A STUDY ON THYROID PROFILE AND ITS PROGNOSTIC VALUE IN PATIENTS PRESENTING WITH ST ELEVATION MYOCARDIAL INFARCTION

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT

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CERTIFICATE FROM THE DEAN

This is to certify that the dissertation entitled **"A STUDY ON THYROID PROFILE AND ITS PROGNOSTIC VALUE IN PATIENTS PRESENTING WITH ST ELEVATION MYOCARDIAL INFARCTION"** is a bonafide work submitted by **Dr. SIVA SUNDAR.A**, in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical university, Chennai, for M.D. General Medicine Branch I examination to be held in MAY 2023.

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CERTIFICATE FROM THE HOD

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DECLARATION

I, **Dr. SIVA SUNDAR** declare that, I carried out this work on, **"A STUDY ON THYROID PROFILE AND ITS PROGNOSTIC VALUE IN PATIENTS PRESENTING WITH ST ELEVATION MYOCARDIAL INFARCTION"** at the Department of Medicine, Govt. Rajaji Hospital during the period of Nonmember 2021 to August 2022. I also declare that this bonafide work or any part of this work was not submitted by me or any others for any award, degree or diploma to any other University, Board either in India or abroad.

This is submitted to The Tamilnadu Dr.M.G.R.Medical University, Chennai in partial fulfillment of the rules and regulations for the M.D degree examination in General Medicine.

Date: 13/12/2022

Place: MADURAI

Dr. SIVA SUNDAR

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LIST OF ABBREVIATIONS

STEMI	-	ST elevation Myocardial Infarction
NSTEMI	-	Non ST elevation Myocardial Infarction
CAD	-	Coronary artery disease
T3	-	Tri iodo thyronine
T4	-	Thyroxine
TSH	-	Thyroid stimulating hormone
TRH	-	Thyrotropin releasing hormone
DM	-	Diabetes mellitus
HT	-	Hypertension
SES	-	Sick euthyroid state
MACE	-	Major adverse cardiac events
TIMI	-	Thrombholysis in myocardial infarction
IHD	-	Ischemic heart disease
EF	-	Ejection fraction
LDL	-	C Low density lipoprotein cholesterol
VLDL	-	C -Very low density lipoprotein cholesterol
HDL	-	C - High density lipopreotein cholesterol

TGL	-	Triglyceride
Tg	-	Thyroglobulin
NIS	-	sodium iodide symporter
TPO	-	thyroperoxidase
MIT	-	Mono iodo thyronine
DIT	-	Di iodo thyronine
FSH	-	Follicle stimulating hormone
LH	-	Lutenising hormone
hCG	-	Human chorioninc gonadotropin
IYD	-	Iodotyrosine deiodinase
TBG	-	Thyroid Binding globulin
TTR	-	Transthyrethrin
TSHR	-	TSH receptor
MCT8	-	Monocarboxylate transporter 8
OATP1C1	-	Organic anion transporting polypeptide 1C1

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INTRODUCTION

Coronary artery disease is one of the leading causes of mortality in the world today-contributing to almost 13% of all the deaths annually. It is the most common cause of mortality in the non- communicable disease category. In India, cardiovascular disease accounted for 26% of all deaths in 2008. The proportion of Indians who develop CAD during their productive years is more when compared tothe western countries. This is because CAD occurs at an earlier age in Indians. Over the last 30 years, the prevalence of CAD in India has increased from 6 to12% in urban areas and 4 to 6% in the rural areas.

Atherosclerosis can affect all the arteries in the body leading to multiple consequences. CAD is a growing epidemic in the world because of the increase in sedentary lifestyle and increase in the consumption of high-fat, energy rich food. The number of younger individuals presenting with CAD is increasing today.

ST elevation myocardial infarction occurs when there is complete thrombotic occlusion of an already diseased coronary artery. Patient presents to the emergency department with chest pain. ECG

shows ST elevation in 2 or more contiguous leads. It is an emergency where treatment has to be initiated at the earliest as time means muscle.

The thyroid is an important endocrine gland in our body. It has effects on almost every system in our body. The relationship between the thyroid and cardiovascular system is complex and present at many levels. Hypothyroidism and hyperthyroidism are both known risk factors for the development of coronary artery disease. Thyroid disorders have also been implicated in influencing the outcome in heart failure, atherosclerosis, dyslipidaemia and arterial hypertension.

Any systemic illness can be associated with certain changes in the thyroid hormone levels. This is known as the Euthyroid sick syndrome or the low-T3 syndrome or non-thyroidal illness. This syndrome is characterised by a normal TSH, normal free T4 , reduced free T3 and increased reverse T3.

There are numerous prognostic factors for ST elevation MI such as the TIMI risk score, the LV ejection fraction etc. The thyroid status of a patient at the time of presentation to the hospital also affects the recovery. Patients with a sick euthyroid state at the time of presentation have a higher risk of complications- including heart failure, ventricular arrhythmias and death.

AIMS AND OBJECTIVES

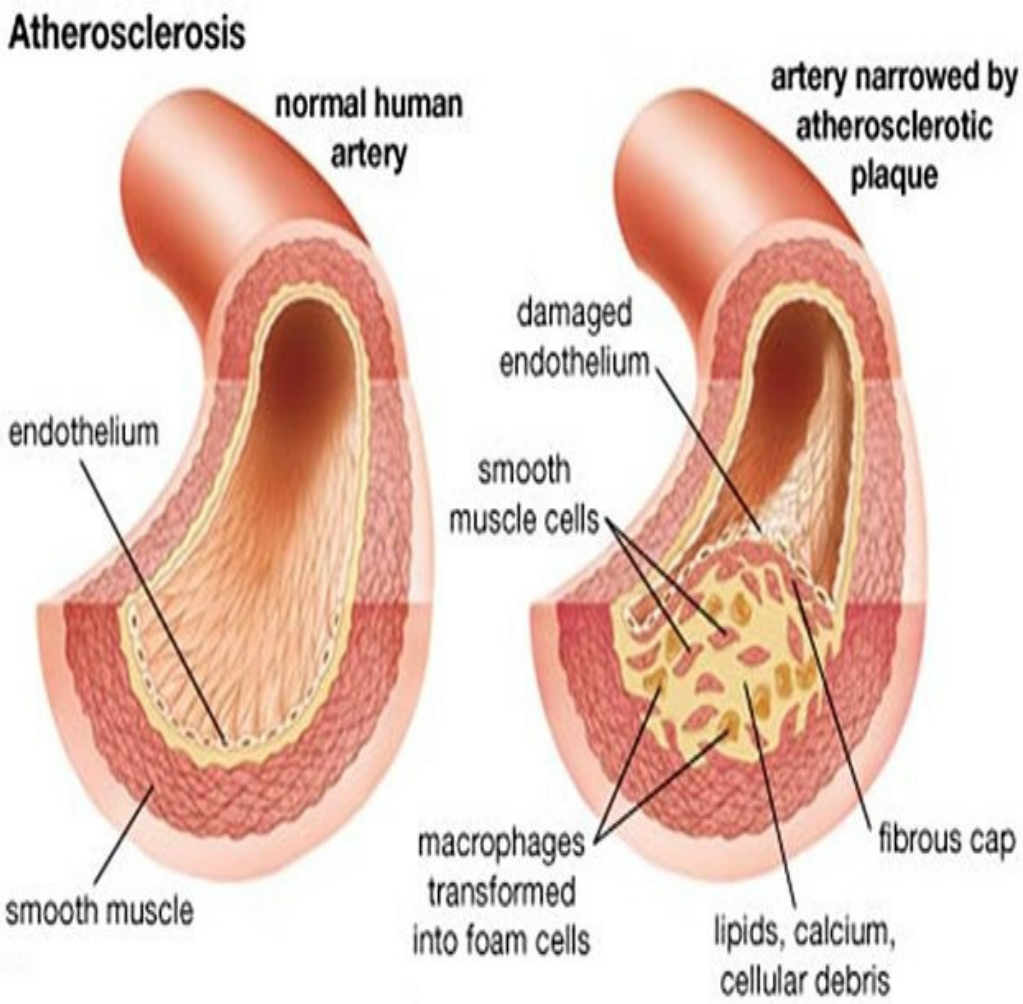
- To study the levels of TSH, fT3 and fT4 in patients presenting with ST elevation Myocardial Infarction
- To study the association, if any, between the presence of the Sick euthyroid state- characterised by reduced fT3 and normal TSH,fT4 levels and the incidence of MACE (Major adverse cardiac events), namely ventricular arrhythmias, cardiac failure and death.
- To evaluate whether thyroid hormone profile can be used to predict prognosis in ST elevation myocardial infarction.

REVIEW OF LITERATURE

ATHEROSCLEROSIS

The term “atherosclerosis” was coined in Germany as “atherosklerose “in early 20th century. It was derived from the Greek word athere and sklerosis meaning hardening of vessels.

Atherosclerosis is the leading cause of mortality in the developed world today. Atherosclerosis refers to the formation of atheromas or fibrofatty plaques in the intima of blood vessels. These plaques protrude into vascular lumens and cause obstruction. They occur mainly in elastic arteries (e.g., aorta, carotid and iliac) and muscular arteries (e.g., coronary and popliteal arteries). Symptomatic disease usually occurs when atherosclerosis affects the arteries of the heart, brain, kidneys and extremities. Deposition of atherosclerotic plaques in the coronary arteries leads to coronary artery disease. Reduction in the blood supply to the myocardium alters the supply-demand ratio. This leads of ischemia of the myocardium. Certain conditions can aggravate ischemia by either increasing the cardiac energy demand (e.g.hyerptrophy) or by decreasing the oxygen bioavailability (e.g.anemia).



ATHEROSCLEROSIS- RISK FACTORS

Advanced age, smoking, hypertension, diabetes mellitus, dyslipidaemia, sedentary lifestyle, metabolic syndrome, obesity are all important riskfactors for atherosclerosis.

SMOKING

Other than age, smoking is the most important risk factor for CAD. It is the leading preventable cause of death. The risk of CAD is directly proportional to the number of cigarettes smoked per day.

Smoking also increases the risk of ischemic stroke, sudden death, aortic aneurysm formation and peripheral vascular disease. In the past smoking used to be prevalent among men. However over the past few decades smoking has become increasingly prevalent among women. In young women who are on oral contraceptives, smoking has an adverse synergetic effect increasing the risk for CAD[27,28].

Smoking has acute undesired effects on blood pressure and sympathetic tone. It also accelerates atherosclerosis, enhances the oxidation of low-density lipoprotein (LDL) cholesterol and impairs endothelium-dependent coronary artery vasodilation. Smoking also contributes to adverse hemostatic and inflammatory effects including increased levels of CRP, soluble intercellular adhesion molecule-1 (ICAM-1), fibrinogen, and homocysteine. It also provokes spontaneous platelet aggregation, increases monocyte adhesion to endothelial cells and adversely alters endothelial-derived fibrinolytic and antithrombotic factors, including tissue-type plasminogen activator and tissue pathway factor inhibitor.

Cessation of cigarette smoking remains the single most important intervention in the prevention of CAD[27].

HYPERTENSION

Hypertension remains the silent killer of our time. It remains underdiagnosed and undertreated. The prevalence of hypertension is also increasing and it confers a silent risk for CAD. Both elevated systolic and diastolic BP jointly contribute to cardiovascular risk. Reductions of blood pressure as little as 4-5mm hg have been shown to result in a large and clinically significant reduction in risk for stroke, CAD, peripheral vascular disease.

DYSLIPIDEMIAS

High LDL-C

Elevations in Low density lipoprotein cholesterol confer an increased risk for CAD.LDL is intimately involved in the process of atherosclerosis. Patients with familial hyperlipoproteinemias with an elevated LDL are found to have accelerated atherosclerosis with early-onset CAD, The current target LDL for patients with evidence of established atherosclerosis or Diabetes is <100mg/dl. Intensive treatment is recommended for the same[38].

The major risk factors, the presence of which can modify LDL targetgoals include-

- Cigarette smoking
- Hypertension (BP more than 140/90)
- Diabetes Mellitus
- Low HDL cholesterol (less than 40mg/dl)
- Family history of premature CAD- In male 1st degree relative <55years, In female 1st degree relative <65 years
- Age >45 years for men, >55 years for women
- Lifestyle risk factors- obesity-BMI>30kg/m2, Physical inactivity, Atherogenic diet

RISK CATEGORY	**TARGET LDL (mg/dl)**
Very High- ACS, CAD with DM or multiple cumulative risk factors	<70
High-CAD or CAD risk equivalents	<100
Moderately high- 2+ risk factors	<130
Low risk- 0-1 risk factor	<160

HDL cholesterol

An inverse relationship exists between levels of HDL and the risk for CAD.HDL <40 md/dl is a major risk factor for CAD. The exact mechanism by which HDL cholesterol reduces the risk for CAD is not known. HDL functions in reverse cholesterol transport- it transports cholesterol from the peripheral tissues to the liver[31]. Hence it may ferry cholesterol out of the atherosclerotic plaques in the coronary arteries. It is also believed to be rich in antioxidant enzymes which may reduce the oxidised phospholipids in atheromatous plaques[38].

METABOLIC SYNDROME, DIABETES MELLITUS AND INSULINRESISTANCE

Diabetes Mellitus is a major risk factor for CAD. Ischemic heart disease is the leading cause of death in diabetics. Patients with diabetes have an altered lipoprotein profile- also termed as *diabetic dyslipidemia.*Even though most diabetics have LDL cholesterol levels in the normal range, the LDL particles are smaller, denser and more atherogenic. HDL is low and TGL are elevated . Furthermore insulin resistance itself promotes atherosclerosis even before the development of overt diabetes. Hypertension also commonly accompanies diabetes and dyslipidaemia. This cluster of risk factors is also known as the metabolic syndrome[29,30].

Metabolic syndrome- presence of any 3 of the following risk factors

- Abdominal obesity(waist circumference) >102cm in men : >88cmin women
- Fasting glucose >110mg/dl
- Triglycerides > 150mg/dl
- Blood pressure >130/>85 mm Hg
- HDL cholesterol < 40mg/dl in men : <50mg/dl in women

Therapeutic lifestyle changes (TLC) are a must for people with metabolic syndrome to counter the harmful effects of inadequate physical activity and obesity. The blood pressure goal in diabetic patients is 130/80 mm Hg.

OBESITY AND EXERCISE:

The levels of physical activity have been shown to have an inverse relation to risk for CAD. Studies have shown that even modest exercise such as 30 minutes of walking every day reduces the risk of CAD and stroke. Exercise acts in multiple ways to reduce cardiovascular risk. Aerobic exercise results in a mean reduction of BP by 5mm Hg. It also leads to an increase in HDL cholesterol and a decrease in TGL. Though LDL concentrations are not affected by exercise, the average size of LDL particles is increased, hence making them less atherogenic.

Exercise also improves insulin resistance and leads to better glycaemic control. It also helps lower CRP levels.

Obesity, irrespective of activity levels is associated with increased vascular events. A higher BMI is associated with an increased risk of adverse cardiovascular events. Thus, weight management must play an important role in all cardiac preventive strategies.

MENTAL STRESS AND DEPRESSION

The adrenergic surge associated with mental stress can increase myocardial oxygen requirements and aggravate myocardial ischemia. Stress can also lead to coronary vasoconstriction further reducing blood supply. Acute stress such as that associated with a natural disaster or an untoward event is also associated with increased risk. In today's age, job related stress plays a very important role as more people are taking up high-profile, stressful jobs[37].

Depression is associated with an increased risk for CAD. This risk is independent of the greater prevalence of hypertension, smoking and lack of physical activity among patients with depression.

AGE AND GENDER:

Increasing age is a non-modifiable risk factor for CAD.

Male gender is associated with an increased risk of CAD when

compared to premenopausal women. After menopause, coronary risk accelerates in women[26].

The protection in premenopausal women is probably due to the relatively higher HDL level which is due to the effect of estrogen on lipoproteins. However estrogen therapy in the postmenopausal age group has failed to demonstrate a net benefit in risk reduction[25].

NOVEL MARKERS OF ATHEROSCLEROSIS

Almost 50% of individuals who have a myocardial infarction have a normal lipid profile. Although the use of major risk factors for screening the general population is recommended, 20% of CAD events occur in patients who do not have even a single risk factor. There is a need to improve detection of people at risk of vascular events.

hsCRP

Inflammation plays an important role in many stages of atherosclerosis. CRP or c-reactive protein is a simple downstream marker of inflammation which is now used as a cardiovascular risk marker. CRP is synthesised mainly from the liver but can also be synthesised by other tissues. It is still not clear whether CRP is just a marker of atherosclerosis or whether it contributes to the process. It appears to have some effects – increase in the endothelial expression of plasminogen activator inhibitor type-1, reduced endothelial NO bioavailability, altered

LDL uptake by macrophages and colocalisation with complement inside atherosclerotic plaques. Studies have shown that CRP measured by highly sensitive assays- hsCRP is a strong and independent predictor for adverse events- MI, peripheral vascular disease and ischemic stroke. This is true even in patients with normal levels of LDL-C and plasminogen activator inhibitor. At all levels of LDL-C hsCRP has a prognostic value[30].

HOMOCYSTEINE

Homocysteine is an amino acid derived from the demethylation of methionine. Patients who have rare inherited defects of methionine metabolism develop severe hyperhomocysteinemia (plasma levels higher than 100 mol/liter). They have a markedly increased risk of premature atherosclerosis and venous thromboembolism. Insufficient dietary folate intake can have mild to moderate elevations of homocysteine. Fortification of food with folate in industrialised countries has led to a reduction of patients with homocystinemia due to folate deficiency[30].

PATHOPHYSIOLOGY

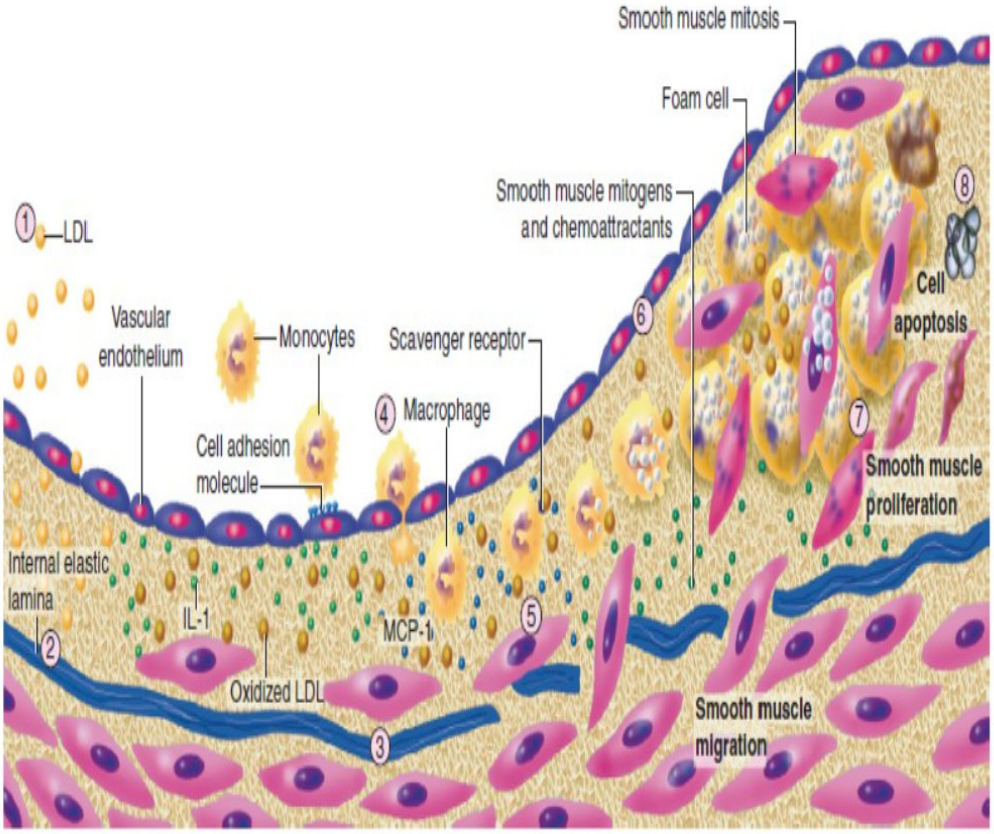
The major determinants of oxygen demand of the myocardium are- heart rate, myocardial contractility and wall tension. The oxygen supply to the myocardium depends on the oxygen carrying capacity of blood (which depends on level of oxygen in inspired air, pulmonary function,

haemoglobin concentration and function) and on coronary blood flow. Majority of the blood flow to the coronaries occurs during diastole and blood flow is phasic. To some extent, the myocardium can control the flow through coronaries by altering the resistance offered by the coronaries. There are 3 main types of resistance vessels- R1- large epicardial arteries, R2- prearteriolar vessels and R3- arteriolar and intramyocardial capillary vessels. In normal coronaries, majority of the resistance is determined by R2 and R3. The heart can regulate its blood flow by altering the level of resistance- this can occur as a response to emotional stress or exercise that increases the oxygen demand of the heart. This is known as *metabolic regulation*[8].

