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Review

Cardiovascular risk in rheumatoid arthritis

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ABSTRACT

The objectives of this review are to discuss data on the cardiovascular risk increase associated with rheumatoid arthritis (RA), the effects of RA treatments on the cardiovascular risk level, and the management of cardiovascular risk factors in patients with RA. Overall, the risk of cardiovascular disease is increased 2-fold in RA patients compared to the general population, due to the combined effects of RA and conventional risk factors. There is some evidence that the cardiovascular risk increase associated with nonsteroidal anti-inflammatory drug therapy may be smaller in RA patients than in the general population. Glucocorticoid therapy increases the cardiovascular risk in proportion to both the current dose and the cumulative dose. Methotrexate and TNFα antagonists diminish cardiovascular morbidity and mortality rates. The management of dyslipidemia remains suboptimal. Risk equations may perform poorly in RA patients even when corrected using the multiplication factors suggested by the EUropean League Against Rheumatism (EULAR) (multiply the score by 1.5 when two of the following three criteria are met: disease duration longer than 10 years, presence of rheumatoid factor or anti-cyclic citrullinated peptide (CCP) antibodies, and extraarticular manifestations). Doppler ultrasonography of the carotid arteries in patients at moderate cardiovascular risk may allow a more aggressive approach to dyslipidemia management via reclassification into the high-risk category of patients with an intima-media thickness greater than 0.9 mm or atheroma plaque.

The cardiovascular risk increase associated with rheumatoid arthritis (RA) has been extensively investigated. The objectives of this review are to discuss data on this risk increase, the effect of RA treatments on the level of cardiovascular risk, and cardiovascular risk management in patients with RA.

1. Epidemiological data

Excess mortality has been convincingly documented in patients with RA compared to the general population [1]. Cardiovascular disease explained about 50% of the excess mortality in RA patients in a meta-analysis of 24 mortality rate studies published between 1970 and 2005 [2]. Both cardiac and cerebrovascular events contributed to the excess mortality, in both females and males [2]. The relationship between disease duration and cardiovascular risk remains debated. A meta-analysis found no cardiovascular risk increase among patients with recent-onset RA [2]. The excess risk was detectable within a few years after disease onset in some studies and only after 10 years in others [3]. The excess mortality is greater in patients with rheumatoid factors or anti-cyclic citrullinated peptide (CCP) antibodies [3,4]. The presence of extraarticular manifestations is also associated with a higher risk [4]. Despite data showing lower mortality rates in patients with RA and decreased cardiovascular mortality in the general population, recent cohort studies of RA patients failed to show a decrease in the risk of death from cardiovascular disease [4].

Cardiovascular morbidity is also increased in RA, whose effect on the cardiovascular risk is similar to that of diabetes [5,6]. In the most convincing study published to date, 4,311,022 individuals in Denmark were followed-up from January 1997 to December 2006 [6]. RA developed in 10,447 individuals and diabetes in 130,215. The risk of myocardial infarction (MI) was similar in these two groups: RA, 1.7 (1.5–6.9); and diabetes, 1.7 (1.6–1.8) ($P = 0.64$) [7]. The risk of MI in patients with RA is similar to that in non-RA patients who are older by 10 years [6]. As with cardiovascular mortality, the relationship of disease duration with the risk increase is unclear. In a case-control study from the Mayo Clinic, risk increases were identified 2 years before the patients met criteria for RA, for both symptomatic MI (odds ratio [OR], 3.17; 1.16–8.68) and asymptomatic MI (OR, 5.86; 1.29–26.64), and the risk remained elevated after the definite diagnosis of RA (OR, 2.13; 1.13–4.03) [4]. However, no risk increase was found before the diagnosis of RA in two cohort studies from Sweden [3,4]. In other studies, the risk increase was detectable at the diagnosis of RA, within the first year after the

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diagnosis, or only 7 years after the diagnosis [3,4]. Coronary artery disease in RA patients is both more often asymptomatic and more severe, with a higher frequency of multivessel involvement and increased risks of recurrence and death after the first MI [4].

Many studies have assessed subclinical atheroma in RA [8]. Endothelial dysfunction has been shown to antedate the development of structural alterations [3,8]. Diminished arterial compliance, a predictor of cardiovascular events, has been reported in RA [8]. Intima-media thickness (IMT) is a marker for vascular alterations due to atheroma and a predictor of cardiovascular risk. Thus, IMT improves the results of cardiovascular risk prediction using the Framingham equation [9]. IMT was increased in RA patients in 21 of the 22 available studies, and the difference versus controls was statistically significant in 17 studies [10]. The IMT increase is detectable within the first few years after RA onset [3].

