Introduction

Coronary heart disease (CHD) is a leading cause of morbidity and mortality in many countries world-wide. Despite the search for novel risk factors for CHD, established risk factors still play a major role. These are the dyslipidaemias, hypertension, cigarette smoking, diabetes, obesity and physical inactivity *(**Lee et al., 2001**)*.

Acute coronary syndrome encompasses a spectrum of coronary artery diseases, including unstable angina, ST-elevation myocardial infarction and non ST-elevation myocardial infarction *(**Braunwald et al., 1994**)*. Haemostasis plays an important role in the development of cardiac complications ***(Lisowski et al., 2004).*** Platelets activation is a hallmark of acute coronary syndrome ***(Van de Werf et al., 2003).***

Drug trials have demonstrated that antiplatelet drugs including aspirin, clopidogrel and glycoprotein (Gp) IIb/IIIa inhibitors provide substantial therapeutic benefit in patients with acute coronary syndrome. Thus, numerous lines of evidence suggest that platelets play a dominant pathogenic role in the development and outcome of acute coronary syndrome ***(Fuchs et al., 2006).***

The potential utility of measuring platelet function in patients with coronary artery disease includes monitoring antiplatelet therapy and predicting clinical outcome *(**Paul et al., 2007**)*.

Platelet function is increased under high shear stress in acute coronary syndrome patients ***(Harison et al., 2005).*** Several studies have found increased platelets function, as measured by shortened closure time (CT)-values with the platelet function analyzer ***(Ziegler et al., 2002).***

Platelet function analyzer measures the time needed for a platelet plug to form after activation of platelets by pathophysiological relevant stimuli (eg, collagen and adenosine diphosphate or collagen and epinephrine), which is a prognostic in peripheral arterial occlusive disease ***(Ziegler et al., 2002).***

Aim of the Work

The purpose of this study is to:

Assess the platelet hyperactivity in patients with acute coronary syndrome and correlate it with the severity and outcome of these patients.

Acute Coronary Syndrome

Acute coronary syndromes are a major heath problem and represent a large number of hospitalization annually. Studies conducted in the 1960s and 1970s showed a rate of major adverse clinical events (death/myocardial infarction) ranging from 10% at 3 months to 17% at 24 month. Even in the late 1990s the prognosis of ACS remains unfavourable ***(Bertrand et al., 2000)***.

Definition of Acute Coronary Syndrome (ACS):

The term ACS refers to a spectrum of acute severe cardiac disorders that include UA (unstable angina), non ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) figure (1). These disorders are characterized by myocardial oxygen demand and supply mismatch, most often caused by atherosclerotic coronary artery disease ***(Antman and Braunwald, 2005)***.

According to WHO's definition, a myocardial infarction occurs if at least two of three criteria are fulfilled:

a. Typical ischemic chest pain.

b. Raised concentrations of serum Creatine kinase-MB.

c. Typical electrocardiographic findings, including development of pathological Q-waves.

(Tunstall-Pedoe et al., 1999).

