"ASSESSMENT OF SERUM PROLACTIN LEVELS AS A RISK FACTOR IN ACUTE MYOCARDIAL INFARCTION"

By

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Dissertation submitted to BLDE (DU) 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 ABBREVIATIONS

ACS	-	Acute Coronary Syndrome
IHD	-	Ischemic Heart Disease
AMI	-	Acute Myocardial Infarction
CAD	-	Coronary Artery Disease
UA	-	Unstable Angina
TRH	-	Thyrotropin Releasing Hormone
PRL	-	Prolactin
PDA	-	Posterior Descending Artery
RCA	-	Right Coronary Artery
LAD	-	Left Anterior Descending artery
LCx	-	Left Circumflex Artery
TG	-	Triglycerides
CHO	-	Cholesterol
LDL	-	Low Density Lipoprotein
VLDL	-	Very Low Density Lipoprotein
HDL	-	High Density Lipoprotein
NADPH	-	Nicotinamide Adenine Dinucleotide Phosphate
LBBB	-	Left Bundle Branch Block
PCI	-	Percutaneous Coronary Intervention
CABG	-	Coronary Artery Bypass Grafting
RISK	-	Reperfusion Injury Salvage Kinase
PTP	-	Permeability Transition Pore
ATP	-	Adenosine Triphosphate
ADP	-	Adenosine Diphosphate

cTn	-	Cardiac Troponin
hs-Tn	-	High sensitive Troponin
CRP	-	C-Reactive protein
BNP	-	Brain Natriuretic Peptide
Ca	-	Calcium
LMWH	-	Low Molecular Weight Heparin
UFH	-	Unfractionated Heparin
aPTT	-	Activated Partial Thromboplastin Time
TIMI	-	Thrombolysis In Myocardial Infarction
LVEF	-	Left Ventricular Ejection fraction
REPAIR-AMI	-	Reinfusion of Enriched Progenitor cells and Infarct Remodelling in Acute Myocardial Infarction
AIP	-	Atherogenic Index of Plasma
MPV	-	Mean Platelet volume
VIP	-	Vasoactive Intestinal Peptide
TIDA	-	Tuberoinfundibular Dopamine
ELISA	-	Enzyme Linked Immuno Sorbent Assay

ABSTRACT

BACKGROUND:

Acute Coronary Syndrome is the most common form of heart disease world-wide and the single most important cause of premature death. The disease of the coronary arteries is almost always as a resultant of atheroma formation and its associated complications. One of the precipitating factors for the progression of atherosclerosis is presence of inflammation.

Prolactin is synthesized and secreted from the anterior pituitary lactotrophic cells. Neuroendocrine stress reaction to acute coronary syndromes may be reflected by hyperprolactinemia, which induces acute endothelial dysfunction, insulin resistance, and induction of vascular immune reactions. Hyperprolactinemia leads to dyslipidemia, augmentation of platelets aggregation and amplification of vascular thrombosis leading to increased risk score of acute coronary syndrome.

OBJECTIVES OF THE STUDY:

- To evaluate serum prolactin levels as a risk factor in acute myocardial infarction.
- To compare the serum prolactin levels in patients of acute myocardial infarction with age and gender matched healthy controls.

METHODOLOGY:

A prospective cross-sectional comparative study was conducted by studying 38 patients of Acute Myocardial Infarction and 38 patients of age and sex matched controls who attended the outpatient department or those who were

admitted in the wards of Shri B. M. Patil Medical College and Hospital. The patients who were considered into the study were to satisfy the inclusion and exclusion criteria. Serum prolactin levels were determined by using sandwich ELISA method and the levels were compared between both the groups.

RESULTS:

In our study, out of 38 patients of acute myocardial infarction, 31 patients showed raised serum prolactin levels with a mean of 43.1 ng/ml and a p-value of <0.001. Out of 38 controls, only 3 subjects had raised serum prolactin levels with a mean value of 12.7 ng/ml. We also observed that, among the cases of acute MI, the mean troponin-I levels were significantly elevated in patients with raised serum prolactin compared to patients with normal serum prolactin levels.

CONCLUSION:

Serum prolactin levels are significantly elevated in cases of Acute Myocardial Infarction. Serum prolactin levels are positively correlated with levels of Troponin-I, reflecting the underlying cardiovascular complications. MPV values are increased in cases of acute MI with raised serum prolactin levels, indicating the effect of prolactin on platelet aggregation. Thus, serum prolactin levels can be used as predictor of Acute Myocardial Infarction with sensitivity and specificity of 84.2% and 81.6% respectively.

KEYWORDS:

Acute Myocardial Infarction, Prolactin, Atherosclerosis, Platelet aggregation

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INTRODUCTION

Acute Coronary Syndrome is the most common form of heart disease world-wide and the single most important cause of premature death. The disease of the coronary arteries is almost always as a resultant of atheroma formation and its associated complications. Atherosclerosis is an advancing inflammatory disorder of the arterial wall which is characterized by formation of atheroma, leading to occlusion of the vessel. It can affect any artery in the body and it begins in early life. One of the precipitating factors for the progression of atherosclerosis is presence of inflammation. Atherosclerosis begins with deposition of focal lipid rich deposits of atheroma that remain clinically dormant until they enlarge and impair tissue perfusion. A vulnerable atherosclerotic plaque is characterized by a lipid rich core, a thin fibro-cellular cap and increased inflammatory cells that release specific enzymes to degrade the matrix proteins. As the vulnerable plaque ruptures, it consecutively leads to thrombus formation and occlusion of the affected coronary vessel, causing ischemia and necrosis of the subtended myocardium. These events that occur in the coronary arteries are termed as Acute Coronary Syndrome. [1]

Acute Coronary Syndrome (ACS) includes acute myocardial infarction (STEMI and NSTEMI) and unstable angina pectoris (UAP). ST-Elevation Myocardial Infarction (STEMI) and Non-ST elevation Myocardial Infarction (NSTEMI) are the components of Acute Myocardial infarction.

Prolactin is synthesized and secreted from the anterior pituitary lactotrophic cells. [2] Thyrotropin releasing hormone (TRH) stimulates prolactin secretion and dopamine inhibits it. [3] Extra-pituitary prolactin is found in the cerebral cortex, amygdala, spinal cord, immune cells,

sweat glands, myometrium, lacrimal glands, thymus, and skin fibroblast. This extra pituitary prolactin is not regulated by dopamine. [4]

Neuroendocrine stress reaction to acute coronary syndromes may be reflected by hyperprolactinemia, which induces acute endothelial dysfunction, insulin resistance, and induction of vascular immune reactions. Thus, prolonged hyperprolactinemia lead to arteriosclerosis, augmentation of arterial stiffness, and hypertension. [5] Hyperprolactinemia leads to dyslipidemia, augmentation of platelets aggregation and amplification of vascular thrombosis leading to increased risk score of acute coronary syndrome. [6] Serum prolactin is positively correlated with blood pressure and cardiovascular complications. [7]

Immunohistological studies, implicate prolactin in the pathogenesis of acute coronary syndrome by local paracrine effects of prolactin on vascular smooth muscle hyperplasia in the development of coronary atherosclerosis. [8,9] High serum prolactin levels cause a significant vasoconstriction and induction of oxidative stress in the coronary vessels as prolactin receptors are overexpressed in atherosclerotic plaque macrophage and this indicates the association between prolactin and induction of inflammatory markers that may explain the connection between serum prolactin and cardiovascular mortality. [10]

AIMS AND OBJECTIVES OF STUDY

- To evaluate serum prolactin levels as a risk factor in acute myocardial infarction.
- To compare the serum prolactin levels in patients of acute myocardial infarction with age and gender matched healthy controls.

REVIEW OF LITERATURE

CORONARY VASCULATURE:

From the left and right aortic sinuses arise the left and right coronary arteries, respectively, and their ostia, which normally originate about two-thirds the distance from the aortic annulus to the sino-tubular junction and about midway between the aortic commissures. [11,12,13] The right coronary artery arises almost perpendicularly from the aorta and the left arises at an acute angle.

Rarely, the anterior descending and circumflex arteries arise separately from a double-barrel left coronary ostium.

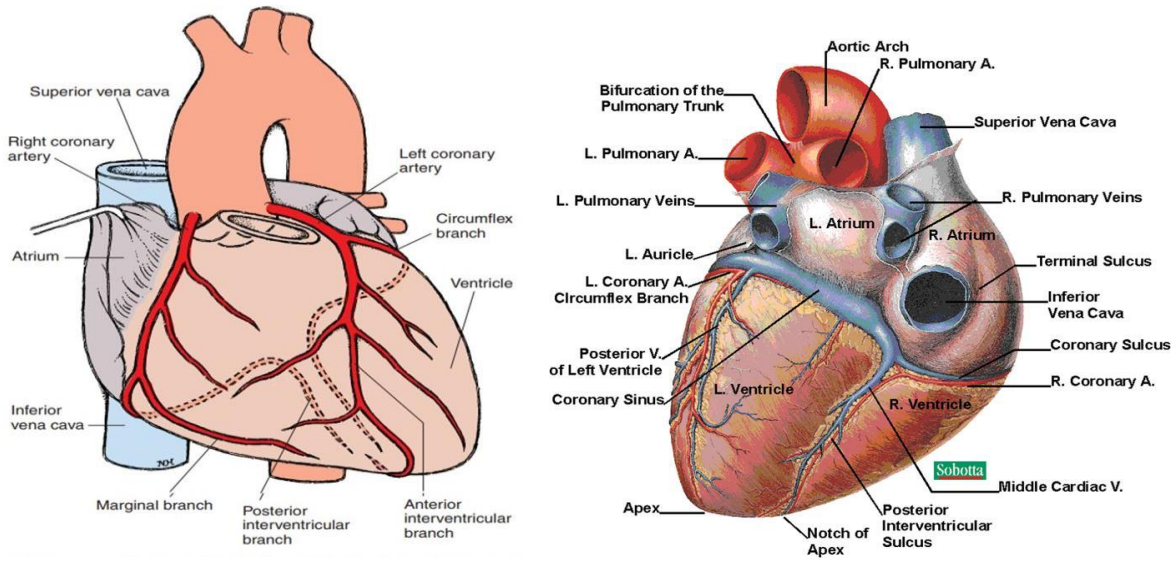


Fig. 1: Coronary circulation. Anterior and posterior view of coronary arteries

DOMINANCE:

In general, the RCA will be dominant in 60–65% of cases as it gives off a PDA branch (balanced coronary circulation). In about 10–15% of cases, the LCx gives off the PDA (left predominant circulation). In about 20- 25% of cases, the RCA, in addition to supplying the

PDA, crosses the posterior interventricular septum to reach as far as the left marginal artery and thereby supplying the diaphragmatic surface of the left ventricle (right predominance). [14,15] However, it does not distinguish this condition from balanced coronary circulation.

AREAS SUPPLIED:

Right coronary artery	**Left coronary (LAD) artery**	**Left circumflex coronary artery (LCX)**
Right ventricle	Anterior and lateral wall of LV	SA node (40-45%)
Right atrium	Most of the left ventricle	Left atrium
Diaphragmatic surface/ inferior wall of left ventricle (LV)	Interventricular septum (anterior 2/3rd)	AV node and bundle of His (10%)
Posterior wall of left ventricle (90%)	Right and left bundle branches	Lateral wall of LV
Posterior third of interventricular septum (90%)	-	Posterior third of interventricular septum (10%)
SA node (55-60%)		
AV node and bundle of His (90-90%)		

Table – 1: Areas supplied by coronary arteries

VENOUS DRAINAGE OF HEART:

The venous drainage of the heart is from the coronary sinus, anterior cardiac veins and the lesser cardiac (thebesian) veins. The epicardium and myocardium will be drained by coronary sinus and it opens into right atrium. [11,12,14,16]

CORONARY COLLATERALS AND LYMPHATIC SUPPLY: [17]

Coronary collaterals:

1. Provide communication between major coronary arteries and branches.
2. May dilate and provide blood supply beyond the obstructed/stenosed epicardial vessel.
3. May develop between the terminal extension of two arteries, between side branches of two arteries, between branches of same artery or within the same branch.
4. Most common in the ventricular septum, ventricular apex, anterior right ventricular free wall, anterolateral left ventricle free wall, cardiac crux and atrial surfaces.

Cardiac lymphatics

1. Lymphatics drain towards the epicardial surface and they merge to form the right and left channels.
2. Left and right channels travel in a retrograde fashion with their respective coronary arteries.
3. The left and right channels travel along the ascending aorta and merge before draining into the pretracheal lymph node.

The merged single lymphatic chain travels through a cardiac lymph node and finally empties into the right lymphatic duct.

CORONARY AUTOREGULATION: [18]

Coronary arterioles possess α adrenergic receptors, which mediate vasoconstriction and β-adrenergic receptor which mediate vasodilatation. In a normal human being, activity in the nor adrenergic nerves to the heart and injection of nor epinephrine causes coronary vasodilation, because of the fact that nor epinephrine increases the heart rate & the force of cardiac contraction. Similarly, when the systemic BP reduces, the effect of reflex increase in sympathetic discharge is increased coronary blood flow secondary to the metabolic changes in the myocardium at a time when the cutaneous, renal and splanchnic vessels are constricted. In this way, the circulation of heart, like that of the brain, is maintained when blood flow to other organs is compromised.

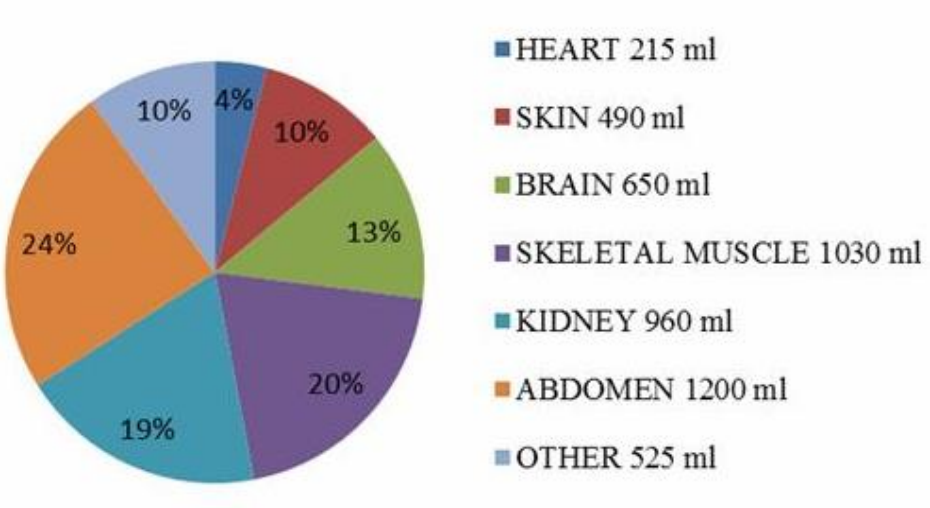


Fig. 2: Distribution of systemic blood flow to various organs of the body during rest

INFLAMMATION AND ATHEROSCLEROSIS:

Atherosclerosis is defined as a chronic inflammatory response to accumulation of lipid in the wall of arteries and is characterized by clinically intimal plaques that develop in arteries. Atherosclerosis is the leading reason for most of the myocardial infarction, ischemic strokes

and peripheral arterial disease, dementia and chronic heart failure. The major risk factors that facilitate the progression of atherosclerosis are hyperlipidaemia, Obesity, smoking, type 2 diabetes mellitus, hypertension, high plasma levels of lipoprotein, psychosocial stress, and sleep disturbances, elevated levels of serum homocysteine, elevated C - reactive protein and family history of coronary artery disease.

Inflammation plays a significant role at all the stages of development of atherosclerosis. The pathogenesis of atherosclerosis begins with interaction of endothelial cells and circulating leukocytes, resulting in T cell and macrophage recruitment and activation. As a consequence of this, smooth muscle cell accumulation and proliferation takes place, varying amounts of matrix production overlying an atheromatous lipid core, cholesterol, calcifications and necrotic debris; this constitutes an atheromatous plaque. Plaques vary in size and composition, most plaques remain asymptomatic, some become occlusive, and a few, become susceptible to rupture and lead to atherothrombotic events such as lethal cardiac arrest or incapacitating stroke.

The phenomenon of atherosclerosis commences when LDL accumulate in the vascular intima and get trapped in the wall of the artery. The trapped LDL particles are now attacked on by myeloperoxidase and NADPH oxidases. This leads to non-enzymatic oxidation of LDL, which further activates the macrophages and endothelial cells. This activation lead to T cell recruitment to the intimal layer of the arteries. The macrophages are known take up oxidized LDL and through the scavenger receptors, begin to gather cholesterol that eventually get converted to foam cells. The T cells identify the antigens presented by the macrophages (mostly LDL), and thus the accumulation of lipid in the intimal layer of arteries, triggers the chronic inflammatory process. The lipid rich plaques often have a hostile effect on the functioning of the endothelium, thus leading to exaggerated retention of lipid particles into the endothelium and there by inhibiting the clearance.

Most of the plaques remain stable, but a disruption of a partially occlusive plaques leads to thrombus formation and haemorrhage in to the core of plaques. This expands the plaque volume and thereby causing acute occlusion of the lumen of the arteries. [19,20,21,22]

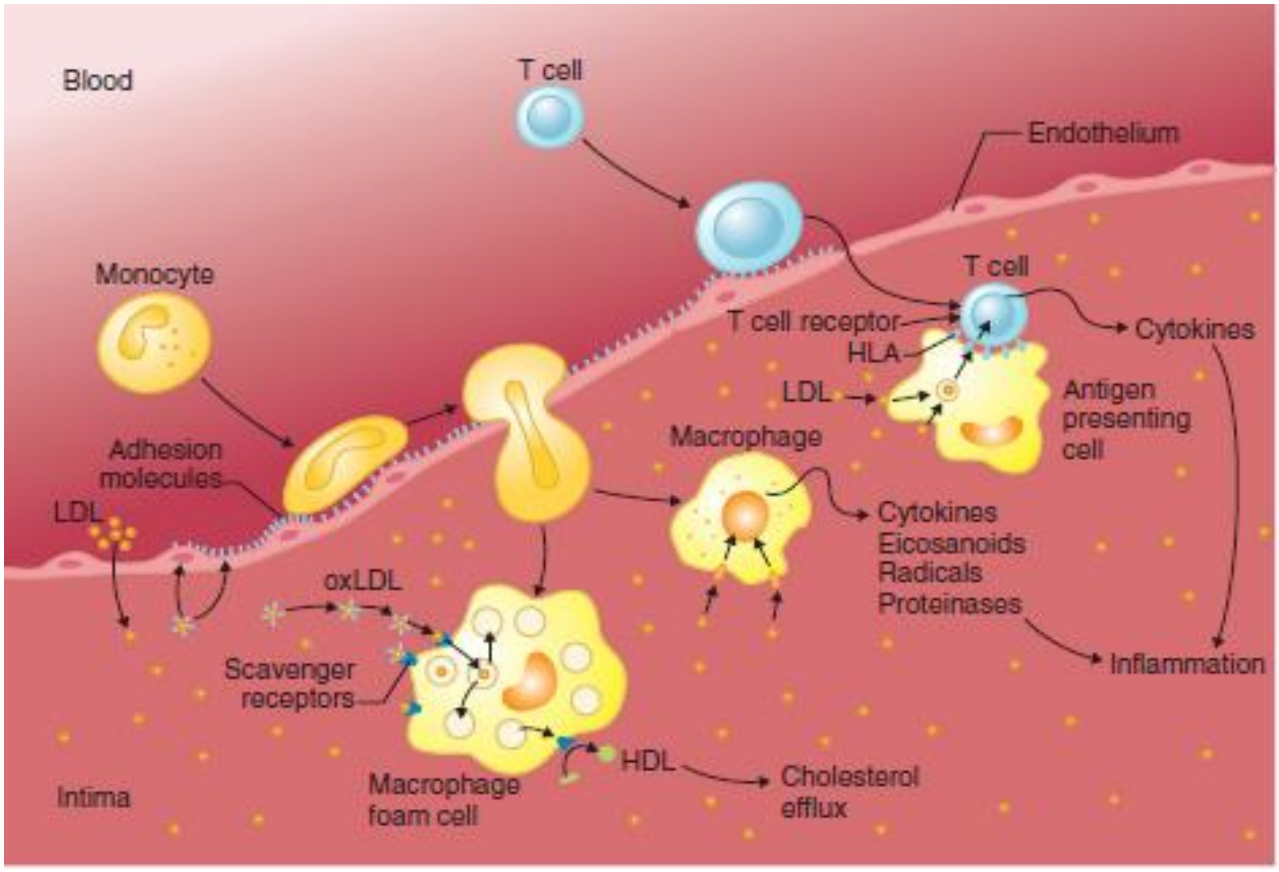


Fig. 3. Process of plaque formation

GROWTH AND PROGRESSION OF ATHEROSCLEROSIS:

The lesions of atherosclerosis gradually expand because of gathering of cholesterol, dissemination, activation and proliferation of inflammatory cells; further the core of the plaque grows due to the deposition of cellular debris and lipids. The collagen cap stabilizes the plaque mechanically but narrows the arterial lumen and the arteries undergo remodelling thus causing paradoxical vasoconstriction.

