

## Cardiovascular risk in women with autoimmune rheumatic diseases

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**Summary.** Cardiovascular (CV) disease is the main cause of death in the general population, as well as in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). In recent years, many female-specific CV risk factors have been recognized, including pregnancy morbidity and autoimmunity. Different autoantibodies have been associated with CV disease in patients with and without autoimmune disease.

Atherosclerosis and RA share many common pathogenic features, starting from the pre-clinical stage of the diseases: genetic background, environmental factors and post-translational modification of antigens. Although CV morbidity appears to be equally distributed between men and women with RA, some studies suggest a higher risk among female patients with RA. Besides the traditional risk factors, disease-specific autoantibodies (antibodies to citrullinated and carbamylated proteins) and disease activity contribute to CV morbidity. It is worth noting that female patients have more active disease and show poorer response to treatment.

Amongst SLE patients, younger females are at highest risk of death for CV events. Although survival has improved, long-term mortality is still mainly attributable to CV events. As in RA, SLE patients show higher CV morbidity and mortality that are not fully explained by the excess of traditional CV risk factors. The inflammatory burden and different autoantibodies, in particular the anti-phospholipid antibodies, contribute to the atherosclerotic process. Moreover, disease activity and medications further contribute to CV risk.

**Key words.** Cardiovascular risk, rheumatoid arthritis, systemic lupus erythematosus.

### *Il rischio cardiovascolare nelle donne con malattie reumatiche autoimmuni*

**Riassunto.** La malattia cardiovascolare (CV) è la principale causa di morte nella popolazione generale così come nei pazienti affetti da artrite reumatoide (AR) e lupus eritematoso sistemico (LES). Negli ultimi anni sono stati descritti diversi fattori di rischio CV associati al sesso femminile; tra questi rientrano la patologia gravidica e l'autoimmunità. Nei pazienti con e senza malattie autoimmuni diversi autoanticorpi sono stati associati alla malattia CV.

L'aterosclerosi e l'AR condividono diversi aspetti patogenetici, a partire dalle fasi precliniche: substrato genetico, fattori ambientali, modificazioni post-traduzionali degli antigeni. Sebbene la morbilità CV sembri essere egualmente distri-

buita nei due sessi, esistono alcune prove a supporto di un eccesso del rischio CV nelle donne affette da AR. Accanto all'eccesso di fattori di rischio CV tradizionali, gli autoanticorpi specifici dell'AR (antipeptidi citrullinati e carbamylati) e l'attività di malattia contribuiscono all'eccesso di malattia CV. È importante notare che le donne affette da AR hanno una malattia più attiva ed una prognosi peggiore.

Tra i pazienti affetti da LES, le giovani donne presentano il rischio più elevato di andare incontro ad eventi CV. A fronte di un aumento della sopravvivenza, la mortalità dei pazienti affetti da LES è tuttora causata principalmente da eventi CV. Come nell'AR, nei pazienti con LES l'eccesso di morbilità e mortalità CV non è del tutto spiegabile con il solo eccesso di fattori di rischio CV tradizionali. Il carico infiammatorio e diversi autoanticorpi, in particolare gli anticorpi anti-fosfolipidi, contribuiscono al processo aterosclerotico. Inoltre, l'attività della malattia e la terapia contribuiscono ulteriormente al rischio CV.

**Parole chiave.** Rischio cardiovascolare, sesso femminile, artrite reumatoide, lupus eritematoso sistemico.

### Introduction

Cardiovascular disease (CVD) is the main cause of death in men and women and is one of the major causes of comorbidity and mortality in patients with autoimmune rheumatic diseases; accelerated atherosclerosis accounts for most of the excess cardiovascular (CV) risk<sup>1-3</sup>.

Traditionally, CVD has been considered a male-specific disease; on the contrary, autoimmune rheumatic diseases mostly affect female subjects. In recent years, awareness of the increased cardiovascular risk among females has grown and more attention has been paid to female-specific CV risk factors. Of these factors, autoimmunity is one of those that has attracted the attention of clinicians and scientists. Most literature data on cardiovascular disease and autoimmune rheumatic diseases concerns rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). This narrative review will focus on these two diseases and attempts to underline certain aspects that may account for the gender difference in cardiovascular risk in RA and to address the factors responsible for the higher frequency of CV disease in SLE.

