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Cardiovascular and autoimmune diseases in females: The role of microvasculature and dysfunctional endothelium

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ABSTRACT

Cardiovascular (CV) diseases are becoming increasingly frequent and associated with a high incidence of CV events, disability and death. It is known that there is a relationship between CV burden and systemic autoimmune diseases (SADs) that is mainly due to inflammation and autoimmunity, but the other mechanisms underlying the high CV risk of SAD patients have not yet been fully clarified.

The aim of this review article is to discuss some of the specific factors associated with the accelerated atherosclerosis (ATS) characterising SADs (female sex, the microcirculation and the endothelium) in order to highlight the importance of an early diagnosis and the prompt implementation of preventive measures, as well as the possible role of new therapeutic strategies such as vaccine immunomodulation.

Finally, as the natural history of ATS begins with endothelial injury (a potentially reversible process that is influenced by various factors) and microvascular damage plays a central role in the etiopathogenesis of SADs, it underlines the crucial need for the development of reliable means of detecting subclinical abnormalities in the microcirculation, particularly coronary microcirculation dysfunction.

1. Introduction

Cardiovascular disease (CVD) is an increasingly frequent indirect cause of lost productivity [1], and one of the leading causes of death worldwide [2,3]. It is therefore essential to improve our prevention strategies because, although they are still not as efficacious as they might be, the feasibility of large-scale preventive interventions such as those promoted by the World Health Organisation (WHO) [4], should improve cardiovascular (CV) outcomes [5]. In order to do this, it is necessary to act not only on traditional CV risk factors such as smoking, diabetes, hypertension, hypercholesterolemia [6], and atherosclerosis (ATS) and its complications [7], but also on specific items such as CV involvement in systemic autoimmune diseases (SADs) [8–10].

Furthermore, growing interest in sex studies has improved our understanding of the need for more specific sex-related treatments for various conditions, including CVD [11]. Little is known about the relationships between SADs and sex, but it it is known that SADs are generally more prevalent among female subjects [12].

The primary aim of this paper is therefore to summary our knowledge about CVD in females with auto-immune diseases, concentrating on the microcirculation and endothelial dysfunction.

1.1. Old and new insights into the relationships between CVD and SADs

It is known that SADs are associated with major CV morbidity, and that CV mortality accounts for 40–50% of all deaths among patients with rheumatoid arthritis (RA) [13]. Furthermore, CVD seems to occur at a younger age than in the general population, is often asymptomatic (at least in the early stages), and also involves specific risk factors such as chronic inflammation, the duration and activity of the autoimmune disease, and the effects of immunosuppressive therapy (glucocorticoids and methotrexate) [14]. Wolfe et al. assessed the prevalence of minimal disease activity and remission in 18,062 patients with RA and found that the former and

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a short disease duration are associated with better outcomes [15].

Most research has underlined the role of systemic inflammation but Hollan et al. have recently both vascular and peri-vascular inflammatory responses [16], and found that inflammatory cell infiltrates in the adventitia and media were more frequent (47% *vs* 20%; odds ratio 3.6, $p = 0.002$) and extensive in patients with than in those without SADs. Inflammation in the deeper vascular and peri-vascular layers may also be involved in plaque formation and destabilisation [17] or the formation of aortic aneurysms [18,19].

The presence of inflammatory mediators is more frequent in the perivascular layers of SAD patients than in the general population, and a number of published studies have also found that they have underlying microvascular lesions and/or macrovascular damage (e.g. scleroderma) [20]. Au et al. [21] have published a meta-analysis of 14 studies assessing carotid intima-media thickness (IMT) and seven assessing percentage brachial artery flow-mediated dilation (FMD). In comparison with the healthy controls, the patients with systemic sclerosis (SSc) showed a higher prevalence of coronary ATS, peripheral vascular disease, and cerebrovascular calcification, increased carotid IMT (summary mean difference 0.11 mm, 95% confidence interval [95% CI] 0.05−0.17 mm; p = 0.0006) and less FMD (summary mean difference −3.07%, 95% CI 5.44% to −0.69%; $p = 0.01$).

Before attempting to clarify what is said above, it is worth worth mentioning some differences among the various forms of SADs. Over the years, most studies have investigated the relationship between RA and ATS, but it is necessary to remember that RA is a type of paradigmatic inflammatory arthritis that is substantially different from other systemic rheumatic diseases (SRDs) such as systemic lupus erythematosus (SLE), SSc and psoriatic arthritis (PsA) [22,23].

