopausal women, the C282Y carrier status was assessed among 531 (57 carriers; 10.7%) women who died of cardiovascular disease and 555 (43 carriers; 7.7%) randomly selected women who did not die of cardiovascular disease (6). This study reported a 1.5-fold increased risk of myocardial

infarction death (95% CI, 0.9–2.5), a 2.4-fold increased risk of cerebrovascular death (95% CI, 1.3–4.4), and a relative risk of 1.6 (95% CI, 1.1–2.4) for total cardiovascular death. However, the numbers of C282Y carriers in the cause-specific subgroups were not given. In this study, a subgroup analysis suggested that C282Y heterozygotes who were both smokers and had hypertension had a strongly increased risk of cardiovascular death (relative risk, 18.9; 95% CI, 8.4–42.4). The wide CI reflects the small number of deaths in the smoker/hypertensive category; further study is needed to confirm or refute this finding. The third study, the United States Atherosclerosis Risk in Communities study , reported a C282Y carrier frequency of 9.9% among 243 CHD cases and 6.1% among 535 selected noncases. The crude relative risk of CHD associated with C282Y carrier status was 1.6 (95% CI, 0.9–3.0) and was 2.7 (95% CI, 1.2–6.0) after controlling for other risk factors, especially lipid concentrations. In addition to the current study by Bonzini et al.[80] all six previous case-control studies reported no association between atherosclerosis or cardiovascular events and heterozygosity for HFE C282Y.[89-94] Although survival bias could not be ruled out in all these case-control studies, the three prospective studies did not specifically report a stronger impact of C282Y heterozygosity on fatal CHD.

It has been reported that heterozygotes for hereditary hemochromatosis have slightly but significantly increased serum ferritin and serum iron.[95] However, it remains uncertain whether heterozygotes of C282Y indeed have increased iron stores because some studies, including the Finnish KIHD study and the study in this issue, found that serum ferritin concentrations were not correlated with C282Y carrier status. One recent

study[96] suggested that non-transferrin-bound iron or low-molecular weight iron is increased in circulation of C282Y heterozygotes, leading to higher transferrin saturation. However, transferrin saturation was not associated with increased risk of CHD in epidemiologic studies as discussed previously. Moreover, in all three cohort studies and seven case-control studies of HFE mutation and CHD risk, the numbers of individuals homozygous for C282Y were too small to evaluate a gene-dose effect, and a larger study is needed to address this issue.

In summary, the totality of available evidence from a variety of studies using different measures of body iron stores (ranging from blood donation, biochemical and genetic markers to hemochromatosis patients) do not provide persuasive evidence to support the iron hypothesis, although further studies are warranted. The majority of HFE heterozygotes have distributions of iron storage indicators that overlap substantially with controls. The potential influence of nongenetic factors (such as gender, chronic blood loss, regular blood donation, excessive iron intake, or other dietary modifiers that increase or decrease iron stores) on phenotype expression needs to be carefully evaluated. Previously published studies either lacked comprehensive nongenetic information or were too small to examine gene-environment interactions. A larger comprehensive prospective study or a pooled analysis of existing genetic studies might provide a more coherent picture before a large and expensive trial of genetic screening and iron depletion can be seriously entertained.

ASSESSMENT OF IRON OVERLOAD:

Estimation of the iron overload at regular intervals is essential as it provides a guide towards the dose regulation of the chelation drugs. The various methods are classified as invasive and non-invasive.

INVASIVE METHODS:

a) Biopsy:
   i] Endomyocardial biopsy
   ii] Hepatic biopsy
b) Hepatic iron concentration
c) Serum Ferritin levels

NON-INVASIVE METHODS:

a) Magnetic Susceptometry (SQUID- superconducting quantum interference device)
b) Cardiac MRI

Endomyocardial Biopsy:

It is done via a percutaneous internal jugular vein approach, using a 7-F bioptome. According to percentage of myocytes involved, the severity of iron overload is classified into 4 stages as follows:[97]

Table 5 : Severity of myocardial iron overload with percentage of myocytes involved

Grade	Percentage of Myocytes Involved
1	< 25%

2	25 to 50 %
3	50 to 75 %
4	> 75%

Hepatic Biopsy:

Percutaneous biopsy from the centre of the right lobe of the liver is under ultrasound guidance.[98] The progression of fibrosis or the activity of hepatitis; are some of the histopathological parameters which are assessed. Absorption spectrophotometry is used to measure the hepatic iron concentration.

Hepatic Iron Concentration:

Hepatic iron concentration (HIC) is the most useful method for estimating iron load in chronically transfused patients.[99-101] However, while the method is generally safe, it requires a liver biopsy and an undefinable risk of morbidity (and rarely of mortality) is reported.[102] Thus alternative procedures for detecting iron load in the body in order to make proper decisions concerning chelation therapy are warranted. Attempts to correlate serum ferritin with HIC have failed to demonstrate a linear relationship between the two parameters[103] and discrepancies have frequently been observed.

Serum Ferritin Levels:

A diagnosis of iron overload using serum ferritin requires serial measurements and/or combination with other indicators of iron overload.

Nevertheless, this practical and inexpensive method can provide valuable information with regard to dynamic trends in iron levels over time.

Maintaining serum ferritin levels < 2,500 µg/L reduces the risk of cardiac complications, but a target value of ≤ 1,000 µg/L is recommended. Serum ferritin is not as reliable as liver iron concentration (LIC) for estimating total body iron stores, as serum ferritin levels are affected by common processes, such as:[104]

- Infection
- Inflammation
- Vitamin C deficiency
- Oxidative stress

In patients requiring regular blood transfusions, maintaining serum ferritin < 2,500 µg/L reduces the risk of cardiac complications, but a target value of ≤ 1,000 µg/L is recommended.[105]

However, estimation of serum ferritin as a marker of iron overload has certain advantages and disadvantages.[106]

Advantages:

- Inexpensive and easily measured
- Allows for frequent monitoring
- Positive correlation with morbidity and mortality

Disadvantages:

- Indirect measurement of iron burden
- Requires serial measurements and/or combination with other indicators of iron overload
- Levels are influenced by many factors, including infection and inflammation.

Magnetic Susceptometry (SQUID - superconducting quantum interference device):

The amount of magnetization is measured by our instrument, called a superconducting quantum interference device (SQUID) susceptometer. In patients with iron overload, our previous studies have shown that magnetic measurements of liver iron in patients with iron overload are quantitatively equivalent to biochemical determinations on tissue obtained by biopsy. The safety, ease, rapidity, and comfort of magnetic measurements make frequent, serial studies technically feasible and practically acceptable to patients.[107]

Other studies have focused on evaluating whether magnetic susceptometry (SQUID) could be proposed as a substitute for HIC in monitoring iron in the liver and in other tissues, but convincing results were obtained only in cases where hepatic iron levels were five times greater than the normal upper limit.[108-111] With the aim of contributing to the general understanding of iron overload in thalassemia, hepatic iron levels may be studied by MRI, liver biopsy and HIC in most cases. Biopsy and HIC data may be compared with serum ferritin; in addition, a correlation between qualitative MR images and serum ferritin may be attempted.

Pathophysiology of Iron Overload & Toxicity:

Iron is sequestered within intracellular lysosomes in the form of ferritin, which subsequently degrades into hemosiderin. When this storage mechanism becomes saturated or compromised, free iron levels increase within the cells, causing oxidative damage through the production of hydroxyl radicals.[112] Tissue damage in the myocardium causes conduction

disturbances and left ventricular hypertrophy. The resulting cardiac complications, including ventricular arrhythmias and congestive heart failure, remain the leading cause of death in patients with thalassemia major.[113] To minimize myocardial injury, transfusion-dependent patients must undergo lifelong chelation therapy and periodic monitoring of iron burden.[114]

Holay MP et al in 2012[115] in a hospital based case-control study assessed the relationship of serum ferritin with acute myocardial infarction (AMI) in univariate and multivariate analysis and to assess the relationship of high serum ferritin with established conventional risk factors. The authors found Median serum ferritin levels were significantly higher in cases (220 µg/L) than controls (155 µg/L) ($P \leq 0.0001$. In univariate analysis in addition to ferritin > 200 µg/L (odds ratio [OR] 6.71, 95% confidence interval [CI] = 3.22–12.89, $P<0.05$), diabetes (OR=7.68, 95% CI=2.95–19.13, $P<0.05$), hypertension (HTN) (OR=2.36, 95% CI=1.02–5.14, $P<0.05$) high-density lipoprotein (HDL) < 35 mg/dL (OR = 11.9, 95% CI = 2.66–52.57, $P<0.05$) and smoking (OR=2.17, 95% CI = 1.12–3.87, $P< 0.05$) were found to be significantly associated with AMI. After controlling for all conventional risk factors, in multiple logistic regression analysis, high ferritin was significantly associated with AMI. (adjusted OR=5.72, 95% CI=2.16–15.17, $P < 0.001$). Serum ferritin was significantly higher in diabetics than non-diabetics ($P < 0.01$). The authors concluded that High serum ferritin is strongly and independently associated with AMI.

Morad R et al in 2013[116] in a cross-sectional study determined the relationship between serum iron and ferritin with AMI and its role on early

coronary vessels disorder. The authors found There were significant difference ($p < 0.00001$) between the mean iron and ferritin levels in male group compared to healthy men (173.6 ± 31.4 vs. 115.3 ± 28.5 µg/dl ($p < 0.00001$) and 196.6 ± 94.2 vs. 82.7 ± 61.7 µg/L, respectively). There were significant difference ($p < 0.00001$) between the mean iron and ferritin levels in the female group compared to healthy women, (112.2 ± 38.3 vs. 78.4 ± 33.1 µg/dl ($p < 0.00001$) and 140.7 ± 85.6 vs. 77.5 ± 69.3 µg/L ($p < 0.00001$), respectively).

Shipra G et al in 2014[117] studied the relation of lipid profile and Serum Ferritin with myocardial infarction (MI). The authors found Mean ± SD of TC level was 250.64 ± 25.61, of HDL-c was 36.52 ± 2.86, of LDL-c was 165.69 ± 26.80, of VLDL-c was 42.35 ± 8.53 and of TG was 211.83 ± 42.65 in study group while these values were 174.46±47.68, 43.2±12.52, 98.37±41.13, 32.88±21.45 and 164.42±107.29 respectively in control group. All the parameters were found not only raised in patients of acute myocardial infarction (AMI) but were also statistically significant when compared with control group ($p=<0.01$). Mean ± SD of SF levels was 268.43±30.17 ng/ml in study group and 110.96±56.5 ng/ml in control group; this level was found not only raised in patients of AMI but were also statistically significant when compared with control group ($p=<0.01$). The authors concluded that 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. It can be concluded that there exists an association in lipid profile and SF with AMI therefore dyslipidemia and raised SF levels are the features of AMI.

Ishran R et al in 2016[118] in a hospital based case control analytic study determined the difference in serum ferritin level among Acute Myocardial Infarction (AMI) patients and healthy subjects. The authors found Mean serum ferritin was higher in MI patients (202.1±81.2 µg/L) as compared to controls (135.4±90µg/L), and this difference was statistically significant ($p<0.001$). ROC curve analysis found that Serum ferritin level more than was145 µg/L was a good predictor of AMI with Sensitivity 74% and specificity 68%. The authors concluded that Body iron (serum ferritin) was found to significantly higher in AMI and was a good predictor of AMI. They can be used as a simple and economical method for predicting an impending acute coronary event

Lokary V et al in 2016[119] in a cross-sectional comparative study evaluated iron status in cases of acute MI (AMI) (ST-elevated MI [STEMI] and non-STEMI [NSTEMI]). The authors found Mean serum ferritin and iron levels were significantly increased in case of AMI when compared with healthy participants. The authors concluded that Serum ferritin and iron levels were increased in AMI and the increase was more pronounced in patients with STEMI.

Gill D et al in 2017[120] in a Mendelian randomization technique investigated whether there was any causal effect of iron status on risk of coronary artery disease (CAD). The authors found evidence of a protective effect of higher iron status on CAD risk (iron odds ratio, 0.94 per SD unit increase; 95% confidence interval, 0.88-1.00; P=0.039; transferrin saturation odds ratio, 0.95 per SD unit increase; 95% confidence interval, 0.91-0.99;

P=0.027; log-transformed ferritin odds ratio, 0.85 per SD unit increase; 95% confidence interval, 0.73-0.98; P=0.024; and transferrin odds ratio, 1.08 per SD unit increase; 95% confidence interval, 1.01-1.16; P=0.034). The authors concluded that Mendelian randomization study supported the hypothesis that higher iron status reduces CAD risk. These findings may highlight a therapeutic target.