### Gender-specific differences in cardiovascular risk

For a long time, cardiovascular disease has been considered a male-specific disease; however, whereas men have a significantly higher prevalence of coronary heart disease (CHD) before the age of 50, in women the CV risk starts to increase after the menopause and becomes similar to the CV risk in men in the seventh decade<sup>4</sup>. There is now a growing awareness of the CV risk in females. In addition to the traditional cardiovascular risk factors, female-specific factors contribute to coronary heart disease in women. Firstly, life expectancy is longer in women than in men, and consequently the elderly population – which has the highest risk of CV morbidity and mortality – is mostly feminine<sup>1</sup>. Overall, the absolute number of women with CV disease is higher than in men; however, the proportion is unbalanced towards men under the age of 75<sup>5</sup>. Menopause is the best known ‘risk factor’ accounting for the increase in cardiovascular morbidity following the loss of the cardio-protective effect of estrogens. Animal models and *in vitro* studies have demonstrated that estrogen receptors (ER) alpha and beta exert many cardio-protective effects. Indeed, estrogens exert their cardio-protective properties by reducing myocardial pro-inflammatory cytokines, inhibiting cardiomyocyte apoptosis, and regulating vascular smooth muscle cells and nitric oxide synthesis in endothelial cells<sup>6</sup>. Consequently, post-menopausal women have a greater risk of myocardial infarction, which is higher even than in age-matched men<sup>7-8</sup>.

Besides the ‘physiological’ increase in CV risk after the menopause, other female-specific conditions, unique to women, contribute to CV risk. Pregnancy complication seems to contribute to the maternal risk of future CVD. Hypertensive disorders during pregnancy – chronic or gestational hypertension and pre-eclampsia – are associated with an increase in traditional CV risk factors later in life. Moreover, pre-eclampsia and eclampsia increase the risk of cardiovascular heart disease, stroke and CV-related mortality<sup>9-11</sup>. Besides pre-eclampsia, other ischemic placental diseases as well as growth restriction, preterm delivery and recurrent miscarriages seem to influence the mother’s cardiovascular history<sup>6</sup>. Whether the pregnancy outcome itself is responsible for the increase in CV risk or pregnancy morbidity shares common mechanisms with atherosclerosis is questionable. For instance, anti-phospholipid antibodies are a well-known risk factor for both obstetric complications (recurrent miscarriage, fetal loss, premature delivery, growth restriction) and accelerated atherosclerosis<sup>12</sup>.

Autoimmune diseases are more prevalent among women, with a female to male ratio ranging from 2-3:1 for RA to 9-11:1 for SLE and Sjögren syndrome<sup>13</sup>. Interestingly, the isolated (non-specific) positivity for auto-antibodies, in the absence of any systemic autoimmune

disease, also seems to increase the risk of atherosclerotic CV events. In 2002, Grainger and Bethell were the first to investigate the presence of ANA amongst patients with coronary atherosclerosis: compared to those without coronary atherosclerosis, patients with stenotic lesions of the three main arteries showed a significantly higher prevalence of ANA (70% vs 15%;  $p < 0.001$ ), without any difference between men and women<sup>14</sup>. A few years later, the association between systemic autoimmunity and atherosclerosis was further confirmed<sup>15</sup>. In a large population-based study on nearly 15,000 patients screened for anti-nuclear antibodies (ANA), rheumatoid factor (RF) or anti-citrullinated peptide antibodies (ACPA), RF- and ANA-positivity emerged as predictors of CV morbidity – mainly myocardial infarction – and mortality, in those subjects with but also in those without a diagnosis of autoimmune rheumatic disease; more specifically, in women, ANA were associated with death for CV events<sup>15</sup>. In a study on 2,278 healthy Finnish subjects aged 24-39, the authors observed that ANA positivity was associated with reduced carotid elasticity in women, even after adjusting for traditional CV risk factors and C-reactive protein (CRP)<sup>16</sup>.

More recently, RA-specific antibodies (i.e. ACPA) have been associated with the development of atherosclerotic plaques. In 2013, Cambridge et al. detected a higher prevalence of ACPA at baseline in patients who subsequently developed CHD; even after adjusting for traditional CV risk factors (including cigarette smoking) and CRP, ACPA was confirmed as an independent risk factor for CVD in patients without concomitant RA<sup>17</sup>. These findings are not surprising, since citrullinated proteins have been detected in the atherosclerotic plaques of patients not affected by RA<sup>18</sup>.

