INTRODUCTION

Atherosclerosis, the leading cause of morbidity and mortality worldwide, is a complex disease initiated and propagated by lipoprotein deposition and inflammation. Later stages of atherosclerosis are characterized by progressive deposition of calcium in the coronary arterial vessel wall ***(Fukuda et al., 2001)***.

Conventional coronary angiography and myocardial perfusion imaging detect anatomically significant and hemodynamically relevant luminal stenosis, respectively, but perform less well in depicting atherosclerotic disease in its earlier stages when luminal integrity has not yet been compromised by positive vascular remodeling ***(Schoenhagen et al., 2000)***.

Using intravascular ultrasonography (IVUS), cardiac magnetic resonance, and cardiovascular computed tomography (CT) have suggested that coronary plaque rupture could occur in positively remodeled lesions. Recently, the usage of positively remodeled lesions as predictors of plaque rupture are the subject of active research ***(Schoenhagen et al., 2001)***.

The early development of coronary artery disease was described as a gradual growth of plaques within the intima of the vessel. The outer boundaries of the intima, the media and the external elastic membrane, were thought to be fixed in size.

In this model, plaque growth would always lead to luminal narrowin and the number and severity of angiographic stenoses would reflect the extent of coronary disease. However, histological studies demonstrated that certain plaques do not reduce luminal size, presumably because of expansion of the media and external elastic membrane during atheroma development. This phenomenon called "arterial remodeling ***(Zhen et al., 2011)*.**

We are aiming to measure coronary artery diameters in patients who had been referred for coronary artery calcium (CAC) scoring and then using these measurements to study the relationship of increased coronary artery diameter to the degree of coronary artery calcium (CAC) and also the relationship of increased coronary artery diameters to traditional cardiovascular (CV) risk factors to predict the early development of coronary artery disease.

AIM OF THE WORK

TO study the relationship of increased coronary artery diameter to the degree of CAC and also the relationship of increased coronary artery diameters to traditional CV risk factors

ATHEROSCLEROSIS

Definition

The term ***atherosclerosis*** is derived from the Greek "athero," meaning gruel, or wax, corresponding to the necrotic core area at the base of the atherosclerotic plaque, and "sclerosis" for hardening, or induration, referring to the fibrous cap of the plaque's luminal edge ***(Virmani et al., 2000).***

The earliest pathologic descriptions of atherosclerotic lesions focused on morphologies of fatty streaks to fibroatheromas (FAs) and advanced plaques complicated by hemorrhage, calcification, ulceration, and thrombosis. In the mid 1990s the terminology used to define atheromatous plaques was refined by the American Heart Association (AHA) Consensus Group headed by Dr. Stary ***(Virmani et al., 2000).***

The classification consists of 6 different numeric categories to include early lesions of initial type I adaptive intimal thickening, type II fatty streak, type III transitional or intermediate lesions and advanced plaques characterized as type IV, atheroma type V fibroatheroma or atheroma with thick fibrous cap and type VI complicated plaques with surface defects, and/or hematoma-hemorrhage, and/or thrombosis ***(Virmani et al., 2000).***

A modified version of the AHA classification was developed to include important pathologic lesions responsible for luminal thrombosis other than plaque rupture, such as plaque erosion and calcified nodule. In this modified classification, numeric AHA lesions types I to IV are replaced by descriptive terminology to include adaptive intimal thickening, intimal xanthoma, pathologic intimal thickening, and fibroatheroma ***(Virmani et al., 2000).***

Epidemiology

Despite advances in medical, interventional, and surgical treatment, atherosclerotic disease remains the most important cause of death in developed and developing nations ***(Roger et al., 2012).***

In the United States alone, coronary artery disease causes approximately 1 of every 6 deaths, accounting for more than 400,000 deaths annually ***(Celermajer et al., 2012).***