Kadoglou NPE et al in 2017[121] in a English Longitudinal Study of Ageing investigated the sex-specific associations of ferritin levels with all-cause and cardiovascular mortality in a population-based cohort. The authors categorized ferritin in sex-specific quartiles. In men, the following categorization was done: lowest (2-69ng/ml), second lowest (70-118ng/ml), second highest (reference category) (119-193ng/ml) and highest (194-598ng/ml) ferritin quartiles. In women, ferritin was categorized as follows: lowest (2-44ng/ml), second lowest (45-73ng/ml), second highest (reference category) (74-115ng/ml) and highest (116-341ng/ml) ferritin quartiles. 841 deaths of which 262 cardiovascular disease-related were recorded over a mean follow-up time of 7.7 years. Risk for all-cause mortality was found increased in men with hyperferritinemia (194-598ng/ml) and no history of major chronic diseases compared with the reference group [fully-adjusted HR: 1.49 (95%CI 1.03–2.16)]. Among women, those in the lowest ferritin quartile (2-44ng/ml) had increased risk for all-cause mortality [fully-adjusted HR: 1.59 (95%CI 1.18–2.13)] compared with the reference group after adjustment for all covariates. Regarding cardiovascular mortality, the authors observed a positive association with ferritin levels in men, which was blunted after adjustment for inflammatory markers and lifestyle parameters. Men with no

major chronic diseases who were in the highest ferritin quartile had a significantly increased risk of cardiovascular mortality. No association between ferritin levels and cardiovascular mortality was detected in women. The authors concluded that Circulating ferritin levels showed sex-specific prognostic patterns. High ferritin levels in men with no major chronic disease and low ferritin levels in all women were associated with increased all-cause mortality after adjusting for covariates. High ferritin levels in men with no major chronic diseases were also independently associated with an increased risk of cardiovascular mortality. Future research is needed to clarify the prognostic role of ferritin.

MATERIAL AND METHODS

Study design: A total of 200 patients (100 cases and equal number of controls) were enrolled in a case control study to assess the levels of serum ferritin in acute myocardial infarction.

Study Site: BLDEU'S Shri B. M. Patil Medical college Hospital and Research Centre, Vijayapur.

Study population: Patients admitted to BLDEU'S Shri B. M. Patil Medical college Hospital and Research Centre, Vijayapur with acute myocardial infarction.

Study duration: The study was carried out for a period of October 2015 to January 2018.

Sample size:

In a study done by Regnström J et al[122] with mean difference of serum TIBC (micromol/l) between cases and controls as 2.63 and with common SD 6.3 at 95% confidence level and with 80% power in study, the sample size calculated is 92.

$$n = \frac{(Z_\alpha + Z_\beta)^2 \times 2 \times S^2}{d^2}$$

Z_α = Z value at α level =95%

Z_β = Z value at β level = 80%

S – Standard deviation

d – Difference between parameters

Hence to compare serum ferritin level, 92≡100 cases were included in the study. Equal number of age and sex matched controls were taken. So total sample size was 100+100=200 patients.

Inclusion Criteria

The diagnosis of AMI was based on European society of cardiologists/American college of cardiology Definition of AMI.

1. Ischaemic symptoms (sudden onset of chest pain lasting ≥30 min; often associated with shortness of breath, weakness, nausea, vomitting).
2. Electrocardiogram changes indicative of ischemia (ST segment elevation or depression).
3. Increased cardiac bio-markers (CKMB, Trop T and or Trop I),
4. Presumably new onset bundle-branch block.
5. Age group > 18 years

Exclusion Criteria

1. Patients with high ferritin levels like haemochromatosis, liver disease, tuberculosis, chronic inflammatory diseases, those on iron therapy.
2. Past history of AMI or CHD
3. Age group < 18 years

METHODOLOGY

All subjects were subjected to detailed history, physical examination and relevant investigations. Cases and controls were investigated for conventional risk factors (BMI, blood sugar, lipid profile). Study subjects were evaluated for serum creatine kinase-MB fraction (CK-MB),Trop-T, serum ferritin along with complete blood counts, renal function , liver function etc.

All patients were interviewed as per the prepared proforma and then complete clinical examination and laboratory investigations was done.

INVESTIGATIONS

The following investigations were done.

1. CBC with peripheral smear
2. Urine examination
3. FBS and PPBS
4. HbA_1C
5. Lipid profile
6. Blood urea and serum creatinine
7. ECG
8. CPKMB and Troponin T
9. Echocardiography
10. Serum ferritin

Other investigations were done wherever necessary.

Serum ferritin estimation:

Principle- The assay principle combines a one step enzyme immunoassay sandwich method with a final fluorescent detection(ELFA).

The solid phase receptacle(SPR) serves as the solid phase as well as the pipetting device for the assay. Reagents for the assay were ready to use and predispensed in the sealed reagent strips.

During the final detection step, the substrate was cycled in and out of SPR. The conjugate enzyme catalyzes the hydrolysis of this substrate into a fluorescent product, the fluorescence of which is measured at 450nm. The intensity of the fluorescence is proportional to the concentration of antigens present in the sample. At the end of the assay, results were automatically calculated by the instrument in relation to the calibration curve stored in memory and then printed out.

PROCEDURE-

- Required reagents were taken out from the refrigerator and then allowed to come to room temperature for at least 30 minutes.
- Use one FER strip and one FER SPR for each sample, control or calibrator were tested. The storage pouch had been carefully resealed after the required SPRs have been removed.
- The test is identified by the FER code on the instrument. The calibrator must be identified S1 and tested in duplicate. If the control needs to be tested, it should be identified by C1.

- Mix the calibrator, control and samples using a vortex type mixer.
- For this test, the calibrator, control and sample test portion is 100µl.
- Insert the FER SPRs and FER strips into the instrument. Check to make sure the colour labels with the assay code on the SPRs and the reagent strips match.
- Initiate the assay and all the assay strips are performed automatically by the instrument.
- Re-stopper the vials and return them to 2-8ºC after pipetting.
- The assay was completed within approximately 30 minutes. After the assay was completed, the SPRs and strips from the instrument were removed.
- Used SPRs and reagent strips in an appropriate recipient were disposed.
- Results were automatically calculated by the instrument in relation to the calibration curve stored in memory and then printed out.

STATISTICAL ANALYSIS

Statistical testing was conducted with the statistical package for the social science system version SPSS 20.0. Continuous variables were presented as Mean ± SD or median (IQR) for non-normally distributed data. Categorical variables were expressed as frequencies and percentages.

The comparison of normally distributed continuous variables between the groups was performed using Student's t test else Mann Whitney U test was used for Non-normal distribution data. Nominal categorical data between the groups were compared using Student t-test, Chi-squared test, Fisher's exact test or as appropriate. Multivariate analysis was done wherever necessary.

For all statistical tests, a p value less than 0.05 were taken to indicate a significant difference. Results were graphically represented where deemed necessary. Graphical representation was done in MS Excel 2010.

OBSERVATIONS AND RESULTS

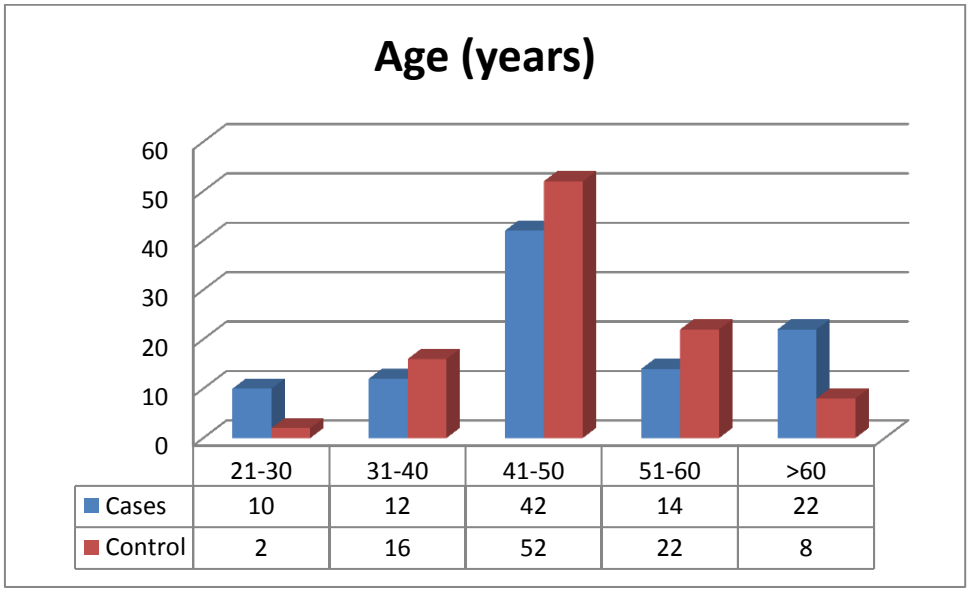
A total of 200 patients (100 cases and equal number of controls) were enrolled in a case control study to assess the levels of serum ferritin in acute myocardial infarction.

Distribution of patients according to Age

Majority of the patients in both the groups were in the age group of 41-50 years (42% and 52% respectively). The mean age of the patients in Cases Group was 48.3 ± 14.24 years as compared to 47.6 ± 8.15 years in Control Group. The mean age of patients between groups were comparable and statistically not significant as per Student t-test ($p>0.05$).

Table 6: Distribution of patients according to Age

Age (years)	Cases		Control		p Value
	N	%	N	%	
21-30	10	10%	2	2%	>0.05
31-40	12	12%	16	16%	
41-50	42	42%	52	52%	
51-60	14	14%	22	22%	
>60	22	14%	8	8%	
Total	100	100%	100	100%	
Mean ± SD	48.3 ± 14.24		47.6 ± 8.15		



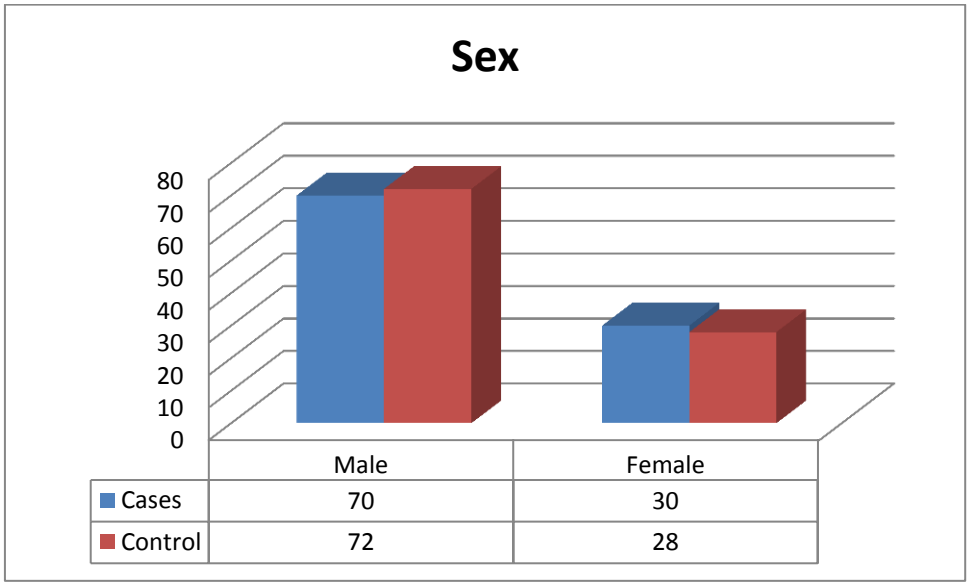
Graph 1: Distribution of patients according to Age

Distribution of patients according to Sex

There were 70 (70%) male and 30 (30%) female patients in Cases Group while Control Group had 72 (72%) and 28 (28%) male and female patients respectively. Majority of the patients in both the groups were males and the difference was statistically not significant as per Chi-square test (p>0.05).

Table 7: Distribution of patients according to Sex

Sex	Cases		Control		p Value
	N	%	N	%	
Male	70	70%	72	72%	>0.05
Female	30	30%	28	28%	
Total	100	100%	100	100%	



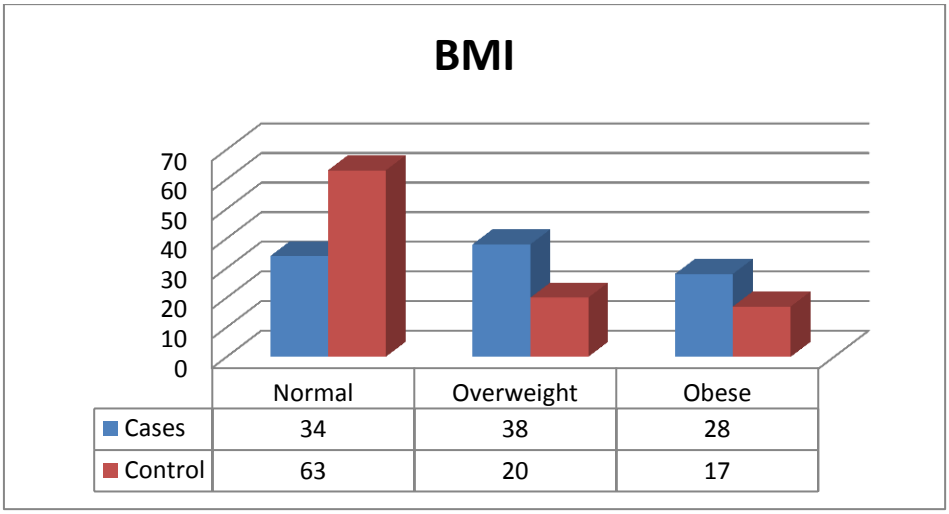
Graph 2: Distribution of patients according to Sex

Distribution of patients according to BMI

Cases Group had 34 (34%) patients in the normal range while 38 (38%) and 28 (28%) patients were overweight and obese respectively. Control Group had 63 (63%) patients in the normal range while 20 (20%) and 17 (17%) patients were overweight and obese respectively. There was significant difference in BMI of the patients between groups as per Student t-test (**p<0.05**).

