INTRODUCTION

Coronary artery disease (CAD) is predicted to be the leading cause of mortality and morbidity by the year 2015 due to the explosive rise in its incidence (***Kumar et al., 2008).*** The disease includes stable angina and acute coronary syndrome which ranges from unstable angina (UA), characterized by myocardial ischemia to acute myocardial infarction (AMI) resulting from myocardial necrosis (***Antman and Braunwald , 2008***).

Atherosclerosis is considered the underlying pathogenic process in coronary artery disease (***Munro and Cotran, 2004)***. Atherosclerosis is a chronic inflammatory disorder resulting from an interaction between biology of arterial wall and various stress stimuli present in circulating blood as oxidized low density lipoprotein cholesterol (LDL-C), infectious agents as chlamydia and enterovirus, tobacco toxins and hyperglycemia ***(Shashkin et al., 2005).*** All previously mentioned factors enhance endothelial injury through release of interferon gamma (INF γ) and adhesion molecules with subsequent accumulation of inflammatory cells, migration and proliferation of smooth muscles resulting in formation of atheromatous plaque ***(Natalia et al., 2005***). In 76% of patients, the plaque is vulnerable to complications such as rupture, calcification and occlusion leading to progressive stenosis of the arterial lumen and ischemia of the perfused organ (***Erling, 2005***).

Nowadays coronary angiography is the most accurate method for diagnosing coronary artery disease through obtaining an image of the interior of the coronary artery, thus helping in defining the patient's coronary anatomy, the extent and the severity of the stenosis**.** However, it is considered an invasive test which has some major complications as stroke, heart attacks and kidney damage. Hence there is an urgent need for an early, sensitive and non invasive laboratory marker that correlates with the degree of severity of coronary artery disease (***Maeder and Zellweger, 2009)***.

CXC Ligand16 (CXCL16) is a protein with both scavenger receptor and inflammatory chemokine like action. There are three forms of CXCL16; a membrane bound form, a soluble form and a cellular form (***Aslanian and Charo, 2007)***. It is expressed in macrophages and aortic smooth muscle cells but not found in normal arteries. CXCL16 has been implicated in a variety of inflammatory diseases such as hepatitis and encephalitis. The function of CXCL16 is mediated through release of proinflammatory stimuli as gamma interferons which increase CXCL16 expression, enhance uptake of oxidized LDL and facilitate foam cell formation. The receptor of CXCL16 has been identified as CXCR6 which is enriched in cells found at site of inflammation as natural killer cells (NK) and T helper cells type 1 (Th1) . The binding between CXCL16 and CXCR6 increases nuclear factor kappa B and tumor necrosis factor which attract NK cells and TH1, thus induces an immune response (***Smith et al., 2008***).

Several researches, have detected the expression of CXCL16 on atheromatous plaques, hence they suggested a potential role for CXCL16 as a prognostic marker in acute coronary syndrome ***(Sun et al., 2008).***

AIM OF THE WORK

The aim of the present study is to evaluate the role of serum CXC ligand 16 (CXCL16) in coronary artery disease through studying its relationship to the severity of coronary artery stenosis.

Chapter (1)

CORONARY ARTERY DISEASE

A. Introduction

Coronary artery disease (CAD) also known as ath erosclerotic heart disease is the No. 1 killer worldwide, affecting more than 13 million individuals every year ***(Grech and Ramsdale, 2011).*** It accounts for nearly 50 percent of all deaths per year ***(Kleinschimdt, 2013)***

The disease is caused by plaque building up along the inner walls of epicardial coronary artery, which narrows the arteries and reduces blood flow to the heart. Atherosclerosis is considered the underlying pathogenic process in CAD (Munro and Cotran, 2004). Atherosclerosis is a progressive disease process that is thought to begin in childhood and has clinical manifestations in middle to late adulthood ***(Crowther, 2005).***

Still, the biological bases of the predilection of certain sites to develop atheroma are not clearly understood. However, atherosclerosis can involve both large and medium-sized arteries diffusely. In the coronaries it causes stenosis and ectasia. Atherosclerosis alone is rarely fatal however superimposed thrombus on a ruptured or eroded atheromatous plaque precipitates the life-threatening clinical

events such as coronary artery disease and cereberovascular stroke ***(Falk, 2006).***

