Dedicated to all my Teachers and my Parents

DR. SRINKANT GADWALKAR & DR SHOBHA GADWALKAR

"HbA1c AS A PROGNOSTIC INDICATOR IN PREDIABETICS WITH ACUTE CORONARY SYNDROME"

By

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Dissertation submitted to

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

MD

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Under the guidance of

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ABSTRACT

BACKGROUND: The role of HbA1C in predicting the outcomes of acute coronary syndrome remains controversial. Lesseris known about it in non diabetic patients. Therefore we conducted a study to seek association between the HbA1C levels and the clinical outcome in non diabetic patients who presented with acute coronary syndrome.

OBJECTIVE:

1. To estimate HbA1C levels in population of prediabetics and non diabetics.
2. To document and correlate major adverse cardiac events in prediabetic and non diabetics.

MATERIALS AND METHODS: This is a case-control study of 68patients without diabetes and who were admitted to RL Jalappa hospital and Narayana Hrudalaya, Tamaka, Kolar with symptoms suggestive of acute coronary syndrome. The diagnosis of ACS was made on the basis of ECG, troponin I. The participants were stratified as per their HbA1C values into two groups. Study group consisting of prediabetics and the control group with a group of non diabetics.Main outcome measures were left ventricular ejection fraction on echo, lipid abnormalities along with complications like arrhythmia, cardiogenic shock and heartfailure.

RESULTS: The mean age of patients in years was 51-60. Out 61.8% were males and females were 38.2%. Of the total, 52.9% were smokers, 64.7% were known to

be hypertensive, 5.9% had family history of Coronary artery disease. The findings of this study found that increased levels of HbA1C was associated with poor outcomes.

CONCLUSION: HbA1C is a predictor of major adverse cardiac events. Measurement of HbA1C levels may improve risk assessment in such patients presenting with ACS.

LIST OF ABBREVIATIONS

AMI	**ACUTE MYOCARDIAL INFARCTION**
ACS	**ACUTE CORONARY SYNDROME**
IHD	**ISCHAEMIC HEART DISEASE**
HbA1C	**GLYCOSYLATED HAEMOGLOBIN**
IGT	**IMPAIRED GLUCOSE TOLERANCE**
ROS	**REACTIVE OXYGEN SPECIES**
eNOS	**ENDOTHELIAL NITRIC OXIDE SYNTHASE**
IL-6	**INTERLEUKIN-6**
IL-18	**INTERLEUKIN-18**
TNF	**TUMOUR NECROSIS FACTOR**
LDL	**LOW-DENSITY LIPOPROTEIN**
HDL	**HIGH DENSITY LIPOPROTEIN**
UA	**UNSTABLE ANGINA**
NSTEMI	**NON ST SEGMENT ELEVATION MYOCAR-DIAL INFACRTION**
STEMI	**ST SEGMENT ELEVATION MYOCARDIAL INFARCTION**
ECG	**ELECTROCARDIOGRAM**
CAD	**CORONARY ARTERY DISEASE**

CK-MB	**CREATINE KINASE-MUSCLE/BRAIN**
TIMI	**THROMBOLYSIS IN MYOCARDIAL ISCHEMIA TRIAL**
UFH	**UNFRACTIONATED HEPARIN**
LMWH	**LOW MOLECULAR WEIGHT HEPARIN**
LBBB	**LEFT BUNDLE BRANCH BLOCK**
RBBB	**RIGHT BUNDLE BRANCH BLOCK**
LDH	**LACTATE DEHYDROGENASE**
MACE	**MAJOR ADVERSE CARDIOVASCULAR EVENTS**
PCI	**PRIMARY PERCUTANEOUS CORONARY IN-TERVENTION**
RBS	**RANDOM BLOOD SUGAR**
cTn	**CARDIAC TROPONINS**
hsTroponin	**HIGH SENSITIVE TROPONIN**
cTnT	**CARDIAC-SPECIFIC TROPONIN T**
cTnI	**CARDIAC SPECIFIC TROPONIN I**
BNP	**BRAIN NATRURETIC PEPTIDE**
DAPT	**DUAL ANTIPLATELET THERAPY**
CRP	**C REACTIVE PROTEIN**
RV	**RIGHT VENTRICLE**
LV	**LEFT VENTRICLE**

JVP	**JUGULAR VENOUS PRSSURE**
ADA	**AMERICAN DIABETES ASSOCIATION**

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INTRODUCTION

Cardiovascular disease has been considered as the important cause of death in industrialized nations.

Acute coronary syndrome (ACS) is encompasses a continuum ranging from unstable angina, STEMI and NSTEMI.

The important risk factors for ACS are hypertension, dyslipidemia, type 2 Diabetes Mellitus (DM), insulin resistance, obesity and cigarette smoking.

Unlike other cardiovascular risk factors, obesity and type 2 diabetes are showing a significantly peaking pattern. Uncontrolled diabetes has high incidence of ACS and poor prognosis. Higher blood sugar value during admission for ACS carries grave prognosis not only in diabetics, but also in non diabetes patients.

Coronary vascular disease which is being considered as the significant complication of DM, presents two to four folds greater risk of mortality compared to the non-diabetic population.[1] Patient with diabetes have coronary artery disease much earlier and show comparatively more widespread atherosclerosis.[2]

Poor glycemic control have high incidence of ACS which inturn have poor outcome. Also it is seen that hyperglycemia without previous history of DM are not uncommon in patients presenting with ACS.[3] Inadequate glycemic control or management is shown by elevated HblAC, and its elevated value during admission for ACS, increases the mortality in first month. Increase in the blood sugars at the time of ACS without the history of DM has increased short term mortality.[4]

Diabetes is a large scale risk factor for the development of ACS & the adverse outcome after ACS. 'Stress hyperglycemia'has been defined in different ways by various studies .Transient hyperglycemia is a noticeable feature in ACS and is thought to be related to stress. (Lakhdar *et al.*, 1984).[5] Sometimes, hyperglycemia can denote pre-existing type 2 diabetes or impaired glucose tolerance which has not been detected before.

In point of fact that elevated blood sugar can be an indicator of already prevailing insulin resistance & defective function of beta cell which can result in poor prognosis. Recently hyperglycemia has been related to increased mortality in diabetics as well as in non diabetic and to an increased incidence of cardiogenic shock(Oswald *et al.*, 1984).[(6)]

Moreover, the stress induced secretion of catecholamine leads to partial inhibition of pancreatic β-cell release of insulin with increase cortisol and glucagon levels, leading to impaired glucose tolerance and elevated glucose levels.[7,8]

There is a rise in inflammatory markers in subjects with impaired glucose tolerance or overt diabetes which is heralded by an acute hyperglycemic event.

Following this school of thought, it might be speculated that the detrimental effect of stress hyperglycaemia in acute MI might also stem from its ability to increase inflammation.

OBJECTIVES :

1. To estimate HbA1C levels in population of prediabetics and non diabetics.

2. To document and correlate major adverse cardiac events in prediabetic and non diabetics.

REVIEW OF LITERATURE

HISTORY:

Claude Bernard observed and explained acute hyperglycemic and intermediate hyperglycemia/prediabetes response to stress more than a century ago.[9]

MECHANISMS OF HYPERGLYCEMIA IN ACUTE MYOCARDIAL INFARCTION

A. Stress Hyperglycemia: [10,11]

Stress plays an important role in the regulation of insulin secretion. Acute insulin response is inhibited by catecholamines by stimulating alpha adrenergic receptors.

Epinephrine blocks secretion of insulin which inturn stimulates the release of glucagons and there occurs breakdown of glycogen which disturbs the action of insulin in target tissues such that the capacity to dispose off an exogenous glucose load is impaired.

The mechanisms that operate during stress are :

The adrenal medulla along with components of sympathetic system help to actuate fatty acids, glucose and lactic acid.

The means by which the glucose increases is:

1. In the liver there is increased glycogenolysis
2. Glucose uptake in the muscle is inhibited
3. Epinephrine inhibiting release of insulin from the pancreas to lessen any sort of rise in the serum insulin.

The second principal endocrine mechanism of maintaining or increasing blood sugars is through dynamizing pituitary adrenocortical axis, clinical studies are not clear in delineating how much or what type of stress gives this corticoid response.[12]

During acute myocardial infarction, hyperglycemia is linked with increased levels of inflammatory markers and enhanced expression of cytotoxic T – cells. This leads to poor outcome in patients with acute myocardial infarction. So, stress hyperglycemia amplifies inflammatory immune reaction and worsens functional cardiac outcome.[13,14]

B. Relative insulin deficiency: [15,16]

The effect counter regulatory hormones such as adrenaline, cortisol,glucagon and growth factors on the pancreas and peripheral cells is thought to cause relative insulin deficiency. They create a state of insulin resistance by decreasing insulin secretion.

C. Impaired glucose tolerance:[17]

IGT not only important in developing overt diabetes and its associated complications, but also have an expanded risk of cardiovascular morbidity and mortality compared with patients with normal glucose tolerance.

D. Undiagnosed diabetes mellitus: [17]

This forms a considerable subset of patients whose diabetic status is detected for the first time after an acute myocardial infarction insult. The true prevalence of diabetes mellitus among people with myocardial infarction might be as high as 45%, since diabetes is present in about 20% of individuals in an unselected population subclinically.

There is an independent association between diagnosed and undiagnosed diabetes and increased mortality. In undiagnosed diabetic population, long term mortality was observed.

Consequently it is of paramount importance to screen for diabetes in all patients admitted with chest pain as a common symptom.

PREDIABETES AND THE HEART

Prediabetes is the precursor stage before diabetes mellitus in which not all of the symptoms required to diagnose diabetes are present, but blood sugar is abnormally high. This phase is often referred to as the "grey area".[18]

Cardiovascular disease accounts for 70 – 75% of deaths in diabetic and prediabetic people, with acute myocardial infarction being responsible for 30%.[19] They are at heightened risk of atherosclerosis associated disease, the contributions of the various cardiovascular risk factors are several abnormalities such as hyperglycemia, insulin resistance, dyslipidemia, hypertension, procoagulant changes and endothelial dysfunction – all appear to play important roles.

EFFECTS OF HYPERGLYCEMIA IN ACUTE MYOCARDIAL INFARCTION

Hyperglycemia is seen as an epiphenomenon that is associated with poor outcomes in acute MI.

The mechanisms underlying the detrimental association between dysglycemia and acute MI are not fully understood, but multiple hypotheses have been proposed.

1. **Endothelial dysfunction** [20]

Vascular endothelial cells plays a vital role in overall homeostasis. The vascular endothelium in health maintains the vasculature in antioxidant, antithrombotic and anti-adhesive state.

During illness, there is endothelial dysfunction which is linked to increased cellular adhesion, disturbed angiogenesis, increased cell permeability, inflammation and thrombosis.

The formation of atheroma is thought to be contributed by increased adhesiveness of the endothelium and enhanced haemostasis.Vasomotor dysfunction of the endothelium is another abnormality that preceeds development of overt atheromatous disease.

In a setting of acute hyperglycemia there is increased production of reactive oxygen species (ROS) and the multiple toxicities of adrenergic response result in abundance of ROS. These interrupt the endothelial nitric oxide reaction resulting in decreased nitric oxide. The uncoupling of eNOS reaction allows the reaction to proceed with endothelium becoming a net producer of superoxide. Hence this reflects a wider damage of endothelium and a more powerful predictor of atherosclerosis and MI.

2. **Reduced collateral coronary** [20,21]

   Due to eNOS dysfunction there is decrease in arteriolar dilatation which obscures the normal increased flow and shear stress responsive element in the collateral vessel which is undergoing remodeling collaterization, as well as decrease endothelial cell permeability blood flow.

3. **Increased thrombus formation** [22,23]

The surge in platelet adhesion and aggregation causes platelet dependent thrombin generation while decreasing vasodilatation mediated by platelets.

Coagulation factors including von willebrand factor, factor VII, factor VIII and fibrinogen are significantly enhanced in a setting of hyperglycemia. Furthermore, the concentrations of plasminogen activator inhibitor I is increased in hyperinsulinemia, insulin resistant states and may account for the decrease in fibrinolysis.

4. Amplification of inflammatory immune reaction [22,23,24]

The activated macrophages release several inflammatory markers like cytokines and growth factors are linked with cardiovascular events. The levels of IL6, IL-18,TNF and induction of

Proinflammatory transcriptional factor is elevated in the existence of increased blood sugars.

Increase in these markers is directly proportional to detrimental vascular defects.

An increased inflammatory immune process seems a likely mechanism linking acute hyperglycemia to poor cardiac outcome in MI patients probable pathologic process.

The effects caused by acute hyperglycemia like endothelial dysfunction, activation of coagulation and inflammation can be hindered by antioxidants,this suggests that free radicals mediate the action of hyperglycemia.

It has been witnessed that during glucose oral challenge, there is a diminution in the antioxidant defences [25] and relatively increase in markers of oxidative stress as observed. This gives a evidence of direct effect of acute hyperglycemia on oxidative stress markers. Hyperglycemia producing oxidative stress by itself can thus worsen outcome in AMI. [26]

ISCHEMIC HEART DISEASE

INTRODUCTION:

Ischemic heart disease is a condition where there is unequal supply of blood and oxygen to a portion of myocardium; it occurs when there is an imbalance between myocardial oxygen supply and demand.The common cause of myocardial ischemia is atherosclerotic disease of an epicardial coronary artery.

Ischemic heart disease (IHD) causes more deaths and disability and incurs greater economic costs than any other illness in the developed world.[27]

With urbanization in the developing world, the prevalence of risk factors for IHD is increasing rapidly in these regions. Large increases in IHD throughout the world are projected, and IHD may be possible cause of death by 2020.[28]

PATHOPHYSIOLOGY:

In normal conditions, for any given level of demand of oxygen, the myocardium will control the supply of oxygen-rich blood to prevent under perfusion of myocytes and subsequent development of ischemia and infarction.

The normal coronary circulation is controlled by requirement of oxygen by the heart. This pursuit is met by the coronary vascular bed which augments its resistance considerably and thereby altering the blood flow, while the myocardium extracts a high and relatively fixed percentage of oxygen.

Normally, intramyocardial resistance vessels demonstrate an immense capacity for dilation. For example, the changing oxygen needs of the heart with exercise and emotional stress affect coronary vascular resistance and in this way the balance of oxygen supply and substrate to the myocardium (metabolic regulation). The resistance vessels also adapt to physiologic alterations in blood pres-

sure in order to maintain coronary blood flow at levels appropriate to myocardial needs (autoregulation).

The large epicardial arteries are referred to as conductance vessels(ability to constriction and relaxation) since they serve as conduits, in health. While the intramyocardial arterioles are reffered to as resistance vessels as they exhibit changes in tone.

Abnormal constriction of these conductance vessels can cause severe ischemia known as Prinzmetal's angina.

Failure of normal dilatation or constriction of coronary resistance vessel can also cause ischemia. When it causes angina, it is referred to as microvascular angina.

By reducing the lumen of the coronary arteries, atherosclerosis limits appropriate increases in perfusion when the demand for flow is augmented, as occurs during exertion or excitement. When the luminal reduction is severe, myocardial perfusion in the basal state is reduced. Coronary blood flow can be limited by arterial thrombi, spasm and rarely coronary emboli as well as by ostial narrowing due to luetic aortitis[29].

Myocardial ischemia can occur if:

1. Myocardial oxygen demands are markedly increased, while the coronary blood flow may be limited by severe left ventricular hypertrophy due to aortic stenosis. The latter can present with angina that is indistinguishable from that caused by coronary atherosclerosis.
2. Minimization in the oxygen-carrying capacity of the blood in patients with moderate coronary obstruction may lower the threshold for ischemia.
3. Increase in oxygen demand due to left ventricular hypertrophy secondary to hypertension and a reduction in oxygen supply secondary to coronary atherosclerosis and anemia.

TABLE 1: RISK FACTORS ASSOCIATED WITH THE DEVELOPMENT OF CAD[30]

Non- Modifiable	Modifiable	New risk factors
• Age • Presence of coronary heart disease • Male gender • Family history of CHD • Menopause • Physical inactivity	• Hypertension • Dyslipidemia • Diabetes • Smoking • Diet	Atherogenic risk factors: • Lipoprotein(a) • Elevated Homocysteine level, Plasma fibrinogen, Tissue plasminogen activator, C-Reactive protein.

CORONARY ATHEROSCLEROSIS

Epicardial coronary arteries are the major site of atherosclerotic disease. The major risk factors for atherosclerosis are [high plasma low-density lipoprotein (LDL), low plasma high-density lipoprotein (HDL), cigarette smoking, hypertension, and diabetes mellitus] that disturb the normal functions of the vascular endothelium

The loss of normal mechanism leads to inadequate constriction, clot formation, and abnormal interactions with blood monocytes and platelets which results in the subintimal

collections of fat, smooth-muscle cells, fibroblasts, and intercellular matrix (i.e., atherosclerotic plaques), which develop at irregular rates in different segments of the epicardial coronary tree and lead eventually to segmental reductions in cross-sectional area.

When a stenosis reduces the cross-sectional area by ~75%, a full range of increase in flow to meet increased myocardial demand is not possible. When the luminal area is reduced by 80%, blood flow at rest may be reduced, and further minor decrease in the stenotic orifice can reduce coronary flow dramatically and cause myocardial ischemia.[31]

The clinical manifestations are brought about by segmental atherosclerotic narrowing which is mostly due to formation of plaque.

