Inflammation-Induced Atherosclerosis as a Target for Prevention of Cardiovascular Diseases from Early Life

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Abstract: Atherogenesis starts from the fetal life, and its natural course consists of interrelations between traditional risk factors and inflammatory, immune, and endothelial biomarkers. Even the early-stages of atherosclerotic lesions, i.e. fatty streaks present the features of chronic inflammation. Markers of inflammation are associated with insulin resistance and major atherosclerosis risk factors. Several studies have confirmed a relationship between surrogate markers of future cardiovascular disease with childhood obesity, notably abdominal obesity, as well as with the degree of obesity. Moreover, functional and structural changes are documented in arteries of children with a familial predisposition to atherosclerotic diseases; these changes are associated with clusters of inflammatory factors and markers of oxidation. In addition to the development of atheromatous plaques, inflammation also plays an essential role in the destabilization of artery plaques, and in turn in the occurrence of acute thrombo-embolic disorders. Markers of inflammation can provide predictive clinical information about outcomes of patients with acute coronary syndromes, independent of the extent of myocardial damage. Moreover, serum levels of the inflammatory markers might add prognostic information provided by traditional risk factors. Platelets have an important role in vascular inflammation and atherosclerosis and in the formation of mural thrombi. As lifestyle modification trials have been successful in decreasing endothelial dysfunction and the level of markers of inflammation among children and adolescents, it is suggested that in addition to expanding pharmacological therapies considered for secondary prevention of atherosclerotic diseases aiming to control the inflammatory process, the importance of primordial/primary prevention of atherosclerosis should be underscored.

Keywords: Atherosclerosis, Inflammation, Primordial, Primary and Secondary Prevention.

INTRODUCTION

Atherogenesis is the developmental process of atheromatous plaques characterized by a remodeling of arteries involving the concomitant accumulation of plaques. During the past decades, numerous theories or hypotheses have been proposed about atherogenesis that was previously considered a cholesterol storage disease. Although none of theories or hypotheses could entirely explain the whole process of the pathogenesis of atherosclerosis, but there is a growing body of evidence about the role of inflammation in this process. It is suggested that atherosclerosis is a specific form of chronic inflammatory process resulting from interactions between plasma lipoproteins, cellular components as monocyte/macrophages, T lymphocytes, endothelial cells and smooth muscle cells as well as the extracellular matrix of the arteries [1-3].

The major risk factors of atherosclerosis induce the secretion of leukocyte soluble adhesion molecules, which facilitate the attachment of monocytes to endothelial cells, and chemotactic factors, which in turn promote the monocytes’ movement into the subintimal space. It is suggested that the transformation of monocytes into macrophages and the uptake of cholesterol lipoproteins initiate the production of fatty streaks. Additional damaging stimuli would maintain the accumulation of macrophages, mast cells, and activated T cells in the growing atherosclerotic lesions [4, 5].

Inflammatory cytokines related to vascular inflammation stimulate the production of endothelial adhesion molecules, proteases, and other soluble mediators. They also induce the generation of the messenger cytokine interleukin-6, which in turn stimulates the liver to increase production of acute-phase reactants such as C-reactive protein (CRP). In addition, platelets and adipose tissue can generate inflammatory mediators relevant to atherogenesis and thrombosis [6].

INFLAMMATORY PROCESS OF AHEROGENESIS FROM FETAL LIFE

The first stages of atherogenesis begin from the fetal life. A local inflammatory process is suggested to contribute in reestablishment of the homeostasis of the vascular wall through promoting the removal of injured tissue and its consequent repair. The endothelial permeability of some arterial segments alters and allows the infiltration of macromolecules, like lipoproteins, in the subintimal space. Oxidized lipoproteins induce the expression of chemokines and adhesion molecules on the luminal surface of the
endothelium, which allow the local recruitment of monocytes-macrophages and T lymphocytes [7].

Even the early-stages of atherosclerotic lesions, i.e. fatty streaks present the features of chronic inflammation. Atherogenic lipoproteins such as oxidized low density lipoprotein (ox-LDL), remnant lipoprotein and lipoprotein (a) have a significant role in the pro-inflammatory reaction, whereas high density lipoprotein (HDL), anti-atherogenic lipoproteins, have anti-inflammatory function [2, 5-7].

Changes in the proteoglycan metabolism of the intima are associated to the early stages of atherosclerosis. Matrix metalloproteinases (MMPs) are a group of zinc-dependent proteases produced by a variety of cell types, including endothelial, smooth muscle cells and monocytes. MMPs exist at low levels in normal adult tissue, and are synchronized in physiological and pathological remodeling processes. They are specialized enzymes involved in various stages of vascular diseases. The imbalance of matrix metalloproteinases (MMPs) and their inhibiting factors, i.e. tissue inhibitors of metalloproteinases (TIMPs) has a crucial role in early changes of atherosclerosis and its progression [8]. Experimental studies have shown that MMPs derived from arterial cells are required for early atherosclerotic plaque development and cellular accumulation [9, 10]. MMPs are considered to mediate the progression of stable atherosclerotic lesions to an unstable plaque prone to rupture [11].

