INTRODUCTION

Myocardial infarction may be defined as the death of the heart muscles. It is a part of the spectrum of acute coronary syndrome, and a consequence of Coronary artery disease (CAD) which leads to decrease in the blood flow to the heart.[1] Unlike other causes of acute coronary syndromes, such as unstable angina(UA), a myocardial infarction occurs when there is cell death, as measured by a blood test of cardiac enzymes such as troponins or CK-MB. [2] When there is evidence of an MI, it may be classified as an ST elevation MI (STEMI) or Non-ST elevation myocardial infarction (NSTEMI) based on the results of an ECG. [3]

Myocardial infarction (MI) or acute coronary syndromes (ACS), the actual term depending on the current definition[4] under which its various presentations are made, remains the major clinical event in patients with atherosclerosis of the coronary arteries.[5] Thrombus formation is a crucial event in the development of coronary artery occlusion.[6] Without it, Coronary heart disease (CHD), also called Coronary artery disease (CAD) or Ischemic heart disease (IHD) would rarely be fatal.[7]

CAD is a major cause of death and disability in developed countries [8]. Although the mortality for this condition has gradually declined over the last decades in western countries, it still causes about one-third of all deaths in people older than 35 years.[9-11] The Framingham Heart Study has perfectly summarized the risk factors that contribute to the development of CAD, providing information regarding objectives for the primary and secondary prevention of CAD.

The 2016 Heart Disease and Stroke Statistics update of the American Heart Association (AHA) has recently reported that 15.5 million persons ≥20 years of age in the USA have CAD[5], whilst the reported prevalence increases with age for both women and men. CAD is the leading cause

of death in adults in the U.S., accounting for roughly one-third of all deaths in subjects over age 35.[10] The 2016 Heart Disease and Stroke Statistics update of the AHA reported that overall death rate from CAD was 102.6 per 100,000 population.[12]

Cardiovascular diseases, especially CHD, are epidemic in India. According to the registrar general of India reports, CHD led to 17% of total deaths and 26% of adult deaths in 2001-2003, which increased to 23% of total and 32% of adult deaths in 2010-2013. The World Health Organization (WHO) and global burden of disease study have also highlighted increasing trends in years of life lost (YLLs) and disability-adjusted life years (DALYs) from CHD in India. Indian studies have reported increasing CHD prevalence over the last 60 years, from 1% to 9%-10% in urban populations and <1% to 4%-6% in rural populations. Using more stringent criteria (clinical ± Q waves), the prevalence varies from 1%-2% in rural populations and 2%-4% in urban populations. In India the age-adjusted CHD mortality rates are 349/100,000 in men and 265/100,000 in women.[13] The incidence and prevalence rates of HF are unreliable in India because of lack of adequate surveillance systems to adequately capture these data.

Chest pain is the most common symptom of acute myocardial infarction and is often described as a sensation of tightness, pressure, or squeezing. Pain radiates most often to the left arm, but may also radiate to the lower jaw, neck, right arm, back, and upper abdomen.Chest pain may be accompanied by sweating, nausea or vomiting, and fainting, and these symptoms may also occur without any pain at all. In women, the most common symptoms of myocardial infarction include dyspnea, weakness, and fatigue. Shortness of breath may occur when the damage to the heart limits the output of the left ventricle, causing LV failure and consequent pulmonary edema.[14]

The heart is a muscular organ responsible for moving blood through a series of vessels to all parts of the body.[15]Acute Myocardial Infarction (AMI) occurs during the period when circulation to a region of the heart is obstructed and necrosis ensues.[16] AMI is characterized by severe pain (angina pectoris), frequently associated with pallor, perspiration, nausea, shortness of breath, and dizziness. A precursor state of AMI is myocardial ischemia, in which obstruction of a coronary artery leads to severe oxygen deprivation of the myocardium prior to necrosis. Angina may be pronounced during myocardial ischemia.[17,18]

Studies suggest that between 40 and 50% of nonfatal AMI are unrecognized by patient and are discovered only on subsequent routine ECG or post mortem examination. [19] Of this unrecognized infarction, half are truly silent, with the patient unable to recall any symptoms whatsoever. [20] The other half of patients with so-called silent infarction can recall an event characterized by symptoms compatible with acute infarction when leading questions are posed after the abnormal ECG is read, unrecognized or silent infarction occurs more commonly in patients without angina, and is more common in patient with diabetes and hypertension.[21]

