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. Atherosclerosis of the non-cardiac vessels is defined as peripheral artery disease (PAD).[1]

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.[2]

Ankle brachial index (ABI), is a simple and non-invasive tool with high specificity and sensitivity for the diagnosis of PAD. Because of the well-established relationship between PAD and coronary artery disease (CAD), a low ABI is associated with higher rates of cardiovascular morbidity and mortality (for each decrement of 0.1 in ABI, mortality increases about 13%).[1,3]

It has been found that patients with PAD who had undergone cardiac catheterization had more extensive and calcified lesions, suggesting a more aggressive form of atherosclerosis. So we hypothesized that low ABI even in asymptomatic PAD can be a useful tool to predict the complexity of CAD.[4, 5]

AIM OF THE WORK

To investigate the correlation between ankle brachial index and the complexity of coronary artery disease.

Chapter 1

ATHEROSCLEROSIS

➢ Definition:

The word Atherosclerosis is of Greek origin and literally means focal accumulation of lipid (i.e., *athere* [gruel]) and thickening of arterial intima (i.e., sclerosis [hardening]).[6]

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.[7]

The most devastating consequences of atherosclerosis, such as heart attack and stroke, are caused by superimposed thrombosis. Therefore, the vital question is not why atherosclerosis develops but rather why atherosclerosis, after years of indolent growth, suddenly becomes complicated with luminal thrombosis. [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.

- **Lipid Hypothesis:**

The lipid hypothesis, proposed initially in 1913 by Anitschkow, holds that the development of atherosclerosis is the result of the gradual accumulation of lipid in the arterial wall, with its presence at that site being responsible for the generation of the characteristic tissue changes of atheroma. [9]

- **Thrombogenic Hypothesis:**

The thrombogenic hypothesis holds that atherosclerotic lesions grow by the gradual incorporation of luminal thrombus into the arterial wall. It is supported by the finding of fibrin and platelet-derived proteins in both developing and mature atherosclerotic plaques. However, thrombus may appear directly as a result of atherosclerosis rather than as a causative factor. [9]

- **Response to Injury Hypothesis:**

The response to injury hypothesis was initially proposed by Virchow in 1856. He believed that the degenerative changes associated with atherosclerosis were due to a healing response of the arterial intima to a prior mechanical injury. [9]

- **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 raise risk for hypertension, diabetes and acute ischemic events.

6. **Stress.**

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

B. <u>Non Modifiable Risk factors:</u> [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.**

➢ Risk Assessment of Atherosclerosis: [12]

The American Heart Association and the American College of Cardiology (AHA/ACC) recommend use of a revised calculator [13] for estimating the 10-year risk of developing a first atherosclerotic cardiovascular disease (ASCVD) event. This is defined as a nonfatal myocardial infarction, death from coronary heart disease, or stroke (fatal or nonfatal) in a person who was initially free from ASCVD. The calculator includes the following risk factors:

- Sex.
- Age.
- Race.
- Total cholesterol.

- HDL cholesterol.
- Systolic blood pressure.
- Treatment for elevated blood pressure.
- Diabetes.
- Smoking. [12]

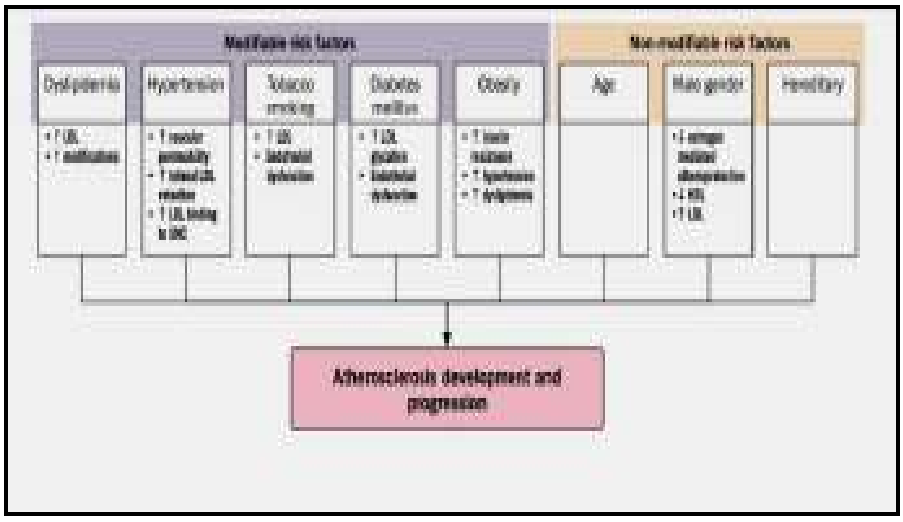

Figure (1): Risk factors of atherosclerosis [11]

