INTRODUCTION

There is a close relationship between type II diabetes and the development of coronary artery disease (CAD). In addition, patients with type II diabetes have a two to four fold higher risk of a cardiovascular event when compared with non-diabetic patients. Moreover, the progression of coronary artery disease appears faster when compared with non-diabetic patients ***(Morrish et al., 2001)*.**

Non-invasive testing, including myocardial perfusion scintigraphy and dobutamine stress-echocardiography, has been used to detect CAD in diabetic patients and a clear association between abnormal test results and worse outcome has been demonstrated similar to the general population. Nonetheless, after normal findings, still elevated event rates are observed in diabetic patients as compared to non-diabetic individuals, indicating a need for further refinement of prognostification in this population ***(Wackers et al., 2004; Sozzi et al., 2003; Giri et al., 2002 and Underwood et al., 2004)*.**

This is probably related to differences in coronary plaque burden and composition. Although Intravascular ultrasound (IVUS) is the gold standard for characterizing morphology plaque or degree of stenosis in patients undergoing coronary angiography, noninvasive detection and characterization of coronary plaque would be an attractive alternative modality. Noninvasive evaluation of coronary atherosclerotic plaques

would improve risk stratification of both symptomatic and asymptomatic patients and also of high risk diabetic patients ***(Loffroy et al., 2009 and Naghavi et al, 2003).***

Atherosclerosis has been non-invasively assessed in patients with type 2 diabetes using coronary calcium scoring revealing extensive atherosclerosis. Still, coronary calcium scoring may seriously underestimate coronary plaque burden as non-calcified lesions are not recognized ***(Mielke et al., 2001, Khaleeli et al., 2001 and Rumberger et al., 1995).***

More recently, contrast-enhanced multi-slice computed tomography (MSCT) coronary angiography has become available which allows, in contrast to calcium scoring, detection of both calcified and non-calcified coronary lesions. As a result, the technique potentially allows a more precise non-invasive evaluation of coronary atherosclerosis, which in turn could be valuable for improving risk stratification ***(Schroeder et al., 2001; Achenbach et al., 2004; Leber et al., 2004 and Leber et al., 2006).***

AIM OF THE WORK

To evaluate whether differences in the extent and composition of coronary plaques in diabetic type II patients and nondiabetic patients can be observed using MSCT Angiography.

Chapter 1

DIABETES MELLITUS "DM" AND CORONARY ARTERY DISEASE

1. A. Definition of DM:

Diabetes mellitus is a group of metabolic diseases in which a person has high blood sugar, either because the pancreas does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst), and polyphagia (increased hunger) ***(Gardner and Dolores, 2011).***

Other symptoms that are commonly present at diagnosis include a history of blurred vision, itchiness, peripheral neuropathy, recurrent vaginal infections, and fatigue. Many people, however, have no symptoms during the first few years and are diagnosed on routine testing. People with type 2 Diabetes Mellitus may rarely present with hyperosmolar hyperglycemic state (a condition of very high blood sugar associated with a decreased level of consciousness and low blood pressure) ***(Gardner and Dolores, 2011).***

Type 1 diabetes

This type can be classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, in which beta cell loss is a T-cell-mediated autoimmune attack ***(Rother, 2007).***

There is no known preventive measure against type 1 diabetes, which causes approximately 10% of diabetes mellitus cases in North America and Europe. Most affected people are otherwise healthy and of a healthy weight when onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults, but was traditionally termed "juvenile diabetes" because a majority of these diabetes cases were in children ***(Rother, 2007).***

Type 2 diabetes

Type 2 diabetes mellitus is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion. The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus cases due to a known defect are classified separately. Type 2 diabetes is the most common type. In the early stage of type 2, the predominant abnormality is reduced insulin sensitivity. At this stage, hyperglycemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver ***(Risérus et al., 2009).***

Epidemiology of type 2 DM:

Globally, as of 2010, an estimated 285 million people had diabetes, with type 2 making up about 90% of the cases

(Williams textbook of endocrinology 2010). Its incidence is increasing rapidly, and by 2030, this number is estimated to almost double ***(Wild et al., 2004).*** Diabetes mellitus occurs throughout the world, but is more common (especially type 2) in the more developed countries. The greatest increase in prevalence is, however, expected to occur in Asia and Africa, where most patients will probably be found by 2030 ***(Wild et al., 2004).*** The increase in incidence in developing countries follows the trend of urbanization and lifestyle changes, perhaps most importantly a "Western-style" diet. This has suggested an environmental (i.e., dietary) effect, but there is little understanding of the mechanism(s) at present, though there is much speculation, some of it most compellingly presented ***(Williams textbook of endocrinology 2010).***

