Atherosclerosis

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Abstract

Atherosclerosis is a chronic inflammatory disease of multifactorial origin that occurs in response to endothelial aggression, affecting mainly the intima of medium and large caliber arteries. It is usually consequent to traditional risk factors such as diabetes mellitus, hypertension, dyslipidemia, obesity and smoking. It is related with several cardiovascular morbidities such as cerebrovascular disease, coronary, peripheral arterial and renovascular diseases. According to the World Health Organization, cardiovascular disease is the main cause of disability and premature death worldwide. An estimated 17.5 million people died from this cause in 2005, representing 30 % of all deaths in the world. This can be explained by understanding that people are more exposed to risk factors and less exposed to prevent efforts. Atherosclerosis prevention is less costly than treating its complications; thus, identification of subclinical disease in the asymptomatic phase has emerged as a public health and economic imperative.

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Introduction

Atherosclerosis is a chronic inflammatory disease of multifactorial origin that occurs in response to endothelial injury, affecting mainly the intima of arteries of medium and large caliber. It is usually consequent to traditional risk factors such as diabetes mellitus, hypertension, dyslipidemia, obesity and smoking habit. However, more rarely, it can be a consequence of inherited diseases such as familial hypercholesterolemia.

Epidemiology

According to the World Health Organization, cardiovascular disease is the main cause of disability and premature death worldwide [1]. An estimated 17.5 million people died from this cause in 2005, representing 30 % of all deaths in the world. This can be explained by understanding that people are more exposed to risk factors and less exposed to prevent efforts. The prevalence of systemic arterial hypertension in the population over 65 years old is approximately 52.3 %, for diabetes mellitus it is about 21 %, obesity is around 27.5 % and for current smokers it is 11.3 % [2]. However, only 24.8 % of North American adolescents from 12 to 15 years old practice at least 60 min of moderate-vigorous physical activity daily, as recommended by the 2008 physical activity guideline [3].

Pathophysiology

Atherosclerosis starts when monocytes migrate from blood stream to the intima (innermost layer of the arterial blood vessel), constituting the foam cells (macrophages that have engulfed lipoproteins). Over time, foam cells accumulate and form an irregular and thick layer distributed along artery lining. Each thickening zone (called atheroma or atherosclerotic plaque) is consisted of cholesterol, smooth muscle cells and connective tissue. The atheroma tends to be formed at large and medium-sized artery, particularly at vessels bifurcation, presumably due to the altered shear stress of such areas, which injures the arterial wall and predisposes to atheroma formation.

Endothelium dysfunction plays a key role in the atherosclerosis pathophysiology. That Endothelial dysfunction downregulates endothelial nitric oxide synthase, the enzyme that generates nitric oxide, which impairs endothelium-dependent vasodilatation and accelerates atherosclerosis. Arteries affected by atherosclerosis lose their elasticity and become narrower. They become progressively damaged and lose their original elastic structure over the years, which can trigger the formation of a blood clot (thrombus). The clot reduces blood flow through the artery and may even cause its complete occlusion. It can also detach and be carried through the blood stream until it reaches a smaller artery, causing an occlusion (embolism). The

disease development occurs mainly in three territories: cerebrovascular, coronary, and peripheral arteries (Fig. 3.1).

Cerebrovascular Disease

It is a pathological narrowing of the intima of the common or internal carotid artery, typically in focal areas called plaques or atheroma. Although the atheroma can remain stable for many years, its surface may rupture leading to formation of local thrombus with subsequent embolization to the territories of the ophthalmic artery, anterior cerebral, or medial cerebral artery.