Coronary artery disease remains the leading cause of death in the Western world. A new or recurrent myocardial infarction affects approximately 1.1 million people in the USA per year, of which 40% are fatal. Sudden cardiac death as a first manifestation of the atherosclerotic process occurs in >450,000 individuals annually. The vast majority of acute myocardial infarctions (approximately 75%) occur from plaque rupture; other causes of coronary thrombosis include erosion and calcified nodules ***(Arbustini et al., 1999).***

Although lesions with rupture occur in men of all ages the frequency of sudden coronary death decreases with advancing age. The incidence of rupture varies with each decade, and the highest incidence of plaque rupture is seen in the 40s in men, whereas in women the incidence increases beyond age 50 years. Approximately 80% of coronary thrombi in women older than 50 years occur from plaque rupture, and there is a strong association with circulating cholesterol. In acute myocardial infarction or sudden coronary death, plaque erosion occurs primarily in patients younger than 50 years and represents the majority of acute coronary thrombi in premenopausal women. Furthermore, 20-25% of acute myocardial infarcts occurring in hospitalized patients are due to plaque erosion ***(Arbustini et al., 1999).***

Countries in Africa and the Middle East bear a heavy burden from CV disease. The prevalence of coronary heart disease is promoted in turn by a high prevalence of CV risk factors, particularly smoking, hypertension (HTN), dyslipidemia (DLP), diabetes (DM), and sedentary lifestyles. Patients in Africa and the Middle East present with myocardial infarction at a younger age, on average, compared with patients elsewhere. The projected future burden of mortality from coronary heart disease in Africa and the Middle East is set to outstrip that observed in other geographical regions ***(Almahmeed et al., 2012).***

Pathopyhsiology:

Over the last dozen years, appreciation of the role of inflammation in atherosclerosis has burgeoned. Although it was formerly considered a bland lipid storage disease, substantial advances in basic and experimental science have illuminated the role of inflammation and the underlying cellular and molecular mechanisms that contribute to atherogenesis. Compelling evidence for the importance of inflammation and atherosclerosis at both the basic and clinical level has evolved in parallel. Accumulating data indicate that insights gained from the link between inflammation and atherosclerosis can yield predictive and prognostic information of considerable clinical utility ***(Peter Libby et al., 2002).***

Main Features of Atherosclerotic Lesions:

Atherosclerotic lesions (atheromata) are asymmetric focal thickenings of the innermost layer of the artery, the intima. They consist of cells, connective-tissue elements, lipids, and debris ***(Göran, 2005).***

Blood-borne inflammatory and immune cells constitute an important part of an atheroma, the remainder being vascular endothelial and smooth-muscle cells. The atheroma is preceded by a fatty streak, an accumulation of lipid-laden cells beneath the endothelium ***(Andrea Mencarelli, 2010).***

Most of these cells in the fatty streak are macrophages, together with some T cells. Fatty streaks are prevalent in young people, never cause symptoms, and may progress to atheromata or eventually disappear ***(Göran, 2005).***

In the center of an atheroma, foam cells and extracellular lipid droplets form a core region, which is surrounded by a cap of smooth-muscle cells(SMCs) and a collagen-rich matrix. T cells, macrophages, and mast cells infiltrate the lesion and are particularly abundant in the shoulder region where the atheroma grows**.** Many of the immune cells exhibit signs of activation and produce inflammatory cytokines ***(Frostegard, 1999).***

Acute myocardial infarction (AMI) occurs when the atheromatous process prevents total blood flow through the coronary artery. It was previously thought that progressive luminal narrowing from the continued growth of SMCs in the plaque was the main cause of infarction, however, angiographic studies, have identified culprit lesions that do not cause marked stenosis ***(Matteo et al., 2006).***

Is now evident that plaque activation, rather than stenosis, precipitates ischemia and infarction. Coronary spasm could be involved to some extent, but most cases of AMI are due to the formation of an occluding thrombus on the surface of the plaque; the two major causes of coronary thrombosis are plaque rupture and endothelial erosion.