When there is rebatement in the cross-section area of proximal epicardial artery by 70%, the resistance vessels that are located distally dilate and build up a pressure gradient across the stenosis, proximally and the post-stenotic pressure falls. The myocardial blood flow becomes dependent on the pressure in coronary artery distal to obstruction when the resistance vessel are dilated maximally.

EFFECTS OF ISCHEMIA

During episodes of inadequate perfusion caused by coronary atherosclerosis, myocardial tissue oxygen tension falls and may cause transient disturbances of mechanical, biochemical and electrical functions of the myocardium.

Coronary atherosclerosis is a focal process that usually causes non uniform ischemia.During ischemia , regional disturbances of ventricular contractility cause segmental hypokinesia, regional disturbances of ventricular contractility cause segmental hypokinesia, akinesia or in severe cases dyskinesia which can reduce myocardial pump function.

With severe oxygen deprivation, fatty acids cannot be oxidized and glucose is converted to lactate, intracellular pH is reduced. Impaired cell memebrane function leads to leakage of potassium and uptake of sodium by myocytes as well as increase in cytosolic calcium.

The extent of the imbalance between myocardial oxygen supply and demand determines whether the damage is reversible (<20min for total occlusion in absence of collaterals) or permanent, with subsequent myocardial necrosis(>20min).

The spectrum of myocardial dysfunction ranges from rapid and full recovery function of myocyte to prolonged contractile dysfunction without necrosis of the myocyte with potential recovery of normal fuctionand ultimately irreversible myocardial necrosis(i.e. myocardial infarction)

FIGURE 1: SHOWING ENTRY OF MONOCYTES AND MACROPHAGES, SMOOTH MUSCLE PROLIFERATION AND FOAM CELL FORMATION WHICH ARE IMPORTANT STEPS IN THE PROCESS OF ATHEROSCLEROSIS.

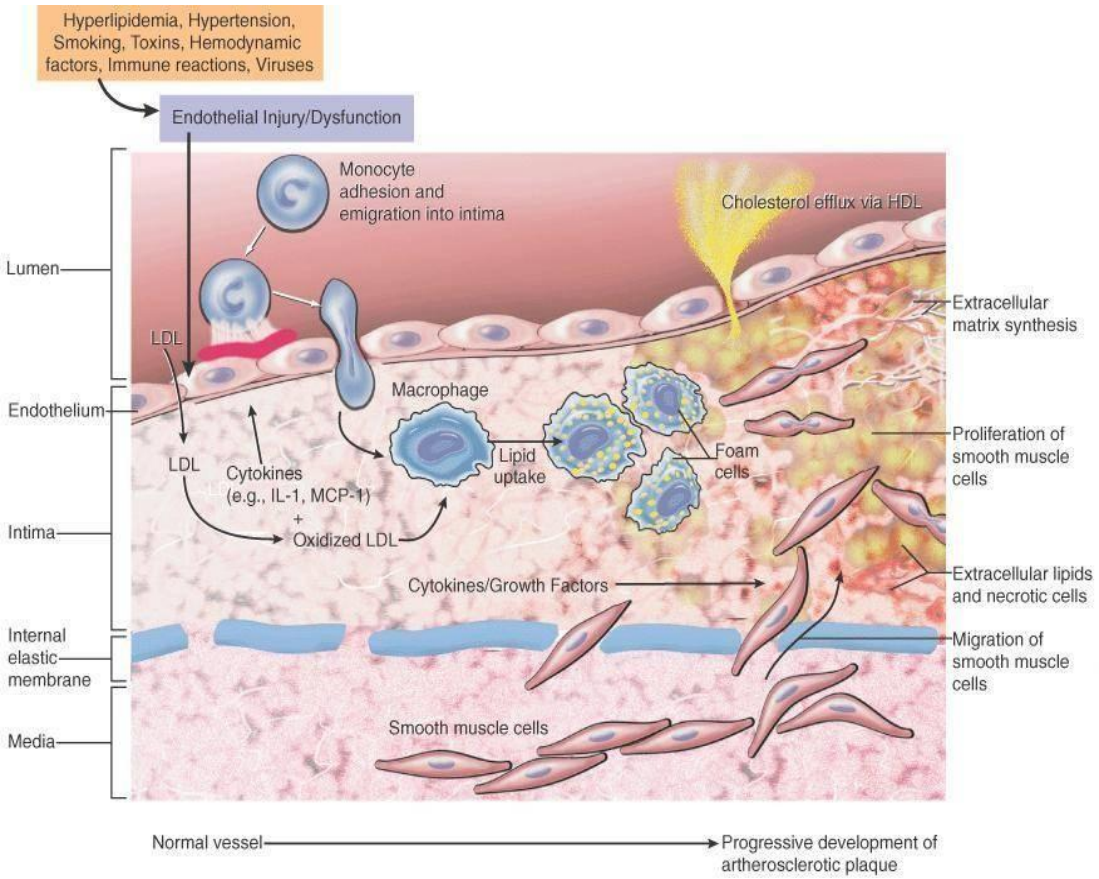
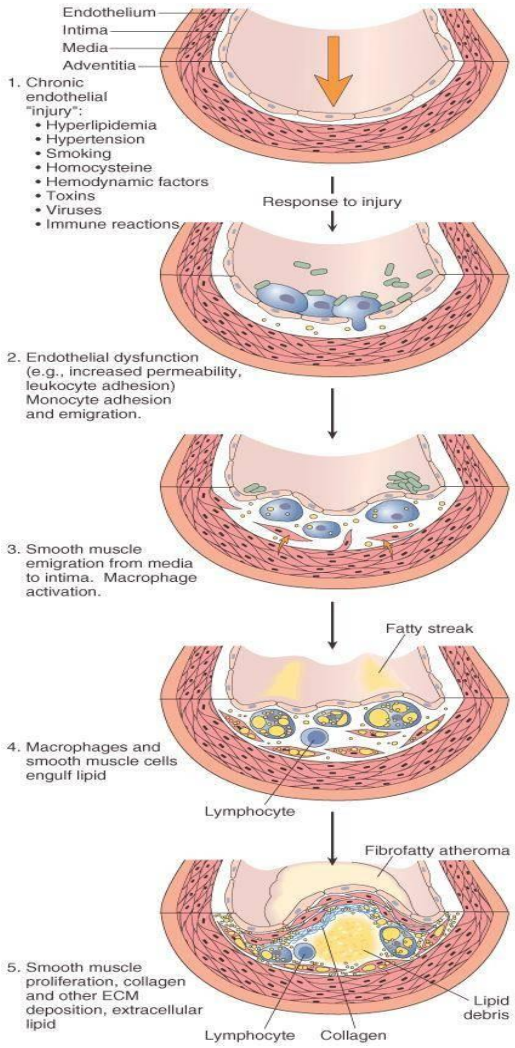


FIGURE 2: SCHEMATIC DIAGRAM SHOWING FORMATION OF A PLAQUE



Evolution of arterial wall changes in the response to injury hypothesis.

1, Normal.

2, Endothelial injury with adhesion of monocytes and platelets (the latter to denuded endothelium).

3, Migration of monocytes (from the lumen) and smooth muscle cells (from the media) into the intima.

4, Smooth muscle cell proliferation in the intima.

5, Well-developed plaque

SPECTRUM OF ACUTE CORONARY SYNDROME

Ischemic heart disease may be manifested clinically as either chronic stable angina or an acute coronary syndrome (ACS). The latter, in turn, can be subdivided into ST-segment elevation myocardial infarction (STEMI), non–ST-segment elevation myocardial infarction (NSTEMI), or unstable angina .

Since NSTEMI and UA are indistinguishable at initial evaluation and the entity of UA is receding as the sensitivity of biomarkers of myocardial injury increases, they are often described together as NSTE-ACS and are discussed together .

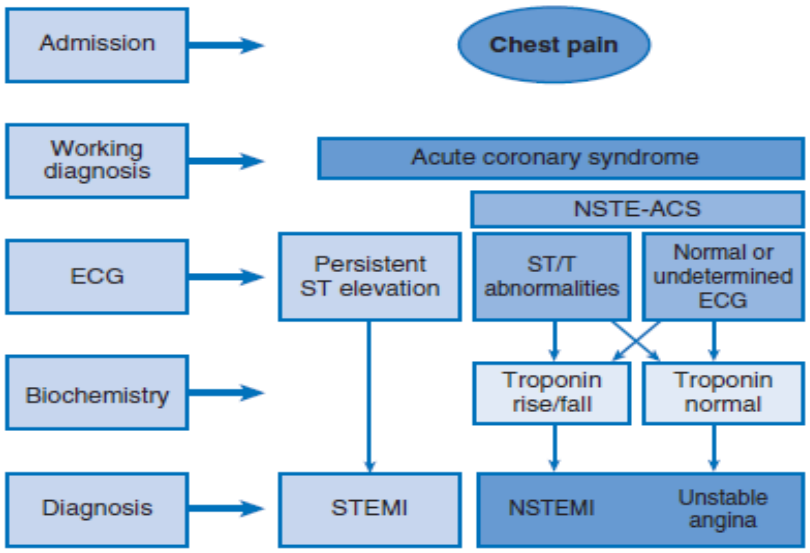


FIGURE 3: SPECTRUM OF ACUTE CORONARY SYNDROME

Features that help differentiate ACS from stable angina are: [32]

(1) Onset of symptoms at rest (or with minimal exertion) and lasting longer than 10 minutes unless treated promptly

(2) Severe, oppressive pressure or chest discomfort

(3) an accelerating pattern of symptoms that develop more frequently, occur with greater severity, or awaken the patient from sleep.

Symptoms alone do not suffice to distinguish the three types of ACS from one another. Patients without persistent (>20 minutes) ST-segment elevation in two or more contiguous leads but with biomarker evidence of myocardial necrosis are classified as having NSTEMI, whereas in patients without such evidence of myocardial necrosis, UA is diagnosed—a condition generally carrying a better prognosis

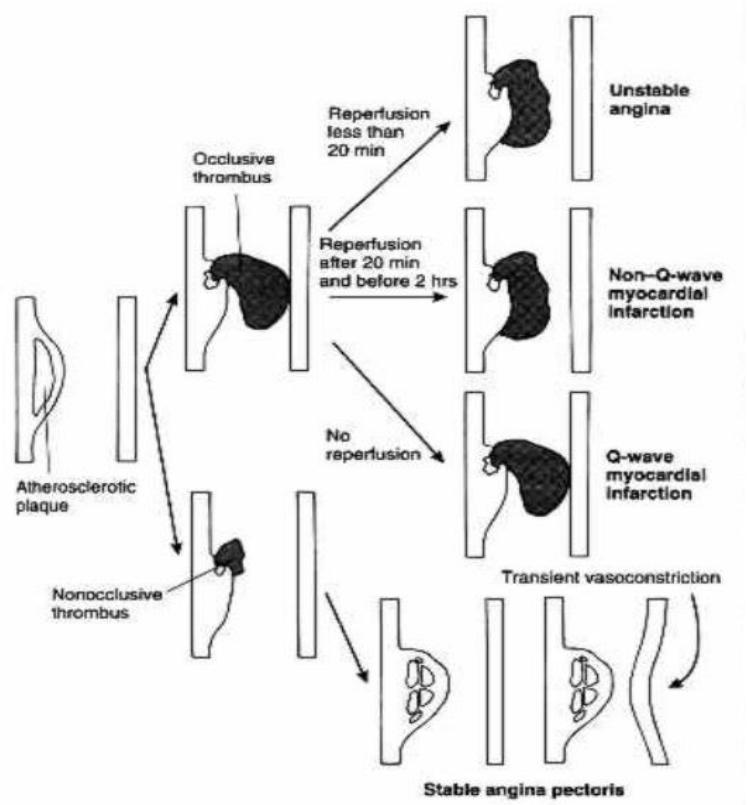


FIGURE 4: CLASSIFICATION OF ACUTE CORONARY SYNDROME

Small surface disruptions lead to non occlusive thrombi, which cause atherosclerotic lesion to increase in size slowly and ultimately limit blood flow in the existence of increased metabolic demand. In addition, flow may be limited by some component of vasospasm. In the other clinical syndromes, a larger intimal surface disruption leads to an occlusive thrombus that causes chest pain at rest. If the thrombus resolves quickly the symptoms resolve after a few minutes and the patientis classified as having unstable angina.

If the thrombus is more persistent but still resolves within several hours, the patient will present with a non Q wave MI.

If the occlusive thrombus is permanent, the patient will develop a Q wave MI.[33]

UNSTABLE ANGINA AND NON ST-ELEVATION MYOCARDIAL INFARCTION

Unstable angina is usually secondary to reduced myocardial perfusion resulting from coronary artery atherothrombosis. In this event, however, the non occlusive thrombus that developed on the disrupted atherosclerotic plaque does not result in any biochemical evidence of myocardial necrosis.[33]

PATHOPHYSIOLOGY: [33]

The pathogenesis of NSTE-ACS involves four processes:

(1) Rupture of unstable atheromatous plaque- Plaque prone to rupture tend to have thin fibrous cap and large lipid pool, which influences the nature of the plaque and accelerates the likelihood of rupture. Conversely, fibrous cap thickening appear to decrease the risk of rupture.

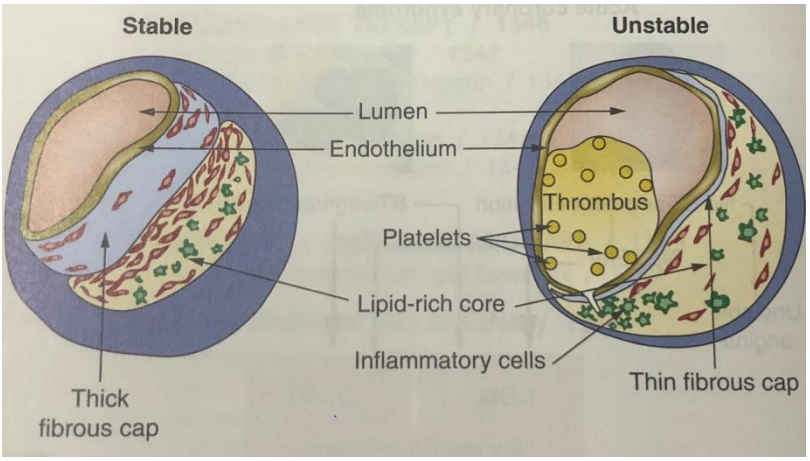


FIGURE 5: STABLE AND UNSTABLE PLAQUE.

(2) Coronary arterial vasoconstriction.

(3) Imbalance between the supply and demand of the myocardium for oxygen.

(4) Gradual intraluminal narrowing of an epicardial coronary artery because of progressive athero-sclerosis or poststent restenosis.

These processes can occur simultaneously in any combination.

CLINICAL PRESENTATION

DIAGNOSIS: The diagnosis of NSTE-ACS is based on clinical presentation.

Typically the chest discomfort is severe and has atleast one of three features:

1.Occurs at rest or with minimal exertion lasting > 10minutes.

2. Recent onset chest discomfort.

3. Occurs with a crescendo pattern.

History and physical examination:

The chest discomfort is often severe described as frank pain, typically located substernally or in the epigastrium and radiates to ulnar aspect of proximalpart of left arm, either shoulder,the neck or the jaw.

Symptoms such as diaphoresis, nausea, abdominal pain, dyspnea, and syncope may accompany the pain. Features that support the diagnosis include exacerbation of symptoms by physical exertion; precipitation by severe anemia, infection, inflammation, fever, or metabolic or endocrinologic (e.g., thyroid) disorders; and importantly, relief with rest or nitroglycerin.

Atypical manifestations, such as dyspnea without chest discomfort, pain limited to the epigastrium, or indigestion, represent “anginal equivalents.” These atypical findings are more prevalent in women, older adults, and patients with diabetes, CKD, or dementia and can lead to underrecognition, undertreatment, and worse outcomes.

ELECTROCARDIOGRAM[34]

The most common abnormalities on the 12-lead electrocardiogram (ECG) are ST-segment depression and T wave inversion; they are more likely to be present while the patient is symptomatic.

Comparison with a recent ECG is important because dynamic ST-segment depressions as little as 0.05 mV are a sensitive marker for NSTE-ACS. Greater degrees of ST-segment depression predict poorer outcomes, however, even when adjusted for other prognostic factors.

Transient ST-segment elevation lasting less than 20 minutes occurs in up to 10% of patients and suggests either coronary vasospasm or an aborted infarction.

Deep (>0.2 mV) T wave inversions are compatible with, but not necessarily diagnostic of NSTE-ACS, whereas isolated T wave inversions of lesser magnitude are not particularly helpful given their low specificity.

In patients with definite NSTE-ACS, findings on the ECG may be normal or nondiagnostic in more than half of patients. Because ischemia may occur in a territory that is not well represented on the standard 12-lead ECG or because the patient may have episodic ischemia that may be missed on the initial ECG, tracings should be repeated every 20 to 30 minutes until the symptoms resolve, the diagnosis of MI is established or excluded, or an alternative diagnosis is made.

