Cardiovascular events in rheumatoid arthritis: challenges and advances

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Кардиоваскулярная патология при ревматоидном артрите: проблемы и достижения

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Abstract: *this review article covers the issue of cardiovascular events in patients with rheumatoid arthritis (RA), sheds light on the molecular mechanism of RA and atherosclerosis comorbidity, current understanding of the role of oxidative stress and lipid disorders in cardiovascular pathology in RA.*
Аннотация: *в обзорной статье рассматривается вопрос кардиоваскулярной патологии у больных ревматоидным артритом (РА), дается объяснение молекулярного механизма коморбидности РА и атеросклероза, современных представлений о роли оксидативного стресса и нарушений липидного профиля в развитии кардиоваскулярной патологии при РА.*

Keywords: *rheumatoid arthritis, atherosclerosis, statins.*
Ключевые слова: *ревматоидный артрит, атеросклероз, статины.*

Rheumatoid arthritis (RA) is known as a systemic autoimmune disorder that affects synovial joints and leads to chronic pain, bone erosions and chronic progressive disability [6]. With a prevalence of 0.5–1% in the general population, RA is the most common chronic inflammatory condition [1]. Beyond joint disease, RA is characterized by high prevalence of comorbidities, such as gastrointestinal, respiratory, and renal diseases. Moreover, metabolic syndrome and its major features (obesity, hypertension, impaired fasting glucose, and hyperlipidemia) have been frequently found in RA patients. RA is also associated with shortened life expectancy, and cardiovascular (CV) disease is considered the leading cause of increased mortality in this clinical setting. Moreover, the association between RA and subclinical atherosclerosis, as a recognized marker of CV disease, is still a matter of study.

Immune-mediated inflammation seems to play a pivotal role in the pathogenesis of atherosclerosis, being involved in endothelial dysfunction, plaque rupture and thrombosis. Patients with RA have elevated levels of C-reactive protein (CRP), a marker of inflammation associated with increased CV risk. The strong correlation between markers of inflammation (CRP, ESR) and those of platelet activation (CD62P, CD63) suggests that disease activity is involved in platelet hyperreactivity in RA patients [3].

The etiology of RA remains unclear. However, it was accepted that autoimmune responses, the dysregulation of T-helper 1-mediated immune responses in particular, play distinct roles in the pathogenesis of RA. Aberrant T-cell activation stimulates monocytes and macrophages to produce inflammatory cytokines and proteolytic enzymes, initiating the destruction. Recently, the attention has been pointed out on interleukin-17 (IL-17); this cytokine, involved in RA pathogenesis, may accelerate myocardial fibrosis and promote atherosclerosis in non-RA animal models. Therefore, elevated circulating IL-17 levels have been detected in patients with acute coronary syndromes [5].

Accordingly, early therapy was based on aggressive biological modification of the disease by controlling the synovial T cells and/or reducing the levels of the cytokines. Unfortunately, this approach has met limited therapeutic success, raising the issue that important regulatory factors were missing in the existing mechanistic model of RA.

Reactive oxygen species (ROS) could be one of the unidentified regulatory factors. The synovial fluid and peripheral blood of RA patients have high levels of ROS and ROS-generated molecules, including superoxide, peroxide, hydroxide radicals and reactive nitrogen species like peroxynitrite [2]. Of these, 8-hydroxyguanine (8-OHdG), which is produced by the oxidation of guanine bases in DNA and in the nucleotide pools, accumulates in diseases related to oxidative stress, such as cancer, diabetes mellitus, Alzheimer's disease, hypertension, metabolic syndrome, and autoimmune pathology. Elevated levels of 8-OHdG have been reported in RA and atherosclerosis [1].

Long-term study of cardiovascular status in young patients with RA in Tashkent Medical Academy during 2008 - 2011 demonstrated a distinct correlation between cardiac and endothelial dysfunction defined by ultrasound parameters (carotid intima-media thickness (CIMT), left ventricular internal diastolic dimension

(LVIDd) etc.), low HDL levels and hypertriglyceridemia, as well as history of CVD risk factors with stage and activity of RA [4].

Along with causing significant morbidity and mortality, RA results in substantial use of medical resource and costs [1]. In spite of the availability of so many conventional disease modifying anti-rheumatic drugs (DMARDs), favorable outcomes are frequently not achieved with combination DMARDs resulting in persistent active disease. Of late, however, newer biologic therapies are the order of the day for successful management of active RA. Adalimumab and rituximab are the popular biologics, which are frequently used either alone or in combination with DMARDs. Despite promising and successful outcome with these newer biologic agents, its benefit largely remains confined to the small subset of patients; moreover, in developing countries very few can afford the high cost of this therapy. Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, mediate significant vascular risk reduction in patients with coronary artery disease by promoting reduction in plasma levels of low-density-lipoprotein cholesterol [4, 6]. Although the action of statins is primarily via this mechanism, recent studies suggest they have broader properties, including alteration in inflammatory pathways and immunomodulatory functions. Statins have been shown to be of some benefit in RA in the randomized clinical trials, therefore, have a plausible bioactivity profile that makes them possible adjunct therapeutic agents in addition to standard antirheumatic treatment to target both vascular risk reduction and synovial inflammation [1].

In addition, it appears that statins can disrupt the oxidative stress/inflammation cycle by decreasing the release of inflammatory mediators and lipid peroxidation [5]. Chronic administration of statins can also inhibit peroxisome proliferator activated receptor α and γ, which are known as inflammatory mediators.

Thus, experimental studies and more recently few clinical trials have strongly suggested statins to possess an important role in RA mainly mediated by their anti-inflammatory and immunomodulatory properties. Nevertheless, these effects are limited. Therefore, they cannot be advocated to be used as a single agent in treatment of RA but can be very useful as an adjuvant therapy. They are proved to modify surrogates for vascular risk, accelerated atherosclerosis, and increased arterial stiffness present in patients with RA thereby providing overall favorable course of disease.

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