



Mechanisms of vascular comorbidity in autoimmune diseases

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Purpose of review

Persuasive statistics support the clinical observation that because of cardiovascular comorbidities patients with inflammatory joint disease die significantly earlier despite anti-inflammatory therapy.

Recent findings

The reason for this earlier death is multifactorial and involves a combination of a complex genetic background, environmental influences, classical cardiovascular risk factors and the impact of anti-inflammatory therapy. We will describe the importance of several new mechanisms, especially the diverse intercellular communication routes including extracellular vesicles and microRNAs that support the development of cardiovascular comorbidities.

Summary

The aim of this review is to give an updated overview about the known risk factors in the development of cardiovascular comorbidities with the latest insights about their mechanism of action. Furthermore, the impact of newly identified risk factors and significance will be discussed.

Keywords

cardiovascular comorbidities, extracellular vesicles, microRNA, psoriatic arthritis, rheumatoid arthritis, systemic lupus erythematosus

INTRODUCTION

Before the appearance of the first disease-modifying drugs (DMARDs), the diagnosis of rheumatoid arthritis inevitably lead to a painful, progressive inflammatory arthropathy with joint erosion, deformation and loss-of-function. Nowadays with aggressive treatment (treat-to-target strategy), low disease activity or even remission have become realistic goals, improving the quality of life of these patients. Despite significant advances in treatment, patients die significantly earlier than the general population because of cardiovascular comorbidities, mostly in connection with accelerated atherosclerosis [1[¶]]. This clinical finding was underpinned by several epidemiological studies, which were followed by a new era of investigations aiming to understand the underlying pathophysiological mechanisms of this phenomenon. Lindhardtsen *et al.* [2] examined the risk of acute myocardial infarction (AMI) in rheumatoid arthritis and stated that the risk of AMI was as high as the risk of AMI in patients with diabetes mellitus. Further results were recently published by Ruscitti *et al.*, presenting the results of a one-year prospective single centre study of patients suffering from rheumatoid arthritis. They quantified the increased risk for cardiovascular events (CVEs) and

showed that the percentage of patients suffering a CVE and/or displaying subclinical atherosclerosis doubled within 12 months [3]. Another epidemiological study from Spain measured comorbidities in rheumatoid arthritis patients with a mean disease duration of 10 years and demonstrated a 51% prevalence of a Framingham Risk Score over 20%, resulting in a frequency of 5 and 1% of AMI and stroke, respectively [4[¶]].

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KEY POINTS

- Despite significant improvements in the treatment of autoimmune diseases, patients die earlier than the general population, mainly because of cardiovascular comorbidities.
- Important new data are available about the complex interactions of genetic and environmental risk factors.
- Emerging data support the role of extracellular vesicles and microRNAs in the development of cardiovascular comorbidities.

With a mean follow-up of 5.8 years in an international cohort, diverse risk factors and CVD outcomes were collected from 5638 patients with rheumatoid arthritis and found that a total of 70% of CVD events were attributable to classical cardiovascular risk factors, Disease Activity Score and seropositivity combined. This demonstrates how important it is to closely monitor disease activity and cardiovascular risk factors in rheumatoid arthritis patients, but it also shows the need for defining the 'missing' 30% responsible for cardiovascular comorbidities [5].

The present review aims to summarize current knowledge about the contributing factors for cardiovascular comorbidities, from the genetic background and known cardiovascular risk factors through to the newest research results, highlighting particularly those related to extracellular vesicles, microRNAs (miRNAs) and their synergy, resulting in the higher morbidity and mortality rates in these patients.

GENETIC BACKGROUND OF CARDIOVASCULAR COMPLICATIONS IN AUTOIMMUNE JOINT DISEASE

The investigation of the genetic background of complex diseases is challenging. The search for genetic components for comorbidities of these autoimmune disorders (which are also of multifactorial origin) is even more challenging. The genetic basis of autoimmune joint disease is confirmed by classical genetic studies, for example twin and family studies [6]. A twin study conducted in 2000, which included over 13 000 twin pairs from Finland and the United Kingdom, estimated a contribution of genetic factors of around 60% [7].