Physiologic alterations in blood pressure can also lead to alterations in the resistance of coronary blood vessels in order to maintain coronary blood flow at appropriate levels. This is known as *autoregulation*.

Atherosclerosis causes narrowing of the lumen of the coronaries. Hence it limits the appropriate increase in blood flow in response to increased demand. If the luminal narrowing is severe, basal blood flow is also affected and the patient can develop chest pain even at rest. With less severe narrowing, the patient is symptomatic during physical activity which increases the oxygen demand and the coronaries are unable to increase the blood flow appropriately.

The normal functions of the endothelium are disrupted by hypertension, diabetes, dyslipidaemia- all of which are the main risk factors for atherosclerosis. Normally the endothelium is involved in control of vascular tone, it provides an antithrombotic surface and also controls inflammation and diapedesis. When these functions are lost, vasoconstriction occurs along with thrombus formation and inflammation with interaction between monocytes, platelets and the damaged, activated endothelium. All these changes lead to the deposition of fat, smooth muscle cells and intercellular matrix in the subintimal region. This leads to the formation of an atherosclerotic plaque. This process occurs at various rates throughout the vascular tree. However certain sites are more prone for these effects- these include sites of increased turbulence such as the branch points[9]. The degree of occlusion of the coronary artery can be correlated to the symptoms to some extent. When luminal narrowing is 50%, the patient is unable to increase coronary blood flow when there is an increased demand. The patient develops chest pain on exertion. When the stenosis is >80%, blood flow at rest is also compromised and a further minor decrease in blood flow can lead to disastrous consequences.



THE EVOLUTION OF THE ATHEROSCLEROTIC PLAQUE

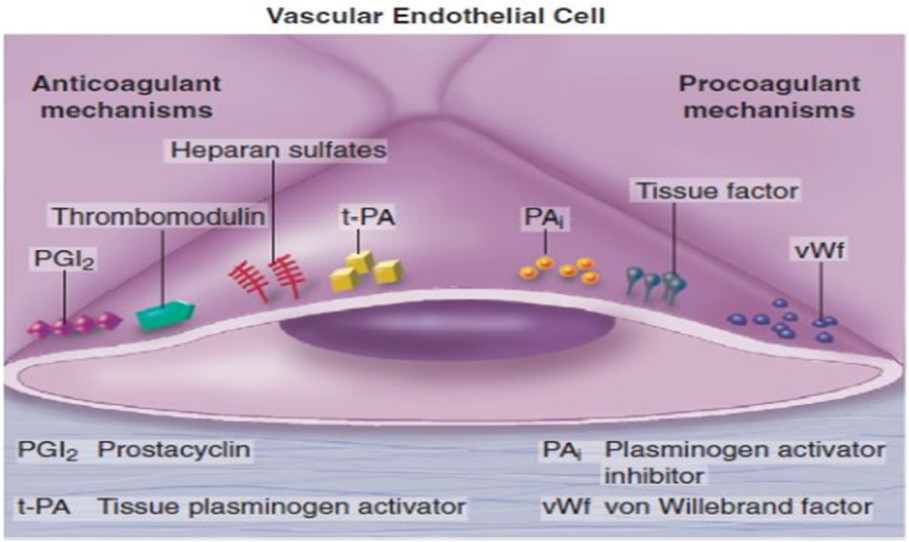
When coronary narrowing is chronic and severe with recurrent episodes of myocardial ischemia, there is time for development of collateral vessels. These collaterals, when they are well developed can provide sufficient blood supply in the basal state but not when demand is increased, as in exercise[11].

The term, Ischemic heart disease encompasses a wide spectrum of disease including Angina pectoris, unstable angina, myocardial infarction, IHD with heart failure and sudden cardiac death.

Acute coronary syndrome is the common term given to ST elevation MI. Non-ST elevation MI and unstable angina. Both STEMI

and NSTEMI are associated with elevation of cardiac biomarkers, whereas in unstable angina these biomarkers are normal.

When the cap of an atherosclerotic plaque erodes or ulcerates, the plaque contents are exposed to blood. This exposes the highly thrombogenic subendothelial collagen to the platelets which adhere, aggregate and are activated[10]. They release potent aggregators like thromboxane A2, serotonin, platelet factor 3 and 4.This leads to vasospasm causing further narrowing and decrease in blood flow. Other factors released activate the coagulation cascade. This leads to the formation of a fibrin rich thrombus and increases the bulk and stability of the thrombus and causes further reduction in blood flow. Soon the entire lumen of the coronary can be occluded. This is the basis of acute coronary syndromes.



THROMBOTIC BALANCE OF THE ENDOTHELIAL CELL

ACUTE PLAQUE CHANGE:

The following changes can take place in a previously present plaque which may only be partially stenosing:

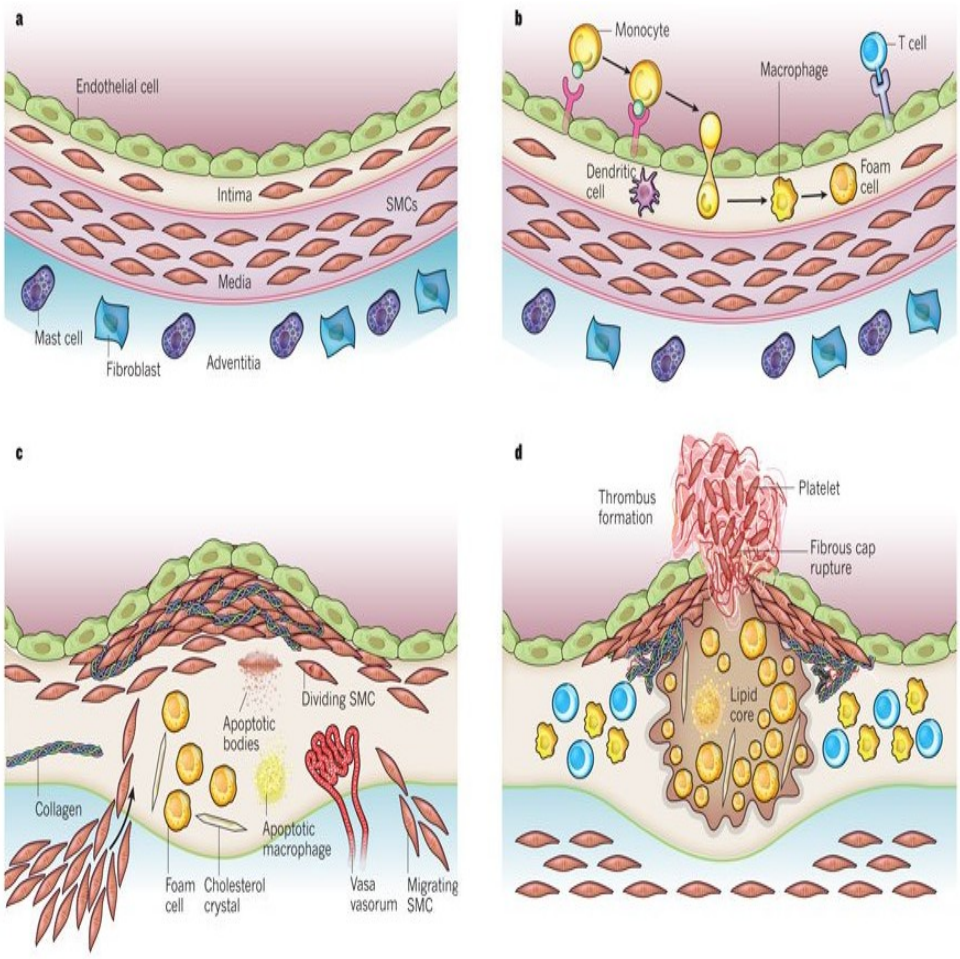
- Rupture or Fissuring
- Erosion or ulceration
- Haemorrhage into the plaque

Intrinsic and extrinsic factors both play a role in triggering changes in plaque configuration. The composition of a plaque is dynamic. *Vulnerable plaques* are those which have a large number of foam cells, extracellular lipid, few smooth muscle cells, large number of inflammatory cells and a thin fibrous cap. These plaques are more prone to rupture[8,9].

Fissuring is more common at the site of the junction of the fibrous cap and the adjacent normal, atheroma-free coronary artery segment. Mechanical stress is maximum within the plaque at this site.

Extrinsic factors such as adrenergic stimulation also play a role in acute plaque change. The surge in the adrenergic drive in the morning as soon as one awakes is one of the main reasons that acute MI occurs with a maximum incidence between 6 AM and 12 noon. Adrenergic drive causes a rise in blood pressure, thereby increasing physical stress on the plaque. Intense emotional stimuli can also contribute to acute plaque change[39].

Most of the acute changes seem to occur in plaques which produce only mild to moderate luminal stenosis. They are not severely stenotic or hemodynamically significant. This signifies that a large number of asymptomatic patients are at risk for developing acute coronary syndrome as the plaque over which thrombus forms would have caused only mild obstruction before the event and hence the patients would have been asymptomatic prior to the event. At present there are no reliable methods by which we can predict plaque disruption or subsequent thrombosis[10].



ROLE OF ACUTE PLAQUE CHANGE

INFLAMMATION

The inflammatory process plays an important role in every stage of atherosclerosis. The formation of the initial lesion requires interaction between leukocytes in blood and the endothelial wall. This leads to the accumulation of macrophages and T-cells in the vessel wall. Release of chemokines by the endothelium and increased expression of adhesion molecules like ICAM-1, VCAM-1, E-selectin and P-selectin leads to the entry of leukocytes into the vessel wall. Once the T-cells enter the vessel wall, they release cytokines like TNF,IL-6 and IFN- gamma that further stimulate the endothelial cells and also activate macrophages which then take on the oxidised LDL and transform into foam cells[8-10].

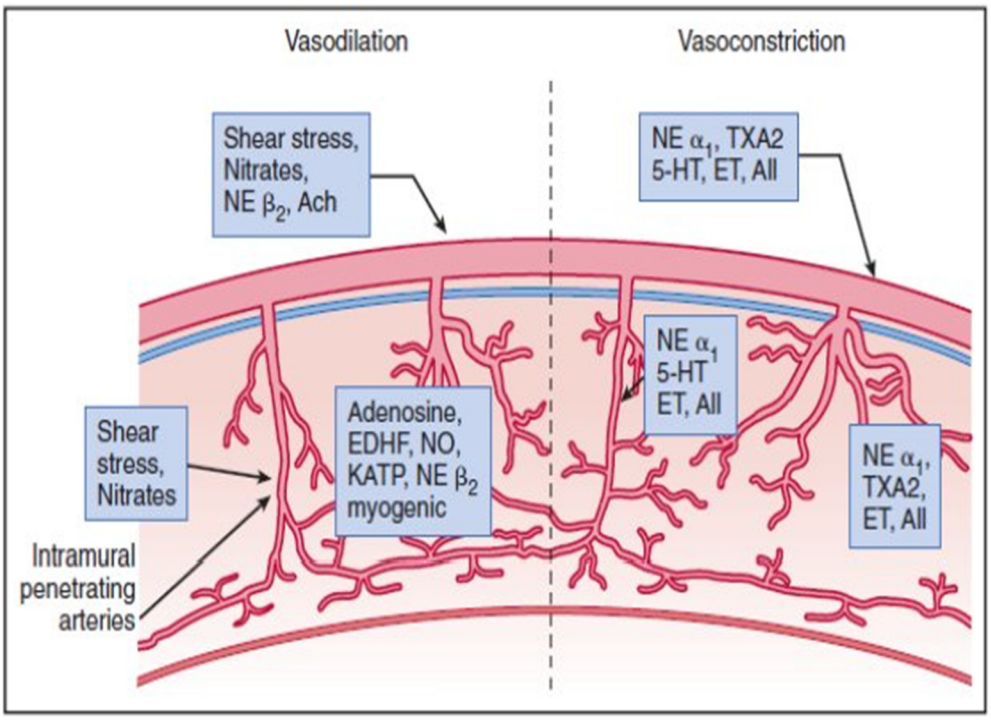
The fibrous cap is a dynamic structure that undergoes continuous remodelling. The major component is collagen which contributes to the strength of the cap. Collagen is continuously synthesised by smooth muscle cells and degraded by metalloproteinases secreted by macrophages. The balance between the synthesis and degradation of collagen determines the strength of the cap and hence the propensity to fissuring. Inflammation tends to destabilise the plaque by increasing the release of metalloproteinases by the macrophages. Because inflammation plays such an important role in atherosclerosis, markers of inflammation like hsCRP in serum have been used as a predictor of riskof CAD.

CORONARY THROMBUS

Following plaque disruption, complete or partial thrombosis of the vessel occurs. If the thrombus superimposed on a disrupted plaque leads to total occlusion of the vessel it leads to the most serious form of ACS-transmural myocardial infarction. If the thrombus leads to an incomplete or partial obstruction ,it leads to subendocardial infarction and unstable angina[9].

VASOCONSTRICTION

Vasoconstriction further aggravates the reduction in blood supply by narrowing the lumen and by increasing mechanical shear stress. Thus it can potentiate the process of plaque disruption. Vasoconstriction may be due to adrenergic agonists, released platelet contents like thromboxane A2, imbalance between endothelial relaxing (eg.nitrous oxide) and contracting (e.g.endothelin) factors or due to mediators released from inflammatory cells



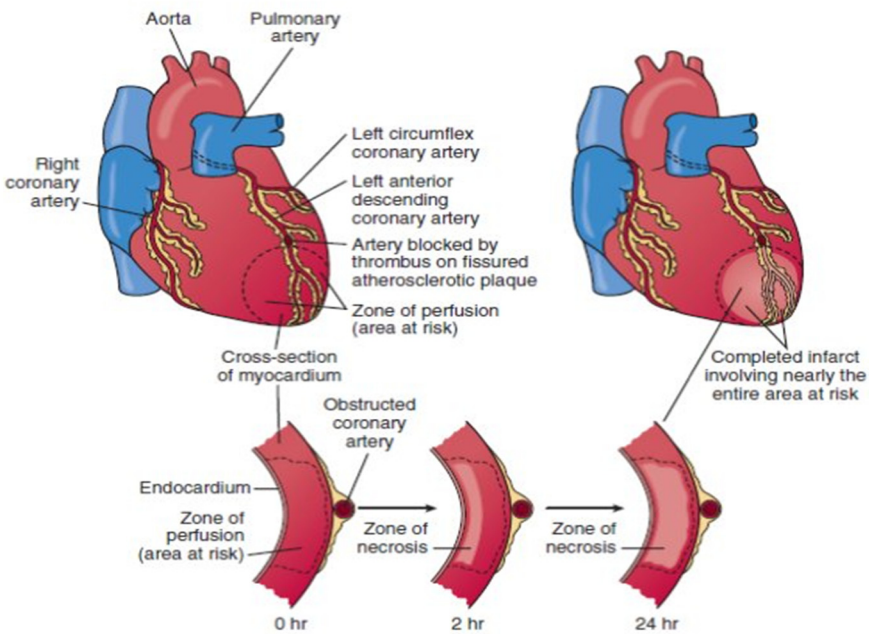
MAJOR VASOCONSTRICTORS AND VASODILATORS

FUNCTIONAL AND METABOLIC CONSEQUENCES OF ISCHEMIA

When a coronary artery is occluded partially or completely, along with the blood supply, the oxygen supply to the myocardium is also lost. Aerobic metabolism in the heart stops, the reserve stores of creatine phosphate are used up and soon the myocardium switches over to anaerobic glycosis. This leads to accumulation of lactate and other metabolites and acidosis develops. Soon there is efflux of potassium into the extracellular fluid[33].

Irreversible injury and myocyte death:

Irreversible injury usually occurs when blood flow has been totally occluded in a vessel for more than 20 minutes and the area under risk is not supplied by collaterals. The injury starts in the subendocardial layer and progresses over time and involves the subepicardial layers[33] . This is because the subendocardium consumes more oxygen and the collateral flow is redistributed to the subepicardial layer of the heart. If there are conditions causing an increased oxygen demand (e.g. Tachycardia) irreversible injury may occur earlier. Prior repeated episodes of reversible ischemia protect against irreversible injury to some extent through preconditioning[35].



PROGRESSION OF MYOCARDIAL NECROSIS AFTER COMPLETE CORONARY OCCLUSION

In chronic CAD, the extent and magnitude of collateral vessels is the most important determinant of the time taken for irreversible injury. The area at risk for ischemia and the infarct size are inversely proportional to the size of collaterals. If the subendocardial flow can be maintained upto 30% of the basal flow by collaterals, irreversible injury may be delayed for more than an hour.

If flow can be maintained upto 50% almost 5 hours may pass without significant necrosis.

Reversible ischemia can be supply or demand induced ischemia. In supply-induced ischemia, coronary vasospasm or transient thrombosis in a critically stenosed coronary artery produces transmural ischemia.

In case of demand-induced ischemia, there is an inability to increase flow in response to increases in myocardial oxygen consumption. Hence ischemia predominantly affects the subendocardium. Both have different effects on myocardial diastolic relaxation. Supply- induced ischemia causes an increase in LV compliance and demand- induced ischemia decreases it. A stereotypical sequence of changes develops during an episode of spontaneous transmural ischemia. Coronary occlusion results in oxygen desaturation[33]. This leads to a decrease in ATP production. A fall in regional contraction occurs within several beats, reaching dyskinesis

within 1 minute. As regional contraction come to a stop, there is a decrease in global LV contractility (dP/dt) leading to a progressive increase in LV end-diastolic pressure, and a fall in systolic pressure. ECG changes including ST segment changes occur in 2 minutes as soon as the potassium efflux into the ECF reaches a critical level. Chest pain occurs at last and it is variable. When perfusion is restored the sequence of events is reversed. Chest pain is resolved in the start followed by resolution of hemodynamic changes. However the contraction of myocardium can remain depressed –this reflects the development of a stunned myocardium[33].

STUNNED MYOCARDIUM

If the restoration of blood supply occurs quickly, within 2 minutes, contractile function also recovers immediately. However if the ischemia persists for a while or is more severe, then even after blood flow is completely restored, the myocardium does not regain full function immediately. This phenomenon is called myocardial stunning. This occurs in the absence of myocardial necrosis. Stunning can also occur following demand-induced ischemia. Exercise-induced ischemia of the subendocardium distal to a coronary stenosis can lead to a depressed function that can persist for hours after the exercise is completed[33].

Stunning may take upto 1 week to resolve. It is an important cause of reversibly dysfunctional myocardium following an acute event like ACS. Stunning is important to recognise as it will recover completely in the absence of further episodes of ischemia. The depressed contractility also normalises on stimulation with beta adrenergic agonists. At the cellular level, stunning probably is explained by free-radical mediated myocardial injury and reduced sensitivity of the myocardium to calcium[34,35].

PRECONDITIONING

Preconditioning can be acute or chronic. Sometimes before a prolonged coronary occlusion occurs, an episode of brief reversible ischemia occurs. This serves to reduce the degree of myocyte necrosis. This phenomenon is known as acute preconditioning. When acute infarction is preceded by angina, preconditioning occurs , which is an endogenous mechanism that can delay the evolution of irreversible myocardial injury. Adenosine A1 receptor stimulation and the use of various agonists that stimulate protein kinase C or open K+-ATP channels can induce acute preconditioning.

When preconditioning occurs on a chronic basis, it is known as delayed preconditioning. It helps in reducing infarct size and prevents the development of myocardial stunning.

Once induced, delayed preconditioning can last upto 4 days. Protein synthesis with upregulation of the inducible form of NO synthase (iNOS), cyclooxygenase 2 (COX-2), and opening of the mitochondrial K+-ATP channel is the mechanism of chronic preconditioning[33].

CHRONIC HIBERNATING MYOCARDIUM

Any myocardial region where contractile function improves after coronary revascularization is defined as viable, dysfunctional myocardium. This spectrum of reversible dyssynergy includes three distinct categories. Function normalises completely after acute ischemia is rare in chronically dysfunctional myocardium.

Prolonged moderate ischemia or brief periods of complete occlusion (short-term hibernation) result in post ischemic stunning in the absence of necrosis, with complete functional recovery occurring within 1 week after reperfusion. This time course of functional recovery is dependent both on severity and duration of the ischemic episode[34].

Delayed functional improvement can also arise from structural remodelling of the heart that is independent of ischemia or a coronary stenosis. Examples include remote myocardial remodelling in heart failure or the reduced infarct volume that occurs over the initial weeks following coronary reperfusion.

In patients with ischemic cardiomyopathy, chronic segmental dysfunction results from episodes of repetitive, often clinically silent ischemia over the territory supplied by one vessel.

