INFLAMMATION IN ATHEROSCLEROSIS AND ARTERIOSCLEROSIS

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Atherosclerotic disease is the fundamental cause of most cardiovascular diseases, atherosclerotic plaque representing the primary asymptomatic lesion of this pathology. The process of oxidized low-density lipoproteins (oxLDL) accumulation at the subendothelial level is recognized as one of the triggering events of atherosclerotic plaque formation.

OxLDL has an important bidirectional contribution in the pathomechanism of atherosclerosis-specific subclinical inflammation. The low-grade inflammation, characteristic for atherosclerotic disease, could be an indicator of the immune responses developed following changes in the arterial wall during the formation of atherosclerotic plaques. These changes are represented by endothelial dysfunction, generation of oxLDL and activation of the immune system. Following immune system activation, innate and acquired immunity cells accumulate in the atherosclerotic plaque, causing antibody formation against both oxLDL and other components.

Arteriosclerosis, an age-related degenerative modification of the arterial wall, which develops in association with atherosclerosis, has also attracted a lot of interest in evaluating the causes of cardiovascular pathologies. This degenerative arterial change has a distinct pathomechanism to atherosclerotic disease, however both pathologies coexist in the same vascular territory and share risk factors, such as inflammation.

The ratio of neutrophils to lymphocytes (NLR), an indicator of subclinical inflammation, has raised much interest as a reliable marker for arterial stiffness and atherosclerotic disease among hypertensive patients. An association between NLR and vascular rigidity has been frequently reported, as well as an association between NLR and atherosclerosis.

The main objectives of the thesis were the following: to investigate the relationship between inflammation and atherosclerosis, to reinforce the role of non-traditional risk factors in the development of atherosclerotic disease and to confirm the inflammation-vascular rigidity relationship. In order to achieve the first objective of the thesis, we evaluated a patient with systemic lupus erythematosus without adequate control of disease activity. The patient also associated advanced atherosclerotic coronary artery disease and chronic kidney disease, however without an important dyslipidemic profile. The influence of inflammation in this individual's advanced atherosclerosis was highlighted by analyzing the classic markers for inflammation alongside serum OxLDL. Meanwhile, we also monitored the prevalence of other non-traditional risk factors for atherosclerotic disease that are specific to systemic lupus erythematosus and renal disorders, such as hyperhomocysteinemia, anticardiolipin antibodies, antibodies against beta 2-glycoprotein I, phosphatidylinositol phosphatidylserine and phosphatidic acid.

In order to support the influence of inflammation in atherosclerosis as well as to achieve the second objective represented by determining the importance of non-traditional risk factors in atherosclerotic disease development, we conducted two retrospective, observational, case-control clinical studies (study 2 and study 3). For these studies we selected hypertensive patients with

chronic kidney disease at a less advanced stage, presenting both traditional and non-traditional risk factors for atherosclerosis. Individuals included in both studies were divided into two groups according to the presence of aortic calcification on chest x-ray. In both studies we followed the prevalence of traditional atherosclerotic risk factors and non-traditional risk factors such as fibrinogen, erythrocyte sedimentation rate, alkaline phosphatase and uric acid. In Study 3 we intended to identify an association between the NLR and advanced atherosclerosis.

For achieving the third objective of the thesis represented by validating the existence of a correlation between inflammation and increased arterial stiffness, we conducted a third research (Study 4). In our last research represented by an observational cohort study, we included hypertensive patients with controlled hypertension who did not associate pathologies characterized by inflammation. Study 4 aimed to establish a correlation between NLR and increased arterial stiffness evaluated by determining pulse wave velocity.

In the first three studies, the importance of evaluating non-traditional risk factors for atherosclerosis is highlighted. The difference in distribution of traditional/non-traditional risk factors for atherosclerotic disease was assessed as well, as different risk factors present different prevalences, depending on the underlying pathology. We emphasized on OxLDL's influence in atherosclerotic disease in the setting of an important inflammatory syndrome and in the absence of an important dyslipidemic profile.

The contribution of inflammation in atherosclerosis has been investigated in different pathologies, presenting different traditional/non-traditional atherosclerotic risk factors and a common element represented by an inflammatory syndrome. For each condition assessed in the thesis, we highlighted the essential contribution of inflammation to the development of calcifying atherosclerotic disease.

The ratio of neutrophils to lymphocytes is a recently recognized inflammatory marker, reported in multiple studies with inflammatory disorders as a risk factor for atherosclerosis and arteriosclerosis. An element of originality of the thesis is given by the fourth study in which the ratio of neutrophils to lymphocytes is reported as a risk factor for arteriosclerosis in a hypertensive population without other determinants of vascular rigidity such as associated inflammatory pathologies.

Prin intemediul aceste lucrări, sperăm să contribuim la validarea inflamației ca factor de risc și țintă terapeutică în ateroscleroză și arterioscleroză. De asemenea, dorim să sensibilizăm în privința factorilor de risc netradiționali, specifici ficărei patologii în parte (oxLDL, viteza de sedimentare a hematiilor, fibrinogen, fosfataza alcalină, hiperhomocisteinemie) care ar trebui să devină o țintă terapeutică primară odată identificați.

The limitations of the first three studies were represented by: small number of patients included in the studies, the absence of prospective studies, absence of a proper calcium phosphate balance characterization, lack of intact serum parathormone and C-reactive protein assessment. The limitations of the fourth study were represented by: limited number of cases, lack of prospective studies and the absence of C-reactive protein evaluation. Taking these aspects into account, the categorical conclusions of the thesis remain limited.

With the help of the present thesis, we hope to contribute in the validation of inflammation as a risk factor and therapeutic target in atherosclerosis and arteriosclerosis. We also want to raise awareness regarding disease-specific non-traditional risk factors for atherosclerosis, such as oxLDL, erythrocyte sedimentation rate, fibrinogen, alkaline phosphatase, hyperhomocysteinemia which should become a primary therapeutic target once identified.