Angiotensin II is a proinflammatory mediator that induces the development and progression of atherosclerosis; it provokes pro-atherosclerotic cytokine and chemokine secretion and increases endothelial dysfunction. Angiotensin promotes macrophage migration into the vascular intima and elastin breaks, it is essential in beginning the atherosclerosis process [12]. Accordingly, the medications inhibiting the rennin-angiotensin system are being used both primary and secondary prevention of atherosclerotic cardiovascular disease [13].

INFLAMMATORY BIOMARKERS AS PREDICTORS OF FUTURE ATHEROSCLEROSIS

The association of inflammatory processes with the development of atherosclerosis provides important links between underlying mechanisms of atherogenesis and risk factors. Therefore, more interest has focused on studies about inflammatory biomarkers as predictors of future clinical events. Several studies have examined different circulating markers of inflammations, such as cytokines and adhesion molecules, as potential predictors of the present and the future risk of cardiovascular diseases, most studies have determined the following factors: ox-LDL, pro-inflammatory cytokines as interleukin-1 and tumor necrosis factor-α, adhesion molecules as intercellular adhesion molecule-1 and selectins, inflammatory stimuli with hepatic effects as interleukin-6 or the products of the hepatic stimulation, such as serum amyloid A (SAA), high-sensitivity CRP (hs CRP) and a host of other acute-phase reactants and leukocyte count. Furthermore, soluble CD40 ligand, adiponectin, interleukin 18, and matrix metalloproteinase 9 are considered to provide additional information for cardiovascular risk stratification and prediction [6]. Elevated plasma levels of molecules such as soluble intercellular adhesion molecule-1, interleukin-6 and hs CRP have been found to represent inflammatory markers of future risk of atherosclerotic diseases. Among these factors, CRP has emerged as the most influential and available marker for clinical and epidemiological use.

An association between this sensitive marker of inflammation and the development of atherosclerotic disease has been documented in different experimental [14-17] and epidemiological studies [18-21]. Some epidemiological studies have confirmed that high-sensitivity CRP (hsCRP) might predict future atherosclerotic diseases among healthy individuals. Moreover, platelets and adipose tissue might produce inflammatory mediators related to atherothrombosis.

It is suggested that cholesterol itself may generate a pro-inflammatory process resulting in atherosclerosis [22]. When trapped in the intima, oxidized products of LDL-C might be active as pro-inflammatory mediators. Human and animal studies have suggested a strong correlation between the auto-antibodies against oxidized LDL and the extent of atherosclerosis [23]. Cholesterol synthesis is associated with interleukin-6 mediated inflammation, which in turn is the common causative factor for aging and age-related disorders including atherosclerosis [24, 25].

INFLAMMATORY BIOMARKERS AND INSULIN RESISTANCE

It is well documented that markers of the acute-phase response, including CRP are associated with insulin resistance [21-29], body mass index (BMI) [21, 26, 27, 29], serum glucose [26] and lipids [21, 26, 27, 29].

Serum hs CRP and interleukin-6 are independent risk factors for atherosclerosis in obese, insulin-resistant adults [30, 31]. However, some studies have documented the association of CRP with cardiovascular disease, independent to insulin resistance [18-21]. Such studies have implicated inflammation as an essential contributor to the progression of atherosclerosis. Elevated serum levels of inflammatory markers, including CRP, are documented in type 2 diabetic patients with components of insulin resistance. It is suggested that insulin insensitivity and/or hyperinsulinemia may be associated with serum CRP levels [28].

CRP level is also related to the risk for future cardiovascular morbidity and mortality among those with documented vascular disease as well as apparently healthy individuals. It is noteworthy to mention that in some studies, the risk prediction of hs-CRP has been independent of traditional risk factors [18]. Longitudinal studies documented a predictive role of elevated circulating levels of soluble (s) intercellular cell adhesion molecule-1 (ICAM-1) in healthy people, of vascular cell adhesion molecule-1 (sVCAM-1) in patients at high risk or with documented cardiovascular diseases [32-34].