As a matter of fact, on the one hand, atherosclerosis has started to be recognized as an immune-mediated disease sharing common mechanisms with traditional autoimmune diseases such as SLE and RA; on the other, it has been ascertained that autoimmune diseases affect female individuals in up to two third of cases<sup>13</sup>. Therefore, the growing interest concerning CVD in autoimmune disease is not surprising. To date, research has focused primarily on SLE and RA.

### Cardiovascular risk in rheumatoid arthritis

The recognition of the excess CV morbidity and mortality amongst patients with RA derives from large population studies and meta-analyses. The risk of myocardial infarction and stroke are increased by 40-70% and death for CV diseases is twice as high in patients with RA than in the general population, and is similar to that observed amongst diabetic patients<sup>19-22</sup>. Moreover, although CV mortality has significantly improved in re-

cent years, CV disease is still the main cause of premature death in RA patients<sup>2</sup>.

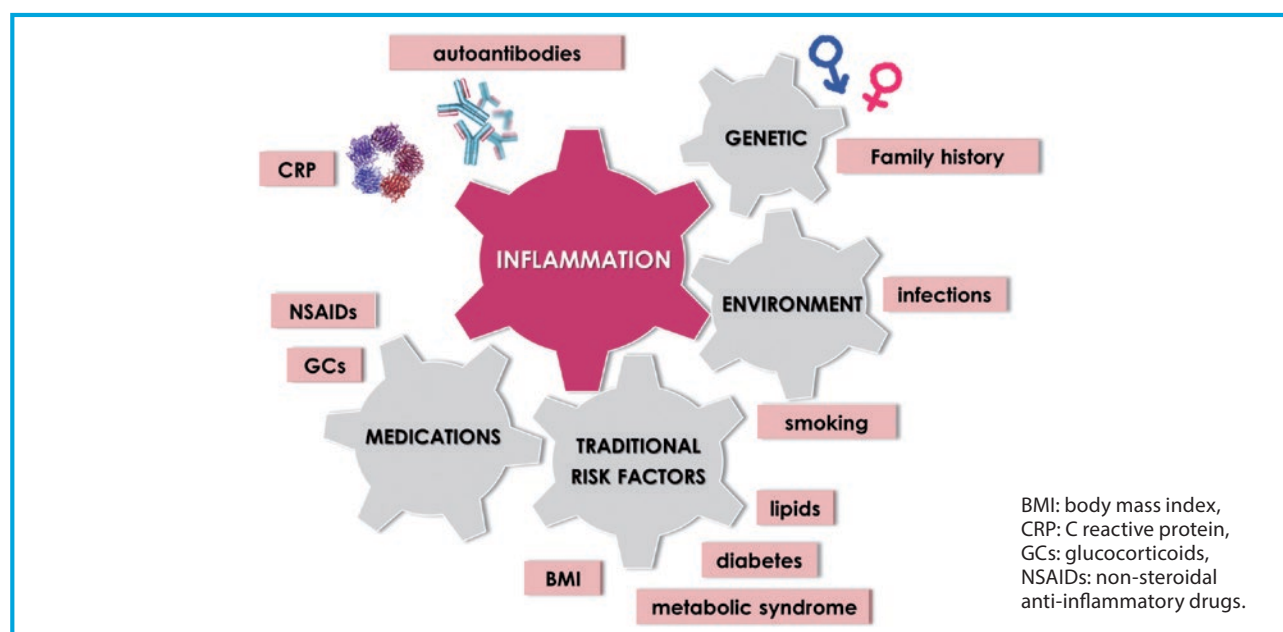
Most observational studies suggest that there is no gender difference in CV morbidity<sup>20,23</sup>. All the common CV risk factors are more prevalent in RA patients than in the general population, regardless of sex; the only exception is the different distribution of body fat, with female RA patients showing an increase in subcutaneous fat compared to controls matched for body mass index (BMI) and waist circumference<sup>23-25</sup>. However, some evidence suggests an excess risk in women. Considering carotid intima media thickness (cIMT) as a surrogate marker of subclinical atherosclerosis, Taverner et al. detected a higher cIMT in male patients with RA than in females, yet the linear regression analysis revealed that disease activity was significantly associated with cIMT in women<sup>26</sup>. Moreover, in a large study on a UK database, the authors confirmed the higher prevalence of traditional CV risk factors in RA patients; interestingly, when gender was added to the traditional risk factors, a significant increase in the incidence of major CV events was detectable only in women<sup>27</sup>. Indeed, it is not surprising that the Q-RISK score 2 adds a multiplication factor of 1.38 for males and of 1.5 for females with RA<sup>28</sup>.