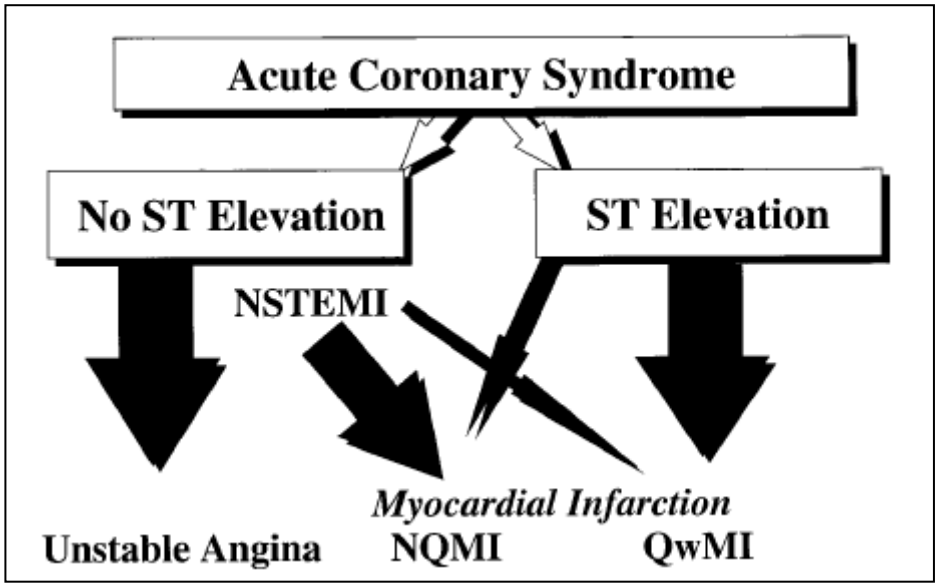

Figure (1): Classification of acute coronary syndrome ***(Braunwald et al., 2002).*** NSTEMI (non ST-segment elevated myocardial infarction), QwMI (Q wave elevated myocardial infarction), NQMI (non Q wave elevated myocardial infarction).

Patients with ischemic discomfort may present with or without ST-segment elevation on the ECG. The majority of patients with ST-segment elevation ultimately develop a Q-wave AMI (Q wave Acute myocardial infarction), whereas a minority develop a non–Q-wave AMI (Non Q wave Acute myocardial infarction). Patients who present without ST-segment elevation are experiencing either UA (unstable angina) or an NSTEMI (non ST-segment elevated myocardial infarction) ***(Braunwald et al., 2002).***

Angina is largely based on the clinical presentation. Stable angina pectoris is characterized by a deep, poorly localized chest or arm discomfort that is reproducibly

associated with physical exertion or emotional stress and relieved within 5 to 15 minutes by rest or sublingual nitroglycerin, or both.

In contrast, unstable angina (UA) is defined as angina pectoris with at least one of three features: First, occurring at rest (or with minimal exertion) and usually lasting more than 20 minutes and second being severe and described as frank pain and of new onset.

Some patients with this pattern of ischemic discomfort, especially those with prolonged rest pain, develop evidence of myocardial necrosis on the basis of cardiac serum markers (such as creatine kinase muscle-brain fraction "CK-MB" or troponin T or I or both) and thus have a diagnosis of myocardial infarction (MI) ***(Cannon and Braunwald, 2005).***

Pathology of Coronary Heart Disease:

Figure (2) shows microscopic findings of normal coronary artery, the lumen is large and without any narrowing by atheromatous plaque. The muscular arterial wall is of normal proportion ***(Klatt, 2002).***

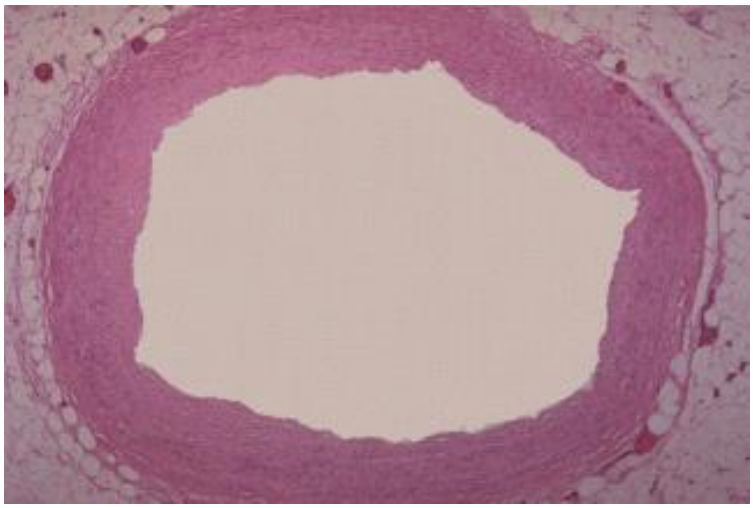

Figure (2): Microscopic findings of normal coronary artery ***(Klatt, 2002).***

Atherosclerosis is an intimal disease of systemic arteries that range in size from the aorta to the epicardial coronary arteries. Atherosclerosis is characterized by discrete intimal plaques, although at an advanced stage, the lesions coalesce. Each plaque has variable combinations of extracellular lipid and connective tissue matrix proteins such as collagen. The American Heart association has recommended a nomenclature for types of plaques and has suggested ways in which they may evolve ***(Stary et al., 1995).***

Type I lesion is the initial lesion, it develops when monocytes adhere to endothelial surface and migrate from the lumen of an artery to accumulate in the intima.