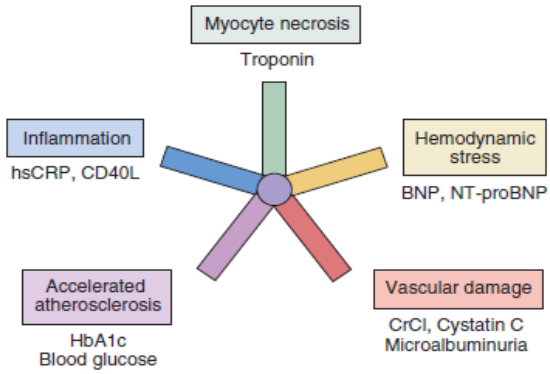
Because the standard 12-lead ECG does not represent this territory well, assessment of posterior leads V7 through V9 should be considered in patients with a history suggestive of ACS and a nondiagnostic initial ECG.

Similarly, ACS caused by isolated involvement of an acute marginal branch of the right coronary artery is often not apparent on the standard 12-lead ECG but may be suspected from leads V3R and V4R.

Therefore it is useful to obtain these extra leads in patients suspected of having ACS but with normal findings on a 12-lead ECG. Continuous monitoring of the ECG in the days following NSTE-ACS can identify patients at higher risk for recurrent events. ST-segment depressions noted on such monitoring within the first week after NSTE-ACS are associated with an increased risk for reinfarction and death.

CARDIAC BIOMARKERS [35]

Biomarkers reflecting the pathogenesis of NSTE-ACS aid in diagnosis and prognosis. They include markers of myocyte necrosis, hemodynamic perturbation, vascular damage, accelerated atherosclerosis, and inflammation.



Biomarker	Independent predictor of risk	Useful as a component in a multimarker strategy	Therapeutic implication
Troponin	+++	++	+++
BNP	+++	++	0
Renal dysfunction	++	+	+
Glucose metabolism*	+	0	+
CRP	++	++	++

FIGURE 6: BIOMARKERS AS AN INDEPENDENT PREDICTOR OF RISK

During the past decade, cardiac specific troponins (cTnI and cTnT) have become the biomarkers of choice to identify myocardial necrosis and hence distinguish NSTEMI from UA.

Several pathobiologic mechanisms can lead to the release of detectable levels of cTn in blood.

TABLE 2: MECHANISMS OF TROPONIN RELEASE [36]

TYPE	EXPLANATION/EXAMPLES
1. Myocyte necrosis	Ischemia, infarction, inflammation, infiltration, trauma, toxic/metabolic(eg.,sepsis)
2. Apoptosis	Programmed cell death because of activation of caspases
3. Normal myocyte turnover	Natural low grade annual turnover of myocyte
4. Cellular release of proteolytic troponin degradation products	Creation of small fragments that pass through the intact myocyte membrane without cell death
5. Increased cellular wall permeability	Reversible injury to myocyte membranes resulting in altered permeability(eg., secondary to stretch ,ischemia)
6. Formation and release of membranous blebs	Active secretion of vesicles or membrane expression with shedding (eg., secondary to hypoxia)

CAUSES OF TROPONIN RELEASE OTHER THAN ACS[37]

1. Pulmonary embolism
2. Myocarditis
3. Congestive heart failure
4. Septic shock

5. Stage IV and V Chronic kidney disease.
6. Chemotherapy(Adriamycin, 5-flurouracil)
7. Cardioversion or radiofrequency ablation

Since troponins are elevated in other conditions as mentioned above utmost care has to be taken in diagnosis of NSTE-ACS.

Patients with clinical findings suggestive of NSTE-ACS should have serial measurements of cTn beginning at initial evaluation.

Other biomarkers also increase in the days to weeks following NSTE-ACS. [38]

a. Natriuretic peptides (i.e., brain natriuretic peptide [BNP] and N-terminal pro-BNP) rise in proportion to the degree of ventricular distention and correlate with the risk for adverse events. In patients with NSTE-ACS, a baseline BNP measured on average 40 hours after the onset of symptoms correlated strongly with risk for death, heart failure, and MI through 10 months in a graded fashion. Baseline natriuretic peptide levels also help identify patients more likely to benefit from more aggressive treatments, including intensive anti-ischemic regimens, aggressive statin therapy and early coronary revascularization.

b. C-reactive protein (CRP) is a marker of inflammation that is elevated following ACS, and persistently elevated levels after discharge are linked with increased long-term cardiovascular risk. Elevated levels of fasting blood glucose and glycosylated hemoglobin indicate the presence of diabetes mellitus or metabolic syndrome and portend accelerated atherosclerosis and an increased risk for cardiovascular events in both the short and long term.

Several novel biomarkers can help improve prognostication in patients with NSTE-ACS. These biomarkers tend to fall into two general categories[39]

(1) Markers that predict death and/or ischemic events

(2) Markers that predict heart failure

TABLE 3: MARKERS THAT PREDICT DEATH/ISCHEMIC EVENTS AND HEART FAILURE

Marker name	Description
Markers That Predict Death and/or Ischemic Events	
Growth differentiation factor-15	Member of the transforming growth factor-beta cytokine superfamily that is released from cardiomyocytes after ischemia and reperfusion injury
Heart-type fatty acid–binding protein	Cytoplasmic protein involved in intracellular uptake and buffering of free fatty acids in the myocardium.
Interleukin-6	Stimulator of hepatic synthesis of C-reactive protein
Secretory phospholipase A2	Hydrolyzes phospholipids to generate lysophospholipids and fatty acids, thereby enhancing susceptibility of the vessel to atherogenesis
Markers That Predict Heart Failure	
Midregional proadrenomedullin	Peptide fragment of the vasodilatory peptide adrenomedullin

Neopterin	Marker of monocyte activation
Osteoprotegerin	Modulator of immune function and inflammation

RISK STRATIFICATION AND PROGNOSIS:[40]

Patients with documented UA/NSTEMI exhibit a wide spectrum of early (30 day) risk, ranging from ~2 to 10%, and of new or recurrent infarction of 3 to 10%.

A 7-point score in patients with acute coronary syndromes derived by summing the presence of these factors (1 point for each)

- Age > 65years
- More than 3 coronary arteries
- Prior coronary angiographic coronary obstruction
- ST segment deviation
- More than two angina episodes within 24 hours
- Use of aspirin within 7days
- Elevates levels of cardiac biomarkers (e.g., troponin)

TABLE 4: TIMI SCORE

TIMI Score	14-day adverse cardiac event rate
0/1	4.7
2	8.3
3	13.2
4	19.9
5	26.2
6/7	40.9

TREATMENT:

TABLE 5: CLASS OF DRUGS AND THEIR ROLES IN NSTE-ACS [41,42]

CLASS OF DRUG	**ROLE IN NSTE-ACS**
Beta blockers	Decreased mortality
Nitrates	No benefit on mortality
Calciumchannel blockers	No clear benefit on mortality or reinfarction
Nicorandil	Decreases arrhythmias and transient ischemia
Trimetazidine	Decreases short-term mortality
Ranolazine	Decreases recurrent ischemia
Cyclosporine	Reduces infarct size in small studies

Medical Treatment:

Patients with UA/NSTEMI should be placed at bed rest with continuous ECG monitoring for ST-segment deviation and cardiac rhythm. Ambulation is permitted if the patient shows no recurrence of ischemia (discomfort or ECG changes) and does not develop a biomarker of necrosis for 12 to 24 h. Medical therapy involves simultaneous anti-ischemic treatment and antithrombotic treatment.

Anti-IschemicTreatment: Nitrates ,ß-adrenergic blockers, calcium channel blockers, e.g., verapamil or diltiazem.

Antithrombotic Therapy:[41,42] Initial treatment should start with the platelet cyclooxygenase inhibitor aspirin. The thienopyridine clopidogrel, which blocks the platelet adenosine receptor (in combination with aspirin), was shown in the CURE trial to confer a 20% relative reduction in cardiovascular death, MI, or stroke compared with aspirin alone in both low- and high-risk patients [41,42]with UA/NSTEMI, but to be associated with a moderate (absolute 1%) increase in serious bleeding, which is more marked in patients who undergo coronary artery bypass grafting. Pretreatment with clopidogrel has also been shown to reduce adverse outcomes associated with and following PCI. Continued benefit of long-term (~1 year) treatment with the combination of clopidogrel and aspirin has been observed both in patients treated conservatively and in those who underwent a PCI. This combination is recommended for all patients with UA/NSTEMI who are not at excessive risk for bleeding.

TICAGRELOR: is a nonethienopyridine direct acting and reversible oral antagonist of P_2Y_{12} receptor. This agent does not require conversion to an active metabolite. It has more rapid onset of action and predictable antiplatelet response than clopidogrel. Ticagrelor achieves rapid antiplatelet activity after a loading dose, with therapeutic activity observed within 30minutes and near to full activity at 2 hours.

GLYCOPROTEIN IIb/IIa INHIBITORS

The role of GP IIb/IIa inhibitors in the contemporary treatment of patients with patients with ACS continues to undergo a reappraisal, and overall usage has decreased in recent years.

The Upstream GP IIb/IIIa treatment with placebo demonstrated a significant benefit for upstream tirofiban and eptifibate but not abciximab. This benefit was confined to high risk patients largely defined by troponin elevation in whom subsequent PCI was performed.

DIRECT THROMBIN INHIBITORS

Bivalirudin is a semisynthetic direct acting antithrombin that differs from hirudin by having a shorter half life, only providing transient reversible inhibition of the active site of thrombin and undergoing only modest renal clearance.

There are several studies which support bivalirudin as a safe alternative to UFH or enoxaparin during PCI.

ANTICOAGULATION THERAPY

Unfractionated heparin (UFH) or low molecular weight heparin (LMWH) should be added to aspirin and clopidogrel. Based on several randomized trials showing the superiority of the LMWH enoxaparin to UFH in reducing recurrent cardiac events

TABLE 6: A BRIEF SUMMARY ON ANTIPLATELETS AND ANTICOAGULANTS FOR NON ST-ELEVATION ACS

<table>
<tr><td colspan="2">Initial treatment</td></tr>
<tr><td colspan="2">DAPT and anticoagulant therapy</td></tr>
<tr><td colspan="2">1. Aspirin
2. P2Y12 inhibitor, clopidogrel or ticagrelor
3. Anticoagulant: Enoxaparin or fondaparinux or bivalirudin(for invasive statergy)

Can consider GP IIb/IIIa receptor inhibitors in high risk patients stratified to early invasive stratergy</td></tr>
<tr><td colspan="2">DURING HOSPITALISATION</td></tr>
<tr><td>Medically treated patients</td><td>PCI-treated patients</td></tr>
<tr><td>1. Aspirin
2. P2Y12 inhibitor, ticagrelor or clopidogrel
3. Anticoagulant: Enoxaparin or UFH or Fondaparinaux</td><td>1. Aspirin
2. P2Y12 inhibitor, clopidogrel ticagrelor or prasugrel.
3. Anticoagulants: Enoxaparin or fondaparinaux or bivalirudin
4. Can consider GBIIb/IIIa receptor inhibitors in high risk patients not on adequately pretreated clopidogrel or in high risk patients adequately pre-treated with clopidogrel.</td></tr>
</table>

LONG TERM TREATMENT	
Medically treated patients	PCI treated patients
1. Aspirin indefinetly	1. Aspirin indefinetly
2. P2Y12 inhibitor, clopidogrel or ticagrelor for upto 12 months	2. P2Y12 inhibitor clopidogrel or ticagrelor or prasugrel for atleast 12months.

ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

ST elevation myocardial infarction (STEMI) usually occurs when coronary blood flow decreases abruptly after a thrombotic occlusion of a coronary artery previously affected by atherosclerosis. Slowly developing, high-grade coronary artery stenosis does not typically precipitate STEMI because of the development of a rich collateral network over time

CLINICAL PRESENTATION:

The classic symptom of acute myocardial ischemia is precordial or retrosternal discomfort, commonly described as pressure , crushing, aching or burning sesnsation. Radiation of the discomfort to the neck, back or arms frequently occurs and the pain is usually persistent rather than fleeting.

The discomfort typically achieves maximum intensity over several minutes and can be associated with shortness of breath, nausea, diaphoresis, vomiting and acute confusion.

Symptoms in elderly (>75years) are more likely to be typical than in younger patients and can be missed. Hence sharp vigilance is very important.

Approximately 20% of AMI patients are asymptomatic or have atypical symptoms. Painless myocardial infarction occurs more frequently in the elderly, women, diabetics and postoperative patients. These patients tend to present with dyspnea as a frank symptom.

PHYSICAL EXAMINATION

Patients are often anxious and uncomfortable.Those with substantial left ventricular dysfunction may hace tachypnea, tachycardia, pulmonary rales, a third heart sound. The presence of systolic murmur suggests ischemic dysfunction of the mitral valve or ventricular septal rupture.

In patients with RV infarction, increased JVP, Kussumaul's sign and a RV third sound may be present. Such patients typically have inferior infarctions due to proximal right coronary artery occlusion, usually without evidence of left heart failure.

In patients with extensive LV dysfunction, shock is indicated by hypotension, diaphoresis , pallor, oliguria, cold extremities and altered mental status.

ELECTROCARDIOGRAM [43]

In presence of ischemic symptoms, diagnosis of MI or ECGS is based on the presence of anyone of the following:

1. Development of new pathological Q waves.
2. Presence of ST segment elevation or depression.
3. Development of new left bundle branch block.

The changes should be present in two contagious leads.

ECG CHANGES AND EVOLUTION OF ECG DURING STEMI [44,45,46]

MI results in myocardial necrosis, injury and ischemia, each of which is reflected by a different and distinctive electrocardiographic manifestation:

TABLE 7:EVOLUTION OF ECG CHANGES DURING STEMI

INFARCTION(NECROSIS)	INJURY	ISCHEMIA
New onset pathological Q waves(QS,Qr or qR complex-es)	Tall and broad based T waves	T wave inversion which are deep and symmetrical
Loss of R wave height	ST segment deviation	ST segment depression
Notch in the QRS complex	Tall R waves	Change in QRS-T axis
Conduction block	J point elevation, loss of S wave, increased ventricular activation time	Abnormality in U wave

The abnormal 'Q' waves appear 8 to 12 hours from the start of symptoms which reflect death of the tissue and there is evolution of a electrical dead zone which is the hallmark of AMI .This is called Q wave infarction. Some of the patients with AMI have ST segment depression or 'T' wave inversion . This type is called as non Q wave infarction.

The non Q wave infarction is diagnosed by a inadequacy in development of abnormal Q waves and by the appearance of reversible ST-T changes with ST segment depression that usually returns to normal over a few days, but is occasionally permanent.

The ECG changes evolve over a period of time and are as described :[47]

1. Hyper acute phase(over minutes-hours)
2. Evolved phase(over hours)
3. Chronic stable phase(over days-weeks)

TABLE 8: BRIEF DESCRIPTION OF EVOLUTION OF ECG DURING STEMI

ECG changes	**Hyper-acute phase**	**Evolved phase**	**Chronic stable phase**
Q wave	_	+	+
R wave height	⇧	⇩	⇩
Increase in ventricular activation time	+	+	+/-
Increase in QRS duration	+	+	+/-
Notch in QRS/Bundle branch block	+/-	+/-	+/-
J point elevation	+	+	_
ST elevation(Convex upwards)	+	+	_
T waves	Tall broad and peaked	Inverted, symmetrical and peaked	Normal
Increase in QT interval	+/-	+/-	_

TABLE9: ELECTROCARDIOGRAPHIC LOCATION OF INFARCTION[48]

SITES	LEADS
Inferior	II, III, Avf
Inferolateral	II, III, aVF, V_4 - V_6
Anteroseptal	V_1,V_2, V_3
Anterolateral	I, aVL, V_4 – V_6
Extensive anterior	I, aVL, V_1 – V_6
High anterolateral	I, Avl
Anterior (apical)	V_2 – V_4
True posterior	Tall R wave in V_1 that has duration of 0.04 sec or more, with an R/S ratio equal to or greater than 1.
Inferoposterior	II, III, aVF, plus tall R wave in V_1 with duration of 0.04sec or more and an R/S ratio equal to or greater than 1.
Posterolateral	V_4 – V_6 plus tall R wave in V_1 with a duration of 0.04 sec or more, with an R/S ratio equal to or greater than 1.
Right ventricular	V_4R with V_4R – V_6R.

New onset LBBB in a setting of chest pain is considered and treated as STEMI.

The diagnosis of STEMI is a setting of old LBBB.[49,50,51]

1.A pathological Q wave in leads I, aVL, V_5 or V_6.

2. Precordial R wave regression

3. Late notching of S wave in V1 to V4.

4. Deviation of the ST segment in the same direction as that of major QRS deflection.

CARDIAC BIOMARKERS[52]

Damaged cardiomyoctes release several proteins in the circulation, including myoglobin, creatine kinase(CK) snd its myocardial band isoenzyme (CK-MB), troponins (I and T), aspartate aminotransferase and lactate dehydrogenase.

Cardiac troponins are currently the preferred biomarkers for myocardial damage because of their high specificity and sensitivity. They regulate the interaction of actin and myosin and are cardiac-specific. There are two isoforms of cardiac troponin: T and I.

Their level starts to rise 3 to 12hours after the onset of ischemia, peak at 12-24hours and may remain elevated for 8 to 21days (troponin T) or 7 to 14days (troponin I).