The diagnosis of AMI, as formally established by the world health organization, requires at least two of the following criteria: a history of chest pain, evolutionary changes on the ECG, and elevation of serial cardiac enzymes. Often, the examining physician is fairly certain after obtaining a patients history and completing a physical examination and performing ECG that an MI has occurred. When the ECG fails to demonstrate an AMI, the cardiac markers must be used.[21]

Electrocardiography

ECG is one of the most important tool in the initial evaluation and triage of patients in whom an acute coronary syndrome (ACS), such as MI, is suspected. It is almost confirmatory of the diagnosis in approximately 80% of cases. For individuals with highly probable or confirmed acute MI, coronary angiography can be used to definitively diagnose the exact blockage or rule out coronary artery disease.

Evidence suggests a number of risk factors for heart diseases: age, high blood pressure, hyperlipidemia, diabetes mellitus, tobacco smoking, processed meat consumption, excessive alcohol consumption, sugar consumption family history, obesity, lack of physical activity, psychosocial factors, and air pollution. While the individual contribution of each risk factor varies between different communities or ethnic groups, the consistency of the overall contribution of these risk factors to epidemiological studies is remarkably strong. Some of the risk factors, such as age, family history, are non-modifiable; however, many important cardiovascular risk factors can be modified by lifestyle change, social change, drug treatment and prevention of Serrano's Cardiac Triad: hypertension, hyperlipidemia, and diabetes.Prevention includes quitting smoking, limit alcohol consumption, lowering cholesterol, controlling high blood pressure, maintaining a healthy weight, decrease body fat (BMI) if overweight or obese, reduce sugar consumptions, exercising and decrease psychosocial stress. For adults without a known diagnosis of hypertension, diabetes, hyperlipidemia, or cardiovascular disease, routine counseling to advise them to improve their diet and increase their physical activity has not been found to significantly alter behavior, and thus is not recommended.[14]

ECG signs that are most commonly associated with acute myocardial ischemia include cardiac arrhythmias, atrioventricular conduction delays, and loss of precordial R wave amplitude.

Coronary artery size and shape of arterial segments, collateral vessels, location, extent and severity of coronary stenosis, and prior myocardial necrosis can all impact ECG manifestations of myocardial ischemia in a patient.[22]

To immediately manage the serious patients with treatment such as reperfusion therapy, it is usual practice to designate MI in patients with chest discomfort, or other ischemic symptoms that develop ST elevation in two contiguous leads on ECG as an 'ST elevation MI' (STEMI). In contrast, patients without ST elevation at presentation are usually designated as having a 'non-ST elevation MI' (NSTEMI). Many patients with MI develop Q waves (Q wave MI), but others do not (non Q-MI). Patients without elevated biomarker values can be diagnosed as having unstable angina and so cardiac markers can be an adjuvant in the right management of the patient.[22]

Certain imaging techniques used in the diagnosis of acute and chronic infarction are echocardiography, radionuclide ventriculography, myocardial perfusion scintigraphy, using single photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI). Positron emission tomography (PET) and X-ray, computed tomography (CT) are less common.[23]

Cardiac markers

Various cardiac markers have been proposed to date some of them are Creatine Kinase (CK); Lactate dehydrogenase (LD); Cardiac Troponin-I and Troponin-T; Myoglobin; Cholesterol; Triglycerides; Low density lipoprotein (LDL); High-density lipoprotein HDL and AST.[21]

AST was the first cardiac biomarker to be used. AST is commonly used in liver function testing and is found in the liver, heart, skeletal muscles, brain and kidneys. Due to its lack of specificity to the cardiac tissue it is no longer used for the diagnosis of AMI. [24,25] In the year 1960, LDH was

being used for diagnosis of AMI.[26] Finally in the year 1979, WHO recommended the panel of cardiac markers consisting of CK, AST and LDH for the diagnosis of AMI.[27]

