Rheumatoid arthritis (RA) is a chronic inflammatory disease that is high on the list of conditions that leads to disability and increases health care costs. RA patients have significantly increased cardiovascular disease (CVD) mortality and morbidity. Different mechanisms have been postulated to explain increased atherosclerosis in RA. One hypothesis is related to the co-integration between RA and traditional CV risk factors, such as lipid abnormalities, hyperinsulinemia and insulin resistance, and hyper-homocysteinemia. On the other hand, laboratory, clinical, and epidemiological studies suggest that immune dysregulation and systemic inflammation play important roles in the accelerated atherosclerosis of RA. Inflammation can work solely, or it can augment the risk of traditional CVD. This review aims at exploring the conventional CV risk factors in RA.

Dyslipidemia
Dyslipidemia is an important risk factor for CVD. Hyperlipidemia is one of several dyslipidemic patterns, and it is considered a major modifiable risk factor, yet half of all coronary events occur without overt hyperlipidemia. Several studies have examined serum levels of lipids in RA, and these show that lipid patterns in RA patients are consistent with those in other inflammatory diseases, namely low total cholesterol (TC), high-density lipoprotein (HDL), and high triglyceride (TG). Low HDL may drive the low TC level. Low-density lipoprotein (LDL) levels are inconsistent, being high in some studies and low in others. Situnayake et al demonstrated low TC in RA patients both on and off disease-modifying antirheumatic drugs (DMARDs) with an inverse relationship between the acute phase response and lipid levels. The majority of data indicated high TG levels in RA patients, showing that RA patients have low TG compared to controls. Structural and functional changes in lipoproteins could explain the possible link between inflammation and atherosclerosis. While circulating levels of TC and LDL are decreased, this decrease in LDL level is associated with an increase in small size dense LDL. Hurt-Camejio et al looked at LDL subclasses in RA patients. They found higher levels of small LDL accompanied by low levels of large LDL in RA patients, and this abnormality was found in conjunction with high levels of secretory group II-A phospholipase-A2 (sPLA2-IIA). sPLA2-IIA protein is classified as an independent risk factor and predictor of coronary heart disease (CHD). The level of this acute-phase protein was reported to correlate with the C-reactive protein (CRP) level in RA. It can hydrolyze the surface phospholipids of LDL, reducing its size and increasing its density.
small, dense LDL, which contains less phospholipid and unesterified cholesterol, has a greater affinity to bind arterial extra-cellular matrix proteoglycans in the vessel wall, with greater susceptibility to oxidative changes resulting in a more rapid uptake and accumulation in the macrophages. In addition, it has a lower binding affinity to LDL receptors, which leads to impaired clearance. All these characteristics of small dense LDL make them more pro-atherogenic and increase atherosclerosis formation despite the reduction in total LDL level among RA.

During inflammation, HDL level decreases markedly, and this low level has pro-atherogenic features. As a result of the impairment of its anti-atherogenic function, circulating HDL during inflammation is known as acute-phase HDL. It has less cholesteryl ester and is rich in free cholesterol. Park et al. demonstrated an inverse relationship between CRP and HDL values in untreated RA patients. Early RA patients exhibited a similar relationship between HDL and CRP levels at disease onset. In an animal model, inflammation was found to decrease HDL cholesterol and apolipoprotein A-1 (apoA1) during the acute phase response. This supports the hypothesis that links lipid abnormalities with inflammation.

Finally, high lipoprotein-a (Lp[a]), a cholesterol-rich modified form of LDL (a distinct lipoprotein consisting of an LDL particle attached to apo[a]) has been classified as an independent CV risk factor. This was found consistently in both active and treated RA patients. Such elevation may be secondary to inflammatory activity in RA, especially as Lp[a] shares structural similarity with plasminogen and may be considered as an acute phase reactant. In addition, this lipoprotein can facilitate the binding of LDL to extracellular matrix proteoglycans.

**Blood pressure**

Hypertension has been identified as a traditional CV risk factor for decades. Patients with RA are at increased risk of hypertension. Hypertension is the most frequently reported comorbid disease in RA, followed by angina pectoris. del Rincón et al. noted higher systolic blood pressure (BP) in RA patients than in population-based controls, while McEntegart et al. found that their RA cohort had significantly higher diastolic BP, and a trend toward higher systolic BP.