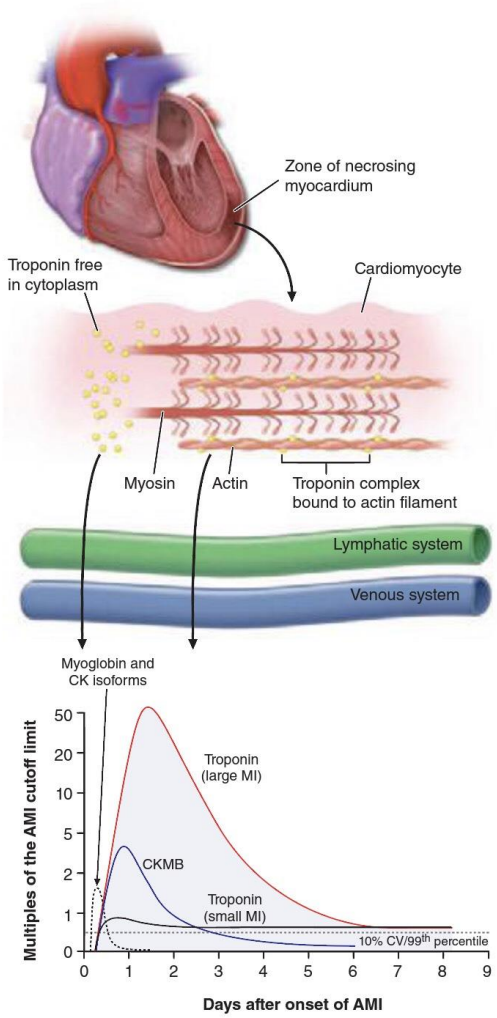


FIGURE 7: The zone of necrosing myocardium is shown at the top of the figure followed in the middle portion of the figure by a diagram of a cardiomyocyte that is in the process of releasing biomarkers.the biomarkers that are released into the interstitium are first cleared by lymphatics followed subsequently by spillover into the venous system. after disruption of the sarcolemmal membrane of the cardiomyocyte, the cytoplasmic pool of biomarkers is released first.

CK-MB is the best alternative, if troponins are not available because of its more rapid appearance and disappearance from the blood. CK rises within 4-8hours and returns to normal by 48-72hours. An important shortcoming of total CK measurement is its lack of specificity for STEMI, as CK may be increased with skeletal muscle disease or trauma.

MYOGLOBIN[53]

Myoglobin is a heme protein found in skeletal and cardiac muscle that has attracted considerable interest as an early marker of MI. Myoglobin typically rises 2-4 hours after onset of infarction, peaks at 6- 12 hours, and returns to normal within 24-36 hours. Rapid myoglobin assays are available, but overall, they have a lack of cardiospecificity. Serial sampling every 1-2 hours can increase the sensitivity and specificity; a rise of 25-40% over 1-2 hours is strongly suggestive of acute MI. However, in most studies, myoglobin only achieved 90% sensitivity for acute MI, so the negative predictive value of myoglobin is not high enough to exclude the diagnosis of acute MI.

TABLE 10: VARIATION OF MYOGLOBIN

Condition where myoglobin increases	Condition where myoglobin does not increase
Acute myocardial infarction	Non cardiac chest pain
Shock	Mild to moderate exercise
Rhabdomyolysis	Cardiac catherization
Progressive muscular dystrophy	

Other prognostic markers during acute coronary syndromes:[53]

1. **C - reactive protein:**

Among the growing list of additional markers that appear to be useful in assessing patients with UA/NSTEMI, CRP holds considerable promise. Elevated levels of high sensitivity CRP relate to increased risk of death, MI, and/or need for urgent revascularization. Elevated levels of CRP in patients with ACS are approximately five times higher than for stable patients.

After stabilization post-ACS measurement of CRP predicts outcome after 3 to 12 months. These studies indicate that inflammation is related to the instability of patients and an increased risk of re-current cardiac events.

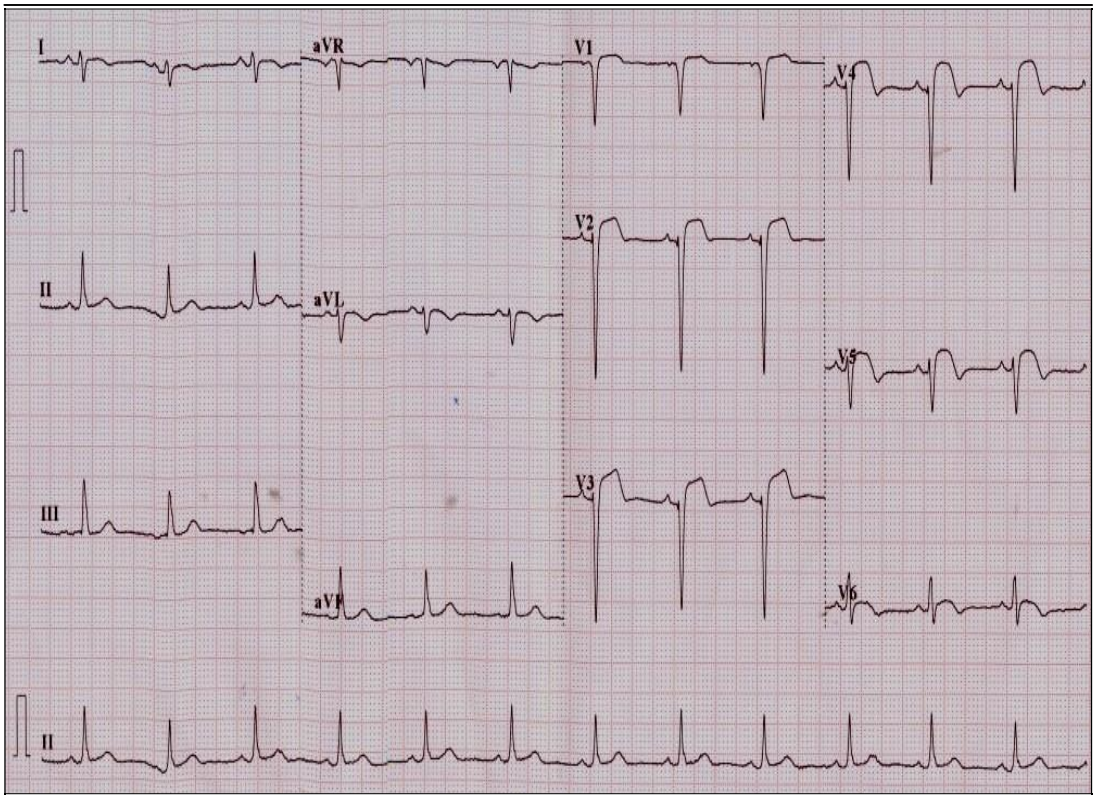
2. B-Type Natriuretic Peptide:

BNP has usefulness as a diagnostic and prognostic marker among patients with congestive heart failure, and in patients with acute MI.BNP has prognostic value across the full spectrum of patients with ACS, including those with UA/NSTEMI.

3. Myeloperoxidase:

Patients presenting to the emergency department with chest pain and in patients with UA/NSTEMI, Myeloperoxidase serum levels predict increased risk for subsequent death or MI, independent of other risk factors and other cardiac markers.

- FIGURE 8: ANTERIOR WALL MYOCARDIAL INFARCTION



- FIGURE 9: ECG SHOWING INFERIOR WALL MYOCARDIAL INFARCTION

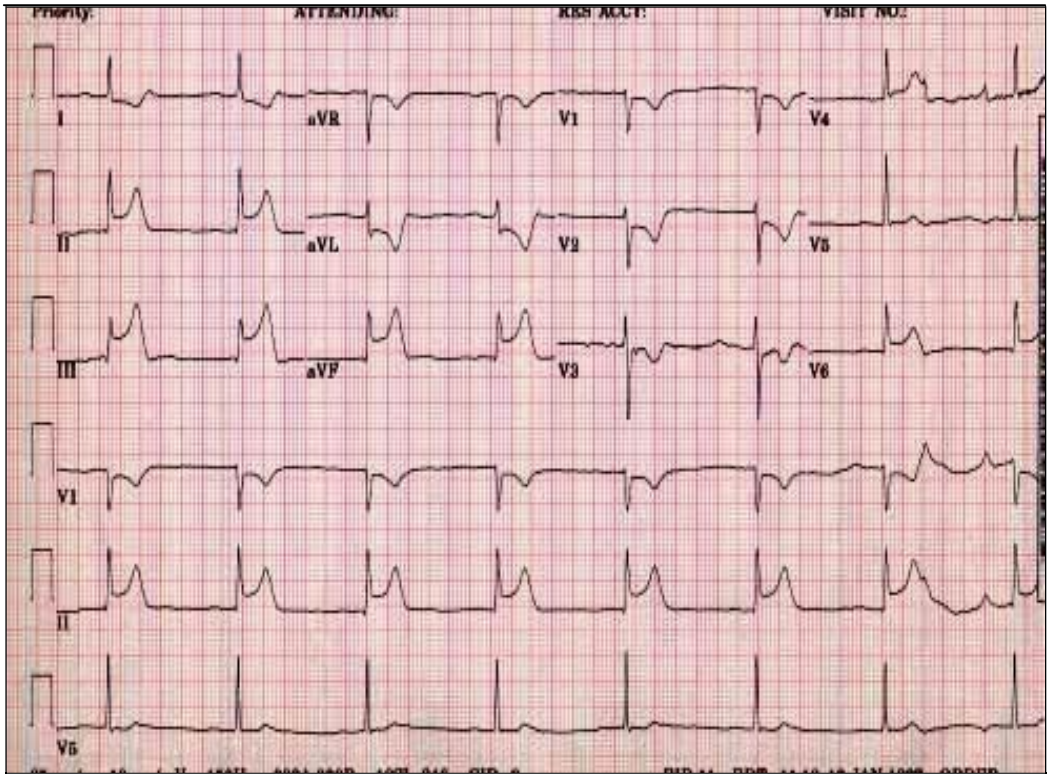


FIGURE 10: ECG SHOWING LEFT BUNDLE BRANCH BLOCK

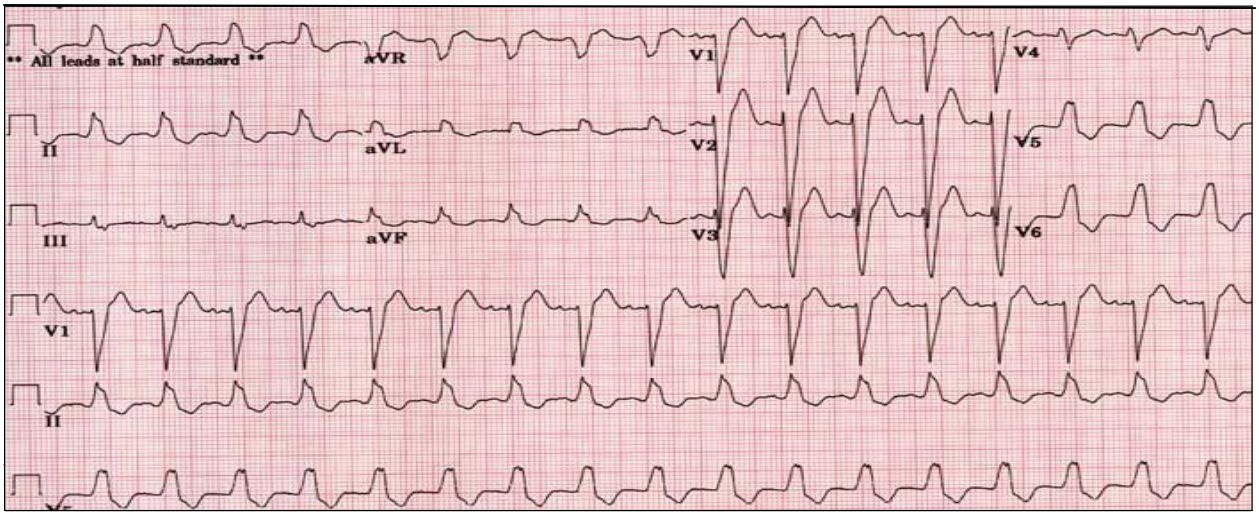
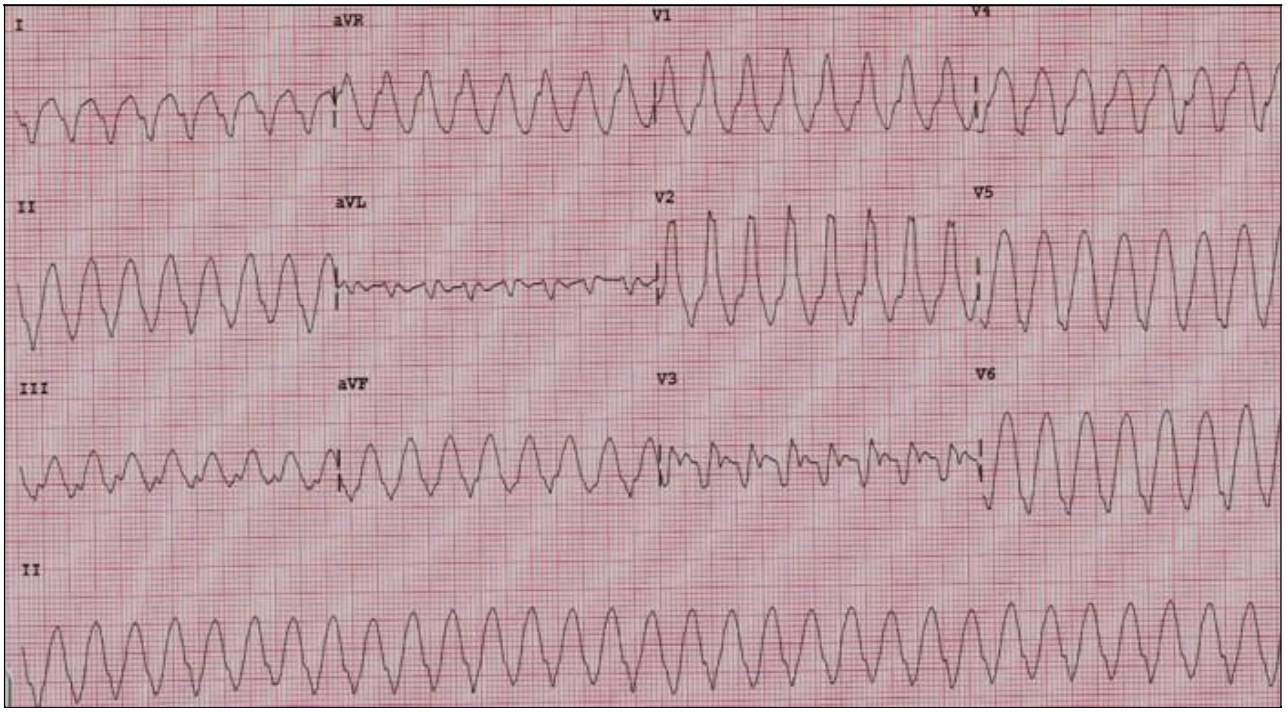


FIGURE 11: ECG SHOWING VENTRICULAR TACHYCARDIA



ASCERTAINMENT OF ADVERSE CARDIAC EVENTS ON FOLLOW-UP[54]

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE): Cardiovascular death, MI, unstable angina pectoris (UAP), coronary revascularization and/or re- hospitalization that are distinct from the qualifying event (after patient's initial ED presentation).

Myocardial infarction

Unstable angina

Cardiovascular Death: Any sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to stroke, and death due to other cardiovascular causes. In addition, any death without a clear non-cardiovascular cause, or a death without known cause will be considered cardiovascular death.

Malignant arrhythmia : was defined as symptomatic sustained ventricular tachycardia and also ventricular fibrillation, irrespective of symptoms or hemodynamic stability.

Cardiogenic shock: defined as systolic blood pressure <90 mm Hg or a drop of mean arterial pressure >30 mm Hg with a pulse >60 beats per minute to exclude shock secondary to bradycardia and/or low urine output (<0.5 mL/kg/h) with or without evidence of organ congestion.

GLYCOSYLATED HAEMOGLOBIN [54,55]

The glycosylation of haemoglobin A to structure into HbA1c occurs all through the lifecycle of the erythrocyte, but occur faster in normal donor red cells given to diabetic recipients, the metabolic conformations in the diabetic patient accomplish glycosylation within red cells circulating in their blood faster than occurs when the transfused red cells circulate in a normal recipient.

The level of glycosylated haemoglobin appears to be a reflection of blood sugars for a period of several weeks prior to the time of sampling. It has therefore been suggested that the measurement of haemoglobin glycosylation would be a more stable indicator of the adequacy of control of diabetic state than occasional measurement of blood and urine glucose.

