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Review

Cardiovascular risk in rheumatoid arthritis: How to lower the risk?

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ABSTRACT

Patients with rheumatoid arthritis (RA) carry an excess risk for cardiovascular disease, which is comparable to the risk in patients with type 2 diabetes mellitus. The mechanisms involved are partly related to traditional cardiovascular risk factors, disease-associated inflammation and undertreatment of traditional cardiovascular disease (CVD) risk factors. Since atherosclerosis is an inflammatory disease, the auto-immune mediated inflammation observed in RA patients contributes to increased endothelial dysfunction, oxidative stress and activation and vascular migration of leukocytes. This concept is underscored by the CVD risk reduction that is seen by anti-inflammatory disease modifying anti-rheumatic drugs such as methotrexate and TNFα inhibitors. The evidence for underdiagnosis and undertreatment of traditional CVD risk factors in RA strengthens the potential benefit of structured CVD risk management in these patients. Current cardiovascular guidelines recommend screening and treatment of CVD risk factors in RA patients, without well defined treatment targets. At present, there is a lack of scientific evidence to establish treatment targets for CVD risk factors in RA. Therefore, expanding research regarding screening and treatment of traditional CVD risk factors in RA patients is needed.

Contents

1. Introduction

The evidence on the excess of cardiovascular disease (CVD) risk in rheumatoid arthritis (RA) has accumulated during the last two decades [1–3]. It has been suggested that the prevalence of CVD in patients with RA is as high as in patients with type 2 diabetes mellitus [1]. Interestingly, the increased CVD risk observed in RA may be independent from traditional risk factors for CVD [1,4].

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These risk factors such as dyslipidemia, hypertension, smoking and obesity have been found in patients with RA in a similar frequency as in the general population [5,6]. It has been shown that these traditional risk factors contribute to the development of atherosclerosis in RA, but their presence alone can not fully explain the increased CVD risk [7,8].

RA-specific factors, such as rheumatoid factor (RF) and/or anti-CCP positivity, joint erosions and extra-articular RA have been linked to the development of premature atherosclerosis in this condition. Since atherosclerosis is an inflammatory disease, it has been proposed that the increased inflammatory state of patients with RA explains, at least in part, the increased CVD risk [2,4,6,7,9]. Furthermore, joint damage and physical inactivity are common in patients with RA and have been associated with an increased prevalence of CVD [8]. In addition, RA is treated with different disease modifying drugs (DMARDs), with anti-inflammatory effects and with potential anti-atherosclerotic consequences [8]. To date, the exact contribution of all of these factors to the development of premature atherosclerosis in RA remains unclear. There is need for studies investigating the pathogenesis of atherosclerosis in RA and a well defined treatment protocol to lower the excess CVD risk is warranted. The purpose of this review is to provide an overview of the current evidence concerning the major determinants of excess CVD risk and the optimal CVD risk management in RA and to explore future scientific directions.

2. RA, inflammation and atherosclerosis

The formation of an atherosclerotic plaque takes place in different stages, which are driven by deposition and oxidation of lipids in the subendothelial space, activation of leukocytes and endothelial cells and finally thrombosis (Fig. 1) [10].

All apolipoprotein (apo) B containing lipoproteins e.g. chylomicrons, chylomicron remnants, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL) and low density lipoproteins (LDL) can enter the subendothelial space via disrupted tight junctions between altered endothelial cells [11,12]. These lipoproteins can be taken up by macrophages converting them to foam cells. LDL needs to become oxidized (oxLDL) before it can induce foam cell formation, whereas chylomicrons and their remnants do not need modification [13]. There is evidence that tumor necrosis factor alpha (TNFα) can directly stimulate the oxidation of LDL [14], and it has been observed that oxLDL levels are higher in patients with RA [15]. Moreover, increased oxLDL concentrations have been linked to increased RA disease activity [15]. The oxidation of LDL is catalyzed by lipoprotein associated phospholipase A2 (Lp-PLA2) [16], but its precise contribution to the development of atherosclerosis in RA is uncertain since reduced levels of Lp-PLA2 have been observed in RA [17], whereas increased Lp-PLA2 activity has been found in association with CVD [18].