Table 8: Distribution of patients according to BMI

BMI (kg/m^2)	Cases		Control		p Value
	N	%	N	%	
Normal	34	34%	63	63%	
Overweight	38	38%	20	20%	
Obese	28	28%	17	17%	**<0.05**
Total	100	100%	100	100%	
Mean ± SD	27.1 ± 3.77		24.9 ± 3.73		



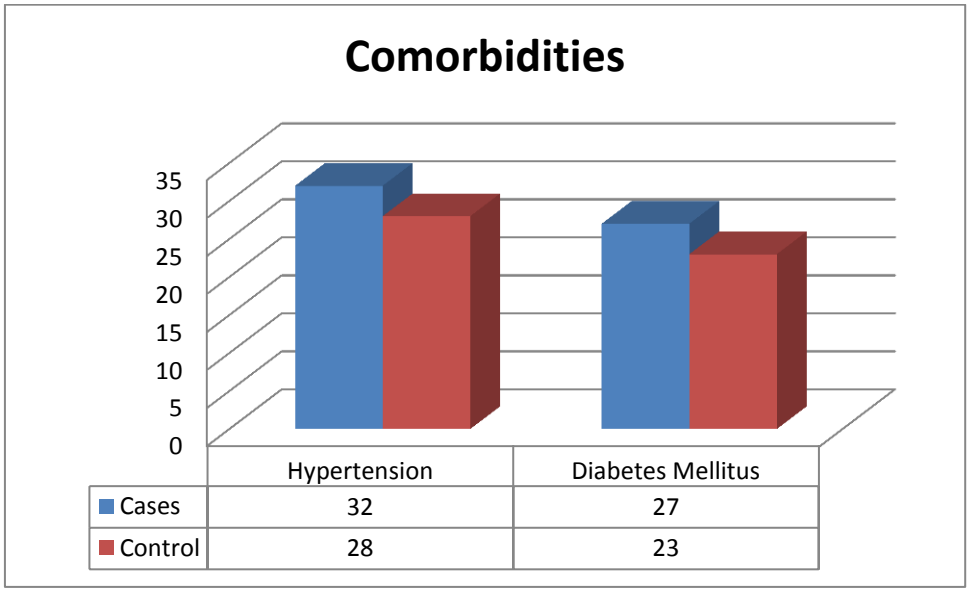
Graph 3: Distribution of patients according to BMI

Distribution of patients according to Comorbidities

Hypertension and diabetes mellitus was more prevalent amongst Cases Group as compared to Control Group (32% vs. 28% and 27% vs. 23% respectively). This difference was statistically not significant as per Chi-Square test (p>0.05).

Table 9: Distribution of patients according to Comorbidities

Comorbidities	Cases		Controls		p Value
	N	%	N	%	
Hypertension	32	32%	28	28%	>0.05
Diabetes Mellitus	27	27%	23	23%	>0.05



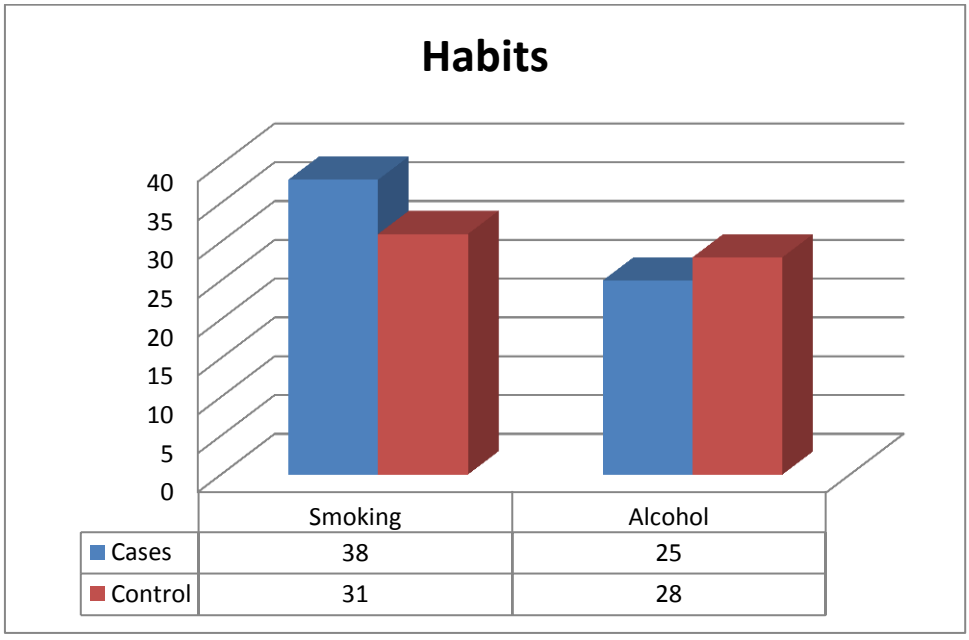
Graph 4: Distribution of patients according to Comorbidities

Distribution of patients according to Habits

In Cases Group, 38 (38%) and 25 (25%) patients smoked and regularly drank alcohol while in Control Group 31 (31%) and 28 (28%) patients smoked and regularly drank alcohol. There was no significant difference as per Chi-Square test (p>0.05).

Table 10: Distribution of patients according to Habits

Habits	Cases		Controls		p Value
	N	%	N	%	
Smoking	38	38%	31	31%	>0.05
Alcohol	25	25%	28	28%	>0.05



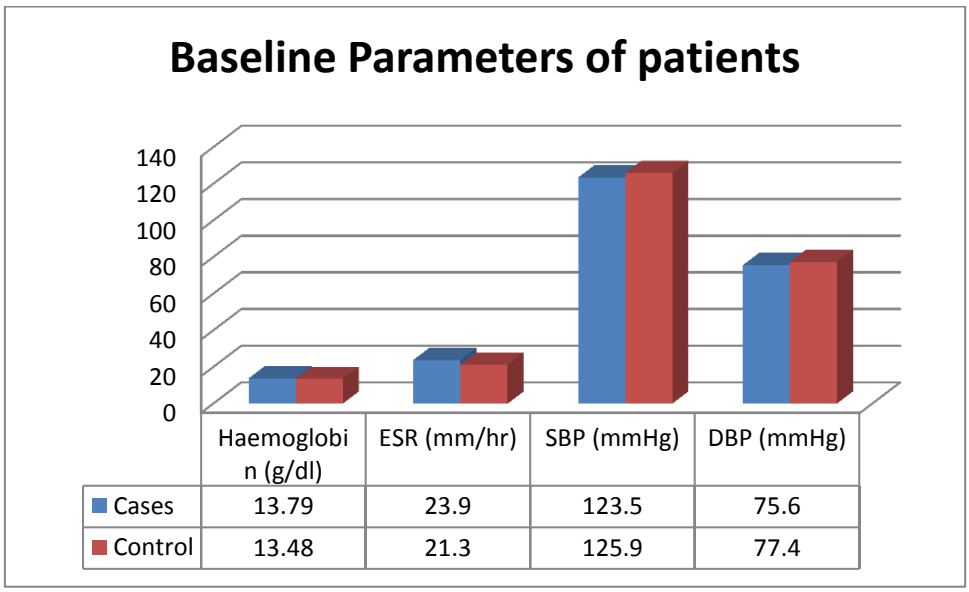
Graph 5: Distribution of patients according to Habits

Baseline Parameters of patients

The baseline parameters (haemoglobin, ESR, SBP, DBP) was comparable between the groups and statistically not significant as per Chi-Square test (p>0.05).

Table 11: Baseline Parameters of patients

Parameters	Cases		Controls		p Value
	Mean	SD	Mean	SD	
Haemoglobin (g/dl)	13.79	3.35	13.48	3.33	>0.05
ESR (mm/hr)	23.9	12.15	21.3	11.22	>0.05
SBP (mmHg)	123.5	15.17	125.9	18.13	>0.05
DBP (mmHg)	75.6	10.79	77.4	10.96	>0.05



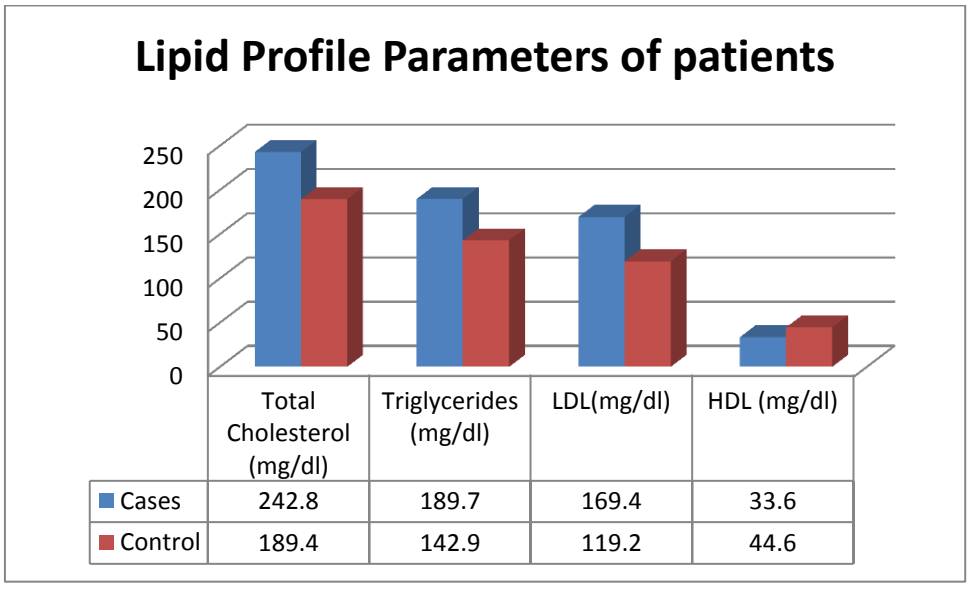
Graph 6: Baseline Parameters of patients

Lipid Profile Parameters of patients

The Total Cholesterol, Triglycerides and LDL values were significantly higher and HDL values were significantly lower in Cases Group as Compared to Control Group as per Student t-test (**p<0.05**).

Table 12: Lipid Profile Parameters of patients

Parameters	Cases		Controls		p Value
	Mean	SD	Mean	SD	
Total Cholesterol (mg/dl)	242.8	32.63	189.4	13.01	**<0.05**
Triglycerides (mg/dl)	189.7	12.46	142.9	24.33	**<0.05**
LDL(mg/dl)	169.4	16.98	119.2	30.71	**<0.05**
HDL (mg/dl)	33.6	4.72	44.6	5.96	**<0.05**



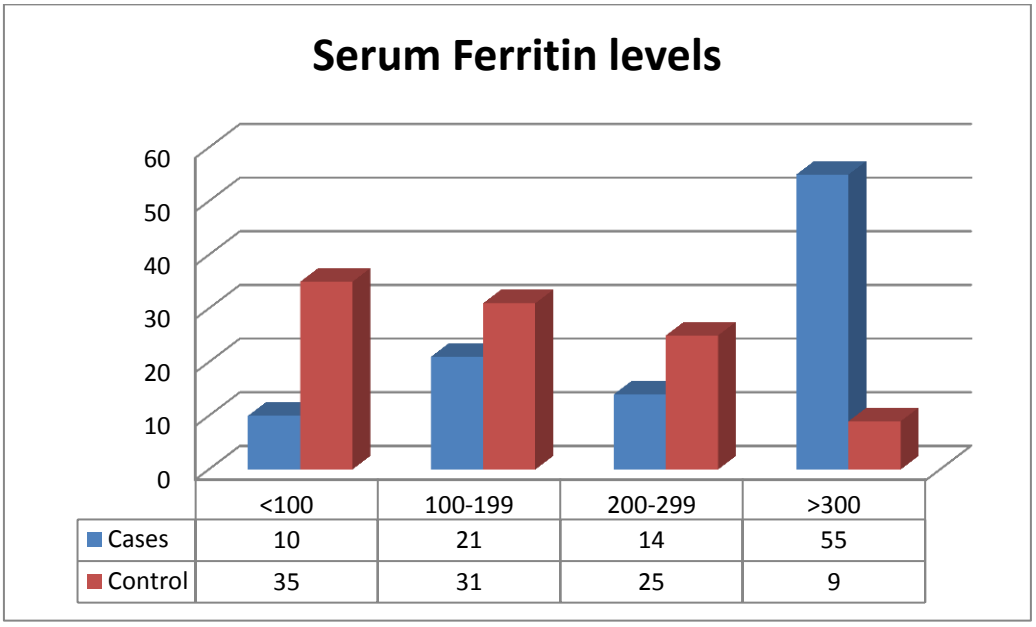
Graph 7: Lipid Profile Parameters of patients

Distribution of patients according to Serum Ferritin levels

It was observed that significantly higher number of patients in Cases Group had serum ferritin level >300µg/l as compared to Control Group (55% vs. 9%). 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**).