There is a suggestion of a link between hypertension, inflammation, and atherogenesis. Angiotensin-II (a highly active octapeptide) is a vasoconstrictor and the most important stimulus for releasing aldosterone by the adrenal cortex. This octapeptide can help atherogenesis formation through an increase expression of certain cytokines, chemokines, and adhesion molecules. Moreover, it can stimulate arterial endothelial cells and smooth muscle cells (SMCs) to produce superoxide anion, a reactive oxygen species. A study of 508 otherwise healthy men noted a significant relationship between BP and interleukin-6 (IL-6) level. This study supports the hypothesis linking inflammation to BP.

Leflunomide is one of the standard DMARDs. Leflunomide-related hypertension is found in 2–4.7% of people receiving the drug. Leflunomide causes a rise in systolic BP after 2–4 weeks of treatment, while the increase in diastolic BP occurs later.

Particular attention should be paid to patients taking leflunomide with non-steroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids. A longitudinal study of RA patients on stable doses of corticosteroids and NSAIDs showed a significant increase in systolic and diastolic BP.

The mechanisms by which leflunomide induces hypertension include an increase in sympathetic drive and the effect of active metabolite of leflunomide on dislodgment of free fraction of ibuprofen or diclofenac from protein binding, thus, increasing the NSAIDs effect on the renal blood flow and salt and water retention. Therefore, though leflunomide is not contraindicated in hypertension, other DMARDs should be considered first in managing RA, especially in the presence of CVD risk factors. The British Society for Rheumatology (BSR) recommends fortnightly BP measurements for the first six months of leflunomide therapy and every two months thereafter. And, if hypertension occurs with leflunomide use, anti-hypertensives medications may be used, but a dose reduction or cessation of leflunomide may be required if BP control is not achieved.

**Smoking**

Smoking has a complicated relationship with RA. Smoking has a complicated relationship with RA. It is recognized as a risk factor for RA development, and the production of rheumatoid factor (RF) production and anti-citrullinated peptide.

It is possible that smoking, a potent risk factor for atherosclerosis, interacts with inflammation...
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Smoking with other traditional CV risk factors was associated with increased CVD morbidity in RA. Others reported increased prevalence and severity of coronary calcification in RA patients, which is related, particularly to smoking and an increased erythrocyte sedimentation rate.

Several studies suggested that smoking is not only a risk factor for seropositive RA development but also for radiographic erosions and rheumatoid nodules. Thus, smoking promotes more severe RA disease along with its effects on the vasculature, promoting CVD. CRP > 5 mg/dL at first presentation with RA found to be significantly associated with a history of smoking. Those who had ever smoked were at greater risk of CRP > 5, with an odds ratio (OR) of 5.6 \((p = 0.019)\), and for those smoking more than 10 years, the OR was 7 \((p = 0.010)\).

**Serum uric acid**

Although the association between serum uric acid (SUA) concentrations and RA inflammatory activity is still controversial, uric acid crystal-mediated gout attacks have been observed in RA. SUA levels are higher in RA with CVD than in those without, even though RA is not usually associated with high SUA levels. Indeed, most of the arthritis patients with CVD have SUA levels in the normal reference range. Consequently, it has been suggested that the reference ranges for patients with RA need to be adjusted, and the elevated levels of SUA, even if within the reference range, may need to be considered more carefully.

The presence of uric acid in the atherosclerotic plaque has been postulated to play a role in the development of atherosclerosis. It is considered an independent CVD risk factor in RA. Uric acid promotes endothelial dysfunction (ED) by increasing oxidative stress and decreasing nitrous oxide \((\text{N}_2\text{O})\) bioavailability. It also increases platelet activation, upregulates the expression of platelet-derived growth factor and monocyte chemoattractant protein-1, increases platelet adhesiveness, stimulate vascular SMC proliferation, and increase inflammatory markers such as CRP.

Furthermore, SUA is associated with many risk factors for CHD. Elevated SUA is often accompanied by hypertension, hyperlipidemia, glucose intolerance, diabetes mellitus, obesity, renal disease, and CVD risk factors clustering. Therefore, SUA works individually or synergistically with other CVD risk factors to increase CVD in RA.

**Hemostatic changes**

Increased plasma levels of certain thrombotic variables such as von Willebrand factor (vWF), a cofactor in platelet adhesion and aggregation, fibrin D-dimer, a marker of increased fibrin turnover, and tissue plasminogen activator (t-PA) antigen, a key regulator of fibrinolysis which inhibits t-PA and acts as a marker of impaired fibrinolysis and atherothrombosis, are associated with increased risk and progression of CHD in the general population.

Clotting potential is increased in RA patients, associated with high plasma levels of thrombotic variables. McEntegart and colleagues reported significantly higher fibrinogen, t-PA antigen, and fibrin D-dimers in RA patients than control patients. These high levels are found even in those with well-controlled RA.