FORMATION OF GLYCOSYLATED HAEMOGLOBIN: [56]

Glucose reacts nonenzymatically with the NH_2 terminal aminoacid of the beta chain of the human haemoglobin by way of keto amine linkage, resulting in the formation of glycosylated haemoglobin. The enhanced electrophoretic mobility of this fast moving minor haemoglobin component is due to the nonenzymatic glycosylation of the aminoacid valine and lysine. The reaction is as follows:

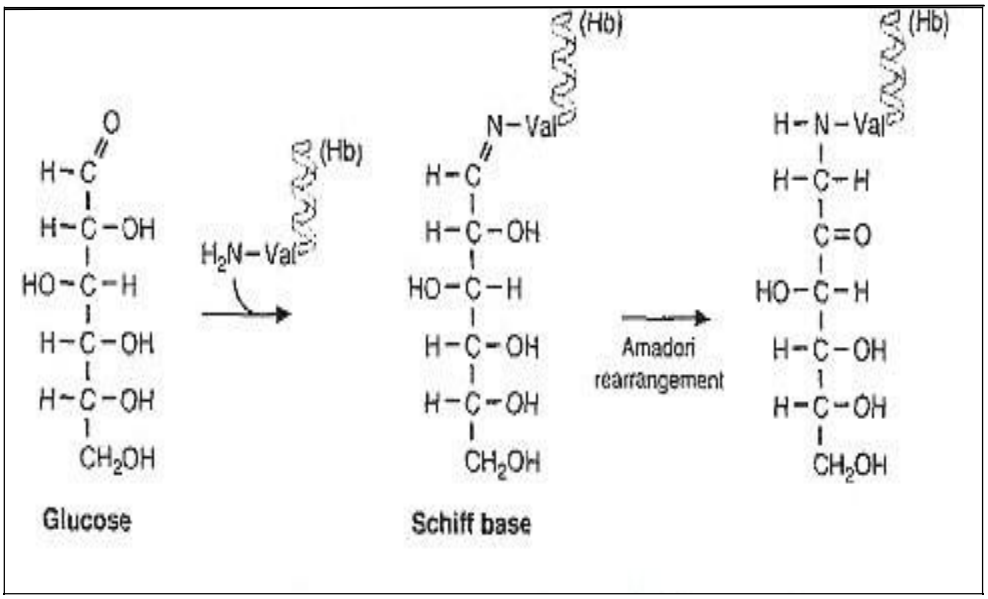


FIGURE 12: NON ENZYMATIC GLYCOSYLATION OF AMINO ACID

HbA ⟷ PreA1C ⟶ HbA1C

RAPID SLOW

NONENZYMATIC GLYCOSYLATION.[57]

Pre A1c must thus be removed to assess true HbA1c values accurately. When properly assayed, the percent of glycosylated haemoglobin gives an estimate of diabetic control for the preceding 3 month period.

The periodic monitoring of HbA1c levels is useful in documenting the degree of control of blood sugars and also helps us asses the relationship of carbohydrate control to the development of sequel.

ASSAY METHODS [58]

The various methods that have been used to determine glycosylated haemoglobin are:

1. Cation exchange chromatography.
2. Batch chromatography.
3. Affinity chromatography.
4. High performance liquid chromatography.
5. Colorimetry.
6. Isoelectric focusing.
7. Radio immuno assay.
8. Spectrophotometric assay.
9. Electrophoresis/Electroendosmosis

TABLE 11: CONDITIONS LEADING TO FALSELY ABNORMAL VALUES FOR THE HBA1C: [59]

FACTORS INFLUENCING HEMOGLOBIN A1C		
COMORBIDITY	EFFECT ON RBC's	EFFECT ON HbA1C
1. Iron deficiency 2. Vitamin B12 deficiency 3. Lack of erythropoietin 4. Pregnancy 5. Renal failure	RBC production decreases	Elevation
6. Hemoglobinopathies 7. Rheumatoid arthritis	RBC destruction increases	Decline

8. Spleenomegaly 9. Elevated erythropoietin 10. Chronic liver disease	RBC production increases	Decline
11. Splenectomy	RBC dectruction decreases	Elevation

TABLE 12: CORRELATION OF HBA1C WITH AVERAGE BLOOD GLUCOSE [6]

HbA1c (%)	**Mean blood glucose (mg/dL)**	**Mean blood glucose (mmol/L)**
5	97	5.4
6	126	7.0
7	154	8.6
8	183	10.2
9	212	11.8
10	240	13.4
11	269	14.9
12	298	16. 5

Even an increase of 1% in HbA1c concentration was associated with about 30% increase in all-cause mortality and 40% increase in cardiovascular or ischemic heart disease mortality, among individuals with diabetes. Whereas reducing the HbA1c level by 0.2% could lower the mortality by 10%. Vaag has suggested that improving glycemic control in patients may be more important than treating dyslipidemia for the prevention of both microvascular and macrovascular complications.

MATERIALS AND METHODS

A total of sixty eight patients with Acute Myocardial Infarction confirmed by electrocardiogram (ECG) or cardiac enzyme were selected consecutively as and when they presented with the following inclusion and exclusion criteria attending General Medicine OPD and Narayana Hrudalaya, RL Jalappa hospital and research centre, Tamaka, Kolar.

SOURCE OF DATA: RL Jalappa hospital and Narayana Hrudalaya hospital, Tamaka, Kolar

METHODS OF COLLECTION OF DATA:

Study design: One year case control study.

Sample size: 68 cases of acute myocardial infarction those are prediabetic and non-diabetic.

Duration: November 2016-October 2017

Procedure:

Study included all prediabetic and non-diabetic patients admitted with raised serum cardiac enzymes, any or all of the symptoms suggestive of myocardial infarction for at least 30 minutes, ECG changes on at least two contiguous leads with ST elevation(>0.1mV) in limb leads or ST elevation (>0.2mV) in chest leads.

The time for beginning of symptoms to admission has to be less than 48 hours. All patients' blood glucose level was measured on admission by glucometer and patients who had no history or treatment for diabetes mellitus at entry were included.

INCLUSION CRITERIA:

Acute coronary Syndrome diagnosed in patients presenting with chest pain and or dyspnoea for >30 minutes and not more than 24 hours with ECG changes

They were classified into

1. **STEMI** - ST segment elevation 1mm or more in two or more contiguous leads with reciprocal ST depression in contralateral leads. ST elevation of 1mm in inferior leads and 2 mm in anterior leads is taken as significant.

2. **Non-STEMI** - ST deviation in the ECG along with elevation of cardiac biomarkers.

3. **Unstable angina**- ST deviation in ECG without elevation of cardiac biomarkers.

A diagnosis of Acute coronary syndrome was established based on clinical features, above ECG findings and cardiac enzymes.

Then the patients were further divided into study group and control group based on the following criteria according to ADA criteria[62]

PARAMETER	STUDY GROUP (PREDIABETES)	CONTROL GROUP (NON-DIABETIC)
Fasting plasma glucose	100-125mg/dl	<100mg/dl
Post-prandial glucose	141-199mg/dl	<140mg/dl
HbA1C	5.7-6.4%	<5.7%

EXCLUSION CRITERIA

1. Known case of diabetes mellitus.
2. Patients on steroids.
3. Patients with chronic kidney disease.
4. Patients with post myocardial infarction.
5. Chronic liver disease
6. Hemoglobinopathy (sickle cell anemia, thalassemia, glucose‑6‑phosphate dehydrogenase deficiency), treatment of anemia with iron or erythropoietin, autoimmune hemolytic anemia
7. Treatment of anemia with iron or erythropoietin
8. Patient's refusal.

The patient's history, and their clinical course was recorded.

ECG of all the patients were read(STEMI, NSTEMI) and recorded.

Patients were followed up during hospital stay. The end point of study was till hospital discharge or till death during hospitalization. Patients were channelized to undergo routine investigations as per protocol of the study.Investigations and interventions conducted on the patients:

1. Routine blood investigations .
2. Random Blood Sugar at admission.
3. Electrocardiogram.
4. Cardiac Enzymes
5. Lipid profile
6. FBS,PPBS, HbA1C.
7. Echocardiography

SAMPLE SIZE

Statistical analysis:

Data will be entered in MS excel and analyzed using SPSS 22 version software. Qualitative data will be presented in the form of Proportions and pie diagrams, bar charts will be used to represent graphically. Quantitative data will be presented as mean, standard deviation. ANOVA will be the test of significance for quantitative data and chi-square test will be the test of significance for qualitative data. p value <0.05 will be considered as statistically significant.

Sample Size:

Was estimated based on the difference in proportions of complications between two groups. Percentage of arrhythmia in control group was 30.77% and in pre diabetic group was 69.23%. These values were obtained from the study by Sushil Singh et.al

$$\text{Sample size} = \frac{r+1}{r}\frac{(p^*)(1-p^*)(Z_\beta + Z_{\alpha/2})^2}{(p_1 - p_2)^2}$$

r = Ratio of control to cases, 1 for equal number of case and control

p^* = Average proportion exposed = proportion of exposed cases + proportion of control exposed/2

Z_β = Standard normal variate for power = for 80% power it is 0.84 and for 90% value is 1.28. Researcher has to select power for the study.

$Z_{\alpha/2}$ = Standard normal variate for level of significance as mentioned in previous section.

$p_1 - p_2$ = Effect size or different in proportion expected based on previous studies. p_1 is proportion in cases and p_2 is proportion in control.

P1 = 30.77% and P2 = 69.23%, ratio of cases to controls as kept as 1. At α error 5% and power at 80% sample size was estimated by using Med calc software. By using the values a sample size of 31 was obtained in each group.

Considering Nonresponse rate of 10%, 31 + 3 = 34 patients in each group will be selected.

Hence a total of 68 subjects will be included in the study

TABLE 13: COMPARISION OF AGE DISTRIBUTION BETWEEN TWO GROUPS

		Group					
		Cases		Controls		Total	
		Count	%	Count	%	Count	%
Age	<40 years	7	20.6%	5	14.7%	12	17.6%
	41 to 50 years	10	29.4%	14	41.2%	24	35.3%
	51 to 60 years	11	32.4%	8	23.5%	19	27.9%
	>60 years	6	17.6%	7	20.6%	13	19.1%
	Total	34	100.0%	34	100.0%	68	100.0%

$\chi 2 = 1.551$, df =3, p =0.671

Among cases majority 32.4% were in the age group 51 to 60 years and among controls majority 41.2% were in the age group 41 to 50 years.

There was no significant difference in age distribution between two groups.

FIGURE 13: BAR DIAGRAM SHOWING COMPARISION OF AGE DISTRIBUTION BETWEEN TWO GROUPS

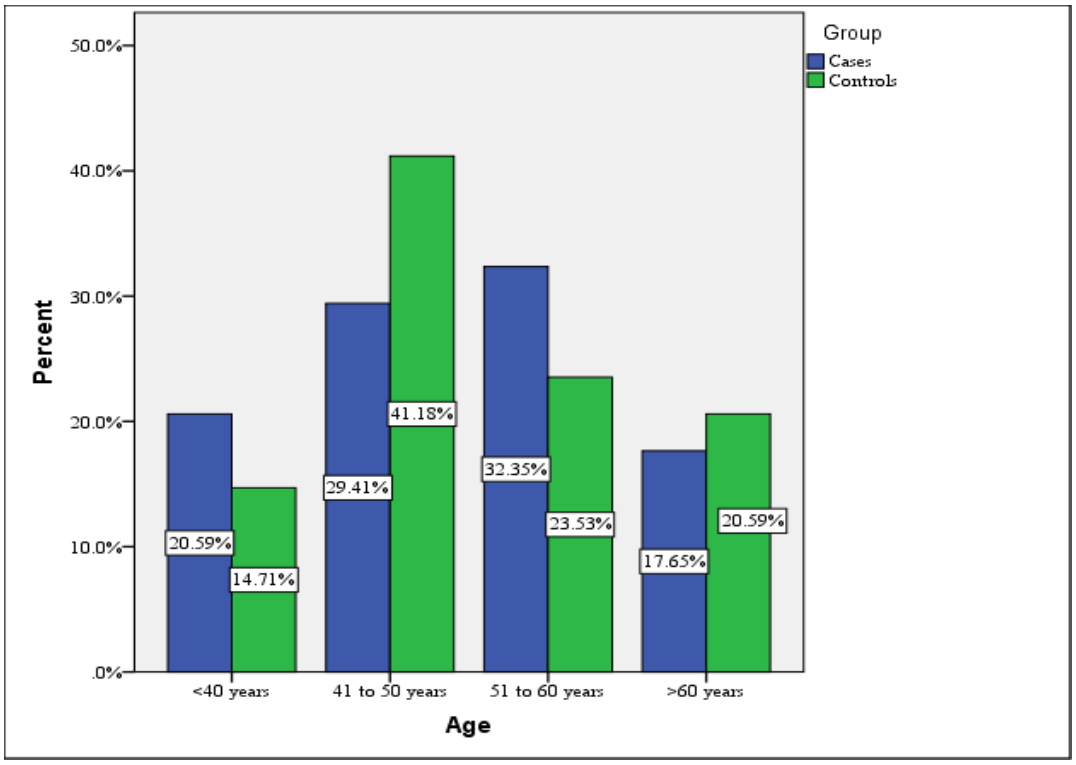


TABLE 14: COMPARISON OF GENDER DISTRIBUTION BETWEEN TWO GROUPS

		Group					
		Cases		Controls		Total	
		Count	%	Count	%	Count	%
Gender	Female	13	38.2%	10	29.4%	23	33.8%
	Male	21	61.8%	24	70.6%	45	66.2%
	Total	34	100.0%	34	100.0%	68	100.0%

$\chi 2 = 0.591$, df =1, p =0.442

In Cases, 61.8% were males and 38.2% were females and in Controls 70.6% were males and 29.4% were females.

There was no significant difference in gender distribution between two groups.

TABLE 15: COMPARISION OF COMORBIDITIES AND PAST HISTORY DISTRIBUTION BETWEEN TWO GROUPS

		Group						P value
		Cases		Controls		Total		
		Count	%	Count	%	Count	%	
Hypertension	No	11	32.4%	13	38.2%	24	35.3%	0.612
	Yes	23	67.6%	21	61.8%	44	64.7%	
Smoker	No	13	38.2%	19	55.9%	32	47.1%	0.145
	Yes	21	61.8%	15	44.1%	36	52.9%	
Family History of CAD	No	34	100.0%	32	94.1%	66	97.1%	0.151
	Yes	0	0.0%	2	5.9%	2	2.9%	
Alcohol	No	24	70.6%	32	94.1%	56	82.4%	0.011*
	Yes	10	29.4%	2	5.9%	12	17.6%	

Among cases, 67.6% had HTN, 61.8% were smokers, 29.4% were alcoholics. Among controls, 61.8% had HTN, 44.1% were smokers, 5.9% had family history of CAD and 5.9% were alcoholics.

There was significant difference in Alcohol consumption between cases and controls.

FIGURE 14: BAR DIAGRAM SHOWING COMPARISION OF COMORBIDITIES AND PAST HISTORY DISTRIBUTION BETWEEN TWO GROUPS.

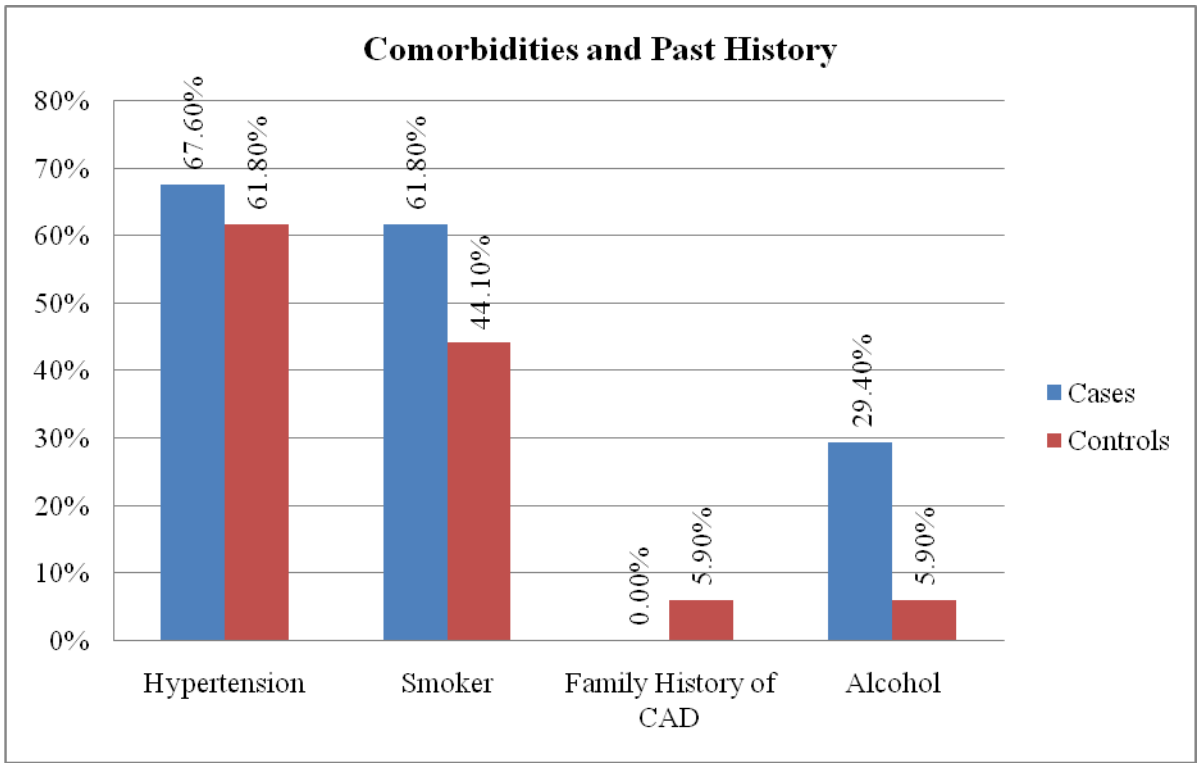


TABLE 16: COMPARISION OF RBS, FBS, PPBS AND HbA1C BETWEEN TWO GROUPS

	Group						P value
	Cases		Controls		Total		
	Mean	SD	Mean	SD	Mean	SD	
RBS at Admission	168.59	77.53	141.74	19.90	155.16	57.78	0.055
FBS	117.09	6.18	92.59	11.16	104.84	15.25	<0.001*
PPBS	164.00	18.85	131.65	12.74	147.82	22.81	<0.001*
HbA1c	6.09	0.27	5.32	0.30	5.70	0.48	<0.001*

In the study there was significant difference in mean FBS, PPBS and HbA1c between cases and controls. All the three glycemic profile parameters were significantly higher in Cases than in controls. There was no significant difference in mean RBS between two groups.

