INTRODUCTION

Atherosclerosis is a disease of the large and medium-sized arteries causing luminal narrowing (focal or diffuse). This occurs as a result of the accumulation of lipid and fibrous material between the intimal and medial layers of the vessel. [1]

Peripheral arterial disease (PAD) is a nearly pandemic condition that has the potential to cause limb loss or even loss of life. PAD manifests as insufficient tissue perfusion initiated by existing atherosclerosis. It most commonly affects the arteries that supply blood to both lower limbs. There is a wide range of modifiable and non-modifiable risk factors for PAD including advanced age, male gender, positive family history, smoking, diabetes, hypertension, hyperlipidemia and obesity. [2]

Because atherosclerosis is a systemic disease, presence of PAD is considered a strong predictor of cardiovascular events which is 5-7% annually. In the AGATHA study, patients with PAD in one vascular bed had a 35% chance of having disease in at least one other territory, and 50% had cerebrovascular or coronary heart disease. There was a 2-3% nonfatal myocardial infarction rate, and a twofold to threefold increase in the occurrence of angina compared with age-matched controls. Risk of cardiovascular mortality increases with asymptomatic PAD and surprisingly the risk may not differ from symptomatic PAD. [3]

Trans Atlantic Inter-Society Consensus II (TASC II) classification is an internationally derived definition that is dedicated for the assessment of peripheral artery disease according to anatomical distribution, number and nature of lesions (stenosis and occlusion). [4]

The SYNTAX score (SS) is a comprehensive scoring system dedicated for the assessment of complexity and severity of coronary artery anatomy and lesion characteristics. SYNTAX score is a valuable marker of major adverse cardiovascular events and cardiovascular mortality. [5&6]

AIM OF THE WORK

The aim of this work was to measure the relationship between coronary artery disease complexity using SYNTAX score and peripheral arterial disease complexity using TASC II score.

ATHEROSCLEROSIS (A SYSTEMIC DISEASE)

Definition:

The word Atherosclerosis is of Greek origin and literally means focal accumulation of lipid (i.e., *athero* [gruel]) and thickening of arterial intima (i.e., sclerosis [hardening]).[7]

Atherosclerosis is a multifocal, immune-inflammatory disease of large and medium-sized muscular arteries fuelled by lipids. Endothelial cells, leukocytes, and intimal smooth muscle cells are the major players in the development of this disease. This results in plaque formation, vascular remodeling, acute and chronic luminal obstruction, abnormalities of blood flow, and diminished oxygen supply to target organs. [8]

Etiology:

The mechanisms of atherogenesis remain uncertain. However, there are many risk factors and theories tried to explain atherogenesis.[9]

Theories of atherogenesis:

Over the years, several theories have been advanced to explain the process of atherosclerosis.

Modified Response to Injury Hypothesis:

In 1973, Russell Ross and John Glomset published a modified version of the response to injury hypothesis. They

suggested that atheroma was the result of excessive smooth muscle cells (SMCs) proliferation in response to an endothelial injury from any cause-not necessarily a mechanical injury-such as hypertension, hyperlipidemia, and smoking.[9]

Inflammation Theory

In his most recent review of the pathogenesis of atherosclerosis, Ross continues to state the importance of endothelial dysfunction in the origin of atherosclerosis. Besides, he also highlights the role played by inflammation at every step of the pathogenesis of atherosclerosis.[9]

Risk factors of Atherosclerosis

A. Modifiable Risk Factors: [10,11]

1. **Dyslipidemia (elevated Low density lipoprotein- LDL, decreased High density lipoprotein-HDL):** Excess LDL accumulates in the intima and undergoes modifications that initiate and perpetuate the development of atherosclerotic lesions.

2. **Smoking:** Enhances oxidative modification of LDL, contributes to endothelial dysfunction via oxidant stress and increases expression of leukocyte adhesion molecules, among other factors.