A large number of candidate gene studies investigated the most different genes and their single nucleotide polymorphisms (SNP) in the development of cardiovascular comorbidities in patients with rheumatoid arthritis [8–10]. Starting points of candidate gene association studies are the physiology

and pathophysiology of genes encoding for proteins with known function and their involvement in the development of a given phenotype. Thus, genetic loci are selected upon their potential biological function. There is a recent excellent summary of the results of these studies [1[¶]] showing that in addition to the well known HLA-DRB1* 01/04 shared epitope, several other genetic variants located inside and outside of the HLA region on the sixth chromosome may be of influence on the risk of cardiovascular disease (CVD) in rheumatoid arthritis. In addition, most variants outside the HLA region with a positive correlation to the elevated cardiovascular risk among rheumatoid arthritis patients on the basis of this review, are connected to genes encoding for proteins of cells and molecules of the immune system, including the tumor necrosis factor (TNF) superfamily genes, cytokines and related genes, chemokines, or adipokines [1[¶]]. Furthermore, correlations have also been found with variants of genes involved in nitric oxide synthesis [11] and vitamin D levels [12]. Finally, there are some additional exciting potential associations with other, seemingly unrelated genes, such as *MTHFR*, important in the homocysteine plasma level homeostasis [13].

Ten genes (*CRP*, *HNF1A*, *LEPR*, *GCKR*, *NLRP3*, *IL1F10*, *PPP1R3B*, *ASCL1*, *HNF4A*, and *SALL1*) known to have an impact on the serum level of CRP in nonrheumatic Caucasians were genotyped in rheumatoid arthritis patients. It was assessed whether they were of influence on the development of CVEs and subclinical atherosclerosis in this special clinical subgroup. Interestingly, no association could be shown between these genes and CVEs in rheumatoid arthritis [14].

CLASSICAL RISK FACTORS OF CARDIOVASCULAR DISEASES ARE MORE COMMON AMONG PATIENTS WITH AUTOIMMUNE DISORDERS

Smoking

Smoking is a well known risk factor of both autoimmune diseases and accelerated atherosclerosis. In autoimmune diseases, smoking was shown to modulate the immune system in various ways, namely the induction of the inflammatory response, alteration of cytokine balance, induction of apoptosis, and DNA damage resulting in the formation of anti-DNA antibodies [15]. There are a variety of studies that have addressed this area [16–18]. The harmful effect of smoking has been described in early atherogenesis especially on endothelial cells [19]. Effects are mediated through low NO bioavailability, followed by increased adhesion molecule expression and

subsequent endothelial dysfunction. A procoagulant and inflammatory milieu is generated by the increased adherence of platelets and macrophages. Macrophages migrate under the endothelial cells, take up oxidized lipoproteins and transform into foam cells.

Several studies reported interactions between smoking and different factors that are predictive of the cardiovascular outcome [rheumatoid factor; anti-citrullinated protein antibodies (ACPA) positivity, rheumatoid nodules, anti-TNF treatment, rheumatoid cachexia] [20]. This complicates the estimation of the extent of contribution of smoking to cardiovascular risk in patients with rheumatoid arthritis. Importantly, not only smoking, but also second-hand (passive) smoking has an impact on disease activity in women with rheumatoid arthritis [21^{*}].

Insulin resistance

Despite the updated recommendations from European League Against Rheumatism (EULAR) for the management of cardiovascular risk factors in patients with inflammatory arthritis, type 2 diabetes (T2D) is still underdiagnosed and undertreated. Ruscitti *et al.* [22] claim the poor clinical response for this as the main risk factor. A recent cross-sectional study demonstrated that the prevalence of both T2D and impaired fasting glucose (IFG) was higher in patients with rheumatoid arthritis compared with age-matched and sex-matched controls [23]. Furthermore, they were associated with both rheumatoid arthritis-specific features and traditional cardiovascular risk factors [23].