Table 13: Distribution of patients according to Serum Ferritin levels

S. Ferritin (µg/l)	Cases		Controls		p Value
	N	%	N	%	
<100	10	10%	35	35%	**<0.05**
100-199	21	21%	31	31%	
200-299	14	14%	25	25%	
>300	55	55%	9	9%	
Mean ± SD	332.5	165.5	153.8	90.5	



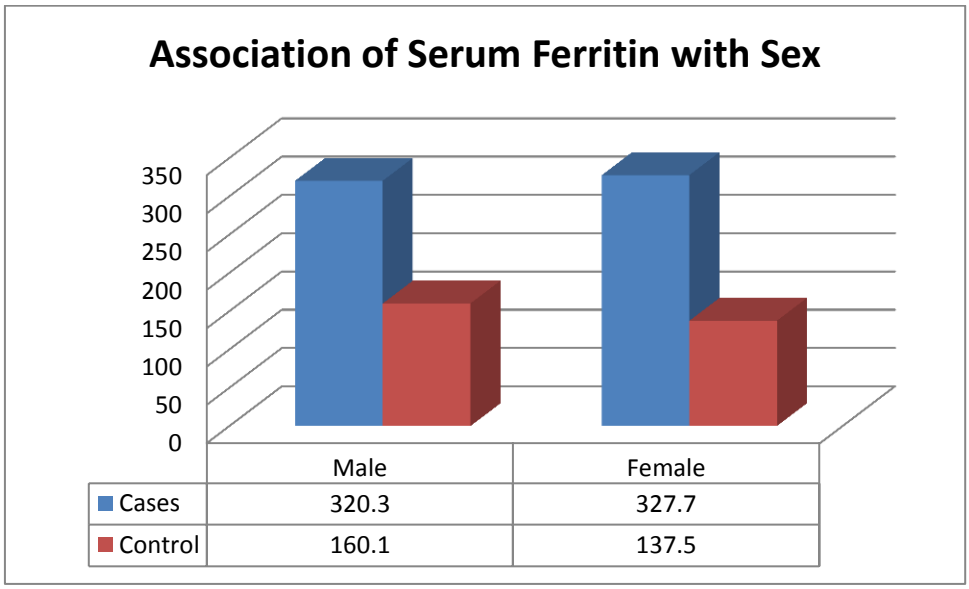
Graph 8: Distribution of patients according to Serum Ferritin levels

Association of Serum Ferritin with Sex

The mean serum ferritin levels of males and females patients in Cases Group were significantly higher as compared to Control Group (320.3 vs. 160.1µg/l and 327.7 vs. 137.5 µg/l respectively) as per Student t-test (**p<0.05**). There was no significant difference of mean serum ferritin levels of males and females patients within the group (p>0.05).

Table 14: Association of Serum Ferritin with Sex

Serum Ferritin (µg/l)	Cases		Controls		p Value
	Mean	SD	Mean	SD	
Male	320.3	165.54	160.1	94.76	**<0.05**
Female	327.7	168.15	137.5	77.75	**<0.05**
p Value	>0.05		>0.05		



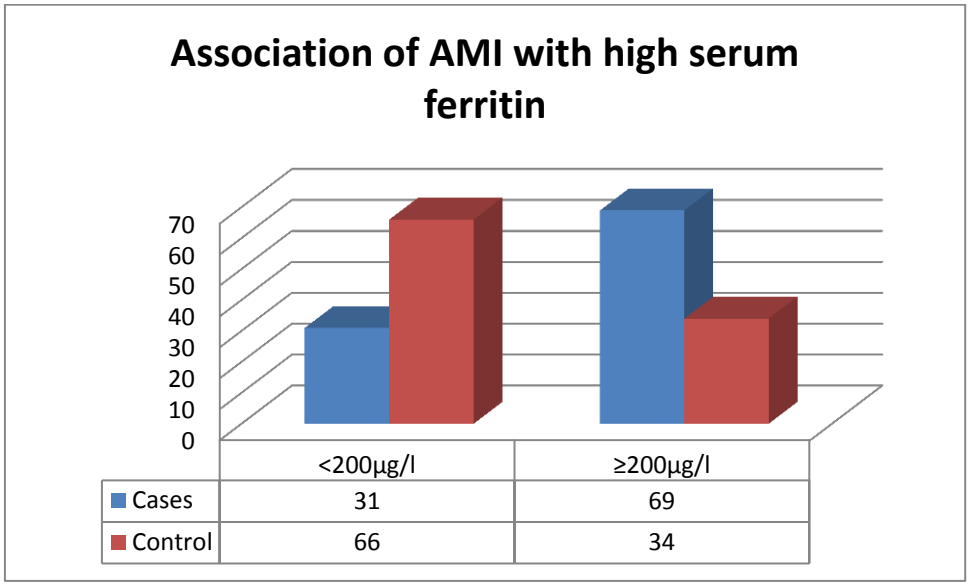
Graph 9: Association of Serum Ferritin with Sex

Association of Acute Myocardial Infarction (AMI) with high serum ferritin

It was observed that significantly more patients in Cases Group (69%) than Control Group (34%) had concentrations above the cut-off of 200 µg/L (**p<0.05**).

Table 15: Association of Acute Myocardial Infarction (AMI) with high serum ferritin

Serum Ferritin (µg/l)	Cases		Controls		p Value
	N	%	N	%	
<200µg/l	31	31%	66	66%	**<0.05**
≥200µg/l	69	69%	34	34%	



Graph 10: Association of Acute Myocardial Infarction (AMI) with high serum ferritin

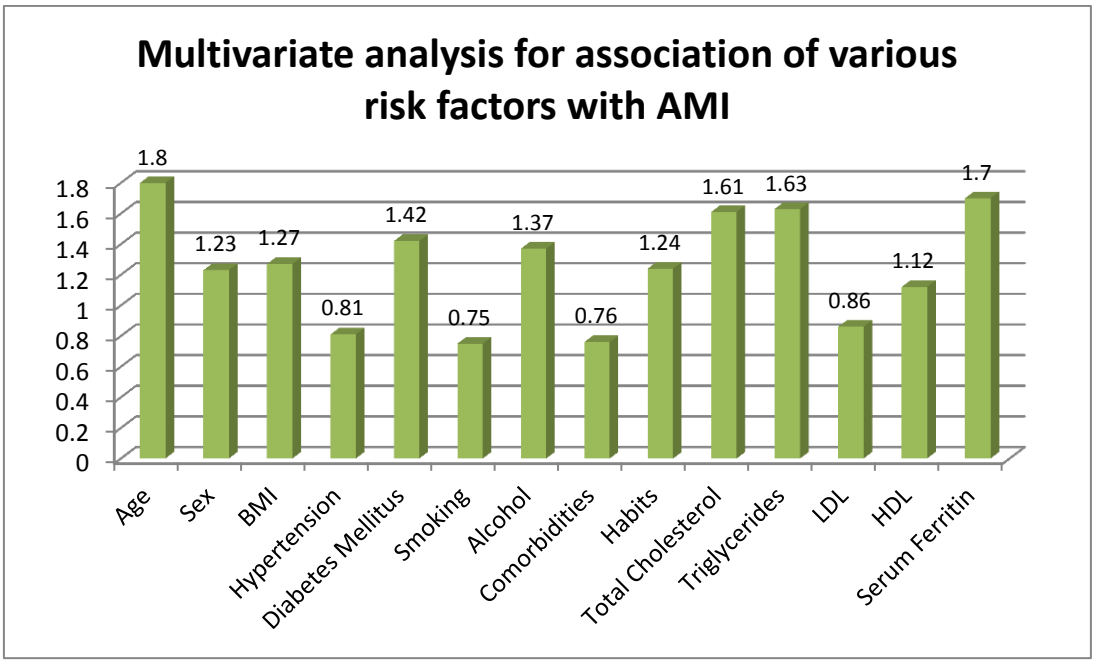
Multivariate analysis for association of various risk factors with Acute Myocardial Infarction (AMI)

In multivariate analysis, Diabetes Mellitus (P = 0.001, OR = 7.64, 95% CI 2.37–24.58), HDL (P < 0.001, OR = 0.86; 95% CI 0.79–0.93) and serum ferritin (>200 µg/L) (P < 0.001, OR = 5.72, 95% CI 2.16–15.17), are found to be independently associated with AMI.

Table 16: Multivariate analysis for association of various risk factors with Acute Myocardial Infarction (AMI)

Parameters	OR	95% CI	p Value
Age	1.8	0.31 - 1.39	p>0.05
Sex	1.23	1.00–1.51	p>0.05
BMI	1.27	0.45–2.85	p>0.05
Hypertension	0.81	0.61–1.09	p>0.05
Diabetes Mellitus	1.42	1.26–1.60	**p<0.05**
Smoking	0.75	0.54–1.03	p>0.05
Alcohol	1.37	1.162-1.235	p>0.05
Comorbidities	0.76	0.681-1.328	p>0.05
Habits	1.24	1.285-2.681	p>0.05

Total Cholesterol	1.61	0.995-1.922	p>0.05
Triglycerides	1.63	1.231-1.782	p>0.05
LDL	0.86	0.742-1.529	p>0.05
HDL	1.12	1.01–1.25	**p<0.05**
Serum Ferritin	1.70	1.15–2.50	**p<0.05**



Graph 11: Multivariate analysis for association of various risk factors with Acute Myocardial Infarction (AMI)

DISCUSSION

A total of 200 patients (100 cases and equal number of controls) were enrolled in a case control study to assess the levels of serum ferritin in acute myocardial infarction.

Incidence of acute myocardial infarction is increasing across the globe among all ages and both sexes with increasing morbidity and mortality. In AMI, irreversible tissue injury occurs due to sustained ischemia and recent pivotal studies have shown that the innate immune system is activated sequentially mediating both injury and repair mechanisms.[123,124] The role of ferritin in pathogenesis of coronary artery disease (CAD) has generated considerable interest in recent times.

Epidemiological studies have found a positive relationship between body iron stores and coronary artery diseases.[12,125] Subsequently, evidence of an association of elevated serum ferritin and increased risk of AMI came from various authors, [16,126] which is similar to our findings. However results of some other studies did not show significant correlation between high ferritin and risk of AMI.[29,127] 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.[128-130] Native low density lipoprotein in contrasts lacks all these atherogenic potentials.[128,130] One study yielded a strong relation between sonographically assessed carotid atherosclerosis and prominent iron stores in both genders particularly when

associated with hypercholesterolemia.[33] 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.[34] High ferritin levels have been associated with established conventional risk factors like diabetes mellitus and hypertension by various authors.[131,132] Reduced extraction of hepatic with increasing iron stores leading to peripheral hyper insulinemia was the proposed mechanism for diabetes mellitus[133] and pronounced metabolic alteration is the proposed mechanism for high ferritin hypertensive.[132]

In the present study, majority of the patients in both the groups were in the age group of 41-50 years (42% and 52% respectively). The mean age of the patients in Cases Group was 48.3 ± 14.24 years as compared to 47.6 ± 8.15 years in Control Group. The mean age of patients between groups were comparable and statistically not significant as per Student t-test ($p>0.05$). There were 70 (70%) male and 30 (30%) female patients in Cases Group while Control Group had 72 (72%) and 28 (28%) male and female patients respectively. Majority of the patients in both the groups were males and the difference was statistically not significant as per Chi-square test ($p>0.05$).

Vijaya BM et al[134] study found the mean age were 45.7±3.8, 46.4±4.1 and 46.2±4.5 in control group and group I and II respectively and the average number of M/F were 82/19.

Bharathi BK et al[135] study found 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.

In our study, Cases Group had 34 (34%) patients in the normal range while 38 (38%) and 28 (28%) patients were overweight and obese respectively. Control Group had 63 (63%) patients in the normal range while 20 (20%) and 17 (17%) patients were overweight and obese respectively. There was significant difference in BMI of the patients between groups as per Student t-test (**p<0.05**). This was similar to the study of Bharathi BK et al[135] study which found significant difference in BMI of patients in controls and cases group.

Hypertension and diabetes mellitus was more prevalent amongst Cases Group as compared to Control Group (32% vs. 28% and 27% vs. 23% respectively) in our study. This difference was statistically not significant as per Chi-Square test (p>0.05). In Cases Group, 38 (38%) and 25 (25%) patients smoked and regularly drank alcohol while in Control Group 31 (31%) and 28 (28%) patients smoked and regularly drank alcohol. There was no significant difference as per Chi-Square test (p>0.05). This correlates to the study of Moradi M et al[136].

The study of Moradi M et al[136] consisted of 100 consecutive patients with first acute myocardial infarction (AMI), and a control group (n = 50) without history of AMI. There was no significant difference in risk factors including diabetes mellitus, hypertension and current smoking between the groups.

It was observed in the present study that the baseline parameters (haemoglobin, ESR, SBP, DBP) was comparable between the groups and statistically not significant as per Chi-Square test (p>0.05). This is concordant to the studies of Moradi M et al[136], Vijaya BM et al[134] and Ishran R et al[118].

Moradi M et al[136] observed that the ESR, CRP and WBC values of patients in both the groups were comparable. Similarly Vijaya BM et al[134] study found that SBP, DBP and Random plasma glucose was comparable between the groups.

The case control analytic study of Ishran R et al[118] was conducted to determine the difference in serum ferritin level among Acute Myocardial Infarction (AMI) patients and healthy subjects. The mean hemoglobin of cases and controls was 14.15±0.81 gm% and 14.30±0.77gm% respectively. No significant difference was observed between cases and controls in relation to hemoglobin level.

It was observed in our study that the Total Cholesterol, Triglycerides and LDL values were significantly higher and HDL values were significantly lower in Cases Group as Compared to Control Group as per Student t-test (**p<0.05**). This correlates to the study of Ishran R et al[118] and Silvia WD et al[137].