Serum lactate dehydrogenase (LDH) is a known pathologic marker for a diversity of diseases, including myocardial ischemia. Strenuous and enduring physical activity can transiently induce a greater total serum LDH level, still within its normal range. To date, however, it has not been determined whether normal-range LDH might be inversely associated with coronary artery disease (CAD) in the low-cardiovascular-risk, physically active, adult population. Lactate dehydrogenase (LDH or LD) is an enzyme with two isoenzymes LDH 1 and 2, whose most important role is catalyzing the interconversion of pyruvic acid and lactic acid. LDH-1 isozyme is normally found in the heart muscle and LDH-2 is found mainly in the blood serum. A high ratio of LDH-1 level to LDH-2 suggest MI. This usually comes back to normal in 10–14 days. Normal level of LDH is usually less than 250 units/liter. However, the exact range of normal value may have some variation among different laboratories and patients.[14]

Myocardial necrosis markers

Troponins. The troponins are a complex of 3 protein subunits, namely troponin C, troponin T and troponin I, located on the thin filaments of the skeletal and cardiac muscle fibers. Troponin C is the calcium-binding component, troponin T is the tropomyosin-binding component and troponin I is the inhibitory component. As the isoforms of troponin C is identical in the skeletal and cardiac muscle, troponin C is not extremely specific for myocardial injury.[28,29] The isoforms of troponin T and troponin I differ in the skeletal and the cardiac muscle, and thus are extremely specific for cardiac tissue necrosis.[30] Troponin T is present chiefly in the bound form to the contractile elements of the myocardial cells; however, it is also present free in the cytoplasm.

Troponin T exhibits a dual release initially of the cytoplasmic component and later of the bound component.[31] Troponin I is extremely specific for the cardiac muscle only and has not been isolated from other skeletal muscles. The absolute specificity makes it an ideal marker for diagnosing myocardial injury as it does not increase in any skeletal injury.[32] They are released into the circulation 6-8 h after myocardial injury, with peak at 12-24 h and remains elevated for 7-10 days in the serum.[33] The only disadvantage is the late clearance that makes it difficult to identify a recurrent myocardial infarction in the same span of time.

Myoglobin (MYO). MYO is a small cytoplasmic oxygen-binding protein found in the skeletal as well as the cardiac muscle. It is released extremely early into the serum, 1 h after the onset of myocardial injury, peaks at 4-12 h and returns to baseline values immediately.[34,35] Myoglobin lacks specificity to the cardiac tissue due to the presence of large amounts of MYO in the skeletal muscle and thus is not an ideal candidate for use as a single diagnostic marker,[36] but can be used in conjunction with the troponins or CK-MB. Thus, serum levels of MYO can be used to rule out, rather than diagnose myocardial infarction for a single attack.[37]

CK and CK-MB. CK was first indicated as a cardiac biomarker in the year 1979. CK is an enzyme that is found primarily in the cardiac muscle and skeletal muscle. This enzyme has 3 isoenzymes: MM, MB and BB. CK-MM is the skeletal muscle fraction, CK-MB is the cardiac muscle fraction and CK-BB is the brain fraction of the total CK.[38] Earlier, the total CK was assessed for myocardial infarction but because the total CK contains 95% of the CK-MM fraction, newer concepts have proposed the use of the relative index score (RI) as follows.[39]

CK-MB RI = [CK-MB (ng/ml)/Total CK (U/l)] x 100

The CK-MB rises in the serum at 4-9 h after the onset of chest pain, peaks ~24 h and returns to baseline values at 48-72 h. CK-MB has an advantage over troponins because of the early clearance that helps in the detection of reinfarction. Thus, the serum level of troponin along with the level of the CK-MB fraction can be used efficiently for the diagnosis of myocardial infarction.[40]

Plaque destabilization markers

Myeloperoxidase (MPO)-MPO is a metalloproteinase produced by the polymorphonuclear leukocytes and macrophages. It initiates the production of reactive oxygen species that are important for the development of atheroma and plaque rupture.[41] Thus, an increased level of MPO is a marker of plaque instability.[42] Furthermore, it serves as a predictive marker for future cardiovascular adverse events. [43]