Dyslipidaemia

Adverse changes in the lipid profile are one of the main risk factors of cardiovascular morbidity and mortality. However, it is not evident to which level targeting the different lipoprotein subpopulations reduces the risk of CVDs. In a recently published prospective study based on data from over 50 000 patients with hypertension, dyslipidaemia or diabetes mellitus, an association was found between high-density lipoprotein (HDL)-cholesterol, total/HDL-cholesterol and triglyceride/HDL-cholesterol ratios, and a higher risk for CVD, in contrast to other common lipid profile biomarkers [24]. Recent observations show that small dense low-density lipoprotein (LDL) particles (sdLDL) are elevated not only in diverse metabolic disorders, but also in rheumatoid arthritis and psoriatic arthritis (PsA) [25]. This lipoprotein subgroup is especially important as it seems to be particularly atherogenic, and seems to be a good predictor of significant

coronary artery stenosis. This is because of its high susceptibility to oxidation, high endothelial permeability, and decreased LDL receptor affinity [26].

Sudden cardiac death is twice as common among rheumatoid arthritis patients as in the general population. Regarding this, the importance of close lipid management is highlighted by the recent results of Turk *et al.* [27], showing a close relationship between prolonged QRS time and elevated total cholesterol.

Arterial hypertension

A study of cross-sectional design with multistage sampling, involving 2455 Chinese hypertensive patients, clearly demonstrated the importance of patient compliance. The percentage of non-compliant patients and the rate of suboptimal blood pressure control were both above 45%. In addition, multimorbidity was also more frequent in these patients, accentuating the importance of more clinical attention to this subgroup of patients [28^{**}].

Among classical cardiovascular risk factors, hypertension has the highest incidence and prevalence both in rheumatoid arthritis (74 cases per 1000 patient-years; 18.6% of patients) and psoriatic arthritis (79.8 cases per 1000 patient-years; 19.9% of patients) [29]. Not only blood pressure itself but arterial inflammation is more prevalent in patients with rheumatoid arthritis and is independently associated with both traditional cardiovascular risk factors and rheumatoid arthritis-disease characteristics [30^{**}].

Another important aspect of close cardiovascular risk management is demonstrated in a recent analysis of retrobulbar blood flow and choroidal thickness of rheumatoid arthritis patients, which showed a significantly higher peak systolic velocity of the ophthalmic and central retinal artery in rheumatoid arthritis patients compared with healthy controls [31].

Physical activity

Carlsson *et al.* stimulated peripheral blood mononuclear cells from children with high versus average physical activity. The authors found that high physical activity was associated with lower immune reactivity toward autoantigens GAD65, HSP60, and IA-2 and also with lower spontaneous pro-inflammatory immune activity [32^{*}].

However, physical activity in juvenile idiopathic arthritis (JIA) patients can be a double-edged sword as at times of acute flare, exercise may be very painful for these patients. Also, physical activity may exacerbate underlying inflammatory

processes. Through exercise, the secretion of various hormones, miRNAs, and peptides are influenced and it seems that muscle cell-derived IL-6 has a central role in the fine balancing of anti-inflammatory and pro-inflammatory cytokines [33].

Hyperhomocysteinaemia

Taking into consideration that the risk for cardiovascular comorbidities is still underestimated in patients with rheumatoid arthritis, it is thought-provoking that in the *Journal of Rheumatology* in 1998, attention had already been drawn to the importance of folic acid supplementation to prevent folate deficiency and hyperhomocysteinaemia and, if necessary, to prevent Methotrexate (MTX) toxicity [34]. Essouma and Noubiap [35] emphasized the importance of the bidirectional link between immunoinflammatory activation and hyperhomocysteinaemia. Hyperhomocysteinaemia may lead to nuclear kappa B enhancement and vice versa, chronic immune activation causes hyperhomocysteinaemia through vitamin B (including folic acid) depletion. The authors also underline the importance of folic acid supplementation in preventing cardiovascular complications in rheumatoid arthritis [35]. In cutaneous lupus erythematosus, the level of homocysteine is correlated with disease severity [36]. The C677T polymorphism in the *MTHFR* gene, important in the re-methylation of homocysteine, varies depending on geography and ethnicity [37].

Vitamin D level

The CIMESTRA trial has recently shown the importance of optimal vitamin D serum levels in patients with rheumatoid arthritis. The study found that low baseline vitamin D metabolite levels associate with long-term CVEs in patients suffering from rheumatoid arthritis [38^{*}]. Neuropathic pain is often a therapeutic challenge in chronic inflammatory diseases. In a recent cross-sectional study, patients suffering from rheumatoid arthritis filled out the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire and their serum vitamin D levels were measured. An association was shown between low-serum vitamin D levels and increased neuropathic pain, which underlines again the importance of optimal vitamin D serum levels [39].