Lp(a), which is a pro-atherogenic lipoprotein that consists of an LDL-like particle and apo(a), can become oxidized and provoke an immune response similar to oxLDL. Apo(a) promotes thrombosis and inhibits fibrinolysis due to its homology with plasminogen [19,20]. An increase in Lp(a) has also been associated with inflammation, but data are inconsistent [21–23]. Lp(a) is an independent risk factor for CVD [20] that may be disproportionally elevated in RA [19,21,22].

A key event in the development of both atherosclerosis and RA is inflammation [10,24]. Pro-inflammatory cytokines like TNFα and

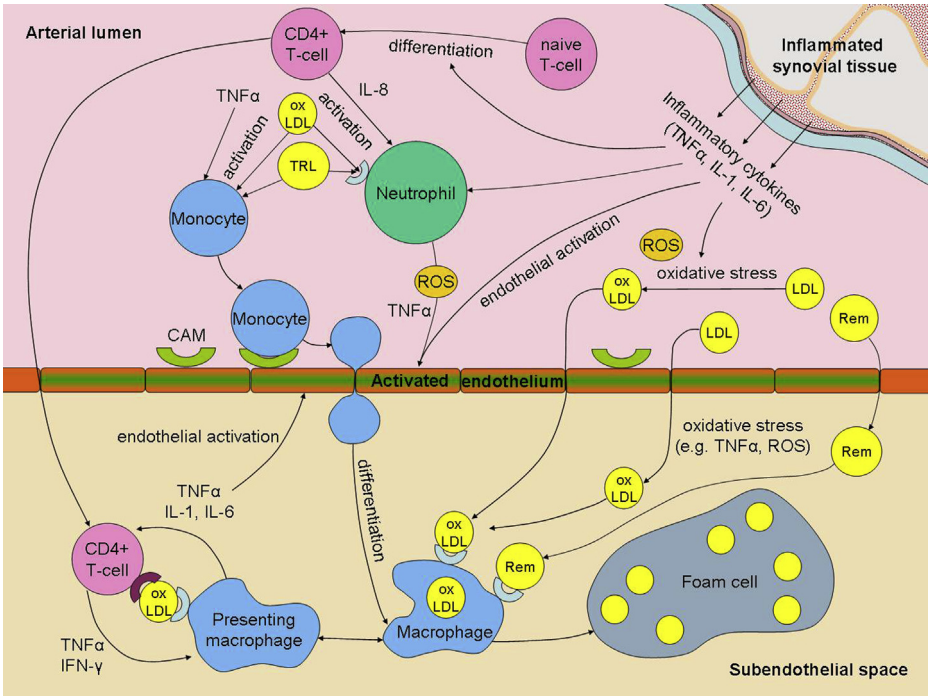

Fig. 1. The inflammation-driven atherogenicity of rheumatoid arthritis (RA). Release of pro-inflammatory cytokines from the synovial tissue in RA has direct effects on systemic inflammation and the initiation of atherosclerosis. The released cytokines modulate the function of the endothelium, leukocytes and the oxidation of lipoproteins. Oxidation of low density lipoproteins (LDL) can be initiated by TNFα and reactive oxygen species (ROS), inducing uptake by macrophages, converting them into foam cells when cholesterol influx exceeds cholesterol efflux. Native chylomicron remnants (Rem) can be taken up by macrophages without modification leading to foam cell formation. Macrophages present atherogenic antigens like oxLDL to CD4+ T cells, which attracts additional leukocytes and leads to T cell proliferation and production of more TNFα and interferon-γ (IFN-γ). These proinflammatory cytokines, and triglyceride-rich lipoproteins (TRL), which include chylomicrons, chylomicron remnants and VLDL, activate monocytes and neutrophils, promote additional lipid uptake by macrophages and increased expression of cellular adhesion molecules (CAM) on the endothelium, which further attracts monocyte derived macrophages and T-lymphocytes and the expression of pro-inflammatory cytokines such as IL1-α, IL1-β, and anti TNFα [31]. All these enhanced cascades in RA contribute to chronic inflammation and the premature development of atherosclerosis in RA.