

REVIEW

Myocardial ischemia in rheumatic inflammatory diseases

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Abstract: Rheumatic inflammatory diseases are a group of disorders characterized by damage to the vascular system and connective tissue as well as damage to the internal organs (kidneys, heart, lungs and spleen). Cardiovascular manifestations of these disorders are followed by substantial morbidity and mortality. The most important risk factor for the development of cardiac pathology, namely myocardial ischemia, is considered to be accelerated atherosclerosis. Leading cause of early atherosclerosis is the presence of chronic inflammation, succeeded by immune and endothelial dysfunction.

Keywords: myocardial ischemia, inflammation, rheumatic inflammatory diseases

Rezumat: Bolile inflamatorii reumatismale reprezintă un grup de afecțiuni caracterizate prin leziuni ale țesutului vasculo-conjunctiv și ale organelor interne precum rinichi, inima, plămâni, splina. Manifestările cardiovasculare din cadrul acestor boli autoimune sunt urmate de o morbiditate și o mortalitate substanțială. Cel mai important factor de risc pentru dezvoltarea patologiei cardiace, în speță ischemia miocardică, este considerat a fi ateroscleroza accelerată. Principala cauză a aterosclerozei precoce o constituie prezența inflamației cronice, urmată de disfuncție endotelială și imună.

Cuvinte cheie: ischemie miocardică, inflamație, boli inflamatorii reumatismale

Collagen is considered to be the main protein in the body that contributes to the mechanical properties of tissues. In pathology, the concept of rheumatic inflammatory diseases was introduced in the 5th decade in order to define a few diseases with vascular system and connective tissue injuries and damage to the internal organs (kidneys, heart, lungs and spleen). This group of diseases includes Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Systemic Scleroderma (SS), Dermatomyositis, Polyarteritis, Systemic Vasculitis and mixed connective tissue disease. The causes of rheumatic inflammatory diseases are not yet fully understood. Their evolution has a chronic course, being interrupted by acute periods, followed by remissions. In the evolution of the lesions we can distinguish the following physiological phenomena: aberrant immune response - hyper- γ -globulinemia, high titers of circu-

lating autoantibodies, autoimmune vasculitis and fibroid degeneration of connective tissue. Clinically, most diseases evolve with multiple manifestations at both a mucocutaneous and a musculoskeletal level as well as at the level of other internal organs such as the cardiovascular, pulmonary, renal, nervous, ocular systems, etc.

Regarding cardiovascular events, these can be more important or clinically silent but they are characterized by substantial morbidity and mortality. The most important risk factor for the development of cardiac pathology, namely myocardial ischemia, is considered to be accelerated atherosclerosis. Chronic inflammation and immune as well as endothelial dysfunction participate in the formation of vascular atherosclerotic plaque^{1,2}. When we mention the term "inflammation" we need to refer to the recruitment of mononuclear cells found in blood, an increased expression of adhe-

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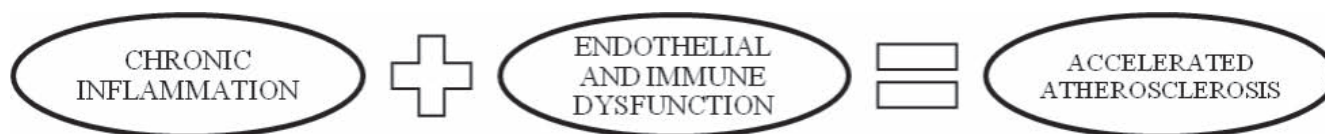


Figure 1. The main pathogenic mechanisms of atherosclerosis.

sion molecules, the production of matrix metallo-proteinase and an increased release of proinflammatory cytokine³ (Figure 1).

Among proinflammatory cytokines, a crucial role is played by the tumor necrosis factor α (TNF α) and interleukin 6 (IL-6). These determine the activation and dysfunction of the endothelium with the help of the nuclear factor κ -B (NF κ -B)⁴, followed by leukocyte infiltration, activation and proliferation in the subendothelial layer^{3,5}. Also, TNF α is closely related to the appearance of insulin resistance, dyslipidaemia, to the stimulation of other inflammatory molecules or to the development of a prothrombotic status^{4,6}. Studies proved that toll-like receptors (TLR) were highlighted at the level of atherosclerotic plaques, thus making the link between atherosclerosis and autoimmunity^{3,7}.

