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Review Article

A review on cardiovascular risk in rheumatoid arthritis

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ABSTRACT

A systemic inflammatory disease known as rheumatoid arthritis (RA) is distinguished by excessive cardiovascular disease (CVD) morbidity and death. Traditional CV risk factors may partially contribute to CV disease in RA. Shared inflammatory mediators, post-translational modifications of peptides/proteins and subsequent immune responses, changes in the composition and function of lipoproteins, increased oxidative stress, and endothelial dysfunction are some of the mechanisms that link RA and CVD. The detailed pathogenetic pathway by which this association between RA and CVD might be explained is still not entirely known. It is crucial for controlling cardiovascular risk in people with RA. Optimizing care of traditional risk factors in addition to those inherent to RA is necessary to lessen the burden caused by CVD. The potential effect of planned Cardiac risk management in these individuals is highlighted by findings for under diagnosis and inadequate treatment of conventional CVD risk factors in RA. Present cardiovascular standards suggest RA patients to be examined for and treated for CVD risk factors without appropriate treatment goals. Utilizing potent anti-rheumatic medications that can reduce disease activity and treating the conventional CV risk factors should both be part of the therapy of CV risk in RA. There is currently insufficient scientific data to develop therapy targets for RA-related CVD risk factors. Thus, more study is required on the traditional CVD risk factor screening and management in RA patients.

Keywords: Cardiovascular risk factors, RA, CVD, Anti-rheumatic medications, Cardiac risk management, Inflammatory mediators

INTRODUCTION

One of the most common chronic inflammatory diseases is RA. It primarily affects the joints includes extraarticular symptoms such rheumatoid nodules, vasculitis or pulmonary involvement, as well as systemic co morbidities. RA is seen mostly in females than males. If three diagnoses (International classification of diseases-9-CM 714) were made during the course of two years, a person was said to have RA.[1]

RA patients are more predisposed to infections, lymphoproliferative disorders, lung cancer, respiratory disease, and cardiovascular (CV) events and a large share of the increased mortality and morbidity of RA is attributable to CV events. RA patients have a 2- to 3-fold greater risk of myocardial infarction (MI) and a 2-fold increased risk of sudden mortality. Both before and after RA diagnosis, typical angina was less frequent among RA patients, while undetected myocardial infarction and sudden cardiac death were common.[2] Increased cumulative inflammation caused by greater innate and adaptive immune system activation may intensify and speed up the

atherogenic process in RA. As a result, either increased atherosclerotic plaque production, increased plaque susceptibility, or both may contribute to the disease's increased risk of CVD.[3]

EPIDEMIOLOGY

When compared to the general population, RA was found to be associated with a 50% greater incidence of CVD - related mortality and a 48% higher risk of cardiovascular events. Patients with RA have a 1.5-2.0-fold higher chance of developing coronary artery disease (CAD). Heart failure is twice as likely to occur in RA patients.[4]

PATHOPHYSIOLOGY OF RA LEADING TO CVD

There are two steps to the path physiological connection between RA and CVD: Role of conventional risk factors and direct vascular injury.

Role of conventional risk factors

Smoking

Smoking is known as a risk factor for the development of RA and contributes to around 25% of the chance of developing CVD. The frequency of ever, present, and previous smokers in RA was as high as 50.6%, 26.5%, and 26.3%, respectively, according to a recent meta-analysis by Sugiyama et al.[5]

Genetic factors

One such example of a gene that appears to be linked to CV mortality in RA is the human leukocyte antigen shared epitope (HLA-DRB1).[6]