Plaque rupture is detectable in 60–70% of cases and preferentially occurs when the fibrous cap is thin and partly destroyed ***(Matteo et al., 2006).***

Ruptures preferentially occur where the fibrous cap is thin and partly destroyed. At these sites, activated immune cells are abundant one of the major challenges in modern cardiology is the knowledge of the factors that induce a silent atherosclerotic plaque shifting from a stable to a vulnerable form.They produce numerous inflammatory molecules and proteolytic enzymes that can weaken the cap and activate cells in the core, transforming the stable plaque into a vulnerable, unstable structure that can rupture, induce a thrombus, and elicit an acute coronary syndrome ***(Van der Wal et al., 2002).***

Lipoprotein Retention and Activation of Immune Cells:

Studies in animals and humans have shown that hypercholesterolemia causes focal activation of endothelium in large and medium-sized arteries. The infiltration and retention of low density lipoproteins (LDL) in the arterial intima initiate an inflammatory response in the artery wall ***(Skalen et al., 2002).***

Modification of LDL, through oxidation or enzymatic attack in the intima, leads to the release of phospholipids that

can activate endothelial cells preferentially at sites of hemodynamic strain ***(Leitinger, 2003).***

Patterns of hemodynamic flow typical for atherosclerosis-prone segments (low average shear but high oscillatory shear stress) cause increased expression of adhesion molecules and inflammatory genes by endothelial cells. Therefore, hemodynamic strain and the accumulation of lipids may initiate an inflammatory process in the artery ***(Dai G et al., 2004).***

The platelet is the first blood cell to arrive at the scene of endothelial activation. Its glycoproteins Ib and IIb/IIIa engage surface molecules on the endothelial cell, which may contribute to endothelial activation. Inhibition of platelet adhesion reduces leukocyte infiltration and atherosclerosis ***(Massberg et al., 2002).***

Once the blood cells have attached, chemokines produced in the underlying intima stimulate them to migrate through the interendothelial junctions and into the subendothelial space. Genetic abrogation or pharmacologic blockade of certain chemokines and adhesion molecules for mononuclear cells inhibits atherosclerosis in mice ***(Lutters et al., 2004).***

Macrophages in the Developing Plaque:

A cytokine or growth factor produced in the inflamed intima, macrophage colony-stimulating factor, induces monocytes entering the plaque to differentiate into macrophages. This step is critical for the development of atherosclerosis and is associated with up-regulation of pattern-recognition receptors for innate immunity, including scavenger receptors and toll-like receptors ***(Peiser et al., 2002)***.

The activated macrophage produces inflammatory cytokines, proteases, and cytotoxic oxygen and nitrogen radical molecules. Similar effects are observed in dendritic cells, mast cells, and endothelial cells, which also express toll-like receptors. Bacterial toxins, stress proteins, and DNA motifs are all recognized by various toll-like receptors ***(Janeway et al., 2002)*.**

Cross-Talk between Inflammation and Metabolism:

The balance between inflammatory and anti-inflammatory activity controls the progression of atherosclerosis. Metabolic factors may affect this process in several ways. Obviously, they contribute to lipid deposition in the artery, initiating new rounds of immune-cell recruitment. Furthermore, the adipose tissue of patients with the metabolic syndrome and obesity produces inflammatory cytokines, particularly tumor necrosis factor and interleukin-6 ***(Yudkin et al., 2004).***

Infections and Coronary Artery Disease:

Several studies have linked infections to atherosclerosis and coronary artery disease (CAD). Elevated titers of antibodies against chlamydia were found in patients with CAD, and it was speculated that this microbe causes atherosclerosis ***(Rosa, 2014).***

However, *Chlamydia pneumoniae* infection does not cause atherosclerosis in animals, although it may stimulate disease progression and plaque activation ***(Caligiuri et al., 2001).***