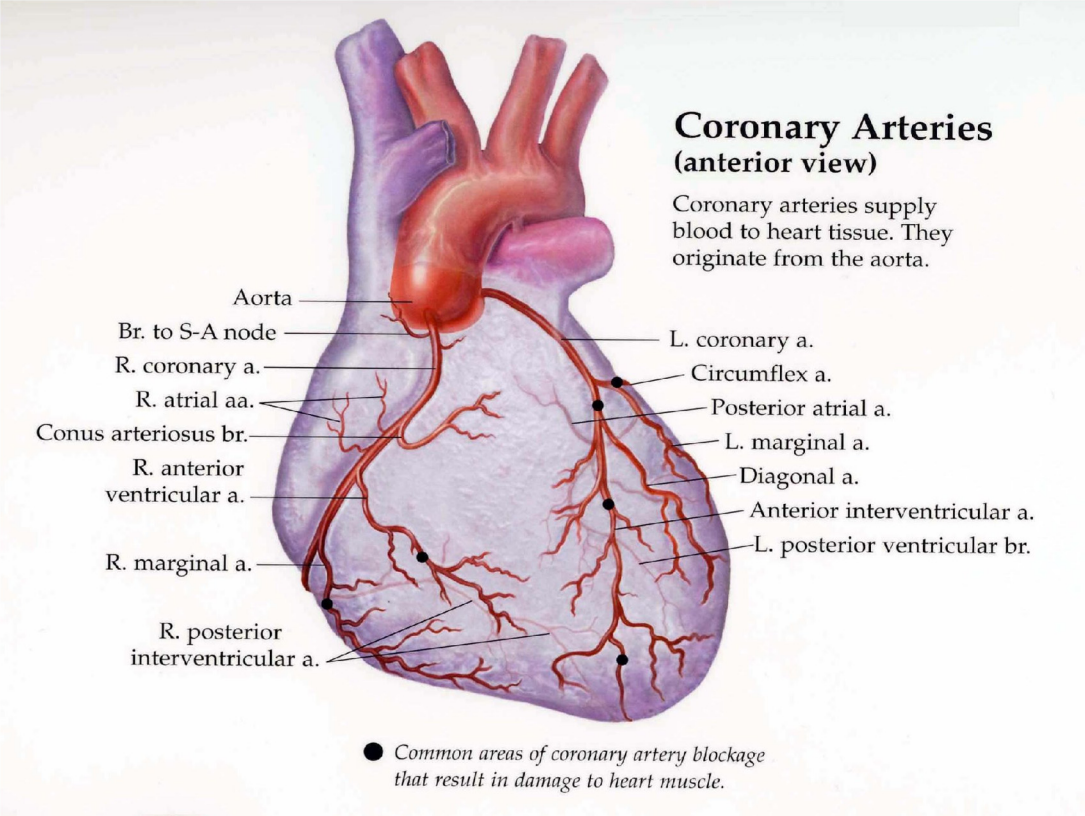
When the resting flow to a dysfunctional myocardium distal to a fixed stenosis, relative to a normal segment of myocardium, is found to be normal, the myocardium is said to be chronically stunned. However if the relative resting flow is reduced then the myocardium is hibernating.

The progression from chronically stunned myocardium to hibernating myocardium is related to the functional significance of the chronic stenosis supplying the region .It is probably a reflection of its propensity to develop repetitive supply or demand-induced ischemia. This progression can develop in as soon as 1 week after a critical stenosis

As dysfunction progresses from chronically stunned to hibernating myocardium, the myocyte takes on regional characteristics similar to those from an explanted heart with advanced failure[33-35].

ANATOMY OF THE CORONARY CIRCULATION

The two main arteries supplying the heart are the right and left coronary artery arising from the aorta. These divide into a number of branches.



The LCA originates from the left coronary sinus, it travels for 1-2 cm and divides into 2 branches-the LCX and the LAD. The LAD descends in the anterior interventricular groove. The LCX runs along the left atrioventric ular sulcus. Branches that arise in between these 2 are the diagonal branches.LCA supplies the left atrium, most of the left ventricle except the part near the posterior interventricular groove, small part of the right ventricle near the anterior interventricular groove and the anterior part of the interventricular system[60].

The RCA originates from the right coronary sinus and runs in the right atrioventricular sulcus. The RCA supplies the Right atrium, most of the right ventricle except a small portion adjoining the anterior interventricular groove and a small part of the left ventricle adjoining the

posterior interventricular groove. It also supplies the posterior part of the interventricular septum and the entire conducting system except the left branch of the AV bundle[60].

Among the coronary vessels, the epicardial arteries are maximally affected by atherosclerosis. Stenosing plaques are found predominantly in the first few centimetres of the Left anterior descending artery (LAD) and the Left circumflex artery (LCX) and the entire length of the right coronary artery(RCA).

Any one of these major vessels or two of them or all three can be involved in atherosclerosis. Sometimes the process may also involve the major secondary epicardial branches like the diagonal branches of LAD, posterior descending branches of the RCA or the marginal branch of LCX. However marginal branches are very rarely involved[60].

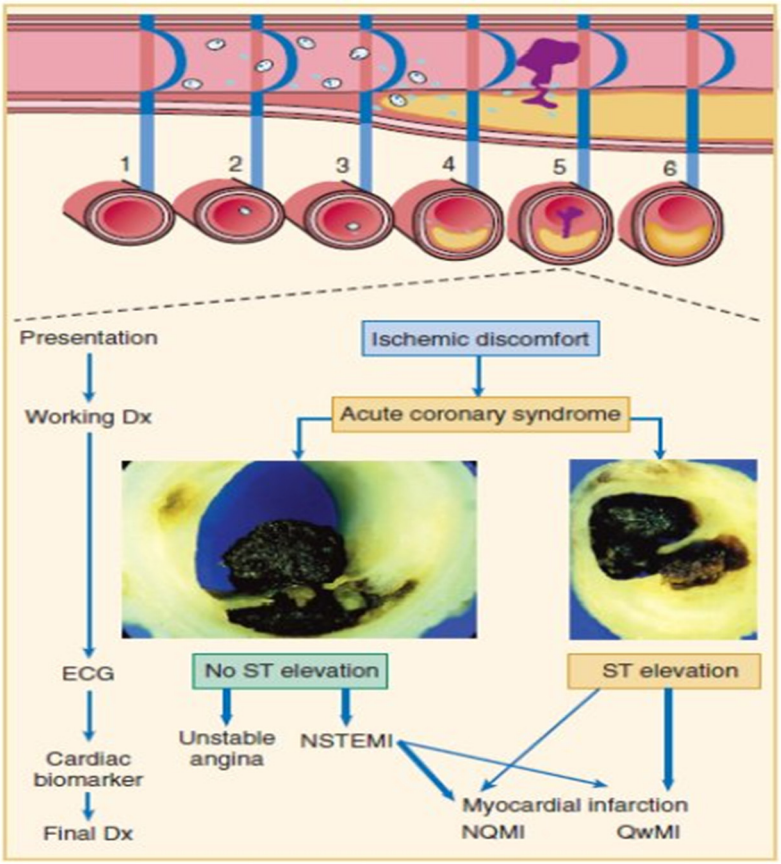
CLINICAL FEATURES

Patients commonly present with chest pain. Typical angina refers to left sided or retrosternal pain which is compressive or squeezing in nature, associated with palpitations or sweating, radiating to the jaw or either shoulder, hand and aggravated by exertion and relieved by rest. This is stable angina. The chest pain of myocardial infarction has similar characteristics but is more severe, may be associated with vomiting and a sense of impending doom and is not relieved with rest.

Unstable angina refers to chest pain with at least one of three features:

- occurs at rest (or with minimal exertion), usually lasting >10 minutes
- more severe and of new onset (i.e., within the prior 4–6 weeks)
- it occurs with a crescendo pattern - distinctly more severe, prolonged, or frequently than before.

Non ST elevation myocardial infarction is the term used in a patient who presents with features suggestive of Unstable angina but who has elevated biomarkers of myocyte necrosis.



POSSIBLE OUTCOMES OF ACUTE PLAQUE CHANGE

In diabetics silent MI is more common. In the elderly a MI may present with sudden-onset breathlessness or an episode of palpitations with syncope.

On examination the patient is restless. He shows pallor with diaphoresis and cool extremities. In case of anterior wall MI patient may present with tachycardia and hypertension due to sympathetic overactivity whereas in inferior wall MI patient presents with bradycardia due to parasympathetic overactivity[40].

Myocardial Infarction can be classified into 5 types-

1. Spontaneous MI due to ischemia caused by a primary coronary event such as plaque erosion and/or rupture, fissuring, ordissection
2. MI secondary to ischemia caused by increased oxygen demand or decreased supply e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, hypotension
3. Sudden unexpected cardiac death, including cardiac arrest, with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST-segment elevation, or new LBBB, or presumably new major obstruction in a coronary artery by angiography and/or pathology, but death occurring before blood samples could be obtained, or before the appearance of cardiac

biomarkers in the blood

4. A. MI associated with PCI B. MI associated with stent thrombosis, as documented byangiography or autopsy
5. MI associated with CABG

DIAGNOSIS

In a patient presenting with the typical history with risk factors,a 12-lead ECG can be used to make the diagnosis of acute coronary syndrome. Cardiac enzymes and various imaging modalities can be used to confirm the diagnosis in doubtful cases[42].

WHO and American Heart association requires at least 2 of the following 3 criteria for diagnosis of Myocardial infarction:

- typical symptoms of ischemia
- ECG changes
- Classical rise and fall in cardiac biomarkers.

When interpreting the tests used for diagnosis of MI this temporal sequence must be kept in mind. There are 4 main groups of tests used in diagnosis:

- ECG
- Cardiac biomarkers

- ❖ Cardiac imaging
- ❖ Nonspecific markers of inflammation and necrosisECG

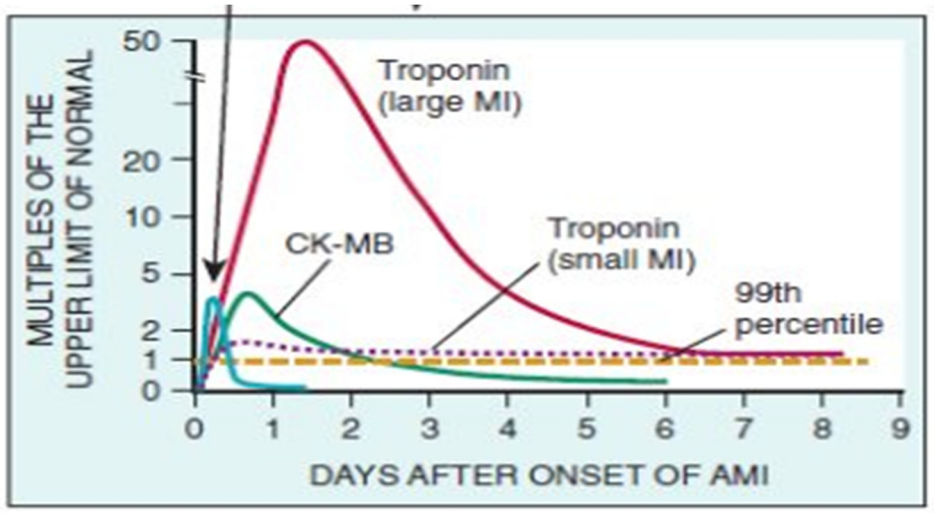
In the initial stage, when an epicardial artery is completely occluded, the ECG shows a ST segment elevation in leads overlying the infarcted area. The leads opposite the affected area will show a reciprocal ST segment depression.

As MI evolves, Q waves may form. The magnitudes of these Q waves vary and sometime they may be present only transiently.

The evidence of an old MI on ECG may be just a loss of R wave amplitude with or without Q waves. On the other hand NSTEMI and unstable angina presents with ST-T changes other than ST segment elevation along with elevated cardiac biomarkers in NSTEMI and normal markers in UA.

CARDIAC BIOMARKERS

When a MI occurs and myocyte necrosis occurs, certain proteins present in myocytes are released into blood. The rate of this release depends on the molecular weight of the protein, their location intra-cellularly and the local lymphatic and blood flow. When the capacity of the cardiac lymph to clear the interstitial spaces of the infarct zone is exceeded, these markers spill over into venous blood.



The most commonly used cardiac biomarker today is cardiac specific troponin-I (cTnI)and troponin-T (cTnT). They have different amino acid sequences than their muscle counterparts. Normally they are not detectable in blood[41,42]. After a MI, their levels can increase to >20 times their normal limit. They remain elevated for 7-10 days.

Creatine Kinase levels begin to rise in 4-8 hours and return to normal in 48-72 hours.CK-MB isoform is more specific for cardiac myocyte necrosis. It is mainly used for the diagnosis of reinfarction within the 1st week as troponins return to normal only after 7 days[44,45].

CARDIAC IMAGING

In 2-D Echocardiography, MI appears as abnormalities of wall motion. Though echo may not be able to differentiate between acute severe ischemia, an old myocardial scar and a STEMI, it is still a very useful instrument that can help with the diagnosis when ECG

changes are not typical and also help in management decisions. It is simple and safe.

Radionuclide imaging can also be used to diagnose STEMI, however they are rarely used as they lack the necessary sensitivity and specificity and are cumbersome.

THYROID

The thyroid is an important endocrine gland in our body. It is one of the largest endocrine glands in the body and has capacity for tremendous growth. It has 2 lobes joined by an isthmus. Each lobe is 4*2*2cm and the isthmus is 1.5* 2*0.5cm.The gland weighs around 15-20gm in an average individual.

The right lobe is normally larger and more vascular than the left. The thyroid is supplied by 2 main pairs of arteries- superior thyroid artery from the external carotid and the inferior thyroid artery from the subclavian artery.

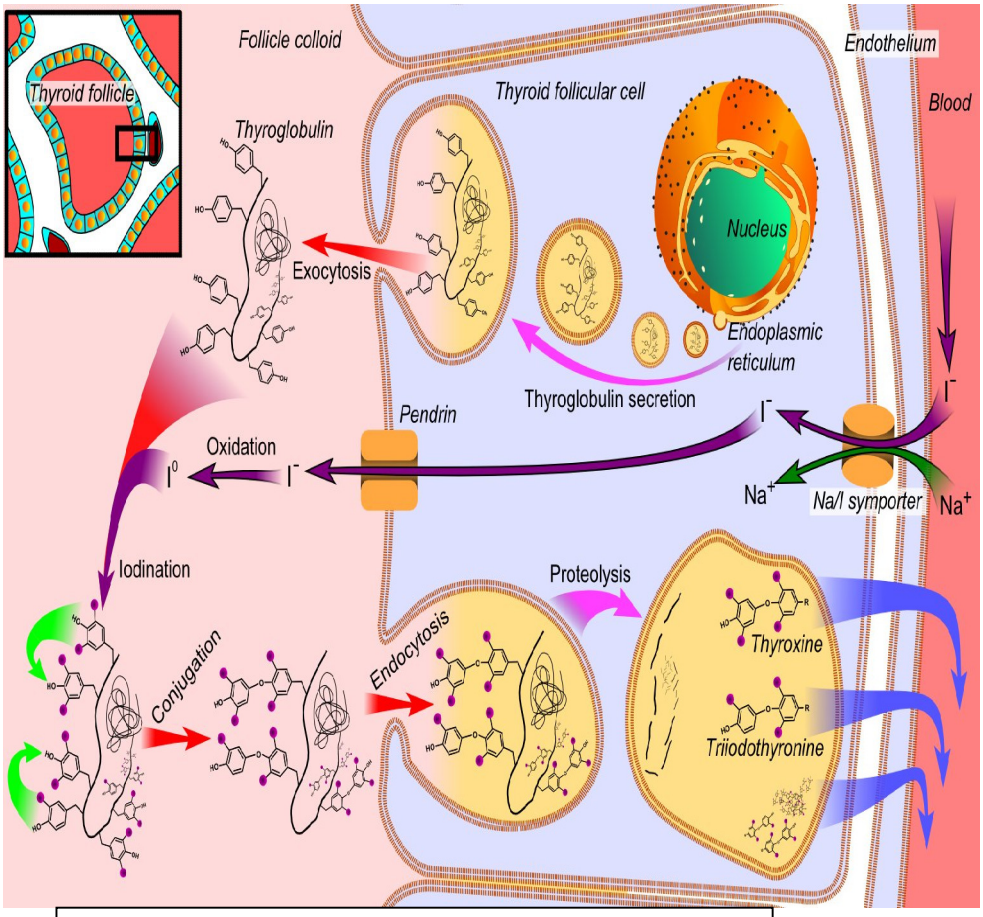
The gland is composed of multiple spherical structures called follicles. At the centre of each follicle we have the proteinaceous substance called colloid. On cross section each follicle is lined by a single layer of thyroid cells surrounding the colloid. These cells are columnar when they are active and secreting, cuboidal when inactive. The epithelium of the follicular cells has multiple microvilli at its apex.

They extend into the colloid. Iodination, exocytosis and resorption of colloid occur at this surface. 20-40 follicles are grouped together by connective tissue septa and form lobules. The thyroid also has parafollicular or C cells that are derived from the neural crest and secrete calcitonin.

THYROID HORMONE SYNTHESIS

The function of the thyroid gland is to secrete thyroid hormones- Thyroxine (T4) and Triiodothyronine (T3) to meet the needs of the body. There are numerous steps involved in the synthesis of the thyroid hormones:

- ❖ Iodine trapping
- ❖ Oxidation of iodine to iodide
- ❖ Organification
- ❖ Release of hormones



STEPS IN THROI HORMONE SYNTHESIS

Iodine Trapping

Synthesis of thyroid hormones requires adequate quantities of exogenous iodine. Dietary iodine intake must allow for a thyroidal uptake of approximately 60 -75 µg/day, for faecal losses of about 10 to 20 µg iodine as glucuronides and for urinary losses of 100 to 150 µg.

In the body iodine is mainly found in the form of iodide. In normal healthy adults, almost 90% of the dietary iodide is absorbed. Iodine intake varies from region to region depending on the soil and water

content of iodine and also on dietary practices. Iodine deficiency is common in mountainous regions and in glaciated areas where the soil and water are poor in iodine content. In these places TSH induced compensatory enlargement of the thyroid is common- endemic goitre. In the body iodide is mainly concentrated in the extracellular fluid[12].

The normal concentration of iodide in the ECF is 10-15 ug/L. The iodide content in the thyroid gland in 8000 μg which is the maximum in the body. Hence iodide uptake into the thyroid has to take place against the concentration gradient and is an active process. This is enabled by means of a membrane protein -*NIS-sodium iodide symporter.* The transport of iodide depends on the presence of a sodium gradient across the basal membrane of the thyroid cell. The downhill transport of 2 Na+ ions results in the entry of one iodide atom against an electrochemical gradient. The NIS is also found in other cells like the salivary and lactating mammary glands, choroid plexus, and gastric mucosa which concentrate iodine and in the cytotrophoblast and syncytiotrophoblast[12].

This NIS can also transport perchlorate, thiocyanante and pertechnatate. This accounts for the use of potassium perchlorate to block iodine uptake in the treatment of hyperthyroidism. TSH stimulation increases the transcription and prolongs the half-life of NIS.

In addition to iodine trapping, intracellular iodide can also be generated by the action of the enzyme- iodotyrosine dehalogenase 1 (DEHAL1), also known as iodotyrosine deiodinase (IYD). IYD is a membrane protein concentrated at the apical cell surface that acts as a catalyst for the (NADPH)-dependent deiodination of MIT and DIT.The iodide thus released is immediately reconjugated to newly synthesized Tg after exiting the apical membrane of the cell. This process can be inhibited by the thiourea class of antithyroid drugs, including methimazole, carbimazole, and propylthiouracil (PTU) [12].

IODIDE OXIDATION AND ORGANIFICATION

Inside the thyroid the iodide is oxidised and the intermediate is incorporated into the iodothyrosines, Monoiodothyrosine and diiodothyrosine-MIT and DIT.This process is called organification. Oxidation of iodide is mediated by the heme-containing enzyme TPO.The enzymes requires H_2O_2 generated by the calcium dependent. DUOX1 and DUOX2 enzymes. This enzyme-protein is located in the apical membrane of the thyroid cells. The product of the peroxidation of iodide (i.e., the active iodinating form) may be free hypoiodous acid, I_2, or iodinium (I^+).This product is evanescent as it immediately reacts with the MIT and DIT within the Thyroglobulin in the colloid to form T3 and T4 respectively. This is also mediated by TPO.

COUPLING

T4 and T3 are the hormonally active iodothyronines .MIT and DIT are precursors of the same.2 molecules of DIT combine to form T4, whereas one molecule of MIT and one DIT combine to form T3.

The coupling reaction is the fusion of 2 DIT molecules to yield T4 which has 2 diiodinated rings linked by an ether bridge. This process is catalysed by TPO. Normally every molecule of thyroglobulin contains 3-4 molecules of T4 but only one in five molecules of thyroglobulin contains a T3 residue[25].

RELEASE OF THYROID HORMONE

The thyroid gland is the only endocrine gland in the body to store its hormones in such large quantities. The turnover rate is also very low-1% per day. This ensures that even when synthesis ceases completely, a euthyroid state can be maintained for upto 50 days.

The initial step in the release of thyroid hormones is the endocytosis of colloid containing the thyroglobulin into the cell. This is accomplished by pinocytosis. This process is stimulated by TSH. The endocytic vesicles now fuse with lysosomes and T3 and T4 are released. The iodotyrosine residues released within the lysosome are immediately acted upon by NADPH-dependent IYD and the iodine released is recycled. The exact process by which the released thyroid hormones enter

the blood stream is not known but the transporter MCT8 is believed toplay a role[51].

