

Atherosclerosis and Rheumatic Diseases

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Abstract

Until recently, patients with chronic autoimmune diseases were dying at a young age from their disease. However, with the emergence of biologic drugs and disease-targeted therapies, longevity in this patient population has increased. In addition, physicians have become more aware of the long-term sequelae of chronic inflammation focusing mainly on the development of premature atherosclerosis. In this review we will systematically analyze the most relevant published papers for the PubMed Central database and other validated-internet sources that have relevance to the role that atherosclerosis plays in several autoimmune diseases including Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA) and Ankylosing Spondylitis (AS). We also examined the effects of disease modifying agents on the development of atherosclerosis in patients with autoimmune diseases as well as identifying strategies or interventions which can prevent or retard the development of cardiovascular disease in these patients.

Keywords: Atherosclerosis; Rheumatic diseases; Autoimmune diseases

Introduction

The role of inflammation in the pathophysiology of atherosclerosis

It is now widely recognized and established that atherosclerosis is a chronic inflammatory disorder which involves innate and adaptive immune responses with the caveat that we don't yet know precisely what factors trigger the initiation of an immune response within the intima of the blood vessels which contributes to the progression to atherosclerosis.

Most studies on vascular inflammation in atherosclerosis have focused on inflammation in atherosclerotic lesions and elsewhere in the intima, however the Feiring Heart Biopsy Study (FHBS) revealed a surprisingly high occurrence of fibrosis and inflammatory cell infiltrates (mainly lymphocytes) in the outer vascular and perivascular layers of the aorta of patients with coronary artery disease. Inflammatory cell infiltrates in the adventitia and media were more frequent and extensive in patients with autoimmune rheumatic diseases than in patients without autoimmune rheumatic diseases. Thus, inflammation in the outer vascular layers might be a common phenomenon in autoimmune rheumatic diseases and contribute to the increased cardiovascular risk [1].

In the general population the development of atherosclerosis arises from endothelial injury. This results in endothelial dysfunction which permits invasion of sub-endothelial regions by inflammatory cells with subsequent lipid deposition and narrowing of the arterial lumen which following plaque rupture results in thrombosis formation [2,3]. The deposition of low density cholesterol [(LDL-cholesterol)] in the intimal layer of blood vessels is facilitated by proteoglycans which are

components of the blood vessels extracellular matrix that bind LDL particles. Thus, within the intima LDL particles are "attacked" by oxygen radicals and oxidizing enzymes resulting in chemical modifications of the LDL protein as well as lipids. This event can lead to endothelium activation and the secretion of chemokines such as Monocyte Chemoattractant Protein-1 (MCP-1), Regulated Upon Activation Normal T Cell Expressed Secreted (RANTES), fractalkine and others chemokines/chemokine receptor network such as CXCL1, CCL2, MIF (macrophage migration inhibitory factor), CXCL16, and CX3CL1 and of their receptors CXCR2, CCR2, CXCR2 and CXCR4, CXCR6, and CX3CR which result in the increased expression of the Vascular Cell-Adhesion Molecule-1 (VCAM-1) [4], inter-cellular adhesion molecule and E-selectin. As such these adhesion proteins recruit inflammatory cells, including T lymphocytes, Dendritic Cells (DCs) and monocytes to sites of endothelial injury [5]. Under these conditions, intimal monocytes are stimulated by Monocyte-Colony Stimulating Factor (M-CSF) and cause monocytes to differentiate into macrophages which express a class of cellular Pattern-Recognition Receptors (PRRs) called scavenger receptors that phagocytize oxidized LDL. Cholesterol molecules contained in these LDL particles accumulate in the macrophage cytoplasm and form large droplets which transform the macrophage into a foam cell; the prototypic cell of the atherosclerotic lesion [4].

Although some of the macrophages turn into foam cells, others promote arterial inflammation through signals generated by PRRs, as well as other pro-inflammatory cytokines [6]. Toll-Like Receptors (TLRs) are abundantly found in these lesions which can bind Pathogen-Associated Molecular Patterns (PAMPs), such as endotoxins, endogenous molecules, such as Heat-Shock Proteins (HSPs) and oxidized LDL (ox-LDL), all of which have been implicated in atherosclerosis [6]. In a manner similar to TLRs, Tumor Necrosis Factor- α (TNF- α), produced by neighboring immune cells, and Interleukin-1 (IL-1), produced by vascular and immune cells, trigger signal transduction that can lead to the production of cytokines,

chemokines, proteases and vasoactive agents [6]. Of note, genetic epidemiologic analyses have identified associations between polymorphisms in the genes encoding TNF-Like Receptor-4 (TLR4), TNF- α and IL-1 and the increased risk of developing atherothrombotic diseases, including stroke and Myocardial Infarction (MI) [7,8]. As discussed above T-lymphocytes are also recruited into the injured endothelium. The most prevalent T-lymphocyte type in the vascular lesion is CD4⁺-Th1 cell which are activated by specific antigens such as ox-LDL, Heat Shock Protein-60 (Hsp-60) and microbial antigens. Th1 effector responses to antigenic stimulation include secretion of Interferon- γ (IFN- γ), which leads to the activation of macrophages and endothelial cells [3]. Epidemiological studies have also identified 2 additional genes which control T-cell activation, including the TNF superfamily member, OX40L, and the MHC II transactivator, MHC2TA (MHC II Transactivator) or CIITA (Class II Transactivator), as important risk factors for developing myocardial infarct.