3. **Hypertension:** Increases permeability of vessel wall to lipoproteins and promotes retention of LDL in the vessel

intima by accentuating production of LDL-binding proteoglycans by SMCs.

4. **Diabetes mellitus (DM):** Enhances glycation of LDL and is associated with endothelial dysfunction.

5. **Obesity and lack of physical activity:** Contribute to dyslipidemia, hypertension and insulin resistance. Obesity is associated with **Sleep apnea** which increases the risk for development of hypertension, diabetes and acute ischemic events.

6. **Stress.**

7. **Alcohol:** Heavy consumption worsens other risk factors for atherosclerosis.

B. Non Modifiable Risk factors: [10,11]

1. **Advanced age.**

2. **Male gender.**

3. **Positive family history** of coronary artery disease (CAD) among first-degree relatives at a young age (before 55 for males and before 65 for females).

C. Novel risk factors: [10,11]

1. **Homocysteine** High levels may promote oxidative stress, vascular inflammation and platelet adhesiveness.

2. **Lipoprotein particle Lp (a).**

3. **C-reactive protein (CRP) and other markers of inflammation** activates complement and contributes to a sustained inflammatory state.

4. **Small, dense LDL-C particles.**

5. **Fibrinogen.**

Stages of Atherosclerosis

A. Fatty Streak development:

Areas of yellow discoloration on artery's inner surface; blood flow is not yet impeded at this stage. Its formation begins with:

1- Endothelial dysfunction:

It is triggered by injury to the arterial endothelium due to exposure to **Physical forces** e.g. shear stress, and **Chemical toxins** resulting from smoking, elevated circulating low density lipoprotein (LDL) levels and diabetes. [11, 12, 13]

2- Lipoprotein entry and modification:

Endothelial dysfunction allows for entry of LDL into the vessel intima to be modified by oxidation and glycation. [11, 12, 13]

3- Leukocyte recruitment:

Oxidized LDL activates endothelial cells to express adhesion molecules and release chemo-attractants which recruit monocytes and T cells. [11,12,13]

4- Foam cell formation:

Monocytes differentiate into phagocytic macrophages and they engulf the oxidized LDL and become foam cells which produce additional cytokines that contribute to atherosclerotic plaque formation. [11, 12, 13]

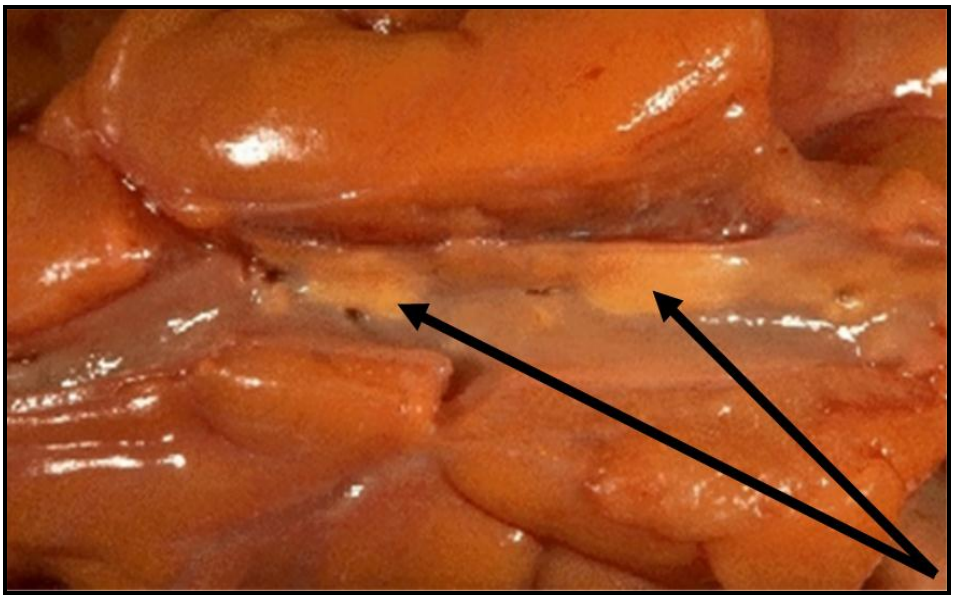

Figure (1): Fatty Streaks [14]