B. Classification :

Ischemic heart diseases include a wide spectrum of conditions, ranging from silent ischemia and chronic stable angina (exertion induced angina), through unstable angina (UA), to acute myocardial infarction (AMI). UA occupies the center of this spectrum, causing disability and risk greater than that of chronic stable angina but less than that of AMI ***(Rifai, and Wornick, 2012).***

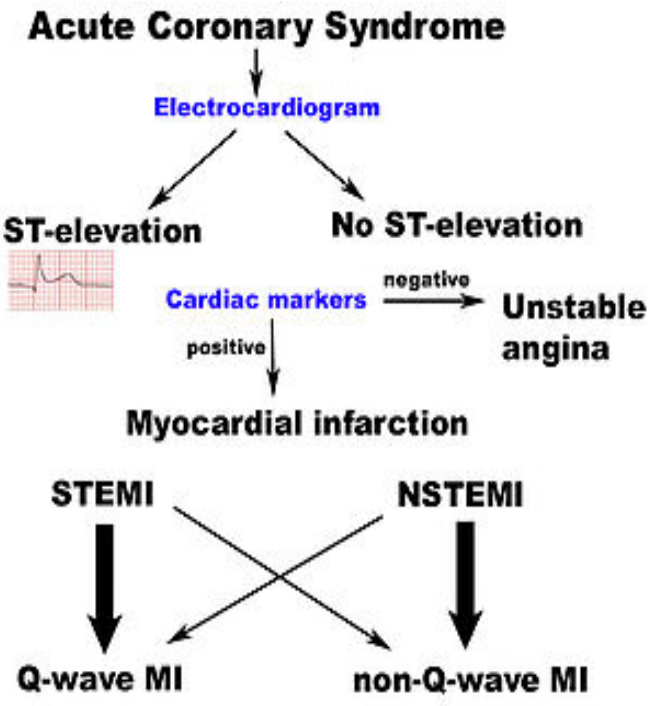

Fig. (1): Classification of acute coronary syndrome ***(Braunwald and Cannon, 2007).*** STEMI: ST- segment elevation myocardial infarction, NSTEMI: non-ST- segment elevation myocardial infarction.

C. Path physiology of Acute Coronary Syndrome:

Acute coronary syndrome occurs due to acute or subacute primary reduction of myocardial oxygen supply provoked by disruption of an atherosclerotic plaque associated with inflammation, thrombosis, vasoconstriction and micro-embolization ***(Senes et al., 2011).*** Atherosclerosis contributes to significant narrowing of the artery lumen and a tendency for plaque disruption and thrombus formation ***(Singh and Muller, 2012).***

D. Risk Factors for CAD

Risk factor of CAD can be classified into traditional and non traditional risk factor as shown in table 1.

Table (1): Traditional and Non Traditional Risk Factors of CAD ***(Mallika et al., 2007).***

Traditional Risk Factors
Dyslipidemia Hypertension Diabetes mellitus Obesity Cigarette Smoking Family history Physical inactivity
Non Traditional Risk Factor
Homocysteine Fibrinogen Infections

1. Traditional Risk Factors:

a. Dyslipidaemia

Dyslipidaemia is a term used to describe abnormal metabolism of plasma lipids that can be due to genetic, dietary or secondary to a disease ***(Goff et al., 2006).***

i. Hypercholesterolemia

Morphologic studies of the atherosclerotic plaques revealed that cholesterol is a major gradient in all of these plaques and it is not made within the vessel wall but it is derived from circulating lipoproteins (Libby and Aikawa, 2008). The levels of the cholesterol subtypes which can affect heart disease risk according to the National Cholesterol Education Program and Adult Treatment Panel III (NCEP-ATP III) are shown in (table 2).