Hypertension

Pro-inflammatory cytokines including interleukin (IL) 1, IL-6, and tumor necrosis factor (TNF-alpha) are typically present in RA patients. Large amounts of RF and ACPA are produced by plasma cells, aberrant immune response has been developed, which could take several years. In the joints, these auto-antibodies link to Fc receptors and activate macrophages via complement. The synovium is damaged by the local inflammation, may lead to vascular endothelial cell injury. TNF-alpha and IL-6 block the activity of COX-1 and nitric oxide (NO), which are needed to maintain a healthy endothelium and cause damage to endothelial cells.[7] Peripheral vascular resistance (PVR) and arterial stiffness are both brought on by endothelial NO inhibition causing hypertension in RA patients. Glucocorticoids, nonsteroidal anti-inflammatory medicines (NSAIDs), cyclooxygenase II inhibitors (Cox IBs), disease-modifying antirheumatic drugs (DMARDs) like lefunomide, and cyclosporine are also thought to contribute to the development of hypertension in RA patients.[8]

Dyslipidemia

Proatherogenic dyslipidemia is yet another factor that connects RA to CVD. Low levels of high-density lipoprotein cholesterol (HDL-C) and total cholesterol (TC) are common in RA patients. An increase in very low-density lipoprotein (VLDL) and a decrease in HDL-C are the two factors that cause high triglyceride (TG) levels.[9] The levels of TC, LDL, and HDL cholesterol have been shown to be inversely correlated with serum CRP.[10] The "lipid paradox" refers to the fact that increased lipoprotein catabolism from inflammation in RA frequently causes HDL and LDL levels to drop while yet being linked to an increased risk of developing CVD. Inflammation lowers HDL's cholesterol export capability, or its capacity to absorb cholesterol from macrophages, an independent risk factor for CVD, making HDL levels pro-atherogenic.[11] The development of atherosclerosis is accelerated by glycation of lipoproteins, which is linked to a decrease in nitric oxide production and endothelial cell death. Increased carotid plaque and worsening CVD outcomes were both linked to elevated apo-B levels and a greater ratio of apo-B to apo-A in RA patients.[12]According to genomic studies, variations in the lipoprotein(a)(LPA) gene that cause elevated levels of lipoprotein(a) are linked to coronary heart disease, stroke, heart failure, aortic stenosis, and renal dysfunction. Patients with RA frequently have high lipoprotein (a) levels (>300 mg/L concentration). Proatherogenic dyslipidemia is characterized by low TC, LDL-c, and HDL-c values as well as a high atherogenic index and a high ApoB: ApoA ratio eventually results in atherosclerosis and CVD.[13]

Body weight

Another significant RA-specific trait that raises the risk of CVD is rheumatoid cachexia. In RA patients, a low BMI has been linked to an increased CV mortality. With less muscle mass and a higher amount of fat (rheumatoid cachexia), especially abdominal fat, than the overall population, the body composition of RA patients appears to be different than that of the general population.[14] R. cachexia's pathophysiology can be explained in two different ways.

Due to the activation of the transcriptional nuclear factor-kappa B cells (NF-kB) pathway and the promotion of the ubiquitin pathway, which leads to catabolism/proteolysis, it is characterized by the loss of muscle mass, which is primarily brought on by an increase in inflammatory cytokines.[15]

In women, the prevalence of central obesity or abdominal obesity is 20-57%, while in men; it is 80-90%. Because of this, RA develops visceral adiposity, which worsens CVD. However, increased adiposity also causes RA to produce inflammatory cytokines, which makes the situation worse. Low body mass index (BMI), reduced muscle mass and increased adiposity is the three factors that can explain this condition.[16]

Insulin resistance and diabetes

A substantial correlation between RA, metabolic syndrome, and insulin resistance (IR) has been reported in epidemiological research. Carotid intimal thickness (cIMT), which is evaluated by carotid ultrasound, determines IR as an independent predictive risk factor that indicates the presence of subclinical atherosclerosis in RA patients.[17] Long-term inflammations brought on by RA encourages oxidative stress, endothelial dysfunction, and atherosclerosis in this population. The risk of getting diabetes is increased by raised levels of CRP and interleukin (IL)-6.[18] By reducing the tyrosine kinase activity of the insulin receptor and obstructing glucose absorption in skeletal muscle, tumor necrosis factor (TNF-alpha) production may lead to insulin resistance.[19]