Obstructive sleeping apnoea

A current population-based study showed that obstructive sleep apnoea has a higher incidence in

patients with rheumatoid arthritis as compared with age-matched and sex-matched controls. Considering the importance of obstructive sleep apnoea in predicting the future CVD risk, it may be important to screen patients for obstructive sleep apnoea [40^{*}].

Diet

The higher risk of cardiovascular comorbidities among patients with inflammatory joint disease consuming higher amounts of sodium is not the only consequence: sodium has an impact on the Th17 pathway activation and it can, thus, promote autoimmunity. A recent study shows an increased sodium excretion in patients with early rheumatoid arthritis [41]. Not only in-vitro evidence shows an anti-inflammatory effect of *trans*-resveratrol, the major cardioprotective component of red wine, but in preclinical models of osteoarthritis and rheumatoid arthritis. A joint protective effect through decreased production of pro-inflammatory and pro-degenerative soluble factors of *trans*-resveratrol was shown [42]. Fish consumption seems to be protective not only in decreasing the CVD risk through, for example, lowering triglycerides and increasing HDL serum levels [43], but has also been shown to impact on rheumatoid arthritis, associated with lower disease activity [44].

INFLAMMATION

Neutrophil to lymphocyte ratio is not only a reliable marker for inflammation in neoplastic and cardiovascular disorders, but a recent study shows its reliability also for disease activity in rheumatoid arthritis [45]. Low disease activity, defined by a disease activity score (DAS, 28) lower than 3.2 results in a reduced risk in cardiovascular complication in patients suffering from rheumatoid arthritis [46^{*}]. The magnitude and period of time of elevated CRP serum levels correlates with an increased risk of cardiovascular complications in rheumatoid arthritis [47]. Myocardial infarction is one of the main complications of accelerated atherosclerosis in rheumatoid arthritis patients and CRP serum level is also associated with AMI [48]. Thus, Meissner *et al.* declare that it is seemingly irrelevant which DMARD is administered but the goal must be the quickest effective disease control.

Symmetric dimethylarginine (SDMA) and asymmetric dimethylarginine (ADMA) emerge as novel biomarkers of CVDs. Their levels are also abnormal in patients with rheumatoid arthritis. Dimitroulas *et al.* [49] analyzed their presence in

rheumatoid arthritis patients and the results revealed that these molecules may promote endothelial injury in rheumatoid arthritis patients as a result of systemic inflammation during active disease periods.

DOES TREATMENT INFLUENCE CARDIOVASCULAR RISK?

Treatment of inflammatory joint disease should aim to reduce the cardiovascular risk accompanied with the disease, which is best achieved with a treat-to-target approach [50]. This is underpinned by a time-dependent Cox regression analysis of the Nijmegen early rheumatoid arthritis inception cohort, which showed that low disease activity was significantly associated with reduced risk of first CVE [46[¶]]. The effect of glucocorticosteroids on the cardiovascular risk is still questionable. On the one hand, glucocorticosteroid-induced hypertension, insulin resistance, and metabolic effects (especially insulin resistance and obesity) increase the cardiovascular risk, but on the other hand, attenuating inflammation is beneficial [51,52]. Nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk of CVD in the general population; diclofenac has a similar cardiovascular risk to rofecoxib [53]. The cardiovascular safety profile of COX2 selective and nonselective NSAIDs in rheumatoid arthritis and osteoarthritis was recently published; celecoxib was found to be noninferior to naproxen or ibuprofen in this study [54]. NSAIDs, especially COX2 inhibitors, increase the cardiovascular risk in rheumatoid arthritis [51].

Probably because of a blood pressure lowering and anti-inflammatory effect, methotrexate therapy seems to decrease the cardiovascular risk in rheumatoid arthritis [55].