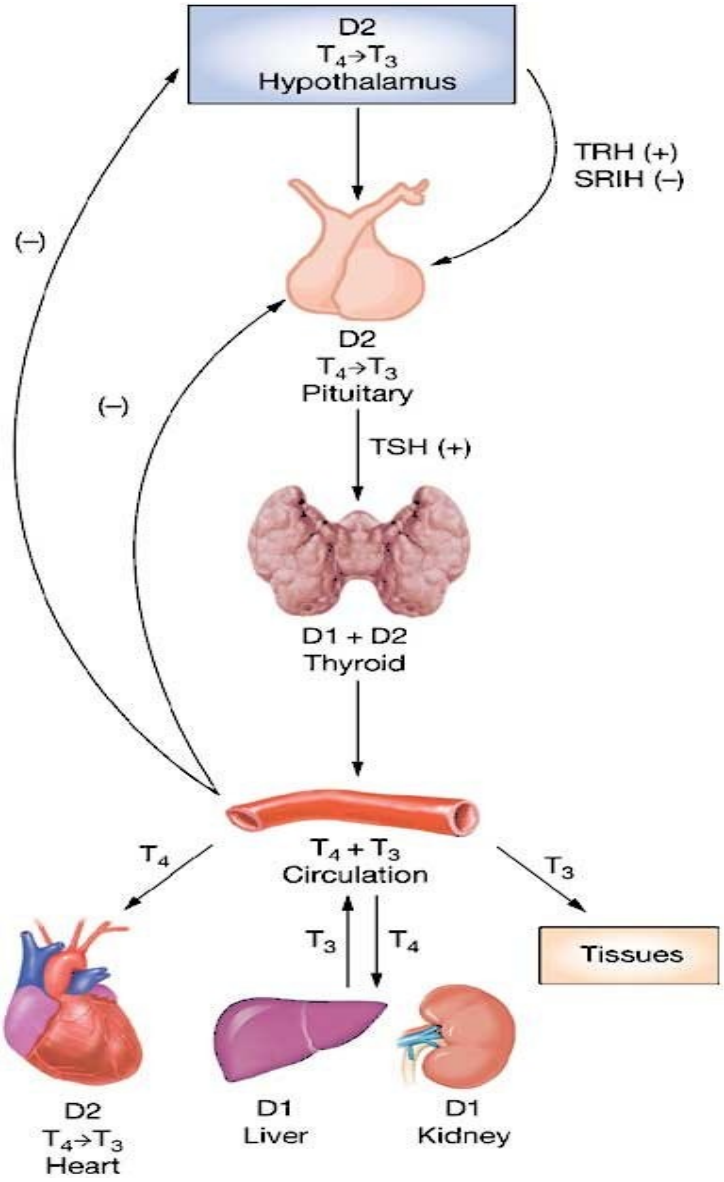
The normal ratio of T4 to T3 in thyroglobulin is 15:1 whereas in the serum it is 10:1.This implies that some of the T4 immediately after release from the thyroglobulin is acted upon by deiodinase and converted into T3 before release into the bloodstream.

T4 release from the thyroid can be inhibited by iodide. The exact mechanism is not known but excess iodination of thyroglobulin can make it resistant to hydrolysis. Also iodide inhibits the stimulation ofthyroid adenylate cyclase by TSH.

REGULATION OF THYROID HORMONE SECRETION

The regulation of thyroid hormones is a classic example of a feedback loop. Thyrotropin releasing hormone (TRH) is a modified tripeptide released by neurons in the hypothalamus. TRH is synthesised by neurons in the parvocellular region of the paraventricular nuclei of the hypothalamus. The gene encoding TRH has elements responsive to glucocorticoids, cAMP for mediating TRH release and for negative feedback by thyroid hormones. After synthesis TRH travels along the axons of hypothalamic-pituitary plexus through the median eminence and is released in the portal system formed by the hypothalamic-pituitary plexus[44].

Axons containing catecholamine, Melanocyte stimulating hormone, Leptin agouti related peptide, somatostatin all innervate the neurons that synthesise TRH and influence the rate of synthesis and release of TRH. T3 suppresses the production of TRH by inhibiting the production of pre-pro-TRH. It also blocks the ability of TRH to stimulate the synthesis and release of TSH from the thyrotrophs[45].



REGULATION OF THYROID HORMONE SYNTHESIS

TSH is a glycoprotein hormone secreted by the thyrotrope cells situated in the anterior pituitary. It plays an important role in the regulation of the thyroid axis. It has 2 subunits- alpha and beta.

The beta subunit is unique to TSH whereas the alpha iscommon to TSH, LH, hCG and FSH. Glycosylation of the protein is essential to prevent its intracellular degradation and for its full biologic activity. Glycosylation of the TSH molecule requires TRH. Secretion of TSH shows a circadian rhythm with peak levels in the night before sleep.

Removal of the hypothalamus is not associated with as severe thyroid dysfunction as that seen after hypophysectomy. This shows that T3 and T4 both have a negative feedback on TSH secretion, however TRH sets the set point for this feedback.

Somatostatin, dopamine, bromocriptine all cause inhibition of TSH release on an acute basis.

TSH STIMULATORY AGENTS	TSH INHIBITORY AGENTS
TRH	Thyroid hormones & analogues
Alpha-adrenergic agonists	Dopamine & its agonists
Prostaglandins	Gastrin
Opioids	Serotonin
Arginine vasopressin	Cholecystokinin
Glucagon like peptide (GLP-1)	Gastrin-releasing peptide
Galanin	Neuropeptide-y
Leptin	IL-1beta, IL-6
	TNF-alpha
	Bexarotene
	Phenytoin
	Somatostatin & analogues

TSH acts on almost every step in the synthesis of thyroid hormones. The TSH receptor (TSH-R) is present on the cell surface of the thyroid cells. This receptor protein consists of a large extracellular N-terminal domain,

7 membrane-spanning domains, and an intracellular domain that transduces the signal by phosphorylation of the α-subunit of G proteins.

The TSHR mainly couples to the stimulatory protein, G_s. However, when activated by high concentrations of TSH (100 times the physiologic level), it can also couple to G_q/G_{11}, activating the inositol-phosphate diacylglycerol cascade.

- Signalling via the phospholipase C (PLC) and intracellular Ca^{2+} pathways- leads to regulation of iodide efflux, H_2O_2 production,and Tg iodination
- Signalling via the protein kinase A (PKA) pathway mediated by cAMP – leads to regulation of iodine uptake and transcription of Tg, TPO, and NIS mRNAs- leads to thyroid hormone production .

The TSHR also binds with thyroid-blocking antibodies and neutral antibodies to the TSHR[46]. Lutenising hormone and human chorionic gonadotropin can also bind to the TSHR and lead to its activation- this is the cause for the physiological hyperthyroidism in pregnancy.

TRANSPORT AND METABOLISM OF THYROID HORMONES

Both T3 and T4 are bound to albumin, thyroid binding globulin (TBG) and transthyretin (TTR) in the serum. This binding leads to decreased clearance, increased circulatory pool and selective delivery to tissues.

TBG has very high affinity towards thyroid hormones. So even though it is present in small quantities (1-2mg/dl), it carries upto 80% of the total thyroid hormones in serum. Albumin is present in large quantities (3.5g/dl) but has lesser affinity. It binds 30% of T3 and 10% of T4. TTR binds 10% of T4 and very little T3.Upto 99.98% of T4 and 99.7% of T3 is present in the bound form with proteins. A greater fraction of T3 is unbound but the total T3 is less than T4 and is cleared more rapidly than T4.

The free form of the hormones is the active form. When a change in TBG occurs, to maintain the free T4 and T3 concentrations at the normal level, the bound hormone changes in the same direction. For example, when we administer estrogen , TBG concentrations are increased with a reduction in free T4.This leads to a decrease in T4 clearance, allowing an increase in the plasma total T4 concentration. This interactive process eventually brings the free T4 levels to normal at a new equilibrium without a change in T4 secretion rate. The transient fall in free thyroid hormones also slightly decreases the negative

feedback on the hypothalamic-pituitary-thyroid axis. This whole processis known as the *free thyroid hormone hypothesis.*

The entry of the thyroid hormones into cells is mediated by various membrane transporters. Some of the important ones are

Monocarboxylate transporter 8 (MCT8) and organic anion transporting polypeptide 1C1(OATP1C1).Defects in MCT8 have been shown to be associated with a severe neurologic disease.OATP1C1 is believed to be involved in the transport of thyroid hormones across the blood brain barrier.

IODOTHYRONINE DEIODINATION

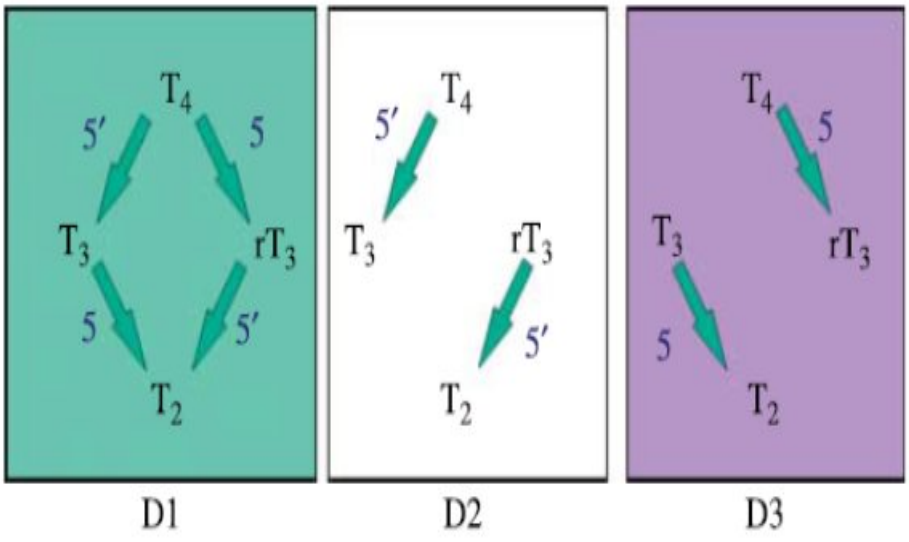
Metabolism of both T3 and T4 occurs mainly via deiodination by a group of selenium-containing deiodinases. Hence T4 undergoes monodeiodination of its external ring (5') to the active thyroid hormone, T3. This reaction is catalysed by both D1 and D2.This is the main source of almost 80% of the circulating T3 in humans[16].

Inner ring deiodination leads to inactivation of the hormones and is catalysed primarily by D3, which inactivates T3 and converts T4 to rT3.

The three human deiodinases are structurally similar. They are all homodimers and they contain the amino acid selenocysteine in the active catalytic center. Selenium is believed to be the iodine acceptor during these reactions.

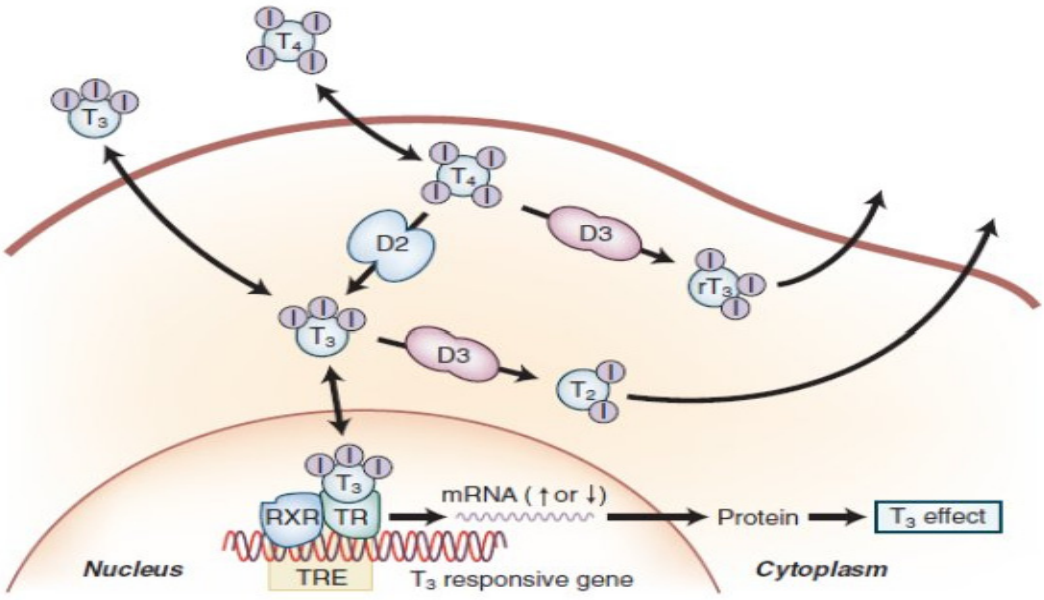
D1 catalyses both 5′ and 5 deiodination of T4 to form T3 and rT3, respectively. However the Michaelis-Menten constant (Km) for these reactions is approximately 3 orders of magnitude greater than that of D2 and D3 for this substrates[16].

The preferred substrates of D1 are rT3 (5′ deiodination) and T3SO4(5 deiodination). D1 can be inhibited by PTU, unlike D2 and D3. D1levels are markedly increased when thyroid hormone levels are high through increased gene transcription. On the other hand D2 mRNA and protein are reduced by increase in thyroid hormones. D2 has a very short half-life of only 20 to 30 minutes, whereas that of D1 and D3 is more than 12 hours. This is because D2 undergoes rapid ubiquitination, a process that is accelerated by interaction with its substrate T4 or rT3.



THE SUBSTRATES AND PRODUCTS OF THE 3 DEIODINASE ENZYMES

D2 is located close to the nucleus intracellularly and the T3 formed by its catalytic action has better access to the nucleus than that formed by D1.It can easily enter the nucleus and carry out its actions. D1 is located in the plasma membrane and the T3 produced by this enzyme is usually secreted into the plasma. The action of D2 is especially important in the maintenance of the hypothalamic-pituitary axis. As the levels of T4 falls, the levels of D2 increase much before the serum T3 falls[16-18].



THYROID HORMONE ACTIVATION AND INACTIVATION IN A CELLEXPRESSING D2 AND D3

PARAMETER	D1	D2	D3
Physiological Role	rT3 &$T3SO_4$ degradation, source of plama T3	Provides intracellular T3 in some tissues, source of plasma T3	Inactivates T3 and T4
Tissue Location	Liver, Kidney, Thyroid, ?Pituitary	CNS, Pituitary, Brown adipose tissue, thyroid, placenta, skeletal muscle, heart	Placenta,CNS, Fetal and adult liver, skeletal muscle, Hemangiomas
Subcellular Location	Plasma Membrane	Endoplasmic reticulum	Plasma Membrane
Preferred substrate	rT3,$T3SO_4$	T4,rT3	T3,T4
Susceptibility to PTU	High	Absent	Absent
Response to increased T4	Increase in levels	Decrease in levels	Increase in levels
Km	rT3, 10^{-7}; T4, 10^{-6}	10^{-9}	10^{-9}

MECHANISM OF THYROID HORMONE ACTION

Thyroid hormones act by binding to a specific nuclear thyroid hormone receptor (TR).This complex now binds to DNA, usually as a heterodimer with retinoid X receptor (RXR).The binding takes place at specific sequences called thyroid hormone response elements, or TREs. The DNA binding-site preferences of the RXR-TR (or TR-TR) complex determines the binding[11].

As T3 has a 15-fold higher binding affinity for TRs than T4, it functions as the active thyroid hormone. In humans, 2 TR genes are found, α and β. They are present on chromosome 17 and 3, respectively. When these genes are alternatively spliced many products are formed, both active and inactive. The active proteins are TRα1, TRβ1, TRβ2, and TRβ3[47,48].

The protein structure of TRs has 3 major functional domains— one that binds DNA, one that binds ligand, and a major transcriptional activation domain in the C-terminus.

Various tissues express each of these receptors.

- TRα especially TRα2 is important in the hypothalamus and pituitary for regulation of thyroid axis.
- TRβ2 is expressed in the cochlea.

- TRα1 is expressed in all tissues- however mRNA is especially highly expressed in the kidney, liver, brain and heart.
- TRα3 is expressed in lungs, liver and kidneys

Studies have shown that TRβ is involved in the feedback regulation of thyroid hormone effects and cochlear development, whereas cardiac function and energy metabolism are more likely to be regulated by TRα[47,48].

THYROID FUNCTION IN ILLNESS AND FASTING

Fasting and illness are associated with a number of changes in thyroid function which are similar in both conditions.

There is a central reduction in TSH secretion with a decreased T3 level in plasma and decreased binding of T4 and T3 in serum. This pattern of findings in the clinical background of illness is termed the *euthyroid sick syndrome* or *low T3 syndrome.* There is a reduction in serum fT3 with a corresponding increase in rT3.In the initial stages thereis no change in the levels of fT4 or total T4 or TSH[50].

The exact mechanism behind the sick euthyroid syndrome is not known.Various mechanisms have been proposed. These include:

- modifications to the hypothalamic–pituitary axis

- altered binding of thyroid hormone to circulating binding proteins
- modified entry of thyroid hormone into tissue
- changes in thyroid hormone metabolism due to modified expression of the intracellular iodothyronine deiodinases
- Changes in thyroid hormone receptor (THR) expression or function.

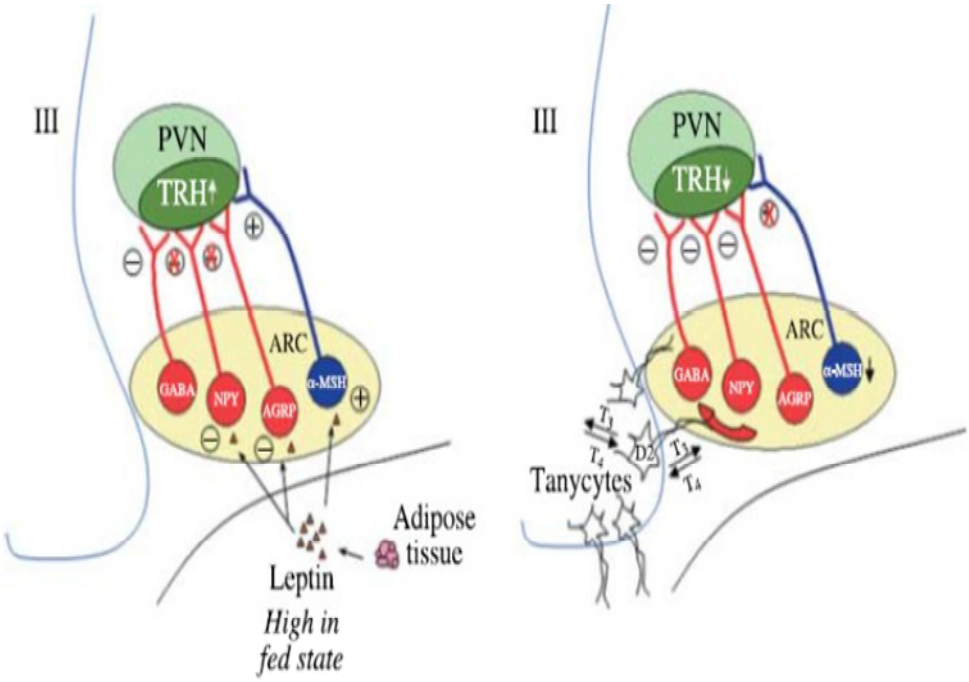
Variations in the levels of various deiodinases are proposed to play a role. Decrease in D1 and D2 mediated conversion of T4 to T3 with an increase in D3 levels in liver and muscle leading to increased formation of rT3 from T4 and 3,3′ diiodothyronine from T3 have been noted in many studies.

In mice with genetically absent D1 and D2, levels of T3 were maintained. This suggests that normally the regulation of serum T3 levels is under strict control with multiple compensatory mechanisms in place. However during fasting or illness, all compensatory mechanisms are reduced, probably mediated by the hypothalamus and the T3 levels fall.

This fall in T3 levels may be beneficial for the patient while fasting or during illness. The fall in T3 contributes to a reduction in the basal oxygen consumption and heart rate and contributes to a negative nitrogen balance, all of which are beneficial during fasting[52,53]. If the illness

progresses, a series of changes takes place. There is further suppression of the HPA axis with reduction in fT4 levels. This signals the development of a complex syndrome with worsening prognosis as fT4 levels decrease further. In the brain there is a reduction in TRH mRNA in the paraventricular nuclei. There is also increased conversion of T4 to T3 by D2 in the tanycytes lining the 3rd ventricle. This leads to a blunted response of TSH to the fall in T3 and T4 levels[58]. This is seen mainly with infections and may be because of the increased levels of cytokines such as IL-6.All these changes may be further aggravated by drugs used commonly in the treatment of serious illnesses- like dopamine and glucocorticoids that further suppress the TRH-TSH axis[56].