Atherosclerosis progression and direct vascular injury in RA

T-cell and mast cell activation is elevated in RA. Production of cytokines that promote inflammation, namely IL-1, TNF-alpha and IL-6. These pro-inflammatory cytokines activate smooth muscle cells and endothelial cells (ECs) (SMCs) in the endothelium through producing intercellular adhesion molecule (ICAM) and other cell adhesion molecules, such as vascular cell adhesion molecule 1 (VCAM) (ICAM) and through generating chemokines such as macrophage colony-stimulating factor (MCSF) and monocyte chemo attractant protein (MCP) (M-CSF).

Endothelial cell activity enables LDL-c to move into the sub-endothelial layer, where it is oxidized and sets off an inflammatory response that attracts immune cells like T lymphocytes and monocytes to the intimal layer. Monocytes become macrophages once they reach the intimal layer, where they pick up the oxidized LDL-c and develop into foam cells. Atherosclerotic plaque eventually develops when this intricate process is finished. Additionally, macrophages start the growth of smooth muscle cells and cause their migration from the tunica media to the tunica intima. To stop atherosclerotic plaque from encroaching on the lumen, the SMCs create a thin fibrous cap. However, with time, the fibrous cap begins to erode and the plaque becomes more prone to rupture due to pro-inflammatory cytokines, enzymes, and free radicals. The inflammatory reaction is amplified, which accelerates the production of plaque and ultimately causes plaque rupture and thrombotic events, which harm the blood vessels.[20]

CLINICAL PICTURE OF CV EVENTS IN RA

Acute chest, epigastric, neck, jaw, or arm discomfort with ECG abnormalities and positive biomarkers are common symptoms of acute coronary syndrome (ACS). The clinical picture in RA is different from that of the general population, with patients describing usual symptoms less frequently and more frequently collapsing, dying suddenly, and having silent ischemia attacks.[21]

DIAGNOSIS

Non-invasive imaging techniques

Magnetic resonance imaging (MRI): The composition of the plaque, including its calcification, lipid-rich necrotic core, and thickness of the fibrous cap, is measured by MRI.[22]

Computed tomography (CT)

Carotid artery stenosis is typically detected.[23]

F-Fudeoxyglucose: positron emission tomography (FDG-PET)

Measures the inflammation in carotid atherosclerotic plaque.[24]

Ultrasound

Using carotid intima-media thickness (cIMT), carotid intima-media thickness variability (IMTV), and plaque area, non-invasive carotid ultrasound is a widely used imaging method that may detect morphological variations in the atherosclerotic plaque and it is cheaper and simpler to utilize. Carotid intima-media thickness shows the overall atheromatous burden in the arterial system in addition to local atheroma formation in the carotid artery and to other locations of the same artery. Patients with RA have higher cIMT and carotid plaque area compared to non-RA groups.[25]

Erythrocyte sedimentation rate (ESR)

Patients with elevated ESR levels had a significantly greater rate of CVD events. Studies have also recommended the use of additional well-known RA-specific inflammatory markers, such as CRP, or hsCRP, and IL-6, to enhance the CVD risk assessment in addition to ESR.[26]

Aortic pulse wave velocity (aPWV)

The most reliable indicator of arterial stiffness is aortic PWV, which is evaluated noninvasively by recording the carotid and femoral pulse-wave forms. This measurement is frequently used to gauge "vascular health." In end-stage renal illness, diabetes, hypertension, and healthy patients older than 70 years, aortic PWV has been demonstrated to be a potent predictor of cardiovascular death.[27]

Aortic augmentation index (AIx)