PLAQUE ACTIVATION, INFARCTION:

An atherosclerotic plaque usually remains stable and does not cause any clinical manifestations for days to years. However, if the surface of the plaque undergoes damage due to fissuring or plaque rupture, surface erosion can lead to sudden cardiac death. These events lead to formation of atherothrombosis. These atherothrombi rapidly expand and fill the lumen of the arteries leading to ischemia and infarction.

Thrombosis-prone atherosclerotic plaques, also known as high-risk or vulnerable plaques, are the main cause of death and severe disability worldwide. Although causal risk factors are known and constitute important therapeutic targets, their usefulness in risk assessment and finding people at the risk for an atherosclerotic event is limited. Most of the heart attacks and strokes occur in people who are not identified as being at particular high risk by conventional risk factor scoring. Atherothrombotic events are however, always preceded by a long pre-clinical phase in which sub-clinical atherosclerosis evolves and can be detected by non-invasive techniques and thereby offering unique opportunities for timely and individualized preventive care. [23]

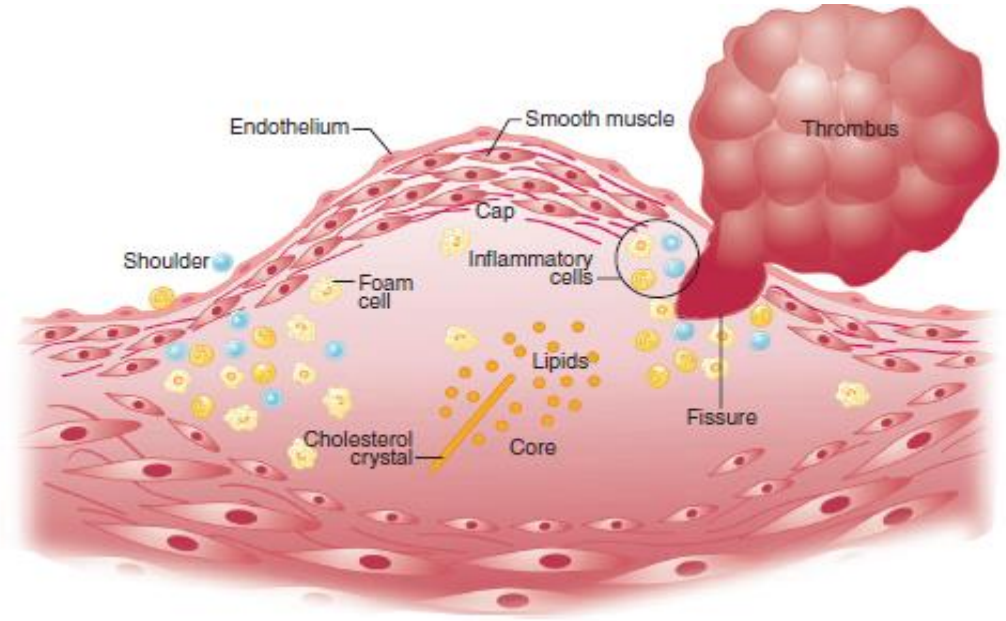


Fig. 4. Formation of thrombus

ACUTE MYOCARDIAL INFARCTION:

DEFINITION:

Myocardial infarction (MI) is the irreversible necrosis and death of cardiac muscle due to diminished blood supply to the heart which leads to myocardial cell damage and ischemia supplied by that artery. It happens mainly due to prolonged ischemia. [24] The atheromatous plaque rupture followed by thrombus formation is the hallmark event to develop MI.

The term Acute Coronary Syndrome (ACS) encompasses a spectrum of ST-elevation Myocardial Infarction (STEMI), Non-ST elevation Myocardial Infarction (NSETMI), and Unstable Angina (UA).

EPIDEMIOLOGY:

Acute MI is one of the single largest killer of male and female. An American suffers a Ischemic heart disease [IHD] event every 29 seconds, and dies of one every minute. 47% of people having a IHD event will die from it that year. More than 4,50,000 people die each year from a IHD event without being hospitalized, most from cardiac arrest, 84% of IHD deaths are among people aged ≥65 years and greater than 7 million have sustained a myocardial infarction. IHD is likely to become leading cause of death worldwide by 2020. Half of the death rate are reduced due to prompt diagnosis, treatment and life style modification. Global burden of diseases analysis showing there is shift from communicable diseases to non-communicable diseases. [24]

TYPES OF MYOCARDIAL INFARCTION:

CLASSIFICATION:

Based on the ECG morphology:

1. ST ELEVATION MYOCARDIAL INFARCTION
2. NON-ST-ELEVATION MYOCARDIAL INFARCTION

On the basis of pathological / gross examination:

1. TRANSMURAL
2. SUB ENDOCARDIAL (NON-TRANSMURAL)

On the basis of anatomical involvement:

1. ANTERIOR WALL MYOCARDIAL INFARCTION
    - ANTEROSEPTAL
    - ANTEROLATERAL
    - EXTENSIVE ANTERIOR WALL

2. INFERIOR WALL MYOCARDIAL INFARCTION
3. POSTERIOR WALL MI
4. RIGHT VENTRICULAR MI

Revised definition classifies MI in to five types depending on the circumstances on which it occurs. [25]

1. Spontaneous; this is related to ischemia caused by plaque erosion and/ or rupture, fissuring or dissection.
2. Myocardial infarction Secondary to ischemia caused by demand-supply mismatch (coronary spasm, embolism, arrhythmias, anaemia, hypertension, hypotension).
3. Sudden unexpected cardiac death, including cardiac arrest, with symptoms suggestive of myocardial ischemia, and presumably accompanied by new LBBB, or new ST-segment elevation, or a new major obstruction in a coronary artery angiographically and/or pathology, but death occurring before blood samples are taken, or before the cardiac biomarkers appear in blood.
4. 4a. Myocardial infarction associated with primary coronary intervention (PCI)
   4b. Myocardial infarction associated with stent thrombosis.
5. Myocardial infarction associated with CABG.

To be noted that patients may have more than one type of MI simultaneously or sequentially. Type 1 and 3 and 4b MIs have got the highest short- and long-term mortality rates and should be treated very aggressively with both medical and mechanical therapies. Type 2, 4a, and 5 MIs are associated with generally better short- and long-term outcomes.

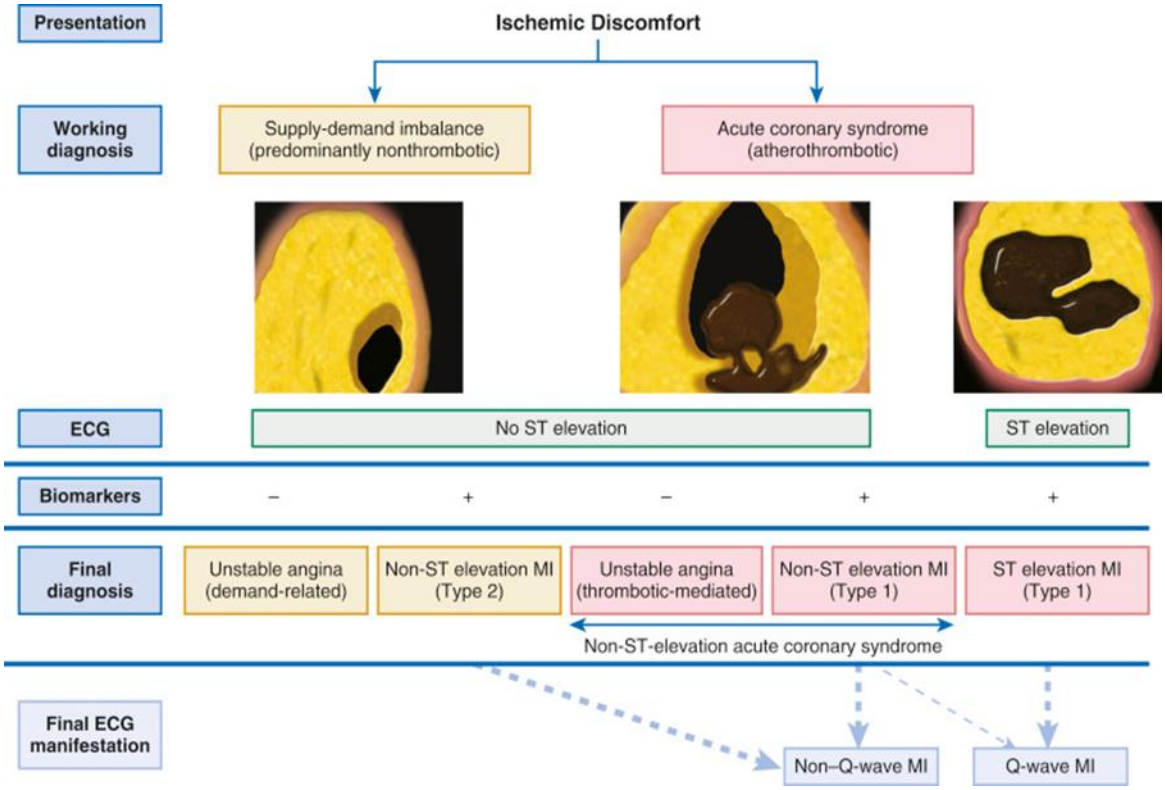


Fig. 5. Types of MI

Criteria for acute, Evolving or Recent MI: [25]

Any one of the criteria following below fulfils the diagnosis of acute, evolving, or recent myocardial infarction:

1. Rise and fall of biochemical markers of myocardial injury with atleast one of the following:
    a. Symptoms of ischemia
    b. Pathologic Q wave formation in the ECG
    c. Changes in the electrocardiogram consistent with ischemia (ST segment elevation or depression).
    d. New loss of viable myocardium or new regional wall motion abnormality evidenced by imaging methods.
2. Evidence of acute myocardial infarction documented pathologically.

Criteria for Healing or Healed Myocardial Infarction:

Any of the following criteria needs to be fulfilled for the diagnosis of healing or healed myocardial infarction.

1. New pathologic Q waves in serial ECGs. The patient may or may not remember previous symptoms. Cardiac injury markers of may have normalised.
2. Healed or healing infarction by pathological examination.

RISK FACTORS:

Table – 2: Risk factor

Lifestyle	**Biochemical or physiological characteristics (modifiable)**	**Personal characteristics (non-modifiable)**
-Diet high in saturated fat, cholesterol and calories -Tobacco smoking -Excess alcohol consumption -Physical inactivity	-Elevated blood pressure -Elevated plasma total cholesterol (LDL cholesterol) -Low plasma HDL cholesterol -Elevated plasma triglycerides -Hyperglycaemia/diabetes -Obesity -Thrombogenic factors	-Older age -Male gender -Family history of CHD or other atherosclerotic vascular disease at early age (men <55 years, women <65 years). -Personal history of CHD or other atherosclerotic vascular disease.

CAUSES OF MYOCARDIAL INFARCTION:

- Injury Related to Primary Myocardial Ischemia
    - Plaque rupture
    - Intraluminal coronary artery thrombus formation
- Injury Related to the Supply-Demand Imbalance of Myocardial Ischemia
    - Tachyarrhythmias/bradyarrhythmia
    - Aortic dissection or severe aortic valve disease
    - Hypertrophic cardiomyopathy
    - Cardiogenic, hypovolemic, or septic shock
    - Severe respiratory failure
    - Severe anaemia
    - Hypertension with or without left ventricular hypertrophy
    - Coronary spasm
    - Coronary embolism or vasculitis
    - Coronary endothelial dysfunction without significant coronary artery disease
- Injury Not Related to Myocardial Ischemia
    - Cardiac contusion, surgery, ablation, pacing, or defibrillator shocks
    - Rhabdomyolysis with cardiac involvement
    - Myocarditis
    - Cardiotoxic agents (e.g., anthracyclines, trastuzumab [Herceptin])
- Multifactorial or Indeterminate Myocardial Injury
    - Heart failure
    - Stress (takotsubo) cardiomyopathy
    - Severe pulmonary embolism or pulmonary hypertension
    - Sepsis and critically ill patients

- Renal failure
- Severe acute neurologic diseases (e.g., stroke, subarachnoid haemorrhage)
- Infiltrative diseases (e.g., amyloidosis, sarcoidosis)
- Strenuous exercise.

ETIOPATHOGENESIS:

The primary cause of acute myocardial infarction (MI) is coronary atherosclerosis with superimposed luminal thrombus, which accounts for more than 80% of all infarcts.

Eccentric plaque causes total variation in lumen leading to variable luminal stenosis. Concentric plaque will be having fixed stenosis. [26]

Fatty streaks – earliest lesion in atherosclerosis can be found in coronaries of children. [27] With increasing age these fatty streaks may evolve into fibro muscular plaques. Platelet adherence, platelet aggregation and release of smooth muscle growth factors, causes embryonic atherosclerotic plaque to increase in its size. Abnormal lipid deposition, necrosis and calcification occur in atherosclerotic plaque. Clinical presentation and prognosis of coronary AS depend on the type of plaque rather its size.[28]

PLAQUE MORPHOLOGY:

The majority of MIs occur in patients with coronary atherosclerosis, with almost more than 90% are associated with the superimposed luminal thrombi. Arbustini et al [29] found that coronary thrombi in 98% of patients dying with clinically documented acute MI, and of those thrombi, 75% were caused due to plaque rupture and 25% by plaque erosion. The culprit coronary artery of infarction at autopsy most commonly is the LAD (~50%) and then the right coronary artery (30%-45%) and the left circumflex artery (15%-20%). [30]

Table – 3: Differences between stable and unstable plaque

Stable plaque	Unstable plaque
▪ Small lipid pool. ▪ Thick fibrous cap. ▪ High grade stenosis. ▪ Not at bend or branch	▪ Large lipid pool. ▪ Younger, less stenosis. ▪ Located at branch points. ▪ Thin plaque cap. ▪ Numerous macrophages. ▪ Paucity of smooth muscle cells in cap.

PATHOPHYSIOLOGY:

Myocardial ischemia occurs when there is mismatch between oxygen supply and myocardial demand, and necrosis or infarction occurs when ischemia is severe and prolonged. Although biochemical and functional abnormalities begin almost immediately at onset of ischemia, severe loss of myocardial contractility occurs within 60 seconds, other changes take a more protracted course.

Reperfusion Injury:

The process of restoring blood flow to ischemic myocardium has shown utility in limiting cell death in the presence of severe ischemia. At the time of myocardial reperfusion, there is an abrupt increase in intracellular Ca++, leading to a disturbance in the normal mechanisms that regulate Ca++ within the cardiac myocyte which is known as the *calcium paradox*. [31,32,33]

The RISK (reperfusion injury salvage kinase) pathway refers to a group of protein kinases that when activated during myocardial reperfusion confer cardio protection by preventing lethal reperfusion injury. [34] The RISK pathway inhibits mitochondrial PTP opening and activates anti-apoptotic pathways and may also represent a mechanism for programmed cell survival reducing myocardial infarct size by up to 50%. [35]

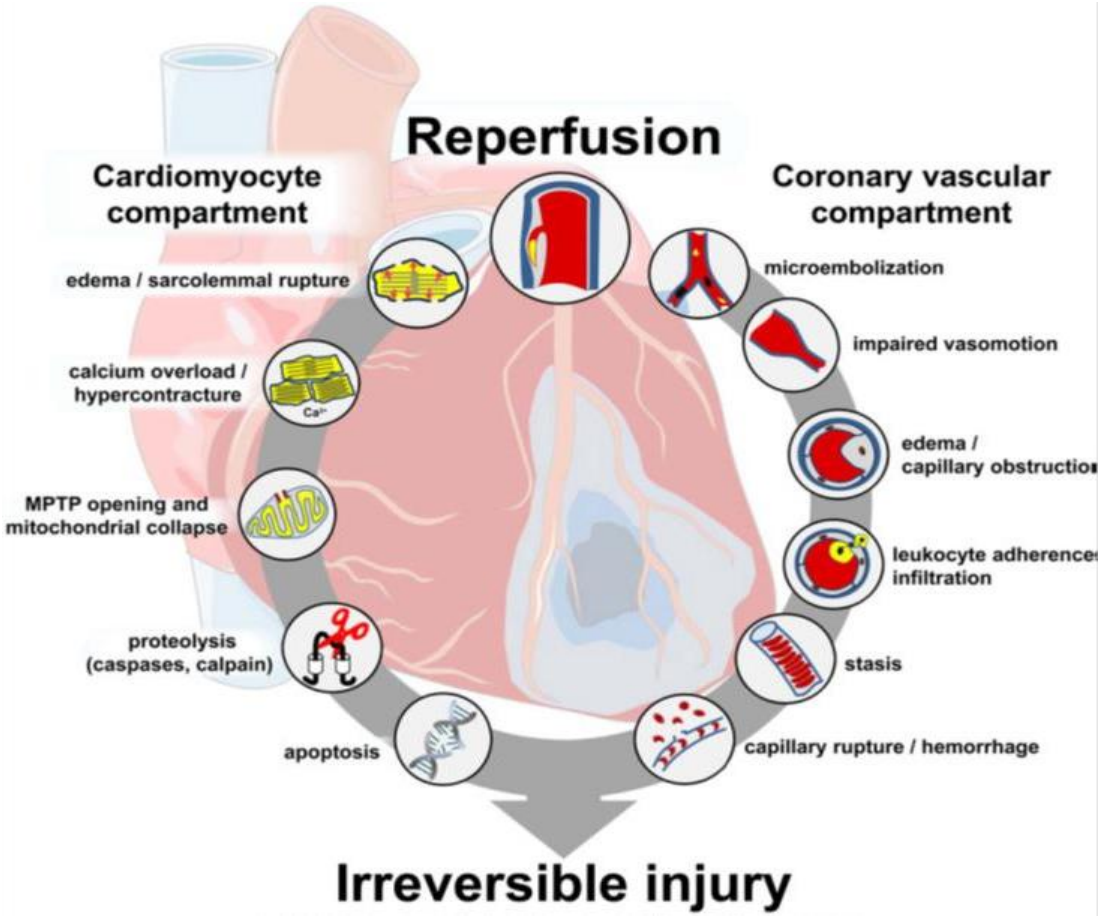


Fig. 6: REPERFUSION INJURY

HIBERNATING MYOCARDIUM: [36]

Stunned myocardium is a condition of transient left ventricular dysfunction following an ischemic event to the myocardium. It occurs if coronary blood flow was impaired for a brief period of time (5 to 15 minutes). Usually, stunned myocardium persists for hours or days

following the re-establishment of coronary blood flow.

However, prolonged exposure of the myocardium to an ischemic state, results in an impairment of its contractile function, which can be partial or complete, this is known as myocardial hibernation, and is reversible with revascularization.

Both myocardial stunning and hibernation occur because of loss of essential metabolites required for normal myocardial contractility, such as adenosine, which is needed for adenosine triphosphate (ATP) – dependent contraction.

CLINICAL FEATURES:

Chest pain is the most common presenting symptom in patients with myocardial infarction. Pain of acute myocardial infarction is severe & in some instances intolerable. It is prolonged, usually lasting for more than 30 minutes & frequently for a number of hours. The pain is usually retrosternal in location spreading frequently to both sides of the anterior chest with predilection for the left side. Often the pain radiates down the ulnar aspect of the left arm producing a tingling sensation in the left wrist, hand & fingers. Pain of acute MI is thought to arise from nerve endings in ischemia or injured, but not necrotic myocardium. [37]

Nausea & vomiting occur in more than 90% of patients with transmural myocardial infarction with severe chest pain. These symptoms occur more commonly in patients with anterior myocardial infarction than in those with inferior myocardial infarction. [38]

Other symptoms include feeling of profound weakness, dizziness, pain abdomen, palpitations, cold perspiration, sudden onset of breathlessness & sense of impending doom. On occasion, symptoms arising from an episode of cerebral embolism or other systemic arterial embolism are the first signs of STEMI.

Silent infarction occurs more commonly in patients without antecedent angina pectoris & in patients with diabetes & hypertension.

Atypical presentation of STEMI includes:

1) Heart failure i.e., dyspnoea without pain
2) Classic angina pectoris without a particularly severe or prolonged episode.
3) Atypical location of the pain.
4) CNS manifestations, resembling those of stroke, secondary to a sharp reduction in cardiac output in a patient with cerebral arteriosclerosis
5) Apprehension & nervousness.
6) Sudden mania or psychosis.
7) Syncope.
8) Overwhelming weakness;
9) Acute indigestion and,
10) Peripheral embolization

KILLIP CLASSIFICATION:

Killip and Kimball, in 1967, proposed a prognostic classification scheme on the basis of severity of rales detected in patients with STEMI. It classifies the heart failure in acute MI patient.

