Coronary Artery Disease: Pathogenesis, Progression of Atherosclerosis and Risk Factors

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Introduction

Coronary artery disease

Coronary artery diseases (CAD) known as atherosclerotic heart disease, atherosclerotic cardiovascular disease, coronary heart disease (CHD), or ischemic heart disease (IHD) [1]. CAD is the largest contributor of cardiovascular diseases (CVDs) and mortality rate is due in prevalence to atherosclerosis, a chronic inflammatory condition of the arterial wall. Unfortunately, myocardial infarction (MI) is still a first common manifestation of CHD and, in about 50% of patients; angina pectoris is the first symptom of the pathology [2].
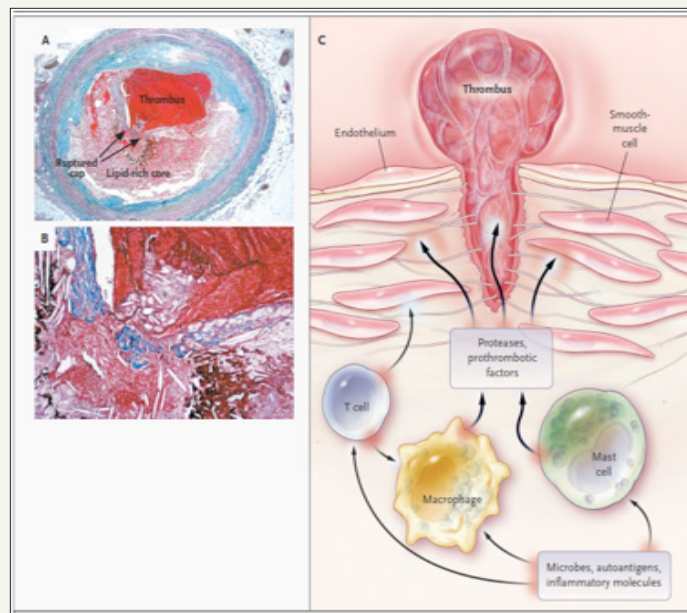
Atherosclerosis

Figure 1: Atherosclerotic lesion in a human artery.

Atherosclerosis is derived from the Greek words 'athera' meaning soft gruel-like (porridge-/mush-/paste-like) fatty deposit and 'sclerosis' which means hardening. Atherosclerosis is a pathological process that affects large- and medium-sized arteries and causes coronary artery disease (angina pectoris and myocardial infarction), cerebrovascular disease (ischemic stroke and vascular dementia) and peripheral vascular disease (intermittent claudication and gangrene) [3]. Atherosclerosis is a chronic cumulative disease progressing over years. It is characterized by atherosclerotic plaques formed in the wall of the vessels, consisting of necrotic cores, calcified regions, accumulated modified lipids, and inflamed smooth muscle cells (SMCs), endothelial cells, leukocytes, and foam cells (Figure 1). Lesions begin early as fatty streaks and progress into pathologic lesions under the influence of both genetic and lifestyle insults [4,5].

Panel A shows a cross-sectioned coronary artery from a patient who died of a massive myocardial infarction. It contains an occlusive thrombus superimposed on a lipid-rich atherosclerotic plaque. The fibrous cap covering the lipid-rich core has ruptured (area between the arrows), exposing the thrombogenic core to the blood. Trichrome stain was used, rendering luminal thrombus and intra-plaque hemorrhage red and collagen blue. Panel B is a high-power micrograph of the area in Panel A indicated by the asterisk and

shows that the contents of the atheromatous plaque have seeped through the gap in the cap into the lumen, suggesting that plaque rupture preceded thrombosis (the asterisk indicates cholesterol crystals). (Panels A and B courtesy of Dr. Erling Falk, University of Aarhus, Aarhus, Denmark.)

Panel C illustrates the consequences of the activation of immune cells in a coronary plaque. Microbes, autoantigens, and various inflammatory molecules can activate cells, macrophages, and mast cells, leading to the secretion of inflammatory cytokines (e.g., interferon- and tumor necrosis factor) that reduce the stability of plaque. The activation of macrophages and mast cells also causes the release of metalloproteinases and cysteine proteases, which directly attack collagen and other components of the tissue matrix. These cells may also produce pro-thrombotic and pro-coagulant factors that directly precipitate the formation of thrombus at the site of plaque rupture.