In the study of Ishran R et al[118] mean cholesterol level (mg/dl) among Myocardial Infarction (MI) cases and controls was 230± 53.81 and 200.48 ±50.96 respectively, and this difference was statistically significant. LDL cholesterol (mg/dl) level was also significantly higher among MI cases (126.44±49.54) as compared to controls (106.38±38.48). VLDL cholesterol

(mg/dl) was also significantly higher in MI case (57.74 ± 22.35) as compared to controls (37.42 ±14.36). MI cases had significantly higher serum Triglycerides (mg/dl) (173.1 ± 67.27) as compared to controls (112.52 ±43.17). Serum HDL cholesterol level (mg/dl) was significantly lower among MI cases (36.92 ± 6.96) as compared to controls (44.06 ± 7.10).

The case control study of Silvia WD et al[137] involved 145 patients (100 cases and 45 healthy control subjects) in the age group of 30-70 years. The mean value of controls and cases for cholesterol (mg/dl) 186.9 ± 36.55 and 242.81 ±40.60, LDL cholesterol (mg/dl) 117.58 ± 38.35 and 170.96 ±39.75, VLDL cholesterol (mg/dl) 28.36 ± 11.77 and 38.41 ±19.53, triglycerides (mg/dl) 143.49 ± 57.11 and 190.68 ± 97.67, HDL cholesterol (mg/dl) 41.51 ± 11.36 and 33.34 ± 10.50 respectively was found to be significantly different.

In the present study, significantly higher number of patients in Cases Group had serum ferritin level >300µg/l as compared to Control Group (55% vs. 9%). 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**).

Ishran R et al[118] observed that most (74%) of the myocardial infarction (MI) cases had ferritin level >200 µg/L, while most (74%) of the control subjects had ferritin level below 200 µg/L. Serum ferritin level (>200 µg/L) was significantly associated with AMI (P<0.01). Median serum ferritin level of MI cases (211µg/L) was significantly higher than controls (111µg/L).

Vijaya BM et al[134] reported measured parameters were significantly elevated in the AMI patients except HDL which was found to be decreased when compared to controls. And also serum ferritin and malondialdehyde

levels were significantly elevated Group II AMI patints compared to Group I AMI patients (P<0.001).

Bharathi BK et al[135] study reported 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.

In our study, the mean serum ferritin levels of males and females patients in Cases Group were significantly higher as compared to Control Group (320.3 vs. 160.1µg/l and 327.7 vs. 137.5 µg/l respectively) as per Student t-test (**p<0.05**). There was no significant difference of mean serum ferritin levels of males and females patients within the group (p>0.05).

In the study of Holay MP et al[115], the mean value of serum ferritin (µg/L) in controls and cases were found to be 155.65 ± 79.76 and 324.4 ± 256.8 respectively (P<0.001). The distribution of serum ferritin for cases and control subjects indicated a shift towards higher concentration in patients with AMI. Correspondingly, more patients with AMI (62.66%) than control subjects (20%) had concentrations above the cut-off of 200 µg/L. There was no significant difference of mean serum ferritin levels in males and females.

Bharathi BK et al[135] study reported mean value of serum ferritin (µg/L) in controls and cases were found to be 96.3 ± 69.5 and 408.7± 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 µg/L)

was significantly associated with AMI (OR = 11.67 (95% CI 5.37–74.5, P < 0.001).

It was observed in our study that significantly more patients in Cases Group (69%) than Control Group (34%) had concentrations above the cut-off of 200 µg/L (**p<0.05**). In multivariate analysis, Diabetes Mellitus (P = 0.001, OR = 7.64, 95% CI 2.37–24.58), HDL (P < 0.001, OR = 0.86; 95% CI 0.79–0.93) and serum ferritin (>200 µg/L) (P < 0.001, OR = 5.72, 95% CI 2.16–15.17), are found to be independently associated with AMI.

In univariate analysis done by Holay MP et al[115], Diabetes Mellitus, hypertension, serum cholesterol, high-density lipoprotein (HDL) < 35 and smoking were found to be significantly associated with AMI. In multivariate analysis, high serum ferritin (> 200 µg/L) (P < 0.001, OR = 5.72, 95% CI 2.16–15.17), DM (P = 0.001, OR = 7.64, 95% CI 2.37–24.58), low HDL (< 35 mg%) (P < 0.001, OR = 0.86; 95% CI 0.79–0.93) are found to be independently associated with AMI. When ferritin, cholesterol, BMI and HDL were taken as continuous variables, then also mean serum ferritin (P = 0.001) was found to be significantly associated with AMI.

Bharathi BK et al[135] study reported 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.

Vijaya BM et al[134] reported Serum ferritin levels showed strong positive correlation with CRP and MDA in both groups of AMI patients (P<0.01). Triglycerides and LDL levels were showed strong positive

correlation with serum ferritin in both the groups of AMI patients and group II AMI patients exhibited positive correlation with cholesterol and negative correlation with HDL.

Silvia WD et al[137] noted that serum ferritin was significantly directly associated with haemoglobin ($r=0.586$, $p < 0.01$), serum cholesterol ($r=0.439$, $p< 0.01$), serum LDL cholesterol ($r=0.381$, $p < 0.01$), serum triglycerides ($r=0.280$, $p < 0.01$) and serum VLDL cholesterol ($r=0.286$, $p < 0.01$). Serum ferritin was significantly inversely correlated with serum HDL cholesterol ($r=-0.210$, $p < 0.05$).

Free Iron, as well as other transition metals, can catalyze free radical formation. For this reason iron is tightly bound to transport and storage proteins to prevent their involvement in free radical formation. It has been hypothesized that increased iron intake or iron stores may promote atherogenesis by increasing free radical formation and oxidative stress[24]. Oxidative stress increases the peroxidation of low-density lipoprotein (LDL) thereby increasing its uptake by macrophages with increased foam cell formation and atherosclerosis.[138,139]

SUMMARY

A total of 200 patients (100 cases and equal number of controls) were enrolled in a case control study to assess the levels of serum ferritin in acute myocardial infarction. The following observations were noted:

1. Majority of the patients in both the groups were in the age group of 41-50 years (42% and 52% respectively). The mean age of the patients in Cases Group was 48.3 ± 14.24 years as compared to 47.6 ± 8.15 years in Control Group. The mean age of patients between groups were comparable and statistically not significant as per Student t-test ($p>0.05$).
2. There were 70 (70%) male and 30 (30%) female patients in Cases Group while Control Group had 72 (72%) and 28 (28%) male and female patients respectively. Majority of the patients in both the groups were males and the difference was statistically not significant as per Chi-square test ($p>0.05$).
3. Cases Group had 34 (34%) patients in the normal range while 38 (38%) and 28 (28%) patients were overweight and obese respectively. Control Group had 63 (63%) patients in the normal range while 20 (20%) and 17 (17%) patients were overweight and obese respectively. There was significant difference in BMI of the patients between groups as per Student t-test (**$p<0.05$**).
4. Hypertension and diabetes mellitus was more prevalent amongst Cases Group as compared to Control Group (32% vs. 28% and 27% vs. 23% respectively). This difference was statistically not significant

as per Chi-Square test (p>0.05). But it is significant as risk factor in Multivariate analysis for risk factors for MI.

5. In Cases Group, 38 (38%) and 25 (25%) patients smoked and regularly drank alcohol while in Control Group 31 (31%) and 28 (28%) patients smoked and regularly drank alcohol. There was no significant difference as per Chi-Square test (p>0.05).
6. The baseline parameters (haemoglobin, ESR, SBP, DBP) was comparable between the groups and statistically not significant as per Chi-Square test (p>0.05).
7. The Total Cholesterol, Triglycerides and LDL values were significantly higher and HDL values were significantly lower in Cases Group as Compared to Control Group as per Student t-test (**p<0.05**).
8. It was observed that significantly higher number of patients in Cases Group had serum ferritin level >300µg/l as compared to Control Group (55% vs. 9%). 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**).
9. The mean serum ferritin levels of males and females patients in Cases Group were significantly higher as compared to Control Group (320.3 vs. 160.1µg/l and 327.7 vs. 137.5 µg/l respectively) as per Student t-test (**p<0.05**). There was no significant difference of mean serum ferritin levels of males and females patients within the group (p>0.05).

10. It was observed that significantly more patients in Cases Group (69%) than Control Group (34%) had concentrations above the cut-off of 200 µg/L (**p<0.05**).
11. In multivariate analysis, Diabetes Mellitus (P = 0.001, OR = 7.64, 95% CI 2.37–24.58), HDL (P < 0.001, OR = 0.86; 95% CI 0.79–0.93) and serum ferritin (>200 µg/L) (P < 0.001, OR = 5.72, 95% CI 2.16–15.17), are found to be independently associated with AMI.

CONCLUSION

Iron is considered as an essential dietary constituent till now, is considered a pro-oxidant. According to “iron hypothesis”, iron is believed to be detrimental for the cardiovascular system in promoting atherosclerosis development and progression. Iron, in its catalytically active form, can participate in the generation of reactive oxygen species and induce lipid peroxidation, triggering endothelial activation, smooth muscle cell proliferation and macrophage activation; all of these processes are considered to be proatherogenic.

Higher levels of ferritin, seems to be a strong risk factor for AMI. Patients with higher ferritin level can easily be identified during routine haematological analysis along with other risk factor estimation. Regular monitoring of serum ferritin levels may help in reduction of cardiovascular morbidity and mortality.

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Annexure 1

Ethical certificate

B.L.D.E.UNIVERSITY'S

SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR – 586103

INSTITUTIONAL ETHICAL COMMITTEE

No/58/2015
20/11/15

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 17-11-2015 *at* 03 pm *scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has accorded Ethical Clearance.*

Title "Serum ferritin in acute myocardial infarction: A case control study in BLDE University's Shri. B.M.Patil Medical college, Hospital and Research center Vijayapur"

Name of P.G. Student : Dr. Mudiyappa Herakall
Dept in Medicine

Name of Guide/Co-investigator : Dr. M.S. Biradar
Professor & Principal

DR.TEJASWINI VALLABHA
CHAIRMAN

Following documents were placed before E.C. for Scrutinization
1)Copy of Synopsis/Research Project
2)Copy of informed consent form.
3)Any other relevant documents.

CHAIRMAN
Institutional Ethical Committee
BLDEU's Shri B.M. Patil
Medical College,BIJAPUR-586103.

Annexure 2

Ethical certificate

INFORMED CONSENT FORM

BLDE (Deemed to be University) SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR- 586103

TITLE OF THE PROJECT - SERUM FERRITIN IN ACUTE MYOCARDIAL INFARCTION : A CASE CONTROL STUDY

PRINCIPAL INVESTIGATOR - Dr MUDIYAPPA HERAKALL

P.G.GUIDE NAME - Dr. M S BIRADAR M.D
Vice Chancellor and
PROFESSOR OF MEDICINE

CHAIRMAN ETHICAL COMMITTEE

All aspects of this consent form are explained to the patient in the language understood by him/her.

I) **INFORMED PART**

1) PURPOSE OF RESEARCH:

I have been informed about this study. I have also been given a free choice of participation in this study.

2) PROCEDURE:

I am aware that in addition to routine care received I will be asked series of questions by the investigator. I have been asked to undergo the necessary investigations and treatment, which will help the investigator in this study.

3) RISK AND DISCOMFORTS:

I understand that I may experience some pain and discomfort during the examination or during my treatment. This is mainly the result of my condition and the procedure of this study is not expected to exaggerate these feelings that are associated with the usual course of treatment.

4) BENEFITS:

I understand that my participation in this study will help to know the role of newer risk factors(serum ferritin) for acute myocardial infarction which will help in identifying and treating this condition in a better way and the better outcome of acute myocardial infarction.

5) CONFIDENTIALITY:

I understand that the medical information produced by the study will become a part of hospital record and will be subjected to confidentiality and privacy regulation of hospital. If the data is used for publication the identity will not be revealed.

6) REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. Dr. MUDIYAPPA HERAKALL is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation.

7) REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital. I also understand that Dr. MUDIYAPPA HERAKALL may terminate my participation in the study after he explains the reasons for doing so and will help to arrange for my continued care by my own physician or physical therapist, if this is appropriate.

8) INJURY STATEMENT:

I understand that in the unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly, the appropriate treatment would be available to me, but no further compensation would be provided. I understand that by my agreement to participate in this study I am not waiving any of my legal rights.

I have explained to _____the purpose of the research, the procedures required and the possible risks and benefits to the best of my ability in patient's own language.

_____ _____

Dr.MUDIYAPPA HERAKALL Date-

(Investigator)

II) STUDY SUBJECT CONSENT STATEMENT:

I confirm that Dr. MUDIYAPPA HERAKALL has explained to me the purpose of research, the study procedures that I will undergo, and the possible risks and discomforts as well as benefits that I may experience in my own language. I have read and I understand this consent form. Therefore, I agree to give consent to participate as a subject in this research project.