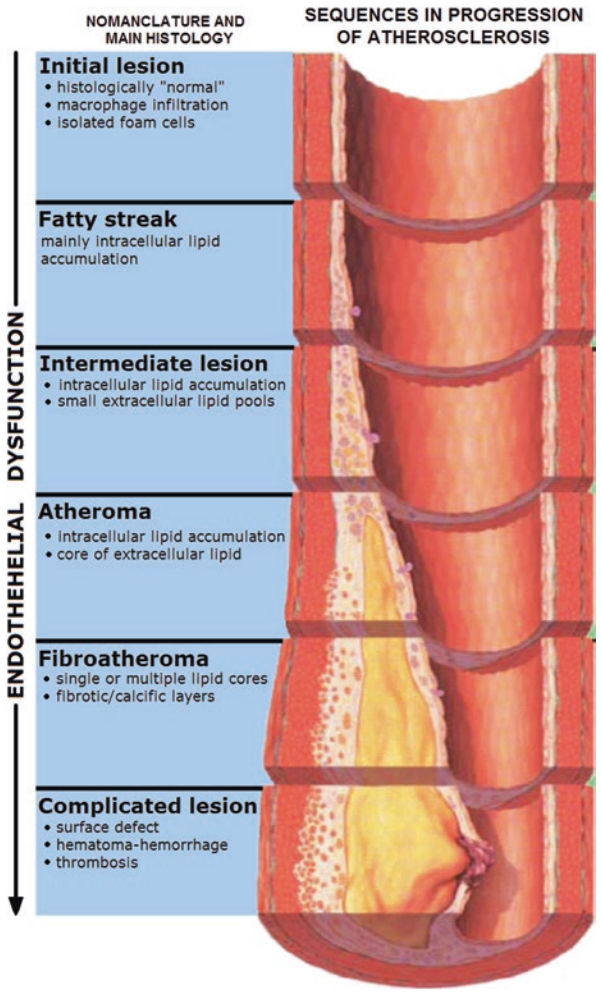

Fig. 3.1 Pathophysiology of atheromatous plaque

The main symptoms depend on the affected territory. At the ophthalmic circulation, symptom of amaurosis fugax or retinal infarction may be seen. On the other hand, the medial cerebral artery embolism can be seen as transient symptoms in the contralateral hemisphere body (called 'transient ischemic attack') or even stroke.

However, it is usually diagnosed on non-invasive imaging studies in asymptomatic individuals [4].

Patients with atrial fibrillation have a threefold to fivefold increased risk of cardioembolic ischemic stroke. Hyperlipidemia is a risk factor for the disease development in this territory, being associated with the presence of atherosclerotic stenosis and the stroke occurrence observed when total cholesterol level is greater than 5.20 mmol/L (200 mg/dL) [5]. Hypertension is an independent risk factor for the development of cardiovascular disease and has a great association with hyperlipidemia [6]. The presence of diabetes mellitus is associated with increased chances of having ischemic stroke in two to three times and its proper control is related to risk reduction [7, 8].

Coronary Artery Disease

Atherosclerosis reduces coronary blood flow leading to symptoms of myocardial ischemia. In recent years, advanced knowledge of the atheroma pathophysiology and the rupture of atherosclerotic plaques was have been achieved. The atheroma is responsible for acute coronary syndromes causes, in more than half of the cases, produces a stenosis lower than 50 % of the vessel diameter. Therefore, they are vulnerable plaques with a large lipid core, inflammatory cells and thin fibrous caps, subject to biomechanical stress. This knowledge of plaques vulnerability has led to change in treatment, with new therapeutic options such as antiplatelet, antithrombotic drugs, statins and beta-blockers drugs [9].

In this territory, the genetic factor is strongly associated with plaque formation and complication, especially in individuals with a history of premature familial disease. This correlation is significant for those with a first-degree relative who had atherosclerotic cardiovascular disease or died due to it before 55 years old for men or 65 years old for women [10]. Dyslipidemia is directly related to the occurrence of coronary artery disease due to its important role in the formation of atherosclerotic plaque. Higher levels of non-high density lipoprotein are associated with higher incidence of coronary events, particularly in patients with earlier manifestations [8, 11, 12]. Nicotine and tar are directly related to deaths from coronary artery disease and higher doses of these toxins are associated with progressive increase in mortality [13]. Patients with diabetes mellitus have higher chance of developing coronary artery disease and developing it in an early age when compared to the general population [14]. Diabetes mellitus also increases the risk of complications. The incidence of acute coronary syndrome is higher in patients with diabetes mellitus when compared to individuals without the disease [15]. Moreover, mortality of patients with diabetes mellitus is mostly related to coronary artery disease complications [16]. A study conducted in 52 countries showed a significant association

between hypertension and coronary artery disease, consistent with the vast data related to the Framingham study. It shows that this is an important target for the reduction of myocardial infarction, especially when it occurs early in life [17, 18].

Peripheral Artery Disease

Atherosclerosis is the leading cause of peripheral arterial disease, in which there is a blockage or stenosis in the arteries that supply lower limbs. Approximately 80 % of patients with peripheral artery disease are asymptomatic. The main symptoms of the ischemia are muscular atrophy, ulcers, pallor and intermittent claudication, and the main finding in the physical examination is the reduction or absence of peripheral pulses. In some cases, the disease can have an acute worsening, characterized by severe pain, sudden onset, associated with reduced limb temperature, decreased temperature and paraesthesia, featuring acute arterial ischemia that must be treated immediately in an attempt to avoid amputation and death.