In addition to CD4⁺ Th1 cells, other T-cell subtypes are recruited, which include Natural Killer (NK) T cells which have been found to accelerate early disease [9] and CD8c T cells that can aggravate atherosclerotic disease when triggered by vascular antigens [10]. Conversely, Regulatory T (Treg) cells inhibit atherosclerosis by producing the anti-inflammatory cytokines IL-10 and TGF- β [11,12].

Systemic reactivity also occurs besides the activity of local immune responses within the atherosclerotic plaque. These include increased levels of several acute phase reactants such as C-Reactive Protein (CRP), Serum Amyloid A (SAA), fibrinogen, pentraxin-3 and others [4]. However, it is now well-established that a modest elevation in CRP levels is an independent risk factor for coronary artery disease [13].

Of note microbial antigens such as components of Chlamydia pneumoniae and Cytomegalovirus (CMV) might also be important, in accelerating the atherosclerotic process by increasing plaque inflammation [4].

The precocious atheromatous plaque grows silently for months or years without producing any clinical symptoms. However the chronic production of inflammatory cytokines and proteases during this time may lead to thinning of the plaque wall and eventual plaque rupture, which results in exposure of the blood to phospholipids, tissue factor and platelet-adhesive matrix molecules, eventually promoting thrombosis and acute cardiovascular disease [14].

There are additional contributing factors that result in perpetuating the vicious cycle of atherosclerotic changes the most prominent of which is the lack of repair of damaged endothelium. This leads to deleterious effects on vascular health, including the loss of nitric oxide, generation of phosphatidyl serine-rich microparticles with significant tissue factor activity, and potential predisposition to acute coronary events [11,15]. It was previously proposed that vasculature repair is primarily driven by bone marrow-derived Endothelial Progenitor Cells (EPCs) and Myelomonocytic Circulating Angiogenic Cells (CACs) [16]. Reactive oxygen species, telomere shortening as a biomarker of senescence, and cytokines such as TNF have been implicated in EPC/CAC dysfunction [17]. Indeed, decreased numbers of or dysfunction in these cell types may contribute to cardiovascular disease as EPC numbers inversely correlate with cardiovascular disease risk, time to first cardiovascular disease event, and in-stent restenosis risk [18].

Finally there are emerging roles for other cytokines in atherosclerosis but more studies are needed. Particular emphasis could

be on the role of IL-37 which is anti-inflammatory cytokine of the IL-1 ligand family. IL-37 is normally expressed at low levels in Peripheral Blood Mononuclear Cells (PBMC), mainly in monocytes, and DCs, but this cytokine is rapidly up-regulated in the context of inflammation, and IL-37 inversely inhibits the production of inflammatory cytokines in PBMC and DC. Thus, IL-37 may play a protective role in atherosclerosis by inhibiting the production of inflammatory cytokines and by suppressing macrophage and DC activation [19], IL-17A is another cytokine which is also involved in the pathology of several autoimmune diseases such as RA and PsA. In that regard, IL-17 was shown to regulate chemokine expression and leukocyte migration to a site of inflammation. There is also increasing evidence indicating an association between elevated levels of IL-17A and cardiovascular diseases, although the precise role of IL-17A⁺ cells in atherosclerosis is controversial [20].

It is also noteworthy to mention that HMGB1 (High Mobility Group Box 1) has been implicated in the pathogenesis of inflammatory vascular diseases including systemic vasculitis and atherosclerotic disease. Its levels are significantly increased in patients with subclinical CAD and in those who develop acute ischemic events in cardiac and cerebral vascular beds. In human atherosclerotic lesions from the aorta, carotid and coronary arteries, the expression of HMGB1 is markedly increased in the nuclei and in the cytoplasm of macrophages and smooth muscle cells localized near the intima, as well as in areas adjacent to the necrotic core of atherosclerotic lesions.