TABLE 4: KILLIP CLASSIFICATION

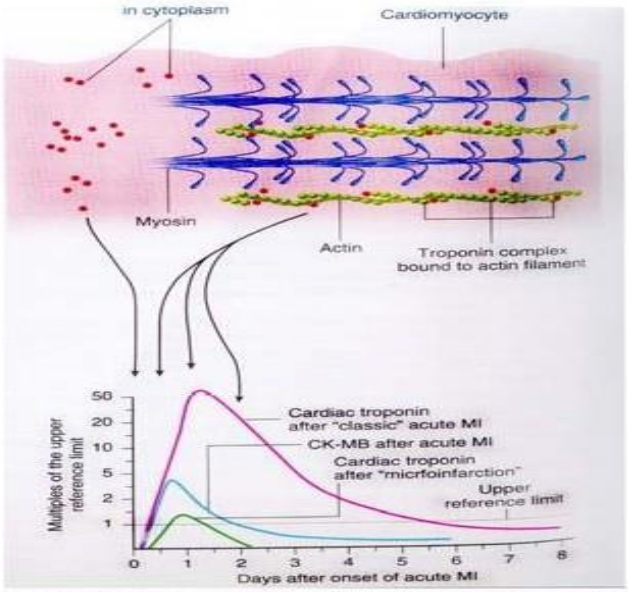
CLASS	DEFINITION	30 DAY MORTALITY
1	No S3 and Clear lung	5%
11	S3 or crackles <50% of lung	14%
	Crackles > 50% of lungs	
	Cardiogenic Shock	
111		32%
1V		57%

DIAGNOSIS:

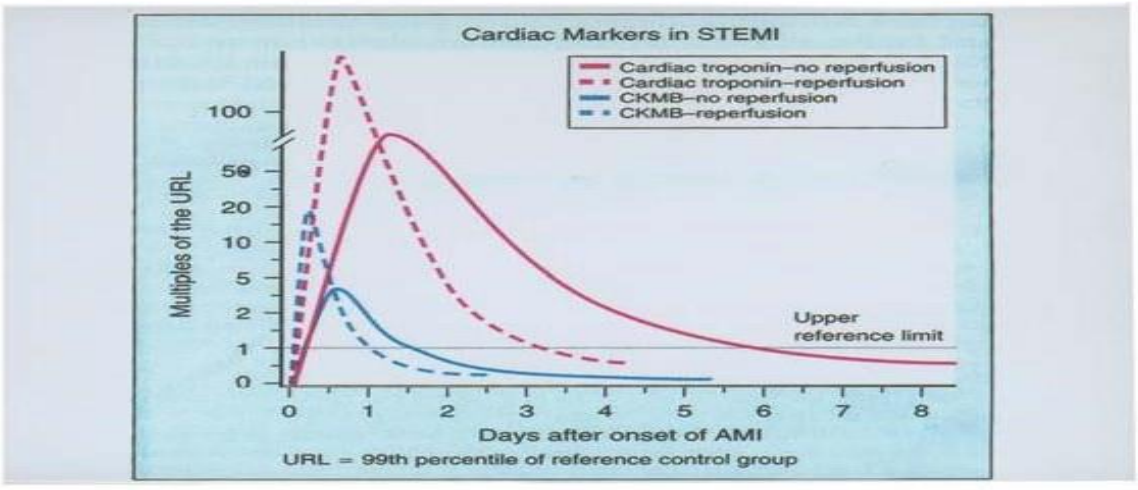
CARDIAC BIOMARKERS:

This is the main diagnostic criteria for detection of injury to myocardium. The markers of myocardial injury include CK, CK-MB, aspartate amino transferase, and lactate dehydrogenase and have limitations.

There is lack of specificity, limited sensitivity and short diagnostic window as they are expressed in skeletal muscles too. Due to these limitations and the presence unique amino acid sequence of myofibrillar cardiac troponin-I, monoclonal antibodies were developed for detection of cardiac troponin-I through immunoassay. [39]



CARDIOMYOCYTE IN THE PROCESS OF RELEASING BIOMARKERS



CARDIAC MARKERS IN STEMI

Fig. 7. Cardiac markers in STEMI

CREATININE PHOSPHOKINASE: [40-43]

There are 3 isoenzymes (MM, BB, MB). BB subtype is seen in brain and kidneys. The skeletal muscle contains the MM subtype and the cardiac muscles contain both MM and MB subtypes. The MB isoenzyme is also present in small quantities in the intestine, tongue, diaphragm, uterus and prostate. Strenuous exercise is associated with rise in both the CK-MB

and total creatinine kinase. For practical purposes, the elevation of CK-MB may be considered due to myocardial infarction unless proved otherwise. CK-MB is analysed by specific enzyme immunoassays which use monoclonal antibodies against CK-MB. At present, cardiac specific troponins play he vital role in diagnosing myocardial infarction because of its specificity towards the cardiac muscle.

Sensitivity and specificity of CPK is not as high as Troponins.

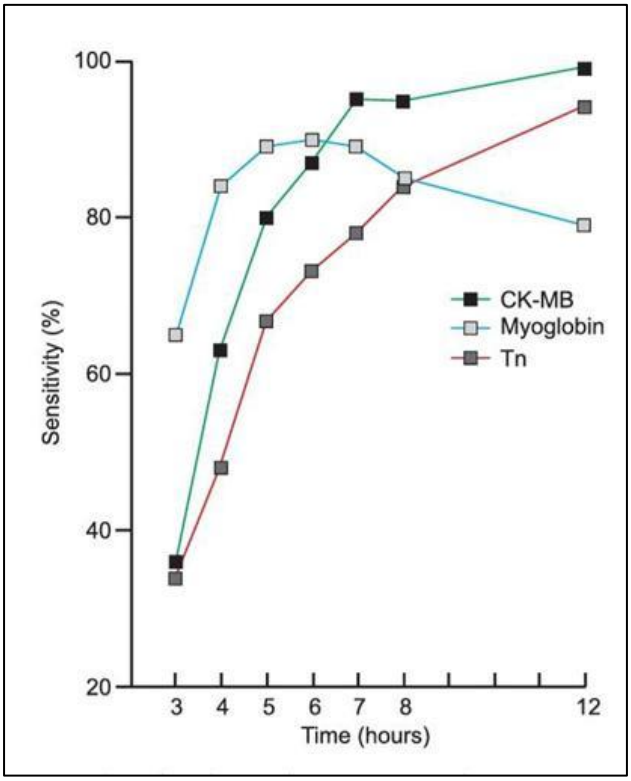


Fig. 8: Sensitivities of cardiac biomarkers over a 12-hour time course

TROPONINS:

Cardiac troponin (cTn) is a structural component of cardiac myocyte which is found at small quantities in the cytoplasm and very large quantities in the thin filaments. Among its three subunits (C, I, and T), the I and T subunits are highly specific to cardiac cells. They are the gold standard for detecting ischemic myocardial event and remote infarction.

TROPONIN I:

Three isoforms of TnI have been described, a cardiac (cTnI) and two skeletal muscle [slow twitch (sTnI) and fast twitch (fTnI)]. cTnI is 100% tissue-specific for the myocardium. cTnI has been shown to be a very sensitive and specific marker for acute myocardial infarction (AMI).

cTnI peaks between 14 and 36 h after onset of AMI and remains elevated for 10–14 days afterward, the result of continued proteolysis of the myocardial contractile apparatus. [44,50] Balk et al. [45] showed that when diagnosing AMI, initial troponin I and T (threshold range 0.1–0.6 ng/mL) had poor sensitivity (39%), but adequate specificity (93%). And serial measurements of cTn raised the sensitivity by nearly 2.5-fold, resulting in a sensitivity of 90–100% and a specificity of 83–96%.

Table – 5: Possible causes of troponin elevation, except in acute myocardial infarction

Cardiac causes	Noncardiac causes
Acute and chronic heart failure	Acute pulmonary oedema
Acute inflammatory myocarditis, endocarditis/pericarditis	Acute pulmonary embolism
Aortic dissection	Cardiotoxic drugs
Aortic valve disease	COPD
Apical balloon syndrome	Chronic renal failure
Bradyarrhythmia, heart block	Difficult exercise/excessive effort

Cardiac contusion	Infiltrative diseases (amyloidosis)
Cardiac surgery, post–percutaneous coronary intervention, endomyocardial biopsy	Nonacute critical cardiac disease
Cardioversion	Pulmonary hypertension
Hypertrophic cardiomyopathy	Rhabdomyolysis
Myocardial trauma	Sepsis
Tachycardia/tachyarrhythmia	Stroke, subarachnoid haemorrhage

HIGH SENSITIVE TROPONIN:

It is highly efficacious in predicting ACS detecting 27% more ACS cases compared to normal troponins. [46] Hs-Tn is slowly gaining use because of its improved ability to diagnose and detect infarcts of even minimal size.

Serum lipids:

It is mandatory to obtain lipid profile in all patients admitted with STEMI within 24 to 48 hours of symptoms. Studies tell that hypolipidemic therapy improves the endothelial function and inhibits thrombus formation.

This forms the basis of instituting early hypolipidemic therapy in patients who are admitted with STEMI. [47]

Hematologic findings:

White blood count starts increasing within 2 hours of chest pain and peaks in 2 to 4 days after infarction. The levels can range from 12,000 to 15,000. Sometimes even higher.

There is propensity of differential count to shift towards the band forms.

The ESR may be normal during the first two days and after that it rises reaching a peak on fourth or fifth day and remain elevated for weeks. There is also elevated haematocrit and CRP levels. Presenting haemoglobin values also predicts major cardiovascular events. [48] Cardiovascular mortality increases at values less than 14 to 15 mg/dl and more than 17 mg/dl. Former is due to anaemia resulting in diminished tissue delivery of oxygen and latter is due to the increased blood viscosity.

BNP:

B-type natriuretic peptide (BNP) is released from ventricular myocardium. BNP release can be stimulated by systolic and diastolic left ventricular dysfunction, acute coronary syndromes, stable coronary heart disease, valvular heart disease, acute and chronic right ventricular failure, and left and right ventricular hypertrophy secondary to arterial or pulmonary hypertension. BNP is a marker for heart failure.

CRP:

C-reactive protein (CRP) is an acute phase protein elevated when inflammation is present. Since inflammation is part of atheroma formation, then CRP may reflect the extent of atheromatous plaque formation and predict risk for acute coronary events. However, CRP lacks specificity for vascular events.

ECHOCARDIOGRAPHY:

Echocardiography is a non-invasive, rapid, portable, and inexpensive imaging modality, making it the preferred technique for the assessment of patients with myocardial infarction (MI). [49] ECG changes always do not correlate with the quantity of damaged myocardium, and the extent of the dysfunction often is considerably greater than expected relative to the size of the necrotic area, because it encompasses not only the zone of the actual

infarct but also stunned and hibernating segments and dysfunction from previous coronary events. Consequently, echocardiography is a better predictor of the extent and location of the MI and associated ventricular dysfunction than the ECG.

MANAGEMENT:

The initial management for patients with acute MI has the following aims:

- Restoration of the balance between oxygen supply and demand to prevent further ischemia
- Pain relief
- Prevention and treatment of complications

Non-pharmacological:

- Absolute Bed rest
- Continuous ECG monitoring for patients with ongoing chest pain at rest.
- Supplemental oxygen for patients with cyanosis or patients with respiratory distress or cyanosis

Pharmacological:

- Administer loading dose of T. Aspirin 325 mg, T. Clopidogrel 300mg, T. Atorvastatin 80mg.
- Give sublingual T. Nitroglycerine 5 -10 mg (if SBP >90)
- Chest pain may be relieved with morphine sulphate.

ANTI-PLATELET THERAPY:

ASPIRIN: [50,51]

Thromboxane A2 is blocked by aspirin which irreversibly inhibits cyclooxygenase 1, thereby diminishing platelet aggregation.

"The ACC/AHA guidelines" recommend an initial daily dose of 325mg followed by daily dose of 75mg to 162mg for long term secondary prevention.

Contraindications for aspirin therapy include aspirin allergy (asthma or anaphylaxis), active bleeding and platelet disorders.

CLOPIDOGREL: [52]

Clopidogrel decreases platelet activation and aggregation. It blocks the P2Y12 ADP receptor on the surface of platelets. It also increases bleeding time, and reduces blood viscosity.

Treatment with clopidogrel and aspirin is recommended for essentially all patients with UA/STEMI.

NEWER P2Y12 ADP INHIBITORS:

Ticagrelor is a reversible oral P2Y12 receptor antagonist with half-life of around 12hrs. Loading dose of 180mg followed by 90mg twice daily. Prasugrel is an irreversible P2Y12 ADP receptor antagonist that is given at 60mg of loading dose and 10mg of daily maintenance dose.

GP2B/3A INHIBITORS: [53]

These are specific and potent inhibitors of platelet aggregation. They interrupt the final common pathway of fibrinogen mediated cross- linkage of platelets. IV Eptifibatide or

Tirofiban is the preferred choice. Abiciximab is indicated only if angiography is appreciably delayed and PCI is likely to be performed.

The benefit of this inhibition appears to be greatest for the patients at a risk of complications i.e. those with a TIMI risk score 4 or higher, ST segment changes, recurrent angina, elevated troponin concentrations and diabetes.

ANTICOAGULANT THERAPY:

The aim of administering anticoagulants in STEMI patients are as follows -

1. Prevention of deep venous thrombosis.
2. Prevention of pulmonary embolism
3. Preventing thrombus formation in the ventricle.
4. Preventing emboli to brain.
5. Establishment and maintenance of infarct related artery patency

Anticoagulants should be continued for at least 48 hours after thrombolysis and maintained to an aPTT of 1.5 to 3 times the normal.

Unfractionated Heparin (UFH) was used initially. Disadvantages in using UFH are that it depends on ant- thrombin III for inhibiting thrombin activity, its sensitivity to platelet factor 4, inability to inhibit clot bound thrombin and inter patient variability. In contrast, the Low Molecular Weight Heparins (LMWH) are stable, have reliable anticoagulant effect and have high bioavailability.

STEMI MANAGEMENT: [54]

All patients with STEMI should be evaluated for reperfusion therapy and have a method implemented promptly after contact with the medical system.

The main aim is to recognize and treat the patients with STEMI so that door to balloon time for PCI to be kept as 90min and door to needle time for starting fibrinolytic therapy within 30min.

The severity of MI, the outcome and the size of MI depends on the duration between the onset of symptoms to the initiation of fibrinolytic therapy. As the time passes by the capacity of the fibrinolytic agents to lyse the clot reduces. If the fibrinolytic therapy is administered with 2 hrs of symptoms MI can be aborted. The effectiveness of fibrinolytic agents in dissolving the thrombus diminish with the passage of time. Fibrinolytic therapy administered within the first 2hrs (especially the first hour) can occasionally abort MI and dramatically decrease the mortality.

FIBRINOLYSIS:

In the absence of contraindications, fibrinolysis should be started within 30min of presentation (i.e. door to needle time<30min)

Restoration of coronary artery patency is the principal goal of treatment. Fibrinolytic agents include Streptokinase, Tenectaplase (TNK) and Reteplase (rPA), Tissue plasminogen activator (TPA), which are approved.

Thrombolysis in myocardial infarction (TIMI) grading system described angiographically is as follows:

“Grade 0 - indicates complete occlusion of the involved artery.

Grade 1 - penetration of obstruction by contrast but no distal perfusion.

Grade 2 - Perfusion of entire infarct vessel into the distal bed but with flow that is delayed compared with that of normal artery

Grade 3 - indicates normal flow with full perfusion of the infarct vessel".

Contraindications to fibrinolysis:

Absolute contraindications:

- Prior ICH
- Patients with structural cerebral vascular lesion
- Malignant intracranial neoplasm
- Ischemic stroke within 3months EXCEPT acute ischemic stroke within 3hours Active bleeding or bleeding diathesis (excluding menses)
- Significant closed head or facial trauma within 3months

Relative contraindications:

- History of poorly controlled hypertension.
- Uncontrolled hypertension on presentation (>180/110)
- History of prior ischemic stroke more than 3months, dementia, or known intracranial pathology not covered in contra-indications.
- Recent internal bleeding (within 2 to 4 weeks)
- Non compressible punctures of the vasculature
- Pregnancy
- Active peptic ulcer
- Use of anticoagulants currently, the higher INR, the higher the risk of bleeding.

Fibrinolytic Agent	Dose	Fibrin Specificity	Antigenic	Patency Rate
Non-fibrin specific				
Streptokinase (no longer marketed in the US)	1.5 million units IV given over 30–60 min	No	Yes	60%–68%
Fibrin specific				
Tenecteplase (TNK-tPA)	30 mg for weight < 60 kg 35 mg for 60–69 kg 40 mg for 70–79 kg 45 mg for 80–89 kg 50 mg for >90 kg	++++	No	85%
Reteplase (rPA)	10-U IV boluses given 30 min apart	++	No	84%
Alteplase (tPA)	Bolus 15 mg followed by infusion 0.75 mg/kg for 30 min (maximum 50 mg), then 0.5 mg/kg (maximum 35 mg) over the next 60 min; total dose not to exceed 100 mg.	++	No	73%-84%
IV = intravenous; rPA = recombinant human tissue plasminogen activator; STEMI = ST-elevation myocardial infarction; tPA = tissue plasminogen activator;				

Table – 6: Fibrinolytic agents

PERCUTANEOUS CORONARY INTERVENTION: [54,55]

The fundamental indication of PCI is the presence of one or more coronary stenosis thought to be responsible for a clinical syndrome, that warrant revascularization, is approachable by catheter-based techniques, with risk and benefit compare favorably with those of bypass surgery. In patient with multivessel coronary CAD, particularly those with reduced left ventricular function or diabetes, there may also be survival advantage to surgical revascularization. Trials randomizing patient with multivessel disease in whom either balloon angioplasty or bypass surgery is possible have suggested that the two procedures have essentially equivalent in hospital and 3 to 5 year mortality rates.

In patient with acute coronary syndromes, the benefits of PCI include reduced death and MI. In unstable angina and NSTEMI, recent studies employing platelet 2b/3a receptor blockers and coronary stenting have shown >20% reduction in death or MI at 6months with a parallel reduction in hospital readmission, compared to a conservative strategy in which PCI was reserved for strongly positive exercise.

In patients who present within 12 hours on onset of symptoms, the current PCI guidelines recommend that primary PCI should be performed. It performed in a timely fashion by persons skilled in procedure, working in an appropriate laboratory environment.

Largely through the introduction of newer interventional devices, PCI has advanced well beyond the treatment of proximal, discrete, subtotal, concentric, non-calcified lesion. Even chronically totally occluded coronary arteries can be crossed and dilated effectively and when treatment with drug-eluting stents, have a 90% long term patency rate. In addition to lesion in the native coronary tree, obstructions in the saphenous vein bypass grafts can also be dilated successfully to treat recurrent post- bypass angina, making use of distal embolic protection

devices to reduce the incidence of peri-procedural MI caused by the tendency of atheroembolic debris to be liberated during stenting of such lesions.

REDUCTION OF INFARCT SIZE:

Bed rest with both physical and emotional stability is needed and this is achieved by using mild sedation and treating in a quiet atmosphere. Beta blockers reduce the infarct size and they should be used unless otherwise contraindicated. Congestive cardiac failure should be always treated with inhibitors of RAAS unless contraindications are present.

CORONARY ARTERY BYPASS GRAFTING (CABG): [56]

CABG is indicated for cardiogenic shock, failed PCI, high-risk anatomy, surgical repair of a mechanical complication of STEMI (e.g., ventricular septal rupture, free-wall rupture, or severe mitral regurgitation from papillary muscle dysfunction or rupture). CABG is also the preferred revascularization strategy for patients with unprotected left main disease.

Emerging therapy: [57,58]

Local injection of progenitor cells, growth factors, or stem cells may stimulate vascular development. Stem cell therapies for acute myocardial infarction (MI) remain a major target of research, with some data showing modest results. Investigators in the Reinfusion of Enriched Progenitor Cells And Infarct Remodelling in Acute Myocardial Infarction (REPAIR-AMI) study examined 204 patients with acute ST-elevation MI (STEMI) and reported greater improvement in left ventricular ejection fraction (LVEF) among patients who received intracoronary progenitor cell infusion than among those given placebo.

COMPLICATIONS:

TABLE - 7 : COMPLICATIONS OF ACUTE MI

COMPLICATIONS	TYPES
Mechanical complications	Cardiogenic shock, FWR, VSR, acute MR, and true ventricular aneurysm
Electrical complications	Bradyarrhythmias, tachyarrhythmias, bundle branch blocks and fascicular blocks
Inflammatory complications	Peri infarction pericarditis and Dressler Syndrome
Ischemic complications	Post infarction angina (infarct extension and re infarction)
Embolic complications	Mural thrombus and systemic embolism.

PROLACTIN

Stricher and Greuter in 1928 demonstrated the lactogenic effect of prolactin by injecting anterior pituitary extracts into virgin rabbits. [59] In 1933, Riddle and his peers purified this hormone and named it prolactin.