FIGURE 15: BOX PLOT SHOWING FBS LEVELS COMPARISON BETWEEN TWO GROUPS

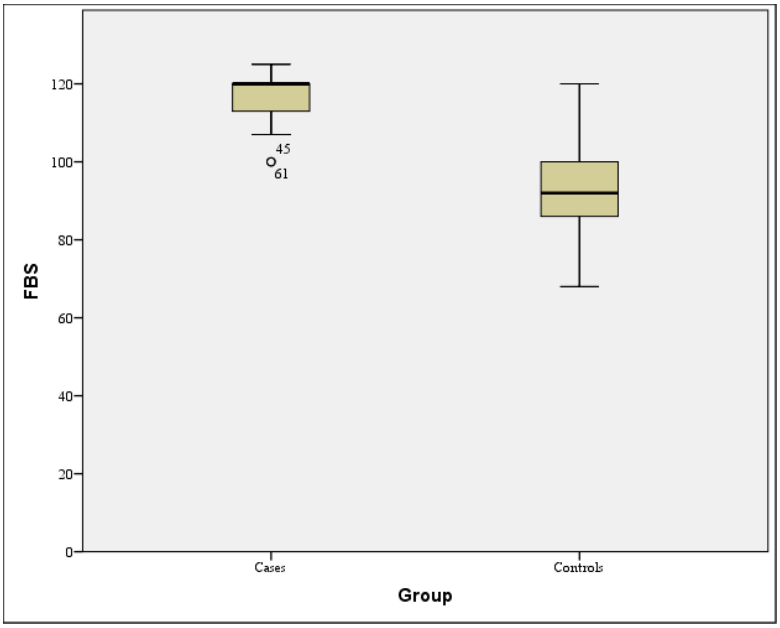


FIGURE 16: BOX PLOT SHOWING PPBS LEVELS COMPARISON BETWEEN TWO GROUPS

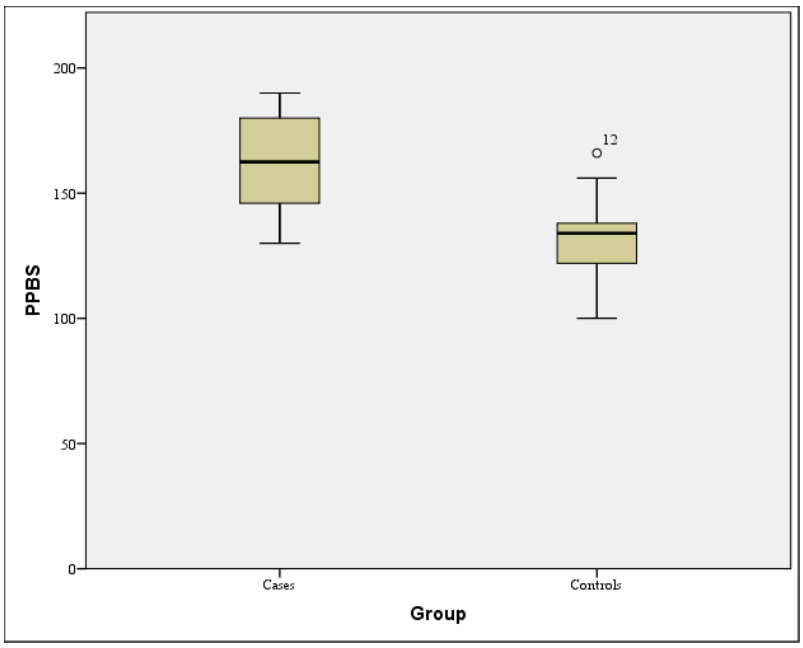


FIGURE 17: BOX PLOT SHOWING HbA1C LEVELS COMPARISON BETWEEN TWO GROUPS

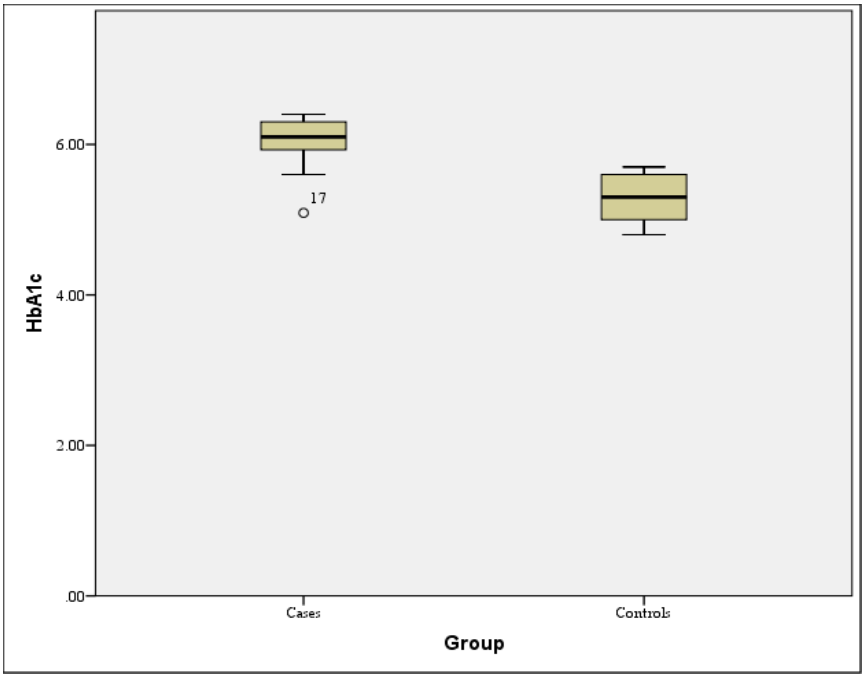


TABLE 17: RENAL PROFILE COMPARISON BETWEEN TWO GROUPS

	Group						P value
	Cases		Controls		Total		
	Mean	SD	Mean	SD	Mean	SD	
Blood Urea	32.41	13.03	32.74	6.85	32.57	10.33	0.898
Serum Creatinine	0.89	0.21	0.79	0.23	0.84	0.22	0.075

There was no significant difference in mean blood urea and serum Creatinine between two groups

TABLE 18: BMI COMPARISON BETWEEN TWO GROUPS

		Group			
		Cases		Controls	
		Count	%	Count	%
BMI	Normal (18.5 to 24.9)	2	5.9%	3	8.8%
	Overweight (25 to 29.9)	22	64.7%	23	67.6%
	Obese I (30 to 34.9)	9	26.5%	8	23.5%
	Obese II (35 to 39.9)	1	2.9%	0	0.0%

There was no significant difference in BMI between two groups.

TABLE 19: HbA1c and Lipid profile comparison between two groups

		Group				P value
		Cases		Controls		
		Count	%	Count	%	
HbA1c	>5.7	34	100%	0	0.0%	<0.001*
	<5.7	0	0%	34	100.0%	
Total Cholesterol	>200 mg/dl	24	70.6%	5	14.7%	<0.001*
	<200 mg/dl	10	29.4%	29	85.3%	
Triglycerides	>150 mg/dl	28	82.4%	22	64.7%	0.099
	<150 mg/dl	6	17.6%	12	35.3%	
LDL	>129 mg/dl	31	91.2%	23	67.6%	0.016*
	<129 mg/dl	3	8.8%	11	32.4%	
HDL	<60 mg/dl	34	100.0%	34	100.0%	

In the study there was significant association between HBA1c, Total Cholesterol, LDL with cases and controls.

Among cases 100% had HbA1c >5.7, 70.6% had Total Cholesterol >200 mg/dl, 82.4% had Triglycerides >150 mg/dl and 91.4% had LDL >129 mg/dl.

Among Controls 100% had HbA1c <5.7, 14.7% had Total Cholesterol >200 mg/dl, 64.7% had Triglycerides >150 mg/dl and 67.6% had LDL >129 mg/dl.

FIGURE 18: BAR DIAGRAM SHOWING TRIGLYCERIDES COMPARISON BETWEEN TWO GROUPS

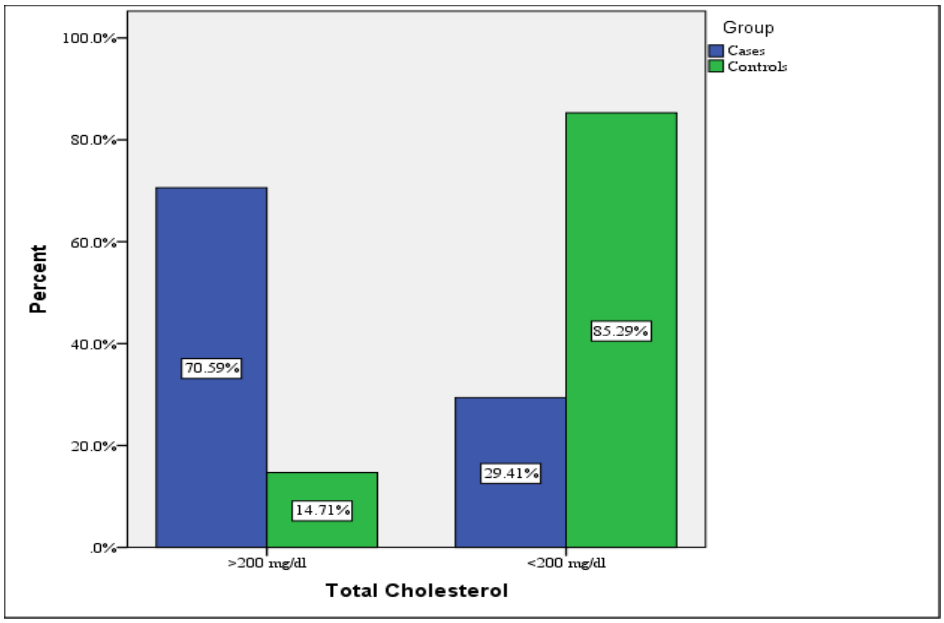


FIGURE 19: BAR DIAGRAM SHOWING LDL COMPARISON BETWEEN TWO GROUPS

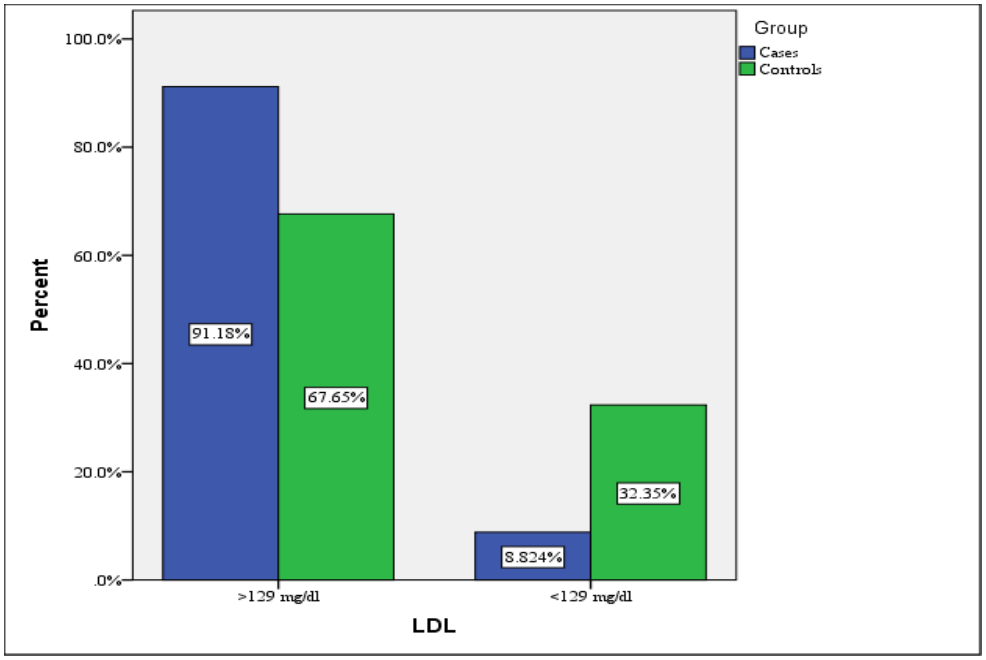


TABLE 20: ASSOCIATION BETWEEN HBA1C, LIPID PROFILE WITH MACE AMONG CASES

		Mace								P value
		Cardiogenic Shock		Congestive Heart Failure		No Complications		Ventricular Tachycardia		
		Count	%	Count	%	Count	%	Count	%	
Total Cholesterol	>200 mg/dl	8	33.3%	5	20.8%	3	12.5%	8	33.3%	0.044*
	<200 mg/dl	0	0.0%	1	10.0%	5	50.0%	4	40.0%	
Triglycerides	>150 mg/dl	8	28.6%	6	21.4%	3	10.7%	11	39.3%	0.002*
	<150 mg/dl	0	0.0%	0	0.0%	5	83.3%	1	16.7%	
LDL	>129 mg/dl	8	25.8%	6	19.4%	5	16.1%	12	38.7%	0.014*
	<129 mg/dl	0	0.0%	0	0.0%	3	100.0%	0	0.0%	
a. Group = Cases										

Among cases there was significant association between Total Cholesterol, Triglycerides and LDL with MACE

TABLE 21: ASSOCIATION BETWEEN HBA1C, LIPID PROFILE WITH MACE AMONG CONTROLS

		Mace								P value
		Cardiogenic Shock		Congestive Heart Failure		No Complications		Ventricular Tachycardia		
		Count	%	Count	%	Count	%	Count	%	
Total Cholesterol	>200 mg/dl	1	20.0%	2	40.0%	2	40.0%	0	0.0%	0.217
	<200 mg/dl	2	6.9%	3	10.3%	23	79.3%	1	3.4%	
Triglycerides	>150 mg/dl	1	4.5%	3	13.6%	17	77.3%	1	4.5%	0.571
	<150 mg/dl	2	16.7%	2	16.7%	8	66.7%	0	0.0%	
LDL	>129 mg/dl	2	8.7%	5	21.7%	15	65.2%	1	4.3%	0.316
	<129 mg/dl	1	9.1%	0	0.0%	10	90.9%	0	0.0%	
a. Group = Controls										

Among cases there was significant association between Total Cholesterol, Triglycerides and LDL with MACE

TABLE 22: ASSOCIATION BETWEEN HBA1C AND LIPID PROFILE

		HbA1c				P value
		>5.7		<5.7		
		Count	%	Count	%	
Total Cholesterol	>200 mg/dl	24	70.6%	5	14.7%	<0.001*
	<200 mg/dl	10	29.4%	29	85.3%	
Triglycerides	>150 mg/dl	28	82.4%	22	64.7%	0.099
	<150 mg/dl	6	17.6%	12	35.3%	
LDL	>129 mg/dl	31	91.2%	23	67.6%	0.016*
	<129 mg/dl	3	8.8%	11	32.4%	
HDL	<60 mg/dl	34	100.0%	34	100.0%	-

In the study there was significant association between HbA1c and Total cholesterol and LDL. Among those with HbA1c >5.7, 70.6% had Total cholesterol >200 mg/dl and 91.2% had LDL >129 mg/dl. There was no significant association between HbA1c<5.7 and Triglycerides and HDL.