_____ _____

Participant / Guardian Date

Cell no if available-

_____ _____

Witness to signature Date

BLDE (DEEMED TO BE UNIVERSITY), SHRI B.M.PATIL MEDICAL COLLEGE

HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR

Scheme of case taking

Name:	CASE NO:
Age:	OP/IP NO:
Sex:	DOA:
Religion:	DOD:
Occupation:	
Address:	

Presenting complaints with duration:

History of presenting complaints:

Past History: Hypertension/Diabetes Mellitus/IHD/TB/Malignancy/Hepatic or Renal disease/blood transfusion/COPD/Bronchial Asthma

Family History: Diabetes Mellitus /Hypertension/IHD/TB/Dyslipidemia

Personal History:

Diet

Appetite

Sleep

Bladder and bowel habits:

Smoking/Tobacco chewing

Duration

Number of cigarettes/beedis pack year smoked

Amount of tobacco chewed

Categories : Non smoker

Past smoker

Current smoker

Alcohol

Duration

Quantity/Frequency

Type

Categories : Non drinker

Light drinker (1-20gm of alcohol / day)

Moderate drinker (21-40gm of alcohol / day)

Heavy drinker (>41gm of alcohol / day)

Others

Treatment History: Treatment for anemia with iron suppliments within previous 3 months or on treatment for diabetes/hypertension

General Physical Examination

Height : Weight: Body Mass Index :

Vitals:

PR:	Pallor
Supine and standing BP:	Icterus
RR:	Cyanosis
Temp:	Clubbing
	Lymphadenopathy
	Oedema
	Xanthomas

SYSTEMIC EXAMINATION.

1. Cardiovascular System

2. Respiratory System

3. Per abdomen

4. Central Nervous System

Provisional diagnosis:

INVESTIGATIONS:

- CBC with peripheral smear study
- Urine examination
- ECG
- Echocardiography
- Chest X-ray if required
- CPKMB and Trop T
- FBS, PPBS and HbA_1C
- Lipid profile, Blood urea, Serum Creatine, LFT
- Serum Ferritin in all patients

FINAL DIAGNOSIS

TREATMENT GIVEN

COMPLICATIONS

OUTCOME:

SUMMARY

								CASES																	
S.NO	Name	AGE	SEX	IP NO.	PR	SBP	DBP	RR	TEMP	Habits	BMI	Comorbidities	Hb	TC	ESR	Ferritin	T.Ch	TG	LDL	HDL	TROP T	CPK MB	RWMA	LVEF	VALV ABN	DD
1	CHANNABASAPPA	58	M	39217	130	132	62	14	37	Smoking	23.95	Diabetes Mellitus	14.6	21970	33.0	319	229	199	143.2	38	POSITIVE	28	ANTERIOR WALL	45%	G-II MR,G-II TR	GRADE 1
2	ASHOK BASAVARAJ	23	M	39437	72	136	80	14	37.1	Alcohol	23.42	Hypertension	11.4	7240	7.0	120	279	166	145.9	26	NEGATIVE	32	ANTERIOR WALL	50%	NILL	GRADE 1
3	SHANTABAI	35	F	8409	80	135	72	16	37	-	23.59	-	14.9	11980	18.0	596	251	199	155.2	38	POSITIVE	132	INFERIOR WALL	50%	NILL	NILL
4	SAVITHRI	44	F	1768	80	115	61	14	36.9	-	32.39	-	18.8	11510	13.0	462	214	206	169.1	36	POSITIVE	34	INFERIOR WALL	50%	G-2 MR	NILL
5	NAGAPPA	65	M	15210	74	109	65	14	37.2	Alcohol	25.28	Diabetes Mellitus	8.0	18100	42.0	467	230	200	163.5	38	POSITIVE	160	ANTERIOLATERAL WALL	40%	NILL	GRADE 1
6	DEVANAGOWDA	53	M	16070	180	125	84	16	37	Smoking	24.31	Hypertension	8.1	15830	8.0	75	251	176	182.6	38	POSITIVE	53	ANTERIOR WALL	26%	G-I MR	NILL
7	BASAPPA	33	M	16221	70	147	96	14	37	Alcohol	26.06	Diabetes Mellitus	12.8	5600	37.0	488	220	205	159.0	29	NEGATIVE	58	INFERIOR WALL	50%	NILL	GRADE 1
8	MALAGAPPA	60	M	17645	90	144	82	15	37.1	Smoking	26.49	-	11.7	19360	43.0	434	252	184	156.1	32	POSITIVE	78	ANTERIOR WALL	40%	NILL	NILL
9	SAIDA	42	F	4809	96	129	69	14	36.8	Smoking	31.21	Diabetes Mellitus	9.2	17320	40.0	101	214	179	183.7	27	POSITIVE	56	INFERIOR WALL	45%	MILD PAH	NILL
10	PARVATHI	23	F	16198	80	132	69	22	37	-	23.66	Hypertension	12.8	9480	32.0	523	279	186	153.3	27	NEGATIVE	22	ANTERIOSEPTAL WALL	40%	G 1 MR	G 2
11	NEELAMMA	28	F	2388	80	129	84	14	37	Alcohol	24.16	Diabetes Mellitus	8.6	12100	24.0	524	204	193	181.8	30	POSITIVE	35	ANTERIOR WALL	40%	G 1 MR	G 1
12	SUGHAKAR	44	F	9056	102	105	96	16	36.8	Alcohol	33.32	Hypertension	15.2	13600	35.0	212	209	166	187.2	30	POSITIVE	53	INFERIOLATERAL WALL	55%	NILL	NILL
13	BALAPPA	48	M	3882	64	136	80	14	36.8	Alcohol	27.34	Diabetes Mellitus	11.4	12680	26.0	287	220	206	166.1	38	POSITIVE	43	ANTERIOR WALL	40%	NILL	NILL
14	RAMACHANDRA	46	M	4635	90	115	61	16	37.1	-	25.10	Hypertension	18.8	9300	26.0	512	248	191	199.2	30	POSITIVE	45	ANTERIOR WALL	45%	NILL	NILL
15	SIDDU	65	M	4754	100	116	79	22	37	Smoking	32.30	-	10.3	11860	7.0	573	314	187	159.1	24	POSITIVE	51	ANTERIORWALL	50%	NILL	GRADE 2
16	GURANNA	76	M	5779	84	125	63	15	37	Smoking	31.47	-	13.6	9600	3.0	180	244	176	152.8	33	NEGATIVE	45	ANTERIOLATERAL WALL	50%	NILL	GRADE 1
17	NINGAMMA	42	F	91	82	150	76	16	37.2	Smoking	21.97	Diabetes Mellitus	13.9	13290	28.0	595	249	208	182.1	32	NEGATIVE	26	NORMAL	60%	G-1 MR,TR	GRADE 1
18	LAKKAWWA	43	F	11028	80	137	78	14	37	Alcohol	26.85	Diabetes Mellitus	12.1	4420	38.0	237	214	196	144.1	37	POSITIVE	18	INFERIOLATERAL WALL	60%	NILL	NILL
19	ALISAB	65	M	7989	88	122	78	16	37	-	24.51	-	10.5	11530	29.0	170	254	181	166.4	35	POSITIVE	95	ANTERIOSEPTAL WALL	45%	NILL	GRADE 1
20	PARVATHI	41	F	18523	80	126	69	15	37	Smoking	24.17	-	17.5	7620	35.0	447	311	185	122.0	38	NEGATIVE	16	ANTERIOLATERAL WALL	45%	NILL	G 1
21	YEMKAWWA	42	F	17831	76	144	82	14	37	Smoking	22.03	Diabetes Mellitus	11.7	17650	10.0	92	305	177	172.5	37	POSITIVE	234	INFERIOR WALL	45%	NILL	NILL
22	SAIBANNA	23	M	10311	100	132	54	14	37.2	-	24.06	-	16.4	11400	16.0	387	222	182	170.1	38	NA	78	INFERIOR WALL	55%	G 3 MR	NILL
23	YELLAPPA	48	M	11078	70	132	69	16	37.1	Alcohol	27.69	Diabetes Mellitus	12.8	3830	15.0	544	218	196	159.0	25	POSITIVE	69	INFERIOR WALL	45%	NILL	NILL
24	GOLLAPPA	76	M	11399	86	132	68	26	37	-	23.73	Hypertension	18.6	12200	18.0	123	274	176	175.5	33	POSITIVE	114	ANTERIOSEPTAL WALL	45%	G 1 MR	G 2
25	GOURAMMA	42	F	1151	80	132	78	13	37	Smoking	24.09	Hypertension	18.6	13020	35.0	371	239	206	159.1	34	POSITIVE	135	ANTERIOR WALL	45%	NILL	NILL
26	MALAKAWWA	46	F	27774	72	109	65	14	37.1	Smoking	32.81	Hypertension	8.0	17710	22.0	505	264	181	180.9	39	POSITIVE	300	ANTERIOR WALL	40%	NILL	N
27	CHANDRABAGH	46	F	25819	66	138	56	16	37	Smoking	22.66	Hypertension	14.6	16760	30.0	159	251	185	110.0	38	POSITIVE	80	INFERIOLATERAL WALL	45%	G 1 MR	G 1
28	DHARAKABAI	42	F	27056	140	138	86	14	37	Alcohol	22.10	Diabetes Mellitus	10.9	19100	42.0	237	213	198	179.8	39	NEGATIVE	300	ANTERIOR WALL	40%	G 1 MR	N
29	MALLIKARJUNA	31	M	13708	80	137	78	14	37.1	-	23.05	-	12.1	10140	33.0	124	299	182	181.3	38	POSITIVE	55	ANTERIOSEPTAL WA;;	50%	NILL	NILL
30	BHEERAPPA	79	M	14012	80	138	56	14	37.1	-	26.84	-	14.6	10200	26.0	56	178	206	172.4	38	NEGATIVE	34	INFERIOLATERAL WALL	40%	G 1 MR	NILL
31	BHEEMAVVA	35	F	22206	140	117	84	20	37	Smoking	24.68	Hypertension	14.7	21660	30.0	166	252	185	157.1	36	POSITIVE	40	ANTERIOR WALL	35%	G 1 TR, MR	G 3
32	LALSAB	53	M	14432	120	96	66	30	36.8	Smoking	34.01	-	16.7	17570	24.0	106	256	205	143.4	27	POSITIVE	133	GLOB HYPOKINESIA	25%	NILL	NILL
33	GADEPPA	33	M	15360	92	102	82	14	37.1	-	33.36	-	13.9	4730	13.0	232	212	179	169.8	30	NEGATIVE	48	ANTERIOR WALL	40%	G 1 MR	G 2
34	NINGAPPA	48	M	15620	80	140	70	16	37	Smoking	26.84	Hypertension	11.9	11960	37.0	507	219	181	189.6	31	POSITIVE	39	INFERIOR WALL	30%	G 2 MR	G 2
35	MAHABOOB	45	M	16147	40	108	89	14	37.1	Smoking	25.28	-	12.3	16430	40.0	570	265	186	164.9	24	POSITIVE	129	INFERIOR WALL	60%	G 1 MR	G 3
36	CHANDRAWWA	28	F	22080	88	117	73	18	37.2	-	24.73	-	13.3	15540	18.0	498	234	176	164.8	33	POSITIVE	243	ANTERIOR WALL	45%	NILL	NILL
37	CHENNAMMA	44	F	17381	96	111	80	14	36.8	Alcohol	32.79	Hypertension	13.2	10850	39.0	79	300	192	152.3	35	POSITIVE	45	ANTERIOSEPTAL WALL	40%	NILL	G 1
38	KAMALA BAI	42	F	20558	84	143	89	16	36.9	-	22.03	-	11.9	20970	4.0	188	258	181	168.9	39	NEGATIVE	33	INFERIOR WALL	50%	NILL	G 2
39	APPANNA	38	M	820	86	141	88	14	37	Alcohol	26.67	Hypertension	9.1	11530	5.0	81	307	206	147.1	34	POSITIVE	128	INFERIOLATERAL WALL	50%	NILL	NILL
40	VIJAY KUMAR	31	M	14404	82	141	88	22	37.1	Smoking	22.03	Hypertension	9.1	14930	27.0	306	237	206	169.0	34	NEGATIVE	23	ANTERIOR WALL	35%	NILL	NILL
41	VITTAL	45	M	21453	54	150	76	16	36.9	-	25.91	-	13.9	10800	28.0	402	294	200	200.8	38	POSITIVE	60	ANTERIOR WALL	50%	NILL	G 1
42	SIDDRAMAPPA	46	M	22397	88	116	79	18	37.2	Smoking	25.10	-	10.3	12580	32.0	84	317	165	163.2	34	POSITIVE	30	ANTERIOSEPTAL WALL	40%	NILL	NILL
43	SEETH DEVULU	65	M	23178	62	139	70	16	36.9	Alcohol	26.84	Diabetes Mellitus	13.5	13880	33.0	397	216	189	185.5	37	POSITIVE	56	ANTERIOLATERAL WALL	40%	NILL	G 2
44	CHANNABASAPPA	51	M	18225	90	147	96	16	37.1	Smoking	21.97	-	12.8	5600	13.0	425	249	177	182.9	26	POSITIVE	70	INFERIOR WALL	50%	G-1 MR	GRADE 1
45	BASAVARAJ	65	M	21085	82	114	82	15	37	Smoking	25.10	Diabetes Mellitus	9.5	13100	29.0	581	216	206	181.0	34	POSITIVE	91	ANTERIOLATERAL	30%	NILL	NILL
46	DEVAPPANNAGOUDA	76	M	18534	80	117	73	16	37.1	-	31.93	Hypertension	13.3	8950	37.0	352	244	206	188.1	26	NEGATIVE	28	ANTERIOSEPTAL WALL	35%	NILL	NILL
47	KEMPAYYA	47	M	20657	88	102	82	16	37	Smoking	25.40	Hypertension	13.9	9640	13.0	366	315	192	164.3	35	NEGATIVE	64	INFERIOLATERAL WALL	45%	G 1 MR	G 1
48	KALLAPPA	71	M	26934	140	90	62	14	37	Smoking	25.71	-	17.9	3600	6.0	530	178	190	199.4	34	POSITIVE	21	INFERIOR WALL	35%	G 3 MR, TR	N
49	HANAMANTH	56	M	27519	84	140	64	16	37	-	22.03	-	18.8	11400	44.0	387	252	165	175.2	34	POSITIVE	45	ANTERIOSEPTAL	40%	NILL	G 1
50	PARAPPA	65	M	27619	46	132	62	14	37.9	Smoking	27.69	Hypertension	14.6	12600	19.0	351	210	176	194.6	38	POSITIVE	31	INFERIOLATERAL WALL	45%	NILL	N
51	NEELAKANTAYYA	65	M	27516	130	121	64	16	37	Smoking	31.53	-	8.6	1000	8.0	523	307	191	173.8	39	POSITIVE	30	ANTERIOR WALL	40%	NILL	N
52	RAMJAN SAB	48	M	28409	120	146	89	20	37	Smoking	26.22	-	10.0	17300	21.0	335	218	199	181.7	25	NEGATIVE	31	ANTERIOR WALL	40%	G 1 MR	N
53	SAHEBGOUDA	48	M	28716	80	132	54	14	37	Smoking	27.77	Hypertension	16.4	9200	16.0	168	253	206	157.1	36	NEGATIVE	37	ANTERIOR WALL	40%	NILL	N
54	YAMANNUR	66	M	28462	90	146	89	16	37.2	Alcohol	21.97	Diabetes Mellitus	10.0	12100	5.0	579	259	163	176.9	38	NEGATIVE	42	NORMAL	60%	NILL	N
55	MALLIKARJUN B B	38	M	28409	60	126	69	16	37	-	31.35	-	17.5	9640	36.0	250	216	188	193.1	37	POSITIVE	78	ANTERIOR WALL	50%	NILL	G 1
56	MD ISUF	48	M	1767	170	102	80	14	37	-	25.48	-	17.6	14700	39.0	127	248	184	174.7	31	POSITIVE	60	ANTERIOR WALL	50%	NILL	G 1
57	SOMANNA M B	56	M	13303	78	96	66	16	36.9	Alcohol	25.71	Diabetes Mellitus	16.7	10800	25.0	291	221	176	172.0	34	POSITIVE	30	ANTERIOSEPTAL WALL	40%	NILL	NILL
58	DONDILAL N K	47	M	17737	80	111	80	18	37.2	-	25.28	-	13.2	12580	22.0	390	258	177	184.5	37	POSITIVE	56	ANTERIOLATERAL WALL	40%	NILL	G 2
59	MITALAYYA H	21	M	19151	80	116	72	16	36.9	Smoking	24.73	-	14.2	13880	15.0	565	222	188	184.0	34	NEGATIVE	26	LATERAL WALL	60%	NILL	NG 1
60	BHEERAPPA N P	65	M	14012	120	140	70	16	37.1	Alcohol	22.03	Hypertension	11.9	9550	18.0	300	214	185	147.1	24	POSITIVE	46	ANTERIOR WALL	45%	NILL	N
61	BABUGOUDA N P	48	M	16425	92	140	64	14	37	-	26.71	-	18.8	6180	6.0	424	238	184	186.7	31	POSITIVE	30	ANTERIOR WALL	35%	G 1 TR, G 2 MR	N
62	LACHU R R	53	M	14902	80	98	67	34	36.8	-	25.71	Hypertension	9.8	10000	14.0	411	218	166	157.9	26	NEGATIVE	82	ANTERIOR WALL	45%	NILL	N
63	MALAKAPPA B N	48	M	13966	40	102	88	16	36.8	Alcohol	25.45	Hypertension	13.8	12650	36.0	305	293	188	164.9	38	POSITIVE	21	INFERIOR WALL	35%	G 3 MR, TR	N
64	MALLIKARJUN S P	76	M	13708	80	115	74	14	37	Alcohol	32.60	Hypertension	11.7	3600	20.0	112	254	205	151.4	37	POSITIVE	45	ANTERIOSEPTAL	40%	NILL	G 1
65	BALASAHIB N Y	58	M	8854	130	132	68	16	37	-	27.69	Diabetes Mellitus	18.6	11400	15.0	395	209	205	155.4	27	POSITIVE	31	INFERIOLATERAL WALL	45%	NILL	N
66	DUNDAPPA M B	21	M	10759	80	102	80	14	37.9	-	33.76	-	17.6	12600	41.0	262	217	192	167.2	37	POSITIVE	30	ANTERIOR WALL	40%	NILL	N
67	SIDAPPA D P	79	M	9406	88	105	96	16	37	-	25.28	Hypertension	15.2	1000	32.0	405	250	205	163.4	37	NEGATIVE	31	ANTERIOR WALL	40%	G 1 MR	N
68	GURAPPA B H	39	M	8958	98	104	74	20	37	Alcohol	33.32	Diabetes Mellitus	15.8	17300	9.0	548	237	195	178.1	38	NEGATIVE	37	ANTERIOR WALL	40%	NILL	N