Type II lesion is the fatty streaks that consist of focal accumulation of lipid-filled foam cells largely of monocyte origin immediately beneath the intact endothelium (Figure 3) ***(Stary et al., 1995).***

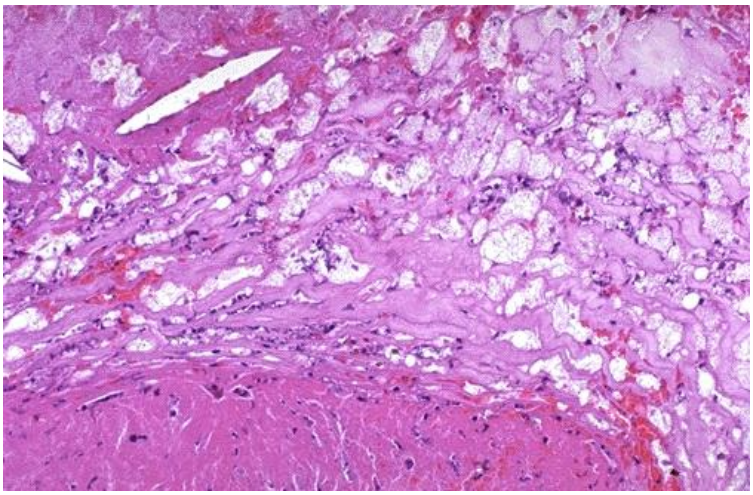

Figure (3): This is high magnification of the atheroma shows numerous foam cells and numerous dark blue inflammatory cells scattered within the atheroma ***(Klatt, 2002).***

Type III lesion contains in addition small pools of extracellular lipid. Although type I to type III plaques are the precursors of more advanced lesions, they do not cause clinical symptoms ***(Stary et al., 1995).***

Type IV lesion is characterized by two additional features, smooth muscle cells appear within the lesion beneath the endothelium and pools of extra cellular lipid coalesce to form a lipid core.

Type V lesion shows significant connective tissue deposition and the formation of a fibrous capsule containing the lipid core. The portion of this capsule separating the core from the lumen is the plaque cap. Plaques with lipid core and fibrous cap are designated as type Va. Some plaques have heavy calcification (type Vb) (Figure 4).

Another form of advanced plaque (type Vc) is almost entirely composed of collagen and smooth muscle cells. **Type VI** plaques are those complicated by thrombosis ***(Stary et al., 1995).***

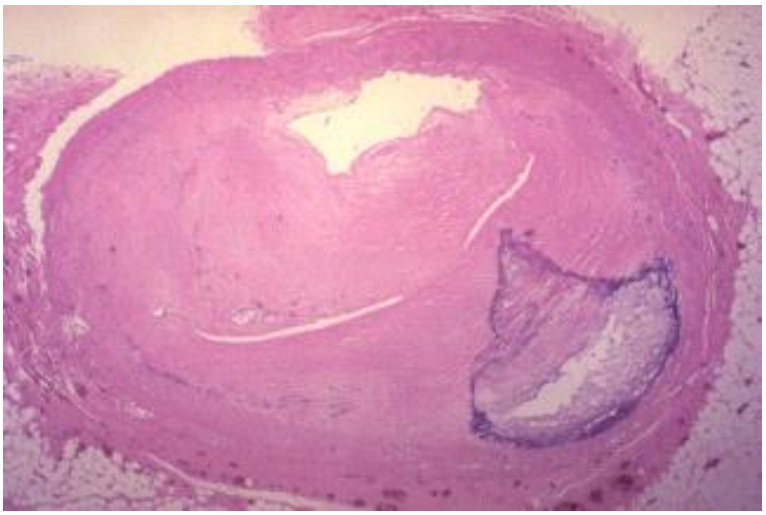

Figure (4): Severe degree of narrowing in coronary artery. There is a large area of calcification on the lower right, appears bluish on this H&E stain ***(Klatt, 2002).***

Pathogenesis of ACS:

The process central to the initiation of an acute coronary syndrome is disruption of an atheromatous plaque. Fissuring or rupture of these plaques and consequent exposure of core constituents such as lipids, smooth muscles and foam cells leads to the local generation of thrombin and deposition of fibrin. This in turn promotes platelet aggregation, adhesion and formation of intracoronary thrombus ***(Grech and Ramsdale, 2003).*** This will be discussed later in chapter (2).