RA patients have a reduced life expectancy: according to Van Doornum et al. [24], standardised mortality ratios range from 0.87 to 3.0, and CVD is the main cause of death in clinical and community-based cohorts of RA populations. SLE is an autoimmune disease that may involve any organ of the body and has a broad spectrum of clinical manifestations. It predominantly affects young women, a group of subjects who are generally not affected by ATS. However, the prevalence of coronary artery disease (CAD) among SLE patients is 6−10%, and the risk of developing CAD is 4−8 times greater than in the general population [25]. The prevalence of CAD seems to be even higher in SSc patients as Akram et al. studied 172 patients who underwent coronary angiography because of suspected CAD, and found that its observed prevalence was 22% (38/172): 17% in males (6/36) and 23% in females (32/136) [26]. Finally, one study of PsA patients found that, in comparison with controls, they had a significantly reduced coronary flow reserve (CFR) (CFR: 2.86 ± 0.70 *vs* 3.3 ± 0.43; p < 0.01) and greater common carotid IMT, although this difference was not statistically significant (0.64 ± 0.26 *vs* 0.62 ± 0.5 mm; p = 0.65) [27].

Returning to the relationship between SADs and ATS, it is important to underline that atherosclerosis needs to be treated early in order to obtain better outcomes [28], which is why every effort should be made to identify potentially reversible endothelial dysfunction as early as possible [29]. The many parameters that can be used to evaluate endothelial dysfunction and early ATS include arterial distensibility and stiffness [30], which are mainly assessed by measuring IMT and pulse wave velocity (PWV) [31]. It has also recently been suggested that asymmetric dimethylarginine (ADMA) may be involved in endothelial dysfunction because it is the main endogenous inhibitor of all three nitric oxide (NO) synthases [32].

The various methods used to assess endothelial dysfunction in patients with SADs include transthoracic echocardiography and the non-invasive evaluation of CFR, which is also capable of revealing much about the cardiac macro- and microcirculation [33]. The CFR of the left anterior descending coronary artery (LAD) is a strong and independent indicator of mortality, and has additional prognostic value over wall motion analysis in patients with known or suspected CAD [34].

Coronary microvascular dysfunction describes abnormalities in the regulation of myocardial blood flow (MBF) that cannot be attributed to epicardial CAD. Recio-Mayoral et al. [35] carried out a case−control study in which positron emission tomography (PET) was used to study MBF and CFR at rest and during adenosine-induced hyperemia in patients with SLE and RA. Coronary angiography showed that none of the patients had a significant epicardial stenosis, but they all had a lower CFR and less MBF during hyperemia.

About two years ago, an interesting review concluded that a multi-parametric approach is the best means of recognise subclinical ATS in patients with rheumatic conditions [36].

1.2. ATS in patients with SADs: is the culprit inflammation or autoimmunity?

Our knowledge of the pathogenic mechanisms and possible treatments of SADs has significantly increased over the last ten years. It has long been known that inflammation is a major CV risk factor, and there is now substantial evidence indicating that it contributes to the onset and pathogenesis of ATS and CVD in the general population [37], and that reducing inflammation decreases the risk of CVD in patients with SADs, especially those with RA [38]. Epidemiological studies have found that pro-inflammatory molecules such as C-reactive protein (CRP), fibrinogen and cytokines are involved in mediating the process of inflammation [39], and the increased levels of these molecules in patients with SADs not only promotes endothelial dysfunction and structural vessel abnormalities, but also induces other CV risk factors such as changes in lipid levels, insulin resistance and oxidative stress [40].

It is also interesting to note that genome-wide association studies (GWAS) have successfully identified a number of gene variants that influence CRP levels, although the results of Mendelian randomisation studies indicate that they are not significantly associated with the risk of CAD [41].

Inflammation contributes to all stages of atherosclerosis, from plaque formation to plaque instability and final plaque rupture [42], but it is still unclear whether it is inflammation or autoimmunity that triggers ATS. As things stand, it is known that innate immune mechanisms are present in humans ando so in patients with ATS, particularly during the early stages of the disease, but it is becoming increasingly important to clarify the role of autoimmunity mechanisms in the genesis of plaques and atherosclerotic injury [43].

Recent studies of the molecular factors and signalling systems activated by a variety of pathogens and/or endogenous signals have highlighted the prominent role of pro-inflammatory inflammasome/IL-1 cytokines, and drawn attention to the role of auto-inflammatory mechanisms in ATS [44,45]. It is not yet known whether these progress to atherogenic adaptive immune responses in the later stages of the disease or represent two independent pathological processes, but understanding their nature and interrelationship in patients with ATS may provide new clues to assist not only early and accurate diagnoses, but also preventive programmes and perhaps more effective therapeutic interventions.

However, ATS can now be considered an “auto-inflammatory” rather than an autoimmune disease that triggers the production of auto-antibodies against substances such as oxidised LDL [46].

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