Causes of type 2 DM:

Type 2 diabetes is due primarily to lifestyle factors and genetics. A number of lifestyle factors are known to be important to the development of type 2 diabetes, including obesity (defined by a body mass index of greater than thirty), lack of physical activity, poor diet, stress, and urbanization. Excess body fat is associated with 30% of cases in those of Chinese and Japanese descent, 60-80% of cases in those of European and African descent, and 100% of Pima Indians and Pacific Islanders. Those who are not obese often have a high waist–hip ratio ***(Risérus et al., 2009).***

Dietary factors also influence the risk of developing type 2 diabetes. Consumption of sugar-sweetened drinks in excess is associated with an increased risk. The type of fats in the diet is also important, with saturated fats and trans fatty acids increasing the risk and polyunsaturated and monounsaturated fat decreasing the risk ***(Malik et al., 2010).*** Eating lots of white rice appears to also play a role in increasing risk. A lack of exercise is believed to cause 7% of cases ***(Lee et al., 2012).***

Table (1): The following is a comprehensive list of other causes of diabetes ***(Mitchell et al., 2008).***

• Genetic defects of β-cell function o Maturity onset diabetes of the young o Mitochondrial DNA mutations	• Endocrinopathies o Growth hormone excess (acromegaly) o Cushing syndrome o Hyperthyroidism o Pheochromocytoma o Glucagonoma
• Genetic defects in insulin processing or insulin action o Defects in proinsulin conversion o Insulin gene mutations o Insulin receptor mutations	• Infections o Cytomegalovirus infection o Coxsackievirus B
• Exocrine pancreatic defects o Chronic pancreatitis o Pancreatectomy o Pancreatic neoplasia o Cystic fibrosis o Hemochromatosis o Fibrocalculous pancreatopathy	• Drugs o Glucocorticoids o Thyroid hormone o β-adrenergic agonists

Complications

All forms of diabetes increase the risk of long-term complications. These typically develop after many years (10–20), but may be the first symptom in those who have otherwise not received a diagnosis before that time. The major long-term complications relate to damage to blood vessels. Diabetes doubles the risk of cardiovascular disease ***(Emerging Risk Factors Collaboration 2010).***

The main "macrovascular" diseases (related to atherosclerosis of larger arteries) are coronary artery disease (angina and myocardial infarction), stroke, and peripheral vascular disease. About 75% of deaths in diabetics are due to coronary artery disease Diabetes also damages the capillaries (causes microangiopathy) ***(O'Gara et al., 2013).***

Diabetic retinopathy, which affects blood vessel formation in the retina of the eye, can lead to visual symptoms including reduced vision and potentially blindness ***(Boussageon et al., 2011).***

Diabetic nephropathy, the impact of diabetes on the kidneys, can lead to scarring changes in the kidney tissue, loss of small or progressively larger amounts of protein in the urine, and eventually chronic kidney disease requiring dialysis ***(Boussageon et al., 2011).***

Diabetic neuropathy, the impact of diabetes on the nervous system most commonly presents in numbness, tingling, pain in the feet, and also increases the risk of skin damage due to altered sensation. Together with vascular disease in the legs, neuropathy contributes to the risk of diabetes-related foot problems (such as diabetic foot ulcers) that can be difficult to treat and occasionally require amputation. Additionally, proximal diabetic neuropathy causes painful muscle wasting and weakness ***(O'Gara et al., 2013)*.**

Diabetic heart disease (DHD) may include coronary heart disease (CHD), heart failure, and/or diabetic cardiomyopathy. At least four complex processes, alone or combined, can lead to diabetic heart disease (DHD). They include 1-coronary atherosclerosis; 2-insulin resistance in people who have type 2 diabetes 3-metabolic syndrome and 4-the interaction of coronary heart disease (CHD), high blood pressure, and diabetes ***(Health and Human Services, 2011)*.**

Coronary artery disease (**CAD**) also known as atherosclerotic heart disease, is the most common type of heart disease and cause of heart attacks. The disease is caused by plaque building up along the inner walls of the arteries of the heart, which narrows the lumen of arteries and reduces blood flow to the heart ***(Bhatia and Sujata, 2010)*.**

While the symptoms and signs of coronary artery disease are noted in the advanced state of disease, most individuals

with coronary artery disease show no evidence of disease for decades as the disease progresses before the first onset of symptoms, often a "sudden" heart attack, finally arises. Symptoms of stable ischaemic heart disease (IHD) include angina (characteristic chest pain on exertion) and decreased exercise tolerance. Unstable IHD presents itself as chest pain or other symptoms at rest, or rapidly worsening angina. The risk of artery narrowing increases with age, smoking, high blood cholesterol, diabetes, high blood pressure, and is more common in men and those who have close relatives with CAD ***(Rezkalla and Kloner, 2007).***