Regarding the role of leukocytes, first place is occupied by activated T cells. These T cells were found both in stable and unstable atherosclerotic plaques, mentioning that a subset of CD25 positive T cells were found in an increased titer in unstable lesions⁸.

Inflammation is also characterized by an increased expression of adhesion molecules. An activated endothelium determines the expression of a large number of adhesion molecules which favors early atherosclerosis through leukocyte recruitment into the subendothelial layer³. Clinical trials on patients with large-vessel vasculitis, SLE or RA sustained that vascular cell adhesion protein 1 (VCAM-1) is directly involved in the occurrence of cardiovascular events⁵.

Monocyte-chemotactic protein-1 (MCP-1) is expressed by activated endothelium cells under the influence of TNF α and promote atherosclerosis by attracting leukocytes and monocytes to the vascular endothelium⁹. The presence of MCP-1 correlated with coronary calcifications in patients diagnosed with SLE can even be observed in healthy people with an increased risk of coronary artery disease^{3,10}.

Figure 2 reiterates both common and rare cardiovascular risk factors in inflammatory rheumatic diseases.

Due to the presence of inflammation, many inflammatory rheumatic disorders are associated with the inflammation of coronary arteries and with cardiovascular events such as: myocardial infarction, angina, coronary angioplasty and stroke (Figure 3)¹¹⁻¹³.

Systemic lupus erythematosus is a complex disease associated with premature atherosclerosis and early deaths due to cardiovascular events or severe infections¹⁴. In the pathogenesis of SLE a very important role is played by type I interferon which is considered to determine the instability of atherosclerotic lesions, aortic stiffness or dysfunction of the endothelium¹⁵. Studies demonstrated that 40% of patients have myocardial perfusion defects¹⁶ and 50% of patients have impaired endothelial vasodilatation¹⁷. Clinical trials using ultrasound at carotid artery level, sustained the early appearance of atherosclerotic plaques which were related to SLE activity which was quantified by the SLE-DAI index¹⁸. The cardiovascular events occurred with

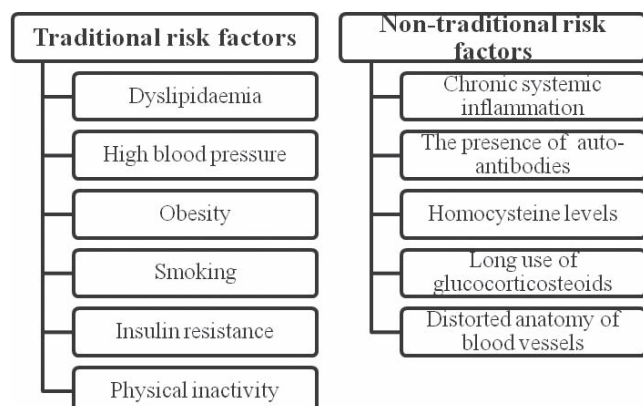


Figure 2. Common and rare cardiovascular risk factors in inflammatory rheumatic diseases.

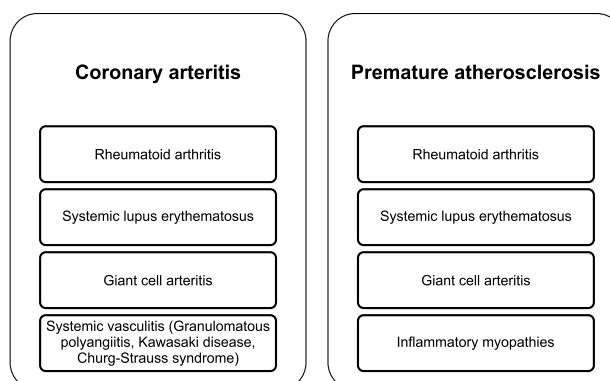


Figure 3. Inflammatory rheumatic diseases and coronary involvement.

a higher frequency in people under 40 years of age, the risk of myocardial infarction being 50-fold greater in women ages 35 to 44 than the general population¹⁹. Another important fact related to cardiovascular risk is corticosteroid use which is considered to be dose-dependent (a 5-fold increase in cardiovascular risk at a dose more than 20mg/day)²⁰. Other factors involved in the occurrence of cardiac events are considered to be: high titer of anti DNA double-stranded antibodies, renal complications such as lupus nephritis, duration and disease activity²¹.