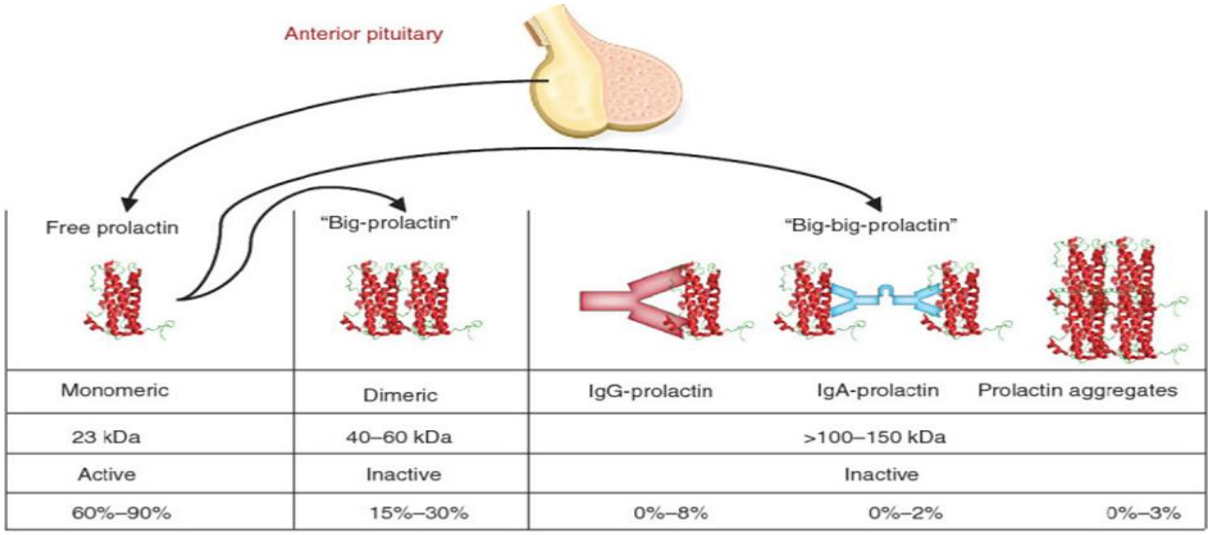
Structure of Prolactin:

Prolactin (PRL) is encoded by a single gene, found on chromosome 6. The gene is composed of 5 exons and 4 introns and is 10 kb in size. Two independent promoter regions regulate the transcription of the prolactin. The proximal region directs pituitary- specific expression. An upstream promoter region is responsible for extra pituitary expression. Mature human prolactin is composed of 199 amino acids. According to three-dimensional model, prolactin comprises of four long α-helices that are arranged in antiparallel fashion. [60] The molecular weight of mature form is 23 kDa (kilodalton) containing 199 amino acids.

According to size, it circulates three different forms:

- Small molecular size (22kDa)
- Big molecular size (50kDa)
- Larger molecular size(100kDa)

80% of the hormones are biologically active, small molecular forms.



Monomeric	Dimeric	IgG-prolactin	IgA-prolactin	Prolactin aggregates
23 kDa	40–60 kDa	>100–150 kDa		
Active	Inactive	Inactive		
60%–90%	15%–30%	0%–8%	0%–2%	0%–3%

Fig. 9: Molecular forms of Prolactin

Distribution of Prolactin-R, a cell surface receptor:

We know that mRNA and prolactin receptors are found in the mammary gland and the ovary, surprisingly, its mRNA are also found in numerous parts of the CNS (choroid plexus, bed nucleus of the stria terminalis, amygdala, the central gray of the midbrain, thalamus, hypothalamus, cerebral cortex and olfactory bulb). In addition to the pituitary gland, the receptors are also found in other organs like the heart, lung, thymus, spleen, liver, pancreas, kidney, adrenal gland, uterus, skeletal muscle and skin. [60]

The hormone acts as both in autocrine and in a paracrine manner through its prolactin receptor and a cytokine receptor.

REGULATION OF SECRETION

The hypothalamic factor that inhibits prolactin secretion is the neurotransmitter dopamine, secreted from arcuate nucleus through D2 receptors. Thyrotropin releasing hormone

stimulates release of prolactin; however, it is a pituitary hormone which is mainly under inhibitory control.

The prolactin production is mainly controlled by oestrogens, which directly stimulate prolactin production as well as acts by suppressing dopamine. It synthesises milk from the mammary gland by its enlargement (lactation), during pregnancy and also prepare for milk production. Lactation starts when the levels of progesterone fall by the end of pregnancy and a suckling reflex starts.

Vasoactive intestinal peptide and peptide histidine isoleucine are involved in the regulation of prolactin secretion in humans. It has diurnal and ovulatory cycles. Its levels increase during REM sleep and in the early morning. High levels of oestrogen and progesterone increase prolactin levels by 10- to 20-fold during pregnancy. In vertebrates such as mice, similar actions with tissue specific effect is attained by a group of prolactin-like proteins. The sudden fall in level of oestrogen and progesterone levels after the delivery of baby will allow prolactin to induce lactation in the women.

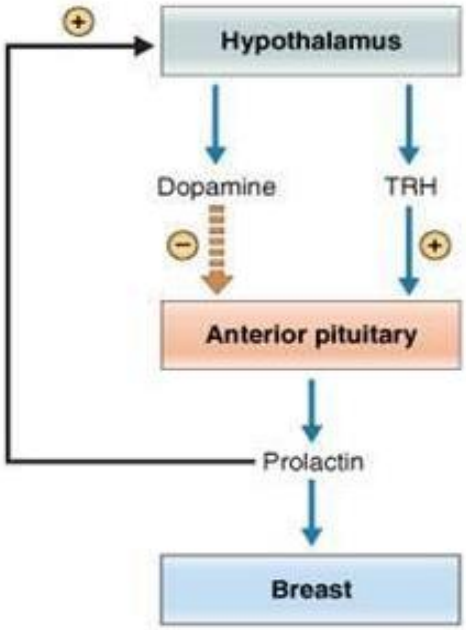


Fig. 10: Feedback regulation of prolactin hormone

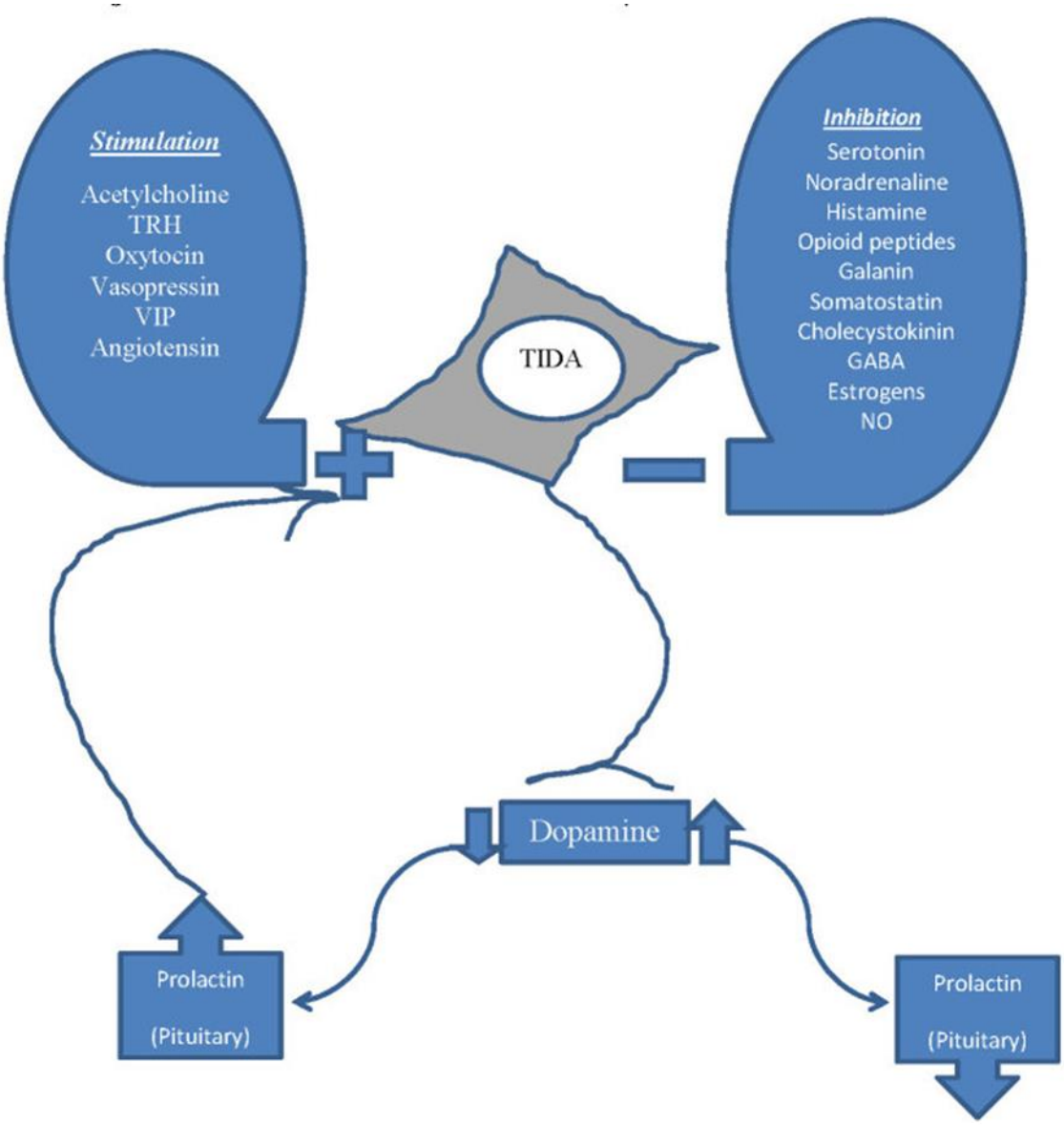


Fig. 11: Factors affecting dopamine neurons and control of prolactin secretion and short loop feedback. [61]

TIDA = Tuberoinfundibular dopaminergic neurons, TRH = Thyrotropin releasing hormone, VIP = Vasoactive intestinal polypeptide, GABA = ɣ amino butyric acid, NO = nitric oxide

BIOLOGICAL ACTIONS OF PROLACTIN: [60]

REPRODUCTION:

Prolactin is best known due to its action on the mammary gland. However, it also exerts effects on other targets with respect to the reproduction of the mammalian species. Prolactin is also important for the maintenance and secretory activity of the corpus luteum particularly in rodents. It also affects mating and maternal behaviours.

With respect to lactation prolactin is responsible for the growth and development of the mammary gland (mammogenesis), synthesis of milk (lactogenesis) and maintenance of milk secretion (galactopoiesis).

In most rodents, prolactin maintains the structural and functional integrity of the corpus luteum for 6 days after mating by acting as a luteotrophic hormone and such "luteotrophic" action which has been best described in the rat, is characterized by enhanced progesterone secretion that is essential for the implantation of the fertilized ovum (along with estrogen), maintenance of pregnancy and inhibition of ovulation.

Prolactin-R present in the ventromedial nucleus of the hypothalamus, is responsible for controlling female sexual behaviour. The literatures depict the effects of prolactin on the induction and maintenance of these maternal behaviours in mice, rabbit, hamsters, and sheep. But it does not initiate a maternal behaviour, it decreases the latency to the onset of maternal behaviour.

HOMEOSTASIS:

Prolactin maintains the constancy of the internal environment by regulating the immune system, osmotic balance and angiogenesis.

Prolactin has been a common mediator of the immune neuroendocrine network, where

endocrine, nervous and immune systems communicate with each other. It plays a significant role in regulating the humoral and cellular immune responses in physiological as well as pathological states (autoimmune diseases).

Studies with respect to osmoregulatory function of prolactin, have suggested that that prolactin stimulates solute transport across cell membranes. The proteolytic fragments of native prolactin exhibit antiangiogenic activity that is inherent to the 16- kDa fragment.

METABOLIC EFFECTS:

Pituitary-derived prolactin is a known regulator of the lactating mammary gland. According to the recent finding, human adipose tissue produces PRL as well as expresses the PRL receptor (PRLR) through unappreciated action of PRL, as a cytokine involved in adipose tissue function. The depots of adipose tissue (breast, visceral and subcutaneous) secrete biologically active PRL and its expression is regulated by a non-pituitary, alternative super distal promoter. During early pre-adipocyte differentiation, PRL expression and release increases and is stimulated by cyclic AMP activators, including beta adrenergic receptor agonists. Adipose PRL production is altered by the metabolic state as its release is attenuated during obesity. The literatures also suggest that, PRL suppresses lipid storage as well as the release of adipokines such as adiponectin, interleukin-6 and possibly leptin. PRL also regulates adipogenesis. Through its action as an adipokine, PRL is also involved in the manifestation of insulin resistance. [62]

OTHER FUNCTIONS:

- Prolactin helps in the proliferation of oligodendrocyte precursor cells and its differentiation, which is involved in the synthesis of myelin.
- It affects the fetal lung surfactant synthesis, it also helps in building up of the immunity level in the fetus.

- Fetal brain and maternal neural development is also controlled to many extents by the prolactin. The site of synthesis of prolactin is not only in the anterior pituitary, but is also produced in other sites like decidua, myometrium, breast, lymphocytes, leukocytes and prostate.

HYPERPROLACTINEMIA AND HYPOPROLACTINEMIA:

Fig. 12: Causes of hyperprolactinemia [63]

- Physiological
  - Pregnancy
  - Lactation
  - Nipple stimulation
- Analytical
  - Macroprolactinaemia (hyperprolactinaemia with a predominance of macroprolactin)
- Pathological
  - Prolactinomas and mixed secreting adenomas
  - Hypothalamic and pituitary stalk disorders (compressive macroadenoma, hypophysitis, granulomatous disease, Rathke cleft cyst, irradiation and/or trauma, and tumours including cranio-pharyngiomas, germinomas and metastases)
- Medications
  - Dopamine antagonists (antipsychotics, anti-emetics and α-methyldopa antihypertensives)
  - Other (antidepressants, oestrogens and opiates)
- Chronic renal failure
- Ectopic prolactin secretion
  - Ovarian dermoids
  - Hypernephroma
  - Bronchogenic carcinoma
- Genetic
  - *PRLR* loss-of-function mutation
- Idiopathic
  - Unknown

Fig. 13: Causes of hypoprolactinemia: [63]

- Abnormal lactotroph cell development (genetic causes)
  - *POU1F1*, *PROP1*, *LHX3*, *LHX4*, *HESX1*, *OTX2* and *IGSF1* loss-of-function mutations
- Destruction of pituitary tissue
  - Sheehan syndrome
  - Inflammation or hypophysitis (or autoimmune lactotroph damage)
  - Tumour or surgery
  - Infection (tuberculosis)
- Pseudohypoparathyroidism
- Idiopathic prolactin deficiency
- Medications
  - Dopamine agonists (cabergoline, bromocriptine, quinagolide and pergolide)

CLINICAL FEATURES:

HYPOPROLACTINEMIA	HYPERPROLACTINEMIA
• Ovarian Diseases • Impotence • Delayed Puberty • Abnormal Spermatogenesis. • Infertility	**Women:** • Amenorrhea and Oligomenorrhoea • Galactorrhea • Infertility • Hirsutism • Osteoporosis **Men (Late Onset):** • Gynecomastia • Impotence. • Osteoporosis

DIAGNOSIS:

- Detailed History including medications, menstrual cycle
- Local Examination (galactorrhoea)

LABORATORY INVESTIGATIONS:

- Measurement of serum Prolactin level
- Thyroid function test
- LH and FSH assay
- Pregnancy test

IMAGING MODALITIES:

- MRI scan is the best image of choice.it detect very minimal lesion even 3 to 5mm size.
- High speed helical- CT scan also very useful.

MEDICAL AND SURGICAL MANAGEMENT:

HYPERPROLACTINOMA MANAGEMENT GUIDE:

- Dopamine agonist: Bromocriptine, Lisuride, Quinagolide, Cabergoline.
- Large pituitary tumour treated with surgical removal or radiation therapy.
- If needed, replacement of thyroid hormone or other hormonal replacement therapy like estrogen and progestins in ovarian insufficiency is advised.

PATHOGENESIS OF PROLACTIN IN ACUTE MI:

1) Hyperprolactinemia causes
    - Arteriosclerosis
    - Augmentation of arterial stiffness
    - Hypertension [6]
2) Prolactin augments adhesion of immune cells into the endothelium via intergrin mediated effects, which cause proliferation of vascular smooth muscle cells, leading to atherosclerotic expansion. [64]

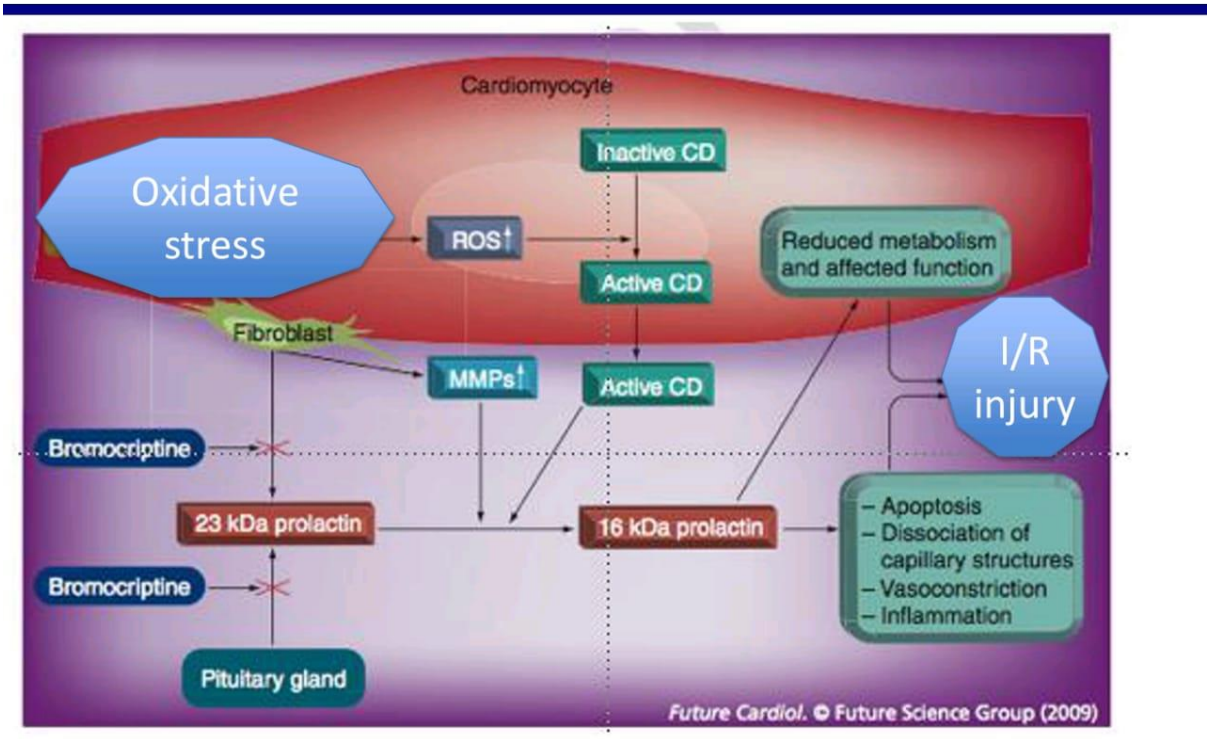


Fig. 14: Mechanism of cardiac ischemia or reperfusion injury (I/R) caused by 16 kDa prolactin

VARIOUS MECHANISMS BY WHICH PROLACTIN CAUSES MYOCARDIAL INFARCTION: [65,66,67]