Pathogenesis of atherosclerosis

The pathologist Felix Marchand first introduced the term "atherosclerosis" in 1904, describing the association of fatty degeneration and vessel stiffening [6]. This process affects medium and large-sized arteries and is characterized by patchy intramural thickening of the sub-intima that encroaches on the arterial lumen. Each vascular bed may be affected by this process; the etiology, treatment and clinical impact of atherosclerosis varies from one vascular bed to another [7]. The earliest visible lesion of atherosclerosis is the fatty streak, which is due to an accumulation of lipid-laden foam cells in the intimal layer of the artery (Figure 2). With time; the fatty streak evolves into a fibrous plaque, the hallmark of established atherosclerosis. Ultimately the lesion may evolve to contain large amounts of lipid; if it becomes unstable, denudation of overlying endothelium, or plaque rupture, may result in thrombotic occlusion of the overlying artery [7,8].
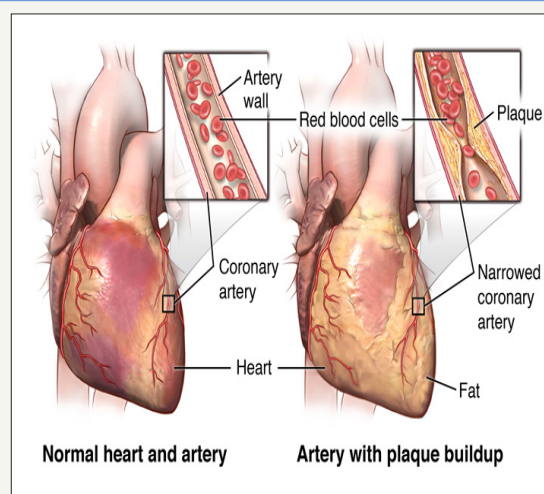

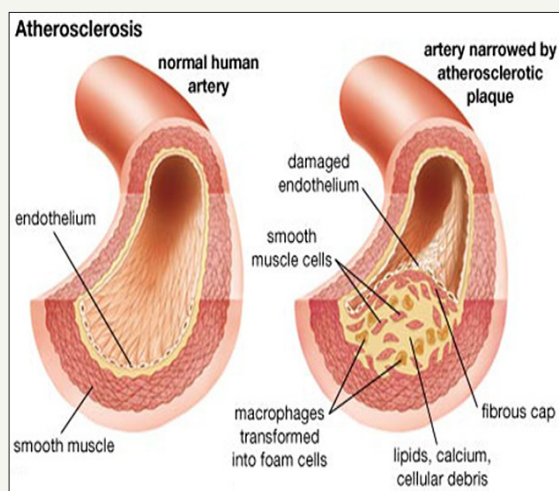**Figure 2:** Normal heart, normal artery and artery with plaque.

Figure 3: Atherosclerotic plaque formation.

Atherosclerotic lesions (atheromata) are composed of three major components. The first is the cellular component comprised predominately of smooth muscle cells and macrophages. The second component is the connective tissue matrix and extracellular lipid. The third component is intracellular lipid that accumulates within macrophages, thereby converting them into foam cells (Figure 3). Atherosclerotic lesions develop as are sult of inflammatory stimuli, subsequent release of various cytokines, proliferation of smooth muscle cells, synthesis of connective tissue matrix, and accumulation of macrophages and lipid [9,10].

There are 2 major types of vascular pathology leading to stroke, stroke subtypes and IHD. One is atherosclerosis, a large vascular pathology typically observed in the aorta, coronary arteries, carotid arteries and basal cerebral arteries, and characterized by lipid accumulation with proliferative changes leading to plaque formation [11]. The other pathology is arteriolosclerosis, a small vascular pathology typically occurring in small penetrating arterioles in the basal ganglions of the brain, characterized by necrosis or apoptosis of smooth muscle cells within the media, leading to the formation of micro-aneurysms (intra-parenchymal hemorrhage) and fibrous proliferative changes (lacunars stroke) (Figure 4) [11].
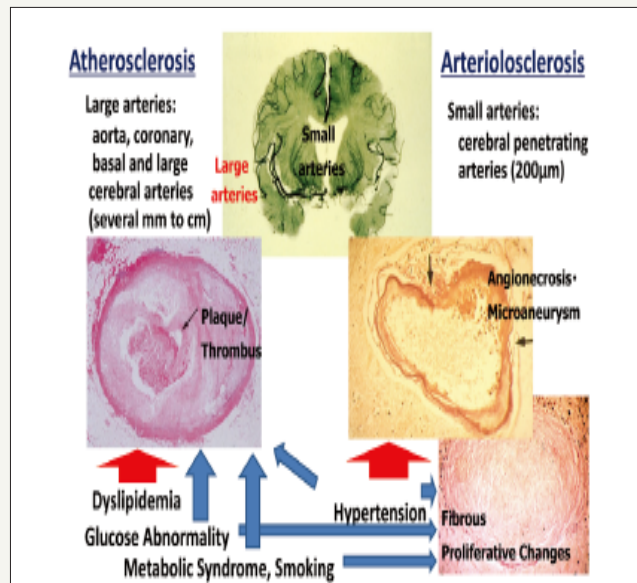