HMGB1 may be released from several cell types in the atherosclerotic plaque including smooth muscle cells, endothelial cells, foam cells, macrophages and activated platelets. Once released, HMGB1 induces a cascade of inflammatory effects on endothelial cells, smooth muscle cells and macrophages. Recombinant HMGB1 has been shown to activate vascular endothelial cells leading to expression and secretion of Intercellular Adhesion Molecule 1 (ICAM-1), Vascular Cell Adhesion Molecule 1 (VCAM-1), E-selectin, Granulocyte Colony Stimulating Factor (G-CSF), RAGE (the Receptor For Advanced Glycation End Products), TNF- α , Monocyte Chemotactic Protein 1 (MCP-1), IL-8, plasminogen activator inhibitor 1, and tissue plasminogen activator. Regarding smooth muscle cells from atherosclerotic plaques, HMGB1 promotes their proliferation, migration to the intimal layer, their release of more HMGB1 as well as C-reactive protein, and their expression of MMP2, MMP3 and MMP9. Experimental studies showed that HMGB1 participates also in tissue remodeling during the late phase after ischemic injury [21].

Atherosclerosis and SLE

SLE is an autoimmune disease that predominantly affects women of childbearing age group. SLE can cause damage to many internal organs with resultant co-morbidities and premature death. The most common cause of death in SLE is cardiovascular disease from atherosclerosis, arteritis, thrombosis, embolization, spasm, and abnormal coronary flow [22,23]. The risk for atherosclerotic disease increases with each year of disease duration [4]. This observation suggested that chronic exposure to dysregulated immune cells promotes cardiovascular disease in SLE [24,25].

One important finding is that the increased cardiovascular risk in SLE is mainly seen in young age patients who have an estimated risk of myocardial infarction between 9- and 50-fold over that in the general population [23,26]. In that regard, SLE patients also have an increased prevalence of sub-clinical atherosclerosis, with up to 40% of SLE patients having evidence of a carotid plaque, nuclear imaging

abnormalities or increased coronary calcification. Thus the Framingham risk factors (i.e. hypertension, hypercholesterolemia, diabetes mellitus, older age, and postmenopausal status) cannot fully account for or explain this increased risk of premature cardiovascular disease among SLE patients, and many factors that are non-traditional risk factors or SLE-related factors may constitute an equal or even greater risk [26]. These factors include but are not limited to renal manifestations of SLE, cytokines and inflammatory mediators, and drug therapy used for SLE.

However, among the Framingham risk factors hypertension, dyslipidemia and hypercholesterolemia have been shown to be more prevalent in SLE [27]. In several studies metabolic syndrome which is considered an independent predictor of cardiovascular morbidity and mortality has been shown to have increased prevalence in SLE [28,29]. As for SLE-related factors, a study conducted by Rho et al, reported that the adhesion molecules VCAM, ICAM, E-selectin, and the cytokine TNF- α are associated with subclinical atherosclerosis in patients with SLE independent of Framingham risk score, while other potentially atherogenic inflammatory mediators-MPO, IL-1 α , MMP-9, VEGF, CRP and SAA were not significantly associated with coronary atherosclerosis after adjustment for Framingham risk score, diabetes and corticosteroid exposure [30].

SLE patients have increased numbers of circulating apoptotic endothelial cells, which correlates with endothelial dysfunction and the production of tissue factor. In addition vascular repair is significantly compromised in lupus patients [31]. This has been demonstrated to be secondary to "IFN (interferon) signature in SLE". In fact patients with SLE have an increased expression of type I IFN-regulated genes because of a continuous production of IFN α that could lead to endothelial dysfunction by promoting a reduction in the number of endothelial progenitor cells, and by significant impairments in the capacity of EPCs/CACs-circulating angiogenic cells to differentiate into mature ECs (endothelial cells) and synthesize adequate levels of the proangiogenic molecules, Vascular Endothelial Growth Factor (VEGF) and Hepatic Growth Factor (HGF) [32,33]. Thus increased IFN α expression in SLE patients contributes to endothelial dysfunction and induce pro-inflammatory responses that promote development of atherosclerosis. However, the precise role of type II IFN (IFN γ) in the development of atherosclerosis in SLE remains to be elucidated.

TNF- α has differential and pleiotypic effects on monocytes, B cells, T cells, and on dendritic cells with elevated levels of TNF α found in SLE patients [34]. In addition, TNF α was found in SLE to be associated with high triglyceride and low HDL levels. Thus due to its immunomodulatory and pro-inflammatory properties TNF- α may be considered a major factor in SLE-related cardiovascular disease, acting by contributing to hypertriglyceridemia and by promoting atherosclerosis-related inflammation [35].

A role for IL-6 in the pathogenesis of SLE-related atherosclerosis is more controversial. Some investigators consider elevated IL-6 levels in SLE to be an epiphenomenon and to be part of the acute phase response [36]. However other studies have reported that IL-6 has a pro-inflammatory role in the development of atherosclerosis in lupus patients [37].