Severity of Illness	fT3	fT4	rT3	TSH	Proposed mechanism
Mild	↓	N	↑	N	Decreased D1, D2
Moderate	↓↓	N or ↑↓	↑↑	N or ↓	Further decrease In D1, D2 with? Increase in D3
Severe	↓↓↓	↓	↑	↓↓	Further decrease In D1,D2 with? increasein D3
Recovery	↓	↓	↑	↑	Not known



MODIFICATION OF THE HPA AXIS DURING FASTING/ ILLNESS

The neurons of the paraventricular nucleus (PVN) that secrete TRH are innervated by neurons from the arcuate nucleus (ARC) that contain melanocyte-stimulating hormone (MSH), neuropeptide Y (NPY), agouti-related protein (AGRP), and the inhibitory neurotransmitter GABA. Both NPY and AGRP inhibit TRH gene expression, an action prevented by leptin. During fasting, when leptin decreases, the inhibitory actions of NPY of AGRP can prevail leading to diminished TRH. The expression of TRH in the PVN is stimulated by MSH, and this effect is enhanced by leptin[57]. Thus, in fasting (low leptin), the stimulatory action of MSH on TRH expression in the PVN is diminished.

T3 produced by deiodinase D2 in tanycytes has important feedback inhibitory actions on TRH production in the PVN[58]. During sepsis and trauma, there is an increase in tanycyte D2, which is postulated to lead to an increased generation of T3 from T4. Tanycyte processes may extract T4 from portal capillaries, blood vessels in the arcuate nucleus or the CSF (in the third ventricle). The T3 can then be released back into the CSF or the blood stream. TRH neurons may take up T3 via diffusion from the CSF, by axonal terminals of the TRH neurons present in the median eminence, or the release of T3 into the arcuate nucleus may influence the activity of arcuate neurons that project into the PVN[56].

Irrespective of the mechanism under play, the sick euthyroid state is associated with a poor prognosis. Treatment of the sick euthyroid state with T3 or TRH is associated with biochemical improvement. However no improvement has been seen in the clinical state or prognosis. Hence at present no treatment is recommended for the sick euthyroid state.

LABORATORY I NVESTIGATIONS USED FOR THE EVALUATION OF THYROID DISORDERS:

- Tests of the hypothalamic-pituitary-thyroid axis- measurement ofTSH, Total T4,T3, FreeT3,T4
- Tests that measure the metabolic impact of thyroid hormones- Basal Metabolic rate, Serum LDL cholesterol
- Tests that help determine etiology- Thyroid autoantibodies
- Radioiodine uptake and thyroid scanning
- Ultrasound of the thyroid

Quantitation of the TSH and Thyroid hormone levels:

Measurement of TSH levels is the most widely used screening test for detection of thyroid disease. This is because TSH secretion is extremely sensitive to the plasma concentrations of free thyroid hormones, thus it provides a precise and specific barometer of the thyroid status of the patient.

The immunometric assay is most commonly used as it is more sensitive and specific than the radioimmunoassay. In this assay, the TSH molecule is used to link a TSH antibody bound to an inert surface (e.g., particles, the side of a test tube) to a second antibody (directed against a different TSH epitope).This 2^{nd} antibody is labelled with a detectablemarker such as ^{125}I, an enzyme, or a chemiluminescent reagent. The concentration of TSH in the serum is proportional to the intensity of the signal generated.

When the TSH values are abnormal, T3 and T4 measurements must be done next to confirm the abnormality. Total T3 and T4 can be measured sensitively and specifically by radioimmunoassay.

The thyroid status of a patient depends on the concentration of the free hormone rather than the total hormone levels. Hence measurement of fT3 and fT4 may be necessary in some cases. Direct measurements of the concentrations of fT4 and fT3 in serum, which are most accurate are performed by assay of these hormones in a dialysate or ultra-filtrate of serum. This is impractical and hence alternative methods have been developed[12].

Two categories of methods are used- comparative free T4 methods and FT4 Index methods

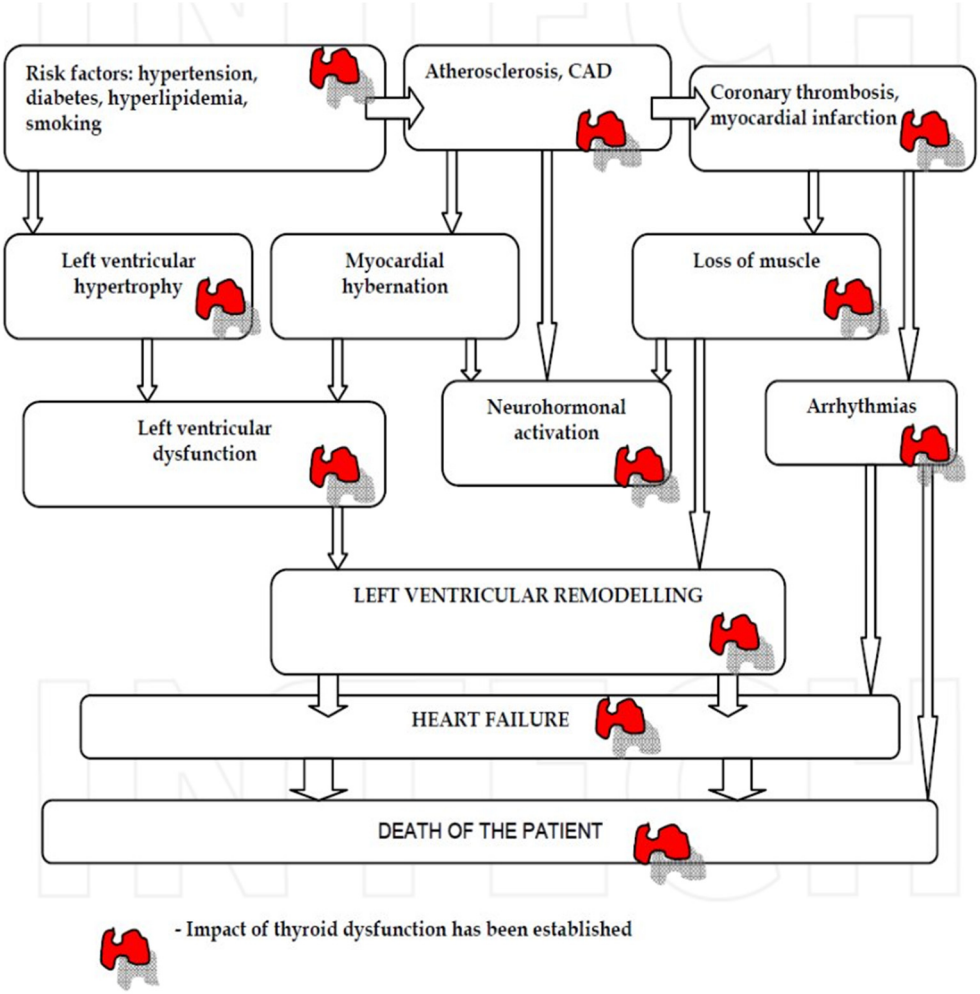
The *Thyroid hormone binding ratio* (THBR) - This is derived from the *T_3-resin uptake test*. Here the distribution of radiolabeled T_3 between the unoccupied thyroid hormone binding proteins in the sample and an absorbent resin is determined. The binding of the labelled T_3 to the resinis increased when there is reduced unoccupied protein binding sites (e.g., TBG deficiency) or increased total thyroid hormone in the sample; it is decreased under the opposite circumstances[9].

The free T4 index: This is obtained by finding the thyroid hormone–binding ratio (THBR) and multiplying that result by the total T4 (or T3). In this test, a tracer quantity of labelled T4 (or T3) is added to serum, which is then exposed to a solid phase matrix coated with T4 or T3 antibody or to an inert matrix that binds the iodothyronine irreversibly.The proportion of labelled T4 or T3 bound by the solid phase is then quantitated. This value, like the free fraction of T4 quantitated directly in a dialysate, varies inversely with the concentration of unoccupied TBG sites in the serum[8].

THE THYROID HORMONE AND THE CARDIOVASCULAR

SYSTEM: Cardiovascular diseases have similar pathophysiologic mechanisms which lead patients from risk factors, such as dyslipidaemia, smoking, high blood pressure etc. to congestive heart failure and finally – to death.

Thyroid Hormones have multiple effects on the cardiovascular system and also on the important cardiovascular risk factors like hypertension and dyslipidaemia.



The treatment of CAD also becomes complicated when a thyroid disorder is associated with the CAD. Hence thyroid hormones have an impact on cardiovascular diseases right from the risk factors and pathogenesis up to the treatment modalities[13].

EFFECTS OF THE THYROID HORMONE ON THE NATURAL HISTORY OF CAD:

Effects on Cardiomyocytes:

On the genome level (long term effects)– T3contributes to

- Synthesis of proteins and activation of transcription of the genes for alpha-isoform of myosin heavy chain, sarcoplasmic reticulum Ca activated ATPase, alpha1-adrenergic receptors, guanine-nucleotide-regulatory proteins, Na+/K+-adenosine triphosphatase, some of voltage gated K+ channels[4].
- repression of transcription of the genes for the beta-isoform of myosin heavy chain, phospholamban, nuclear receptor alpha1 Extra nuclear cellular effects (short term)

Membrane effects	
➢ Augments the activity of the SA node by increasing the conductance density of I(f)-channels	Increases the heart rate and oxygendemand of myocardium
➢ Activates the transmembrane transfer of sodium and potassium, glucose and calcium	cardiomyocytes' metabolism activated
sarcoplasmic reticulum effects	
➢ Activates calcium reuptake in diastole, up-regulates of Ca-activated ATPase, down-regulates phospholamban expression	Augments contraction of cardiomyocytes, enhances myocardial relaxation

OTHER EFFECTS THAT INFLUENCE THE NATURAL HISTORYOF CAD

Effects on heart: Increases the density of Beta1-adrenoreceptors in the heart & the response to catecholamines	Increase in cardiac output
Effects on vascular wall: Causes Relaxation of smooth muscle cells	Vasodilatation, decreases preload as well as afterload on the heart, decreases the peripheral vascular resistance
Metabolic effects Activates metabolism	Increases oxygenDemand of myocardium
Effects on lipid profile	Maintaining serum VLDL,LDL andHDL cholesterol, triglyceride and apo-B 100 levels within normal range
Modulates the production of glucose and storage of glycogen in the liver and heart	Cardiomyocytes' metabolism activated
Increases reabsorption of sodium in the kidney	Increases circulation blood volume

HYPOTHYROIDISM AND CAD:

Overt hypothyroidism is associated with hyperlipidemia, coagulation abnormalities, endothelial dysfunction, hypertension, LV hypertrophy, diastolic dysfunction of heart ventricles, and abnormalities of insulin resistance. All of these factors can alter the atherosclerotic process and modify morbidity and mortality rates for CAD[4].

Hypothyroidism and Hyperlipidemia:

Hypothyroidism leads to elevated plasma total cholesterol and LDL cholesterol levels. Elevation of TGL is also seen along with increased concentration of HDL cholesterol (mainly because of elevated concentration of HDL–2 particles). Hence, the lipid profile in patients with hypothyroidism is associated with atherogenic properties, and may be characterized by the unusual condition with simultaneously elevated TGL and HDL cholesterol levels. This elevated plasma concentration of HDL cholesterol may partly diminish the atherogenic lipid profile in patients with overt hypothyroidism. Patients with hypothyroidism also have increased concentration of lipoprotein (a) which is highly atherogenic[4].

Hypothyroidism and Hypertension:

The prevalence of hypothyroidism among the general population of patients with hypertension is around 3-4%. Patients with

hypothyroidism and hypertension have higher blood pressure levels compared with those without thyroid dysfunction.

At the same time hypertension is more common in hypothyroid patients – its prevalence reaches 20-40%. So, hypertension is frequently associated with hypothyroidism. Hypothyroidism is associated with predominantly diastolic hypertension[4]. This is believed to be a result of increased systemic vascular resistance, increased arterial stiffness and impaired endothelial function.

HYPERTHYROIDISM AND CAD:

Hyperthyroidism affects the natural history of CAD in many ways. Primarily it increases myocardial oxygen demand along with sinus and/or supraventricular tachycardia (as well as atrial fibrillation) – these factors can contribute to decompensation of underlying CAD and lead to manifestation of angina pectoris and heart failure (mostly with high cardiac output). Furthermore, systolic BP is usually increased, while diastolic BP is decreased in patients with hyperthyroidism. This causes the pulse pressure to become wider and mean blood pressure becomes moderately decreased[4].

Hence there is an increase in cardiac output with a reduction in peripheral vascular resistance; resulting in the classic hyperdynamic cardiovascular status. Hyperthyroidism affects another aspect of the

cardiovascular system, the renin-angiotensin aldosterone system. This is activated in patients with thyroid hyperfunction. This contributes to the hypertension and the ventricular remodelling[4].

Hyperthyroidism is also associated with an increase in von Willebrand factor levels as well as enhanced function of platelets and thus, a reduced collagen epinephrine- induced closure time (platelet plug formation measure). This may lead to increased platelet aggregation.

On the other hand, the presence of CAD may compromise the ability of myocardium to respond to the metabolic demands of hyperthyroidism. Hyperthyroidism may lead to MI even in patients without coronary stenosis. In hyperthyroid patients above 50 years of age on treatment, cardiovascular complications are the leading cause of death[4].

Dysrhythmias (especially atrial fibrillation) with thromboembolic complications and hypertension are the most important confounding factors for cardiovascular morbidity and mortality in hyperthyroid patients.

THE EFFECT OF SICK EUTHYROID STATE ON PROGNOSIS OF ACUTE MYOCARDIAL INFARCTION.

Acute myocardial infarction is a leading cause of mortality in the world today. There are multiple scoring systems and factors used to

prognosticate patients with STEMI. Systems like the TIMI- thrombolysis in Myocardial infarction score are commonly used.

However, the presence of the sick euthyroid state at the time of admission or within the first 3 days is an independent prognostic indicator that can be used to predict higher rates of mortality and major adverse cardiac events like ventricular arrhythmias and cardiac failure.

The pathogenesis is probably multifactorial. The role of some cytokines has been studied. These cytokines are also elevated in patients with STEMI. There appears to be a negative correlation between the elevation of these cytokines- CRP and IL-6 and the fall in fT3 levels[6].

In patients with prior angina, the sick euthyroid state may be present even before the acute event and when this is the case, may play a protective role when MI occurs. This is because the decreased fT3 helps to reducethe oxygen demand of the myocardium[55].

However if the sick euthyroid state develops after the acute STEMI, it is actually associated with higher mortality rates and poor prognosis. The mechanism by which thyroid dysfunction leads to a worse prognosis is not known completely. Thyroid hormones can affect ventricular function through stimulation of sarcoplasmic Ca-ATPase activity and expression. This ATPase removes the calcium from the cytoplasm during diastole and allows for the uncoupling of actin-

myosin cross-bridging. Hence it playsa major role for diastolic function of the heart. It is also involved in the regulation of the quantity of calcium in the sarcoplasmic reticulum. This calcium is needed for systolic contraction and is thus, also important for the systolic heart function. When there is a downregulation of the thyroid hormone system in the short term in STEMI, the change in intracellular calcium handling may contribute to myocardial stunning and reperfusion injury due to calcium overload. Down-regulation of the thyroid hormones also leads to an increase in systemic vascular resistance and increases the cardiac afterload. In an already weakened heart, the cardiac output will be reduced[55].

The Sick Euthyroid State is also seen in patients with chronic heart failure and in patients who go into cardiac arrest and are revived. Hence the thyroid hormone affects the cardiovascular system at multiple levels and in multiple ways. Hence it is prudent to screen every patient with CAD for the presence of thyroid dysfunction as this has an effect on treatment and prognosis.

MATERIALS AND METHODS

PARTICIPANTS

75 Patients admitted with ST elevation Myocardial Infarction at Govt. Rajaji Hospital >18 years of age fulfilling all the inclusion criteria.

STUDY POPULATION:

The study was conducted among 75 patients admitted in Government Rajaji Hospital with history, clinical features and ECG changes of ST elevation Myocardial Infarction.

INCLUSION CRITERIA:

- Age > 18 years
- History of chest pain with ECG changes of ST elevation Myocardial Infarction.

EXCLUSION CRITERIA:

- Patients presenting as Non ST elevation MI or unstable Angina
- Known case of hypothyroidism/hyperthyroidism
- Known case of any other endocrine disorder excluding Diabetes Mellitus
- Known case of Chronic Kidney disease
- Known case of Chronic Liver disease

- Known case of malignancy
- Patients with Renal failure
- Patients taking amiodarone, steroids, propranolol, oral contraceptives
- Patients who have received iodinated contrast in past week

DATA COLLECTION:

A previously designed proforma was used to collect the demographic and clinical details of the patients. A detailed history was taken and a complete clinical examination was performed. ECG was taken at the time of admission. Blood samples for thyroid profile were taken at the time of admission. Clinical course of all patients were followed up till discharge.

LABORATORY INVESTIGATIONS

Blood samples for analysis of TSH, fT3 and fT4 were taken at the time of admission. Samples were taken in a container with no added anticoagulant. Serum was analysed for the levels of TSH,fT3 and fT4 by chemiluminescence method.

The reference levels used were : Serum fT3 – 2.3 – 4.2 pg/ml

Serum fT4- 0.89 – 1.76 ng/dl Serum TSH – 0.35 – 5.50 mIU/ml

STUDY PROTOCOL:

- Patients with ECG changes suggestive of ST elevation MI were included in the study.
- Serum fT3, fT4 and TSH were analysed for all the patients.
- Depending on the thyroid profile, patients were divided into 3 groups- those with a normal thyroid function- controls, those with a hypothyroid profile (decreased fT3/fT4 and/or elevated TSH) and those with a sick euthyroid state (normal fT4,TSH and low fT3).
- All the 3 groups were followed up till discharge.

STUDY DESIGN: Prospective analytical study.

DATA ANALYSIS: All the data was entered onto Microsoft excel sheet 2010 version. The statistical analysis was done using SPSS software. The statistical tools applied were mean, standard deviation, and chi – square test with Yates' correction. The results were considered very significant with p value < 0.01 and significant with p value <0.05.

PERIOD OF STUDY:

November 2021 to August 2022

COLLABORATING DEPARTMENTS:

Department of General Medicine, Department of Cardiology, Department of Endocrinology.

ETHICAL CLEARANCE: obtained

CONSENT:

Individual written and informed consent

ANALYSIS: statistical analysis- chi square

CONFLICT OF INTEREST: NIL

FINANCIAL SUPPORT: NIL

OBSERVATION AND RESULTS

Table 1-Age distribution vs Thyroid

Age	Euthyroid	Sick Euthyroid	Hypothyroid
< 50 (18)	13	5	0
51 - 60 (42)	18	17	7
> 60 (15)	9	3	3
Total	40	25	10
p value	0.133 Not significant		

Myocardial infarction is more common in the 51-60 years age group and > 60 years age group. The youngest patient was 35 years old and the oldest was 68 years old. No significant difference between age and thyroid p value is 0.133 Not sig.

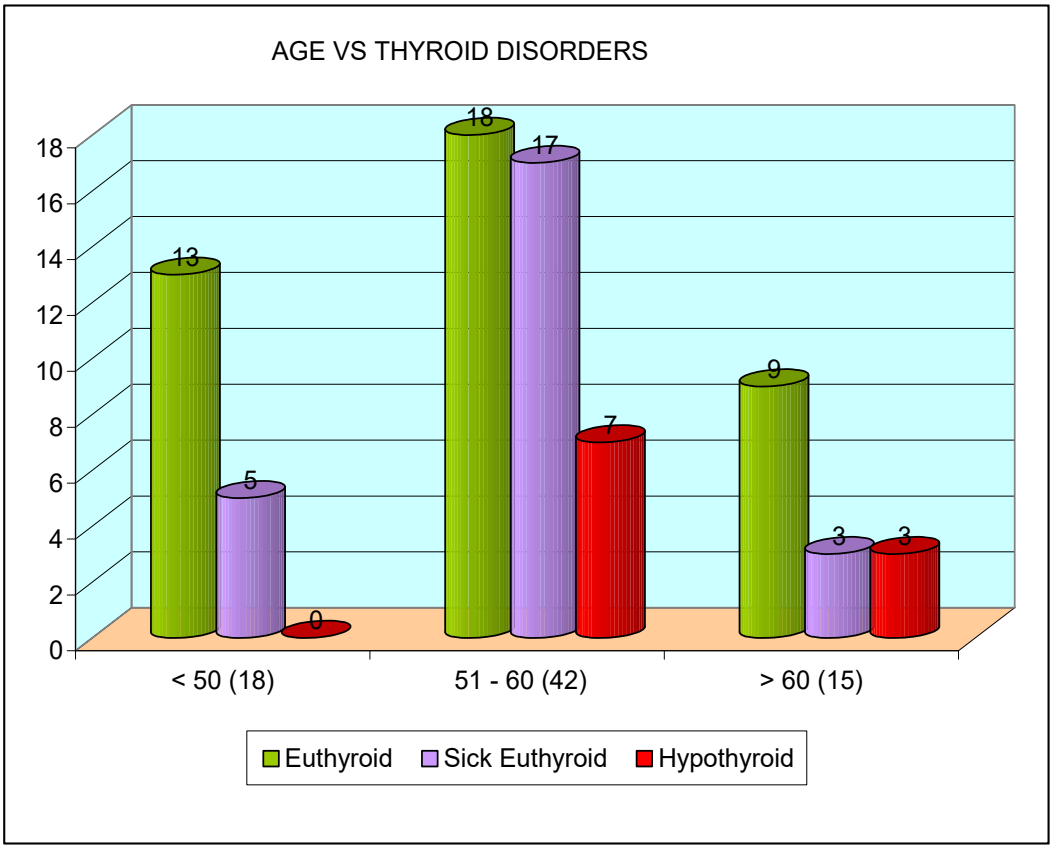

AGE VS THYROID DISORDERS
18
16
14
12
10
8
6
4
2
0
13
5
0
18
17
7
9
3
3
< 50 (18)
51 - 60 (42)
> 60 (15)
Euthyroid
Sick Euthyroid
Hypothyroid

Table 2 :Gender distribution vs Thyroid

Gender	Euthyroid	Sick Euthyroid	Hypothyroid
Male (49)	27	17	5
Female (26)	13	8	5
Total	40	25	10
p value	0.549 Not significant		

Comment: Myocardial infarction is more common in males (65.3%) compared to females (34.7 %). No significant difference regarding gender p value is 0.549 Not significant.

