ScieniQ Publishers

Japan Journal of Medical Science

Review Article

Historical overview of lipid metabolism and ath erosclerosis from its origin to the Covid 19 era

Sidney Carvalho Fernandes[1], Anita L. R. Saldanha[1], Ana Paula Pantoja Margeotto[1], Abel Pereira[1], André Luis Valera Gasparoto[2], Tania Leme da Rocha Martinez[1]*

[1]Nephrology Department, BP - A Beneficência Portuguesa de São Paulo, São Paulo, Brazil

[2]Intensive Care Unit, BP - A Beneficência Portuguesa de São Paulo, São Paulo, Brazil

***Corresponding author**
Tania Leme da Rocha Martinez, BP - A Beneficência Portuguesa de São Paulo. Rua Comandante Ismael Guilherme, 358 - Jardim Lusitânia. CEP 04031-120 - São Paulo – SP, Brazil

Receiveed: 22 Dec 2020
Accepted : 24 Dec 2020
Published: 02 Jan 2021

Abstract

This review aims at the historical path for understanding the atherosclerotic process and the role of dyslipidemias in their pathophysiology. Responsible for about 33% of the world's mortality, followed by afar by neoplastic diseases in some countries and violent deaths in others, atherosclerotic disease was already present at least 3,500 3500 before Christ (BC), as morphological findings in Egyptian mummies verified by anatomical studies show. Hippocrates described sudden death and Erysisths symptoms of intermittent claudication, both around 300 BC. In 1904 Felix Marchand introduced the term atherosclerosis and suggested that it was responsible for most of the obstructive processes of the arteries. The oldest descriptions of atherosclerotic lesions focused on morphologies from fatty striae to fibroatheromas and advanced plaques complicated with hemorrhage, calcification ulceration and thrombosis, however, there is no description of how the plaques developed to trigger an acute coronary syndrome. The pathophysiology of atherosclerosis involves the transformation of a normal artery into an atherosclerotic artery, through several steps, such as: activation or endothelial lesion, absorption and retention of LDL particles with subsequent oxidation, infiltration of monocytes and their conversion into macrophages and then in fatty cells, proliferation of smooth muscle cells of the arterial wall, proliferation of the middle tunic and migration to the intimate region and finally thrombosis. The higher the lipid nucleus, the number of inflammatory cells, the higher concentration of cytokines and proteinases (peptidases, collagenases and gelatinases) formed by these inflammatory cells, the greater the vulnerability of the plaque, with thinning of its fibrous layer, and can more easily lead to its rupture. Presently in the COVID-19 pandemic era the process is accelerated by cytokines storms leading to the precipitation of cardiovascular events linked to the inflammatory and pro thrombotic stimuli.

Keywords: Atherosclerosis, Fat cells, Inflammation, Cholesterol, LDL Cholesterol, Biomarkers, Atheroma, C Reactive Protein

Abbreviations

CRP: C-reactive protein
HDL: High Density Lipoprotein
IL-6: Interleukin 6
IL-17: Interleukin 17
LDL: Low Density Lipoprotein
NF-kB: Nuclear Factor kB
Th 1: Auxiliary T 1 lymphocytes
Th 17: Auxiliary T 17 lymphocytes
TMAO: Trimethylamine-N-Oxide
TNF-α: Tumor Necrosis Factor Alpha
VEGF: Vascular Endothelial Growth Factor
VLDL: Very Low Density Lipoprotein

With the exception of some developing countries where infectious diseases and malnutrition still predominate, cardiovascular diseases represent the greatest cause of morbidity and mortality in the rest of the world. Among these, cerebrovascular disease, whether ischemic or hemorrhagic and ischemic heart disease are the most important and have a common etiopathogenesis that is atherosclerotic disease.

When studying the treatment of dyslipidemias and atherosclerosis it is necessary to review some concepts that, if not well understood, can generate some distortions. To do so, the terms arteriosclerosis, atherosclerosis and arteriolosclerosis should initially be defined [1].

The term arteriosclerosis comes from the Greek and literally means hardening of the arteries and was first used in the literature in 1835 by Lobstein [2], and this process is caused by many diseases that have in common the increase in thickness and the loss of elasticity of the arterial wall, which may involve large and small arteries and the various layers of them. Within this term, there are three variants:

1. Atherosclerosis, characterized by the formation of plaques in the intimate layer of the arteries, consisting of fat deposits, inflammatory cells, fibrous connective tissue, smooth muscle cells and sometimes

calcium, often leading to a narrowing of the vessel light, and may involve different arterial groups, such as coronary arteries, carotid arteries, renal arteries and arteries of lower limbs.
2. Arteriosclerosis characterized by thickening of the walls of small arteries or arterioles, either by cell proliferation or by deposition of hyaline material and which has arterial hypertension as its main cause.
3. Calcified medial sclerosis of Mönckeberg presenting calcification of the middle layer of muscular arteries, usually occurring in conjunction with atherosclerosis and in the old people.