IL-6 can increase levels of fibrinogen and tumor necrosis factor (TNF) and induces the expression of tissue factors by monocytes and possibly endothelium, thereby initiating the coagulation cascade. Activated factor-XII is associated with an increased risk of CHD. These factors are all found to be elevated in RA patients. Finally, thrombocytosis induced by inflammation contributes to a hypercoagulable state in RA.

**Homocysteine**

Homocysteine is a thiol-containing amino acid derived from methionine in the diet through its conversion to cysteine. It has been demonstrated to be an independent risk factor for atherosclerosis. This amino acid is elevated in general and particularly in RA patients with CVD comorbidities. There is strong evidence suggesting a potential link between inflammatory activity in RA and the homocysteine pathway. For example, Lazzerini et al. demonstrated a reduction in plasma homocysteine levels in RA patients given pulsed glucocorticoid treatment.

Several hypotheses have been proposed to explain the cellular mechanisms by which hyperhomocysteinemia promotes CVD, including oxidative stress and activation of pro-inflammatory factors. Elevated levels of homocysteine can elicit other effects that contribute to atherogenesis. For example, homocysteine can stimulate the proliferation of cultured vascular SMCs, upregulate...
SMCs collagen, impair t-PA binding to its endothelial cell receptor, and increase the procoagulant activity of cultured endothelial cells by enhancing tissue factor. It also causes direct endothelial cell injury through oxidative inactivation of NO or inhibition of NO production by asymmetric dimethylarginine; an endogenous endothelial NO synthase inhibitor.55

Methotrexate (MTX), the most commonly used drug for RA, reduces plasma and red cell folate through inhibition of dihydrofolate reductase, which increases the level of homocysteine. Increased serum levels of homocysteine have been shown in RA patients treated with MTX. Folic acid (≥ 5 mg/wk) replacement reduces homocysteine levels in MTX-treated patients.36

Lifestyle
A sedentary lifestyle is more frequent among RA patients as a result of physical impairment with inflammation of the joints and tendons, resulting in pain, swelling, and restricted movement, eventually leading to radiological changes and deformities. Exercise therapy is an important cornerstone of the treatment of RA in all stages of the disease. The current guide to reduce CVD risk includes physical activity, with the minimum goal of 30 minutes three or four times per week. To date, no study has examined the relationship between RA lifestyle and the incidence of CVD,57 and it might be expected that a sedentary lifestyle would increase RA patients’ risk for CVD.

Hyperinsulinemia Diabetes is a known risk factor for atherosclerosis. Another interesting suggestion has linked diabetes to inflammation and atherosclerosis. Hyperglycemia causes the formation of advanced glycation end (AGE) products39 that bind to its receptor. These AGE proteins promote the production of cytokines. In addition, the diabetic state enhances oxidative stress mediated by reactive oxygen species and carbonyl-groups.59 The prevalence of diabetes is not increased in RA, although insulin resistance has been reported in patients with RA.40

Both basal hyperinsulinemia and insulin resistance are present in RA patients, with both abnormalities correlating to the degree of inflammation.40 Steroid or sulfasalazine therapy leads to a paradoxical and rapid improvement in insulin sensitivity. As worsening insulin sensitivity with impaired glucose tolerance is a well-known steroid side effect, this unexpected effect in RA patients implicates the inflammatory response as an underlying cause of insulin abnormalities in RA.

Atherogenic side effects and cardioprotective effect of antirheumatic medications

Corticosteroid
Corticosteroids have a recognized atherogenic effect, mediated through their effects on plasma lipids,41 glucose metabolism, and BP. Corticosteroids could theoretically decrease the risk of atherosclerosis by controlling inflammation. Perhaps, because of these dual effects, studies so far have failed to demonstrate a clear association between steroid use in RA and CV mortality.42

Non-steroidal anti-inflammatory drugs and selective cyclooxygenase-2 inhibitors

Non-Steroidal Anti-Inflammatory Drugs
Among the non-selective cyclooxygenase (COX), the highest CV risk was seen with diclofenac, which is relatively COX-2 specific.43 Ibuprofen has been found to block the cardioprotective benefits of aspirin.44 Several (but not all) observational studies have suggested that ibuprofen may be associated with increased CV risk in patients taking aspirin.45 Indomethacin is a non-selective NSAID associated with elevated CV events. Data on the relatively COX-2-specific meloxicam did not allow any definite conclusion.46