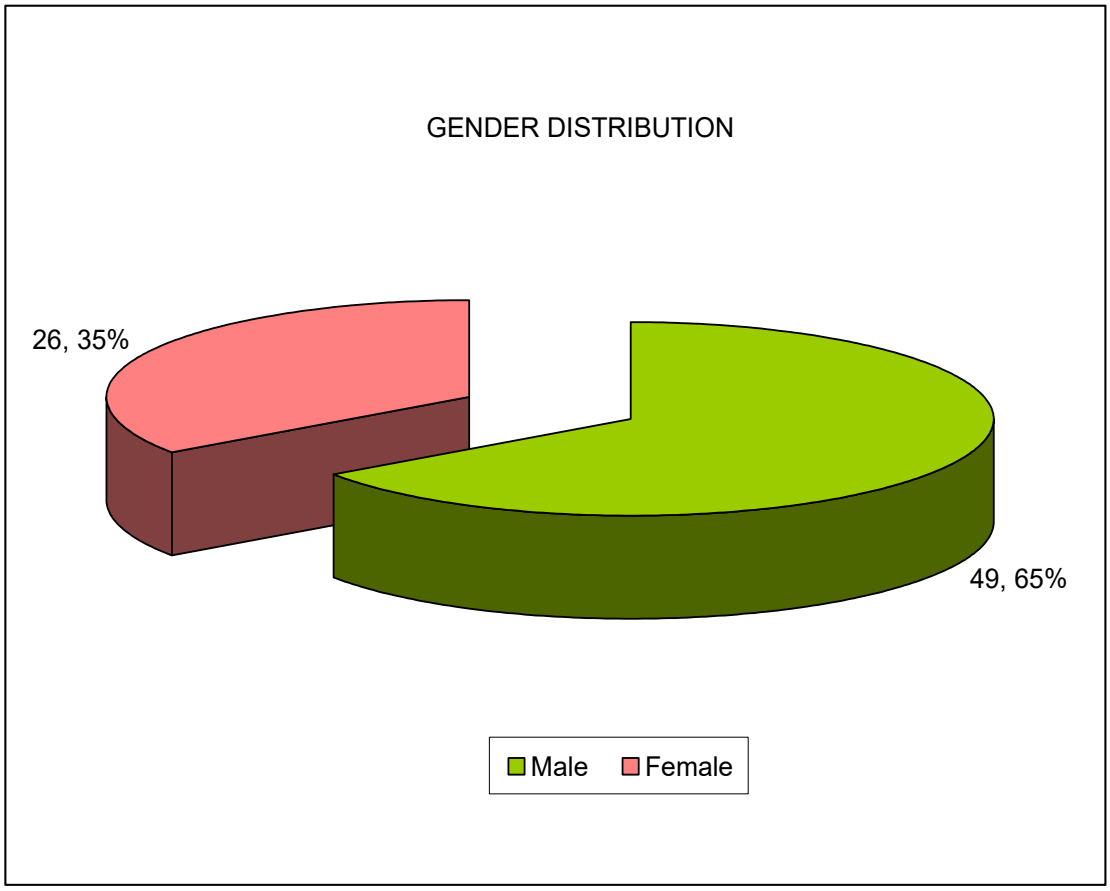

GENDER DISTRIBUTION
26, 35%
49, 65%
Male
Female

Table 3 :Diabetes mellitus vs Thyroid

DM	Euthyroid	Sick Euthyroid	Hypothyroid
Yes (16)	12	3	1
No (59)	28	22	9
Total	40	25	10
p value	0.146 Not significant		

In our study, 16 cases are diabetic and remaining 59 cases are non diabetic. No significant difference between diabetes and thyroid disorder.

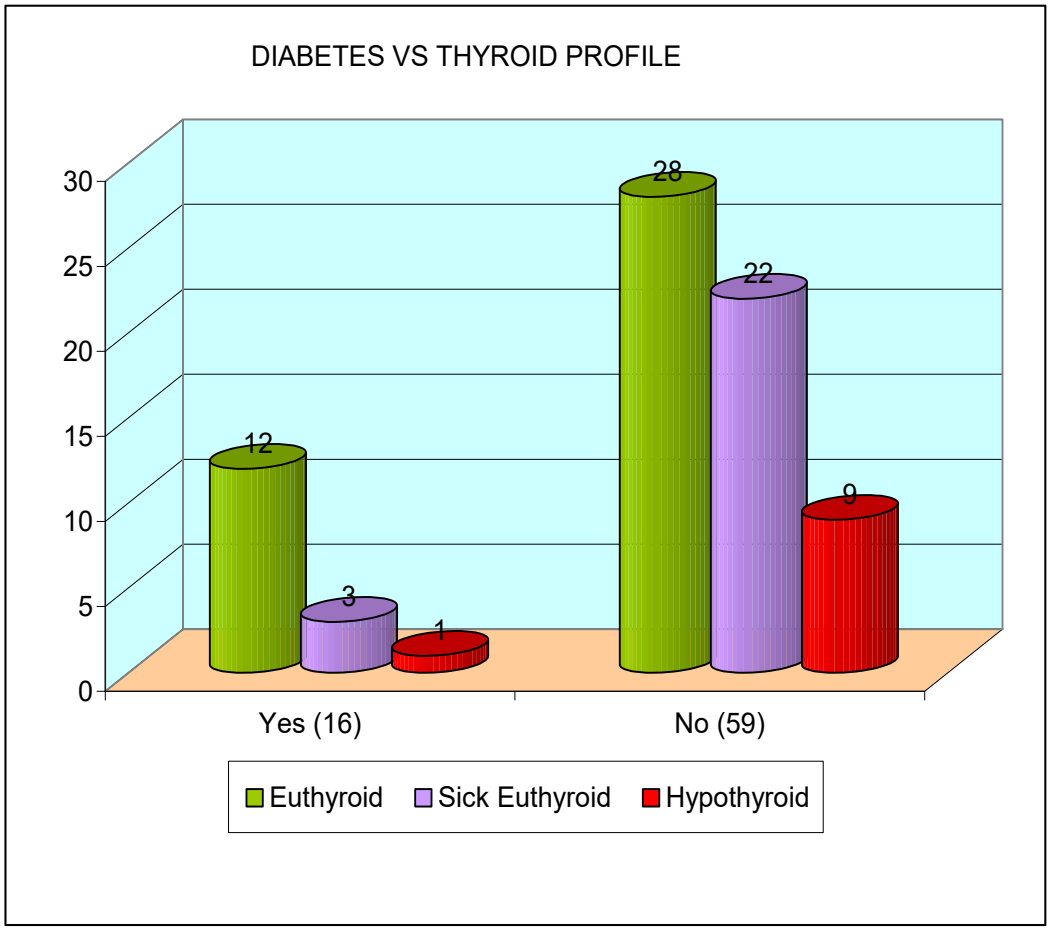

DIABETES VS THYROID PROFILE
30
25
20
15
10
5
0
12
3
1
28
22
9
Yes (16)
No (59)
Euthyroid
Sick Euthyroid
Hypothyroid

Table 4 :Hypertension vs Thyroid

SHT	Euthyroid	Sick Euthyroid	Hypothyroid
Yes (24)	16	6	2
No (51)	24	19	8
Total	40	25	10
p value	0.276 Not significant		

In our study, 24 cases are hypertensive and remaining 51 cases are non hypertensive. No significant difference between hypertension and thyroid disorder. P value is 0.276 not significant.

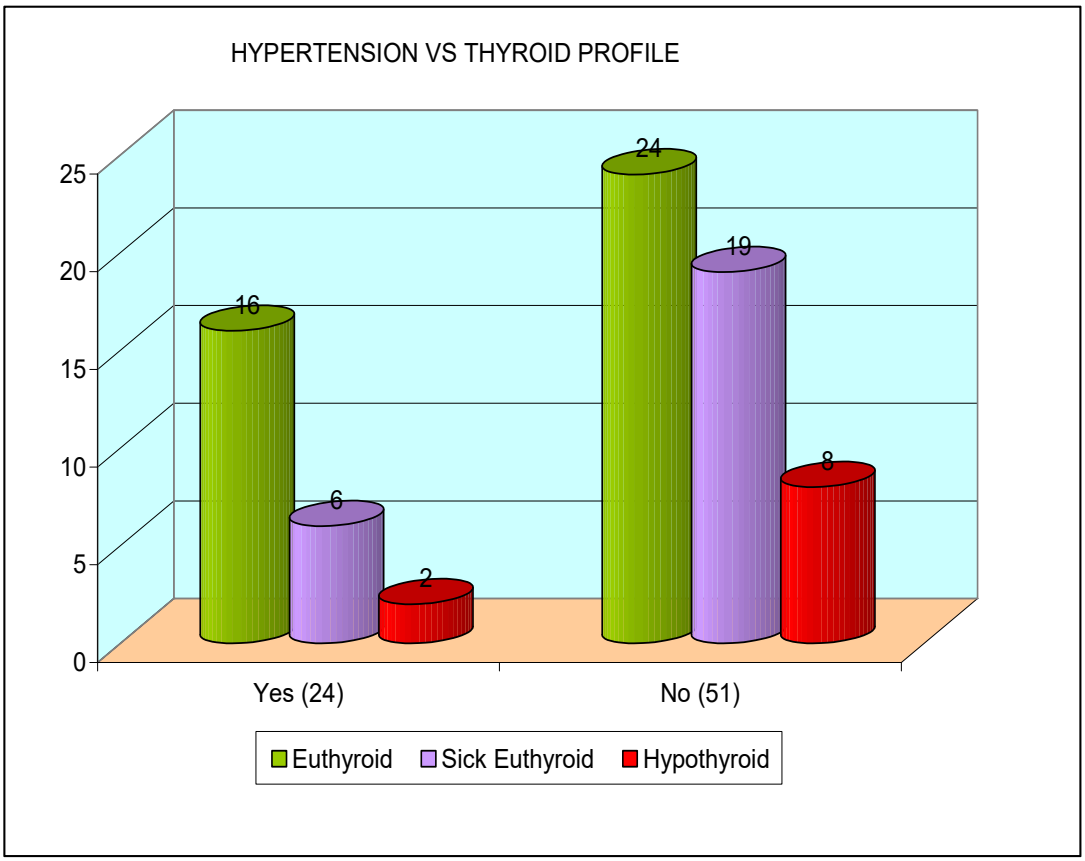

HYPERTENSION VS THYROID PROFILE
25
20
15
10
5
0
16
6
2
24
19
8
Yes (24)
No (51)
Euthyroid
Sick Euthyroid
Hypothyroid

Table 5 :Thrombolysis vs Thyroid

Thrombolysis	Euthyroid	Sick Euthyroid	Hypothyroid
Yes (40)	23	11	6
No (35)	17	14	4
Total	40	25	10
p value	0.514 Not significant		

Out of 75 cases, 40 cases had thrombolysis, no significant difference between thrombolysis and thyroid disorder.

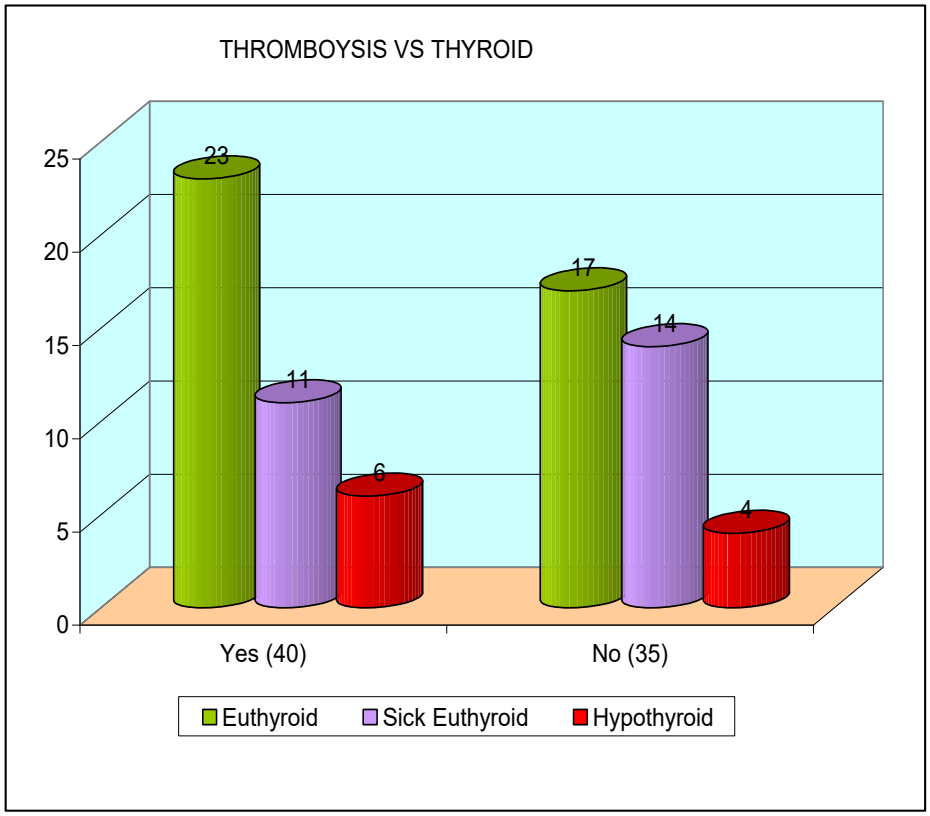

THROMBOYSIS VS THYROID
25
20
15
10
5
0
23
11
6
17
14
4
Yes (40)
No (35)
Euthyroid
Sick Euthyroid
Hypothyroid

Table 6 :Smoking vs Thyroid

Smoking	Euthyroid	Sick Euthyroid	Hypothyroid
Yes (43) only males	22	16	5
No (32) females (26)	18	9	5
Total	40	25	10
p value	0.683 Not significant for overall male and females < 0.001 for males alone		

Smoking is one of the most important risk factors for CAD. The prevalence of smoking in our study was 57.3%. but exclude females, smoking 87.7% In our study all the females were non-smokers, whereas among the males only 6 were non-smokers.

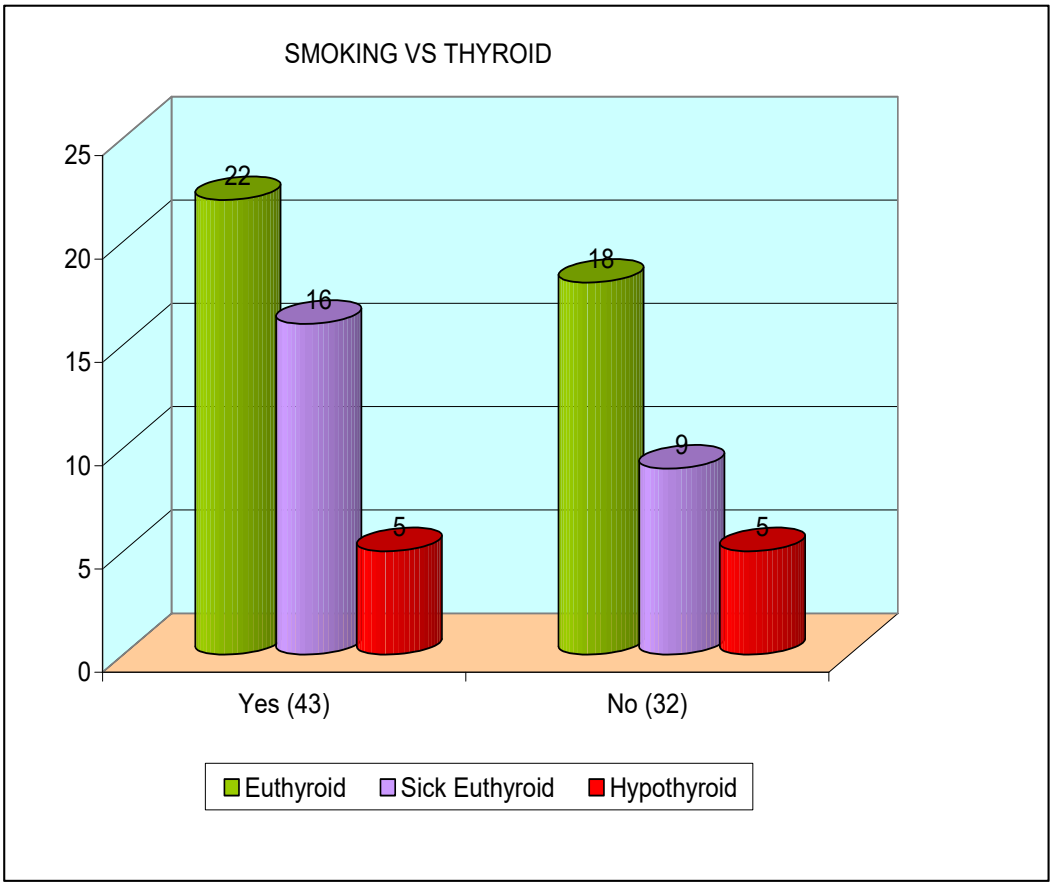

SMOKING VS THYROID
25
20
15
10
5
0
22
16
5
18
9
5
Yes (43)
No (32)
Euthyroid
Sick Euthyroid
Hypothyroid

Table 7: fT3 vs Thyroid

fT3	Euthyroid	Sick Euthyroid	Hypothyroid
Mean	2.262	0.498	2.544
SD	0.202	0.105	0.476
p'value	<0.001 Significant		

Mean fT3 values are significantly higher in sick euthyroid cases 3.362 when compared with hypo and euthyroid cases 2.54 and 2.26. p value is < 0.001 significant.

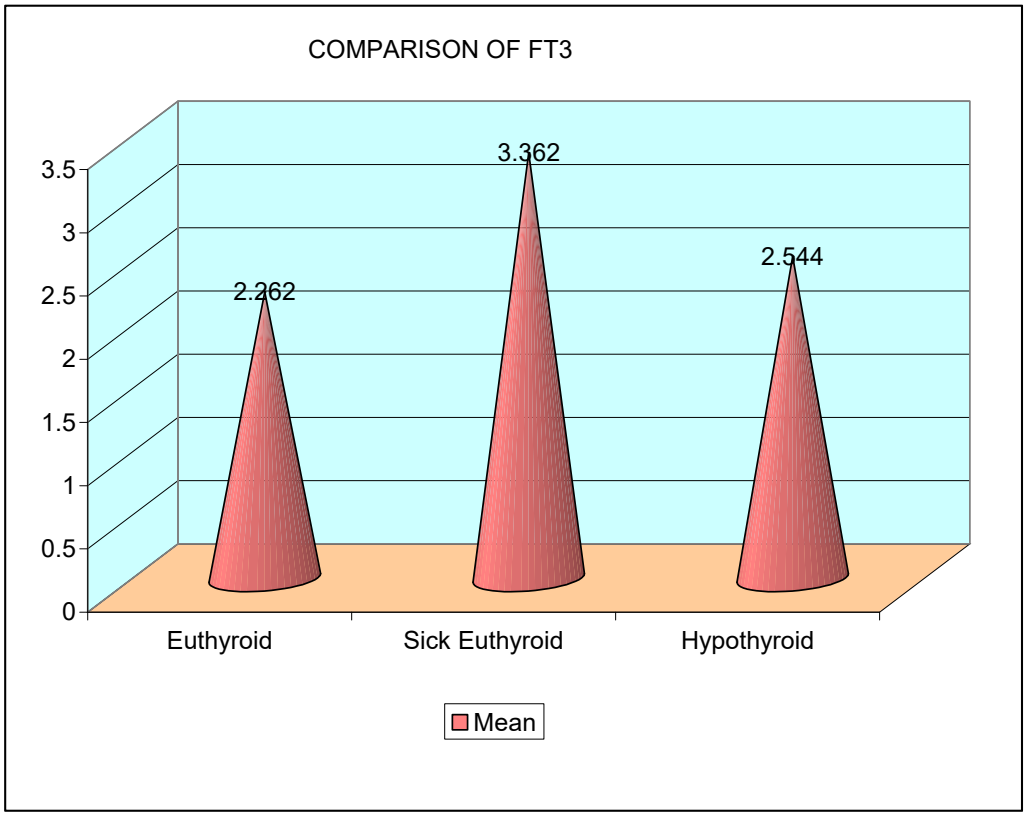

COMPARISON OF FT3
3.5
3
2.5
2
1.5
1
0.5
0
2.262
3.362
2.544
Euthyroid
Sick Euthyroid
Hypothyroid
Mean

Table 8: fT4 vs Thyroid

fT4	Euthyroid	Sick Euthyroid	Hypothyroid
Mean	1.212	1.312	1.138
SD	0.228	0.249	0.198
p'value	0.093 Not significant		

Mean fT4 values are higher in sick euthyroid cases 1.312 when compared with hypo and euthyroid cases 1.14 and 1.21. but not statistically significant. p value is 0.093 Not significant.