At the end of the 20th century, it became an important public health problem due to its high incidence and high morbidity and mortality, coronary artery disease, which can lead to angina pectoris and acute myocardial infarction, was one of the major responsible for the increased interest in the study of atherosclerotic disease. However, atherosclerosis may also manifest in other arterial territories, which may lead to cerebral vascular disease, peripheral arterial disease, kidney disease, aortic aneurysms or even manifest in other arterial territories.

Responsible for about 33% of the world's mortality, followed by afar by neoplastic diseases in some countries and violent deaths in others, atherosclerotic disease was already present at least 3,500 3500 before Christ (BC), as morphological findings in Egyptian mummies verified by anatomical studies show. Hippocrates described sudden death and Erysisths symptoms of intermittent claudication, both around 300 BC. In 1575 Fallopius observed certain pathological findings in arteries that characterized as bone degeneration suggesting the presence of calcified lesions. Around 1719 Potain interpreted the symptoms of angina pectoris as a result of myocardial ischemia, and in 1799 Parry related these symptoms to coronary artery lesions. In 1904 Felix Marchand introduced the term atherosclerosis and suggested that it was responsible for most of the obstructive processes of the arteries. In 1910 Windaus showed that atheromatous lesions contained 6 times more cholesterol free and 20 times more esterified cholesterol than the walls of normal arteries. From there, epidemiological, clinical and laboratory research have been unveiling the entire atherogenesis process, with its risk factors, pathophysiology, evolution and clinical manifestations, leading to effective therapeutic strategies for the prevention and treatment of atherosclerotic diseases.

Anitschkow in St. Petersburg, Russia in 1913 was the first scientist to demonstrate the role of cholesterol in the development of atherosclerosis and his research is often cited among the great discoveries of the 20th century. Unlike other research groups that conducted experiments with protein-enriched diets, Anitschkow used rabbits fed a high cholesterol diet and observed atherosclerotic alterations in the intimate layer of the arteries of these animals that were very similar to those that occurred in human arteries [3]. Analyzing plaque development and histology, it demonstrated the different cell types in which recent research on atherosclerosis has focused through immunohistochemical studies, especially smooth muscle cells, macrophages and lymphocytes.

The oldest descriptions of atherosclerotic lesions focused on morphologies from fatty striae to fibroatheromas and advanced plaques complicated with hemorrhage, calcification ulceration and thrombosis, however, there is no description of how the plaques developed to trigger an acute coronary syndrome. In the 1990s, a consensus of the American Heart Association developed a classification of the plates, classifying them into six categories[4].

1. adaptive intimal thickening
2. greasy streaks
3. intermediate (transition) lesion
4. Atheroma
5. Fibroatheroma or atheroma with thickened fibrous capsule and
6. Complicated lesions with capsule rupture, hemorrhage or thrombosis.

The pathophysiology of atherosclerosis involves the transformation of a normal artery into an atherosclerotic artery, through several steps, such as: activation or endothelial lesion, absorption and retention of Low Density Lipoprotein (LDL) particles with subsequent oxidation, infiltration of monocytes and their conversion into macrophages and then in fatty cells, proliferation of smooth muscle cells of the arterial wall, proliferation of the middle tunic and migration to the intimate region and finally thrombosis. Endothelial dysfunction begins in the presence of so-called cardiovascular risk factors, such as age, heredity, hypercholesterolemia, smoking, diabetes mellitus, insulin resistance, hypertension and inflammatory processes.

LDL oxidation is one of the factors that most contributes to the activation of the vascular endothelium. Macrophages express relatively few non-oxidized LDL[5], receptors, but in the meantime, oxidized LDLs are abituously absorbed by macrophages through endocytosis by cleanse receptors (LOX 1, scavenger), facilitating the transformation of macrophages into foam cells [5]. The cytotoxicity of oxidized LDLs can be induced by peroxidation of lipids by free radicals. These LOX 1 receptors are also expressed in endothelial cells and smooth muscle cells of the arterial wall and the presence of oxidized LDL and other proinflammatory cytokines increase the expression of these receptors. The interaction of oxidized LDL with LOX 1 receptors increases the level of reactive oxygen species, reduces the level of nitric oxide, activates the nuclear factor kB (NF-kB) and the chemoattractive protein of monocytes (facilitates the binding of monocytes in the endothelium) and also induces apoptosis. In addition, oxidized LDL causes a molecular change in Apoprotein A-I (Apo A-I), the largest lipoprotein in High Density Lipoprotein (HDL) that facilitates the outflow of cholesterol from macrophages, leading to the transformation of HDL into dysfunctional HDL and impairing the reverse transport of cholesterol [6].