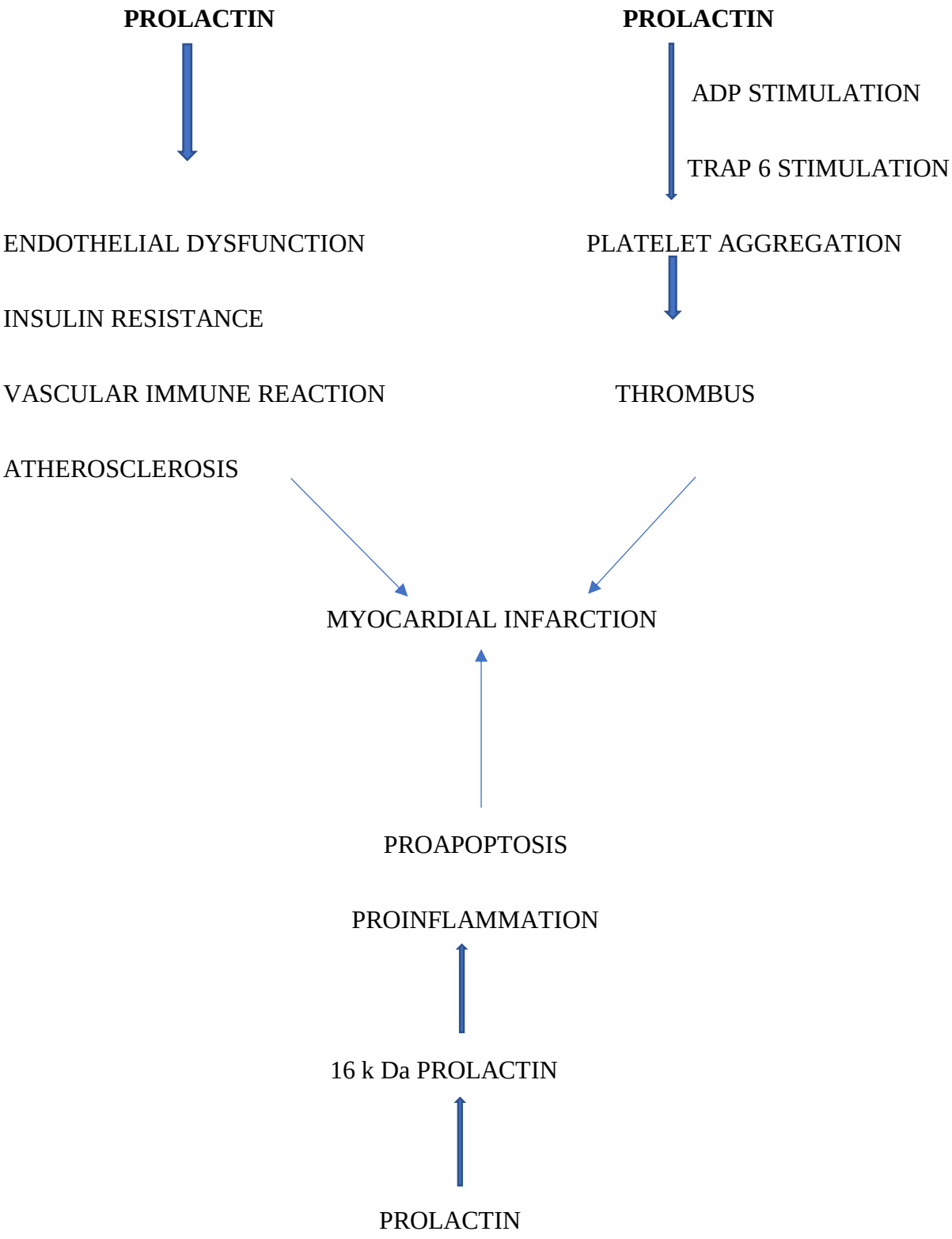


Fig. 15: Possible mechanisms by which prolactin causes MI

VARIOUS STUDIES RELATED TO PRESENT STUDY:

- Hayder M. Al-Kuraishy *et al* (2016), concluded that serum prolactin level increased in acute MI, and positively correlated with cardiac troponin level and reflects underlying cardiovascular complications. [65]

- Robin Haring *et al* (2014), studied that higher serum prolactin concentration within the physiological range are associated with an increased risk of all-cause and cardiovascular mortality. [68]

- Raaz D *et al* (2006), concludes that there is an association between increased prolactin values and enhanced P-selectin expression on platelets in patients with acute coronary syndromes. Therefore, stress hormone prolactin could be a co-stimulator of platelet activation in these patients. [69]

- Hisham Elgayar *et al* (2011), studied that hyperprolactinemia may be associated with increased risk of myocardial infarction but the levels of prolactin are variable among diabetics. In addition, the increase in both prolactin and hs-CRP increases the atherosclerotic process and hence the macrovascular complications revealing a new mechanism for atherosclerosis in diabetics. [70]

- Reuwer,A.Q. *et al* (2011), concluded that prolactin is involved in the systemic inflammatory response, which takes place during myocardial infarction. [71]

- Juan Jesus Carrero *et al* (2012), studied that prolactin levels are directly associated with endothelial dysfunction / stiffness and with increased risk of cardiovascular events and mortality in two independent cohorts of CKD patients. [72]

MATERIALS AND METHODS:

SOURCES OF DATA

1. The patients admitted in the medicine ICU/wards of B.L.D.E (DEEMED TO BE UNIVERSITY), Shri B. M. Patil Medical College, Hospital and Research centre, Vijayapura and who fulfill inclusion criteria.
2. Patients attending the medicine OPD/executive health checkup schemes who fulfill the inclusion criteria.

METHODS OF COLLECTION OF DATA :

- By detailed history
- Investigations like Complete blood count, Fasting blood sugar, Post prandial blood sugar, lipid profile, thyroid profile, urine examination, blood urea, serum creatinine.
- Electrocardiography and Echocardiography.
- Determination of ischemic cardiac biomarkers like CPK-MB and Cardiac Troponin I
- Subjects are divided into 2 groups. 38 subjects with Acute MI in one group, with 38 healthy controls as the other group.
- Determination of serum prolactin levels using sandwich ELISA method.
- Serum prolactin levels of the two groups are then compared.
- The serum prolactin levels are compared with serum troponin among Acute MI patients.

1.INCLUSION CRITERIA:

CASE-

Patients fulfilling the criteria for acute Myocardial Infarction

- Detection of a rise and/or fall of cardiac biomarker values with at least one of the following.
    - Symptoms of ischemia
    - New or presumed new significant ST-segment T wave (ST-T) changes or new Left Bundle Branch Block (LBBB)
    - Development of pathologic Q waves
    - Imaging evidence of new loss of viable myocardium or regional wall motion abnormality

CONTROL- Age and sex matched subjects with no clinical signs or symptoms suggestive of acute myocardial infarction.

2. EXCLUSION CRITERIA:

- Smokers
- Patients using various drugs that have effects on prolactin metabolism such as antipsychotics like chlorpromazine, risperidone, trifluperazine, fluphenazine, haloperidol and anti-depressants like chlorimipramine, amitriptyline, fluoxetine and oral contraceptives.
- Hypothyroidism
- Diabetes Mellitus
- Essential Hypertension

3. TYPE OF STUDY:

Prospective cross-sectional comparative study.

4. SAMPLE SIZE:

Time period of study from November 2018 to June 2020

With Anticipated Mean Difference of mean prolactin level between the cases and control in acute myocardial infarction as 19.6 and Anticipated SD as 23.1, the minimum sample size per group is 38 with 90% power and 5% level of significance based on the study done by Al-Kuraishy HM [65].

Total sample size 38+38=76

By using the formula:

$$n = \frac{(z_\alpha + z_\beta)^2 \, 2\,SD^2}{MD^2}$$

Where Z= Z statistic at 5% level of significance

MD= Anticipated mean difference

SD= Anticipated Standard deviation

Statistical analysis

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean± standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Chi-square (χ^2) test was used for association between two categorical variables.

The formula for the chi-square statistic used in the chi square test is:

$$\chi_c^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

The subscript "c" are the degrees of freedom. "O" is observed value and E is expected value.

C= (number of rows-1)* (number of columns-1)

The difference of the means of analysis variables between two independent groups was tested by unpaired t test.

The t statistic to test whether the means are different can be calculated as follows:

$$t = \frac{(\overline{x_1} - \overline{x_2}) - (\mu_1 - \mu_2)}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$$

where $\bar{x}_1$ = mean of sample 1

$\bar{x}_2$ = mean of sample 2

n_1 = number of subjects in sample 1

n_2 = number of subjects in sample 2

s_1^2 = variance of sample 1 = $\frac{\Sigma(x_1 - \bar{x}_1)^2}{n_1}$

s_2^2 = variance of sample 2 = $\frac{\Sigma(x_2 - \bar{x}_2)^2}{n_2}$

ROC analysis for Sensitivity- specificity was done to check relative efficiency.

sensitivity or true positive rate (TPR)

eqv. with hit rate, recall

$$TPR = TP/P = TP/(TP + FN)$$

specificity (SPC) or true negative rate

$$SPC = TN/N = TN/(FP + TN)$$

precision or positive predictive value (PPV)

$$PPV = TP/(TP + FP)$$

negative predictive value (NPV)

$$NPV = TN/(TN + FN)$$

If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analyzed using SPSS software v.23 (IBM Statistics, Chicago, USA) and Microsoft office 2007.

RESULTS AND ANALYSIS

Our Study was conducted in Shri B. M. Patil Medical College and a total of 76 subjects are studied, out of which 38 were cases and 38 were controls who satisfied the inclusion criteria and the following observations were made:

Table 8: Distribution of Age between Study and Control Groups

Age(yrs)	Cases		Controls		p value
	N	%	N	%	
41-50	4	10.5%	4	10.5%	0.996
51-60	20	52.6%	19	50.0%	
61-70	12	31.6%	13	34.2%	
>70	2	5.3%	2	5.3%	
Total	38	100.0%	38	100.0%	

Figure 16: Distribution of Age between Study Groups

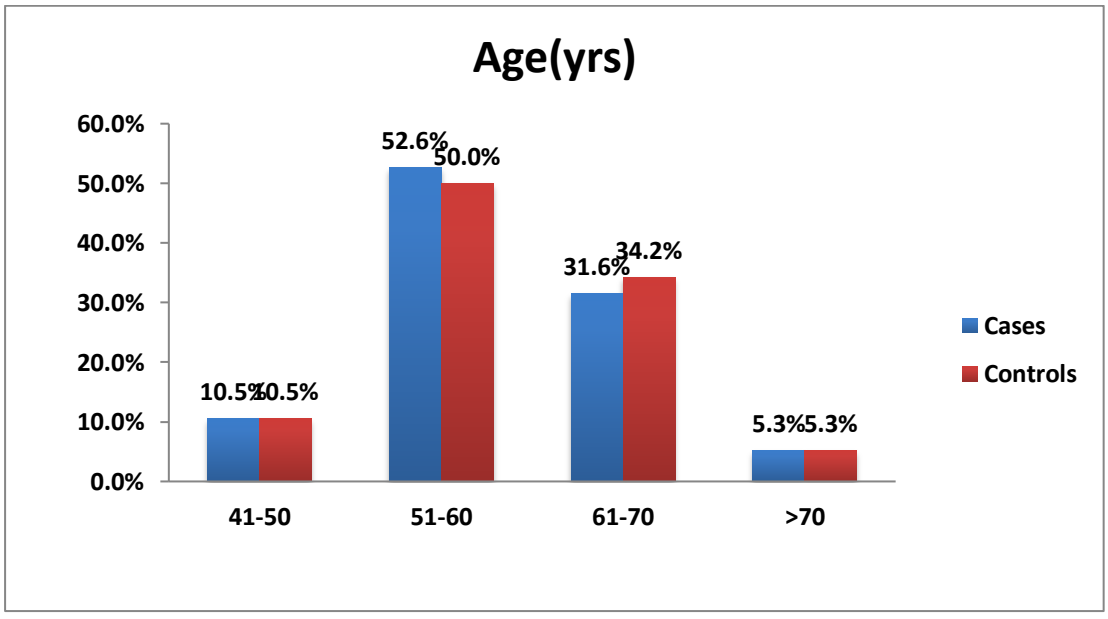


Table 9: Distribution of Mean Age between Study and Control groups

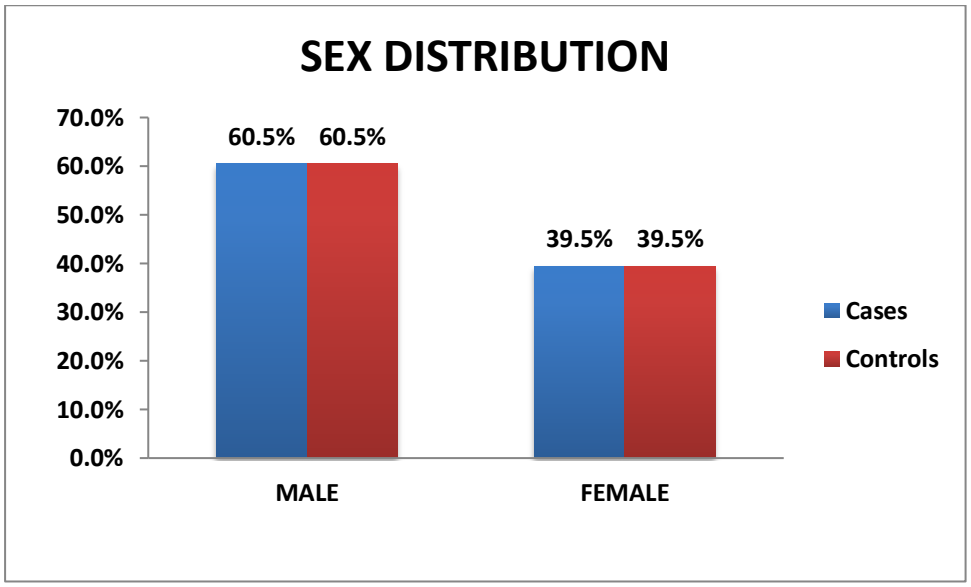
Parameters	Cases		Controls		p value
	Mean	SD	Mean	SD	
AGE	58.9	6.7	59.4	7.0	0.739

- Maximum number of patients belonged to age group of 51-60 in both study and control groups, constituting to 20 subjects and 19 subjects respectively in each group.
- Least number of patients belonged to age group of >70 years in both study and control groups, constituting to 2 subjects in each group.
- The mean age group among study group is 58.9 years, and that of controls is 59.4 years.

Table 10: Distribution of Sex between Study Groups

SEX	Cases		Controls		p value
	N	%	N	%	
MALE	23	60.5%	23	60.5%	-
FEMALE	15	39.5%	15	39.5%	
Total	38	100.0%	38	100.0%	

Figure 17: Distribution of Sex between Study Groups



- Among the study groups and controls, 23 subjects are males and 15 subjects are females.

Table 11: Distribution of BMI between Study and Control Groups

BMI	Cases		Controls		p value
	N	%	N	%	
Normal	18	47.4%	27	71.1%	0.100
Overweight	17	44.7%	10	26.3%	
Obese	3	7.9%	1	2.6%	
Total	38	100.0%	38	100.0%	

Figure 18: Distribution of BMI between Study and Control Groups

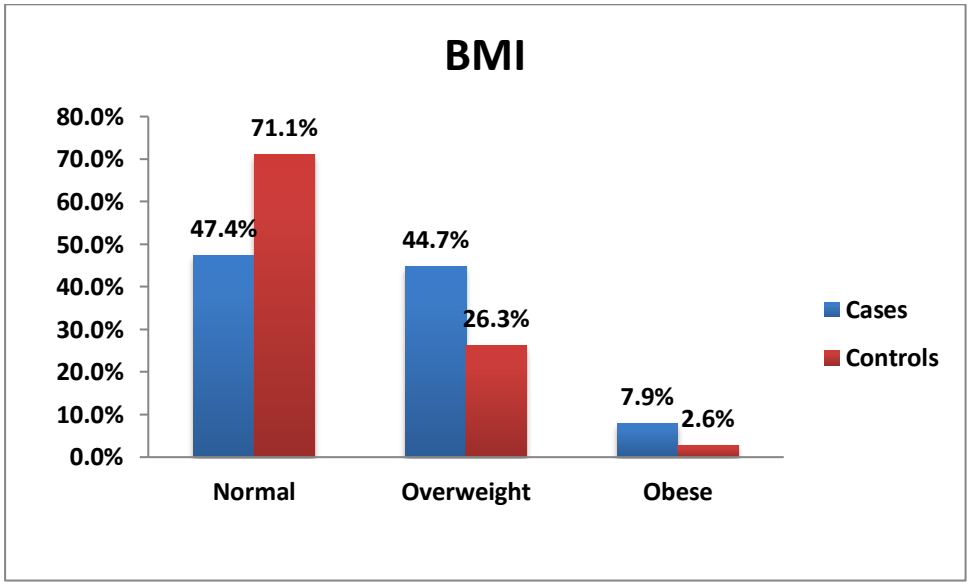


Table 12: Distribution of Mean BMI between Study and Control groups

Parameters	Cases		Controls		p value
	Mean	SD	Mean	SD	
BMI	25.3	2.5	23.6	3.2	0.014*

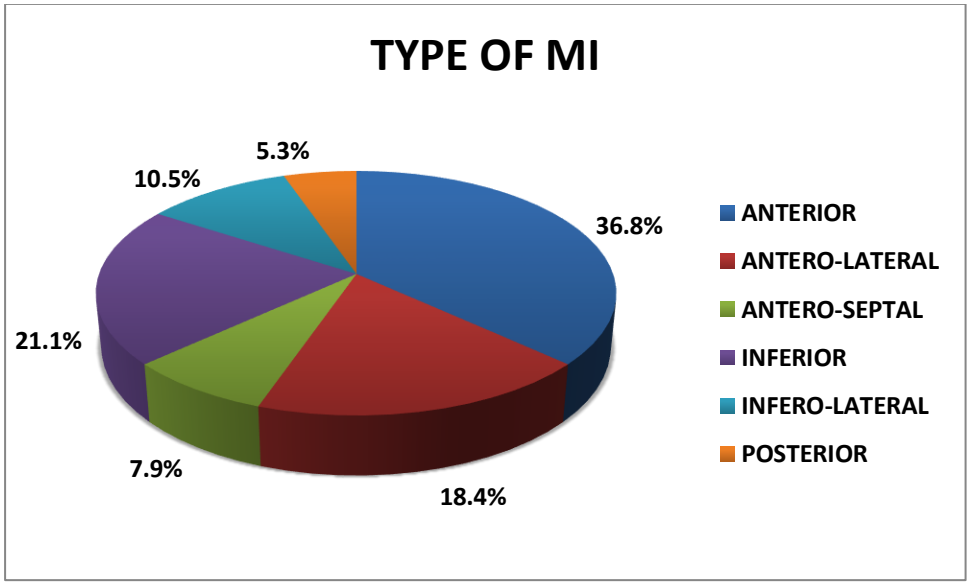
Note: * significant at 5% level of significance ($p<0.05$)

- Among the cases, 17 patients belong to Overweight category and 3 patients belong to Obese category.
- Among control group, 10 subjects belong to Overweight category and 1 subject belongs to Obese category.
- The mean BMI is 25.3 kg/m^2 among cases and 23.6 kg/m^2 among control groups.

Table 13: Distribution of Cases according to type of MI

TYPE OF MI	N	%
ANTERIOR	14	36.8
ANTERO-LATERAL	7	18.4
ANTERO-SEPTAL	3	7.9
INFERIOR	8	21.1
INFERO-LATERAL	4	10.5
POSTERIOR	2	5.3
Total	38	100.0

Figure 19: Distribution of Cases according to type of MI



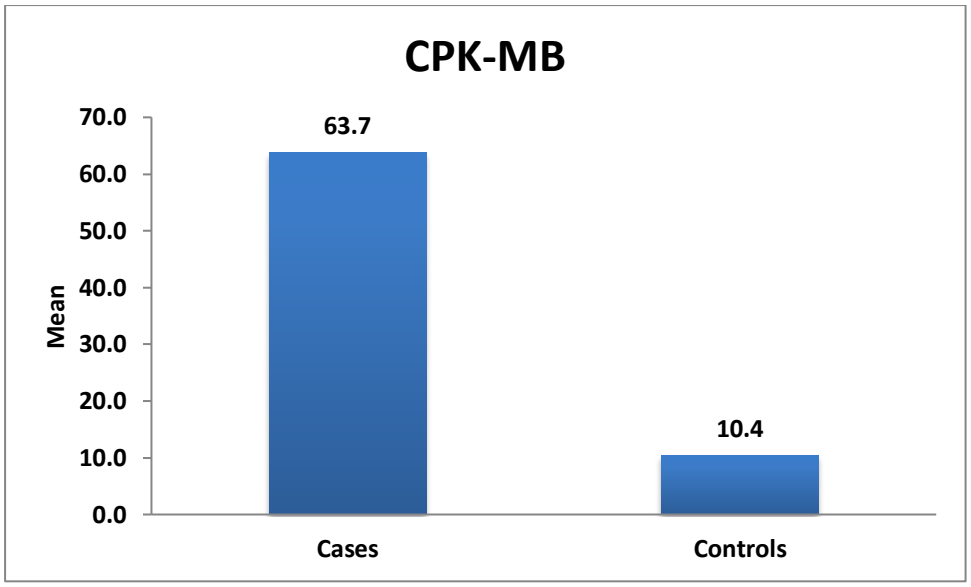
Among the cases of acute MI, 36.8% of patients had anterior wall MI (AWMI), 21.1% of patients showed inferior wall MI (IWMI), 18.4% of patients showed antero-lateral wall MI (ALWMI), 10.5 % of patients showed infero-lateral wall MI (ILWMI), 7.9% of patients showed antero-septal wall MI (ASWMI) and the rest 5.3% of patients showed posterior wall MI.