The excess CV risk in RA can be only partially attributed to the excess of traditional risk factors, and the inflammatory disease itself strongly contributes to the accelerated atherosclerosis (Figure 1). From a pathogenetic standpoint, atherosclerosis and RA are diseases that mirror one another. Starting from the pre-clinical phase, the two diseases share many different aspects: genetic background, environmental factors accounting for post-

translational modifications of proteins, endothelial involvement and inflammatory cell infiltration of the target structures (vessels and joints)<sup>25,29</sup>.

Besides RF, antibodies recognizing citrullinated peptides are nowadays considered the most specific biomarker of RA. ACPA are involved in the pathogenesis of the disease and are a good prognostic marker as they are associated with a more active and aggressive disease, as well as with a higher mortality rate<sup>30</sup>. Indeed, both in female and male RA patients, ACPA positivity is associated with subclinical atherosclerosis, CV morbidity and mortality for CV events<sup>31-36</sup>. As regards gender discrepancy and ACPA positivity, in a Dutch population-based study on more than 40,000 individuals with and without RA, van Zanten et al. detected a correlation between female gender and ACPA positivity, regardless of age, smoking habits and female-based variables (parity, menopause, age of menarche and menses regularity)<sup>37</sup>. Similarly, in subjects at risk of developing RA (seropositive first-degree relatives of RA patients), female gender was significantly associated with ACPA positivity<sup>38</sup>. The association was stronger in females aged 45-55 and in those who were in the menopause, especially in the early post-menopausal period, soon after the estrogen levels decrease; moreover, after stratification for menopausal status, the effect of age was no longer detectable, suggesting that estrogen levels could have a direct influence on the development of ACPA<sup>39</sup>.

Citrullination is an enzymatic post-translational modification catalyzed by peptidyl-arginine deiminases<sup>40</sup>. In genetically predisposed individuals carrying the HLA-DRB1 allele, environmental factors can increase



**Figure 1.** Traditional and disease-related cardiovascular risk factors contributing to the atherosclerotic process in autoimmune rheumatic diseases.

citrullination; considering the factors responsible for citrullination, atherosclerosis and RA have two common risk factors i.e. cigarette smoking and chronic periodontitis<sup>29</sup>. It would be superfluous to discuss the role of smoking as a CV risk factor here. Similarly, since the early 1990s, cigarette smoking has been recognized as a risk factor for RA<sup>41</sup>. Smoking is more prevalent amongst patients with RA than in the general population and it is associated with RF- and ACPA-positivity<sup>25</sup>. There is limited literature data on the contribution of cigarette smoking to CV morbidity and mortality in women with RA; however, although smoking is more prevalent amongst male patients, it seems to be associated with an increase in mortality (including CV mortality) amongst females<sup>42</sup>.

In recent years, a new subset of autoantibodies has been described in RA patients: the antibodies directed against carbamylated proteins (anti-CarP). Carbamylation is a mainly non-enzymatic post-translational modification that leads to the generation of homocitrullinated peptides<sup>43</sup>. Carbamylation involves proteins and lipoproteins both high- and low density by increasing their atherogenicity<sup>29</sup>. To date, there are no data suggesting gender differences in the prevalence of anti-CarP antibodies. One recent study demonstrated that anti-CarP antibodies, like ACPA, are associated with sub-clinical atherosclerosis in RA patients without clinical evidence of CV disease, regardless of patient gender<sup>36</sup>. It remains to be clarified whether antibodies to carbamylated proteins or lipoproteins are also associated with worse CV outcomes in RA patients.

Another aspect to be considered when addressing the topic of CV risk in RA concerns the impact of disease activity on CVD and its relationship with female gender. The modern management of RA aims to achieve disease remission or low disease activity; to quote the title of an editorial published in 2015: "Treat to target in rheumatoid arthritis: good for the joints as well as for the heart?"<sup>44</sup>. Therefore, the strategy, more than the type of treatment, is important for controlling inflammation and disease activity.