Although TNF inhibitors frequently increase the total cholesterol, triglyceride, HDL and LDL cholesterol levels, accumulating evidence suggest the beneficial effect of these biologicals on cardiovascular risk [51]. Interestingly, whenever compared with TNF inhibitors, tocilizumab is associated with an even higher increase in blood cholesterol and triglyceride levels [56]. A recently published multidatabase cohort study suggests that the cardiovascular risk of rheumatoid arthritis patients treated with tofacitinib versus TNF inhibitors is similar [57]. These observations suggest that glucocorticosteroids and NSAIDs should be tapered as soon as possible. Appropriate combinations of synthetic and biological DMARDs, in addition to optimizing lipid levels and hypertension, may provide the best cardiovascular outcome in rheumatoid arthritis.

NEW PARTICIPANTS IN THE COMPLEX BACKGROUND OF CARDIOVASCULAR COMORBIDITIES IN AUTOIMMUNE DISEASES: EXTRACELLULAR VESICLES

In addition to cytokines and chemokines, extracellular vesicles are new mediators of intercellular communication [58]. Extracellular vesicles are highly diverse, heterogeneous, membrane-surrounded, subcellular structures that can be found in all body fluids. Currently, there is no molecular marker or marker panel that precisely discriminates extracellular vesicle subpopulations; based on their size, extracellular vesicles can be classified as small extracellular vesicles/exosomes (30–150 nm), intermediate sized extracellular vesicles/microvesicles/microparticles (100–1000 nm) and large extracellular vesicles such as apoptotic bodies (1–5 μ m). Extracellular vesicles may target both neighbouring or remote cells, and by transferring DNA, RNA or proteins, extracellular vesicles may regulate multiple functions of target cells [58,59].

Extracellular vesicles are secreted by all human cells; blood-derived extracellular vesicles mainly originate from platelets, red blood cells, monocytes, lymphocytes, granulocytes, and endothelial cells. In addition to their broad physiological functions, extracellular vesicles play a central role in the pathogenesis of several diseases including cardiovascular and immunological conditions [60,61]. Although the lack of standardized isolation and characterization methods still hampers the widespread use of extracellular vesicles as diagnostic and prognostic biomarkers, a characteristic extracellular vesicle profile has been described in autoimmune diseases [60,62]. Increased levels of both phosphatidylserine-positive and phosphatidylserine-negative microvesicles, without association with the disease activity, was recently described in SLE [63].

Numerous observations support the multifaceted role of extracellular vesicles in CVD as well [64[¶]]. Extracellular vesicles have been claimed to promote plaque stability [65]. Small extracellular vesicles containing insulin-like growth factor 1 receptor (IGF-1R) and miR-29a have been found to have a cardioprotective effect in rats [66]. On the other hand, mainly platelet-derived human microvesicles are thrombogenic [67]. Elevated levels of endothelial cell-derived and platelet-derived extracellular vesicles were observed in acute coronary syndrome [68]. Interestingly, according to recently published observations, although smoking promoted both extracellular vesicle release by leukocytes, platelets and endothelial cells, and vascular inflammation, these effects were prevented by red wine [69]. Extracellular vesicles may also significantly modulate the effect of cytokines [70].

A highly unexpected observation was recently found by Sodar *et al.* [71], namely that LDL mimics