Table 14: Distribution of Mean CPK-MB between Study Groups

Parameters	Cases		Controls		p value
	Mean	SD	Mean	SD	
CPK-MB	63.7	64.5	10.4	3.9	<0.001*

Note: * significant at 5% level of significance (p<0.05)

Figure 20: Distribution of Mean CPK-MB between Study Groups



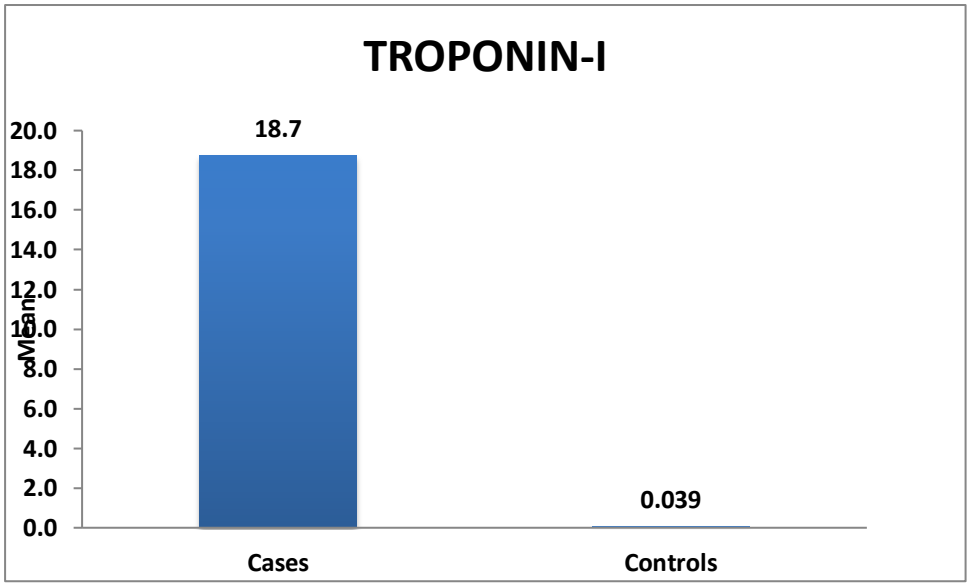
The mean CPK-MB values among cases is 63.7, whereas that of control group is 10.4.

Table 15: Distribution of Mean TROPONIN-I between Study Groups

Parameters	Cases		Controls		p value
	Mean	SD	Mean	SD	
TROPONIN-I	18.7	26.8	0.039	0.01	<0.001*

Note: * significant at 5% level of significance (p<0.05)

Figure 21: Distribution of Mean TROPONIN-I between Study Groups



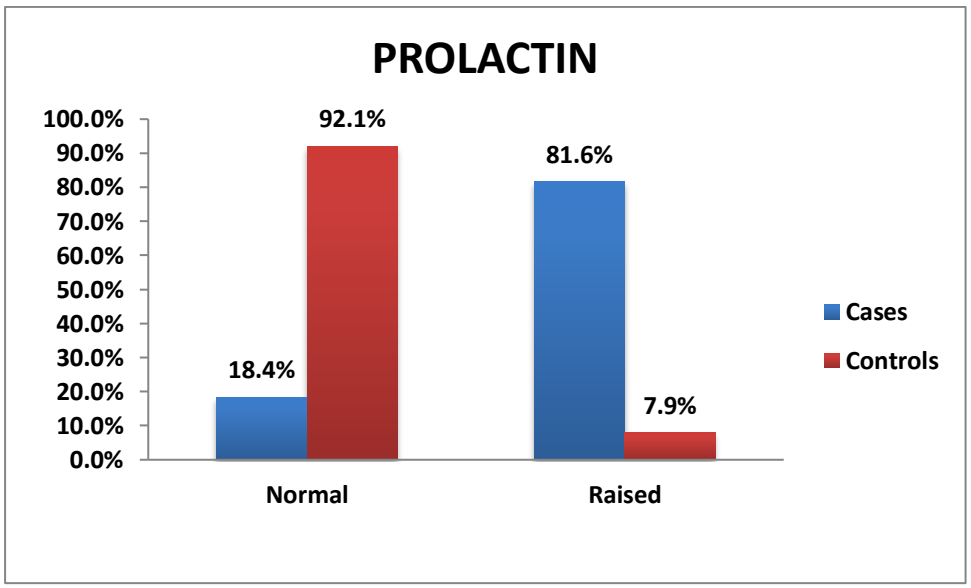
The mean troponin-I levels among the cases is 18.7 ng/ml, while that of the control group is 0.039

Table 16: Distribution of Prolactin between Study Groups

PROLACTIN	Cases		Controls		p value
	N	%	N	%	
Normal	7	18.4%	35	92.1%	<0.001*
Raised	31	81.6%	3	7.9%	
Total	38	100.0%	38	100.0%	

Note: * significant at 5% level of significance (p<0.05)

Figure 22: Distribution of Prolactin between Study Groups



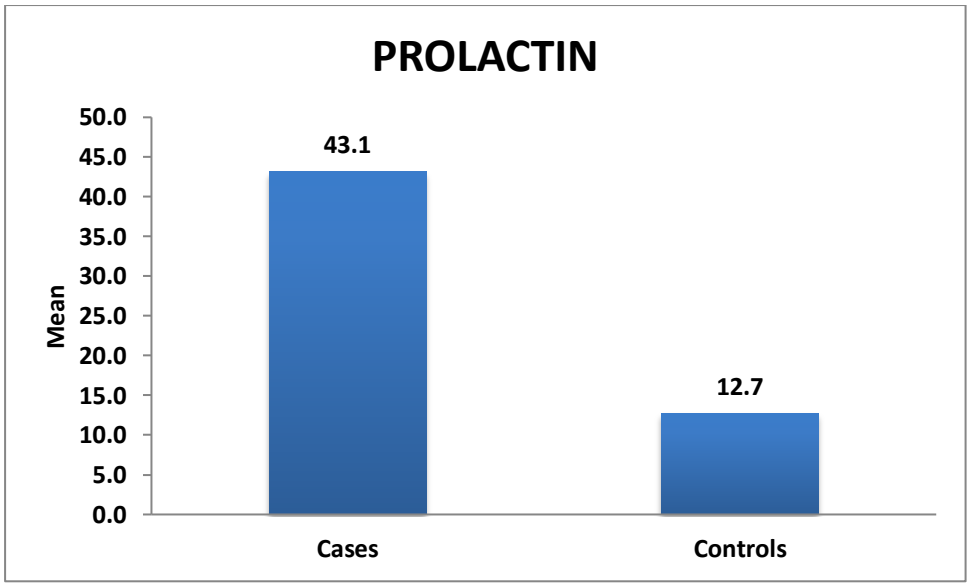
- Among 38 cases of acute MI, 31 patients (81.6%) had raised serum prolactin levels and the other 7 (18.4%) patients had normal serum prolactin levels.
- Out of 38 subjects in the control group, 3 subjects (7.9%) had raised serum prolactin and the other 35 subjects (92.1%) had normal serum prolactin levels.

Table 17: Distribution of Mean Prolactin between Study Groups

Parameters	Cases		Controls		p value
	Mean	SD	Mean	SD	
PROLACTIN	43.1	22.1	12.7	3.9	<0.001*

Note: * significant at 5% level of significance (p<0.05)

Figure 23: Distribution of Mean Prolactin between Study Groups



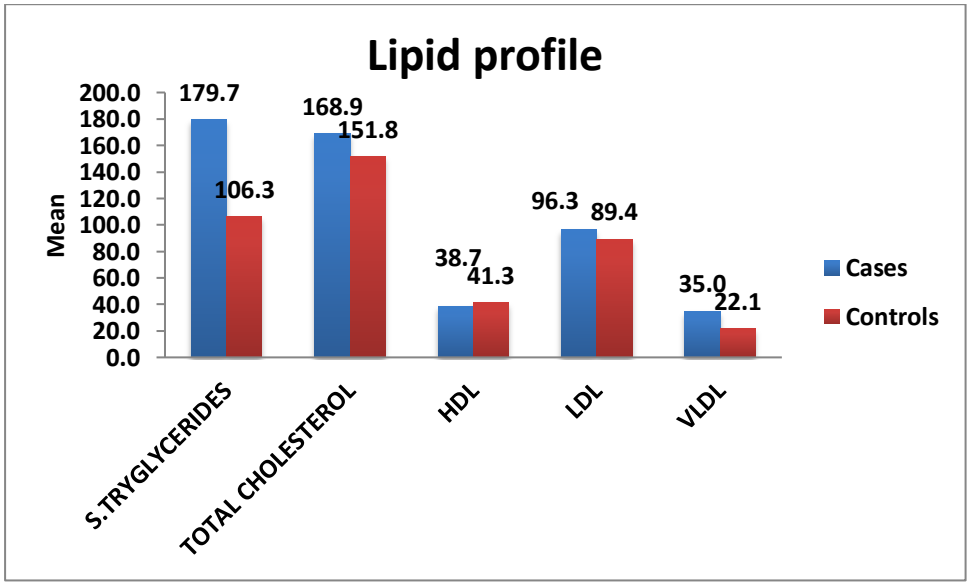
The mean prolactin levels among the cases is 43.1 ng/ml, and the mean prolactin levels among the control group is 12.7 ng/ml.

Table 18: Distribution of Mean Lipid profile between Study Groups

Lipid profile	Cases		Controls		p value
	Mean	SD	Mean	SD	
S. TRYGLYCERIDES	179.7	79.7	106.3	30.7	<0.001*
TOTAL CHOLESTEROL	168.9	35.3	151.8	25.8	0.018*
HDL	38.7	11.8	41.3	9.4	0.290
LDL	96.3	33.1	89.4	22.5	0.288
VLDL	35.0	16.4	22.1	6.8	<0.001*

Note: * significant at 5% level of significance (p<0.05)

Figure 24: Distribution of Mean Lipid profile between Study Groups



- Among the cases, the mean serum TG is 179.7 mg/dl, mean total cholesterol is 168.9 mg/dl, mean HDL is 38.7 mg/dl, mean LDL is 96.3 mg/dl and the mean VLDL is 35 mg/dl.
- Among the controls, the mean serum TG is 106.3 mg/dl, mean total cholesterol is 151.8 mg/dl, mean HDL is 41.3 mg/dl, mean LDL is 89.4 mg/dl and the mean VLDL is 22.1 mg/dl.
- The mean serum TG levels, mean total cholesterol levels and the mean VLDL levels among cases are elevated compared to that of controls and are found to be statistically significant.
- The mean HDL levels are elevated among control group compared to that of cases.
- The mean LDL levels are raised among cases compared to control group but it was not statistically significant.

ATHEROGENIC INDEX OF PLASMA:

Atherogenic Index of Plasma (AIP) is a marker to predict the risk of atherosclerosis and the coronary heart disease. It gives the relationship between protective and atherogenic lipoprotein. It is associated with the size of pre-atherogenic and anti-atherogenic lipoproteins. It is calculated by using the following formula

$$Log_{10} (TG/HDL\_C)$$

AIP values are interpreted as follows:

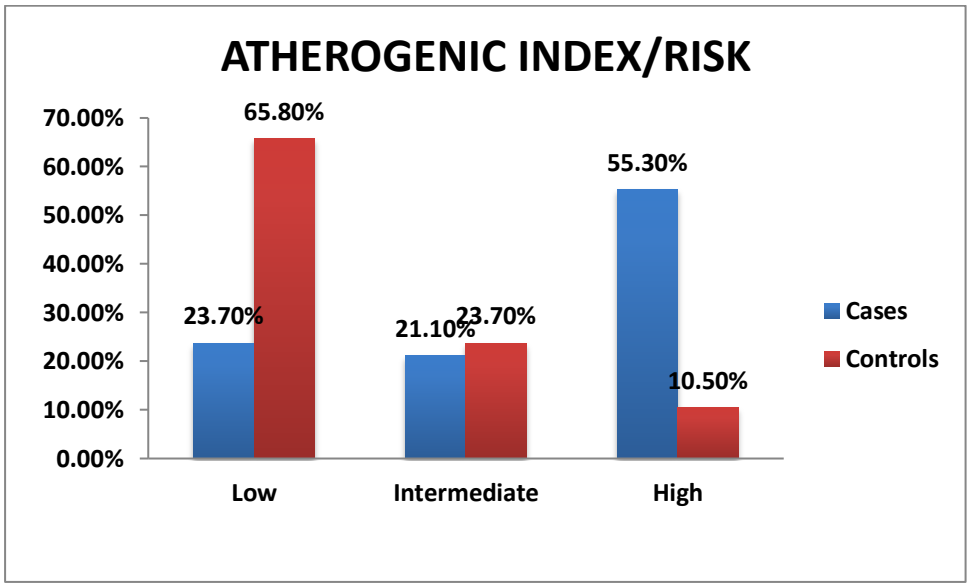
- AIP < 0.11 - Low Risk
- AIP 0.11 – 0.21 - Intermediate Risk
- AIP >0.21 - High Risk

Table 19: Distribution of Atherogenic Index/Risk between Study Groups

ATHEROGENIC INDEX/RISK	Cases		Controls		p value
	N	%	N	%	
Low	9	23.7%	25	65.8%	<0.001*
Intermediate	8	21.1%	9	23.7%	
High	21	55.3%	4	10.5%	
Total	38	100.0%	38	100.0%	

Note: * significant at 5% level of significance ($p<0.05$)

Figure 25: Distribution of Atherogenic Index/Risk between Study Groups



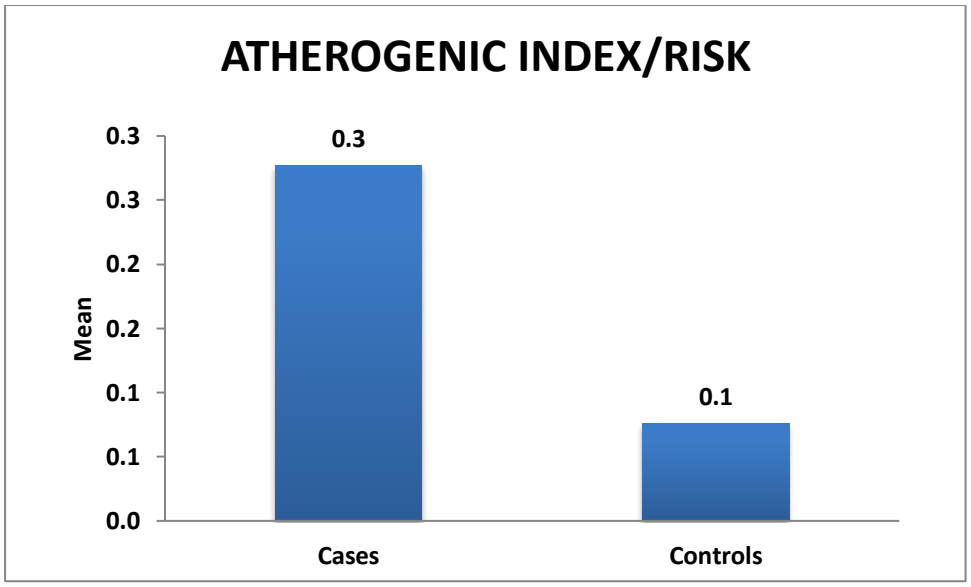
- Among the cases, 9 patients (23.7%) belonged to Low risk group, 8 patients (21%) belonged to Intermediate risk group and 21 patients (55.3%) belonged to High risk group.
- Among the control group, 25 subjects (65.8%) belonged to Low risk group, 9 patients (23.7%) belonged to Intermediate risk and 4 subjects (10.5%) belonged to High risk group.

Table 20: Distribution of Mean Atherogenic Index/Risk between Study Groups

Parameters	Cases		Controls		p value
	Mean	SD	Mean	SD	
ATHEROGENIC INDEX/RISK	0.3	0.2	0.1	0.1	<0.001*

Note: * significant at 5% level of significance (p<0.05)

Figure 26: Distribution of Mean Atherogenic Index/Risk between Study Groups



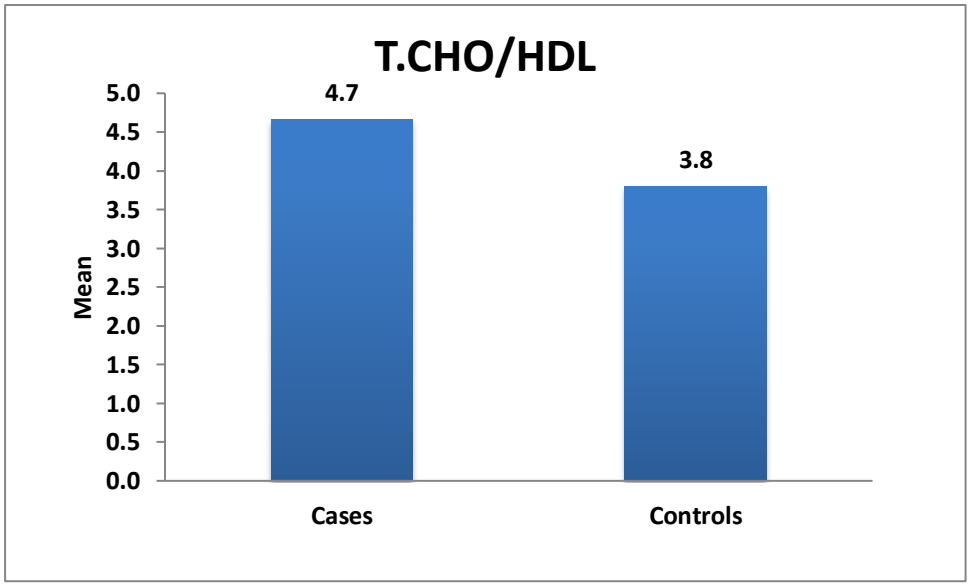
The mean Atherogenic Index among cases of acute MI is 0.3 and that of control group is 0.1 and is found to be statistically significant.

Table 21: Distribution of Mean T.CHO/HDL between Study Groups

Parameters	Cases		Controls		p value
	Mean	SD	Mean	SD	
T.CHO/HDL	4.7	1.5	3.8	0.9	0.003*

Note: * significant at 5% level of significance (p<0.05)

Figure 27: Distribution of Mean T.CHO/HDL between Study Groups



Among the cases, the mean T.CHO/HDL ratio is 4.7 and that of controls is 3.8.

MEAN PLATELET VOLUME AND P-LCR:

Mean platelet volume (MPV) is a marker of platelet size which reflects the activity of the platelet. Larger platelets with higher MPV values are hemostatically more reactive and produce large amounts of prothrombotic factor which leads to atherothrombosis. Normal MPV range is 7.4 fl -11.4 fl.

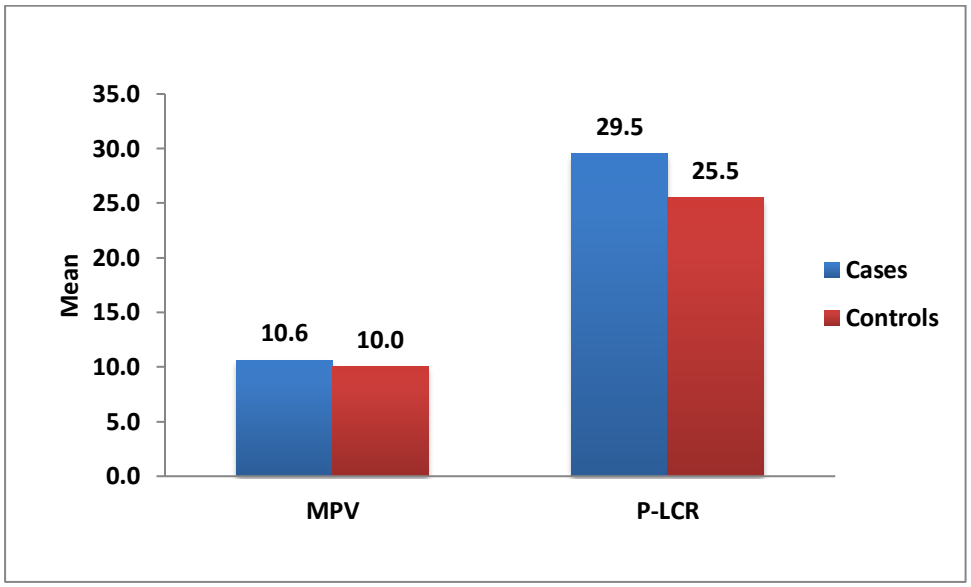
P-LCR is defined as the percentage of platelets that exceed the normal value of platelet volume in the total platelet count. Normal P-LCR value range is 11-33%.