FIGURE 20: BAR DIAGRAM SHOWING ASSOCIATION BETWEEN HbA1C AND TOTAL CHOLESTEROL

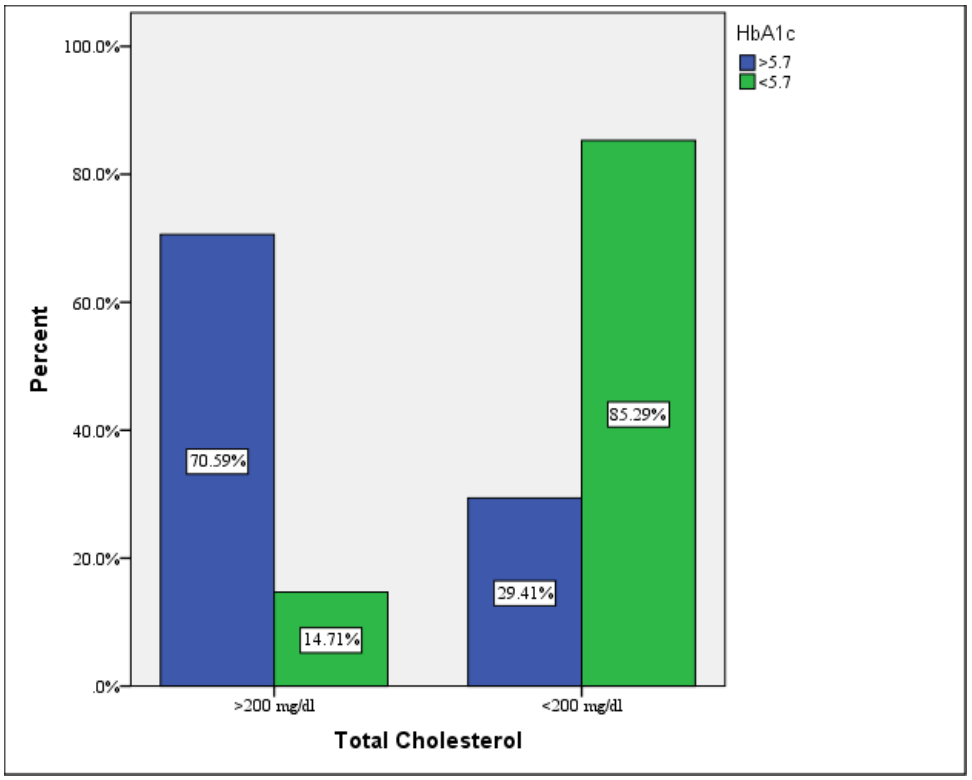
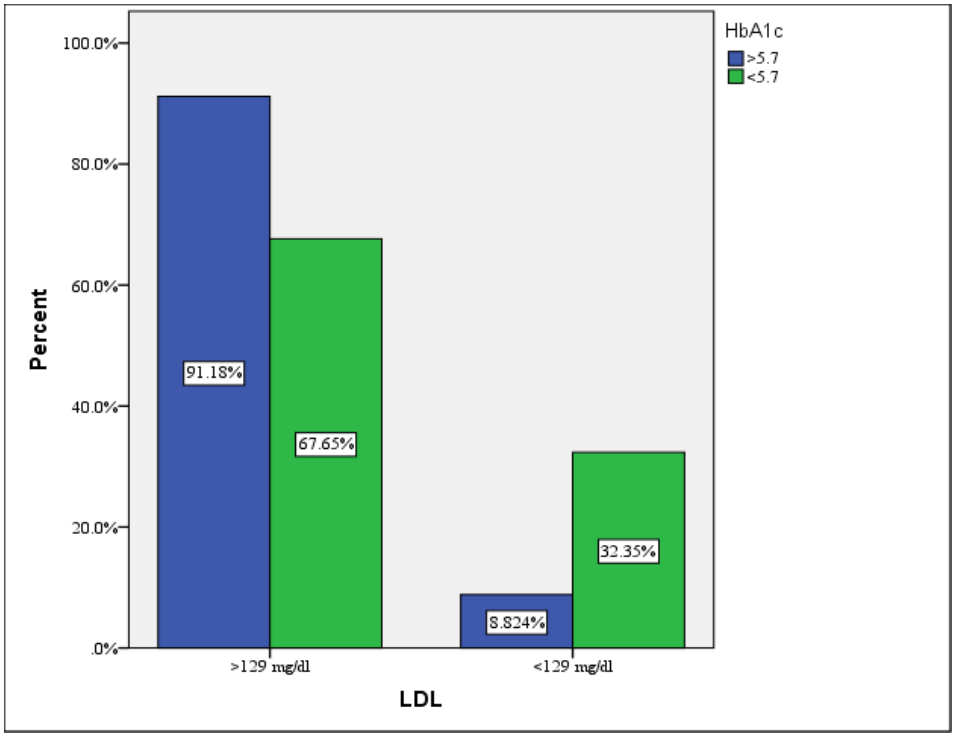


FIGURE 21: BAR DIAGRAM SHOWING ASSOCIATION BETWEEN HBA1C AND LDL



From the study it can be concluded that cases (i.e. those with HbA1c >5.7%), had significantly higher levels of Total cholesterol, triglycerides and LDL and complications was significantly high compared to controls (i.e. those with HbA1c <5.7%).

TABLE 23: COMPLICATIONS AMONG CASES WITH HbA1C >5.7% AND RBS >140 MG/DL

		Group			
		Cases		Controls	
		Count	%	Count	%
Mace	Cardiogenic Shock	6	26.1%	0	0.0%
	Congestive Heart Failure	6	26.1%	0	0.0%
	No Complications	4	17.4%	0	0.0%
	Ventricular Tachycardia	7	30.4%	0	0.0%
a. RBS at Admission = >200 mg/dl, HbA1c = >5.7					

Among cases with HbA1c >5.7 and RBS >140 mg/dl, 26.1% had Cardiogenic shock and Congestive heart failure respectively, 17.4% had no complications and 30.4% had Ventricular Tachycardia.

TABLE 24: COMPARISION OF WALL INVOLVEMENT BETWEEN TWO GROUPS

		Group					
		Cases		Controls		Total	
		Count	%	Count	%	Count	%
Wall Involvement	Anterior Wall	19	55.9%	11	32.4%	30	44.1%
	Inferior Wall	9	26.5%	15	44.1%	24	35.3%
	No	6	17.6%	8	23.5%	14	20.6%
	Total	34	100.0%	34	100.0%	68	100.0%

Among cases, 55.9% had anterior wall involvement, 26.5% had inferior wall MI and among controls, 32.4% had anterior wall, 44.1% had inferior wall MI. There was no significant difference in wall involvement between two groups

TABLE 25: DIAGNOSIS COMPARISON BETWEEN TWO GROUPS

		Group					
		Cases		Controls		Total	
		Count	%	Count	%	Count	%
Diagnosis	NSTEMI	14	41.2%	16	47.1%	30	44.1%
	STEMI	14	41.2%	10	29.4%	24	35.3%
	Unstable Angina	6	17.6%	8	23.5%	14	20.6%
	Total	34	100.0%	34	100.0%	68	100.0%

$\chi 2 = 1.086$, df =2, p =0.581

Among cases, 41.2% had NSTEMI, 41.2% had STEMI and 17.6% had Unstable Angina and among controls, 47.1% had NSTEMI, 29.4% had STEMI and 23.5% had Unstable angina. There was no significant difference in diagnosis between two groups.

TABLE 26: 2D ECHO COMPARISON BETWEEN TWO GROUPS

		Group					
		Cases		Controls		Total	
		Count	%	Count	%	Count	%
2D Echo	Normal LV Function	5	14.7%	9	26.5%	14	20.6%
	Mild LV Dysfunction	10	29.4%	18	52.9%	28	41.2%
	Moderate LV Dysfunction	15	44.1%	4	11.8%	19	27.9%
	Severe LV Dysfunction	4	11.8%	3	8.8%	7	10.3%
	Total	34	100.0%	34	100.0%	68	100.0%

$\chi 2 = 9.940$, df =3, p =0.019*

Among cases,

14.7% had Normal LV Function

29.4% had Mild LV Dysfunction

44.1% had Moderate LV Dysfunction

11.8% had Severe LV Dysfunction.

Among controls,

26.5% had Normal LV Function

52.9% had Mild LV Dysfunction

11.8% had Moderate LV Dysfunction

8.8% had Severe LV Dysfunction.

There was significant difference in 2D Echo findings between two groups.

TABLE 27: MORTALITY COMPARISON BETWEEN TWO GROUPS

		Group					
		Cases		Controls		Total	
		Count	%	Count	%	Count	%
Mortality	No	32	94.1%	34	100.0%	66	97.1%
	Yes	2	5.9%	0	0.0%	2	2.9%
	Total	34	100.0%	34	100.0%	68	100.0%

$\chi 2 = 2.061$, df =1, p = 0.151

Among cases, 5.9% had mortality and in controls none had mortality.

There was no significant difference in mortality between two groups.

TABLE 28: ASSOCIATION BETWEEN MACE AND HBA1C

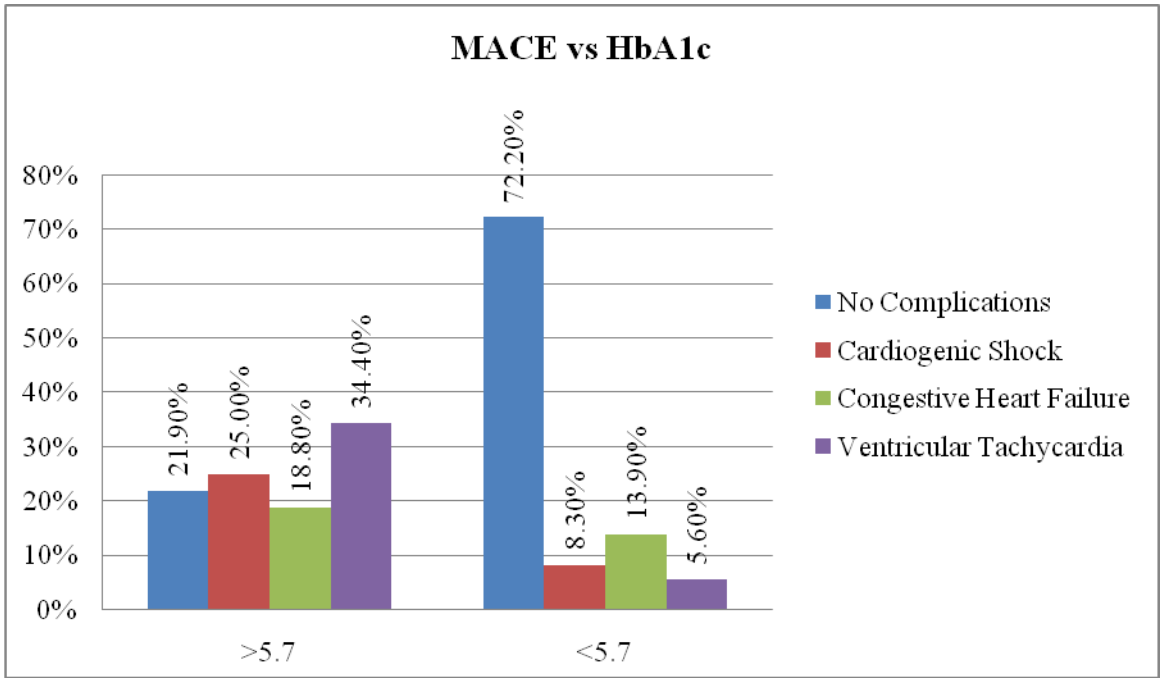
		Mace							
		No Complications		Cardiogenic Shock		Congestive Heart Failure		Ventricular Tachycardia	
		Count	%	Count	%	Count	%	Count	%
HbA1c	>5.7	7	21.9%	8	25.0%	6	18.8%	11	34.4%
	<5.7	26	72.2%	3	8.3%	5	13.9%	2	5.6%

$\chi 2 = 19.366$, df =3, p <0.001*

In the study among those with HbA1c >5.7, 21.9% had no complications, 25% had Cardiogenic shock, 18.8% had CCF and 34.4% had Ventricular Tachycardia. Among those with HbA1c <5.7, 72.2% had No complications, 8.3% had Cardiogenic Shock, 13.9% had Congestive Heart Failure and 5.6% had Ventricular Tachycardia.

There was significant association between HbA1c and MACE.

FIGURE 22: BAR DIAGRAM SHOWING ASSOCIATION BETWEEN MACE AxzzzzzzND HBA1C



DISCUSSION:

THE STUDY SAMPLE

Our study population included only patients admitted with ACS without history of type 2 diabetes.

Comorbidities such as renal disease, Cerebrovascular accident, previous history of Ml concurrent infections were excluded, so as to study the prognosis related to the blood sugars and their clinical outcome.

A Total of 100 patients were recruited for the study. Out of which 34 patients satisfied the inclusion criteria and were included. The history was taken, physical examination was carried out and was noted. At admission ECG, cardiac enzymes,FBS,PPBS and HbA1C were done. The patients were followed up for complications during the hospital stay till discharge.

AGE AND GENDER BETWEEN PREDIABETIC AND NON DIABETICS

In our study the mean age in prediabetic ACS patient was 51 to 60 years and that of non diabetic 41 to 50 years indicating the absence of a statistically significant difference between age of diabetic patients when compared to non diabetic patients.

In cases, 21 were male patients and 13 were female patients. Among controls 24 were male patients and 10 were female patients. The male and female comparision between the two groups was not statistically significant.(p=0.442).

There was no gender and age preponderance between the prediabetics and non diabetics

MODE OF PRESENTATION IN ACS

In our study, Among cases, 41.2% had STEMI , 41.2% had NSTEMI and 17.6% had Unstable Angina and among controls, 47.1% had NSTEMI, 29.4% had STEMI and 23.5% had Unstable angina. There was no significant difference in mode of presentation between two groups.

ACS AND CLINICAL FINDINGS

In our study,Among cases: 23 patients had hypertension, 21 patients were smokers and 10 patients were alcoholic. Among controls, 44 patients had hypertension, 36patients were smokers, 2 patients had family history of coronary artery disease and 12 were alcoholics. There was no statistically significant difference between number of smokers and prevalence of hypertension between the groups. . There was significant difference in Alcohol consumption between cases and controls.

Similar observations were noted in several other studies which have proven that hypertension and alcohol consumption were common co-morbidities.[63]

ACS AND CLINICAL OUTCOME

Our study showed that 41.2% had ST Elevation MI , 41.2% had Non ST Elevation MI and 17.6% had Unstable Angina. While population based studies have shown that up to 23.1% of patients presented with ACS has ST elevation Ml.

In our patients, HbA1c >5.7, 25% had Cardiogenic shock, 18.8% had CCF and 34.4% had Ventricular Tachycardia. In this study, the most common adverse cardiac event observed was ventricular tachycardia. Study by Vinita Elizabeth Mani and John [64], in which 47.1% patients

having arrhythmia were in low HbA1C group and 52.9% patients having arrhythmia were in high HbA1C group also support this.

In our study, we found that most of the patients with HbA1C>5.7% had lower EF i.e. 29.4% had Mild LV Dysfunction, 44.1% had Moderate LV Dysfunction and 11.8% had Severe LV Dysfunction as compared to patients with HbA1C<5.7%, who had higher LVEF.

A study done by Razzaq et al [65], demonstrated that the mean EF was significantly lower in a group of HbA1C 6.5-8.5 and in HbA1C> 8.5 as contrasted with that group <6.5. A linear decline in EF was seen with increasing HbA1C level in patients with ACS. 16 out of 100 patients had heart failure. 11 patients belong to high normal HbA1C and 5 belong to normal HbA1C group. This is supported by the study given below.

A study by John and Mani ,[66] 27% patients of heart failure were in low HbA1C group(<7%) and 73% patients with heart failure were in high HbA1C group(>7%). In our study 18.8% patients of heartfailure were in high HbA1C(>5.7%) and 13.9% patients of heart failure were in low HbA1C group(<5.7%). These findings suggests that as there is rise in HbA1C value the chance of heart failure rises in both the studies.

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LIPID PROFILE AND MACE

In a study done by Rahbar et al [67] showed that pre-diabetics are at higher risk of having low level of HDL cholesterol (HDL-c). Impaired lipid profile i.e. dyslipidemia associated with CVD in type 2 diabetes and can also occur in pre-diabetics.

A study carried out by Gaziano et al and Boizel et al [68,69]showed that TG/HDL were significantly higher in IFG/ IGT compared to NFG/NGT. The same was observed in a study conducted by Miyazaki et al [70]that IFG/IGT subjects had higher TG/ HDL ratio (4.0 ± 2.5 for cases and 2.7 ± 1.9 for controls). These results suggested that elevation of postprandial levels of plasma glucose and insulin based on whole body insulin resistance contributed to atherogenic lipids profile.

In our study, subjects with HbA1C levels > 5.7 ,70.6% had Total cholesterol >200 mg/dl and 91.2% had LDL >129 mg/dl and had higher chances of MACE probably attributing to acceleration of macrovascular atherosclerosis.

LIMITATIONS OF THE STUDY

1. This study was limited with respect to population size and the patients were followed only till the time of discharge. This leaves us blind about the long term complications which could be effected by HbA1C.
2. With this study, a scope for further investigation regarding long term complications and complications associated with fluctuating levels of blood sugars may be considered.
3. Large sample size is required to confirm the age, and gender difference in ACS outcome

CONCLUSION

Our study showed that HbA1C is a significant predictor of MACEs after AMI in prediabetic patients.

1. The risk for ventricular tachycardia is 34.4%, cardiogenic shock is 25% and CCF is 18.8% in prediabetics when compared to non diabetics which was statistically significant in this study.

2. It was also observed that there was a significant difference in 2DECHO findings between the two groups.14.7% had normal LV function, 29.4% had mild LV dysfunction, 44.1% had moderate LV dysfunction, 11.8% had severe LV dysfunction among patients with HbA1C > 5.7%.

This biomarker may strengthen the accuracy of clinical care in early intervention and secondary prevention. HbA1C may be considered as an effective indicator that facilitates the early detection of patients with potential adverse prognosis

SUMMARY

This prospective study was conducted on 34 prediabetic patients and 34 non diabetic patients with acute coronary syndrome admitted to RL jalappa hospital , Narayana Hrudalaya, Tamaka, Kolar.

The cases were divided on the basis of presentation into STEMI, NSTEMI and unstable angina. All cases were subjected to investigations, and in-hospital complications were noted. Every patient was then followed up till their discharge.

The results are as follows:

1. Age and sex were comparable between the groups.
   There was no statistically significant difference across the groups in mean age.
2. There was no statistically significant difference in number of smokers, prevalence of hypertension between the groups. Alcohol consumption was found to be significant.
3. In-hospital complications were more common in subjects with high HbA1C values. Incidence of developing ventricular tachycardia was more in patients with high HbA1C values.
4. Subjects with HbA1C > 5.7 had low ejection fraction
5. In our study, subjects with HbA1C levels > 5.7 ,70.6% had Total cholesterol >200 mg/dl and 91.2% had LDL >129 mg/dl and had higher chances of MACE probably attributing to acceleration of macrovascular atherosclerosis.
6. There was significant association between HbA1c > 5.7 and major adverse cardiac events.