Figure 4: Two types of vascular pathology in large and small arteries: Atherosclerosis (Left) and Arteriosclerosis (Right).

Progression of atherosclerosis

Excess generation of (ROS) represents an important pathological process in atherogenesis. Each component of the atherosclerotic blood vessel has been demonstrated to increase production of ROS, primarily superoxide anion (O_2^-) [12]. Important sources of ROS are vascular smooth muscle cells, endothelial cells, fibroblasts, and infiltrating leukocytes [13]. Production of ROS affects gene transcription, damages DNA, and increases production of inflammatory transcription factors [14]. The two best-characterized effects include oxidation of LDL and scavenging of endothelium-derived NO•. The progression of atherosclerotic disease has been described as moving from an early lesion (phase1) to a more advanced fibro-lipid lesion (phase 2) (Figure 5). The formation of thrombus or hematoma can advance into an acute phase (phase 3 and 4) or even to total occlusion (phase 5). Although there is substantial evidence for this process in the coronary circulation, it is highly likely that it also occurs in peripheral artery disease (PAD). Magnetic resonance imaging (MRI) has allowed better characterization of lesions and has shown the importance of plaque composition to subsequent clinical events [15,16].
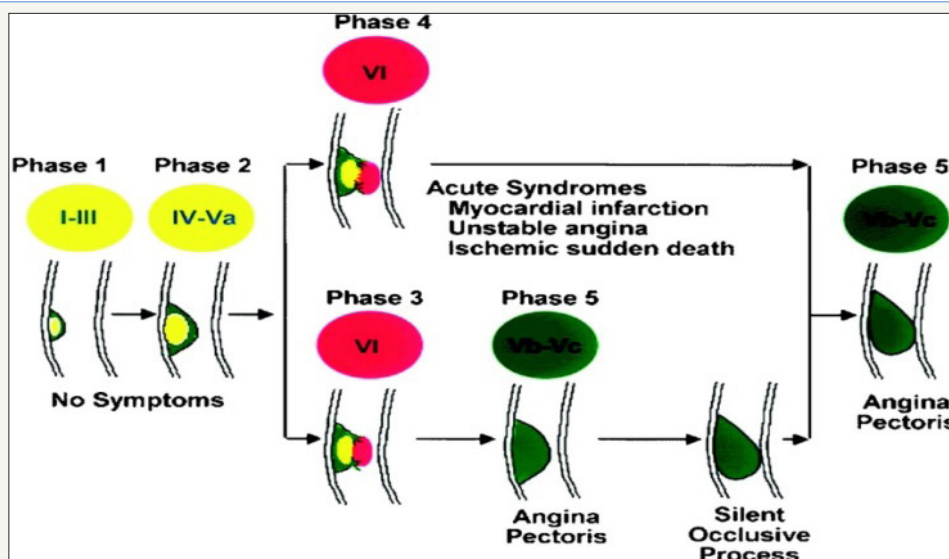

Figure 5: Phases of lesion development.

Risk Factors Influencing Coronary Artery Disease

A risk factor can be defined as a characteristic that is associated with increased or decreased likelihood of subsequent development of CVD [17].

Types of risk factors

Non-modifiable risk factors: Risk factors that cannot be prevented, changed or controlled such as: age and gender, because they are not modifiable, they are less determining in terms of risk factor management [17].

A. Age

Ageing is an un-modifiable risk factor for CAD, with males clinically manifesting this condition at 50-65 years of age and females about 10 years later, following menopause. The WHO reports that the principal cause of death of people over 65 years is CAD, and as age increases, a substantial proportion of deaths are among females [18]. In many developed countries, the number and proportion of older people (over 65 years) is increasing, which is largely explained by declines in fertility and mortality. The ageing population of many countries has accelerated the contribution of CAD to total disease burden. It is predicted that the global ageing population will maintain CAD as a predominant cause of death worldwide [18]. Among countries with high but declining CAD mortality, it is suggested that these trends are changing with respect to younger age subgroups [19].