Table 22: Distribution of Mean MPV and P-LCR between Study Groups

Parameters	Cases		Controls		p value
	Mean	SD	Mean	SD	
MPV	10.6	1.2	10.0	0.8	0.010*
P-LCR	29.5	8.9	25.5	6.6	0.027*

Note: * significant at 5% level of significance ($p<0.05$)

Figure 28: Distribution of MPV and P-LCR between Study Groups



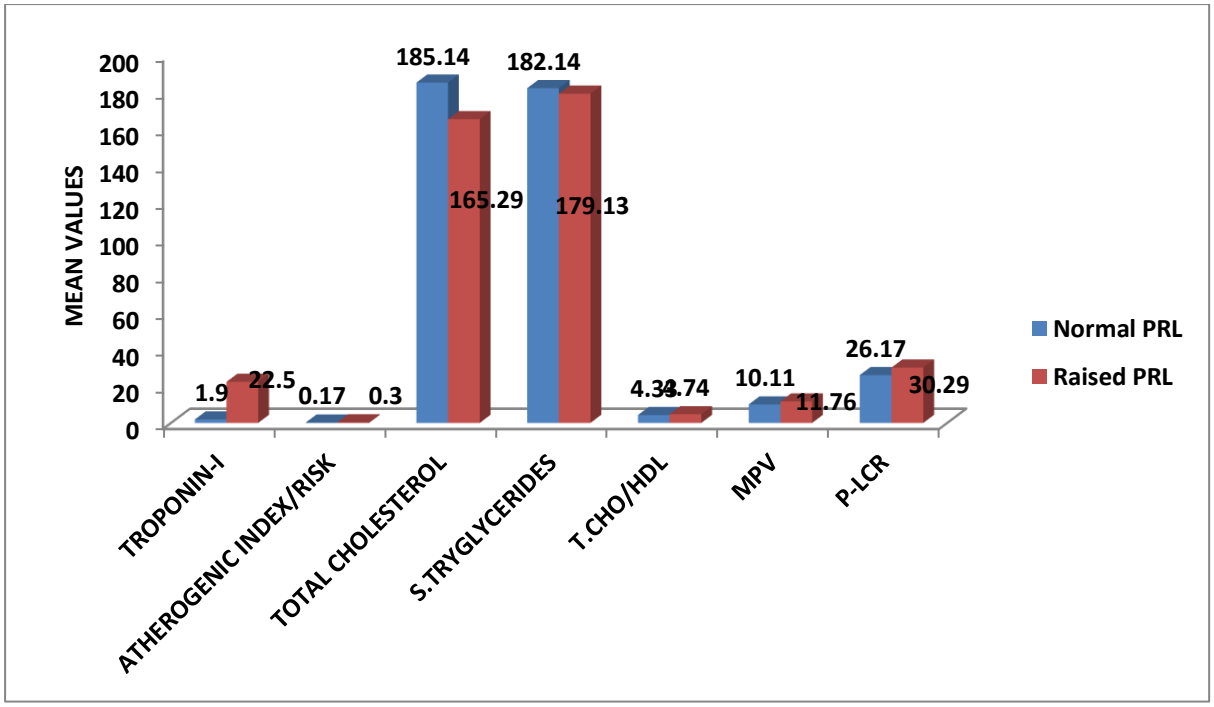
- The mean MPV value among cases is 10.6 fl and that of the control group is 10 fl and the difference is found to be statistically significant.
- The mean P-LCR value among cases is 29.5% and that of the control group is 25.5% and the difference is found to be statistically significant.

Table 23: Distribution of Mean Parameters according to Prolactin level among cases

Parameters	Prolactin Normal		Prolactin raised		p value
	Mean	SD	Mean	SD	
TROPONIN-I	1.9	2.5	22.5	8.3	<0.001*
ATHEROGENIC INDEX/RISK	0.17	0.16	0.30	0.23	0.150
TOTAL CHOLESTEROL	185.14	47.23	165.29	31.86	0.182
S.TRYGLYCERIDES	182.14	60.54	179.13	84.20	0.929
T.CHO/HDL	4.33	1.77	4.74	1.45	0.523
MPV	10.11	1.03	11.76	1.19	0.047*
P-LCR	26.17	8.55	30.29	8.96	0.275

Note: * significant at 5% level of significance (p<0.05)

Figure 29: Distribution of Mean Parameters according to Prolactin level among cases



In our study, we divided the cases into raised prolactin group and normal prolactin group and we compared the mean values of Troponin-I, Atherogenic Index of Plasma, Total Cholesterol, Serum Triglycerides, T.CHO/HDL, MPV and P-LCR among both the groups.

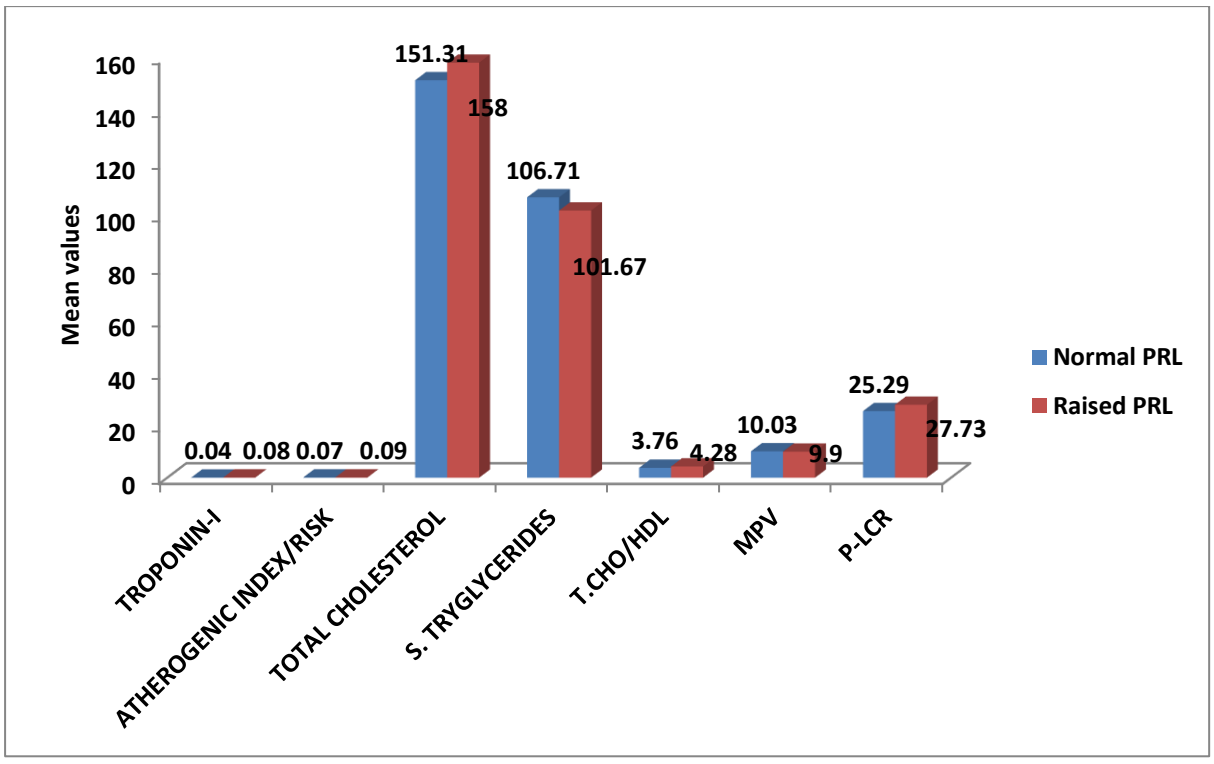
- The mean Troponin-I levels among raised prolactin group is 22.5 ng/ml and that of normal prolactin group is 1.9 ng/ml and it is found to be statistically significant.
- The mean Atherogenic Index among raised prolactin group is 0.3 and that of normal prolactin group is 0.17.
- The mean Total Cholesterol levels among raised prolactin group is 165.29 mg/dl and that of normal prolactin group is 185.14 mg/dl.
- The mean serum triglycerides level among raised prolactin group is 179.13 mg/dl and that of normal prolactin group is 182.14 mg/dl.
- The mean T.CHO/HDL ratio among raised prolactin group is 4.74 and that of normal prolactin group is 4.33.
- The mean MPV values among raised prolactin group is 11.76 fl and that of normal prolactin group is 10.11 fl and it is found to be statistically significant.
- The mean P-LCR values among raised prolactin group is 30.29% and that of normal prolactin group is 26.17%.

Table 24: Distribution of Mean Parameters according to Prolactin level among controls

Parameters	Prolactin Normal		Prolactin raised		p value
	Mean	SD	Mean	SD	
TROPONIN-I	0.04	0.03	0.08	0.04	0.023*
ATHEROGENIC INDEX/RISK	0.07	0.13	0.09	0.09	0.804
TOTAL CHOLESTEROL	151.31	25.64	158.00	32.74	0.673
S. TRYGLYCERIDES	106.71	31.66	101.67	17.56	0.788
T.CHO/HDL	3.76	0.84	4.28	1.43	0.334
MPV	10.03	0.84	9.90	0.66	0.790
P-LCR	25.29	6.76	27.73	4.71	0.545

Note: * significant at 5% level of significance (p<0.05)

Figure 30: Distribution of Mean Parameters according to Prolactin level among controls



In our study, we divided the controls into raised prolactin group and normal prolactin group and we compared the mean values of Troponin-I, Atherogenic Index of Plasma, Total Cholesterol, Serum Triglycerides, T.CHO/HDL, MPV and P-LCR among both the groups.

- The mean Troponin-I levels among raised prolactin group is 0.08 ng/ml and that of normal prolactin group is 0.04 ng/ml and it is found to be statistically significant.
- The mean Atherogenic Index among raised prolactin group is 0.09 and that of normal prolactin group is 0.07.
- The mean Total Cholesterol levels among raised prolactin group is 158 mg/dl and that of normal prolactin group is 151.31 mg/dl.
- The mean serum triglycerides level among raised prolactin group is 101.67 mg/dl and that of normal prolactin group is 106.71 mg/dl.
- The mean T.CHO/HDL ratio among raised prolactin group is 4.28 and that of normal prolactin group is 3.76.
- The mean MPV values among raised prolactin group is 9.90 fl and that of normal prolactin group is 10.03 fl.
- The mean P-LCR values among raised prolactin group is 27.73% and that of normal prolactin group is 25.29%.

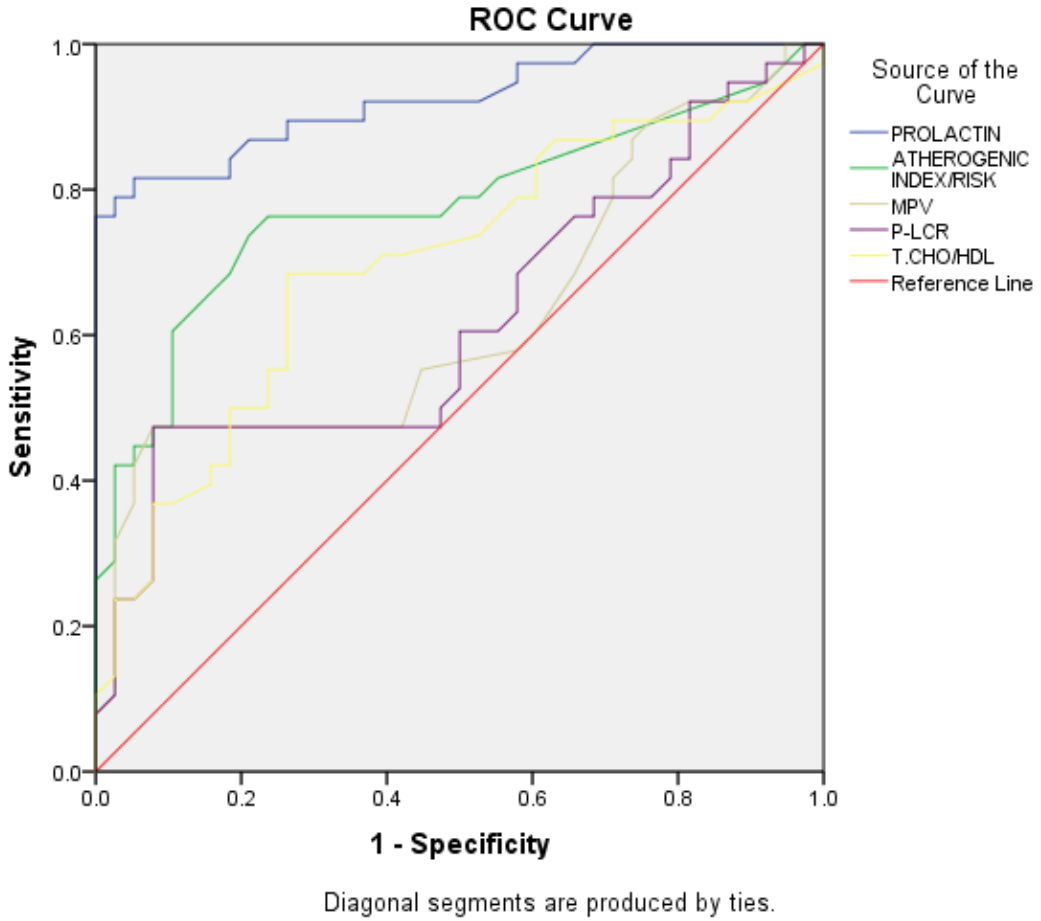
Table 25: ROC Analysis of Scores in Predicting MI

Parameters	Area Under the Curve	SE	p value	95% Confidence Interval	
				Lower	Upper
PROLACTIN	0.92	0.031	<0.001*	0.86	0.99
ATHEROGENIC INDEX/RISK	0.78	0.056	<0.001*	0.67	0.89
T.CHO/HDL	0.70	0.061	0.003*	0.58	0.82
MPV	0.63	0.066	0.049*	0.50	0.76
P-LCR	0.62	0.066	0.066	0.49	0.75

Note: * significant at 5% level of significance (p<0.05)

Parameters	Cut off value	Sensitivity	Specificity	PPV	NPV	ACCURACY
PROLACTIN	16.06	84.2%	81.6%	82.8%	83.1%	82.9%
ATHEROGENIC INDEX/RISK	0.14	76.3%	71.1%	72.5%	75.0%	73.7%
T.CHO/HDL	3.94	71.1%	60.5%	61.8%	69.9%	65.5%
MPV	9.95	57.9%	42.1%	42.1%	57.9%	48.8%
P-LCR	25.40	55.3%	50.0%	51.2%	54.1%	52.6%

Figure 31: ROC curve of Scores in Predicting MI



- According to above table and figure, we can say that, with a confidence interval of 95%,
- prolactin can be used as a predictor of acute MI, with a cut off value of 16.06 ng/ml, sensitivity of 84.2%, specificity of 81.6%, with the area under the curve being 0.92 and sit is found to be statistically significant.
- With a confidence interval of 95%, Atherogenic Index can be used as a predictor of acute MI, with a cut off value of 0.14, sensitivity of 76.3%, specificity of 71.1%, with the area under the curve being 0.78 and it is found to be statistically significant.

- With a confidence interval of 95%, T.CHO/HDL ratio can be used as a predictor of acute MI, with a cut off value of 3.94, sensitivity of 71.1%, specificity of 60.5%, with the area under the curve being 0.70 and it is found to be statistically significant.
- With a confidence interval of 95%, MPV can be used as a predictor of acute MI, with a cut off value of 9.95 fl, sensitivity of 57.9%, specificity of 42.1%, with the area under the curve being 0.63 and it is found to be statistically significant.
- With a confidence interval of 95%, P-LCR can be used as a predictor of acute MI, with a cut off value of 25.40%, sensitivity of 55.3%, specificity of 50% and with the area under the curve being 0.62, but was not statistically significant.
- So, according to the above table and graph, we can infer that Prolactin has a better sensitivity and specificity in predicting acute MI, followed by Atherogenic index, followed by T.CHO/HDL ratio, followed by MPV.
- P-LCR has least sensitivity and specificity in predicting acute MI.

DISCUSSION

The present study was conducted on 76 subjects of Acute Myocardial Infarction. Serum prolactin levels were measured to evaluate as a risk factor in Acute MI. The study subjects were divided into 2 groups, which consists 38 patients of acute MI and 38 controls who did not have any signs and symptoms suggestive of myocardial infarction. Our study also compared prolactin levels with levels of troponin I, Atherogenic index, T.CHO/HDL ratio, MPV and P-LCR.

AGE:

In a study done by Hayder M. Al-Kuraishy et al [65], 44 patients of acute MI and 22 controls of healthy individuals were studied for serum prolactin levels. Among the study group, 2 patients belonged to the age group of 40-49 years, 8 patients were between 50-59 years, 12 patients were between 60-69 years and patients were above 70years. The mean age in the study group was 60.2 years. In a study conducted by Saurabh et al [73], the mean age of cases was 59 years. In the study conducted by Reuwer et al [66], 40 patients of acute MI and 39 patients of controls were studied. The mean age group among cases was 66.4 years among cases and that among control group was 65.4. Our study involved 38 cases of acute MI and 38 healthy controls. Among the study group, 4 patients belonged to age group of 41-50 years, 20 patients belonged to the age group of 51-60 years, 12 patients belonged to age group of 61-70 years and 2 patients belonged to age group of greater than 70 years. The mean age in our study group is 58.9 years.

SEX:

In a study done by Hayder M. Al-Kuraishy et al [65], among 44 patients with acute MI, 20 patients were males while the remaining 24 were female patients. The male to female ratio (%) was 45:55. In the study conducted by Reuwer et al [66], among 40 patients of acute MI, 29

were males and 11 were females. The male to female ratio (%) was 72.5:27.5. In a study conducted by Saurabh et al [73], the male to female ratio (%) was 57:43. In our study, among 38 patients with acute MI, 23patients were male and the remaining 15 patients were female. The male to female ratio (%) among cases and controls was 60.5:39.5.

BMI:

In a study done by Hayder M. Al-Kuraishy et al [65], the mean BMI in cases was 29.6 kg/m^2 and that of controls was 25.0 kg/m^2. In the study conducted by Reuwer et al [66], the mean BMI was 27.4 Kg/m^2 among cases and 26.8 kg/m^2 among control group. In our study, mean BMI is 25.3kg/m^2 in cases and 23.6kg/m^2 in controls.

TROPONIN-I:

In a study done by Hayder M. Al-Kuraishy et al [65], among the study group, the mean troponin-I level was 76.70 pg/ml. Among the control group, the mean troponin-I level was 13.43 pg/ml. In our study, the mean troponin I level in cases was 18.7ng/ml and in controls the mean troponin I level was 0.039 ng/ml.

PROLACTIN:

In a study done by Hayder M. Al-Kuraishy et al [65], of the 44 patients with acute MI, 22 patients had raised serum prolactin, while the remaining 22 patients had normal serum prolactin levels. Among the control group of 22 individuals, only 1 subject had raised serum prolactin levels while the other 21 patients had normal serum prolactin levels. The mean serum prolactin levels among the study group was 22.01ng/ml and in the control group, it was 3.4 ng/ml. The comparison between the study and the control groups with regard to the mean prolactin levels, yielded a p value of 0.0032. In our study, among the study group of 38 patients, 31 patients had raised serum prolactin, while the rest 7 patients had normal serum prolactin. Among 38 individuals in the control group, 3 subjects had raised serum prolactin

levels, while the rest 35 subjects had normal serum prolactin levels. Among the study group, the mean prolactin level is 43.1ng/ml and among the control group, the mean prolactin level was 12.7ng/ml. In our study, the comparison between the study and the control groups with respect to mean prolactin levels obtained a p value of <0.001 which is highly statistically significant. In contrast to the present study, in the study conducted by Reuwer et al [66], the mean prolactin level among cases was 7 mcgm/l, and that of the control group was 6 mcgm/l.

LIPID PROFILE:

In a study done by Hayder M. Al-Kuraishy et al [65], the lipid profile was deranged among cases when compared to that of control group and it was found to be statistically significant with p value <0.001. In a study done by Naresh et al [74], similar findings were found. In our study the mean triglycerides, total cholesterol and VLDL are elevated among cases of acute MI compared to that of control group and it was found to be statistically significant. The mean level of HDL among cases was less when compared to that of control group stating the protective role of HDL cholesterol in reducing cardiovascular events.

ATHEROGENIC INDEX OF PLASMA:

In a study done by Hayder M. Al-Kuraishy et al [65], the atherogenic index was elevated among cases in comparison to control group and it was found to be statistically significant. In a study conducted by Gaojun Cai et al [75], Atherogenic index of plasma (AIP) was higher among cases of CAD than in controls, where the mean AIP value among cases was 0.17 and that of the control group was 0.12. Similar findings were found in a study conducted by Zhan Y et al [76], in which mean AIP value was higher in cases of ACS. In our study, the mean AIP levels was significantly elevated among cases which was 0.3, compared to that of control group which was 0.1. In our study, we also found that, among the 38 cases of acute MI, 21 patients (55.3%) belonged to high risk group of AIP, 8 patients (21.1%) belonged to intermediate risk

group and the rest 9 patients (23.7%) belonged to low risk group.

T.CHO/HDL ratio:

In a study done by Hayder M. Al-Kuraishy et al [65], the mean T.CHO/HDL ratio among cases was 6.36 and that of controls was 1.89 and the mean difference was found to be statistically significant. In a study conducted by Gaojun Cai et al [75], the mean T.CHO/HDL ratio was 4.51 among cases of CAD and that of controls was 4.19 and the mean difference was found to be statistically significant. In our study, the mean T.CHO/HDL ratio among cases of acute MI was 4.7 while that of control group was 3.8 and it was found to be statistically significant with p value of 0.003.

MEAN PLATELET VOLUME AND P-LCR:

Mean platelet volume (MPV) is a marker of platelet size which reflects the activity of the platelet. Larger platelets with higher MPV values are hemostatically more reactive and produce large amounts of prothrombotic factor which leads to atherothrombosis. Normal MPV range is 7.4 fl -11.4 fl. P-LCR is defined as the percentage of platelets that exceed the normal value of platelet volume in the total platelet count. Normal P-LCR value range is 11-33%.

In a study conducted by Khandekar et al [77], the mean MPV among cases of acute MI was 10.43 fl and the mean MPV among controls was 9.20 fl and it was found to be statistically significant. In a study conducted by Yekeler et al [78], the mean MPV value among cases of ACS was 10.43 fl and that of the controls was 10.11 fl and it was statistically significant.