Women would seem to have higher disease activity and a lower response rate to the different treatment strategies<sup>45-51</sup>. Data from a large international cohort of more than 6,000 RA patients demonstrated that female patients have higher scores in all the core data set measurements including the activity indices (number of tender and swollen joints, evaluation of pain and global health evaluation, acute phase reactants) and, consequently, a higher composite disease activity score on 28 joints (DAS28); the effect of gender was mild to moderate for all the variables and the swollen joints count was the most similar between men and women<sup>52</sup>. A significantly greater percentage of male patients – almost double – showed disease remission; however, the distribution of therapies for RA was similar in men and women<sup>52</sup>. If the

measurements included in the activity indices differ between the genders, they likely account for higher disease activity in females. Besides clinical variables, most of the activity indices include acute phase reactants (i.e. ESR or CRP). One recent paper suggested that the level of high-sensitivity CRP before the clinical onset of RA could be a predictive maker of incident RA, as well as a marker of CV death amongst female, but not male, patients<sup>53</sup>.

As a matter of fact, hormones would seem to affect RA activity: most patients show an improvement of their disease during pregnancy, and estrogen-based therapies (oral contraceptives and hormone replacement therapy) also seem to improve the disease<sup>54,55</sup>.

### Cardiovascular risk in systemic lupus erythematosus

Addressing the topic of gender differences and their effect on CV disease in SLE is more complex. Indeed, of the systemic autoimmune diseases, SLE is one of those with the greatest gender-discrepancy with a female: male ratio of approximately 9:1<sup>13</sup>. Many epidemiological studies as well as translational research have involved only female patients with SLE.

Since the late 1970s, CVD has emerged as the main cause of death in patients with long-standing disease<sup>56</sup>. Patients with SLE have a 2-3-times greater risk of CVD than the general population<sup>57</sup>. Data from large population-based studies support the notion that the survival of SLE patients has dramatically improved in recent decades. As a consequence, in line with better survival there has been an increase in CV morbidity and mortality. In a Swedish study published in 2004, the authors recorded a decline in all-cause mortality over the time, with the only exception of CVD, which remained unchanged and is still the main cause of death in SLE patients – with younger patients showing the most pronounced increase<sup>58</sup>.

Although older patients with long-standing disease are at a higher risk of CVD than the general population, younger patients with lupus have the highest risk<sup>57</sup>. In 1997, Manzi et al. published a milestone paper comparing the rate of cardiovascular events in 498 women with SLE with age-matched healthy females of the Framingham Offspring Study: women with lupus aged 35-44 were at the highest risk of CHD, showing a 50-fold increase in the relative risk of myocardial infarction<sup>59</sup>. Other studies confirmed the highest risk of myocardial infarction amongst SLE patients in the fourth decade of life<sup>60-61</sup>. Similarly, patients with SLE, especially younger females, are twice as likely to have a cerebrovascular accident than the general population<sup>57</sup>. One very recent paper comparing two inception cohorts of SLE patients followed up between 1975 and 1992 and between 1999 and 2011 showed a significant decrease in the incidence

of atherosclerotic CV events (from 1.8 to 0.44 per 100 patient-years) due to a reduction in the traditional risk factors (hypertension, diabetes and smoking) as well as disease-related disease activity in the second cohort<sup>62</sup>. The results of this study are consistent with the decline in CV events detected in the general population and seem to be partially attributable to a better management of traditional CV risk factors, together with a more widespread use of antimalarials and immunosuppressants<sup>62</sup>. The subclinical features of atherosclerosis can be detected in approximately 30-40% of SLE patients: a meta-analysis published in 2016 showed a higher prevalence of atherosclerotic plaques and increased cIMT amongst SLE patients<sup>63</sup>. Moreover, most of the studies evaluating flow mediated dilation (FMD), an ultrasonographic measurement of endothelial dysfunction, detected an impairment of brachial artery dilatation in SLE patients<sup>64</sup>.