Risk Factors for Atherothrombotic Diseases:

1. Non Modifiable Risk Factors:

a. Age:

Increasing age has been shown to be associated with a significant increase in adverse outcomes in patients with ACS. About 85% of people who die from heart disease are over the age of 65 years ***(Watkins et al., 2005).***

b. Gender:

Coronary artery disease and heart attacks are much more common in middle-aged men. Women have (on average) 10 - 15 more years of heart disease-free life than men. This is due to the cardioprotective effect of estrogen in females. At 15 years postmenopause, the incidence of angina occurs with equal frequency in both sexes. Evidence exists that women more often have coronary events with atypical symptoms such as sudden dyspnea and nausea. This explains the frequent failure to initially diagnose ACS in women ***(Watkins et al., 2005).***

c. Ethnicity:

Of all major ethnic groups, Afro-American women face the highest risk for death from heart disease. Native American men have a lower risk for heart disease than Caucasian men ***(Watkins et al., 2005).***

2. Modifiable Risk Factors:

a. Serum lipids:

Cholesterol is an essential nutrient necessary for many functions. However, low-density lipoprotein (LDL) cholesterol is considered the "bad" cholesterol responsible for many heart problems. While, high-density lipoprotein (HDL) cholesterol is the "good" cholesterol that helps to protect against heart disease. The ratio of these cholesterol subtypes can affect heart disease risk. Triglycerides are another type of lipids (fat molecule) that can be bad for the heart ***(Wang et al. 2006a).***

Clinical trials have been made to lower cholesterol levels using the hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. These drugs lower LDL cholesterol more effectively than previously available agents ***(Ridker and Libby, 2005).***

b. Obesity:

The effect of obesity on cholesterol levels is complex. Obesity does not appear to be strongly associated with overall cholesterol levels. Among obese individuals triglyceride levels are usually high while HDL levels tend to be low, both are risk factors for heart disease. Obesity, in any case has other effects as hypertension and increase in liability to inflammation that pose major risks to the heart ***(Yusuf et al., 2005).***

c. High blood pressure:

Hypertension is defined as systolic blood pressure of 140 mmHg or greater, diastolic blood pressure of 90 mmHg or greater, or both ***(Van den Hoogen et al., 2000).***

Hypertension is a silent cardiovascular risk factor. Most epidemiological studies now recognize the joint contributions of systolic and diastolic blood pressures to the development of cardiovascular risk; an issue that has markedly changed strategies for risk detection. These effects are greatest among older individuals and those with known cardiovascular disease. Isolated systolic hypertension in particular appears to represent a distinct pathophysiological state in which elevated blood pressure reflects reduced arterial elasticity not necessarily associated with increased peripheral resistance or an elevation in mean arterial pressure ***(Ridker and Libby, 2005).***

d. Metabolic syndrome, insulin resistance and diabetes:

Patients with diabetes have 2-8 fold higher rates of future cardiovascular events as compared with age and ethnicity matched non diabetic individuals. Three fourths of all deaths among diabetic patients result from coronary heart diseases. Compared to unaffected individuals, diabetic patients have a greater atherosclerotic burden both in the major arteries and in the microvascular circulation. Thus insulin resistance and diabetes rank among the major cardiovascular risk factors ***(Henry et al., 2002).***

Although hyperglycemia is associated with microvascular disease, insulin resistance itself promotes atherosclerosis even

before it produces frank diabetes and available data confirm the role of insulin resistance as an independent risk factor for atherothrombosis. This finding has prompted recommendations for increased surveillance for the metabolic syndrome, a cluster of glucose intolerance and hyperinsulinemia accompanied by hypertriglyceridemia, low HDL levels, hypofibrinolysis, hypertension, microalbuminuria, a predominance of small dense LDL particles and central obesity ***(Ridker and Libby, 2005).***

The definition adopted by the National Cholesterol Education Program adult treatment panel requires at least three of the following five criteria:waist circumference >102 cm in men and 88 cm in women, serum triglyceride levels =150 mg/dl, HDL cholesterol <40 mg/dl in men and <50 mg/dl in women, blood pressure of =130/85 mm Hg and serum glucose concentration =110 mg/dl ***(Ridker and Libby, 2005).***

e. <u>Smoking:</u>

Cigarette consumption remains the single most important modifiable risk factor for coronary artery disease ***(Ridker and Libby, 2005).***