2. Pathophysiology

Conventional risk factors, which are best evaluated using cardiovascular risk equations, are more common in RA but do not fully explain the increased cardiovascular risk [4], as adjusting for conventional cardiovascular risk factors induces only a very small decrease in the relative risk (RR) of cardiovascular events in RA patients [4–6]. Proinflammatory cytokines (IL-1, TNF-α, IL-6, and IL-17) promote atherogenesis and may explain the increased development of atheroma in RA [11]. Thus, CRP elevation is associated with an excess cardiovascular risk not only in patients with coronary artery disease or a high cardiovascular risk, but also in healthy individuals [12]. Nevertheless, the role for CRP in the cardiovascular risk increase remains debated [13]. Because CRP levels are significantly associated with conventional cardiovascular risk factors (obesity, hypertension, hypertriglyceridemia, and low high density lipoprotein [HDL]-cholesterol), whether CRP exerts causal effects or is a mere marker for atheroma remains unclear [13]. This point probably explains the conflicting data about the potential additive effect of CRP levels to that of conventional cardiovascular risk factors [12]. Finally, that statin therapy diminishes the cardiovascular risk in patients with CRP elevation does not prove a role for CRP in atheroma [14]. Genetic studies based on Mendelian randomization are more relevant for resolving this issue. The objective of Mendelian randomization studies is to assess associations linking the genotype, phenotype, and risk of coronary artery disease, based on the working hypothesis that genetic susceptibility to a cardiovascular risk factor should result in a proportionate increase in cardiovascular risk. This study results do not confirm this hypothesis, indicating that CRP elevation per se probably has no noticeable causal effect in atheroma [15]. In contrast, genetic studies support a role for IL-6 in atheroma. The Asp358Ala polymorphism of the IL-6 receptor results in cleavage of this receptor at the surface of effector cells and in increased levels of the soluble IL-6 receptor. This polymorphism decreases the effect of IL-6 on hepatocytes, monocytes, and macrophages; diminishes CRP and fibrinogen levels; and is clearly associated with a decreased risk of cardiovascular disease [16]. Tocilizumab produces a profile identical to that associated with the Asp358Ala polymorphism [17]. These two hypotheses do not seem mutually exclusive, and incontrovertible evidence exists for an interaction between conventional cardiovascular risk factors and inflammation. In addition, inflammation induces a pro-atherogenic lipid profile.

In patients with RA, inflammation decreases both total- and HDL-cholesterol levels and increases the atherogenic index [18]. However, total- and HDL-cholesterol levels fluctuate in lockstep and the atherogenic index varies less with RA activity compared to each of its two components taken separately [18]. In addition, in patients with RA, HDL acquires proinflammatory effects mediated by increased LDL oxidation and decreased reverse cholesterol transport [18]. The numerous studies evaluating the effects of TNF-α antagonists on the lipid profile showed increased total- and HDL-cholesterol levels with no change in the atherogenic index [18–20]. TNF-α antagonist therapy restores the anti-inflammatory properties of HDL-cholesterol [18]. Conflicting effects of rituximab have been obtained, with no change in the atherogenic index in a study by our group contrasting with an improved atherogenic index and anti-inflammatory HDL-cholesterol effects reported by others [18,21,22]. Tocilizumab therapy increases the total cholesterol/HDL-cholesterol ratio in 12% to 17% of patients, as early as the sixth treatment week [18]. Tocilizumab does not seem to improve the anti-inflammatory properties of HDL-cholesterol [23]. Tocilizumab-induced dyslipidemia may be ascribable to decreased cholesterol clearance due to loss of hepatic LDL-cholesterol receptors [23]. Data are scarce on the effect of synthetic disease-modifying antirheumatic agents on lipid metabolism. Lipid profiles were determined in the Treatment of Early Rheumatoid Arthritis trial that randomized patients with early RA to methotrexate alone, methotrexate plus sulfasalazine and hydroxychloroquine, or methotrexate plus etanercept [24]. Lipid level changes showed no significant differences, with increases in total-, LDL- and HDL-cholesterol levels and a decrease in the atherogenic index [24]. Hydroxychloroquine improved the lipid profile by decreasing the total- and LDL-cholesterol levels and the atherogenic index [25].

Among other conventional cardiovascular risk factors, smoking was more prevalent among RA patients than among controls (OR, 1.56; 95% confidence interval [95%CI], 1.35–1.80) in a meta-analysis of four case-control studies with 1415 patients in all [26]. However, although smoking is associated with a cardiovascular risk increase in RA patients, the RR is not as high as in the general population [4]. Hypertension, although common among RA patients, does not seem more prevalent than in the general population. Thus, in a meta-analysis of seven case-control studies with 1053 RA patients in all, the prevalence of hypertension was identical in the RA and control groups (OR, 1.09; 95%CI, 0.91–1.31) [26]. It is worth noting that hypertension may be frequently underdiagnosed and undertreated in RA patients and may be more common in those with poor joint disease control despite treatment [3,4]. The many other factors that may influence blood pressure control in RA patients include physical inactivity; obesity; and the use of nonsteroidal anti-inflammatory drugs, glucocorticoids, and leflunomide. The prevalence of diabetes was increased in patients with RA compared to controls (OR, 1.74; 95%CI, 1.22–2.50) in the meta-analysis of seven case-control studies with 1230 RA patients [26]. Diabetes may result from abdominal obesity, disease activity, and glucocorticoid therapy. In contrast, hydroxychloroquine therapy decreased the risk of developing diabetes by 46% (hazard ratio [HR], 0.54; 95%CI, 0.36–0.80) in one study and by 77% (HR, 0.23; 95%CI, 0.11–0.50) in another [27,28]. Similarly, TNF-α antagonist therapy diminished the risk of diabetes by 38% (HR, 0.62; 95%CI, 0.42–0.91) [27]. Although among RA patients those with obesity or overweight have higher prevalences of diabetes and hypertension, they are also at lower risk for all-cause and cardiovascular mortality compared to normal weight patients and, to an even greater extent, to underweight patients (BMI < 18.5 kg/m^2) [29].

The respective contributions of conventional cardiovascular risk factors and of markers of RA severity to the occurrence of cardiovascular events were assessed in 10,156 patients with RA who were followed-up for 22 months [30]. Severity markers were defined as disease duration longer than 5 years, erosions, subcutaneous nodule, arthroplasty, HAQ ≥ 2, CDAI > 22, and positive tests for rheumatoid factors. Cardiovascular risk prediction was improved by combining conventional cardiovascular risk factors, age, sex, and RA severity markers instead of using only conventional cardiovascular risk factors or RA severity markers [30].

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