It was as of 2012 the most common cause of death in the world, and a major cause of hospital admissions. There is limited evidence for population screening, but prevention (with a healthy diet and sometimes medication for diabetes, cholesterol and high blood pressure) is used both to prevent IHD and to decrease the risk of complications ***(Finegold et al., 2012).***

Effect of type 2 DM on Coronary artery plaque formation and composition

The effects of diabetes on the vasculature are quite extensive as diabetes affects not only the endothelium and smooth muscle cells, but also platelets, lipoproteins, local vasoactive substance production and function, clotting factors, triglycerides, as well as local arterial response to hypoxia and new collateral vessel formation ***(Beckman et al., 2002)*.**

The pathogenesis of diabetic atherosclerosis involves not only the direct effects of chronic hyperglycemia, but also insulin resistance, nonesterified free fatty acid (NEFA) production, dyslipidemia, hypercoagulability, and impaired response to injury. It is this widespread dysfunction that makes the side effects so deleterious and the treatment so difficult ***(Shrikhande et al., 2010)*.**

Arteries are composed of three layers—the tunica intima, media, and adventitia. The tunica intima is the innermost layer with the luminal side being composed of a single layer of endothelial cells. The next layer of the intima consists of an extracellular connective tissue matrix composed primarily of proteoglycans and collagen. Surrounding the intima is an internal elastic lamina that is composed of elastic cells of varying thickness depending on the vessel size. The tunica media is the next layer composed of primarily vascular smooth muscles cells and it is the thickest layer of the blood vessel.

This layer is surrounded by the external elastic lamina, which separates the tunica media from the tunica adventitia, the outermost layer of the vessel wall. This layer is mainly composed of collagen with interspersed fibroblasts and vascular smooth muscle cells ***(Lusis, 2000)*.**

The development of diabetes-related atherosclerosis follows the same histologic course as atherosclerosis in nondiabetic patients. This includes endothelial injury, smooth muscle cell proliferation, foam cell development and infiltration, platelet activation, and increased inflammation. Sites of lesions are determined by altered hemodynamic forces and external sources of injury to the endothelial cells. Increased endothelial permeability leads to the retention of deleterious low-density lipoproteins (LDL) that interact with the underlying extracellular matrix (ECM). This interaction retains the LDL in the vessel wall where it can undergo oxidation by reactive oxygen species (ROS). This oxidized LDL can then stimulate the overlying endothelial cells to upregulate cellular adhesion molecules, chemotactic proteins, growth factors, and inhibit nitric oxide (NO) production. These activities recruit monocytes and macrophages, which interact with highly oxidized aggregated LDL to form foam cells. Pro-inflammatory cytokine production by activated macrophages stimulates proliferation of vascular smooth muscle cells (VSMCs) (Figure 1). Intimal smooth muscle cells subsequently produce an ECM that gives rise to a fibrous cap. The resulting complex plaque is

vulnerable to destabilization, rupture, and superimposed thrombosis leading to an acute vascular occlusion (Figure 2) ***(Lusis, 2000)*.**