B. Plaque progression:

- Intima continues to thicken due to increase SMCs proliferation and leukocytes recruitment. **Fatty streaks** transform into **fibro-fatty lesions.** [11, 12, 13]

- Smooth Muscle Cells form a **sub-endothelial cap** structure which mechanically stabilizes the plaque and creates a barrier between the hemostatic components of the blood and the thrombogenic material of the plaque. **Calcification** can occur at later stages and fibrosis continues. [11, 12, 13]
- **Fibrous Capsule** is formed due to Apoptosis of SMCs. It surrounds a lipid-rich core. [11,12,13]
- **Late plaque growth** can significantly restrict the vessel lumen and decrease tissue perfusion, causing ischemic symptoms such as Angina pectoris or Claudication. [11,12,13]

C. Plaque disruption:

Fibrous capsule integrity depends on net extracellular matrix metabolism as follow:

- **Smooth Muscle Cells** synthesize constituents of the fibrous cap such as collagen and elastin.
- **Foam cells** synthesize proteolytic enzymes. [11,12,13]

Plaques with thicker fibrous caps tend to cause arterial narrowing, they have low possibility to rupture (**stable plaques**). On the other hand thinner less obstructive plaques tend to be more fragile and rupture (**vulnerable plaques**). [11,12,13]

When the fibrous cap ruptures, pro-thrombotic molecules within the lipid core are exposed and can sometimes, precipitate formation of an acute thrombus which occludes the arterial lumen, leading to ischemia and infarction. [11,12,13]

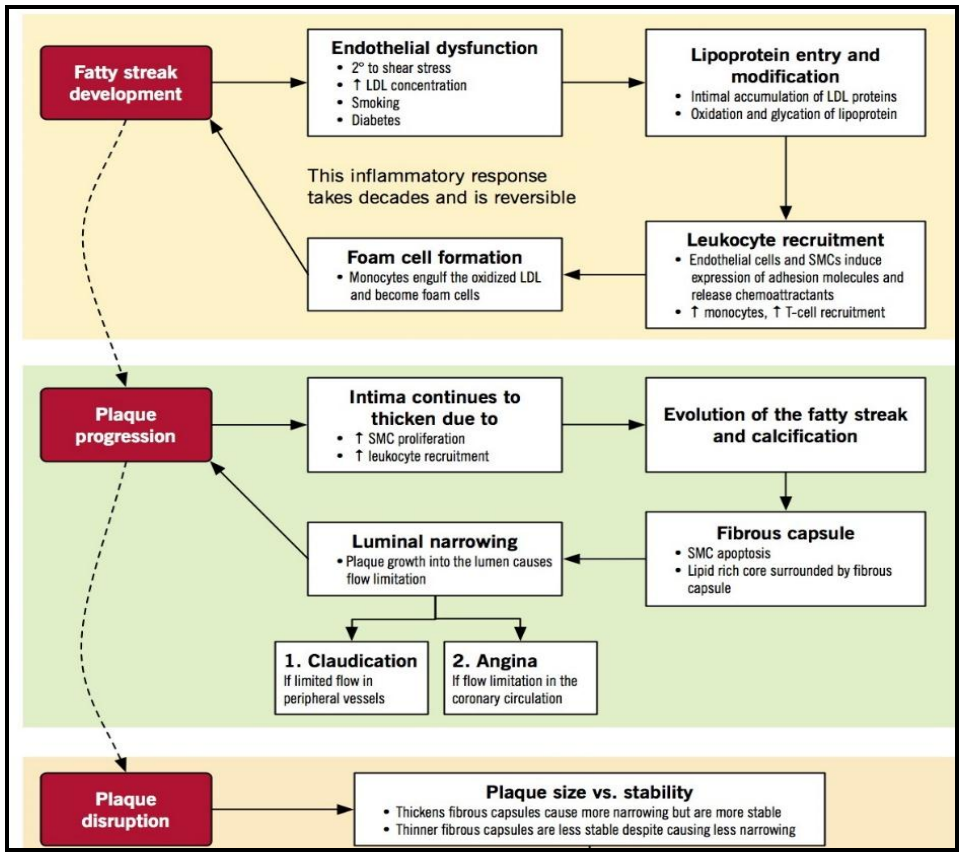

Figure (2): Stages of Atherosclerosis [11]