All the traditional CV risk factors (hypertension, primarily associated with renal involvement as well as with disease activity; diabetes and insulin resistance; metabolic syndrome and cigarette smoking) are more prevalent in SLE patients than in healthy subjects<sup>65</sup>. Moreover, although lupus cohorts are mainly composed of women and the absolute number of women with CV events is higher, male gender seems to account for a nearly 4-fold increase in CV risk<sup>66-68</sup>. Dyslipidemia deserves separate consideration: indeed, patients with SLE, and to a lesser extent, patients with RA, are characterized by a specific lipid profile with an increase in pro-inflammatory HDL (piHDL)<sup>69</sup>. In 2009, Mc Mahon et al. studied the antioxidant function of HDL in 276 women with SLE and demonstrated that almost half showed a pro-inflammatory and pro-atherogenic HDL-cholesterol profile (i.e. HDL lacking the ability to prevent LDL oxidation); piHDL was detectable in a significantly higher percentage of patients with atherosclerotic plaques or increased cIMT<sup>70</sup>. Besides the increase in piHDL, an increase in oxidized LDL (oxLDL), correlating with the presence of carotid plaques, has also been described in female patients with SLE<sup>71</sup>.

As in RA, also in SLE patients the traditional risk factors alone do not explain the excess CV risk. Many lupus-related factors are involved in endothelial activation and dysfunction, thus contributing to the atherosclerotic process from the earliest stage (Figure 1).

Amongst the many pro-inflammatory cytokines, type I interferon (IFN) is one of the most involved in the pathogenesis of lupus and its pathway has been associated with endothelial repair impairment and subclinical atherosclerosis in patients with SLE. Type I IFN affects the differentiation, survival and function of circulating endothelial progenitor cells (EPCs), the bone-marrow derived precursors of mature endothelial cells involved in endothelium repair. Both *ex vivo* and *in vitro*, IFN induces apoptosis of EPCs expressing IFN receptors, thus reducing the number of angiogenic cells and their abil-

ity to form colonies<sup>72-74</sup>. In 2012, Somers et al. studied the relationship between the IFN pathway and CV disease in 95 patients (nearly 98% of whom were female) compared to 38 age- and sex-matched healthy individuals without overt CVD: the authors found that a panel of IFN-related genes were independently associated with impaired endothelial function as measured by FMD and anatomic (increased cIMT) vessel changes, thus promoting the accelerated atherosclerosis<sup>75</sup>. The observation that IFN is crucial in the development of atherosclerosis in lupus patients is becoming more important in the light of the potential opportunity to target IFN for the treatment of SLE patients.

B cells play a pivotal role in both SLE and atherosclerosis. Antibodies reacting to many different self-antigens are the hallmark of SLE and, to date, more than 180 autoantibodies have been described in lupus patients<sup>76</sup>.

Given the atherogenic properties of oxLDL, antibodies directed against oxLDL seem to be a good biomarker of atherosclerotic burden and predictors of CVD; however, data on the protective or detrimental role of anti-oxLDL are still controversial<sup>77</sup>. Oxidized, but not native, LDL may also form stable complexes with  $\beta$ 2 glycoprotein I ( $\beta$ 2GPI) which acts as an autoantigen; antibodies directed against the oxLDL/ $\beta$ 2GPI complex have been detected in patients with SLE and/or antiphospholipid syndrome (APS) and have shown a good correlation with atherothrombosis/atherosclerosis<sup>78-80</sup>. Therefore, IgG anti-oxLDL/ $\beta$ 2GPI could be a good marker of atherothrombotic risk. Evidence of the pro-atherogenic property of anti- $\beta$ 2GPI can be found outside the setting of APS and SLE. Many years ago, Meroni et al. had the opportunity to describe a rare population of 172 young females (<45) who survived myocardial infarction: compared to the age-matched controls, these patients showed a higher prevalence of anti- $\beta$ 2GPI with a significant association between myocardial infarction and IgG/IgM anti- $\beta$ 2GPI antibodies; the association was further confirmed after adjusting for traditional CV risk factors (i.e. smoking and hypertension, which were associated with myocardial infarction)<sup>81</sup>. Besides the B cell response,  $\beta$ 2GPI can also induce a T cell response. A specific T cell reactivity to  $\beta$ 2GPI was detected in patients with SLE and primary APS (32% and 25%, respectively), correlating with cIMT<sup>82</sup>. In the analysis of two long-term cohort studies, anti- $\beta$ 2GPI emerged as one of the predictive factors associated with CV events; along with cigarette smoking, any aPL positivity, high soluble vascular cell adhesion molecule-1 (sVCAM-1) and high-sensitivity CRP were predictive of CV death in patients with SLE<sup>83-84</sup>. The results of these studies corroborate the role of  $\beta$ 2GPI as an antigenic target in atherosclerosis and suggest considering anti- $\beta$ 2GPI antibodies when stratifying SLE and APS patients for CV risk. It is important to remember that the clinical presentations associated with