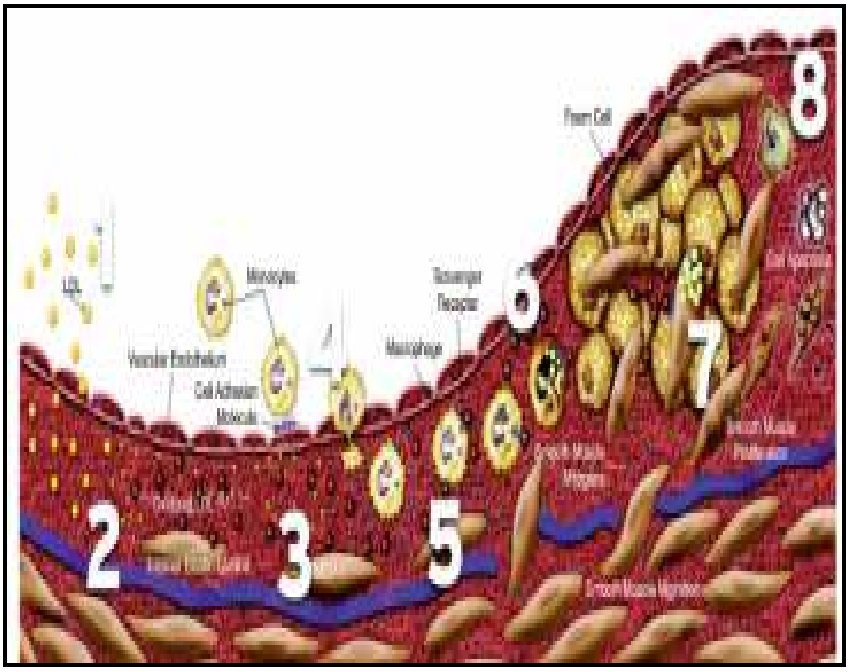

Figure (1): The stages of development of an atherosclerotic plaque. (1) LDL is taken up by the endothelium. (2) Oxidation of LDL by macrophages and VSMCs. (3) Release of growth factors and cytokines. (4) Attraction of additional monocytes. (5) Foam cell accumulation. (6) SMC proliferation. (7, 8) Formation of plaque ***(Faxon et al., 2004)***.

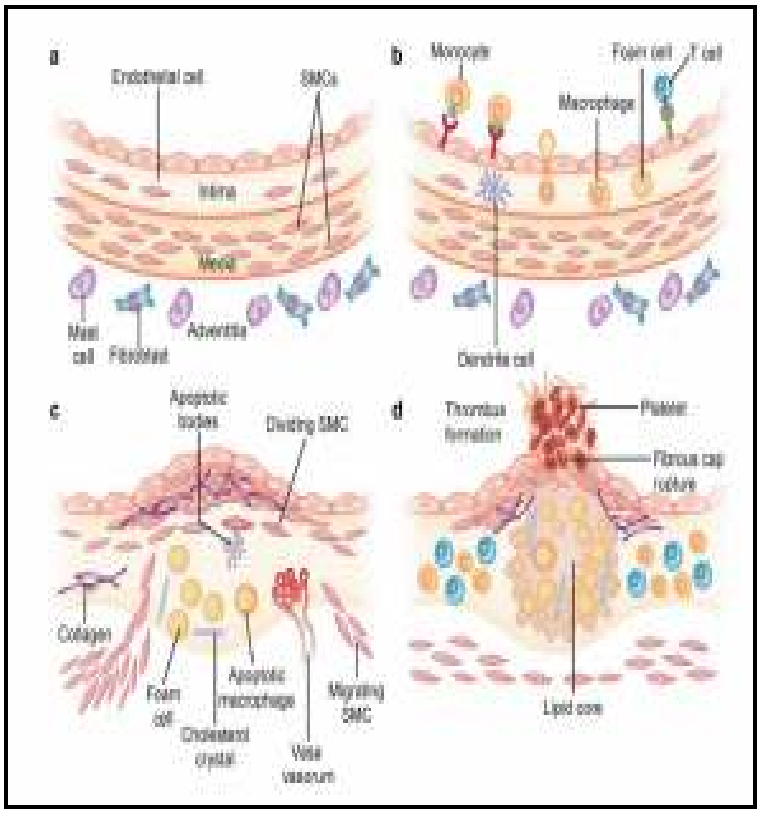

Figure (2): Development of atherosclerotic plaque with superimposed thrombus ***(Libby et al., 2011)***

Atherosclerotic plaques in the presence of diabetes generally have increased calcification, necrotic cores, receptors for advanced glycosylation endproducts (RAGE), and macrophage and T-cell infiltration. There is also a higher incidence of healed plaque ruptures and vascular remodeling. These features can potentially contribute to the more severe atherosclerosis and a higher incidence of acute adverse events ***(Virmani et al., 2006)***.

The vulnerable atherosclerotic plaque is called a "high-risk" or "thrombosis-prone" plaque. Major criteria to characterize such plaques include the presence of active inflammation, a thin inflamed fibrous cap (TCFA) (<65μm) covering a lipid-rich necrotic core (>40% of the total volume of the plaque), the presence of endothelial denudation with superficial platelet aggregation, and the presence of hemodynamically significant stenosis (>90%) ***(Dhawan et al., 2010)***.

A more clinical relevant definition of a vulnerable plaque is a lesion that places a patient at risk for developing future major adverse cardiac events, including death, myocardial infarction, or progressive angina. The identification of such plaques before they become symptomatic would enable prognostic stratification and facilitate primary prevention (e.g., aspirin, statins, and risk factor modification) ***(Sun and Xu, 2014)***.

Previous studies have reported that plaque rupture occurs not only within Acute Myocardial Infarction (AMI) culprit lesions but also in non-culprit lesions in patients with various clinical presentations, suggesting that some plaque ruptures lead to clinical manifestations whereas others remain asymptomatic and heal with subsequent fibrosis ***(Fujii et al., 2003)***.