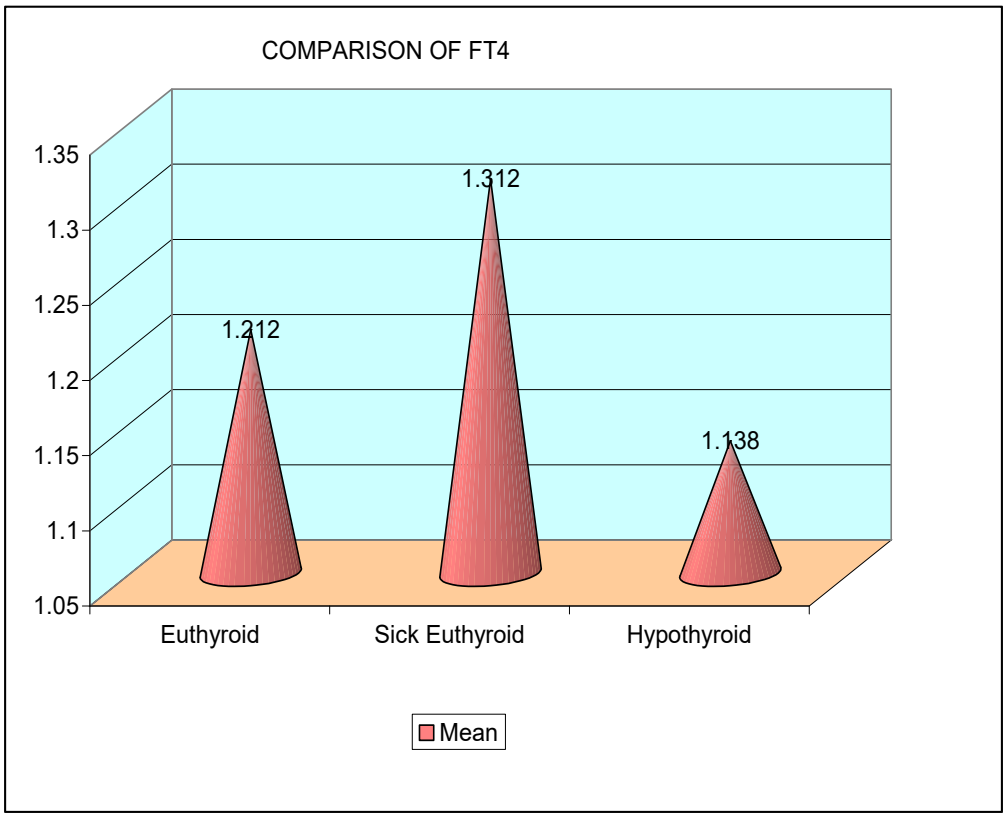

COMPARISON OF FT4
1.35
1.3
1.25
1.2
1.15
1.1
1.05
1.212
1.312
1.138
Euthyroid
Sick Euthyroid
Hypothyroid
Mean

Table 9: TSH vs Thyroid

TSH	Euthyroid	Sick Euthyroid	Hypothyroid
Mean	2.538	3.327	9.645
SD	1.326	1.01	2.307
p'value	<0.001 Significant		

Mean TSH values are significantly higher in hypothyroid cases 9.65 when compared with Sick and euthyroid cases 3.33 and 2.54. p value is < 0.001 significant.

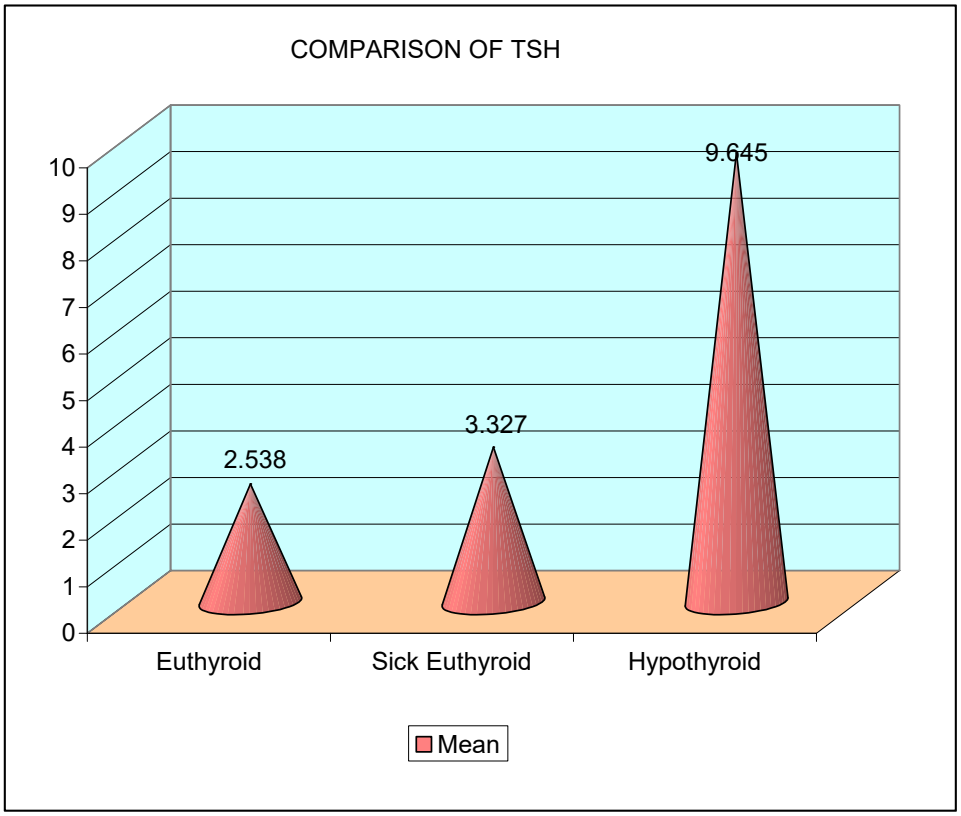

COMPARISON OF TSH
10
9
8
7
6
5
4
3
2
1
0
2.538
3.327
9.645
Euthyroid
Sick Euthyroid
Hypothyroid
Mean

Table 10: MACE vs Thyroid

MACE	Euthyroid	Sick Euthyroid	Hypothyroid
Yes (19)	5	9	5
No (56)	35	16	5
Total	40	25	10
p value	0.017 Significant		

Out of 19 MACE cases, 9 from Sick euthyroid, 5 each from hypo and euthyroid cases. This is statistically significant. p value 0.017.

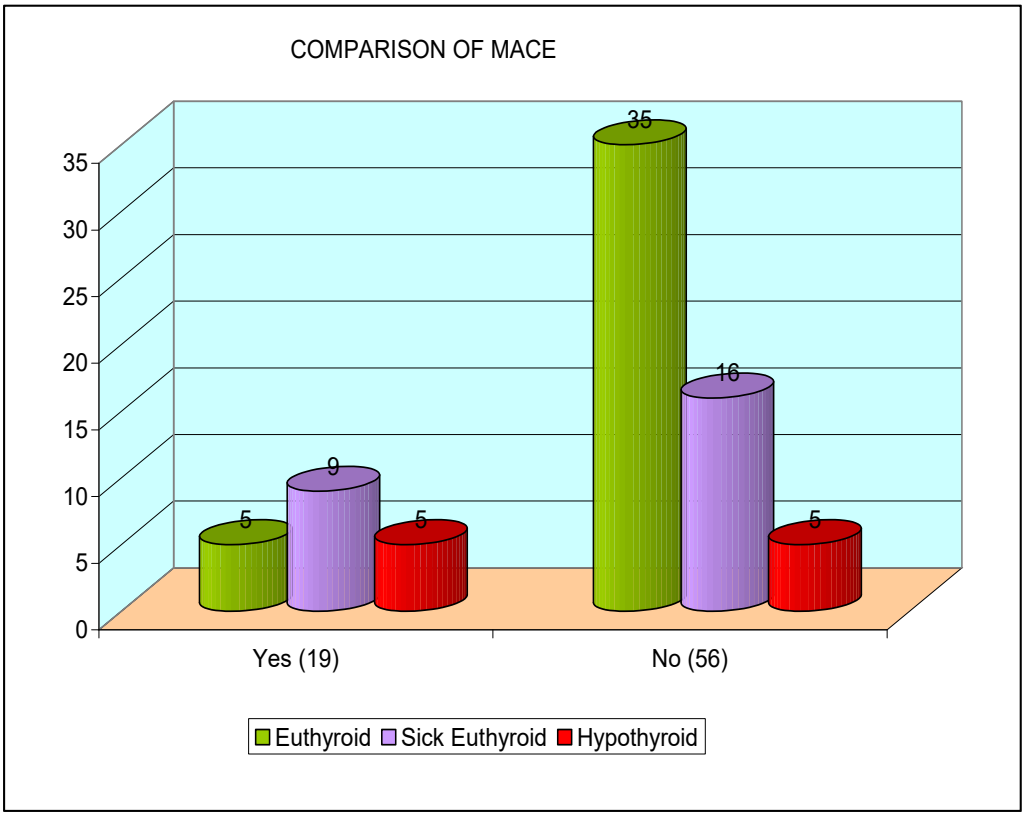

COMPARISON OF MACE
35
30
25
20
15
10
5
0
5
9
5
35
16
5
Yes (19)
No (56)
Euthyroid
Sick Euthyroid
Hypothyroid

Table 11 : Cardiac failure vs Thyroid

CCF	Euthyroid	Sick Euthyroid	Hypothyroid
Yes (15)	3	9	3
No (60)	37	16	7
Total	40	25	10
p value	0.014 Significant		

Out of 15 CCF cases, 9 from Sick euthyroid, 3 each from hypo and euthyroid cases. This is statistically significant. p value 0.014.

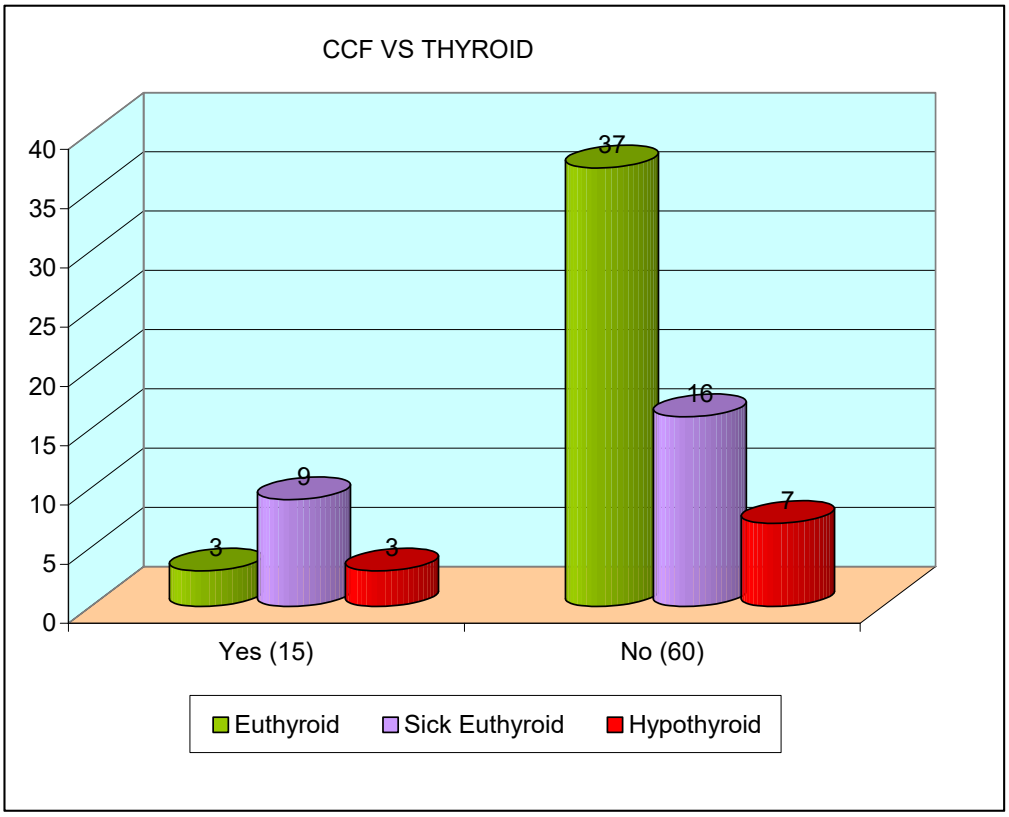

CCF VS THYROID
40
35
30
25
20
15
10
5
0
3
9
3
37
16
7
Yes (15)
No (60)
Euthyroid
Sick Euthyroid
Hypothyroid

Table 12 : Arrhythmia vs Thyroid

Arrhythmia	Euthyroid	Sick Euthyroid	Hypothyroid
Yes (10)	1	8	1
No (65)	39	17	9
Total	40	25	10
p value	0.003 Significant		

Out of 10 Arrhythmia cases, 8 from Sick euthyroid, 1 each from hypo and euthyroid cases. This is statistically significant. p value 0.003.

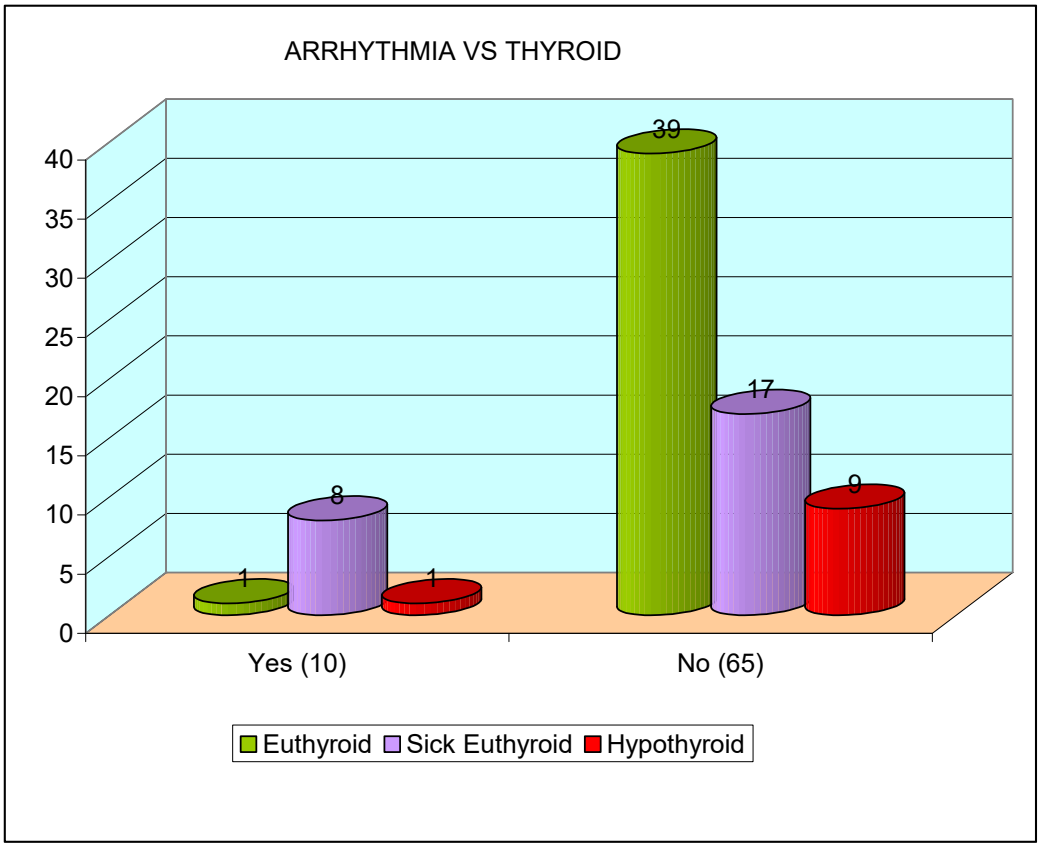
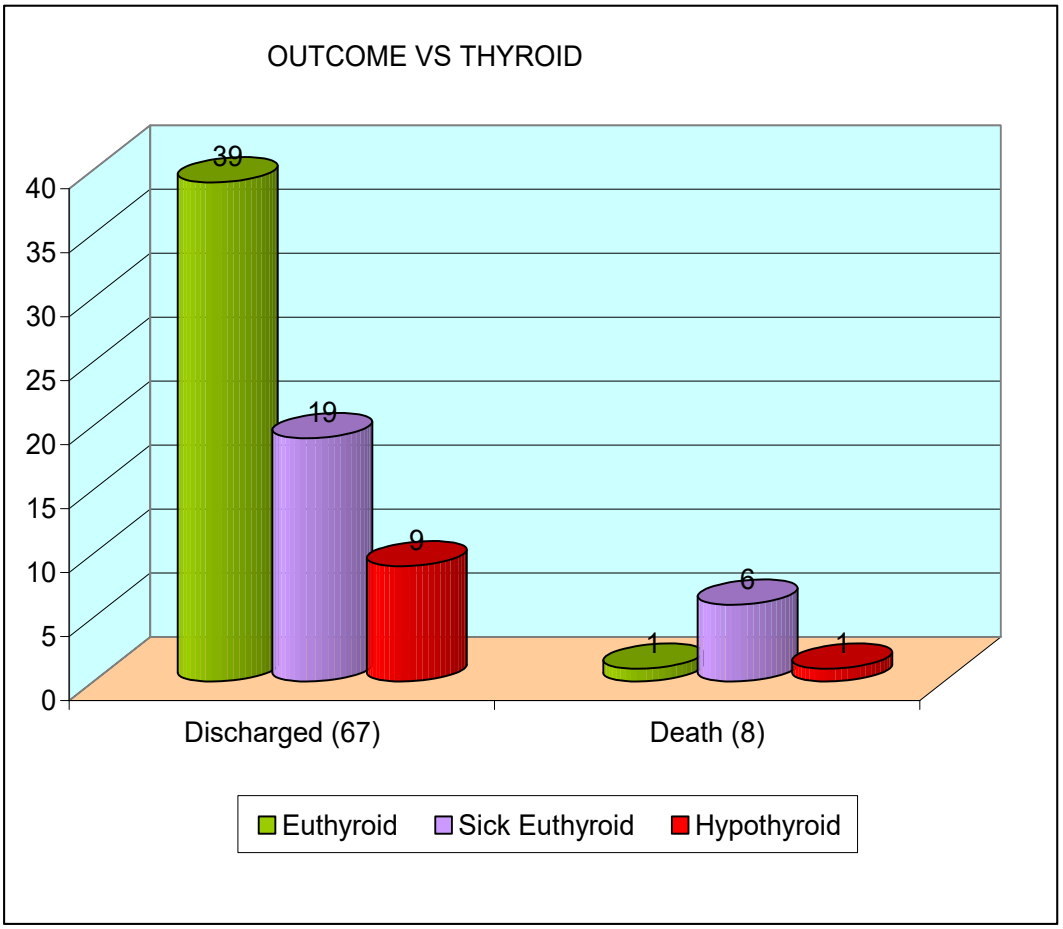

ARRHYTHMIA VS THYROID
40
35
30
25
20
15
10
5
0
1
8
1
39
17
9
Yes (10)
No (65)
Euthyroid
Sick Euthyroid
Hypothyroid

Table 13 : Outcome vs Thyroid

Outcome	Euthyroid	Sick Euthyroid	Hypothyroid
Discharged (67)	39	19	9
Death (8)	1	6	1
Total	40	25	10
p value	0.024 Significant		

Out of 8 deaths, 6 from Sick euthyroid, 1 each from hypo and euthyroid cases. This is statistically significant. p value 0.024.


OUTCOME VS THYROID
40
35
30
25
20
15
10
5
0
39
19
9
1
6
1
Discharged (67)
Death (8)
Euthyroid
Sick Euthyroid
Hypothyroid

DISCUSSION

Myocardial Infarction is one of the most common and dreaded complications of atherosclerosis in the world today. There are numerous scoring systems used to predict prognosis when a patient gets admitted with Myocardial Infarction. The thyroid hormones affect the cardiovascular system in multiple ways and at multiple levels[6]. In this study we analyzed the thyroid profile of 75 patients admitted with features of ST-elevation myocardial infarction.