Table (2): The relationship between risk of developing of CAD and LDL-C, HDL-C and total cholesterol (LDL-C: Low density lipoprotein- cholesterol, HDL-C: High density lipoprotein-cholesterol)

	Level (mg/dL)	Risk
LDL-C	<100	Optimal
	100-129	Near
	130-159	optimal
	160-189	Borderline
	≥190	high
Total cholesterol	<200	Desirable
	200-239	Borderline
	≥240	high
HDL-C	<40	Low
	≥60	High

(Rifai and Wornick, 2012)

Elevated LDL-C is considered a major cause of CAD. LDL-C causes injury to the endothelium and the underlying smooth muscle. When LDL-C particles become trapped in an artery, they can undergo progressive oxidation leading to the formation of oxidized LDL (ox-LDL) that become internalized into the macrophages by the means of receptors present on the surface of macrophages called scavenger receptors, leading to the transformation of macrophages to foam cells. In addition, elevated LDL-C in plasma leads to the stimulation of inflammatory cells to secrete various inflammatory mediators, such as interleukin-1 (IL-1) and chemo-attractants, such as

monocyte chemoattractant protein (MCP-1) which is derived from the endothelial cells. It appears that LDL-C is involved in all the stages of atherosclerosis, from endothelial dysfunction, plaque formation and growth, to plaque instability and disruption ***(Kullo and Ballantyne, 2005).***

ii. Hypertriglyceridemia:

Many epidemiological evidences suggest that triglycerides play an important role in determining CAD risk as elevation of remnants of triglyceride rich lipoprotein found to be correlated with the magnitude of CAD although fasting triglyceride level may be normal. Moreover, post prandial triglyceride level proved to be an independent predictor for CAD. Accordingly, the inability to clear these lipid-rich and potentially toxic remnant particles may play a role in atherogenesis ***(Patel, 2007).***

Elevated triglycerides have been associated in clinical trials with both early coronary and carotid arteries atherosclerosis for persons with normal lipid profile and those with mild to moderate hyperlipidemia, independently of established risk factors ***(Nystrom, 2007).***

Triglycerides may cause a coagulant state involving disturbance of both blood coagulation and fibrinolysis, in particular due to elevation of the plasma level of activated factor VII (VIIa) and plasminogen activator inhibitor (PAI-1).

Therefore, these disturbances of the haemostatic system might account for the link between hypertriglyceridemia CAD ***(Isoda, 2007).***

iii. Lipoprotein a (Lp (a)):

Structurally Lp(a) is identical to LDL-C with the addition of a single apo (a) molecule attached by a disulfide bond to the apo B-100. Lp(a) has been identified as an independent risk factor for CAD ***(Hackam and Anand, 2003).***

The mechanism by which Lp (a) may increase the risk of CAD is complex. Lp (a) has a structural similarity to plasminogen thus may compete with plasminogen for tissue plasmonogen activator. This in turn leads to decreased formation of plasmin and hence impaired fibrinolysis. In addition, Lp (a) may directly bind to fibrin inhibiting its degradation by the fibrinolytic pathway **(*Mallika et al., 2007).***

b- Hypertension

Hypertension follows closely behind lipids on the list of classical risk factors for atherosclerosis. Numerous epidemiological studies have established a direct relation between blood pressure elevation and incidence of CAD and stroke. In addition, hypertension frequently coexists with other risk factors such as central obesity and coagulation abnormalities ***(Mitra and Panja, 2005).***

Hypertension may worsen atherosclerosis by several mechanisms. Elevated blood pressure may modulate gene expression of arterial cells by biochemical forces. Cyclic strain increases the expression of intercellular adhesion molecule-1(ICAM-1) by vascular endothelial cells and enhances adhesion of monocytes to endothelial cells with subsequent development of atherosclerosis ***(Jian-Jun and Ji-Lin, 2005).***

Savola and Schiffrin (2007) proved that an important component in hypertension is the renin / angiotensin system. Activation of this system leads to the production of angiotensin II which in turn plays a key role in the development and pathophysiology of atherosclerosis by several mechanisms. It showed that angiotensin II may generate superoxide anion directly in the vasculature. Also, it cause a marked inflammatory response characterized by recruitment of macrophages into the arterial wall. Moreover, angiotensin II induces expression of the lectin-like ox-LDL receptor by vascular endothelial cells which enhances LDL clearance by endothelial cells. Thus, the interaction of angiotensin II and ox-LDL may provide an additional link between hypertension and atherosclerosis ***(Hattori et al., 2010).***