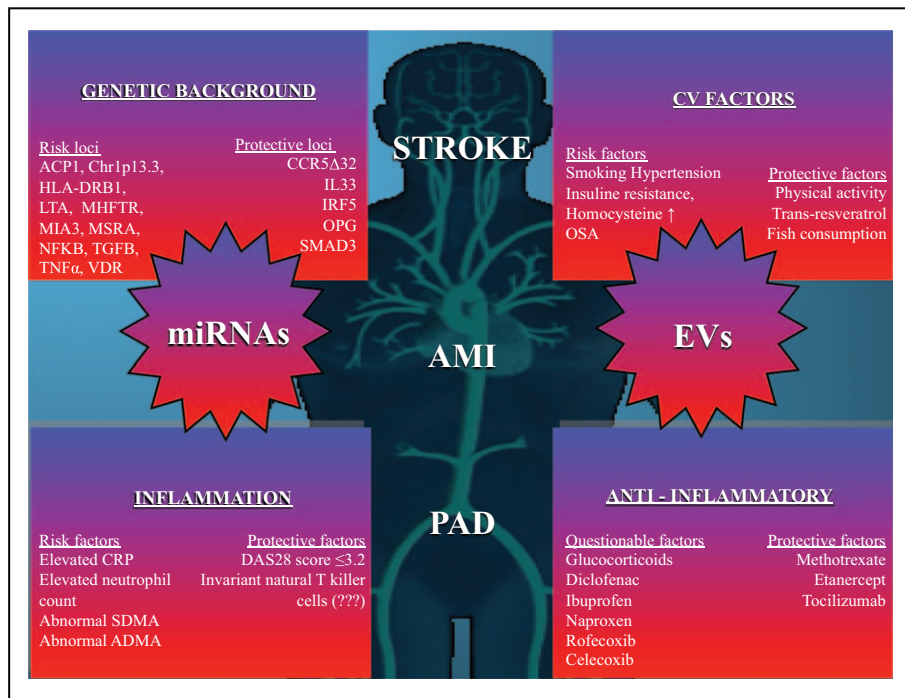


FIGURE 1. The figure demonstrates the known factors to our best current knowledge being of influence on the development of cardiovascular comorbidities such as stroke, acute myocardial infarction or peripheral arterial disease. PAD, peripheral arterial disease.

extracellular vesicles derived from blood plasma and may be copurified, which underlines their potential role whenever examining factors contributing to the development of CVD in rheumatic conditions/disorders.

Although there is little direct evidence, these data strongly support the potential role of extracellular vesicles in vascular comorbidity of autoimmune diseases. Extracellular vesicles may provide a link between inflammation and thromboembolic risk (Fig. 1).

ANOTHER NEW PARTICIPANT: MICRORNAS

Estimates show that as high as 10–30% of protein coding genes are regulated by micro-RNAs [72], which are small regulator RNA molecules composed of 21–24 nucleotides. Salmena *et al.* [73] introduced the term ‘competing endogenous RNAs,’ describing the complex communication system between the different subtypes of RNA molecules. During CD4 T-cell activation, posttranscriptional uridylation by the enzymes TUT4 and TUT7 are responsible for the fine tuning of miRNA levels [74]. MiRNAs are relatively stable molecules and their measurement is reliably reproducible [75]. It also now known that the most diverse illnesses are all characterized by specific changes in the miRNA profile, which makes them a very promising tool for diagnostic purposes [76,77].

Serum miR-210 and miR-155 levels could be shown to be reliable biomarkers for the diagnosis of rheumatoid arthritis [78]. There have been studies looking for miRNA biomarkers for subclinical atherosclerosis in rheumatoid arthritis, but until now only little or no association was found, whenever assessing miR-15a-5p, miR-24-3p, miR-26a-5p, miR-125a-5p, miR-146a-5p, miR-155-5p, and miR-223-3p [79].

An interesting link between different risk factors was found in a study measuring vitamin D levels in SLE patients and correlating them with certain miRNA levels in patients’ T cells. An association between vitamin D concentrations and measured miRNA levels (miRNA-377, miRNA-342, miRNA-10a, miRNA-374b, miRNA-125a, and miRNA-410) was observed – not only comparing SLE patients with healthy controls, but also between patients differing in their vitamin D serum levels and also in cultured T cells from SLE patients, wherever the correlation was dose-dependent and time-dependent [80].

COOPERATION OF DIFFERENT MESSENGERS? EXTRACELLULAR VESICLES TRANSPORT IMPORTANT MICRORNAS

In atherosclerosis, Nguyen *et al.* [81] have demonstrated that extracellular vesicles originating from

Table 1. List of risk factors influencing the development of cardiovascular comorbidities in inflammatory joint diseases