As mentioned previously, IL-17 is a pro-inflammatory cytokine produced by several cell subsets including CD4⁺ T cells, CD8⁺ T cells, NK (natural killers) cells and neutrophils. IL-17 also exerts its biological effects through the recruitment of monocytes and

neutrophils to sites of inflammation by increasing the local production of chemokines and adhesion molecules. In addition IL-17 has been linked to atherosclerotic plaque development in non-lupus-prone models [38]. IL-17 synergizes with other cytokines, in particular with IL-1 β , TNF α , and IFN γ , and recent evidence suggested that IL-17-mediated inflammation might play a role in the pathogenesis of SLE. However, its role in SLE-related atherosclerosis remains to be fully elucidated [3,39].

CD40 ligand (CD40L) also called sCD154) is a member of the TNF family. Through its interaction with CD40 CD40L participates in B cell differentiation and proliferation. CD40L also promotes mononuclear cell recruitment and is believed to be integral part in contributing to thrombosis in atherosclerosis as well as atherosclerotic plaque rupture. It has been found that CD40 and CD40L are over-expressed in T cells and atherosclerotic plaques in SLE patients [39].

The role of Antiphospholipid (APL) antibodies in the development of atherosclerosis in SLE remains unclear and is a matter of debate. However, ischemic events associated with APL are more likely to be caused by pro-thrombotic state than by enhanced atherosclerosis [3].

Of note, genomics and proteomics biomarkers for atherosclerosis and cytokine involvement in SLE have been studied. These biomarkers might be of great importance in determining the high thrombotic risk in SLE patients. Among them, polymorphisms in the region of the TNFAIP3 gene appear to be prominent [34]. TNFAIP3 encodes the deubiquitinating enzyme A20, an endogenous inhibitor of the Nuclear Factor-KappaB (NF κ B) pathway. The latter is activated by TNF or IL-1/TLR signaling pathways, which induces transcription of pro-inflammatory genes. Polymorphisms in TNFAIP3 gene region may cause reduced expression or reduced activity of A20. Therefore A20 could contribute to an already uncontrolled inflammatory response and autoimmunity which potentially accelerates atherosclerosis in these SLE patients [39].

As for treatment related factors, it seems that patients with SLE who received cyclophosphamide had lower aortic atherosclerotic risk compared to SLE patients who did not receive this treatment [40]. Regarding corticosteroids it seems that their role is dual and complex. Corticosteroids have a beneficial effect on reducing inflammation. However, their cumulative dose is associated with weight gain, glucocorticoid-induced diabetes, hypertension, hypertriglyceridemia, which are known to be traditional cardiovascular risk factors [41].

Antimalarials are often employed in the therapy of SLE [42]. In fact antimalarial drugs have several protective effects such as increasing HDL, reducing insulin resistance and inhibiting platelet aggregation, which may improve cardiovascular morbidity [43].

Mycophenolate mofetil inhibits multiple inflammatory mediators and lymphocytes, particularly T cells and macrophages which play major roles in atherogenesis. However, whether this drug has a cardiovascular risk benefit in SLE patients remains unclear and additional research will be needed to address this issue [3].

A role for novel biologic drugs to prevent cardiovascular disease in SLE remains to be determined. Currently, studies targeting type I IFNs, IL-17 and the various anti-B cell therapies are underway in clinical trials in SLE and for other diseases. However, long-term follow-up will be necessary to determine the extent to which these agents are clinically beneficial for preventing atherosclerosis development in these groups [3]. In that regard, a recent study showed that rituximab had a positive effect on traditional cardiovascular risk

factors such as HDL cholesterol, the total cholesterol/HDL ratio and Tissue Factor (TF) levels. The effect of rituximab might be indirectly related to its role in decreasing SLE disease activity as well as reduced inflammation. Therefore, additional studies will be needed to further establish the role of rituximab on the incidence of cardiovascular disease in SLE [44].

As for non-disease modifying agents, it seems that statins have shown a favorable effect on cardiovascular disease development in lupus. Beside their ability to suppress cholesterol synthesis and their pleiotropic effects, statins do have immunomodulatory and anti-inflammatory activity through their capacity to inhibit the production of pro-inflammatory cytokines and soluble mediators, such as TNF- α , IL-1 β , IL-6, IL-8, RANTES, and IL-17, as well as promoting the secretion of Th2 cytokines, including IL-4, IL-5, IL-10 and TGF- β . Statins also appear to suppress IFN-mediated signal transduction pathways such as JAK/STAT [45]. Undoubtedly, more studies will be needed to determine whether and which statin treatment in patients with SLE is associated with decreased cardiovascular disease incidence [46]. Mok et al. [28] reported that treating SLE-prone mice with the peroxisome Proliferator-Activated Receptor- γ (PPAR- γ) agonist, pioglitazone, which is used to treat type II diabetes mellitus in humans, resulted in improved insulin sensitivity, improved endothelial function and restored EPC differentiation. However, how this class of medications would alter the development of cardiovascular disease in SLE patients warrants additional studies.