Angiotensin II is also involved in atherosclerotic lesion progression and plaque instability by stimulating the activation of matrix metalloproteinases (MMPs), which can digest the fibrous cap and thereby participate in the triggering of plaque rupture ***(Dawson et al., 2010).***

c- Diabetes mellitus

Diabetes mellitus is an independent risk factor for CAD. It increases risk by two to three times for men and three to five times for women to the extent that the most important cause of death among diabetic patients is cardiovascular complications. Comparing diabetic patients with non-diabetic patients either with or without prior history of cardiovascular events, studies showed that after a follow-up for 7 years mortality was higher in diabetic patients than in non-diabetics. Also, for diabetic patients with no history of myocardial infarction, the risk of myocardial infarction was similar to that of non-diabetic patients who did have such a history. These data suggest that diabetic patients have already developed vascular disease by the time of clinical diagnosis ***(Barter et al., 2005).***

There are several mechanisms by which diabetes mellitus can cause atherosclerosis. Researchers stated that diabetes frequently exists in the presence of other CAD risk factors such as hypertension and obesity plus the typical dyslipidemias in diabetes as increased triglyceride, decreased HDL-C and elevated Lp (a) concentration. In addition, lipoproteins may be altered by glycation, which affects their recognition and binding by receptors. Glycation of LDL-C causes its accumulation in the circulation and may increase its uptake by macrophage scavenger receptors in the arterial wall and ultimately foam cell formation. In addition,

glycation of HDL-C may interfere with its protective function ***(Munro and Catran, 2004).***

Hyperglycemia and production of advanced glycation end products are probably the most important factors, if not the only factors, in endothelial dysfunction in diabetics. By binding to specific receptors, advanced glycation end products induces the expression of different proinflammatory molecules such as ICAM and selectins ***(Madjid et al., 2004).***

Diabetic patients have impaired endothelium-dependent vasodilatation, hyper-coagulability, with impaired fibrinolysis. Platelets are larger, with an increased number of glycoprotein IIb-IIIa receptors, which are responsible for platelet adhesion. They are hyper-reactive and show enhanced biosynthesis of thromboxane A2. Platelets from diabetic subjects behave abnormally, showing increased adhesiveness as well as spontaneous aggregation, reflected by abnormalities in platelet function tests ***(Schecteret al., 2008).***

d- Obesity

The prevalence of obesity is increasing all- over the world. Obesity promotes glucose intolerance, insulin resistance, hypertension and dyslipidaemia in the form of hypertriglyceridemia and low HDL-C. Many observational studies have found that obesity strongly and positively correlates with the risk of CAD. Health risk of obesity not only

increases with its severity but may also be affected by distribution of body fat. Central obesity, characterized by excessive adipose fat in the abdomen, appears to have a greater risk impact on CHD ***(Despre, 2006).***

e- Cigarette smoking

Studies demonstrated that cigarette smoking provides perhaps the strongest and most consistent correlation with the increased incidence of atherosclerotic disease. They identified agents derived from cigarette smoke that may be injurious to the artery wall. Moreover, they suggested that cigarette smoke inhalation results in the exposure of arterial cells to free radicals or other mutagens that transform the smooth muscle cells and stimulate their proliferation ***(Ott et al., 2006).***

Many studies revealed that smokers have increased levels of oxidation products including ox-LDL. Cigarette smoking also adversely affects the HDL-C metabolism and structure thus lowering its cardio- protective effects. It also causes cross-linking between apolipoprotien A-I and apolipoprotien A-II that may alter the function of HDL-C. In addition, there are the direct effects of carbon monoxide and nicotine, which produce endothelial damage. It also increases platelet aggregability and increases inflammation of the arterial wall which in turn promotes atherogenesis ***(Bassuk and Manson, 2008).***