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Review

Ischemic heart disease in systemic inflammatory diseases. An appraisal

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ABSTRACT

Systemic inflammatory diseases are inflammatory syndromes that are associated with increased cardiovascular morbidity and mortality. The link between inflammatory and cardiovascular diseases can be attributed to coexistence of classical risk factors and of inflammatory mechanisms activated in systemic inflammatory diseases and involving the immune system. Yet, clinical implications of these findings are not entirely clear and deeper knowledge and awareness of cardiac involvement in inflammatory diseases are necessary. The aims of this review are to summarize cardiac involvement in systemic inflammatory diseases and to identify areas where evidence is currently lacking that deserve further investigation in the future.

1. Introduction

Atherosclerosis is a multifactorial disease that can be considered an immune/inflammatory response of intima to tissue damage. In fact, the immune system plays a key role in mediating the development of atherosclerotic lesions, as demonstrated by the presence of macrophages and activated lymphocytes within atherosclerotic plaques and of a low-grade inflammatory component, that parallels the development of the atherosclerotic process [1].

Systemic inflammatory diseases (SIDs) are a heterogeneous group of disorders characterized by an excessive immune response against several self-antigens, due to the interaction between genetic predisposing factors, dysregulation of the immune system and environmental factors [2]. In many SIDs an increased risk of developing ischemic heart disease (IHD) has been reported [3], that is not fully explained by classical cardiovascular (CV) risk factors. In fact, the hyperactivation of the immune system and the potential atherogenic effects of some anti-inflammatory drugs exacerbate low-grade inflammation typical of atherosclerosis, causing a premature occurrence of clinical manifestations [4–6]. Accelerated atherosclerosis and raised CV morbidity and mortality suggest that primary CV prevention aiming to early identify SIDs patients at risk of developing CV events is an important tool.

The aim of this review is to summarize evidence regarding the association between major SIDs, i.e. rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and systemic sclerosis (SSc), and CV disease, identifying pathophysiological and clinical aspects that still need to be investigated in future research.

1.1. Rheumatoid arthritis

RA is a chronic systemic inflammatory disease of unknown etiology that primarily affects synovial joints but may involve other tissues including the skin, eyes, lung, kidney, heart and blood vessels. IHD secondary to coronary atherosclerosis represents the first cause of CV mortality in RA patients [7]. A prospective cohort study conducted among 114,342 women without CV disease and RA at enrolment, participating in the Nurses' Health Study, documented 527 incident cases of RA and 3622 myocardial infarction (MI) and strokes during 2.4 million person-years of follow-up [8]. Compared with those without, women with RA demonstrated an adjusted relative risk of 2.0 (95% CI, 1.23 to 3.29) for MI and 1.48 (95% CI, 0.70 to 3.12) for stroke. Worryingly, RA patients were almost 6 times more likely to have had an undiagnosed ("silent") MI (OR, 5.86; 95% CI, 1.29–26.64) and twice as likely to experience sudden death (HR 2.36, 95% CI 1.30–4.27) than age- and sex-matched controls [9]. In addition, it has been also reported that RA patients usually show more severe coronary involvement. In a retrospective case–control study comparing patients with and without RA with new diagnosis of coronary artery disease (CAD), more severe coronary involvement was observed at time of CAD diagnosis in RA patients, with only 4% of patients with RA having no significant CAD compared to 23% of control patients [10]. Notably, RA remained a significant predictor of multi-vessel CAD after adjustment for age, sex and history of dyslipidemia.

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These data clearly document the burden of IHD on RA morbidity and mortality, suggesting that an accurate knowledge of the presence of CV risk factors and of subclinical vascular damage in patients affected by RA may be useful to foster primary prevention and to not misdiagnose early manifestations of CV involvement.

The development of atherosclerosis in RA is likely accelerated by systemic chronic inflammation. However, occurrence of coronary lesions may also be attributable to coexistence of traditional CV risk factors. Yet, data on the prevalence of CV risk factors in patients with RA are inconsistent. In 2006 Han et al. [11] analyzed the prevalence of CV risk factors in 28,208 RA subjects compared to age, sex, and geographic region-matched control group, and reported increased prevalence of type II diabetes, hyperlipidemia and hypertension in RA patients, as well as of IHD, peripheral vascular disease, congestive heart failure and cerebrovascular disease. In contrast, a recent meta-analysis of Boyer et al. [12], including 7 studies collecting 1053 RA patients and 974 controls, demonstrated that the prevalence of hypertension did not differ between RA patients and controls (OR 95% CI = 1.09; $p = 0.35$).