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ANNEXURE I

TITLE: HBA1C AS A PROGNOSTIC INDICATOR IN PREDIABETICS WITH ACUTE CORONORY SYNDROME

PROFORMA

- NAME:
- PATIENT ID
- AGE:
- SEX
- ADDRESS

CHIEF COMPLAINTS:

PAST HISTORY:

PERSONAL HISTORY:

COMORBID CONDITIONS:

FAMILY HISTORY:

Coronary artery disease

a. GENERAL PHYSICAL EXAMINATION:

Pulse: /min B.P.: / mmHg R.R.:/cpm

Body Mass Index:

Peripheral pulses:

Pallor □ Cyanosis □ Edema□ Lymphadenopathy □ Clubbing□ Icterus □

b. SYSTEMIC EXAMINATION

- Cardiovascular System**:**

Complications: In-Hospital course

-Tachyarrhythmia
-Cardiogenic shock
-Heart failure
- Death

- Respiratory system

- Per Abdomen
- Central nervous system

INVESTIGATIONS**:**

1. Random blood sugar at admission by glucometer

2. Cardiac enzymes:

3. ECG:

   ▪ ST Elevation MI □ NON ST Elevation MI □

4. Echocardiography:
   Ejection Fraction

5. FBS: PPBS: HbA1C:

6. Hemoglobin:

7. Renal function test:

8. Lipid profile:

Serum cholesterol: Triglycerides:

LDL: HDL:

ANNEXURE –II

INFORMED CONSENT FORM

SUBJECT'S NAME:

HOSPITAL NUMBER:

AGE:

If you agree to participate in the study we will collect information (as per proforma) from you or a person responsible for you or both. We will collect the treatment and relevant details from your hospital record. This information collected will be used for only dissertation and publication. This study has been reviewed by the institutional ethical committee. The care you will get will not change if you don't wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

I understand that I remain free to withdraw from the study at any time and this will not change my future care. I have read or have been read to me and understood the purpose of the study, the procedure that will be used, the risk and benefits associated with my involvement in the study and the nature of information that will be collected and disclosed during the study. I have had the opportunity to ask my questions regarding various aspects of the study and my questions are answered to my satisfaction. I, the undersigned agree to participate in this study and authorize the collection and disclosure of my personal information for dissertation.

DATE: **SIGNATURE /THUMB IMPRESSION**

ANNEXURE III

PATIENT INFORMATION SHEET

TITLE OF THE PROJECT:

HbA1c AS A PROGNOSTIC INDICATOR INPREDIABETICS WITH ACUTE CORONORY SYNDROME

PRINCIPAL INVESTIGATOR : DR ARATHI S GADWALKAR

PURPOSE OF RESEARCH:

I have been explained about the reason for doing the study and selecting me as a subject of the study. This study is for better understanding of impact of HbA1C on glycaemic status in non-diabetic patients presenting with acute myocardial infarction.

RISK AND DISCOMFORTS:

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

BENEFITS:

I understand that my participation in the study will have no direct benefits to me other than potential benefit of treatment.

ALTERNATIVES:

Even if you decline the participation in the study, you will get the routine line of management.

CONFIDENTIALITY:

I understand medical information produced by this study will become part of my hospital record and will be subject to the confidentiality and privacy regulations of the said hospital. If the data are used for publication in the medical literature for teaching purposes, no names will be used, and other identifiers, such as photographs and audio or videotapes, will be used only with my special written permission. I understand I may see the photographs and videotapes and hear the audio tapes before giving this permission. For this purpose every effort will be made by publishing person to contact me in the address furnished by me through postal communication. If no response is received within a reasonable time, all the identities will be removed from the photographs and case report before being submitted for publication.

REQUEST FOR MORE INFORMATION:

I understand that, I may ask more questions about the study at any time. Researcher is available to answer my questions or concern in this research period. I understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or my withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital. I also understand that researcher may terminate my participation in the study at any time after I have

been explained the reasons for doing so and has been helped to arrange for my continued care by my own physician, if this is appropriate.

I have explained to _____

(Patient/Guardian Name)

The purpose of research, the procedures required and the possible risk and benefits to the best of my ability.

Investigator **Date:**

I have been explained clearly about the reason for doing this study, reason for selecting me as a subject in the study. I also have been explained about the risks, benefits and confidentiality of the study. Alternative procedures that might be used in the treatment of my disease also explained to me. I am willing to attend any follow up requested to me at a future date. Freedom is given to me for the participation in the study or discontinue participation at any time without prejudice.

ANNEXURE IV

MASTER CHART

CASES

CASES	AGE	GEN	HTN	SMOKER	F/H CAD	ALC	RBS	Hb	FBS	PPBS	HbA1C
623829	68	1	YES	YES	NO	YES	256	10.8	125	189	6.01
620350	45	1	NO	YES	NO	NO	60	13.7	120	150	5.09
255945	40	1	NO	YES	NO	YES	170	13.8	123	146	6.3
620819	55	2	NO	NO	NO	NO	255	10	125	180	6.4
626027	50	2	YES	NO	NO	NO	167	10.6	120	144	5.9
640324	45	1	YES	YES	NO	NO	289	13.3	120	180	6.3
378411	47	2	YES	NO	NO	NO	140	10	120	155	5.93
585537	75	2	NO	NO	NO	NO	123	10	111	150	5.8
641161	60	1	NO	YES	NO	NO	13	10	112	146	5.9
630405	38	2	NO	NO	NO	NO	70	13.7	117	177	6.3
629531	40	1	NO	YES	NO	NO	289	16	111	146	6.4
627143	45	1	YES	YES	NO	YES	70	13.7	119	162	6.4
627621	48	1	YES	YES	NO	YES	68	12	120	190	6.3
630922	56	2	YES	YES	NO	NO	140	10.7	100	165	6.1
357365	50	1	YES	YES	NO	YES	70	14	120	188	5.6
647208	60	1	NO	YES	NO	NO	143	13.7	120	150	5.8
627143	55	1	YES	YES	NO	YES	154	10.8	120	177	6.2
411721	61	1	YES	YES	NO	NO	143	10.7	120	180	6
625145	53	2	YES	NO	NO	NO	150	10.8	122	190	6
607566	60	1	YES	YES	NO	YES	155	10.8	122	186	6
574983	76	1	YES	YES	NO	YES	164	9.8	120	156	6.23
607625	40	1	YES	YES	NO	NO	158	13.2	120	166	6
632122	35	2	NO	NO	NO	NO	68	9	111	160	5.9
641380	56	1	YES	YES	NO	YES	300	14	109	144	6
633165	66	2	YES	NO	NO	NO	160	10	113	156	6.2
589136	52	1	YES	YES	NO	NO	156	9	120	163	6.3
498132	40	1	YES	NO	NO	NO	277	8.9	122	166	6.4
563130	66	1	YES	YES	NO	YES	240	10.8	100	130	6.3
593210	42	1	YES	NO	NO	NO	200	11	107	145	6.4
431682	38	1	NO	YES	NO	NO	266	12	116	133	6
603812	44	1	YES	NO	NO	NO	140	10	119	139	6.2
630798	49	2	NO	NO	NO	NO	156	9.8	120	190	6.3
493129	55	1	YES	YES	NO	NO	267	9	118	188	5.89
572931	58	2	YES	NO	NO	NO	255	10	119	189	6.1

HbA1C	BU	SC	BMI	SCHOL	TRI	LDL	HDL	TROPONIN I	WI	DIAG	2DECHO	MACE
6.01	84	1.2	28	201	180	160	10	NEGATIVE	1	2	3	2
5.09	9	0.8	29.9	210	180	168	30	POSITIVE	1	1	1	1
6.3	20	0.6	30	300	296	200	30	POSITIVE	2		1	2
6.4	35	0.8	30	290	200	190	30	POSITIVE	1	2	2	3
5.9	24	0.4	26	130	200	190	20	NEGATIVE	0	3	0	0
6.3	30	0.8	32	200	209	250	10	POSITIVE	1	2	1	1
5.93	30	0.9	29	140	142	180	10	POSITIVE	1	1	2	0
5.8	30	0.9	26	136	148	160	30	NEGATIVE	0	3	0	0
5.9	22	1	25	236	130	148	20	POSITIVE	1	1	1	0
6.3	40	0.9	26	300	233	304	10	POSITIVE	2	2	1	2
6.4	22	1	27	288	299	200	20	NEGATIVE	2	1	2	1
6.4	20	0.9	28	250	160	180	26	POSITIVE	1	2	2	1
6.3	40	1.2	35	300	304	200	25	NEGATIVE	2	1	2	2
6.1	40	0.9	24.9	220	200	140	10	POSITIVE	1	2	2	1
5.6	35	0.6	27	122	145	122	45	NEGATIVE	0	3	1	0
5.8	36	1	26	150	100	100	50	NEGATIVE	0	3	0	0
6.2	40	1	28	200	205	260	20	POSITIVE	1	2	2	1
6	38	0.8	28.9	230	200	180	15	POSITIVE	2	1	1	1
6	38	0.9	27.7	201	155	140	25	NEGATIVE	0	3	0	0
6	26	0.8	30	260	240	265	20	POSITIVE	2	2	1	1
6.23	24	1.3	28.9	265	200	300	20	POSITIVE	2	1	3	2,4
6	40	0.8	28.9	250	200	200	30	POSITIVE	1	2	1	0
5.9	23	0.9	22	120	100	100	35	NEGATIVE	0	3	0	0
6	33	1	28	299	180	180	10	POSITIVE	1	2	2	3
6.2	40	1.3	29	200	159	269	15	POSITIVE	1	2	2	3
6.3	22	0.3	30	255	168	169	10	POSITIVE	1	1	2	1
6.4	33	0.9	27	299	170	200	20	POSITIVE	1	2	3	2,4
6.3	24	0.7	28	305	200	200	40	NEGATIVE	1	1	2	2
6.4	22	0.9	33	230	170	200	29	POSITIVE	2	2	1	3
6	33	1	32	210	180	201	20	POSITIVE	1	1	2	1
6.2	29	1	31	200	200	195	35	POSITIVE	1	1	2	1
6.3	20	0.9	26	222	210	140	45	POSITIVE	1	1	3	3
5.89	56	1	30	226	200	165	50	POSITIVE	2	2	2	3
6.1	44	0.9	28	220	210	166	33	POSITIVE	1	1	2	2

CONTROLS.

CONTROL	AGE	GEN	HTN	SMOKER	F/H CAD	RBS	ALC	Hb	FBS	PPBS	HbA1C	BU	S
357565	46	1	YES	YES	YES	140	NO	10	120	156	5	39	0
638598	40	1	YES	YES	NO	156	YES	13.2	120	166	5	40	0
649712	60	1	NO	NO	NO	136	NO	11	96	138	5.7	39	0
626114	60	1	NO	YES	NO	103	NO	11	100	140	5.7	40	0
650168	44	1	NO	YES	NO	120	NO	16.9	88	100	5.3	30	
630405	45	1	YES	YES	NO	132	NO	15.6	100	140	5.6	40	0
648656	52	1	YES	YES	NO	144	NO	15	100	138	4.9	40	0
499866	45	2	NO	NO	NO	123	NO	10.6	90	120	5.6	40	0
613544	66	1	YES	YES	NO	169	NO	16	80	130	5	30	0
649969	45	1	YES	YES	NO	178	NO	13.7	100	122	5.3	40	
629051	46	1	YES	YES	NO	179	NO	13.7	100	136	5.7	39	0
640633	75	2	YES	NO	NO	140	NO	9.7	90	150	5.6	30	1
640324	45	1	YES	NO	YES	155	NO	15	94	136	5	24	0
639014	50	2	YES	NO	NO	110	NO	10.6	100	130	5.6	24	0
637246	56	1	NO	NO	NO	172	NO	10	100	134	5.7	24	0
647146	45	1	NO	NO	NO	114	NO	16	89	122	4.8	26	0
627621	32	1	NO	YES	NO	119	NO	16	86	134	5.2	40	0
618765	54	1	YES	YES	NO	150	NO	10	78	125	5.6	40	0
575738	45	2	NO	NO	NO	158	NO	11	88	135	5	33	0
630922	38	1	NO	YES	NO	140	NO	15	99	135	5.4	24	0
629891	65	2	YES	NO	NO	155	NO	15.9	82	140	5.5	34	1
630130	35	2	NO	NO	NO	158	NO	10	68	122	5	33	0
660555	58	1	YES	YES	NO	150	YES	9.7	100	126	5.2	45	0
640088	45	1	YES	NO	NO	145	NO	13	80	114	5.3	30	0
632117	58	1	YES	NO	NO	100	NO	13.9	100	120	5.6	36	0
646739	65	2	YES	NO	NO	120	NO	10.3	98	135	5.6	36	0
649988	72	2	NO	NO	NO	130	NO	12.08	86	146	5	20	0
620812	48	1	YES	YES	NO	137	NO	11	77	122	5	22	0
620811	36	1	NO	NO	NO	140	NO	11.08	90	134	5.3	24	0
547669	42	1	NO	NO	NO	144	NO	15	87	120	5	29	0
520350	70	2	YES	NO	NO	148	NO	9.7	80	130	5.7	30	0
525027	61	1	YES	YES	NO	149	NO	12	100	130	5.7	33	
640633	45	1	YES	NO	NO	150	NO	15.5	99	139	5.3	24	0
443137	55	2	YES	NO	NO	155	NO	10	83	111	5	35	
655314	45	1	YES	NO	NO	153	NO	16	89	133	5.6	40	0

SC	**BMI**	**SCHOL**	**TRI**	**LDL**	**HDL**	**TROPONIN I**	**WI**	**DIAG**	**2DECHO**	**MACE**
0.9	29.9	255	200	189	20	POSITIVE	1	1	2	3
0.8	28.9	250	200	200	30	NEGATIVE	1	2	1	0
0.9	29.9	140	260	180	20	POSITIVE	2	1	1	0
0.8	30	140	260	180	20	POSITIVE	2	1	1	0
1	25	204	160	140	10	POSITIVE	1	1	2	3
0.9	28	122	155	180	40	POSITIVE	1	2	1	3
0.9	32	245	300	130	30	POSITIVE	1	2	1	0
0.9	22	200	205	130	10	POSITIVE	2	2	1	0
0.9	26	200	49	60	40	NEGATIVE	0	3	0	0
1	28.9	133	140	164	30	POSITIVE	1	2	1	0
0.9	32	140	200	190	30	POSITIVE	2	2	1	0
1.2	28	200	160	145	30	NEGATIVE	0	3	1	0
0.6	25	136	140	200	30	NEGATIVE	1	2	3	2
0.9	28	120	155	130	50	NEGATIVE	0	3	0	0
0.8	30	120	160	145	40	NEGATIVE	0	3	0	0
0.7	26	120	150	60	20	POSITIVE	2	2	1	0
0.8	26	120	150	100	20	NEGATIVE	0	3	0	0
0.9	30	124	150	140	30	POSITIVE	2	2	2	3
0.5	26	140	260	180	20	POSITIVE	1	1	1	0
0.5	26	122	150	105	40	POSITIVE	2	2	1	0
1.2	28	140	200	159	20	POSITIVE	2	2	1	0
0.2	28	120	110	100	40	NEGATIVE	0	3	0	0
0.4	25	123	156	100	20	NEGATIVE	0	3	0	0
0.8	29.9	200	160	100	40	POSITIVE	2	1	0	0
0.8	30	200	160	100	20	POSITIVE	1	1	1	0
0.9	28	125	140	120	33	POSITIVE	1	2	3	2
0.9	22	160	200	130	40	POSITIVE	2	2	1	0
0.5	30	130	200	130	40	POSITIVE	2	2	1	0
0.8	24	136	150	120	60	NEGATIVE	0	3	0	0
0.4	26	110	120	130	40	POSITIVE	2	3	1	3
0.9	29	320	245	300	20	POSITIVE	1	1	3	2
1	28	140	260	180	20	POSITIVE	2	1	2	1
0.4	30	130	110	120	35	POSITIVE	2	2	0	0
1	26	136	200	130	40	POSITIVE	1	1	1	0
0.8	29	130	140	90	30	NEGATIVE	0	3	0	0

KEY TO MASTER CHART

GEN: GENDER

HTN: HYPERTENSION

F/H CAD: FAMILY HISTORY OF CORONART ARTERY DISEASE

ALC: ALCOHOL

Hb: HAEMOGLOBIN

FBS: FASTING BLOOD SUGARS

PPBS: POST PRANDIAL BLOOD SUGARS

BU: BLOOD UREA

SC: SERUM CREATININE

SCHOL: SERUM CHOLESTEROL

TRI: TRIGLYCERIDES

LDL: LOW DENSITY LIPOPROTEIN

WI: WALL INVOLVEMENT

DIAG: DIAGNOSIS

GENDER: MALE-1, FEMALE-2

DIAGNOSIS: STEMI-1, NSTEMI-2, UNSTABLE ANGINA-3.

LV DYSFUNCTION [29]:

NORMAL(50-70%)-0,

MILD(40-49%)-1

MODERATE(30-39%)-2

SEVERE(<30%)-3.

MACE: VENTRICULAR TACHYCARDIA-1, CARDIOGENIC SHOCK-2, CONGES-

TIVE HEART FAILURE-3, DEATH-4,NO COMPLICATIONS-0

WALL INVOLVEMENT

ANTERIOR WALL-1, INFERIOR WALL -2