Beyond acute unfavorable effects on blood pressure, sympathetic tone and a reduction in myocardial oxygen supply, smoking affects atherothrombosis by several other mechanisms. In addition to accelerating atherosclerotic progression, long term smoking may enhance oxidation of low density lipoprotein cholesterol and impairs endothelium-dependent coronary artery vasodilatation ***(Ridker and Libby, 2005).***

Additionally, smoking is associated with spontaneous platelet aggregation, increased monocyte adhesion to endothelial cells and a decrease in endothelial derived fibrinolytic and antithrombotic factors ***(Ridker and Libby, 2005).***

f. Sedentary Lifestyle and Exercise:

People who are sedentary are almost twice as likely to suffer heart attacks as those who exercise regularly. Exercise has several effects that benefit the heart and circulation. However, sudden strenuous exercise can put people at risk for angina and heart attack. Patients with angina should never exercise shortly after eating ***(Singh and Muller, 2003).***

g. Stress and Psychologic Factors:

Stress can affect the heart when it activates the sympathetic nervous system. Some studies suggest an association between acute stress and a higher risk for serious cardiac events such as heart rhythm abnormalities and heart attacks, in people with heart disease. Depression increases the severity of heart attack and may even impair a patient's response to medication for heart disease ***(Singh and Muller, 2003).***

h. Alcohol:

Heart disease is the leading cause of death in alcoholics. Heavy alcohol consumption can raise blood pressure and excessive drinking may increase the risk for hemorrhagic

stroke. Large doses of alcohol can trigger irregular heartbeats, which can be dangerous in people with existing heart disease ***(Wang et al., 2006a).***

Diagnosis of ACS:

1. Clinical Picture of ACS:

Symptoms of acute coronary syndrome include chest pain, referred pain, nausea from vagal stimulation, severe weakness, vomiting and dyspnea. Some patients may present without chest pain, sudden dyspnea was the sole presenting feature in 4 to 14 % of patients with acute MI. Pain may be referred to the arm, the jaw, the neck, the back, or even the abdomen. Pain radiating to the shoulder, left arm, or both arms somewhat increases the likelihood of ACS ***(Goodacre et al., 2002).***

A patient may present to the emergency department because of a change in pattern or severity of symptoms. A new case of angina is more difficult to diagnose because symptoms are often vague and similar to those caused by other conditions (e.g., indigestion, anxiety) ***(Goodacre et al., 2002)***.

2. Laboratory Investigations:

Conventional Biomarkers:

1. Creatine Kinase and MB Isonzyme:

Creatine kinase (CK) is a dimeric enzyme that catalyzes the reversible phosphorylation of creatine to creatine phosphate by ATP. CK-MB is one of three dimeric isoenzymes of CK. All

cytoplasmic CK is composed of M and B subunits. They associate to form CK-MM, CK-MB, and CK-BB isoenzymes. CK-MM is found predominantly in striated muscles of both the skeleton and the myocardium (***Panteghini et al., 2006***).

CK-MB isoenzyme comprises approximately 20% of total CK in the myocardium, and about 0% to 3% of CK in the skeletal muscles. However, there exists another form that differs from these forms immunologically and by electrophoretic motility. This is the CK-Mt isoenzyme which is located between the inner and outer membranes of the mitochondria. In the heart, it constitutes about 15% of total CK activity ***(Panteghini et al., 2006).***

The serum CK level rises within three to eight hours after myocardial injury, peaks in 10 to 24 hours, and returns to baseline within three to four days. A serum CK level may be used as a screening test to determine the need for a more specific test. CK-MB is much more cardiac specific than CK alone. CK-MB typically is detectable in serum four to six hours after the onset of ischemia, peaks in 12 to 24 hours and normalizes in two to three days ***(Karras and Kane, 2001).***

2. Lactate Dehydrognase Enzyme:

In addition to heart muscle, lactate dehydrogenase (LDH) occurs in many other parts of the body, including the kidneys, red blood cells, brain, stomach, and skeletal muscle and at least five LD isoenzymes are known LDH is composed of four subunit peptides designated M and H ***(Apple and Jaffe, 2006).***