69	MOULASAB H D	65	M	22740	54	108	89	14	37	Smoking	32.86	Diabetes Mellitus	12.3	9200	42.0	85	249	182	158.1	38	NEGATIVE	42	NORMAL	60%	NILL	N
70	SANGAPPA M S	65	M	2355	88	132	78	16	37.2	Smoking	28.00	-	18.6	12100	19.0	170	255	200	151.5	38	POSITIVE	30	ANTERIOR WALL	40%	NILL	N
71	SIDDABAI	42	F	40187	80	136	66	14	37.1	Alcohol	27.11	Hypertension	17.9	6252	10.0	232	211	181	161.8	39	POSITIVE	92	ANTERIOLATERAL WALL	50%	NILL	NILL
72	BALA SAHEB	21	M	8854	64	121	64	16	36.9	Smoking	24.51	-	8.6	11840	36.0	504	209	194	170.1	38	POSITIVE	112	INFERIOLATERAL WALL	50%	NILL	NILL
73	BAHUBALI	65	M	10063	120	124	89	32	37	Smoking	24.45	-	18.2	17110	11.0	274	218	206	147.0	25	POSITIVE	72	INFERIO LATERAL WALL	55%	G 3 AR	NILL
74	GANGARAM	53	M	11400	88	102	88	14	37	-	33.76	Hypertension	13.8	21150	23.0	129	250	184	144.1	32	POSITIVE	206	ANTERIOSEPTAL WALL	45%	G 1 MR	NILL
75	MACHINDRA	21	M	11608	60	102	66	14	37.4	-	33.76	-	19.5	11620	29.0	537	250	179	179.2	37	POSITIVE	225	ANTERIOSEPTAL WALL	45%	G 1 MR	NILL
76	HEMANTH	48	M	12702	170	102	66	40	37	-	25.71	Diabetes Mellitus	19.5	23300	17.0	524	214	181	191.8	39	N	40	ANTERIOR WALL	35%	G 2 MR	G 1
77	NINGANNA	45	M	13046	78	129	69	16	37.1	Smoking	24.16	-	9.2	9130	8.0	112	244	189	173.5	37	NEGATIVE	34	INFERIOLATERAL WALL	55%	G 1 MR	NILL
78	RAYAWWA	45	F	25005	60	90	62	20	37.1	-	34.67	Diabetes Mellitus	17.9	11810	3.0	392	300	179	195.7	27	POSITIVE	72	INFERIOR WALL	50%	NILL	N
79	JAKAWWA	45	F	24155	70	98	67	14	37	Alcohol	33.91	Diabetes Mellitus	9.8	7600	14.0	463	286	181	178.4	35	POSITIVE	60	INFERIOR WALL	60%	NILL	G 1
80	JANABAI	44	F	25101	80	114	82	14	36	-	32.66	Diabetes Mellitus	9.5	5200	23.0	292	222	165	152.9	24	POSITIVE	56	INFERIOR WALL	50%	NILL	G 1
81	SATAWWA	43	F	24199	128	116	72	30	37	-	32.04	-	14.2	19160	32.0	73	223	199	169.7	25	POSITIVE	55	INFERIOLATERAL WALL	45%	NILL	N
82	KUBUMONU	35	M	23180	56	117	84	16	37.1	Alcohol	31.89	Diabetes Mellitus	14.7	9550	12.0	247	215	194	187.4	34	NEGATIVE	26	LATERAL WALL	60%	NILL	NG 1
83	SAMPATH	45	M	23306	90	116	63	14	37	-	24.80	Hypertension	16.4	6180	31.0	421	210	176	187.5	33	POSITIVE	46	ANTERIOR WALL	45%	NILL	N
84	SOMANNA	48	M	24384	100	143	89	34	36.8	-	26.52	-	11.9	10000	6.0	451	263	185	169.1	36	POSITIVE	30	ANTERIOR WALL	35%	G 1 TR, G 2 MR	N
85	PRAKASH	65	M	25001	90	120	88	16	36.8	Alcohol	31.64	Hypertension	18.4	12650	38.0	112	224	200	188.8	38	NEGATIVE	82	ANTERIOR WALL	45%	NILL	N
86	SHARAWWA	43	F	20731	80	124	89	14	37	-	31.53	-	18.2	9460	13.0	187	251	194	158.1	38	POSITIVE	79	INFERIOLATERAL WALL	40%	NILL	NILL
87	PRAJAWATHI	45	F	21517	68	116	63	14	36	Smoking	32.24	-	16.4	10700	44.0	277	219	208	174.9	35	POSITIVE	157	NORMAL	60%	NILL	G 1
88	TULASABAI	43	F	18647	98	130	97	14	37	Smoking	28.70	-	18.5	15330	37.0	180	223	205	147.0	29	NEGATIVE	34	INFERIOR WALL	50%	NILL	NILL
89	RACHAYYA	35	M	2267	104	120	88	15	37.1	Alcohol	24.56	Hypertension	18.4	36950	43.0	223	210	198	141.3	27	POSITIVE	52	INFERIOR WALL	55%	NILL	NILL
90	SANGANNA GOUDA	39	M	19796	80	138	86	16	36.8	-	26.84	-	10.9	18270	18.0	128	249	177	170.9	26	POSITIVE	20	INFERIOR WALL	60%	NILL	NILL
91	RADHA	41	F	18253	90	125	63	15	37.1	Smoking	24.45	Diabetes Mellitus	13.6	28030	6.0	332	269	206	184.4	38	NEGATIVE	15	ANTERIOSEPTAL	60%	G 1 TR	NILL
92	NANAGOUDA	71	M	19443	130	139	70	15	37	-	22.03	Hypertension	13.5	16190	10.0	76	272	206	176.1	26	POSITIVE	85	ANTERIOR WALL	40%	NILL	NILL
93	TOTAPPA	58	M	3082	90	122	78	14	37	-	31.53	-	10.5	8900	28.0	54	178	208	159.6	37	NEGATIVE	29	ANTERIOR WALL	40%	NILL	NILL
94	TARABAI	23	F	13743	98	130	97	14	37	-	24.14	-	18.5	10530	45.0	537	289	199	205.1	37	NEGATIVE	61	INFERIOLATERAL WALL	55%	NILL	NILL
95	SAHEER AHMAD	60	M	6166	64	115	74	14	37.1	Smoking	25.10	Hypertension	11.7	23720	13.0	306	220	208	170.1	32	POSITIVE	66	ANTERIOR WALL	45%	GRADE 1 MR	GRADE 1
96	SATTAPPA	66	M	6619	74	136	66	16	37.1	-	23.23	Hypertension	17.9	19760	31.0	193	208	181	177.6	31	POSITIVE	85	ANTERIOLATERAL WALL	40%	NILL	NILL
97	SIDDAPPA	51	M	7060	86	129	84	14	37	Smoking	28.94	Hypertension	8.6	17640	12.0	421	230	182	193.3	38	POSITIVE	180	ANTERIOR WALL	45%	NILL	NILL
98	PARVATHI	45	F	16198	120	125	84	16	37	Alcohol	31.38	Diabetes Mellitus	8.1	15490	32.0	544	210	194	186.9	35	POSITIVE	57	INFERIOLATERAL WALL	40%	NILL	NILL
99	SIDDAMMA	42	F	15206	58	104	74	24	37	Smoking	25.39	Diabetes Mellitus	15.8	31540	35.0	329	209	208	171.6	37	POSITIVE	129	ANTERIOSEPTAL WALL	35%	G 3 MR	NILL
100	MAHAVEER	58	M	20668	98	135	72	14	37	Alcohol	27.56	Diabetes Mellitus	14.9	14700	30.0	525	284	178	156.1	37	POSITIVE	78	ANTERIOR WALL	50%	NILL	G 1