Factors	Effect	References
Genetic background		
ACPI – *C haplotype	Risk factor	Teruel <i>et al.</i> [84]
CCR5Δ32	Protective factor	Rodríguez-Rodríguez <i>et al.</i> [85]
Chr1p13.3 – rs599839 – G allele	Risk factor	López-Mejías <i>et al.</i> [86]
HLA-DRB1*01*04	Risk factor	Mattey <i>et al.</i> [87]
IL33 – rs3939286 – T allele	Protective factor	López-Mejías <i>et al.</i> [88]
IRF5 – GTG haplotype	Protective factor	García-Bermúdez <i>et al.</i> [89]
LTA – 252GG	Risk factor	Panoulas <i>et al.</i> [90]
MHFR – rs1801131 – C allele	Risk factor	Abd El-Aziz <i>et al.</i> [91]
MIA3 – rs17465637 – A allele	Risk factor	García-Bermúdez <i>et al.</i> [92]
MSRA – rs10903323 – G allele	Risk factor	García-Bermúdez <i>et al.</i> [93]
NFKB – rs28362491 – -94ATTG ins/del	Risk factor	López-Mejías <i>et al.</i> [94]
OPG – CGA haplotype	Protective factor	Genre <i>et al.</i> [95]
SMAD3 – rs17228212 – C allele	Protective factor	García-Bermúdez <i>et al.</i> [96]
TGFB – rs1800470TC	Risk factor	Chen <i>et al.</i> [97]
TNFα – rs1800629 – A allele	Risk factor	Rodríguez-Rodríguez <i>et al.</i> [8]
VDR – GATG haplotype	Risk factor	López-Mejías <i>et al.</i> [12]
ZC3HC1 – rs11556924 – TT genotype	Risk factor	Lopez-Mejias <i>et al.</i> [98]
Classical cardiovascular risk factors		
Smoking	Risk factor	Murphy <i>et al.</i> [20]
Insulin resistance	Risk factor	Ruscitti <i>et al.</i> [22]
Dyslipidaemia	Risk factor	Gerber <i>et al.</i> [25]
Arterial hypertension	Risk factor	Radner <i>et al.</i> [29], Geraldino-Pardilla <i>et al.</i> [30 [■]]
Physical activity	Protecting factor	Carlsson <i>et al.</i> [32 [■]], Antunes <i>et al.</i> [33]
Hyperhomocysteinaemia	Risk factor	Morgan <i>et al.</i> [34], Essouma and Noubiap [35]
Low baseline vitamin D level	Risk factor	Herly <i>et al.</i> [38 [■]]
Obstructive sleeping apnoe	Risk factor	Wilton <i>et al.</i> [40 [■]]
Sodium intake	Risk factor	Marouen <i>et al.</i> [41]
Trans-resveratrol	Protective factor	Nguyen <i>et al.</i> [42]
Fish consumption	Protective factor	Alhassan <i>et al.</i> [43], Tedeschi <i>et al.</i> [44]
Therapy		
Corticosteroids	Complex effect	Roubille <i>et al.</i> [51], van Sijl <i>et al.</i> [52]
NSAIDs		
Celecoxib	Complex effect	Nissen <i>et al.</i> [54]
Naproxen	Complex effect	Nissen <i>et al.</i> [5]
Ibuprofen	Complex effect	Nissen <i>et al.</i> [54]
Methotrexate	Protective factor	Mangoni <i>et al.</i> [55]
TNF inhibitors	Protective factor	Roubille <i>et al.</i> [51]
Tocilizumab	Complex effect	Gabay <i>et al.</i> [56], Kim <i>et al.</i> [57]
New modalities		
Extracellular vesicles	Complex effect	No publication yet
miRNAs	Complex effect	No publication yet

atherogenic macrophages transfer certain miRNAs (in particular miR-146a). The important role of miRNA-126-3p and miRNA-126-5p, transferred by

extracellular vesicles originating from endothelial cells after AMI, was also demonstrated by Akbar *et al.* [82] and showed that these messengers promote the

recruitment of transcriptionally activated splenic monocytes to the heart.

Systematic characterization of microvesicles and exosomes derived from T lymphocytes of healthy and SLE patients revealed that, depending on stimuli, extracellular vesicles carry a specific RNA profile and a deregulation of miR-155*, miR-34b, and miR-34a could be shown. This again underlines the importance of intercellular communication via extracellular vesicles and miRNAs in autoimmune diseases [83**].

CONCLUSION

Cardiovascular comorbidities of autoimmune diseases are the result of different contributing factors and their synergistic effects

The present review contains numerous studies investigating multiple independent risk factors of cardiovascular comorbidities in autoimmune diseases, focusing on conditions involving the joints. We wish to underline the complex interactions and the importance of their total effect on the phenotype discussed in this review ([84–98]; Table 1). Our suggestion is to focus on new mechanisms emerging, especially the common intercellular communication system of extracellular vesicles and miRNAs as no study yet considers these factors together in the development of cardiovascular comorbidities in patients with inflammatory joint disease.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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