Pregnancy-associated plasma protein A (PAPPA)-PAPPA is also a metalloproteinase that has an active role during the rupture of an atherosclerotic plaque.[44] It is primarily produced by the syncytiotrophoblasts of the placenta, as well as by the fibroblasts, vascular endothelial cells and vascular smooth muscle cells. In atherosclerosis, it has been associated with plaque progression and instability. [45]

Soluble cluster of differentiation 40 ligand (sCD40L)- It belongs to tumor necrosis factor-α (TNF-α) family is upregulated on the platelets located in the intraluminal thrombus. The activation of the inflammatory and coagulant pathways during thrombogenesis causes the release of CD40L into the circulation, thus indicating plaque rupture and subsequent myocardial infarction. [46]

TNF-α- It is a pleiotropic cytokine produced by the endothelial cells, smooth muscle cells and macrophages. TNF-α levels are markedly elevated in advanced heart failure.[47] The role of TNF-α in atherosclerosis is the production of tissue inhibitors of metalloproteinases by the fibroblasts. Thus, the production of excess amounts of metalloproteinases causes rupture of the atheromatous plaque. [48] Additionally, it can stimulate the synthesis of IL-6 by the smooth muscle cells. This confirms the role of TNF-α in the regulation of the inflammatory cascade. Thus, elevated levels of TNF-α are indicative of recurrent non-fatal myocardial infarction or a fatal cardiovascular event. [49]

Inflammatory markers

Coronary plaque disruption with consequent platelet aggregation and thrombosis is the most important mechanism by which atherosclerosis leads to the acute ischemic syndromes of unstable angina (UA), AMI, and sudden death. Inflammation is essential to the initiation, development, and progression of atherosclerosis. The association of increased serum levels of acute-phase proteins with the progression of atherosclerosis and occurrence of atherosclerosis-related adverse events, such as coronary artery disease and MI, has been well documented epidemiologically. These acute-phase protein markers include serum C-reactive protein (CRP), pentraxin 3 (PTX3), amyloid A, homocysteine, and fibrinogen.[50]

C-reactive protein (CRP).CRP is an acute phase protein secreted by the hepatocytes during an inflammatory stimulus. In addition to being an inflammatory marker, CRP has a pro-inflammatory effect causing expression of adhesion molecules and inflammatory cells. It has been shown that CRP is increased in patients with unstable angina; however, owing to lack of

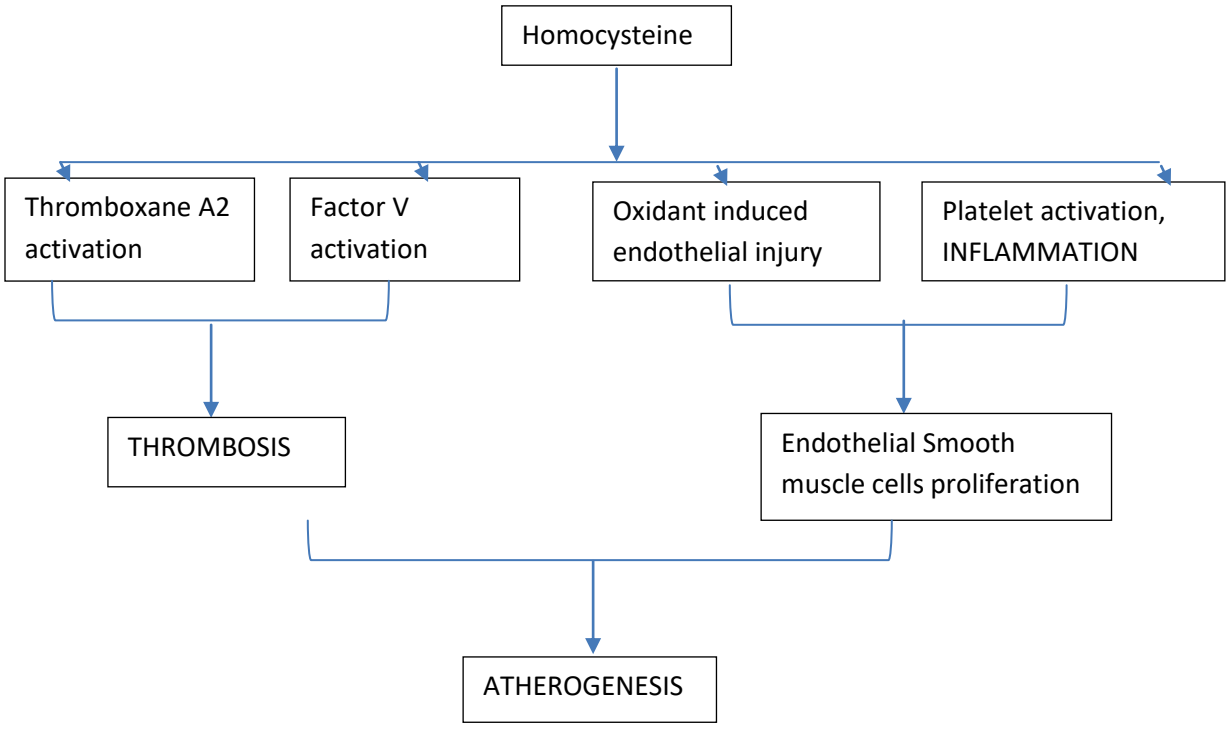
sensitivity and specificity, it cannot be used as a diagnostic marker. As a prognostic indicator, high CRP levels have also been associated with poor outcome.[50]