Rheumatoid arthritis, characterized by chronic inflammation, shows premature atherosclerosis even without common risk factors as well as a high prevalence of ischemic heart disease, namely myocardial infarction²²⁻²⁴. Moreover, events such as sudden cardiac death and silent myocardial infarction are more frequent among these patients²⁵. Many factors are thought to increase mortality in RA patients like: specific antibodies- rheumatoid factor, anti-citrullinated peptide antibodies, the presence of rheumatoid nodules and the level of erythrocyte sedimentation rate, female sex, erosions, synovitis or associated lung disease²⁶⁻²⁸.

Clinical trials have highlighted a poor response to acetylcholine which leads to an impairment of endothelial vasodilatation and a limited number of circulating endothelial progenitors²⁹. One study found a defective relaxation of arterial smooth muscle due to an attenuated response to sodium nitroprusside³⁰. Studies analyzing the morphology of atherosclerotic plaques in patients with RA had important inflammation in the medial and adventitial layers, making the atherosclerotic plaques more unstable which caused an increased number of thromboses^{31,32}. So, patients with RA are at high risk to develop silent cardiac ischemia, myocardial infarction or heart failure. Figure 4

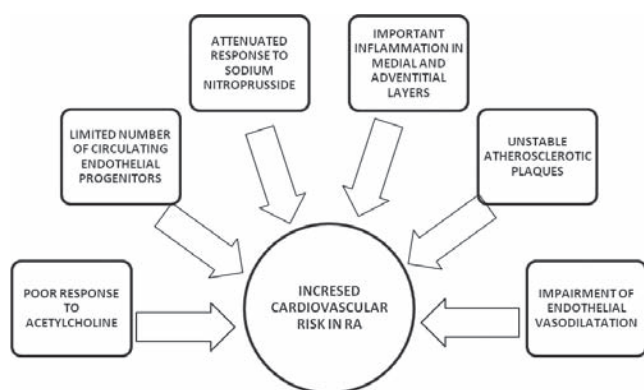


Figure 4. Factors that increase the cardiovascular risk in RA patients.

illustrates the main factors that increase the cardiovascular risk in patients with RA.

Systemic sclerosis is also part of the umbrella group of inflammatory rheumatic diseases, being characterized by an increased risk of premature atherosclerosis. The main mechanisms responsible for cardiovascular impairment are: endothelial cell injury induced by anti-endothelial antibodies, ischemia/reperfusion damage, immune-mediated cytotoxicity and an impaired vascular repair mechanism (Figure 5)³³. The excess of the oxidative phenomena causes the release of pro-inflammatory cytokines, activation and damage of endothelium and inflammation in the vascular wall^{34,35}. Studies highlighted an increased stiffness in the carotid artery wall³⁶ and showed the positive role of statins in the treatment of vascular damage³³.

Systemic vasculitis of small, medium or large blood vessels is a chronic inflammatory disease in the rheumatic disorders subgroup and is characterized by accelerated atherosclerosis and an increased premature mortality rate due to cardiovascular events. Vascular injury has multiple mechanisms such as, activation of endothelial cells which causes increased expression of monocyte adhesion molecules and autoantigens, accumulation in an increased number of oxidized low density lipoprotein (oxLDL) molecules and the formation of foam cells^{37,38}. In patients with Takayasu Arteritis, studies highlighted an important inflammation in the endothelial layer and a distorted arterial anatomy which led to a disturbed arterial blood flow³⁹. Also, this giant arteritis shows early accelerated atherosclerosis, increased aortic stiffness and a high prevalence of silent myocardial infarction^{40,41}.

Regarding ANCA-associated vasculitis, a very important role is played by specific antibodies which can activate neutrophils which can result in the formation of reactive oxygen species that determine increased aortic stiffness and dysfunction of the endothelium⁴²⁻⁴⁴.