B. Gender

Coronary artery disease is the leading cause of mortality for both adult males and females alike worldwide. Although the initial manifestation of CAD is delayed in females by about ten years compared to males, there is not an abrupt increase in CAD mortality rates for females immediately following menopause but a progressive increase over subsequent years [20,21].

C. Family history

Epidemiological studies indicate that family or parental history of myocardial infarction is a risk factor for coronary heart disease [22]. Nasir et al. [23] examined the association of a reported family history of early-onset (before age 55 years) CHD with the presence and burden of coronary artery calcium (CAC) in electron beam computed tomography in 8549 asymptomatic men and women referred for testing. Coronary artery calcium is a surrogate measure of the presence and burden of coronary atherosclerosis that has consistently been associated with increased risks for CHD in selected cohorts [24]. Coronary artery calcium was significantly more common in subjects with a sibling or parental history of CHD. The elevated odds for CAC conferred by the presence of a family history were not significantly different by strata of individual modifiable risk factors, although the prevalence of CAC in subjects with three or more risk factors was higher in those with than in those without a family history [24]. Zlot et al. [25] have reported that parental history of CHD is associated with increased carotid intima-media thickness, even after adjustment for established risk factors.

Modifiable risk factors: Risk factors that can in principle be prevented, changed, or controlled. Major modifiable risk factors include: sedentariness, smoking, dietary imbalance, impaired glucose tolerance and diabetes mellitus, elevated blood pressure, abnormal blood lipids, and obesity [20].

A. Hypertension (Blood pressure)

Hypertension (HTN), one of the most traditional risk factors, has been consistently correlated with increased probability of developing CAD in various populations [26]. Lewington et al. [26] reported that the Prospective Trialists group each 20/10mm Hg increase in blood pressure (BP) doubles the risk of ischemic heart disease and stroke over the range of 115/75 to 185/115mm Hg in individuals from 40 to 90 years of age. The epidemiological studies are supported by experimental evidence postulating that hypertension predisposes to atherosclerosis through a shared synergistic mechanism involving inflammation and oxidative stress in the arterial wall [27,28].

It is conceivable that the effect of hypertension on CAD onset may be modulated by various environmental and genetic factors. However, it is widely accepted that strategies adapted to lower blood pressure play a protective role by delaying atherosclerotic lesion formation [29]. The association of hypertension with CAD manifestations onset has not been thoroughly investigated in Middle Eastern populations [30,31], showed that there is a significant association between hypertension and acute myocardial infarction (MI) in older patients One study however described hypertension as one of the most frequent risk factors for premature CAD [32].

B. Smoking

Smoking is a major factor in both the development and rate of progression of a cardiovascular disease and coronary artery disease [33]. Nicotine and carbon monoxide contents of cigarette have damaging effects on arteries by causing them to lose their compliance and to set up a stage for plaque development. Cigarette smoking results in high levels of circulating non-esterified fatty acids which can be injurious to the cell by eliciting inflammatory response [34]. The free radicals generated from smoking results in oxidative stress and increases oxidation of LDL which trigger the recruitment of monocytes and T-cells; these lead to formation of macrophages and other processes that promote atherosclerosis. Young et al. [35] explained that the toxins in tobacco smoke lower a person's HDL while raising levels of LDL cholesterol or "bad" cholesterol. Specifically, smoking has been associated with a two- to six-fold increase in males in the risk for myocardial infarction, a major form of CHD. It has also been associated with a three-fold increase in the risk for incident angina. There is a clear dose relationship between CHD and the duration (years) of smoking, the number of cigarettes smoked, the degree of inhalation, and the age of initiation of smoking [36].

C. Type 2 diabetes mellitus (T2DM)

One of the risk factors, diabetes, and its predominant form, type 2 diabetes mellitus (T2DM), has a distinctive association with CHD. The number of people with diabetes mellitus (DM) is increasing due

to population growth, aging, urbanization, increasing prevalence of obesity, and physical inactivity, with an estimated number of 200 million patients worldwide [37]. Patients with diabetes have two to four-fold likelihood of developing coronary artery disease with marked morbidity and mortality [38]. CAD in patients with DM is often more advanced at the time of diagnosis compared with patients without DM [39]. In addition, a complex mix of mechanistic processes such as oxidative stress, enhanced atherogenecity of cholesterol particles, abnormal vascular reactivity, augmented haemostatic activation, and renal dysfunction have been proposed as features characteristic of T2DM that may confer excess risk of CHD [40].