Generally, it is documented that all the conditions that increase circulating fatty acids and cause lipid overloading induce a lipotoxic state in non-adipose tissues that predispose insulin resistance and subsequent disorders [35].
ASSOCIATION OF ENDOTHELIAL DYSFUNCTION AND INFLAMMATION FROM EARLY LIFE

Atherogenesis starts from early life, and its natural course is an area under discussion of interrelations between traditional risk factors and inflammatory, immune, and endothelial biomarkers. Excessive production of CRP and other inflammatory biomarkers may accelerate atherogenesis in children and lead to long-term atherothrombotic events [36]. As endothelial dysfunction and atherosclerosis begin from early life, studying the association of their early stages with markers of inflammation would give a better insight of this process, independent of the process of aging. A study that determined the association of hs CRP with vascular endothelial and smooth muscle dysfunction in children with type 1 diabetes mellitus and healthy controls, hsCRP was not associated with early vascular dysfunction in normal-weight diabetic children, but such association was documented in those with higher BMI [37]. Another study investigated the relationship of hs CRP with BMI and cardiovascular risk factors in obese children and adolescents. It found that hs CRP level was correlated with BMI, systolic and diastolic blood pressure and serum leptin levels. It confirmed the relationship between obesity, inflammation and atherosclerosis, and suggested that hs CRP in childhood obesity might be a useful index to predict possible atherosclerotic events [38].

Studies on the relationship between the degree of childhood obesity and surrogate markers of future cardiovascular disease revealed that CRP and interleukin-6 levels increased with the degree of obesity. This finding suggests that the degree of low-grade inflammation may increase as children become more obese. However, C-reactive protein levels did not correlate significantly with insulin resistance or with the metabolic syndrome, suggesting that an underlying inflammation may be an additional factor contributing to adverse long-term cardiovascular outcomes [39].

Endothelial adhesion molecules, including endothelial-leukocyte adhesion molecule (E-selectin), ICAM-1, and VCAM-1 have a crucial role in the earliest stages of atherogenesis by mediating the binding and recruitment of monocytes into arterial intima [40]. Concentrations of hs CRP and soluble adhesion molecules are higher in obese than in other children [41,42]. A population-based study among healthy children and adolescents found a significant correlation between CRP and markers of oxidative stress, as well as between CRP and these markers with abdominal obesity, but not with generalized obesity [43].

Childhood obesity and associated cardio-metabolic risk factors are no more limited to industrialized countries, but also a growing problem in low- and middle-income countries [44]. Therefore, future atherosclerotic diseases in young age would become a major health threat worldwide. Modifiable lifestyle behaviors are associated with childhood obesity [45] and cardio-metabolic risk factors [46]. Given that short-term lifestyle modification programs have been successful in improvement of lipid profile, markers of inflammation and endothelial dysfunction among obese youths [47, 48], early recognition and control of risk factors and in turn inflammation might have long-term impact on prevention and control of atherosclerosis and underlying inflammatory processes. Cardio-metabolic risk factors are not limited to obese individuals, and are documented in some normal weight children and adolescents, termed phenotypically normal metabolically obese youths [49].

In addition to the lipids and apolipoproteins, the markers of inflammation and oxidative stress as well as the carotid-intima media thickness of normal-weight children with a metabolic abnormality are found to be similar to obese children. Furthermore, irrespective of obesity and metabolic abnormality, fitness is shown to have the highest inverse correlation with markers of insulin resistance and non-alcoholic fatty liver diseases among adolescents [50].

Lifestyle modification trial has been successful in reducing serum CRP level among both normal-weight and obese children and adolescents with cardio-metabolic risk factors [51].

Given that cardio-metabolic risk factors track from early life to adulthood, and that childhood CRP value predict adult CRP, and this association is found to be independent of other metabolic risk factors such as serum lipids, blood pressure, smoking, obesity indices, and insulin [52], and that high CRP is one of the youth determinants of adult metabolic syndrome [53], all children and adolescents, and not only those with overweight, should be encouraged to have healthier lifestyle that would help the primordial/primary prevention of atherosclerotic diseases.

INFLAMMATORY CHANGES AND PRECURSORS OF ATHEROSCLEROSIS IN CHILDREN WITH POSITIVE FAMILY HISTORY OF PREMATURE CORONARY HEART DISEASE