➢ Pathophysiology:

Atherosclerosis is a multifactorial disease that usually develops many years before any clinical symptoms are manifest. These factors include, endothelial dysfunction, inflammatory factors, immunologic factors, and dyslipidemia. [11, 15, 16]

➢ 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, 15, 16]

2- Lipoprotein entry and modification:

Endothelial dysfunction allows for entry of LDL into the vessel intima o be modified by oxidation and glycation. [11, 15, 16]

3- Leukocyte recruitment:

Oxidized LDL activates endothelial cells to express adhesion molecules and release chemo-attractants which recruit monocytes and T cells. [11, 15, 16]

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, 15, 16]

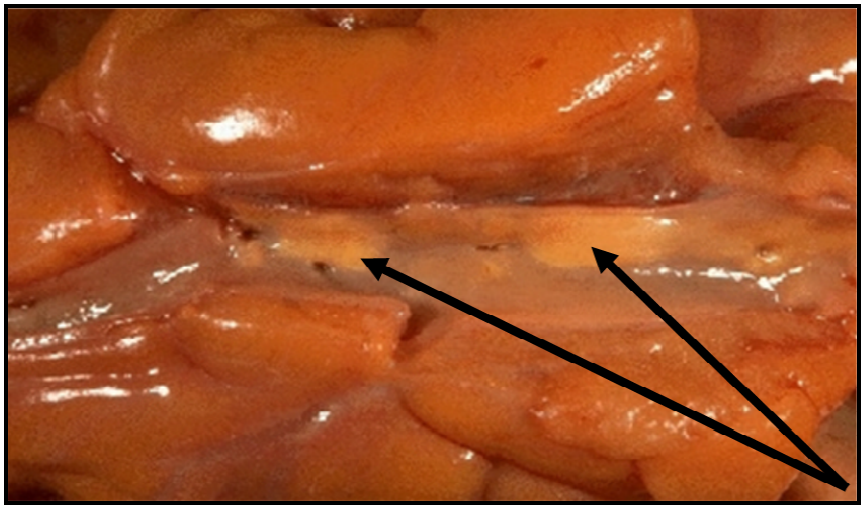

Figure (2): Fatty Streaks [14]

B. Plaque progression:

- Intima continues to thicken due to increase SMCs proliferation and leukocytes recruitment. **Fatty streaks** transform into **fibro-fatty lesions.** [11, 15, 16]
- 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, 15, 16]
- **Fibrous Capsule** is formed due to Apoptosis of SMCs. it surrounds a lipid-rich core. [11, 15, 16]

- **Late plaque growth** can significantly restrict the vessel lumen and decrease tissue perfusion, causing ischemic symptoms such as Angina pectoris or Claudication. [11, 15, 16]

C. <u>Plaque disruption:</u>

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, 15, 16]

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, 15, 16]

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, 15, 16]