anti-phospholipid antibodies include obstetric presentations such as recurrent miscarriage, miscarriage, growth restriction and pre-term delivery, which are associated, as stated previously, with poor maternal CV outcomes<sup>12</sup>. Interestingly, by analyzing 135 women who tested highly positive for anti- $\beta$ 2GPI (108 with APS and 27 aPL carriers without any previous clinical events), Chighizola et al. observed that antibodies directed against domain I of  $\beta$ 2GPI, but not against domains IV and V, were good predictors of pregnancy morbidity, particularly late pregnancy morbidity<sup>85</sup>.

Anti-dsDNA antibodies are SLE-specific autoantibodies that may confer a higher risk of CV events<sup>86</sup>. However, not all studies confirm the association between anti-dsDNA and subclinical atherosclerosis or progression of CVD<sup>87-89</sup>. An interesting subset of autoantibodies is that recognizing ER, which was described few years ago in female patients with SLE. Colasanti et al. detected the presence of ERa, but not anti-ERb in 45% of 86 SLE patients and none of the 90 healthy controls; anti-ERa was also associated with disease activity<sup>90</sup>. Since both ERa and ERb are somehow involved in the cardio-protective effects attributed to sex hormones, it would be interesting to investigate the possible effect of specific antibodies detected in SLE patients on the atherosclerotic process.

Besides autoantibodies, other SLE-related factors could contribute to the atherosclerotic burden. Both disease activity and chronic damage have been variously associated with CV events, as well as with subclinical atherosclerosis. Moreover, the cumulative dose and current dose of glucocorticoids have also been identified as independent predictors of CV events, increased cIMT and atherosclerotic plaque<sup>68</sup>. Glucocorticoids could also account for the onset or worsening of traditional risk factors, even after a short disease duration: in an inception cohort of 260 SLE patients enrolled at the time of diagnosis, the authors observed a significant increase in certain CV risk factors (i.e. obesity and dyslipidemia) after 12 months' follow-up, contrasting with the marked improvement of disease activity<sup>91</sup>. Disease activity and the current glucocorticoid dose reflect the inflammatory load characterizing SLE, which interplay with traditional CV risk factors and contribute to CVD. On the other hand, disease duration and damage accrual, resulting from chronic exposure to disease activity and drugs, may further contribute to vascular damage.

## Conclusions

Atherosclerotic CV disease, once considered a male-specific disease, is the main co-morbidity in patients with autoimmune rheumatic diseases, such as RA and SLE, which mainly affect females. In contrast with the improvement in survival and the better control of dis-

ease activity observed over the past two decades, only a slight decrease in CVD mortality has been observed. Awareness regarding the contribution of both traditional cardiovascular and specific disease-related factors is growing and the topic is attracting the attention of a growing number of researchers.

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## Key messages

- The awareness of the increased cardiovascular risk among females has drawn attention to female-specific CV risk factors: menopause, pregnancy morbidity and systemic autoimmunity.
- The gender-discrepancy is very evident in systemic autoimmune disease showing a female:male ratio ranging from 2-3:1 for rheumatoid arthritis to 9-11:1 for systemic lupus erythematosus and Sjögren syndrome.
- Rheumatoid arthritis and atherosclerosis share many features; the excess cardiovascular morbidity is related to an excess of traditional cardiovascular risk factors, as well as to disease-related factors including positivity for specific autoantibodies (rheumatoid factor, antibodies against citrullinated proteins and antibodies to carbamylated proteins) and disease activity.
- Cardiovascular disease is the main cause of death in patients with systemic lupus erythematosus, especially in younger females; as in rheumatoid arthritis, traditional and disease-related risk factors (interferon-related genes and various autoantibodies, amongst others) contribute to the accelerated atherosclerosis that accounts for the excess cardiovascular morbidity and mortality.
- In contrast with the improvement in survival and the better control of rheumatoid arthritis and systemic lupus erythematosus, the mortality for cardiovascular disease has remained unchanged or has only slightly decreased.

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