Although populations with total cholesterol lower than 150 mg/dL and LDL below 80 mg/dL have a low incidence of atherosclerotic disease, there are other important processes in atherogenesis and inflammation is an important component in this scenario.

Proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) which is secreted by body tissues in response to an infectious process for example, can lead to activation of the endothelium through the release of reactive oxygen species, growth factors, adhering molecules and matrix metalloproteinases. These molecules participate in important phenotypic changes in vascular wall cells, such as cell proliferation, molecular adeation, migration, angiogenesis and apoptosis, events that can cause onset, progression, severity of the atherosclerotic process or even rupture of the atheroma plaque. Other cytokines are also produced through the interaction of vascular wall cells with TNF-α, such as interleukin 6 (IL-6), resulting from the interaction of the vascular wall with arterial smooth muscle cells. Once in the bloodstream IL-6 binds to the hepatocyte stimulating the synthesis and secretion of C-reactive protein (CRP). This increases the bond of oxidized LDL with macrophages. CRP can be found in the serum of patients with bacterial infections, diabetes mellitus, atherosclerosis, visceral adiposity and insulin resistance and leads to the release of free fatty acids and also IL-6 from adipose tissue. The increased supply of free fatty acids to the hepatocyte increases the production of triglycerides and very low density lipoprotein (VLDL), leading to the atherogenic phenotypic of low HDL and small and dense LDL. In recent studies, the measurement of high-sensitivity CRP as an inflammatory marker has been shown to be an important marker of cardiovascular disease regardless of LDL value. In the JUPITER study, the treatment of 17,802 healthy people with an LDL lower than 130 mg/dL and high sensitivity CRP greater than 2 mg/dL with rosu-

vastatin 20 mg per day reduced total mortality by 20% and the incidence of cardiovascular events by 44% when compared with placebo [7].

The immunity cream and also the acquired have the ability to modify lipoproteins in the vascular wall. The different subtypes of $CD4^+$ lymphocytes have opposite roles in the atherosclerotic process. Auxiliary T lymphocytes (Th1) have a proatherogenic role, while regulatory lymphocytes induce the suppression of effector T cells, blocking the activation and function of these lymphocytes, being important in controlling the immune response and having an antiatherogenic action [8]. Auxiliary T 17 lymphocytes (Th 17) cells are a relatively new subtype of $CD4^+$ lymphocytes that produce interleukin 17 (IL-17) which plays an important role in various inflammatory and autoimmune diseases. Although many recent studies have investigated the role of IL-17 in the atherogenic process, there is still no consensus on the real result of its action, whether proatherogenic or atheroprotective.

Adipose tissue is considered today not only a fat depositing organ, but an endocrine organ, producing adipocytoquines. Some of these have a proinflammatory effect while others have an anti-inflammatory effect and the balance between them is an important determinant in vascular homeostasis in physiological or pathophysiological conditions. Overweight and obesity are characterized by dysfunctional adipose tissue with the prevalence of proinflammatory mediators with harmful effect on the arteries.

Unlike adiponectin which is anti-inflammatory, certain proinflammatory adipocytokines such as leptin and resistin promote endothelial dysfunction and inflammatory processes involved in the progression and vulnerability of atherosclerotic plate.

Recently, the role of perivascular adipose tissue has also been demonstrated as an important modulator of atherosclerotic processes due to its interaction with the underlying vascular tissue. With the recent discovery of new adipocytokines with different inflammatory effects, there is talk today in a network of adipocytokines whose real role is not yet fully understood and whose study may lead to the discovery of new markers of cardiovascular risk and potential therapeutic processes.

In addition to these risk factors already widely known and studied, today we speak of the important role of bacteria that live in symbiosis with humans, being part of the homeostasis of this. It is estimated that the number of bacteria residing in our body is 1 to 3 times greater than the very number of cells of this organism. Most of these bacteria inhabit the digestive tract and each part of it has a different composition of the microbial flora. This "organ", called microbiota, has a wide variety of functions that are vital to the host organism. Changes in the intestinal microbiota play an important role in obesity, insulin resistance, dyslipidemia, diabetes mellitus and atherogenesis.

The intestinal microbiota and its metabolic products interact with the host in different ways, influencing the homeostase of the whole organism. The composition of the intestinal microbiota responds to changes in diet, mainly due to competition for substrates and tolerance of intestinal conditions. Metabolic products excreted by the microbiota, such as short-chain fatty acids, are influenced by the supplementation of dietary components and also by the composition of this microbiota determined by the diet. Many metabolic passages responsible for these changes are already being unraveled. For example, the formation of butyrate and propionate from hexoses are due to several bacterial species and the propionate in particular can be formed through alternative passages through lactate and reduced sugars.