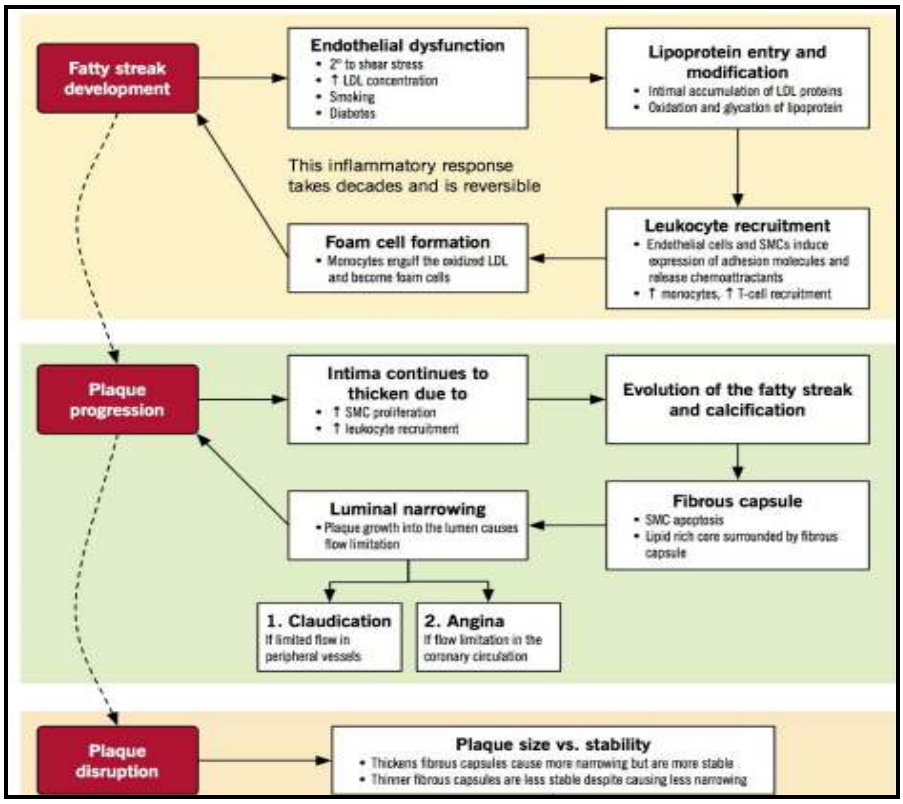

Figure (3): Stages of Atherosclerosis [11]

➢ 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. [17]

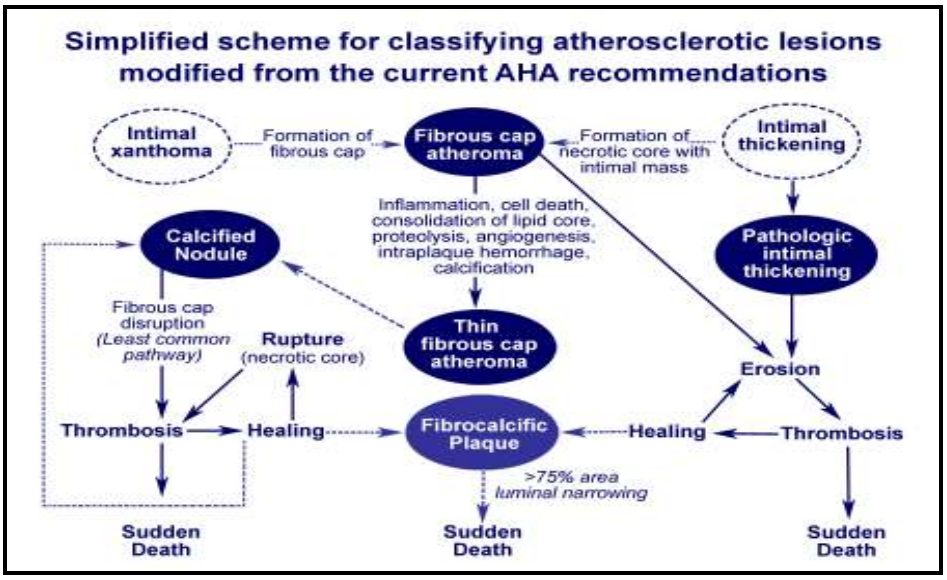

Figure (4): Simplified Scheme for Modified AHA Consensus Classification Based on Morphologic Descriptions [17]

Table (1): Modified AHA Consensus Classification Based on Morphologic Descriptions (Modified from Virmani et al.) [17]

	Description	Thrombosis
Non atherosclerotic intimal lesions		
Intimal thickening	Normal accumulation of smooth muscle cells (SMCs) in the intima in the absence of lipid or macrophage foam cells	**Absent**
Intimal xanthoma	Superficial accumulation of foam cells without a necrotic core or fibrous cap; based on animal and human data, such lesions usually regress	**Absent**
Progressive atherosclerotic lesions		
Pathologic intimal thickening	SMC-rich plaque with proteoglycan matrix and focal accumulation of extracellular lipid.	**Absent**

	Description	Thrombosis
Fibrous cap atheroma	***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.	**Absent**
Thin cap fibroatheroma	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	**Absent**
Lesions with acute thrombi		
Plaque rupture	Fibroatheroma with fibrous cap disruption; the luminal thrombus communicates with the underlying necrotic core	**Occlusive or non-occlusive**
Plaque erosion	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	**Usually non-occlusive**
Calcified nodule	Eruptive (shedding) of calcified nodules with an underlying fibrocalcific plaque with minimal or absence of necrosis	**Usually non-occlusive**
Lesions with healed thrombi		
Fibrotic (without calcification) Fibrocalcific (+/- necrotic core)	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	**Absent**