Classification of Atherosclerosis

Several classifications have been developed to classify atherosclerotic lesions. The American Heart Association (AHA) classification consists of 6 different numeric categories that starts from type I which describes early lesion to type VI which describes complicated plaques. Previous classification was modified by AHA in which numeric AHA lesions types I to IV are replaced by descriptive terminology to include important pathologic lesions responsible for luminal thrombosis

other than plaque rupture, such as plaque erosion and calcified nodule.[15]

Table (1): Modified AHA Consensus Classification Based on Morphologic Descriptions (Modified from Virmani et al.) [15]

Thrombosis	Description	
Non atherosclerotic intimal lesions		
Absent	Normal accumulation of smooth muscle cells (SMCs) in the intima in the absence of lipid or macrophage foam cells	Intimal thickening
Absent	Superficial accumulation of foam cells without a necrotic core or fibrous cap; based on animal and human data, such lesions usually regress	Intimal xanthoma
Progressive atherosclerotic lesions		
Absent	SMC-rich plaque with proteoglycan matrix and focal accumulation of extracellular lipid.	Pathologic intimal thickening
Absent	***Early necrosis***: focal macrophage infiltration into areas of lipid pools with an overlying fibrous cap. ***Late necrosis:*** loss of matrix and extensive cellular debris with an overlying fibrous cap.	Fibrous cap atheroma
Absent	A thin, fibrous cap (< 65 μm) infiltrated by macrophages and lymphocytes with rare or absence of SMCs and a relatively large underlying necrotic core; intra-plaque hemorrhage/fibrin may be present	Thin cap fibroatheroma
Lesions with acute thrombi		
Occlusive or non-occlusive	Fibroatheroma with fibrous cap disruption; the luminal thrombus communicates with the underlying necrotic core	Plaque rupture
Usually non-occlusive	Plaque composition, as above; no communication of the thrombus with the necrotic core; can occur on a plaque substrate of pathologic intimal thickening or fibroatheroma	Plaque erosion

Thrombosis	Description	
Usually non-occlusive	Eruptive (shedding) of calcified nodules with an underlying fibrocalcific plaque with minimal or absence of necrosis	Calcified nodule
Lesions with healed thrombi		
Absent	Collagen-rich plaque with significant luminal stenosis; lesions may contain large areas of calcification with few inflammatory cells and minimal or absence of necrosis; these lesions may represent healed erosions or ruptures	Fibrotic (without calcification) Fibrocalcific (+/- necrotic core)