Wave reflection measurements such as the aortic augmentation index (AIx) must be paired with PWV measurements because it is not thought of as a direct

indicator of arterial stiffness.[28] Both AIxC and PWV rise with age, but AIxC rises more in younger people and PWV rises more in older people, suggesting that the earlier is a more sensitive marker of arterial stiffness in younger people whereas the latter is more sensitive in those over the age of sixty.[29]

Flow mediated dilation

The gold standard for measuring endothelial function is flow-mediated dilatation. The approach is founded on the idea that when shear stress increases due to an increase in flow, arteries respond by dilating. Nitric oxide (NO) produced by endothelial cells serves as the main mediator of the FMD phenomena.[30]

Coronary artery calcification

Circulating endothelial progenitor cells and coronary artery calcification (CAC) are two additional techniques used to measure vascular dysfunction. An accurate noninvasive approach of determining coronary atherosclerosis is coronary artery calcification evaluated by electron beam computed tomography or multidetector-row computed tomography.[31]

Risk variables

high-sensitivity CRP (≥2 mg/L), Lp(a) levels >50 mg/dL, apo-B ≥130 mg/dL, and chronically elevated TG ≥175 mg/mL-are all included as ASCVD "risk enhancers" in the ACC 2018 guideline on management of blood cholesterol.

N-terminal pro-brain natriuretic peptide (NT-proBNP), cardiac troponin T, measurements of markers of systemic inflammation (CRP, IL-6, and TNF-alpha). Anti-cyclic citrullinated peptide (anti-CCP) status, DAS28, erythrocyte sedimentation rate (ESR;mm/hour) and swollen joint count (SJC), tender joint count (TJC).[32]

Models for predicting the risk of CVD in RA

However, only a small number of them are advised by the cardiovascular risk management guidelines. Common cardiovascular risk prediction methods (RRS) are Framingham risk score (FRS), systematic coronary risk evaluation (SCORE), American college of cardiology/American heart association (ACC/AHA) risk score, world health organization (WHO) risk charts, and Reynolds's risk score (RRS).[33]

Traditional risk factors used by these risk calculators include patient demographics (age, gender, and ethnicity), blood biomarkers (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and total cholesterol), behavioral markers (smoking and alcohol use) and physiological markers (height, weight, BMI). Since all of these risk calculators were initially created for people without RA, their usage in RA cohort's results in a significant underestimation of CVD risk.[34]

EULAR Recommendations

The European league against rheumatism (EULAR) published recommendations for CVD risk management specifically for RA and other types of inflammatory arthritis. In an initial effort to account for the underestimated CVD risk in RA patients, the conventional SCORE model and Framingham risk score were modified. For patients with RA, this adjustment entails multiplying the calculated CVD risk (using SCORE or the Framingham risk score) by 1.5 and two of the following three criteria:

RA disease has been present for more than ten years, rheumatoid factor (RF) or anti-CCP is detected, there are severe extra-articular symptoms.[35]

Although recent studies have indicated that the risk for cardiovascular morbidity and mortality increases immediately after the diagnosis of RA.[36] Furthermore, Finck et al demonstrated that adding RF or anti-CCP to the conventional FRS did not increase the precision of CVD risk prediction in RA patients.[37]

Dutch CVD risk management guideline

2011 Dutch CVD risk management guideline also recommends modifying the traditional risk assessment technique for RA patients but this strategy lacks supporting data.[38]

EFFECT OF RA THERAPIES ON CV RISK

Non-steroidal anti-inflammatory drugs

The effects of several NSAIDs on myocardial infarction, stroke, and cardiovascular death were examined in a recent meta-analysis. Naproxen appeared to be less dangerous in terms of CVD risk. It is unclear exactly how NSAIDs raise the risk of a cardiovascular attack. The level of cyclooxygenase-2 inhibition is thought to be a key factor in determining an individual NSAID's cardiovascular risk profile.[39] Rofecoxib was taken off market after the VIGOR study revealed a higher risk of heart disease events.[40]