Molecular mimicry between *C. pneumoniae* antigens and human molecules may contribute to the activation of inflammation. However, several recent secondary prevention trials failed to prevent acute coronary syndromes by administering antibiotics targeting *C. pneumoniae,* suggesting that *C. pneumoniae* infection is not a predominant cause of these syndromes ***(Grayston et al., 2005).***

Herpes family viruses may also contribute to CAD. Cytomegalovirus is found in lesions, can modulate immune-cell as well as vascular-cell activity, and increases experimental atherosclerosis ***(Gredmark et al., 2004).***

ACUTE CORONARY SYNDROMES

Mechanisms of Plaque Rupture

What causes a silent atherosclerotic lesion to rupture? Activated macrophages, T cells, and mast cells at sites of plaque rupture. produce several types of molecules inflammatory cytokines, proteases, coagulation factors, radicals, and vasoactive molecules that can destabilize lesions They inhibit the formation of stable fibrous caps, attack collagen in the cap, and initiate thrombus formation.All these reactions can conceivably induce the activation and rupture of plaque, thrombosis, and ischemia ***(Mach et al., 1997).***

Denudation of the overlying endothelium or rupture of the protective fibrous cap may result in exposure of the thrombogenic contents of the core of the plaque to the circulating blood. This exposure constitutes an advanced or complicated lesion. The plaque rupture occurs due to weakening of the fibrous cap. Inflammatory cells localize to the shoulder region of the vulnerable plaque. T lymphocytes elaborate interferon gamma, an important cytokine that impairs vascular smooth muscle cell proliferation and collagen synthesis. Furthermore, activated macrophages produce matrix metalloproteinases that degrade collagen ***(Irena et al., 2006).***

These mechanisms explain the predisposition to plaque rupture and highlight the role of inflammation in the genesis of

the complications of the fibrous atheromatous plaque. A plaque rupture may result in thrombus formation, partial or complete occlusion of the blood vessel, and progression of the atherosclerotic lesion due to organization of the thrombus and incorporation within the plaque ***(Irena et al., 2006).***

Plaque rupture is the main event that causes acute presentations. However, severely obstructive coronary atheromas do not usually cause acute coronary syndrome (ACS) and myocardial infarction (MI). In fact, most of the atheromas that cause ACS are less than 50% occlusive, as demonstrated by coronary arteriography. Atheromas with smaller obstruction experience greater wall tension, which changes in direct proportion to their radii ***(Ross et al., 1996).***

Most plaque ruptures occur because of disruption of the fibrous cap, which allows contact between the highly thrombogenic lipid core and the blood. These modestly obstructive plaques, which have a greater burden of soft lipid core and thinner fibrous caps with chemoactive cellular infiltration near the shoulder region, are called vulnerable plaques. The amount of collagen in the fibrous cap depends on the balance between synthesis and destruction of intercellular matrix and inflammatory cell activation ***(Liu et al., 2004).***

Inflammatory Markers and the Risk of CAD

Although the degree of active inflammation is increased in activated plaques of patients with acute coronary syndromes, smoldering inflammation characterizes silent plaques. Such lesions may also release inflammatory mediators into the systemic circulation. A moderately elevated C-reactive protein (CRP) level on a highly sensitive immunoassay is an independent risk factor for CAD in a healthy population ***(Danesh et al., 2004).***

Whether this test should be used to screen asymptomatic persons is a matter of debate ***(Danesh et al., 2004).***

Other measures of acute-phase reactants, including the erythrocyte sedimentation rate and levels of fibrinogen and other plasma proteins, also provide information about the inflammatory risk of CAD ***(Engstrom et al., 2004).***

CRP has been show to be an independent risk factor for the development of CV events in both apparently healthy individual and in patients with established coronary artery disease. The exact role that CRP plays in this association has not yet been well characterized. Intially, it was believed that CRP provided an indirect measurement of the inflammatory milieu in at-risk individual. Emerging evidence, however, indicates that CRP itself may have a direct causal influence on the development of atherosclerosis ***(Pearson et al., 2003).***