Our main aim was to study the thyroid profile in these patients and evaluate if the thyroid profile can be used as a predictor of mortality and as a prognostic indicator in them.

Among the 75 patients, 17 were found to have a low fT3 with a normal TSH and fT4- a profile characteristic of the sick euthyroid state. 9 patients were found to have elevated TSH with normal or low fT3 and fT4 values- a picture characteristic of subclinical/overt hypothyroidism.

AGE AND GENDER

Out of the 75 patients admitted with STEMI, 42 patients were in the age group 51-60years. This corresponds to 56% of the study population. The mean age of the males in the study was 52.61 and females was 60.1.

Among the 75 patients, 26 patients were female and 49 were male. Myocardial infarction was more common in males. This was seen in both the normal thyroid profile group and the sick euthyroid groups. However in the hypothyroid group, only 5 of the 10 patients were males. This may be indicative of the fact that hypothyroidism is more prevalent among women than men in the general population[26].

The incidence of MI also increases with age as seen by 56% of the patients falling in the 51-60 years age group. Increasing age and male gender remain important non-modifiable risk factors for CAD.

The mean age was higher among women (60.1 years) in our study. CAD is more common in the postmenopausal group in women.

This is because of the protective effect offered by estrogen in the childbearing years of a woman's life[26].

Other risk factors

In our study, the total number of patients with a history of Diabetes Mellitus was 16 and those with a history of hypertension was 24.This indicates that 53.33% of the patients in our study had at least one modifiable risk factor.

Among the patients with a normal thyroid function, 28 patients had DM or SHT (53.84%). Among the sick euthyroid patients, 9 patients

had DM or SHT (60%). This is not statistically significant (p value-0.276).

SMOKING

46 of the 75 patients had a history of smoking. This is 61.33% of the study population. All the women were non-smokers. Hence smoking remains the most important modifiable risk factor affecting the natural history of CAD.

Among the 3 groups, smoking was less prevalent in the hypothyroid group, probably because this group had more women. No statistical difference was found between the prevalence of smoking in the normal thyroid profile group and the sick euthyroid group[27,28].

But in the male patients, smoking is highly significant in sick and hypothyroid group. P value < 0.001 significant.

INCIDENCE OF MACE

MACE or major adverse cardiac events refers to cardiac failure, ventricular arrhythmias and death. The total number of patients with MACE in our study was 19 (25.3%).Out of these, 13 patients belonged to the sick euthyroid group. Among the sick euthyroid group of 25 patients, 13 had a major adverse cardiac event (52%). In the hypothyroid group, the incidence of MACE was 40%. In the euthyroid group with a normal thyroid profile, the incidence was 5.2%.

The incidence of MACE was found to be statistically significant in the sick euthyroid group with a p value of 0.017. This is in accordance with the results of the study "*Sick euthyroid syndrome is associated with poor prognosis in patients with STEMI undergoing primary percutaneous intervention"* published in the Cardiology journal where 472 patients with STEMI were studied. The incidence of in-hospital MACE was found to be significantly higher in the thyroid dysfunction group and the most common MACE seen was mortality[1].

CARDIAC FAILURE AND VENTRICULAR ARRYTHMIAS

15 patients out of the 75 study population developed cardiac failure. Out of these, 9 patients belonged to the sick euthyroid group (60%), 3 belonged to the normal thyroid profile group (20%) and 3 belonged to the hypothyroid group (20%).

The incidence of cardiac failure in the sick euthyroid group is statistically significant with a p value of 0.014 significant.

Ventricular arrhythmias occurred in 10 people out of 75 cases, 8 people belonged to the sick euthyroid group and among the normal thyroid profile group and the hypothyroid group, the number of patients with arrhythmia was 1 each.

The incidence of ventricular arrhythmias in the sick euthyroid group is found to be statistically significant (80%) with a p value of 0.003.

This is in accordance with the study by *Kazim Serhan Ozcan, et al. "Sick euthyroid syndrome is associated with poor prognosis in patients with STEMI undergoing primary percutaneous intervention"*[1].

MORTALITY

Out of 75 patients in the study, 8 patients died. 6 of these belonged to the sick euthyroid group (75%). One patient from Euthyroid and one patient from hypothyroid group.

The mortality rate among the sick euthyroid group is 75% and this is statistically significant with a p value of 0.024.

This is in accordance to the study "*Evaluation of Thyroid Dysfunction in Acute Coronary Syndrome*" conducted by "*Saurabh Potdal, Hetab Patel and Nivedita Mehta***"** in Baroda Medical College. In this study patients were divided into 2 groups- STEMI and NSTEMI/Unstable Angina. 21% patients were found to have a sick euthyroid syndrome on the day of admission. Mortality rates were found to be higher in the STEMI group who had presented with a sick euthyroid state [3].

This association was also seen in a study "*Association between increased levels of reverse triiodothyronine and mortality after acute myocardial infarction*" by Leif Friberg et al. Here elevated rT3 levels were found to be associated with higher mortality levels.rT3 is another marker of the sick euthyroid state[6].

In a study done in Brazil, *"Thyroid Hormone Profile in Acute Coronary Syndromes" Rodrigo Caetano Pimentel, Gilberto Perez Cardoso, Claudia Caminha Escosteguy et al* studied 70 patients with ACS divided into 2 groups- those with STEMI and those with NSTEMI/Unstable angina. Thyroid hormones were measured on the day of admission and sick euthyroid state was defined as a normal TSH, Total/free T4 with an elevated reverse T3 and a low total/free T3. The group of patients with STEMI were found to have an earlier onset of thyroid hormone dysfunction and a higher mean reverse T3 and lower mean free/total T3 levels. The rates of mortality were also found to be higher in the STEMI group with sick euthyroid state[15].

The exact mechanism by which a sick euthyroid state leads to an increased incidence of MACE and increased mortality is not clear[54]. So far, studies have not shown an improvement in the prognosis following treatment of the sick euthyroid state with levothyroxine.

Irrespective of the mechanism involved, patients with a sick euthyroid state at the time of an acute myocardial infarction are at an increased risk of arrhythmias, cardiac failure and death and hence will benefit fromlonger intensive care and close monitoring during follow-up.

SUMMARY

The cardiovascular system and the thyroid hormones are linked at multiple levels and in multiple ways. This study was conducted in 75 patients presenting with ST elevation Myocardial Infarction. Thyroid profile was done in all of them.

- The number of males in the study was 49 (65.3%) and their mean age was 52.6.
- The number of females was 26 (34.7%) and their mean age was 60.1.
- The total number of patients who were smokers is 46 (61.33%).
- Diabetics constituted 21.33% (16 patients) of the population and hypertension was seen in 24 patients (32%)
- The number of patients with a normal thyroid profile at the time ofpresentation was 40 and 13 of them were females.
- The number of patients with sick euthyroid state at the time of STEMI was 15 and 4 of them were females.
- The number of hypothyroid patients in the study was 10 and 5 of them were females.
- The number of patients who had atleast one major adverse cardiac events (MACE) is 19. Out of this, 13 patients belonged to the sick euthyroid group.

- 15 patients developed cardiac failure, 9 of them belonged to the sick euthyoid group.
- Ventricular arrhythmias were seen in 1 0 patients, with 8 of them in the sick euthyroid category.
- The number of deaths was 8 and 6 of the patients were part of the sick euthyroid group.

The sick euthyoid state was seen in 33.3% of the study population and it was associated with an increased rate of MACE. There was a statistically significant association between the presence of the sick euthyroid state and the occurrence of cardiac failure, ventricular arrhythmias and death.

CONCLUSION

Sick euthyroid is occurs in all age group and gender, not correlated with age, gender, DM and Hypertension.

Sick euthyroid is well correlated with smoking, elevated fT3, TSH value and MACE.

Sick euthyroid cases are significantly correlated ($p<0.05$) with worse prognosis and have an increased risk of developing failure, arrhythmias and death.

The sick euthyroid state is seen when a patient suffers from any serious illness. This study was done to look for any changes in the thyroid profile when a patient presents with an acute ST elevation myocardial infarction. Evaluate if the presence of any such changes has an effect on the course of the illness.

When a patient presents with an acute myocardial infarction, some of them develop a sick euthyroid state. This may be part of the body's compensatory mechanism to try and reduce the metabolic demand of the heart. The sick euthyroid state shows a positive association with the occurrence of MACE.

STEMI patients who present with a sick euthyroid state have a worse prognosis and have an increased risk of developing failure, arrhythmias and death. They may need a longer duration of intensive care and close monitoring during follow-up.

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PROFORMA

Name : Case No. :

Age & Sex :

IP no. :

Occupation :

Address :

Date of Admission :

Date of Discharge :

Chief Complaints :

Chest pain- onset, duration, nature of pain Breathlessness, palpitations, syncope

Past History : History of Diabetes ,Hypertension, CAD History of Thyroid disorder,CKD, CLD History of Drug intake

Personal History : Smoker /Alcoholic Clinical Examination :

General examination Vitals : PR-

BP-

Examination of the Cardiovascular system-Other systems :

ECG changes :

DIAGNOSIS :

Serum TSH -Serum fT3 - Serum fT4 -

Course of patient in hospital :

Treatment given –Anticoagulation alone /Thrombolysis/ PCI/Stenting

Complications : Congestive cardiac failure

Ventricular arrhythmiasCardiac arrest

Duration of stay in ICU :Outcome : Recovered

Expired inspite of treatment

KEY TO MASTER CHART

DM	-	Diabetes Mellitus
HT	-	Hypertension
M	-	Male
F	-	Female
Y	-	Yes
N	-	No
SES	-	Sick Euthyroid State
CCF	-	Cardiac Failure
Dis	-	dischargef
T3	-	Free T3 f
T4	-	Free T4
MACE	-	Major Adverse Cardiac Events

ஆராய்ச்சி ஒப்புதல் படிவம்

பெயர்:

வயது:

தேதி:

நோயாளி எண்:

ஆராய்ச்சி சேர்க்கை எண்:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு விளக்கபட்டது.

எனக்கு விளக்கபட்ட விஷயங்களை நான் புரிந்து கொண்டு எனது முழுமனதுடன் சம்மதிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில்தான் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆராய்ச்சியில் இருந்து எந்த நேரமும் பின்வாங்கலாம் என்றும் அதனால் எந்த பாதிப்பும் எனக்கு ஏற்படாது என்பதையும் புரிந்துகொண்டேன்.

நான் என்னுடைய சுயநினைவுடன் மற்றும் முழுசுதந்திரத்துடன் இந்த மருத்துவ ஆராய்ச்சியில் பங்கு கொள்ள சம்மதிக்கிறேன்.

INSTITUTIONAL ETHICS COMMITTEE
MADURAI MEDICAL COLLEGE &GOVT.RAJAJI HOSPITAL, MADURAI
CDSCO: Reg. No. ECR/1365Inst/TN/2020 &DHR Reg.No.EC/NEW/INST/2020/484

Study Title	:	A study on thyroid profile and its prognostic value in patients presenting with st elevation myocardial infarction.
Principal Investigator	:	**Dr. Siva sundar.A**
Designation	:	PG in MD., General Medicine
Guide	:	Dr.C.Dharmaraj, MD.,DCH., Professor of General Medicine
Department	:	Department of General Medicine Government Rajaji Hospital & Madurai Medical College, Madurai

The request for an approval from the Institutional Ethics Committee (IEC) was considered on the IEC meeting held on **29.10.2021** at GRH Auditorium, Govt. Rajaji Hospital, Madurai at 10.00 A.M

The Members of the committee, the Secretary and the Chairman are pleased to inform you that your proposed project mentioned above is **Approved.**

You should inform the IEC in case of any changes in study procedure, methodology, sample size investigation, Investigator or guide or any other changes.

1. You should not deviate from the area of work for which you had applied for ethical clearance.
2. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions. If encountered during from study.
3. You should abide to the rules and regulations of the institution(s)
4. You should complete the work within the specific period and if any extension is required, you should apply for the permission again for extension period.
5. You should submit the summary of the work to the ethical committee on completion of the study.
6. Serious Adverse Events occurred in the study should be intimated to the IEC within 24 hours of occurrence of the event.

MEMBER SECRETARY,
IEC, Madurai Medical College,
Madurai.

Dr.K.RAADHIKA, M.D(Pharm)
Associate Professor
Member Secretary
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CERTIFICATE – II

This is to certify that this dissertation work titled **"A STUDY ON THYROID PROFILE AND ITS PROGNOSTIC VALUE IN PATIENTS PRESENTING WITH ST ELEVATION MYOCARDIAL INFARCTION"** of the candidate **Dr. A.SIVA SUNDAR** with Registration Number **200120101523** for the award of M.D., in the branch of **GENERAL MEDICINE.I** personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 11 percentage of plagiarism in the dissertation.

Dr.DHARMARAJ DCH, M.D.,

Professor of Medicine

Department of General Medicine

Government Rajaji Hospital

Madurai Medical College Madurai

MASTER CHART

S.No.	Age	Gender	DM	SHT	Thrombolysis	Smoking	fT3	fT4	TSH	Thyroid	MACE	ccf	Arrhythmia	Outcome
1	55	f	y	y	n	n	2.58	1.27	2.04	Euthyroid	Y	Y	n	Death
2	68	m	n	n	n	n	2.32	0.97	2.98	Euthyroid	N	n	n	discharged
3	50	m	n	n	y	n	2.06	0.86	1.15	Euthyroid	Y	y	n	discharged
4	57	m	n	y	y	y	2.39	0.91	3.43	Euthyroid	N	n	n	discharged
5	66	f	y	y	y	n	2.36	1.07	1.29	Euthyroid	N	n	n	discharged
6	51	m	n	n	n	y	0.12	1.38	2.08	Sick Euthyroid	Y	n	y	discharged
7	42	m	n	y	n	y	2.4	1.35	0.31	Euthyroid	N	n	n	discharged
8	59	m	n	n	n	n	2.32	0.94	4.57	Euthyroid	N	n	n	discharged
9	35	m	n	n	y	y	2.2	1.11	2.06	Euthyroid	N	N	n	discharged
10	56	m	n	n	y	y	1.54	0.73	1.65	Euthyroid	Y	y	n	Death
11	65	m	n	n	n	y	2.42	1.19	1.04	Euthyroid	N	n	n	discharged
12	55	f	y	y	n	n	2.27	1.05	0.45	Euthyroid	N	n	n	discharged
13	40	m	n	n	n	y	2.22	1.3	0.58	Euthyroid	N	n	n	discharged
14	56	m	n	n	y	y	2.32	0.99	1.8	Euthyroid	N	n	n	discharged
15	50	m	n	n	y	y	2.34	1.22	3.08	Euthyroid	N	n	n	discharged
16	56	m	n	n	y	n	2.34	1.41	0.63	Euthyroid	N	n	n	discharged

17	50	m	n	n	n	y	0.49	1.14	1.98	Sick Euthyroid	N	n	n	discharged
18	60	f	n	n	n	n	2.3	1.03	3.25	Euthyroid	N	n	n	discharged
19	53	m	n	n	y	y	1.1	1.04	0.84	Sick Euthyroid	N	n	n	discharged
20	58	m	y	y	y	y	2.4	1.23	2.45	Euthyroid	N	n	n	discharged
21	60	m	n	n	y	y	0.12	1.66	4.56	Sick Euthyroid	N	n	n	discharged
22	61	f	y	y	n	n	0.25	1.21	4.12	Sick Euthyroid	N	n	n	discharged
23	62	m	n	n	y	y	2.5	1.43	4.6	Euthyroid	N	n	n	discharged
24	54	m	n	n	y	y	2.16	1.45	3.12	Euthyroid	Y	y	n	discharged
25	55	m	n	n	y	y	0.2	1.54	4.19	Sick Euthyroid	N	n	n	discharged
26	59	f	y	y	n	n	2.34	1.33	8.24	hypothyroid	N	n	n	discharged
27	52	m	n	n	y	y	2.88	1.31	7.8	hypothyroid	N	n	n	discharged
28	49	m	n	n	y	y	2.19	1.74	3.64	Euthyroid	N	n	n	discharged
29	47	m	n	n	y	y	2.08	1.55	2.55	Euthyroid	Y	y	n	Death
30	48	m	y	y	n	n	2.55	1.29	4.26	Euthyroid	N	n	n	discharged
31	63	f	n	n	y	n	2.36	1.22	3.89	Euthyroid	N	n	n	discharged
32	62	f	n	n	y	n	0.9	1.6	2.15	Sick Euthyroid	N	n	n	discharged
33	50	m	y	y	n	y	2.45	1.39	3.48	Euthyroid	N	n	n	discharged
34	51	m	y	y	n	y	2	0.92	1.24	Euthyroid	Y	y	y	discharged
35	60	f	n	n	y	n	2.31	1.28	4.36	Euthyroid	Y	y	n	discharged
36	54	m	n	n	y	y	2.56	1.21	10.26	hypothyroid	N	n	n	discharged

37	52	m	n	y	n	y	0.65	1.33	4.25	Sick Euthyroid	N	n	n	discharged
38	58	f	n	n	n	n	0.58	1.42	3.64	Sick Euthyroid	N	n	n	discharged
39	55	f	n	n	y	n	2.1	1.12	1.69	Euthyroid	N	N	n	discharged
40	60	f	n	n	n	n	0.92	1.78	4.56	Sick Euthyroid	N	n	n	discharged
41	60	m	y	y	n	y	0.9	1.2	4.7	Sick Euthyroid	N	n	n	discharged
42	61	f	n	n	n	n	2.36	1.11	12.54	hypothyroid	Y	n	y	Death
43	56	m	n	y	y	y	2.48	1.26	3.45	Euthyroid	Y	Y	n	discharged
44	64	f	n	n	n	n	2.47	1.13	4.79	Euthyroid	N	n	n	discharged
45	65	f	y	y	y	n	1.98	1.24	2.33	Euthyroid	N	n	n	discharged
46	59	f	n	n	n	n	0.69	1.12	2.45	Sick Euthyroid	N	n	n	discharged
47	55	m	n	n	n	y	3.78	1.22	9.2	hypothyroid	N	n	n	discharged
48	48	m	n	n	y	y	0.55	1.55	4.19	Sick Euthyroid	N	n	n	discharged
49	60	f	n	y	n	n	2.1	1.05	2.4	Euthyroid	Y	y	y	Death
50	62	f	y	y	n	n	2.51	1.36	3.48	Euthyroid	N	n	n	discharged
51	53	m	n	n	y	y	0.12	1.48	3.78	Sick Euthyroid	N	n	n	discharged
52	49	m	n	n	y	y	2.11	1.45	4.09	Euthyroid	Y	y	n	discharged
53	54	m	n	n	y	y	0.15	1.22	3.15	Sick Euthyroid	N	n	n	discharged
54	55	f	n	y	n	n	0.18	1.14	3.79	Sick Euthyroid	N	n	n	discharged
55	58	f	n	n	n	n	0.8	0.9	2.14	Sick Euthyroid	N	n	n	discharged
56	50	m	n	n	y	y	2.19	1.88	3.68	Euthyroid	Y	n	n	Death

57	52	m	n	n	n	y	0.89	1.34	4.12	Sick Euthyroid	N	n	n	discharged
58	38	m	n	y	y	y	0.47	1.26	3.64	Sick Euthyroid	N	n	n	discharged
59	49	m	n	n	n	y	0.1	1.44	2.78	Sick Euthyroid	Y	y	n	discharged
60	55	m	n	n	n	y	0.9	1.08	4.19	Sick Euthyroid	N	n	n	discharged
61	53	m	n	n	y	n	0.18	1.78	3.47	Sick Euthyroid	N	n	n	discharged
62	62	f	y	y	y	n	2.06	1.33	2.5	Euthyroid	y	y	y	Death
63	50	m	n	n	y	y	0.77	1.07	3.25	Sick Euthyroid	N	n	n	discharged
64	52	m	n	n	y	y	2.19	0.66	13.13	hypothyroid	N	n	y	discharged
65	60	f	y	y	n	n	2.36	1.14	0.91	Euthyroid	N	n	n	discharged
66	60	f	n	n	y	n	2.32	1.29	11.44	hypothyroid	N	n	n	discharged
67	65	m	n	n	y	y	2.32	0.99	6.1	hypothyroid	N	n	n	discharged
68	62	f	n	y	y	n	2.24	1.16	7.38	hypothyroid	N	n	n	discharged
69	46	m	n	n	n	y	2.05	1.16	1.28	Euthyroid	Y	N	y	discharged
70	42	m	y	y	y	y	2.04	1.1	0.32	Euthyroid	Y	y	n	Death
71	52	m	n	n	y	y	2.48	1.09	3.47	Euthyroid	N	n	n	discharged
72	60	m	n	n	n	y	2.17	1.26	3.22	Euthyroid	Y	y	y	discharged
73	59	m	y	y	y	y	0.19	0.89	2.69	Sick Euthyroid	N	n	n	discharged
74	63	f	n	n	n	n	0.66	1.23	2.47	Sick Euthyroid	N	n	n	discharged
75	59	f	n	n	n	n	2.45	1.1	10.36	hypothyroid	Y	y	n	discharged