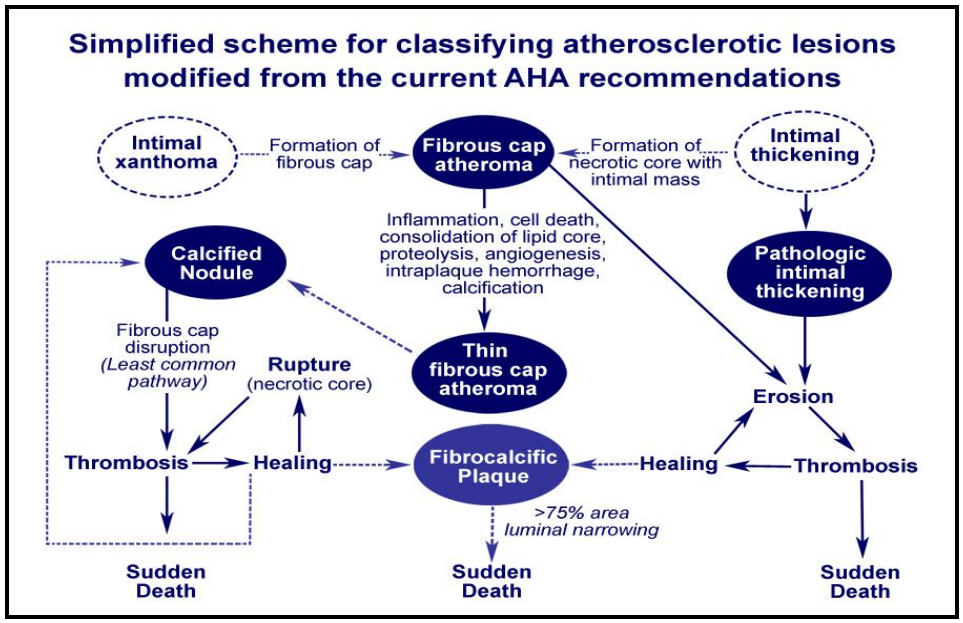

Figure (3): Simplified Scheme for Modified AHA Consensus Classification Based on Morphologic Descriptions [15]

CAD COMPLEXITY (SYNTAX SCORE)

Coronary angiography

Dr. Mason Sones and colleagues at the Cleveland Clinic performed the first selective coronary angiography (CA) procedure. In 1958. Since then, it becomes the clinical gold standard for determining the presence of significant Coronary artery disease.[16]

It provides important information for risk stratification, options for revascularization and prognosis. A cardiac catheterization yields a 2-dimensional rendering of the coronary artery circulation. To assist in circumventing the limitations of a 2-dimensional depiction of 3-dimensional anatomy, multiple views from varying angles are obtained with the extent of CAD severity typically ascribed to the angulation with the greatest stenosis severity within the particular coronary arterial segment. [16]

Coronary angioplasty, also known as Percutaneous Transluminal Coronary Angioplasty (PTCA), was first developed and performed in humans in 1977 by Andreas Gruentzig.

With advances in technology and development of different balloon types, the procedure progressed to being used in very complex lesions. Since the late 1990s, most angioplasties also involve stent implantation, and with this the

nomenclature has changed from PTCA to Percutaneous Coronary Intervention (PCI). [17]

Characterization of coronary artery atherosclerosis by coronary angiography

Types of coronary lesions:

The American College of Cardiology/American Heart Association (ACC/AHA) developed a classification scheme to characterize the complexity of coronary stenosis and the probability of success of a percutaneous intervention. ACC/AHA lesion complexity system provides short-term prognostic information adjunctive to Thrombolysis In Myocardial Infarction (TIMI) flow grade and Myocardial blush Grade (MBG). [18]

Type A lesions (High Success, >85%; Low Risk):

Type A lesions are associated with an anticipated success procedure rate of ≥85% and a low risk of abrupt closure.

Type A lesions demonstrate all of the following characteristics: [19]

1) Discreteness (<10 mm in length).
2) Concentricity.
3) Ready accessibility.
4) Location in a non-angulated segment (<45°).

5) Smoothness of contour.
6) Little or no calcification.
7) Absence of total occlusion.
8) Non-osteal location.
9) Absence of major branch involvement.
10) Absence of thrombus.

Type B Lesions (Moderate Success, 60 to 85%; Moderate Risk):

Type B lesions are associated with an anticipated success procedure rate ranging from 60 to 85% or a moderate risk of abrupt closure. [18]

This classification was modified to subdivide type B lesions into B1 (one adverse characteristic) and B2 (≥ two adverse characteristics). [19]

A) One of the following criteria: Type B1.

B) Two or more of the following criteria: Type B2.

1) Length 10-20mm.
2) Eccentric.
3) Moderate tortuosity of proximal segment.
4) Irregular contour.
5) Presence of any thrombus grade.