Advanced age is also a progressive risk for the disease in this territory. However, it becomes significant higher after 40 years. The risk greatly increases in patients older than 70 years, but only part of them present the symptomatic form of peripheral artery disease [20–22]. Smoking is strongly associated with the development of the disease. Studies like Framingham's showed a two times increased risk of developing intermittent claudication among smokers when compared to non-smokers [23]. Such findings were confirmed by other epidemiological studies that also assigned the risk two to six times greater among smokers [24–26]. Diabetes mellitus is directly associated with the incidence and severity of peripheral artery disease. The prevalence is almost five times greater of peripheral artery disease in diabetic patients older than 40 years when compared to people without the comorbidity [27, 28]. Regarding the affected territory, diabetic patients generally have more distal involvement of the vessels, especially in the popliteal and tibial vessels [29, 30]. Regarding the outcome, the association of these two diseases correlates to a higher risk of lower limb amputations in elderly people [31]. It's well known that patients with peripheral artery disease are more likely to have high levels non-high density lipoprotein cholesterol and/or triglycerides [32] as well as reduced levels of high density lipoprotein [33]. In addition, there is a significant association between hypertension and peripheral artery disease both in symptomatic and asymptomatic individuals [22, 34]. Those patients present a two times higher risk of developing symptoms such as claudication when compared to non-hypertensive patients [35].

Reno-Vascular Atherosclerosis

The initial cause of the endothelial lesion not established that yet, though dyslipidemia, diabetes, hypertension and smoking certainly collaborate to the pathogenic process. It is the leading cause of renal artery stenosis in the elderly. This pathologic process is the main cause of renovascular hypertension, responding for 1–10 % of

all hypertensive disease cases in the United States, and contributing importantly to chronic renal failure progression. The lumen of a renal artery with atherosclerosis gradually reduces, leading to decreased blood flow and renal ischemia. The kidney adaptation to atrophy and reduction of tubular cells, inflammation, fibrosis and glomerular atrophy generates a glomerular filtration rate angiotensin II dependent. This adaptation process can maintain a stable renal function until it reaches high grade renal artery stenosis [36].

Diagnosis

The diagnosis of atherosclerosis is usually established after starting its symptoms in at least one of the above mentioned territories. However, the best approach is to diagnose it in a preclinical phase through risk stratification and laboratory tests, enabling the effective secondary prevention with the correct definition of individual therapeutic goals. Atherosclerotic disease risk stratification results from the sum of all potential increased risks identified in patients; therefore, the first step in clinical risk assessment is to identify any high-risk conditions that obviate the need for further risk assessment, these mainly include established atherosclerotic cardiovascular disease and diabetes. If none of such high-risk conditions is present, the second step is to apply a well stablished risk score, such as Framingham.

Determining the Presence of Significant Atherosclerotic Disease or Its Equivalent

The clinical relevance of detecting subclinical atherosclerosis disease rests on improving prediction of cardiovascular disease risk over traditional factors. A systematic review consisted of 25 studies evaluated the link between cardiovascular events and subclinical atherosclerosis findings in imaging tests. It has been found greater chance of fatal and nonfatal cardiovascular events in individuals with calcification in coronary arteries, carotid plaques and incresed thickness in carotid arteries. Individuals with intermediate risk of cardiovascular disease according to traditional risk assessment factor may benefit from additional images studies [37].

Ankle-Brachial Index

The ankle-brachial index test is an easy and non-invasive way to search for peripheral artery disease risk. It's the ratio of Doppler-recorded systolic blood pressure at the ankle divided by systolic blood pressure in the arm (See Appendix A for detailed information). Individuals without clinically significant peripheral artery disease typically have an ankle-brachial index greater than 1, while an ankle-brachial index < 0.9 is 90 % sensitive and 95 % specific for the presence of peripheral artery disease positive on angiography. A peripheral arterial lesion may be revealed with measurement of lower extremity pressures after exercise. Therefore, exercise

treadmill testing may be performed in order to raise ankle-brachial index test sensitivity [38].

Carotid Ultrasonography

Ultrasound methods have the advantages of being feasible in all individuals, relatively accessible and without exposure to radiation. It is useful in detecting flow reduction, obstructive plaques or to measure intima-media thickness, which represents subclinical atherosclerosis and is associated with adverse cardiovascular events. A novel three-dimensional ultrasound-based approach method identified more carotid plaques compared to other methods and its clinical utility as predictor of future cardiovascular events is comparable to coronary artery calcification score [39, 40].