Concerning Spondylarthropathies, especially Ankylosing Spondylitis (SA) and Psoriatic Arthritis (PsA),

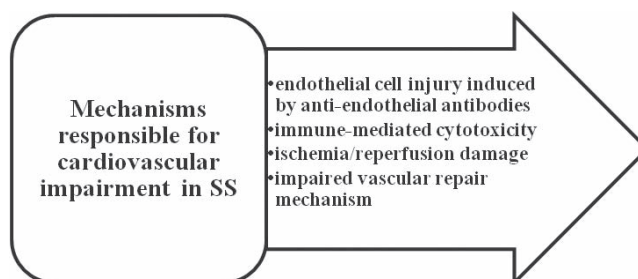


Figure 5. Mechanisms responsible for cardiovascular impairment in SS.

systemic inflammation remains the most important cardiovascular risk factor for developing a cardiac event. In AS patients, aortic regurgitation and aortic disease, was found but could not be correlated with the progression of AS⁴⁵. The genetic background represented by the HLA-B27 antigen increases the risk of a first-degree atrioventricular block⁴⁶. Regarding PsA, we can find accelerated atherosclerosis and arterial dysfunction due to prolonged inflammation leading to an increased secretion of Th1 cytokines, to the formation of foam cells or to endothelial dysfunction^{47,48}. Also, it has been revealed that persistently elevated erythrocyte sedimentation rate (ESR) is associated with the extension of atherosclerotic lesions⁴⁹. PsA is also characterized by increased arterial stiffness through: reduced levels of endothelial progenitor cells, oxidative stress, a decreased release of nitric oxide, advanced glycation end products or increased activation of lytic enzymes such as matrix metalloproteinases^{50,51}. Also, the presence of psoriatic skin lesions is associated with an increased cardiovascular risk.

Pertaining to the treatment of rheumatic diseases, the use of synthetic modifying antirheumatic drugs, mainly Methotrexate, can reduce mortality and cardiovascular risk⁵². It decreases carotid thickening (intima-media thickness) and improves endothelial vasodilatation after one year of treatment⁵³. Concerning biological therapy, particularly anti tumor necrosis factor α (TNF α) antibodies, clinical trials revealed that their use reduces aortic stiffness⁵⁴, improves endothelial function⁵⁵, decreased the risk of stroke, myocardial infarction and heart failure⁵⁶. Symptomatic therapy used for pain relief and for improving the patient's quality of life (non-steroidal antiinflammatory drugs or corticotherapy) is closely linked to the appearance of cardiovascular complications, being a dose-dependent risk^{26,57}.

In the treatment of such patients, the benefits and risks associated with specific drugs should be assessed. Regarding hydroxychloroquine in SLE patients, it is well known that it can improve the cardiovascular outcome due to its antithrombotic, hypolipidemic, hypoglycemic and immunomodulatory effects. This drug has the possibility to decrease Toll-like receptor activation and the systemic inflammation⁵⁸⁻⁶¹.

Methotrexate, in RA, can reduce mortality with approximately 70% due to the decrease of inflammation and cardiovascular events (a decline up to 21%)^{62,63}. Studies highlighted that methotrexate favors the efflux of cholesterol from macrophages thereby decreasing the formation of foam cells and improving the dyslipidaemic profile⁶⁴.

The use of corticosteroids increases the risk of cardiovascular events up to 47%⁶⁵. This can be explained by the effects on blood pressure, on lipid and glucose metabolisms, on body mass index⁶⁶, even though they are used for their antiproliferative and antiinflammatory effects. Both NSAIDs and steroids can cause a dose-dependent risk of cardiovascular manifestations. Among NSAIDs, due to the antithrombotic outcome, naproxen is considered to have the best cardiovascular profile⁶⁷.

Patients diagnosed with inflammatory rheumatic diseases require special attention from both rheumatologists and cardiologists, due to the high cardiovascular risk associated with these diseases. So far, we don't have special methods of active screening in order to prevent cardiovascular events in rheumatic diseases. Depending on the case, we can use low doses of aspirin for an anti-platelet effect or statins to improve the lipid profile. The RORA-AS statin intervention study demonstrated that rosuvastatin can improve endothelial function in patients with inflammatory joint diseases, leading to a decreased mortality and lowering adverse cardiac events⁶⁸.

In conclusion, we strongly support that inflammatory rheumatic diseases have an important role in the development of atherosclerotic cardiovascular disorders and ischemic events due to the presence of systemic inflammation and immune hyperactivity. The rheumatologic patient should be considered as having an elevated cardiovascular risk which requires a well rounded approach in the management of the disease; the treatment pertaining to the patient's comorbidities. A proper and effective collaboration between a cardiologist and a rheumatologist is necessary for optimal treatment of these patients.

Conflict of interests: none declared.

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