Pentraxin 3 (PTX-3).PTX-3 of the PTX family is a specific marker of vascular inflammation produced by the vascular endothelial cells, vascular smooth muscle cells, macrophages, and neutrophils in response to an inflammatory stimulus. The PTX-3 level has been proposed as a prognostic biomarker of adverse outcome in patients with unstable angina pectoris, myocardial infarction and heart failure. However, as opposed to CRP, PTX-3 predicts advanced atherosclerosis and is more specific for vessel wall inflammation.[50]

Interleukin (IL)-6.Another marker of early atherosclerosis is IL-6, which has a major role in the recruitment and activation of inflammatory cells in response to ischemia and further addition, it stimulates the liver to produce the acute phase protein, CRP. Thus, an elevated serum level of IL-6 and CRP are associated with the development of atherosclerosis and additionally to the development of type II diabetes in insulin-resistant individuals.[50]

Homocysteine is a non-protein α-amino acid. It is a homologue of the amino acid cysteine, differing by an additional methylene bridge (-CH_2-). It is biosynthesized from methionine by the removal of its terminal C^{ε} methyl group. The factors known to influence homocysteine metabolism are vitamin B12, vitamin B6, folate and genetic aberration in the methylenetetrahydrofolate reduction genes. Genetic aberrations in the methylenetetrahydrofolate reductase gene may account for reduced enzyme activity and elevated plasma homocysteine concentrations.[51] Since McCully[52] first proposed the homocysteine theory of atherosclerosis, a lot of observational studies have reported a relation between blood levels of homocysteine and CAD.[53]

Homocysteine induces atherogenesis by mechanisms like endothelial injury, platelet activation, smooth muscle proliferation, oxidative modification of low-density lipoproteins, and endothelial leukocyte interactions as shown in Flow Chart 1. High blood homocysteine levels (Hyperhomocysteinemia) makes a person more prone to endothelial cell injury, leading to inflammation in the blood vessels, which in turn leads to atherogenesis, which resulting in ischemic injury. Hyperhomocysteinemia is therefore a certain risk factor for coronary artery disease. [51]



Flow Chart 1 : Role of Homocysteine in atherosclerosis

Hyperhomocysteinemia has been correlated with the occurrence of blood clots, heart attacks and strokes, but it still remains unclear if Hyperhomocysteinemia is an independent risk factor for these conditions because of evidence lacking long individual risk assessment studies.[51]

The analysis of cardiac biomarkers has become the frontline diagnostic tools for AMI, and has greatly enabled the doctors in the rapid diagnosis and treatment planning, thereby reducing the mortality rate by a great extent. However, the future of cardiac biomarkers will follow the analysis of a panel of markers for the diagnosis and prognosis of myocardial infarction. Thus this observational study was undertaken to see the levels of inflammatory marker Homocysteine as an independent predictor of CAD and its relationship with other cardiac biomarkers like CRP, AST, LDH, Troponin and CK-MB to suggest a future panel of cardiac biomarkers for diagnosis of MI.