One of the mechanisms by which the intestinal microbiota can influence cardiovascular morbidity is through the production of trimethylamine-N-Oxide (TMAO), a compound that has been shown to be proatherogenic. It was found that the order Lactobacillales is significantly increased and the filum Bacteroidetes significantly decreased in patients with cardiovascular disease. It is known that TMAO alters the atherogenic process through macrophage recruitment, an increase in the expression of CD36, TNF-α and IL-6 facilitating the formation of foam cells [9].

In addition to the factors exposed so far, we should also comment on the role of two other important factors in atherogenesis: angiogenesis and free radicals.
The rupture of atherosclerotic plates with subsequent acute cardiovascular complications is as has already been seen the main tail of morbidity and mortality in the world. Hypoxia conditions within the plaque activate the vascular endothelium in the vasa vasorum, leading to the production of vascular endothelial growth factor (VEGF), which stimulates angiogenesis. Evidence from studies on routed and unstable plaques show that intraplaque angiogenesis promotes destabilization of this, making it vulnerable.

The class of molecules known as oxygen-reactive species (or free radicals) are important signaling intermediates in the activation of cytokines, such as TNFα, IL-6 and also oxidized phospholipids, and are therefore important signalers in atherogenesis and also in carcinogenesis.

In summary, an artery with an initially normal endothelium, suffering the action of so-called risk factors (age, smoking, diabetes mellitus, dyslipidemia, etc.), passes to a dysfunctional endothelium stage. This over time becomes more permeable, allowing LDL to enter the arterial wall. These, once inserted there, undergo an oxidation process, attracting macrophages, which initially sticking and then crossing the endothelium, absorb them through endocytosis mediated by "scavenger" receptors and turn into foam cells. These, along with oxidized LDL are important cytokine activators that perpetuate the intra-arterial inflammatory process and increase plaque size. These plaques vary in size, lipid content, inflammatory cell content and thickness of their fibrous layer. The higher the lipid nucleus, the number of inflammatory cells, the higher concentration of cytokines and proteinases (peptidases, collagenases and gelatinases) formed by these inflammatory cells, the greater the vulnerability of the plaque, with thinning of its fibrous layer, and can more easily lead to its rupture. Presently in the COVID-19 pandemic era the process is accelerated by cytokines storms leading to the precipitation of cardiovascular events linked to the inflammatory and pro thrombotic stimuli [10]. When this occurs, there is an exposure of its internal environment to circulating platelets, thus initiating the atherothrombosis process, which is ultimately responsible for the dramatic clinical events of acute coronary syndromes, strokes, peripheral arterial ischemia and may also occur in other organs.

Acknowledgments
None.

Conflicts of interest
No conflict of interest.

References
1. Fernandes SC, Fernandes P, Martinez TLR Medicamentos hipolipemiantes. In: Maffei FHA, Yoshida WB, Rollo WA, Moura R, Sobreira ML, et al. (2016) Doenças Vasculares Periféricas. Rio de Janeiro: Guanabara Koogan 679-690.
2. Hanke H, Lenz C, Finking G. (2001) The discovery of the pathophysiological aspects of atherosclerosis - a review. Acta Chir Belg 101: 162-169. https://pubmed.ncbi.nlm.nih.gov/11680058/
3. Finking G, Hanke H. Nikolaj Nikolajewitsch Anitschkow (1885-1964) (1997) established the cholesterol-fed rabbit as a model for atherosclerosis research. Atherosclerosis 135: 1-7.

4. Stary HC, Blankenhorn DH, Chandler AB, Glagov S, Insull W Jr, Richardson M, et al. (1992) A definition of the intima of human arteries and of its atherosclerosis-prone regions. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Arterioscler Thromb 12: 120-134. https://doi.org/10.1161/01.ATV.12.1.120
5. Brown MS, Goldstein JL. (1983) Lipoprotein metabolism in the macrophage: implications for cholesterol deposition in atherosclerosis. Annu Rev Biochem 52: 223-261.
6. Kontush A, Chapman MJ. (2006) Functionally defective high-density lipoprotein: a new therapeutic target at the crossroads of dyslipidemia, inflammation, and atherosclerosis. Pharmacol Rev 58: 342-374.
7. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. (2008) Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 359: 2195-2207.
8. Sojka DK, Huang YH, Fowell DJ. (2008) Mechanisms of regulatory T-cell suppression - a diverse arsenal for a moving target. Immunology 124: 13-22.
9. Geng J, Yang C, Wang B, Zhang X, Hu T, Gu Y, et al. (2018) Trimethylamine N-oxide promotes atherosclerosis via CD-36-dependent MAPK/JNK pathway. Biomed Pharmacother 97: 941-947.
10. Zheng YY, Ma YT, Zhang JY, Xie X. (2020) COVID-19 and the cardiovascular system. Nat Rev Cardiol 17: 259-260.