D. Obesity (Overweight)

Obesity is a predictor of coronary artery disease both as an independent factor and as a progenitor of the multiple atherogenic processes of the metabolic syndrome [41]. Obesity is associated with an increase in both oxidative stress and the pro-inflammatory effects of certain cytokines. Interleukin-6 is produced in adipocytes and increasing adipocyte mass causes an elevated production of IL-6. These higher levels of IL-6 subsequently stimulate production of C-reactive protein in the liver and both play a role in endothelial dysfunction by decreasing nitric oxide ($NO^{\bullet}$), leading to vasoconstriction and increasing vascular resistance [42]. This association remained significant even after adjusting for other risk factors (non-HDL, HDL, smoking and hypertension). These data lead to the ominous realization that obesity in adolescents and young adults accelerates the progression of atherosclerosis decades before the onset of clinical symptoms [43].

E. Dyslipidemia (Hypercholesterimia)

A high level of LDL-C in the blood is the principal cause of injury to the artery and vascular SMCs [44]. With high levels of LDL in vascular endothelium, leukocytes start to 'cling' to the endothelium and cause further accumulation of lipids which result in foam cells formation. Abnormalities in the regulatory mechanisms of LDL-receptors and fatty diet can result in hypercholesterimia which can eventually lead to atherosclerosis [35]. High density lipoprotein-cholesterol (HDL-C) or "good" cholesterol inhibits oxidative modification of LDL and blocks the pro-inflammatory effects of oxidized LDL (ox-LDL) [44]. HDL provides protection against atherosclerosis by promoting the activity of antioxidant enzymes like platelet activation factor, acetyl hydrolase and paraoxonase [45].

F. Sedentariness

Physical activity is a key determinant of energy expenditure and thus fundamental to energy balance and weight control. Physical activity improves endothelial function, which enhances vasodilatation and vasomotor function in the blood vessels [46]. In addition, physical activity contributes to glycaemic control, improved blood pressure, lipid profile and insulin sensitivity [47]. The protective value of physical activity is independent of measures of total cardiovascular risk such as the score estimated using the Framingham risk equation [48].

Other factors are also of importance: psychosocial, such as perceived stress at work, symptoms of depression, low socioeconomic status, as well as indicators of chronic inflammation and haemostatic factors [17].

A. Psychosocial factors

Psychosocial factors contribute independently to the risk of CHD, even after statistical control for the effects of standard risk factors. These factors may act as barriers to treatment adherence and efforts to improve lifestyle, as well as promoting health and well-being in patients and populations [49]. Low socioeconomic status, lack of social support, social isolation, stress at work and in family life, negative emotions including depression and hostility have been shown to influence both the risk of contracting CHD and the worsening of clinical course and prognosis in patients with CHD. Several behavioral and psycho-physiological mediators and moderators of these effects have been identified [48].

B. Socio-economic status

Social determinants such as the distribution of income or the level of education indirectly influence cardiovascular health as well as health in general. These determinants shape a set of socioeconomic positions within hierarchies of power, prestige and access to resources. Several structural mechanisms are responsible for creating the differential social positions of individuals, including governance, education systems, labor market structures and the presence or absence of redistributive welfare policies. Social stratification shapes individual health status as well as CVD outcomes by impacting behavioral and metabolic cardiovascular risk factors, psychosocial status, living conditions and the health system [50].

The final report of the Commission [20] made three overarching recommendations: (i) to improve daily living conditions; (ii) to tackle the unequal distribution of power, money and resources; and (iii) to monitor health inequities. WHO Member States discussed the report and passed a resolution urging action on social determinants at the 2009 World Health Assembly (WHA) [20]. The resolution called for a "Health in All Policies" approach and a renewed commitment to intersect oral action to reduce health inequities as well as the implementation of a social determinants approach across public health programs. Poverty, low rates of literacy, environmental degradation, poor housing and unplanned urbanization have a negative impact on health [51].

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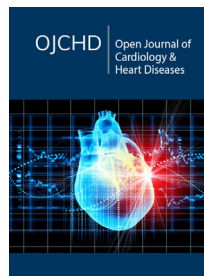
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