Selective COX-2 Inhibitors
Endothelial cells express the COX isoforms COX-1 (constitutive) and COX-2 (inducible), which catalyze the conversion of arachidonic acid to prostaglandin H2 (PGH2). PGH2 is the common substrate for synthases, which produce prostacyclin I2 (PGI2; a vasodilator and inhibitor of platelet aggregation) and thromboxane A2 (a vasoconstrictor and promoter of platelet aggregation).57 The balance between PGI2 and TXA2 is important for vascular and platelet hemostasis. Antithrombotic PGI2 is mainly COX-2 derived while prothrombotic TXA2 is mainly COX-1 derived, making selective COX-2 inhibition which abolishes the PGI2 response while sparing TXA2 an important contributor to the increased rate of CVD associated with the use of selective COX-2 inhibitors.48
Endothelial cells are exposed to reduced oxygen tension (hypoxia) with thrombotic occlusion within the vessels of rheumatoid joints. Hypoxia or other inflammatory stimulus stimulates a COX-2 dependent increase in PGI2 but not TXA2 in endothelial cells, suggesting an anti-thrombotic response to hypoxia which could be suppressed by COX-2 inhibition.

Experimental models suggest that atherogenesis may be enhanced with selective COX-2 inhibition, as mice deficient in the prostacyclin receptor have an exaggerated proliferative response to vascular injury. Moreover, cardiac up-regulation of cardiac-COX-2 in both rabbit and mice was found necessary for the protective adaptive response known as ischemic preconditioning, whereby brief episodes of sublethal ischemia render the myocardium resistant to subsequent ischemic stress.

**Disease-Modifying Antirheumatic Drugs**

Methotrexate (MTX), a commonly used drug in treating RA, has been suggested to contribute to atherosclerosis development through effects on hyperhomocysteinemia, a novel factor described to be associated with atherosclerosis development. In contrast, the beneficial effect of MTX treatment and its early use has been demonstrated. There is no clear evidence that any of the DMARDs increase the risk of atherosclerosis. Choi et al. reported that MTX reduced the overall mortality by 60%, primarily by reducing CHD mortality by 70%. Non-CHD mortality was not significantly altered. Others have shown that using at least one DMARD reduced the risk of death in RA.

Hydroxychloroquine (HCQ) is a DMARD used in RA with beneficial effects on the lipid profile by increasing HDL levels. Treating active RA for one year with HCQ increased HDL cholesterol by 15%. Antimalarials have been postulated to have antithrombotic effects in addition to their effects on HDL level. Park et al. followed 42 patients with newly diagnosed RA who had not been treated with corticosteroids or DMARDs. Their lipid profile was measured at disease onset and after one year of therapy. They found that HDL-cholesterol increased by 21%, apo[a] by 23%, and the ratio of LDL to HDL decreased by 13%. In another study, MTX or other DMARDs therapy, despite some potential toxicity, was found to lessen CHD risk in RA. Following early RA patients over a year with brachial responses recorded at disease onset and then after a year of DMARDs for inflammation control showed a significant improvement in endothelial-dependent and -independent dilatation. Improvement in vascular function was inversely correlated with measures of systemic inflammation, such as CRP, while there were no changes in traditional CV risk factors over the same period of follow-up.

**Anti-TNF Biological Dmards**

Theoretically, anti-TNF could reduce the CVD in RA by reducing inflammation, but so far, the effect of anti-TNF in lowering the risk of CVD in RA is inconsistent. Systematic reviews have demonstrated a decreased risk of CV morbidity in RA with the use of anti-TNF. As well, a large registry study showed significant reductions in the CVD outcomes associated with TNF inhibitors and a decrease in the risk of acute CHD with TNF-inhibitor therapy. The overall reduction in the risk of all CV events was found to be 54%. Others showed no reduction in the rate of composite CVD endpoints. At the same time, there were less definite association found for the risk of the individual events of myocardial infarction, stroke, and heart failure. These analyses had claimed to be confounded by comparisons with patients receiving other DMARDs, including MTX, that known to be associated with a decreased CVD risk in RA.

The adverse effect of anti-TNF might explain such conflict of the results on the lipid profile with an increase in the level of TC, HDL, triglyceride, and LDL.