In addition, a peculiar behavior of CV risk factors has been observed in RA. In-vitro animal models and in-vivo human studies [13] revealed that the interplay between inflammation and lipid components is quite complex. In fact, hyperlipidemia appears to have a paradoxical effect on CV risk in RA patients, whereby decreased lipid levels are associated with increased CV risk [14] (Table 1). In patients affected by RA raised triglycerides, low high-density lipoproteins (HDL) concentration, low levels of total cholesterol and low-density lipoproteins (LDL) have been shown. Reduction of total and LDL cholesterol levels during acute or chronic high-grade inflammation has been described together with a greater reduced high-density lipoprotein (HDL) cholesterol, resulting in a disadvantageous atherogenic index (total:HDL cholesterol ratio) [15]. Yet, although total LDL is normal or low in RA patients, oxidized LDL are higher, compared with healthy subjects, and are further increased by specific RA treatments, such as anti-TNF-α-treatments (infliximab, adalimumab, and etanercept) [16]. In fact, inflammation as well as non-biological and biological drug-induced alterations of the structure and function of lipid molecules require further studies in patients with RA [17].

A paradoxical effect on survival in RA has also been documented for body mass index (BMI) that appears linearly correlated to survival [18]. In fact, among RA patients low BMI, which may indicate uncontrolled active systemic inflammation, is associated with a three-fold increased risk of CV death [19], even after adjustment for cardiac history, smoking, diabetes mellitus, hypertension, and malignancy.

In addition to dyslipidemia and obesity, there is increasing evidence that smoking also has a complicated relationship with RA [20]. Smoking is a well-recognized risk factor for RA, that increases RA specific factor titers, such as rheumatoid factor and anticitrullinated protein antibodies [21]. It has been demonstrated that there is a possible dose-dependent relationship between smoking and disease development, activity and severity [22]. Smokers with RA also appear to have higher rheumatoid factor titers associated with increased risk of major disability, higher radiographic damage, poor RA treatment response [23] and premature CV mortality. This relationship has been attributed to the association between smoking, HLA DR1 shared epitope alleles and production of anticitrullinated protein antibody and development of atherosclerosis [24].

Collectively, these data indicate that CV risk factors behave differently in RA and risk scores developed for the general population based on traditional CV risk factors alone might be unlikely to accurately estimate CV risk in RA. For these reasons, the European League Against Rheumatism (EULAR) [25] has recently proposed the application of a 1.5 multiplier to risk estimates calculated on the basis of standard algorithms for patients with RA. This approach, however, while appealing for simplicity, requires prospective validation. Yet, the underestimation of CV risk in RA patients with available risk charts clearly highlights the need for RA-specific risk prediction tools. Epidemiologic, clinical and laboratory studies have suggested that chronic inflammation and immune dysregulation play a pathogenic role in the development of atherosclerosis in RA, enhancing atherosclerotic plaques vulnerability [26]. Rheological characteristics such as whole blood viscosity, plasma viscosity, erythrocyte deformability, aggregation and erythrocyte nitric oxide production have been increasingly linked to CV risk in the general population [27] and are independently associated with subclinical atherosclerosis in women with RA who did not have previous CV events [28]. Likewise, pro-inflammatory cytokines, such as TNF and interferon γ (INF-γ), in addition to the expression of neo-epitopes on endothelial cells, promote vulnerability and premature rupture of atherosclerotic plaques. Notably, increased mortality is also observed in patients with positive rheumatoid factors and the extent of inflammation in RA has also been linked to increased CV mortality [29], suggesting the relevance of computing the inflammatory and specific RA biomarkers in the risk estimation.

Increased carotid intima–media thickness (IMT) and impaired endothelial-dependent flow-mediated vasodilatation (FMD) are regarded as early markers of systemic atherosclerosis [30,31] and several studies have documented a relation between increased IMT [32,33], impaired FMD and the occurrence of CV events [8,34] (Table 2). In RA patients, Kumeda et al. [35] proved that carotid and femoral IMT were significantly increased in RA patients and the extent of sub-clinical atherosclerosis significantly correlated with the duration and severity of the underlying disease. These observations were consistent with the findings of Ciftci et al. [36] that evaluated 30 RA patients and 52 healthy volunteers undergoing echocardiographic assessment of coronary flow reserve (CFR) and carotid IMT measurements. CFR values were significantly reduced in RA patients compared to controls (2.4 ± 0.5 vs. 2.7 ± 0.4, respectively; $p = 0.002$), whereas IMT values were again significantly increased (0.6 ± 0.1 vs. 0.5 ± 0.1, respectively; $p = 0.001$).

These data point to the potential usefulness of screening for subclinical atherosclerosis to improve primary prevention strategies in RA patients [37]. However, the clinical value and cost-effectiveness of this strategy remain to be investigated.

1.2. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic inflammatory, autoimmune disease that mainly affects young women (90%). Its clinical presentation is highly heterogeneous and a substantial number of patients develop multi-organ involvement (kidney, lung, central nervous system and heart) [38]. Although the etiology of SLE is currently not

Table 1
Lipid abnormalities in SIDs.

	RA	SLE	SSc
TC	↓	↑	↕
HDL	↓	↓	↕
LDL	↓	↑	↑
TG	↑	↑	↕

RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; TC: total cholesterol; HDL: high density lipoproteins; LDL: low density lipoproteins; TG: triglycerides.

Table 2
Subclinical organ damage in SIDs.

	RA	SLE	SSc
IMT	↑	Limited data	↑
Coronary calcium score	Not available	Not available	↑
Endothelial Dysfunction	+	Limited data	+

RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; IMT: intima–media thickness.