Offspring of patients with premature atherosclerotic disease may be at increased risk for atherosclerosis. Screening and control of atherosclerosis’ risk factors are of special concern for these children who are at high-risk for premature atherosclerotic cardiovascular diseases. In addition to higher levels of lipids and lipoproteins [54], markers of oxidation [55], hs CRP [56] and immunologic factors [57], structural and functional changes in arteries are present at an early age in the arteries of individuals with a parental history of premature atherosclerosis [56, 58]. It is documented that the 19-year-old offspring of patients with premature myocardial infarction had lower flow-mediated reactivity of the brachial arteries and greater mean intima-media thickness of the common carotid artery. In those individuals with a parental history of premature myocardial infarction, an inverse association was found between brachial-artery reactivity and carotid intima-media thickness. This study also documented that both brachial-artery reactivity and carotid intima-media thickness were significantly and independently correlated with a parental history of premature myocardial infarction [58]. Vascular structural changes, as increased intima media thickness of the carotid artery, are detectable in children and adolescents, and might occur independently of traditional cardiovascular risk factors [59]. It is documented that in children and adolescents with parental history of premature coronary heart diseases, clusters of inflammatory factors and markers of oxidation as well as carotid-intima media thickness and left ventricular mass were correlated with each other and are associated with a positive parental history of premature coronary heart diseases in youths [60, 61]. These
findings complement the functional and structural changes documented in arteries of adults with a familial predisposition to atherosclerotic diseases.

CRP is one of the best markers for prediction of incident coronary artery diseases; this association is shown to be independent of other established risk factors [62]. CRP and oxidation are correlated; oxidative stress may be a determinant of CRP levels and promote the pro-atherosclerotic inflammatory process [63], and CRP can weaken the antioxidant defenses of endothelial progenitor cells and might predict future vascular events [64]. The relation of inflammatory factors and family history of coronary heart diseases among children and adolescents is a confirmatory finding that subclinical chronic inflammation may have a major role in the development of atherosclerosis. These findings underscore the importance of using a high-risk approach for primordial/primary prevention of atherosclerotic diseases from early life.

INFLAMMATION AND THROMBOEMBOLISM

Inflammation is not only instrumental in the development of atheromatous plaques, but also plays an essential role in the destabilization of artery plaques, and in turn altering chronic atherosclerosis into an acute thrombo-embolic disorder. A number of humoral factors including cytokines, cyclooxygenase-2, matrix metalloproteinases, and tissue factor are involved in the process of plaque destabilization [65].

A growing body of evidence indicate that the association of inflammation with atherosclerosis can provide predictive clinical information. Elevation in markers of inflammation predicts outcomes of patients with acute coronary syndromes, independent of the extent of myocardial damage. Moreover, serum levels of the inflammatory markers as CRP might add prognostic information provided by traditional risk factors [66, 67].

As proposed by Libby and Theroux, “the findings on the widespread nature of inflammation in patients prone to develop ACS challenge the traditional view of coronary atherosclerosis as a segmental or localized disease. Thus, treatment of acute coronary syndromes should involve two overlapping phases: first, addressing the culprit lesion, and second, aiming at rapid stabilization of other plaques that may produce recurrent events” [1].

Platelets have an important role in vascular inflammation and atherosclerosis. They exert essential role in modulating inflammatory and immune processes. During the early stages of atherosclerosis, platelets adhere to endothelial cells, and in later stages they participate in the formation of mural thrombi [68]. They can stimulate the secretion of chemokines in cells of the vascular wall cells [69]; some chemokines accelerate platelet aggregation and adhesion [70], in turn activated platelets release chemokines and precursors which trigger atherogenesis or modulate key processes such as angiogenesis and lipoprotein metabolism [71]. Platelet adhesion depends on the interaction of subendothelial matrix components, such as collagen, fibronectin and von Willebrand factor with other adhesive proteins platelet receptors. Platelet adhesion activates the platelet release of inflammatory substances that will result to firm platelet aggregation and thrombus formation [72]. As supposed by Weber, “An intricate functional relationship between platelets and chemokines emerges from the multiple interactions. The mechanisms provide a framework for synergistic functions and allow insights into the deleterious basis for proatherogenic, proinflammatory, or thrombogenic effects exerted by two prime suspects in the pathogenesis of vascular disease.” [73]. Thus, pharmacological therapies considered for secondary prevention of atherosclerotic diseases aim to control the inflammatory process [74], and they need to be expanded.

CONCLUSIONS

Atherogenesis starts from the fetal life, and its natural course consists of interrelations between traditional risk factors and inflammatory, immune, and endothelial biomarkers. Some studies have suggested a role for genetic polymorphisms associated with inflammation and atherosclerosis [75, 76] but not confirmed by some others [77]. Because of considerable ethnic differences in the role of genetic in atherosclerosis [78], large multi-centric studies should be conducted in this regard.

As lifestyle modification trials have been successful in decreasing endothelial dysfunction and the level of markers of inflammation among children and adolescents, it is suggested that in addition to expanding pharmacological therapies considered for secondary prevention of atherosclerotic diseases aiming to control the inflammatory process, the importance of primordial/primary prevention of atherosclerosis [79, 80] should be underscored. Future studies are needed to find out more details about the role of inflammation in young ages, notably children and adolescents in order to improve strategies for prediction, prevention and treatment of atherosclerotic events.

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Inflammation-Induced Atherosclerosis as a Target for Prevention

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