Regarding risk prediction, Kawai et al. [47] examined the extent to which newer coronary heart disease risk prediction models including the Reynolds Risk Score (RRS), which is of particular interest because it includes a measure of inflammation (i.e. C-reactive protein), and novel risk scores that substitute "coronary age" in place of chronological age would better identify increased risk of cardiovascular disease in women with SLE and in particular in those SLE patients with subclinical coronary atherosclerosis. However, Kawai et al. [47] concluded that the RRS was of limited use in women with SLE. Another model by McMahan et al. [48] aimed to identify lupus patients which were at high risk of current or future carotid plaque, using a combination of traditional risk factors and SLE-related risk factors which consisted of a panel of inflammatory biomarkers (pro-inflammatory HDL, leptin, homocysteine and serum TWEAK). McMahan et al. [48] concluded that the PREDICTS score (the Predictors of Risk for Elevated Flares, Damage Progression, and Increased Cardiovascular Disease in Patients with SLE) can help clinicians in identifying SLE patient that are at higher risk of atherosclerosis. However, the study was limited by the short-term patient follow up and the end point assessed was subclinical atherosclerosis rather than cardiovascular events. The study included SLE patients only in the Los Angeles area suggesting the need for further studies to generalize the PREDICTS score in other SLE cohorts [48]. Thus validating new models which include coronary age to predict the relative risk of cardiovascular events in SLE patients will be valuable [47].

Finally, there are no clinical trials to inform the ideal risk management strategies for cardiovascular disease in SLE patients. Approaches to the screening and management of risk factors are therefore extrapolated from studies in the general population. Whether or not modifying classic risk factors will affect cardiovascular disease outcomes in SLE patients remains an unanswered question. The proposed management of cardiovascular disease in SLE patients aims for an ideal blood pressure of <130/80, an ideal LDL level <100

mg/dl, and an ideal BMI <25 kg/m². Patients are encouraged to use anti-malarial drugs, undergo smoking cessation, and to minimize or even withdraw from steroids, with a goal of stricter control of inflammation [49].

Atherosclerosis in RA

The prevalence of atherosclerosis among RA patients is thought to be higher than general population. It was suggested that cardiovascular disease in RA was 48% higher compared to cardiovascular disease in the general population [50]. The prevalence of atherosclerosis in RA was evaluated in a controlled study by Chung et al using calcium scores, which were higher in patients with established RA compared to the patients with early disease and the control group [51].

In addition, Maradit-Kremers et al. [52] demonstrated in a population-based study that RA patients have a higher relative risk of hospitalization and silent myocardial infarcts prior to the establishment of a diagnosis of RA. This study also showed that RA patients were half as likely as non-RA patients to have a history of angina pectoris, and those RA patients were more than twice as likely to experience sudden death compared to non-RA subjects. Other studies have demonstrated that RA is equivalent to diabetes mellitus II in terms of increased cardiovascular disease [53,54].

The etiology of atherosclerosis in RA is considered multifactorial as was discussed in a recent study by Wu et al. [19]. Although traditional risk factors for cardiovascular disease are highly prevalent among RA patients, there is growing evidence that RA-related risk factors contribute to the increased risk of atherosclerosis in the RA population making RA an independent risk factor for atherosclerosis. It is well established that new risk scores (ACC/AHA 10-year risk score) and standard risk prediction models used in the general population (Framingham risk score) do not adequately identify many RA patients with elevated cardiovascular risk. Thus the need to develop biomarkers CV risk scores in RA patients [55].

Traditional risk factors and CVD risk in RA:

Similar to the findings in the general population, smoking, diabetes mellitus, dyslipidemia, and hypertension are independent risk factors for atherosclerosis in RA. Smoking is considered an independent risk factor for the development of cardiovascular disease in RA patients along with antibody formation, and enhanced active inflammation [56]. However, studies have failed to attribute the increased risk of atherosclerosis to smoking status in RA patients.

Moreover, dyslipidemia in RA has unique characteristics including, increased triglycerides, decreased HDL, and decreased LDL that might enhance cardiovascular disease risk compared to non-RA subjects. AG Semb et al. [57] concluded that total cholesterol and triglyceride levels were significant predictors of myocardial infarction in non-RA subjects whereas the predictive value of these biomarkers in RA patients was inconsistently associated with myocardial infarction. It was also reported in RA patients that there was an increased level of ox-HDL which in turn increased the risk of cardiovascular disease by 2 mechanisms which included the decreased activity of paroxonase which leads to oxidization of LDL as well as promoting LDL oxidization, foam cell formation which results in decreased reverse cholesterol transport.