**Non-Anti-TNF Biological Dmards**

In a similar fashion to anti-TNF medications, there is no clear data to conclude the effect of non-anti-TNF biological DMARDs on CVD risk in RA. Rituximab; a human-murine chimeric monoclonal antibody; anti-CD20 effect on lipid profile and ED showed conflicting results. With no significant differences in CVD events during placebo trials. Tocilizumab (a humanized monoclonal antibody against IL-6 receptor) demonstrated an adverse impact on lipid profiles with persistent elevations of TC, LDL, and HDL years after initiating treatment despite its significant and fast effect on CRP level.
reduction.\textsuperscript{66} At the same time, the ratio of apo B:apoA1, which has been shown to predict CV risk more accurately than any other cholesterol index, remained stable over six months of tocilizumab treatment.\textsuperscript{67} Similarly, tofacitinib, Janus Kinase inhibitor showed to increase the mean of LDL and HDL levels.\textsuperscript{68} Nevertheless, there are no consistent results to indicate whether biological medication prevents or increases CVD risk among the RA population. In the absence of large randomized trials adequately powered to test CV outcomes, definitive conclusions about the CV risks and/or cardioprotective effects of biologic agents cannot be made.

**Use of statin and antihypertensive medications and CVD risk in RA**

**Statin Use**

Adequate control of RA disease activity, as well as management of CVD risk factors, are needed to alleviate the CVD risk in RA. This is reflected in the European League Against Rheumatism guidelines, which recommended aggressive management of traditional CVD risk factors in addition to RA disease activity.\textsuperscript{69} Statins have a dual effect; lipid-lowering and antioxidative/anti-inflammatory properties. The anti-inflammatory properties include reducing N\textsubscript{2}O production, regulating leukocyte-endothelial cell adhesion, and decreasing levels of inflammatory cytokines.\textsuperscript{70}

The data on statin use in RA to reduce CVD risk is limited, and the role of statins in RA remains unclear. Nevertheless, a cohort study of RA patients reported that statin use was associated with a 21% lower risk of all-cause mortality.\textsuperscript{71} Other studies showed that the addition of statins to standard DMARDs resulted in an improvement of a swollen joint count, inflammatory markers, and RA disease activity score.\textsuperscript{72}

On the other hand, CRP reduction with statin might not necessarily be accompanied by improvement in the overall RA disease activity, as shown in a study that evaluated the effects of six-month rosvustatin therapy in RA. In contrast to CRP, a trend toward worsening in IL-6 levels in the rosvustatin group in the same study suggested a rather direct effect of statins on liver production of CRP rather than a global suppression of inflammation.\textsuperscript{73}

Therefore, despite the safety profile of statin that makes them an ideal choice in primary and secondary prevention of CVD, the comprehensive use of statins in all RA patients still cannot be supported by evidence.

**Antihypertensive Medications in RA**

Singh and colleagues reported that with every 20 mmHg increase in systolic BP in RA patients, there are 1572 additional ischemic heart disease events yearly.\textsuperscript{74} Given the increased CVD risk in RA, hypertension needs more attention. Although there are no randomized clinical trials to guide hypertension management among RA patients, several issues should be considered when treating RA patients with hypertension. Panoulas et al,\textsuperscript{22} published a practical approach about prevention, diagnosis, and management of hypertension in RA. The approach state that RA patients are more likely to benefit from angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs). The choice of ACE-I is due to its antihypertensive effect and its suppressive effect on inflammatory mediators, reactive oxygen species, and CRP. β-blockers and thiazide diuretics should be avoided due to their dyslipidemic and diabetogenic effects, particularly in the context of increase of insulin resistance in RA.\textsuperscript{22}

**Subclinical Atherosclerosis Markers**

The atherosclerotic process involves the inner layer of many arteries in the body. Ultrasound (US) can provide information about peripheral arterial anatomy and function that may be relevant to the coronary arteries and can determine the risk of future CVD. The carotid artery intima-media thickness (CIMT) test measured non-invasively using B-mode US has been proposed as an early manifestation of atherosclerosis. Similarly, US testing has provided valuable insights into early atherogenesis by measuring ED, representing early-stage atherosclerosis.\textsuperscript{1,75} RA patients found to have increased subclinical vascular disease compared to their matched controls as was shown by high CIMT and ED.\textsuperscript{1,75} Furthermore, a transthoracic US examination of the left anterior descending coronary-intima had been proposed as a clinically valuable tool for the detection of subclinical CHD in early RA.\textsuperscript{76}
CONCLUSION

Traditional CVD risk factors effect is augmented in RA patients and, therefore, needs careful evaluation. BP needs to be examined regularly, and standard antihypertensive targets should be pursued if needed. Biochemical evidence of hyperlipidemia, glucose intolerance, and diabetes should be sought and these conditions treated. Smoking cessation is critical, and patients should be encouraged to exercise. Control of inflammation is vital, as inflammation has a crucial role independently and on the traditional CVD risk factors.

Disclosure

The authors declared no conflict of interests. No funding was received for this study.

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