Corticosteroids

Glucocorticoids can decrease inflammation associated with RA flares but also cause hypertension, alterations in the lipid profile, and insulin resistance; however, research on this is still preliminary. Research on animals indicates that glucocorticoids have a negative impact on endothelial function in non-inflammatory conditions and a positive impact on endothelial cells during inflammation.[41] An elevated CV risk with glucocorticoids seen in a cohort analysis of 779 RA patients, with minimal threshold of 8 mg of prednisone per day.[42] Glucocorticoids have good anti-inflammatory action but also have negative effects include worsening heart disease outcomes and raising CV risk factors. Increased cholesterol levels, carotid plaque,

arterial stiffness, impaired insulin sensitivity, and hypertension are all linked to usage of glucocorticoids.[43]

MANAGEMENT OF CV RISK FACTORS IN RA

Exercise

Exercise is an important behavioral strategy for the general population to reduce CVD. The endothelial function of RA patients was enhanced by an individual exercise training program that included a 6-month aerobic and resistance exercise programme.[44]

Diet

Mediterranean diet has been demonstrated to lower cardiovascular risk since it is high in omega-3 fatty acids, as compared to Western diets, which tend to be high in omega-6 fatty acids.[45] Omega-3 fatty acids also play preventive impact in CVD, lower inflammation in RA.[46]

Statins

According to a recent study, people with inflammatory joint disease who were taking statins experienced similar reductions in cholesterol and CVD risk as people without the condition.[47] Rosuvastatin decreased the incidence of major cardiovascular events in people who appeared to be in good condition and did not have hyperlipidemia.[48] Atorvastatin treatment for RA reduced the severity of the disease, improved the atherogenic index, and enhanced endothelial function.[49]

ACE inhibitors

In RA patients, endothelial function was measured by FMD of the brachial artery and improved after 8 weeks of treatment with ACE-inhibitors. CD40, a significant inflammatory mediator and a member of the TNF alpha super family, was also reduced.[50]

TNF-alpha inhibitors

Lengthy usage of TNF alpha blockers is directly connected to higher levels of HDL-C, TC, and triglycerides, along with a decline in apo B to apo A-I ratio and augmented endothelium functioning is seen.[51] When compared to RA patients not getting anti-TNF alpha therapy, individuals with inflammatory arthropathies, such as RA, experienced less arterial stiffness and cIMT progression after a year of anti-TNF alpha therapy and anti-TNF alpha medication lowered the risk of CVD in RA.[52]

Conventional DMARDS

Methotrexate either alone or in addition with etanercept, hydroxychloroquine, and sulphasalazine, an improvement in HDL-C, LDL-C, and total cholesterol is seen. Higher HDL-C levels were only seen in patients with RA who reacted to DMARD therapy. Upon receiving MTX treatment for a year, there was a decline in cIMT, which reflected a decrease in atherosclerosis, decreased death and severity from CVD.[53] Increased FMD was seen after adding infliximab to MTX for 12 weeks.[54]

Rituximab

After receiving rituximab therapy, some studies demonstrated improved endothelial function.[55] Given that immature B-lymphocytes (B1) appear to protect against atherosclerosis and mature B-lymphocytes (B2) may make atherosclerosis worse, these contradicting results may be explained by the function of B-cells in the formation of atherosclerosis.[56]

CONCLUSION

According to current research, RA patients should undergo regular screenings for CVD risk factors. Since there is ample evidence that traditional CVD risk factors in RA are under diagnosed and undertreated, people with RA will benefit from routine cardiovascular monitoring. All RA patients may benefit from carotid plaque detection using ultrasonography to further improve risk stratification. It is necessary to conduct randomized controlled studies to compare the effectiveness of the proposed rigorous cardiovascular treatment with existing practice. A multidisciplinary approach is necessary where different specialties can collaborate to improve cardiovascular outcomes and decrease mortality among RA patients. These specialties include rheumatologists, primary care physicians, cardiologists, physical therapists, and pharmacists.

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