In our study, the mean MPV value among cases of acute MI was 10.6 fl and that of the control group was 10 fl and it was found to be statistically significant with a p value of 0.010.

In our study, the mean P-LCR value among cases of acute MI was 29.5% and that of the control group was 25.5% and it was statistically significant with a p value of 0.027.

COMPARISON OF SERUM PROLACTIN WITH OTHER PARAMETERS:

In our study, we compared the mean values of different parameters with respect to serum prolactin levels. This was achieved by dividing the cases of acute MI into 2 groups: Normal prolactin and Raised prolactin groups.

The mean Troponin-I level was significantly elevated among the raised prolactin group in comparison to normal prolactin group and is found to be statistically significant with a p value of <0.001, suggesting the positive correlation between serum prolactin and Troponin-I levels in acute myocardial infarction. Similar findings were seen in a study conducted by Hayder M. Al-Kuraishy et al [65].

The mean MPV value is significantly higher in raised prolactin group compared to that of the normal prolactin group among the cases of acute MI and was found to be statistically significant with a p value of 0.047, reflecting the effect of serum prolactin on platelet aggregation.

In our study, we also found that the mean values of Atherogenic index, T.CHO/HDL ratio and P-LCR were elevated among raised prolactin group compared to those of normal prolactin group, but was not statistically significant.

In our study, we also studied the sensitivity and specificity of serum prolactin, Atherogenic index, T.CHO/HDL ratio and MPV in predicting Acute Myocardial Infarction. We found that serum prolactin level is a better predictor of acute MI, with a sensitivity of 84.6% and a specificity of 81.6%. This is followed by Atherogenic Index, T.CHO/HDL ratio and MPV being the poor predictor of acute MI with a sensitivity and specificity of 57.9% and 42.1% respectively.

Cardiac troponin is an extremely sensitive but; not specific to the myocardial damage it also elevates to noncardiac conditions as in vigorous exercise which leads to stress-induced

myocardial systolic dysfunction, but; it's extremely realistic to exclude non-ST elevation MI but; cannot differentiate between thrombotic and nonthrombotic acute coronary syndrome. [79] Thus, coexistences elevation of both cardiac troponin and serum prolactin in acute MI give an idea about the underlying predisposing factor of occurrences of MI, and the elevated troponin revealed myocardial necrosis due to the coronary vessel complications that appeared in association with dyslipidemia which linked to high prolactin level. [80] Therefore, a positive correlation between cardiac troponin and serum prolactin in this study elucidate that acute MI occurrence is due to long-term vascular complications.

CONCLUSION

- In this study, it was found that the serum prolactin levels are significantly elevated in cases of Acute Myocardial Infarction.
- Serum prolactin levels are positively correlated with levels of Troponin-I, reflecting the underlying cardiovascular complications.
- We also found that, the MPV values are increased in cases of acute MI with raised serum prolactin levels, indicating the effect of prolactin on platelet aggregation.
- Serum prolactin levels can be used as predictor of Acute Myocardial Infarction with sensitivity and specificity of 84.2% and 81.6% respectively.

LIMITATION OF THE STUDY

1) This study has a limited sample size.
2) Patients of Acute Myocardial Infarction with higher serum prolactin levels weren't followed up after discharge to assess the mortality in these patients, which according to us could have added more evidence to our study in proving prolactin as predictor for mortality.
3) We weren't able to compare serum prolactin levels with other inflammatory markers such as myeloperoxidase, C reactive protein, fibrinogen because these makers aren't routinely obtained in our study population.

SUMMARY

A hospital based prospective, randomized, comparative study was conducted from November 2018 to June 2020. A total of 76 subjects were included in the study, divided into 2 groups, with 38 cases of Acute Myocardial Infarction in one group and the other 38 subjects in control group. Demographic characteristics were noted. Detailed history was noted and clinical examination was done. Among cases of acute MI,

- Most patients belonged to age group of 51-60 years, with mean age of 58.9 years.
- Males were predominant in our study.
- Anterior wall MI is seen in 36.8% of cases, Antero-lateral wall MI in 18.4%, Antero-septal wall MI in 7.9%, Inferior wall MI in 21.1%, Infero-lateral wall MI in 10.1% and posterior wall MI in 5.3% of cases.
- Serum prolactin was raised in 81.6% of cases of acute MI, and was statistically significant with a p value of <0.001.
- Serum Prolactin levels were positively correlated with Troponin-I levels among cases of acute MI, suggesting underlying cardiovascular complications.
- MPV values were elevated among patients with raised serum prolactin, reflecting the role of prolactin in platelet aggregation.
- T.CHO/HDL ratio and Atherogenic Index values are also raised among patients with elevated serum prolactin, but it was not statistically significant.
- Serum prolactin can be used as marker for predicting acute MI with a sensitivity of 84.2% and a specificity of 81.6%.

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ANNEXURE 1

ETHICAL CLEARANCE CERTIFICATE

B.L.D.E (Deemed to be University)
SHRI.B.M.PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE
VIJAYAPUR – 586103

IEC. No/286/18
17/11/2018

INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 13-11-2018 at 03-15 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 : Assessment of serum prolactin levels as a risk factor in acute myocardial infarction.

Name of P.G. Student : Dr.Reddivari Leela Mounica
Department of General Medicine.

Name of Guide/Co-investigator: Dr. P.G.Mantur, Associate Professor of General Medicine.

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

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.

ANNEXURE II

INFORMED CONSENT FORM

BLDEU'S SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR- 586103

TITLE OF RESEARCH: **ASSESSMENT OF SERUM PROLACTIN LEVELS AS A RISK FACTOR IN ACUTE MYOCARDIAL INFARCTION**

GUIDE : **DR. P. G. MANTUR**
M.D. MEDICINE

P.G. STUDENT : **DR. REDDIVARI LEELA MOUNICA**

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

PURPOSE OF STUDY:

I have been informed that the purpose of this study is to determine the various clinical and radiological patterns of presentation in geriatric patients who have tested sputum positive for tuberculosis.

PROCEDURE:

I understand that I will undergo detailed history and clinical examination and investigations.

BENEFITS:

I understand that my participation in this study will have no direct benefit to me other than the potential benefit of treatment which is planned to prevent further morbidity and mortality in me.

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.

REQUEST FOR MORE INFORMATION:

I understand that I may ask for more information about the study at any time.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or withdraw from study at any time.

(Signature of Guardian) (Signature of patient)

STUDY SUBJECT CONSENT FORM:

I confirm that **Dr. REDDIVARI LEELA MOUNICA** has explained to me the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience, in my own language.

I have been explained all above in detail in my own language and I understand the same. I agree to give my consent to participate as a subject in this research project.

DATE SIGNATURE OF PARTICIPANT

DATE SIGNATURE OF WITNESS

ANNEXURE III

PROFORMA

BLDE'S DEEMED TO BE UNIVERSITY

SHRI B M PATIL MEDICAL COLLEGE

HOSPITAL AND RESEARCH CENTRE, VIJAYAPURA

NAME: CASE NO:

AGE: IP NO:

SEX: DOA:

RELIGION: DOD:

OCCUPATION:

RESIDENCE:

CHIEF COMPLAINTS:

HISTORY OF PRESENTING ILLNESS:

PAST HISTORY:

HISTORY OF IHD

HISTORY OF HYPERTENSION

HISTORY OF DIABETES MELLITUS

HISOTRY OF THYROID DISEASE

DRUG HISTORY

HISTORY OF SMOKING

PERSONAL HISTORY:

DIET

APPETITE:

SLEEP:

BLADDER AND BOWEL HABITS:

HABITS:

FAMILY HISTORY:

GENERAL PHYSICAL EXAMINATION

HEIGHT:

WEIGHT:

BODY MASS INDEX:

VITALS:

- PULSE RATE
- RESPIRATORY RATE
- BLOOD PRESSURE
- TEMPERATURE

HEAD TO TOE EXAMINATION:

SYSTEMIC EXAMINATION

CARDIOVASCULAR EXAMINATION

RESPIRATORY SYSTEM

PER ABDOMEN

CENTRAL NERVOUS SYSTEM

INVESTIGATIONS:

ECG:

HAEMATOLOGY:

HAEMOGLOBIN:	GM%
TOTAL WBC COUNTS:	CELLS/mm^3
DIFFERENTIAL COUNT	
NEUTROPHILS	%
EOSINOPHILS	%
LYMPHOCYTES	%
MONOCYTES	%
BASOPHILS	%
ESR	mm after 1 hour
MPV	fl
P-LCR	%

URINE EXAMINATION:

- ALBUMIN
- SUGAR
- MICROSCOPY

BIOCHEMISTRY:

- CARDIAC MARKERS
  - CPK-MB
  - TROPONIN I
- SERUM PROLACTIN
- LIPID PROFILE
  - TRIGLYCERIDES
  - TOTAL CHOLESTEROL
  - HDL CHOLESTEROL
  - LDL CHOLESTEROL
  - VLDL CHOLESTEROL
- SERUM CREATININE
- BLOOD UREA
- BLOOD SUGAR LEVELS
  - FBS:
  - PPBS:
- THYROID PROFILE
  - T3
  - T4
  - TSH

2DECHO

TREATMENT

OUTCOME

KEY TO MASTER CHART:

S.NO	-	Serial number
AGE in years		
SEX		
BMI	-	Body Mass Index
TYPE OF MI		
CPK-MB		
TROPONIN-I		
SERUM PROLACTIN		
SERUM TRIGLYCERIDES		
TOTAL CHOLESTEROL		
SERUM HDL		
SERUM LDL		
SERUM VLDL		
ATHEROGENIC INDEX/RISK		
TOTAL CHOLESTEROL/HDL RATIO		
MPV	-	Mean Platelet Volume
P-LCR	-	Platelet larger cell ratio

MASTER CHART

CASES															
	AGE	SEX	BMI	TYPE OF MI	CPK-MB	TROPONIN-I	PROLACTIN	S.TRYGLYCERIDES	TOTAL CHOLESTEROL	HDL	LDL	VLDL	ATHEROGENIC INDEX/RISK	T.CHO/HDL	MPV	P-LCR
1	56	MALE	30.3	ANTERIOR	98	13.3	27.92	178	214	54	144	16	0.16(INTERMEDIATE)	3.96	11.7	36.1
2	64	MALE	30.3	INFERIOR	19	0.787	24.2	189	166	27	101	38	0.48 (HIGH)	6.14	11.6	33.8
3	55	MALE	27.8	ANTERIOR	19	0.264	26.83	189	200	30	132	38	0.44(HIGH)	6.66	13	48.2
4	66	FEMALE	30.5	ANTERO-LATERAL	152	16.6	64.46	158	191	26	133	32	0.42 (HIGH)	7.34	11.6	39.9
5	55	FEMALE	29.4	ANTERIOR	89	80	72.55	152	141	43	67	30	0.19 (INTERMEDIATE)	3.27	12	41.9
6	57	MALE	26.4	INFERIOR	40	18.1	64.31	163	153	31	89	33	0.36 (HIGH)	4.93	10.1	25.2
7	64	MALE	26.2	ANTERO-LATERAL	50	22.6	44.64	156	154	31	92	31	0.34 (HIGH)	4.96	9.8	23.9
8	58	MALE	23.5	ANTERIOR	21.4	14.4	66.45	115	123	44	56	23	0.06 (LOW)	2.79	11.8	37.7
9	58	FEMALE	26.8	INFERO-LATERAL	87	2.14	53.59	153	205	33	141	31	0.31 (HIGH)	6.21	10.1	25.2
10	60	MALE	25.1	ANTERO-SEPTAL	29	4.58	70.48	260	162	38	82	52	0.47 (HIGH)	4.26	10.1	26
11	58	FEMALE	25.5	INFERIOR	24	0.65	46.43	97	150	56	74	19	-0.12 (LOW)	2.67	9.6	20.1
12	52	MALE	24	POSTERIOR	60	3.15	56.06	217	136	29	74	43	0.51 (HIGH)	4.68	11.7	35.6
13	53	MALE	24.2	ANTERIOR	30	0.34	31.07	85	122	46	59	17	-0.09 (LOW)	2.65	9.7	23.5
14	57	MALE	23.6	ANTERIOR	40	0.37	60.74	72	154	32	108	14	-0.01 (LOW)	4.81	11.5	34.2
15	64	FEMALE	25.8	INFERIOR	136	38.8	56.55	114	197	50	124	23	0 (LOW)	3.94	9.7	22.8
16	63	FEMALE	26.1	ANTERO-LATERAL	44	2.79	21.8	53	125	34	80	11	-0.17 (LOW)	3.67	9.7	24.7
17	65	MALE	21.5	ANTERIOR	28	0.34	10.16	116	174	51	100	23	-0 (LOW)	3.41	9.7	20.7
18	54	MALE	24.3	INFERO-LATERAL	36	0.225	37.8	255	194	43	100	51	0.41 (HIGH)	4.51	11.7	37
19	56	MALE	26.5	ANTERIOR	110	80	81.92	405	105	30	6	81	0.64 (HIGH)	3.5	10	26.8
20	66	FEMALE	26	ANTERIOR	46	2.23	72.2	227	145	25	74	45	0.6 (HIGH)	5.8	11.9	35.5
21	53	MALE	22.6	INFERIOR	19	0.258	16.12	120	186	35	127	24	17(INTERMEDIATE)	5.31	8.9	16.4
22	71	FEMALE	25.8	ANTERIOR	295	80	42.86	375	224	29	120	75	0.65 (HIGH)	7.72	11.8	38.7
23	60	MALE	24.2	ANTERO-LATERAL	15	0.792	11.4	170	212	52	126	34	0.15 (INTERMEDIATE)	4.07	9.8	22.9
24	58	FEMALE	24.2	INFERIOR	17	57.3	34.5	121	129	31	75	24	0.23(HIGH)	4.16	11.5	33.3
25	68	MALE	24.5	ANTERO-LATERAL	292	80	31	53	125	34	80	11	0.17(LOW)	3.67	9.3	19
26	65	MALE	24.2	INFERO-LATERAL	33	1.4	11.13	150	139	40	69	30	0.2(INTERMEDIATE)	3.47	9.8	25.6
27	48	MALE	24.2	ANTERIOR	118	80	35	158	172	38	103	32	0.26(HIGH)	4.52	9.2	19

28	75	MALE	18.6	ANTERO-SEPTAL	39	0.93	16	198	150	88	40	22	0.01 (LOW)	1.7	11.7	38.8
29	48	MALE	25.2	POSTERIOR	35	20	43.3	86	154	41	96	17	-0.04(LOW)	3.75	9.9	23.4
30	51	FEMALE	24.9	INFERO-LATERAL	36	12	79.6	189	166	27	101	38	0.48(HIGH)	6.14	8.9	17.1
31	62	FEMALE	26.6	INFERIOR	24	2.48	15	265	277	38	186	53	0.48(HIGH)	7.28	11.4	37.2
32	59	FEMALE	25.7	ANTERIOR	30	12.55	89.27	230	164	41	77	46	0.39(HIGH)	4	8.8	14.3
33	62	FEMALE	24.7	INFERIOR	40	10.3	39.5	260	162	38	82	52	0.47(HIGH)	4.26	12.1	42.1
34	43	MALE	20.8	ANTERO-LATERAL	48	7.38	12.52	256	158	31	76	51	0.17(INTERMEDIATE)	5.09	9.5	21.6
35	57	FEMALE	25.7	ANTERIOR	50	12.2	48.7	168	205	41	130	34	0.25(HIGH)	5	9.4	19.4
36	66	MALE	24.7	ANTERO-SEPTAL	73	21.9	25.9	148	180	45	105	30	0.16(INTERMEDIATE)	4	11.8	34.5
37	50	FEMALE	22	ANTERO-LATERAL	58	5.04	46.3	255	194	43	100	51	0.41(HIGH)	4.51	11.4	38.8
38	60	MALE	27.4	ANTERIOR	42	6.26	51	272	212	25	132	54	0.68(HIGH)	8.48	12.2	41.4
						CONTROLS										
39	48	MALE	19.5		13	0.05	16	104	124	37	66	21	0.09(LOW)	3.35	10.5	28.7
40	70	FEMALE	27.6		12	0.09	12.45	85	122	46	59	17	-0.09 (LOW)	2.65	10.1	27.4
41	55	MALE	24.3		7	0.012	13	140	161	51	87	24	0.08(LOW)	3.15	9.7	21
42	70	FEMALE	23.9		11	0.012	10.12	128	158	40	92	26	0.14(INTERMEDIATE)	3.95	10.7	30.8
43	71	MALE	22.2		10	0.06	15.18	72	154	32	108	14	-0.01(LOW)	4.81	10	28.2
44	56	FEMALE	20.1		8	0.11	22.19	120	186	35	127	24	0.17(INTERMEDIATE)	5.31	10	31.3
45	52	MALE	23.4		13	0.08	9.99	109	124	39	84	22	0.09(LOW)	3.17	11.1	32.4
46	58	FEMALE	25.3		9	0.012	15.95	87	95	27	36	31	0.15(INTERMEDIATE)	3.51	10.7	31.5
47	54	FEMALE	19.8		5	0.072	10.31	121	154	57	83	24	-0.03(LOW)	2.7	11.4	37.2
48	59	FEMALE	20.7		8	0.02	11.92	127	145	45	64	35	0.09(LOW)	3.22	9.1	17.4
49	55	MALE	27.5		6	0.08	16.92	95	114	29	66	19	0.16(INTERMEDIATE)	3.93	10.2	27.1
50	74	FEMALE	22.1		12	0.08	20.49	100	166	34	100	32	0.11(INTERMEDIATE)	4.88	10.5	29.5
51	53	MALE	20.9		16	0.04	11.55	53	125	34	80	11	0.17(LOW)	3.67	10	24.7
52	61	MALE	24.8		8	0.04	16.62	153	198	68	100	31	-0.01(LOW)	2.91	8.7	14.6
53	59	MALE	25.8		12	0.02	9.98	118	170	38	117	24	0.13(INTERMEDIATE)	4.47	10.3	26.9
54	59	FEMALE	27.5		10	0.013	10.16	116	174	51	100	23	0(LOW)	3.41	9.7	20.7
55	64	MALE	19.6		5	0.09	17	93	190	48	123	19	-0.07(LOW)	3.95	9.8	22.9
56	58	MALE	22.7		7	0.017	12.35	54	158	37	109	11	-0.2(LOW)	4.27	10.3	26
57	66	MALE	24.6		14	0.02	13.36	86	154	41	96	17	-0.04(LOW)	3.75	9.5	21.2
58	63	FEMALE	21.3		16	0.012	11.5	153	165	30	104	31	0.35(HIGH)	5.5	8.5	13.2
59	54	MALE	29.9		10	0.012	12.34	104	124	37	66	21	0.09(LOW)	3.35	9.3	20
60	68	FEMALE	24.8		20	0.02	9.54	139	179	54	97	28	0.05(LOW)	3.31	9.1	16.8
61	70	FEMALE	21.6		7	0.04	8.01	86	154	41	96	17	-0.04(LOW)	3.75	10.7	29.7
62	60	MALE	26.4		3	0.012	10	93	190	48	123	19	-0.07(LOW)	3.95	9.2	18.3
63	60	FEMALE	22.5		10	0.02	11.4	86	154	41	96	17	-0.04(LOW)	3.75	9.9	23.4
64	68	MALE	19.8		6	0.01	7.85	53	125	34	80	11	0.17(LOW)	3.67	10	25
65	53	MALE	30.7		20	0.07	10.05	128	158	40	92	26	0.14(INTERMEDIATE)	3.95	10.7	30.8
66	49	MALE	28.7		14	0.06	11	189	200	30	132	38	0.44(HIGH)	6.66	8.9	16.8

67	51	FEMALE	24.6		15	0.07	18	147	145	31	85	29	0.32(HIGH)	4.67	10.4	29.2
68	62	MALE	27.5		10	0.03	10.09	70	136	32	90	14	-0.02(LOW)	4.25	9.8	22.8
69	59	FEMALE	21.9		8	0.012	7.93	115	123	44	56	23	0.06(LOW)	2.79	10.2	27.5
70	61	MALE	26.1		10	0.023	10.11	97	150	56	74	19	-0.12(LOW)	2.67	11.6	37.6
71	49	MALE	23.8		9	0.036	24.26	85	122	46	59	17	-0.09(LOW)	2.65	9.2	22.4
72	57	MALE	18.6		8	0.022	12.81	72	154	32	108	14	-0.01(LOW)	4.81	10	24.9
73	66	MALE	20.4		11	0.012	10.48	153	135	36	69	30	0.27(HIGH)	3.75	12	41.4
74	54	MALE	24.8		12	0.011	8.78	114	197	50	124	23	0(LOW)	3.94	9.1	21.4
75	63	FEMALE	22.6		6	0.07	12.74	97	150	56	74	19	-0.12(LOW)	2.67	11.1	32.2
76	48	MALE	19.5		13	0.013	11.4	98	137	42	75	20	0.01(LOW)	3.26	8.9	15.3