Femoral Ultrasonography

This method may be better than carotid ultrasonography for detection of subclinical atherosclerosis, as showed in a study with 1423 middle-aged men (40–59 years of age) that evaluated the association of subclinical carotid and femoral plaques with risk factors and coronary artery calcification score. The area under the receiver-operating curve for prediction of positive coronary artery calcification score increased from 0.66 when considering only risk factors to 0.71 when adding femoral and carotid plaques ($p < 0.001$). In this model, the femoral odds ratio (2.58) exceeded the carotid odds ratio (1.80) for prediction of positive coronary artery calcification score [41].

Electron-Beam Computed Tomography

It can be used to assess coronary artery calcification score. High coronary artery calcium levels correlates with histological plaque as well as the number of stenosed vessels on studies with invasive angiography [42]. On a study with 6814 participants and over 5.8 years median follow-up, addition of coronary artery calcification score to a prediction model based on traditional risk factors significantly improved the classification of risk. However, this method is limited to detect non calcified plaques and to predict plaque stability [43].

Pressures and Pulse-Volume Recordings

Segmental pressures and pulse-volume recordings are other important tool used to assess the level and extent of obstruction. A series of blood pressure cuffs are placed at multiple levels on the arms or the legs to measure pressures and the amount of blood flow at each level. These tests are performed to localize blockage areas in those territories. An advantage of using pulse volume recording amplitudes is that they are valid when examining calcified vessels, such as in diabetic patients. Exercise test can be necessary to uncover subcritical stenosed sites [44].

Others Cardiovascular Methods of Evaluation

Dobutamine **echocardiography** is more sensitive than adenosine echocardiography, but a positive adenosine echo often represents more severe disease.

A myocardial perfusion **single-photon emission** computed tomography scan of the heart is a non-invasive nuclear imaging test that include perfusion and gated wall motion images. The scans can also be used to accurately determine the left ventricular ejection fraction, the end-systolic volume of the left ventricle, regional wall motion and wall thickening. In addition, solid evidence links these findings to clinical outcomes.

Magnetic resonance imaging offers the advantage of avoiding ionizing radiation and it is capable of identifying specific components of the plaque. However, current magnetic resonance methods suffers from extensive variability of image quality and a longer time for acquiring images.

Utilization of Risk Stratification Scores

Cardiac risk stratification begins with calculating the probability of an incident event using conventional algorithms, such as the Framingham equation.

Framingham Risk Score, for example, estimates the probability of acute myocardial infarction or death from coronary heart disease within 10 years in individuals with no history of clinical atherosclerotic disease and have been validated in multiple countries and populations [45].

Treatment

General Practitioner's Role

Prevention of cardiovascular disease is less costly than treating its complications; thus, identification of subclinical disease in the asymptomatic phase has emerged as a public health and economic imperative. The general practitioner also has an important role in the investigation of peripheral arterial disease through the ankle brachial index (See Appendix A for more details). Behavioral modifications like smoking cessation and exercise has a direct beneficial impact on vascular changes associated with aging. Antiplatelet agents have essential role on prevention of plaque accidents and thrombosis. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE), published in 1996, compared clopidogrel with aspirin in reducing the risk of vascular events in patients with clinical manifestations of atherosclerosis. It found that long-term administration of clopidogrel is more effective than long-term aspirin therapy in reducing the combined risk of ischemic stroke, myocardial infarction or vascular disease. The relative risk reduction provided by clopidogrel is added to the benefit provided by aspirin when compared with placebo. Therefore, rational using of those agents is highly recommended on clinical practice. The pleiotropic effects of statins have beneficial effects on both vascular aging and atherosclerosis. These favorable endothelial effects are attributed to their ability to lower the low-density lipoprotein cholesterol, upregulate endothelial nitric oxide synthase and exert antioxidant activity.

Pharmaceutical agents that block formation of advanced glycation end product have proved efficacious in decreasing vascular stiffness and nephrosclerosis, but clinical trials were halted due to adverse drug effects.

Good medical practice recommends prevent risk factors and behavioral changes associated to pharmacological treatment. Nevertheless, surgical approaches can be necessary.

Medical Specialist Evaluation

The evaluation by the specialist is important when the patient has certain complications of atherosclerosis such as cerebrovascular disease, peripheral arterial disease and other situations. In several cases, surgery becomes necessary. The exact technical procedure will depend on the obstruction grade and its location, but usually some techniques such as open surgery (bypass or endarterectomy) or endovascular surgery can be used. The final objective is to restore the blood flow and stop tissue ischemia. However, the most powerful reduction in atherosclerotic disease results from early recognition and risk factor modification.

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