Other traditional risk factors for atherosclerosis observed in RA patients included insulin resistance, metabolic syndrome, and

hypovitaminosis D. There is growing evidence that inflammation enhances insulin resistance, which was partially explained by the direct effect of TNF- α , expressed in adipose tissue and muscles [58,59], resulting in effects on the insulin receptor by inhibiting autophosphorylation and subsequently by decreasing glucose uptake [60]. Indeed, the prevalence of insulin resistance was higher in RA patients compared with healthy controls and thus insulin resistance was considered as an independent risk factor for cardiovascular disease in RA [61]. However in a most recent study, Giles et al. [62] found that RA patients had a higher levels of insulin resistance compared with controls, but did not detect an association between insulin resistance and higher risk of subclinical atherosclerosis progression in either the coronary or the carotid arteries among a population with increased cardiovascular risk.

Although obesity is usually a main component in metabolic syndrome, Chung et al. [63] concluded that there was a different obesity/metabolic syndrome pattern in RA patients. They found that there was a significantly higher prevalence of metabolic syndrome amongst RA patients when compared to controls but that metabolic syndrome in RA was independent of BMI.

In their cross-sectional cohort study, Haque et al. [64] proposed a possible association between low vitamin D levels and increased cardiovascular disease status in RA patients. They found a high prevalence of low vitamin D levels among RA patients (40%), which was consistent with prior publications. Haque et al. [64] also found that the 25(OH)D level had a significant positive association with HDL, with a significant inverse association with E-selectin and soluble intracellular adhesion molecule-1 (sICAM-1) even after adjusting for possible confounders.

Role of inflammation

There is growing evidence in RA that systemic inflammation, characteristic of RA is a major contributor to increased atherosclerosis and subsequent cardiovascular disease. Thus, the increase in the levels of CRP, TNF- α , IL-6, and IL-17 were found to be directly associated with an increased cardiovascular disease risk. In a meta-analysis performed by Kaptoge et al. [65], CRP was found to have continuous association with ischemic heart disease in the presence of other conventional risk factors and inflammatory markers. In addition, Danesh et al. [13] had also proposed that CRP was a predictor of atherosclerosis. In contrast, Cesari et al. [66] found a non-significant association between CRP and subclinical/clinical cardiovascular disease. However, they and others found an important role for IL-6 and TNF- α in clinical as well as subclinical cardiovascular disease.

To account for a possible role of IL-17 as contributing to cardiovascular disease in RA IL-17 was studied, in RA patients receiving biologic treatment, and the association between IL-17 and endothelial function and arterial compliance. Accordingly IL-17 was shown to be a main predictor of microvascular function and arterial compliance which are 2 measurements of endothelial function [67]. Moreover, Arnod Hot et al. [68] showed using primary human endothelial cells treated with IL-17 alone or in combination with TNF- α , that IL-17 when combined with TNF- α , had pro-coagulant and pro-thrombotic effects on blood vessels.

Serologic factors

The presence of autoantibodies was proposed to be one of the mechanisms contributing to the increased risk of cardiovascular

disease in RA. An association between a positive rheumatoid factor and increased mortality from all causes and cardiovascular disease mortality in the general population (even in the absence of active inflammatory arthritis) was reported by Tomasson et al. [69]. Thus, an excess in mortality among rheumatoid factor positive patients, mostly from cardiovascular disease, was observed [70].

Gerli et al. [71] evaluated the contribution of anti-CCP antibodies to cardiovascular disease in 81 RA patients without overt cardiovascular disease by measuring the carotid intima-media thickness (IMT) and compared the results in these RA patients to sex- and age-matched controls. Firstly, they found that IMT was higher in anti-CCP positive patients compared to anti-CCP negative RA patients. Furthermore, El Barbary et al. [72] measured carotid intima media thickness in RA patients and looked at the relationship between positive anti-modified citrullinated vimentin (anti-MCV) and the risk of atherosclerosis in early RA. They found that the presence of these antibodies correlated with higher risk of atherosclerosis.

Cellular mediators

As in the case with many chronic inflammatory disorders, atherosclerosis and RA share many similarities [73]. One of these is collagen degradation, which is caused by the enzymes produced by active macrophages [38] which are usually activated by INF- γ produced by active T-cells. Other common etiologies that have been documented to be present in both atherosclerosis and RA include, local expressions of adhesion molecules (ICAM-1, VCAM-1, E-selectin), endothelin [74], and neoangiogenesis factors [75,76]. More interestingly, the number of a unique subset of T-cells called CD4⁺CD28⁻ was found to be higher in unstable angina patients as compared to patients with stable angina. It was suggested that CD4⁺CD28⁻, through their unique features (they lack CD⁺40 receptor, have cytolytic characteristics, and produce INF- γ profusely), are responsible of making the atherosclerotic plaque unstable [77].

In view of these findings, Gerli et al. [71] studied the role of CD4⁺CD28⁻ cells in the development of subclinical atherosclerosis in RA patients with no other cardiovascular risk factors. They observed that RA patients with persistent CD4⁺CD28⁻ expansion had arterial endothelial dysfunction and carotid artery intima thickening. They also found that blockade of TNF- α led to a partial reappearance of the CD28 molecule on the CD4 cell surface.