CONTROLS																
S.NO	NAME	IP.NO	Age	Sex	BMI	Comorbidities	Habits	Hb	ESR	SBP	DBP	Ferritin	TCh	TG	LDL	HDL
1	BHIMANNA	7980	59	M	23.41	Hypertension	-	17.32	23	96.1	58.2	196	166	119	63	43
2	SANGANAGOUDA	26214	51	M	24.54	Diabetes Mellitus	Alcohol	11.31	24	144.1	89.8	183	205	142	140	37
3	SAVITRI	13427	38	F	22.15	-	-	13.02	4	131.1	66.8	114	208	148	169	48
4	SURESH	28416	65	M	22.98	Diabetes Mellitus	-	14.59	34	111.1	92.2	82	194	150	142	45
5	KASHIBAI	25889	32	F	22.43	-	-	12.72	38	123.1	69.2	45	205	143	154	37
6	SHANKRAPPA	29051	44	M	22.80	Diabetes Mellitus	Smoking	9.72	8	122.1	75.2	33	165	140	102	38
7	SAMPAD	23306	62	M	29.63	Hypertension	Smoking	11.32	11	111.3	76.4	202	182	119	122	48
8	FATIMA	28312	42	F	32.37	-	Smoking	18.33	14	84.3	65.4	187	205	108	64	42
9	LAALSINGH	23330	46	M	23.18	Hypertension	-	17.01	15	108.1	76.2	312	176	168	135	47
10	SAHEBAGOUDA	28716	46	M	25.47	-	Smoking	10.84	6	137.7	57.8	47	189	161	142	51
11	KALAWATI	26378	41	F	31.02	Diabetes Mellitus	-	13.98	27	99.3	99.4	258	198	77	86	44
12	RAGHAVENDRA	10277	56	M	21.65	Hypertension	Alcohol	13.98	10	138.1	65.8	108	194	150	129	43
13	SANGAPPA	12712	45	M	23.10	-	Smoking	13.32	15	108.1	78.2	215	184	142	135	43
14	NAGARAJ	24182	44	M	23.76	Diabetes Mellitus	Alcohol	12.25	23	153.1	92.2	271	196	149	88	43
15	Sanganagouda	26214	44	M	31.06	-	Alcohol	18.02	39	96.3	85.4	243	181	129	115	55
16	BASAPPA	28584	44	M	22.80	Diabetes Mellitus	-	18.22	20	121.1	57.2	43	177	151	108	30
17	IRAWWA	30143	39	F	21.79	Diabetes Mellitus	Alcohol	18.02	35	138.1	81.8	67	206	160	82	52
18	KASHIBAI	26414	40	F	24.81	Hypertension	Smoking	11.32	38	142.1	69.8	229	205	95	64	40
19	YAMANAPPA	29180	58	M	29.34	-	-	8.50	36	114.3	91.4	318	206	176	155	43
20	SAGAR	1625	47	M	31.46	Diabetes Mellitus	Alcohol	17.91	21	96.3	91.4	173	182	77	94	52
21	SHIVAPPA	3647	46	M	23.41	Hypertension	-	18.92	29	108.1	62.2	202	176	82	122	55
22	BASAVARAJ	26885	65	M	29.17	-	-	17.91	5	119.3	66.4	322	199	180	152	54
23	GANGAPPA	3330	48	M	22.98	-	Alcohol	7.42	10	115.1	61.2	128	185	156	154	52
24	SIDARAYA	11181	56	M	29.23	Hypertension	-	11.12	17	116.3	81.4	161	176	142	81	28
25	SHANKAR	27199	46	M	25.04	-	Smoking	12.92	27	141.7	83.8	212	177	78	143	42
26	NINGAPPA	15620	45	M	22.98	-	-	12.62	9	117.1	76.2	111	192	140	103	52
27	MALAKAPPA	13966	47	M	25.39	Hypertension	Alcohol	11.52	4	137.7	71.8	18	199	154	136	43
28	LAXMI	26971	39	F	19.67	-	-	13.32	6	156.1	79.8	45	179	160	142	43
29	DADAGOND	31606	46	M	24.41	-	Smoking	19.22	33	146.1	67.8	7	208	145	75	45
30	HANAMANTHRAYA	2321	62	M	21.43	Diabetes Mellitus	Alcohol	18.02	33	138.1	71.8	272	194	154	115	43
31	SATAWWA	29598	30	F	21.36	-	Alcohol	12.22	11	138.1	72.8	117	206	156	77	44
32	BHIMASHI	4968	47	M	31.71	-	-	17.11	30	90.3	69.4	171	165	78	88	38
33	MAHESH	27484	44	M	30.51	Diabetes Mellitus	-	12.22	38	103.3	68.4	217	185	142	94	41
34	SATYAPPA	2374	46	M	23.15	-	Alcohol	13.18	20	108.1	84.2	247	166	149	122	43
35	SONABAI	30956	30	F	21.84	-	Alcohol	17.91	28	136.1	100.8	248	181	166	81	43
36	SHOBA	33878	40	F	28.91	-	-	13.98	23	123.3	72.4	47	200	152	149	46
37	GOPAL	8111	57	M	30.00	Hypertension	-	14.02	7	110.3	82.4	159	199	108	122	43
38	MATANSAB	3385	47	M	23.41	Diabetes Mellitus	Alcohol	9.22	36	104.1	63.2	65	185	143	119	28
39	NEELAKANTAYYA	27516	54	M	20.26	-	Smoking	11.32	25	146.1	73.8	149	208	154	154	41

40	BASAPPA	1868	49	M	29.05	Diabetes Mellitus	Smoking	15.82	31	120.3	72.4	31	206	165	75	43
41	PRASHANTH	29632	48	M	24.19	Diabetes Mellitus	Smoking	12.13	8	150.1	78.2	219	185	100	105	28
42	TARASINGH	23336	32	F	21.86	Hypertension	Alcohol	8.03	19	135.1	87.8	108	188	154	149	43
43	BHIMANNA	7980	50	M	29.59	Diabetes Mellitus	Smoking	18.21	33	111.3	87.4	35	182	141	108	52
44	SUGALABAI	31726	41	F	30.09	-	Alcohol	11.52	33	109.3	64.4	122	165	152	154	47
45	SAMIRA	10054	33	F	22.38	-	Smoking	14.12	33	123.1	80.2	96	198	145	82	42
46	SUMATI	2353	40	F	29.23	Hypertension	Alcohol	9.44	8	118.3	92.4	232	176	129	128	43
47	VISHWANATH	34043	65	M	24.54	-	-	8.50	19	144.1	59.8	316	188	174	155	46
48	SUGALABAI	27517	40	F	24.55	-	-	18.21	10	143.1	81.8	63	185	150	108	41
49	PRAKASH	34767	42	M	21.76	Diabetes Mellitus	Alcohol	15.82	19	138.1	57.8	182	179	136	128	43
50	SANGAPPA	2355	50	M	22.43	-	Smoking	13.65	2	122.1	68.2	49	205	145	78	42
51	SHILANATH	6934	50	M	22.26	-	-	17.82	32	126.1	84.2	158	208	102	61	45
52	YALLAPPA	27321	44	M	20.36	-	-	12.92	29	145.1	73.8	166	206	149	61	43
53	VEERAGENSAPPA	33083	53	M	26.64	Hypertension	Smoking	18.02	37	123.3	87.4	206	184	136	128	52
54	AMEENSAB	25037	48	M	22.80	-	-	11.12	19	121.1	70.2	31	192	144	119	42
55	SUBHASH	1469	53	M	19.77	Hypertension	Alcohol	12.25	2	153.1	99.8	159	206	108	155	42
56	TANAJI	3175	65	M	30.30	Hypertension	Alcohol	17.31	14	109.3	77.4	308	206	166	63	44
57	RAGAPPA	33333	57	M	25.70	-	-	14.29	37	126.3	81.4	274	188	154	135	43
58	RACHAPPA	25780	46	M	25.39	-	-	14.02	16	137.7	72.8	226	200	82	122	53
59	MONESH	28160	49	M	22.21	-	-	9.91	38	128.1	81.8	77	181	160	119	43
60	PRABHU	24269	57	M	25.39	-	Alcohol	17.31	36	137.7	65.8	122	176	157	149	47
61	SHIVABAI	31468	40	F	23.09	Diabetes Mellitus	Alcohol	15.22	4	110.1	70.2	77	200	141	136	53
62	LAKKAPPA	44243	54	M	23.41	Hypertension	Alcohol	16.10	19	102.1	62.2	107	196	142	102	43
63	SHIVASHANKAR	37789	58	M	19.87	-	-	11.12	19	150.1	85.8	62	184	154	149	43
64	GOURABAI	2576	42	F	31.61	-	Smoking	10.23	40	92.3	70.4	144	206	140	169	43
65	PRABHAKAR	30347	51	M	22.50	Diabetes Mellitus	-	15.80	14	122.1	59.2	253	179	169	115	42
66	HANUMANTH	27619	65	M	31.46	Diabetes Mellitus	-	19.93	18	96.3	69.4	82	181	161	100	42
67	PARVATI	3085	38	F	21.87	Hypertension	Smoking	16.92	38	132.1	72.8	31	206	148	157	38
68	RAJKUMAR	30154	51	M	21.86	Hypertension	-	8.62	21	135.1	72.8	61	177	154	157	42
69	BABU	43198	47	M	25.26	-	-	10.38	36	140.7	75.8	164	192	142	105	42
70	KALLAPPA	27835	49	M	24.37	Hypertension	Smoking	9.51	34	147.1	91.8	53	182	140	136	48
71	ASHOK KUMAR	3758	57	M	22.80	-	Smoking	8.97	13	120.1	78.2	96	181	155	95	43
72	IRAPPA	29257	50	M	20.16	-	Smoking	18.21	8	146.1	67.8	319	208	178	140	41
73	BASAMMA	32212	40	F	19.80	-	-	9.44	10	152.1	92.8	90	181	160	129	55
74	BHUMANNA	6593	46	M	23.92	Hypertension	-	10.45	30	152.1	85.2	163	206	154	143	38
75	BABUGOND	32824	65	M	22.21	Hypertension	-	8.02	36	127.1	67.8	58	184	157	142	52
76	KANTEWWA	27505	41	F	29.74	Hypertension	Smoking	12.92	14	110.3	75.4	313	165	170	140	47
77	MANAPPA	32823	58	M	20.93	Hypertension	-	17.31	22	142.1	69.8	22	176	157	95	28
78	LATA	8316	39	F	19.97	-	-	11.31	30	149.1	92.8	187	200	149	135	46
79	BASAPPA	27690	58	M	20.36	-	-	10.38	9	144.1	89.8	185	189	157	128	51
80	CHETAN	38897	47	M	22.01	Hypertension	Alcohol	7.57	33	131.1	87.8	241	181	102	86	42
81	SHANTABAI	18040	39	F	20.07	Diabetes Mellitus	Smoking	8.50	13	147.1	91.8	224	181	136	105	43
82	GURULINGAPPAGOUDA	29104	49	M	22.15	Hypertension	Alcohol	17.61	6	130.1	92.8	237	194	100	128	45
83	SANJU	6330	46	M	29.23	-	-	11.31	14	115.3	67.4	93	166	146	136	43
84	LAXMAN	32877	50	M	31.46	-	Smoking	18.02	13	96.3	83.4	292	206	169	152	46
85	MALAKAWWA	27774	42	F	30.36	-	Smoking	10.84	34	108.3	85.4	97	179	150	129	42
86	NEELAKANTHA	20488	48	M	24.54	-	Alcohol	11.12	16	145.1	73.8	247	198	103	68	42

87	LAXMAN	18339	46	M	24.54	Diabetes Mellitus	-	9.44	20	146.1	73.8	81	176	165	142	43
88	SAYEERU	22573	42	F	29.94	Diabetes Mellitus	Alcohol	10.38	30	110.3	66.4	178	177	136	94	30
89	SHANTABAI	29708	51	M	23.61	Hypertension	-	13.32	19	156.1	72.2	100	198	154	100	44
90	MURAGEPPA	24273	42	M	21.12	-	-	10.84	9	142.1	83.8	141	188	164	169	46
91	NEBUSAB	32444	51	M	22.98	-	Smoking	11.78	24	114.1	85.2	284	192	169	89	52
92	ASHOK	21682	50	M	20.75	Hypertension	Smoking	11.52	24	143.1	81.8	52	176	156	136	55
93	VIDYANAND	38856	59	M	20.46	Hypertension	Smoking	14.02	9	144.1	59.8	314	185	172	140	52
94	RAMU	20812	51	M	31.02	Hypertension	Alcohol	15.82	39	98.3	77.4	7	206	146	169	42
95	KAMALABAI	28026	33	F	21.29	Diabetes Mellitus	Smoking	14.29	28	141.1	75.8	222	206	129	68	52
96	SUNIL	32303	46	M	24.22	Diabetes Mellitus	Alcohol	12.32	33	149.1	92.8	78	205	164	78	40
97	BIBIJAN	5358	41	F	26.40	-	Smoking	12.22	16	124.3	100.4	149	199	158	166	54
98	SHRATHAMMA	16612	42	F	29.08	-	Smoking	18.02	6	119.3	87.4	49	166	151	77	43
99	SHANTABAI	29406	42	F	30.49	-	-	14.29	14	105.3	83.4	111	206	150	166	46
100	ADIVEPPA	42713	46	M	30.56	-	Smoking	18.02	7	102.3	92.4	307	208	154	155	48