Medication-induced atherosclerosis

Although the era of treatment with biologic drugs had changed the course of RA and many other rheumatic diseases, traditional agents such NSAIDs and glucocorticoids is still widely used in RA patients. The role of these conventional drugs in atherosclerosis has also been studied extensively with controversial results. In a meta-analysis which evaluated the results of 26 clinical trials, Trelle et al. [78] found that NSAIDs use was associated with increased cardiovascular death (46% of 312 deaths). In a retrospective cohort study, the risk of death and recurrent myocardial infarction was evaluated in 83,677 patients according to the duration of NSAIDs use who presented with their first myocardial infarction. In that analysis, even short-term use of NSAIDs was associated with increased risk of myocardial infarction and death in patients with history of previous myocardial infarction [79]. Then Hudson et al. [80] proposed that the etiology might be explained by NSAIDs decreasing the effect of aspirin on platelet aggregation. Hudson et al. also found that there was an increase in the

risk of recurrent myocardial infarction in patients using ibuprofen and aspirin compared to those using aspirin alone. On the other hand, a longitudinal cohort study evaluated the risk of cardiovascular disease associated with NSAID use in RA patients. This study included 71,320 RA patients who were matched with 69,280 subjects in a control group. It was shown that cardiovascular disease associated with NSAIDs in RA was not only modest, but also was significantly lower in the RA group compared to non-RA subjects [81].

The association between steroid use and increased cardiovascular disease risk in RA patients has been studied over the last decade. Thus, Greenberg et al. [82] showed the use of prednisone (in doses ranging from 1-7 mg/d or more than 7.5 mg/d) was associated with higher cardiovascular disease and furthermore that this association was dependent on the dose of prednisone. However, Davis et al. [83] drew a different conclusion; cardiovascular disease risk was increased in only rheumatoid positive patients when compared to rheumatoid negative patients.

The various mechanisms contributing to atherosclerosis in RA are shown in Figure 1.

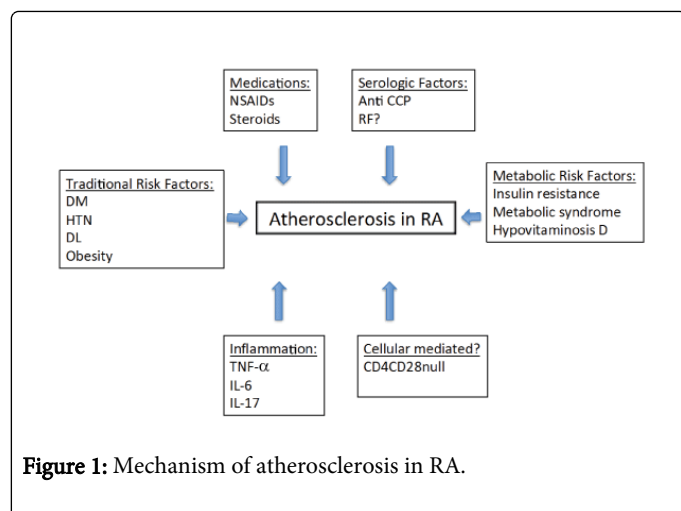


Figure 1: Mechanism of atherosclerosis in RA.

Atherosclerosis in psoriatic arthritis

Epidemiology: Psoriatic Arthritis (PsA) is an inflammatory disease associated with psoriasis. While the prevalence of psoriasis is thought to be around 2-3% in the general population [84], the exact prevalence of PsA is unknown. It was found that the prevalence of arthritis in psoriasis ranges between 30-31% [85] suggesting that PsA prevalence should be around 1%.

A strong association between cardiovascular disease and PsA was found in epidemiological studies where cardiovascular disease was considered one of the leading causes of mortality. However, death from PsA is quite controversial. Thus, Shbeeb et al. [86] found that there was not an increase in mortality in unselected patients with PsA, which is a fairly uncommon disease as their data showed. Taylor et al. [87] drew the same conclusions from their study of unselected patients with PsA compared to the general population.

Risk factors: The prevalence of cardiovascular traditional risk factors in PsA patients has been the subject of multiple studies during the past 2 decades in an effort to address the question of increased cardiovascular disease among PsA patients.

Dyslipidemia: There is a unique pattern of dyslipidemia amongst PsA patients. Thus, it was observed that there was a tendency to have lower levels of cholesterol, HDL, and higher levels of triglycerides in PsA patients [88]. In addition, Tam et al. [88] showed that there was a significant increase in apo A1 and apo B levels with an increased apoA1/apo B ratio. Another important observation was the association between the degree of inflammation and the level of dyslipidemia.

Obesity and Increased BMI: A significant relationship between obesity and increased body mass index (BMI) in PsA patients and the presence of subclinical atherosclerosis was documented in at least 2 studies [88,89].

Hypertension: The prevalence of hypertension amongst PsA patients may reach up to 30%. In that regard, Tam et al. [88] reported an increased prevalence of hypertension even after adjustment for anti-hypertensive medications [90].

Diabetes Mellitus: Diabetes mellitus is a known independent risk factor for cardiovascular disease. The prevalence of diabetes mellitus was studied in PsA patients and was found to be more prevalent in PsA patients compared to controls [88,89,91,92].

Metabolic Syndrome: A cross sectional study by Mok et al. [89] showed an increased prevalence of metabolic syndrome in PsA compared to RA and ankylosing spondylitis patients. However, according to the data there was no association between disease duration in these three rheumatic diseases and the prevalence of metabolic syndrome.

Gender, Smoking, and Hyperuricemia: No significant difference was found between a PsA group and a control group in terms of their smoking status, or gender as suspected risk factors for increased cardiovascular disease [88,91]. Whereas some studies found no increased prevalence among PsA patients other studies found an increased level of uric acid in the PsA population [93,94].

Subclinical atherosclerosis in PsA patients and the role of inflammation: As previously discussed, an observed increased mortality in PsA patients compared to the general population with cardiovascular disease was shown to be one of the leading causes of death in PsA patients. However, it is not clear whether or not the increased mortality could be explained by the presence of the traditional cardiovascular risk factors. In the literature, 6 case control studies evaluated the presence of subclinical atherosclerosis by examining endothelial dysfunction, determined by measuring flow-mediated endothelial dependent vasodilatation (FMD%) [95] and endothelial independent vasodilatation (GTN%) using brachial ultrasonography, or carotid artery intimal-media thickness and carotid plaques by high-resolution carotid ultrasonography [88,96,97], in PsA patients with no cardiovascular disease traditional risk factors. It was evident that in PsA patients FMD% was impaired compared to a control group. In addition, carotid artery intimal-media thickness was also higher by comparison to this control group. The results of these studies suggested that pathophysiologically speaking PsA as an inflammatory disease and an independent risk factor for atherosclerosis.

Atherosclerosis in ankylosing spondylitis

Ankylosing spondylitis (AS) is an inflammatory disease that involves the spine and the axial joints. AS may manifest with extra-articular manifestations such as uveitis and aortitis. AS may also result in serious impairment in spine mobility and in physical activity with

subsequent negative effect on the AS patients quality of life. The prevalence of AS can vary from 7.4/10000 in Africa to 31.9/10000 in North America [98]. However, data on the prevalence of atherosclerosis in AS patients is greatly lacking. In that regard, Sukenik et al. [99] examined the prevalence of ischemic heart disease among 40 AS patients and found it to be present in 17.5% of AS patients. In addition, a cross-sectional comparative study by Han et al. [92] revealed that the prevalence of ischemic heart disease and atherosclerosis was 1.2% and 1.5% respectively.

More recently, an updated meta-analysis and systematic review by Mathieu et al. [100], including 7 longitudinal studies comparing the occurrence of MI among AS patients and the control group, showed a significant increase in the AS group with OR (odds ratio) of 1.6 [101].

Cardiovascular disease traditional risk factors in AS: Data relating the prevalence of cardiovascular disease risk factors in AS is scarce. In a systematic review by Mathieu et al. [101] it was found that in AS patients there is an increase in carotid intima-media thickness, a higher frequency of metabolic syndrome, lower triglyceride levels, and lower total cholesterol and lower HDL levels when compared to controls.

It is not known whether or not AS patients smoke more than the general population, but studies have shown that smoking is associated with worse functional, physical, and radiological outcomes in AS [102].

The prevalence of hypertension was somewhat higher in AS population when compared to the normal population as found by Alves et al. [103] in their cohort of 40 unselected patient. Finally, studies examining cardiovascular disease in AS patients as an independent risk factor for atherosclerosis are also lacking and there is not sufficient evidence to suggest that AS is independently associated with increased atherosclerosis as was shown in RA and PsA.

Conclusion

Despite better knowledge and understanding of atherosclerosis as an inflammatory disease, many crucial questions remain unanswered, what is the direct link between inflammation and initiation and perpetuation of atherosclerosis? What is the best treatment to prevent and delay progression of atherosclerosis?

It is also crucial to understand that there is interplay between various cytokines and inflammatory pathways. Genetic profiles also contribute to disease severity and response to therapy. Thus there is no single agent that is effective for disease prevention and treatment. What might be beneficial in one patient might not produce the same benefit in other patients given the cellular and molecular diversity of each person.

Finally, it would be interesting for future research to validate cardiovascular risk scores to assess clinical and subclinical cardiovascular disease in patients with autoimmune diseases, as well as identifying biomarkers of vascular damage in these groups.

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