Cardiovascular Risk Prediction Parameters in Rheumatic Diseases

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Contributor: Nilima Rajpal Kundnani

Multiple imaging techniques, such as ECG, ultrasound, and cIMT, as well as biomarkers like osteoprotegerin cytokine receptor and angiopoietin-2, can be beneficial in both CV risk prediction and in early subclinical diagnosis. Physical exercise is an essential non-pharmacological intervention that can maintain the health of the cardiovascular system and, additionally, influence the underlying disease. Lipid-lowering drugs (methotrexate from the non-biologic DMARDs family as well as biologic DMARDs such as anti-TNF) were all associated with a lower CV risk; however, anti-TNF medication can decrease cardiac compliance and promote heart failure in patients with previously diagnosed chronic HF. Although they achieved success rates in reducing inflammation, glucocorticoids, NSAIDs, and COX-2 inhibitors were correlated with an increased risk of CVD. When taking all of the aforementioned points into consideration, there appears to be a dire need to establish and implement CVD risk stratification models in rheumatic patients.

rheumatic diseases risk stratification

1. Introduction

Autoimmune-inflammatory rheumatic diseases (ARDs) are a group of systemic immune-mediated disorders with the potential to target various joints, bones, and connective tissues [1]. They are also correlated with a higher risk of developing cardiovascular diseases (CVD) [2]. Additionally, the diagnosis of cardiovascular (CV) involvement is challenging due to the widely varying clinical presentations of CVD, as symptoms range from mild to life-threatening [3]. Furthermore, early detection is crucial, as it helps minimize the resources required in treatment, which lowers the financial burden on the healthcare system [4]. Thus, evaluating the prevalence of CV involvement is of great clinical value as the first step towards individual risk delamination and stratification. In patients with systemic rheumatic diseases, the CVD risk is not solely conditioned by the prevalence of traditional CV risk factors, which include age, sex, smoking, family history, dyslipidemia, obesity, hypertension, and diabetes mellitus [5][6], but, also, by increased genetic risk, long-term uptake of medications, and chronic inflammation [7].

2. Current Insights

The pathophysiological association between RA and CV risk is linked to the traditional risk factors and vascular damage, both of which trigger inflammation in a vicious cycle. In addition to traditional cardiovascular risk factors,

which include age, gender, family history, smoking, sedentary lifestyle, and dyslipidemia, genetic risk has also been shown to play a role when defining global cardiovascular risk.

2.1. Biomarkers

In parallel to the imaging methods, the value of a variety of biomarkers was examined in the CV risk prediction. These biomarkers include inflammation markers, genetic factors, endothelial function, and immunological markers. In patients with RA, for instance, levels of osteoprotegerin cytokine receptor, also known as osteoclastogenesis inhibitory factor or tumor necrosis factor receptor superfamily member 11B, are correlated with the presence of CVD [8], as these have a correlation with carotid ATS and endothelial activation [9]. Angiopoietin-2 is another endothelial function marker that is correlated with CVD in RA patients [10]. Patients with RA also present with high levels of pro-inflammatory cytokines such as interleukin (IL) 1, IL-6, and tumor necrosis factor α (TNF-α). These pro-inflammatory cytokines trigger systemic inflammatory responses, and they inhibit endothelial NO synthesis, leading to arterial stiffness, which adds to CV risk.

The efficacy of B-type natriuretic peptide (heart failure marker NT-proBNP) as a predictor for CV risk in the case of rheumatic diseases has also been evaluated [11]. Some recent studies have been undertaken on the association between NT-proBNP and inflammation in rheumatic diseases, as up-regulation of the neurohormonal axis is linked with inflammation. These patients are considered to be at high risk for developing pulmonary hypertension, because, in connective tissue, disease high right ventricular overload determines increased NT-proBNP synthesis [11]. Serum uric acid levels have been linked to hypertension, renal failure, and CVD in RA patients, although it is uncertain if these correlations are related to unique pathogenic pathways or are an epiphenomenon [12]. In RA patients, mean platelet volume and microalbuminuria are correlated with hypertension, but the usefulness of these measures in predicting CV risk is unclear [13]. Symmetric and asymmetric dimethylarginine are possible biomarkers of inflammatory vascular injury and CVD In RA [14][15]. The use of biomarkers in risk-assessment tools in order to enhance CV risk stratification was shown in a large European population, where enhanced measurement of the combination of N-terminal pro-brain natriuretic peptide, troponin I, and CRP, resulted in an improved 10-year risk assessment when compared to TRF model alone. It is unknown how useful these biomarkers are for risk prediction in the presence of ARDs. The effect of ARDs activity and treatment on biomarker levels has yet to be evaluated, and this complicates the determination of their value. ARDs cohorts are much smaller, insufficient to validate biomarkers against particular endpoints for the entire population, and this implies that international cooperation would be beneficial [7].

2.2. Lifestyle Interventions

The first steps in CV risk control should be lifestyle changes, as they are the most important non-pharmacological interventions in CV prevention in ARDs and chronic inflammatory disorders. Improving the QOL should be one of the main goals. Patients should be encouraged to stop smoking, and they should be encouraged for including daily physical exercise in their schedule. Aerobic activity and physical fitness provide significant impacts on the endothelial system, both acutely and chronically [16]. Exercise has multiple CV benefits in ARD patients, according

to evidence from lifestyle programs [17]. Regulated exercise therapy improves cardiorespiratory health as well as macrovascular and microvascular functionality, and, indeed, it reduces CV risk. Exercise, in fact, can invert endothelial dysfunction by enhancing anti-oxidative processes and increasing vascular endothelial growth factor, endothelial progenitor cell, endothelial nitric oxide synthase (eNOS), and prostaglandins synthesis, thereby boosting angiogenesis, local blood flow, and endothelial growth [18]. The higher eNOS activity is accompanied by a decrease in the up-regulation of adhesion molecules, monocyte chemoattractant protein-1, and endothelin-1, which have all been shown to favor the infiltration of inflammatory cells, especially T cells and monocytes, to the capillary endothelial wall, thereby facilitating atherosclerotic wall injury. Finally, it has been shown that daily physical exercise has a significant systemic anti-inflammatory effect. Undoubtedly, mild muscular exercise decreases the size of adipose tissue, which can lead to an increase in pro-inflammatory molecules like (CRP) and (IL)-6 [17]. Muscular exercise enhances overall muscle hypertrophy and coordination, decreases adipose tissue, and enhances the immune response in RA patients, especially those with structural joint injury. Furthermore, regular exercise has been shown to decrease disease severity and activity, as it is very beneficial for different disease outcomes [19]. Although the CV benefits of physical activity are well documented, there are a few studies that contradict the conclusions pertaining to associations between exercise and subclinical markers of ATS, or those pertaining to the impact of exercise on CV outcomes in patients with ARDS [18]. In a recent study involving women with SLE, poor physical activity was linked to an increased risk of subclinical ATS, as measured by increased carotid IMT and plaque development. Furthermore, in the same population, less physical activity was correlated with the existence of pro-inflammatory HDL, a molecule recently implicated in the induction of subclinical ATS in SLE. Previous research suggests that physical activity may contribute to a decrease in the inflammation associated with ATS, and to influencing inflammation markers in these patients [18][17]. It should be noted: people with RA and other chronic systemic inflammatory disorders are known to have a lower degree of physical activity due to articular discomfort and joint deformity. Given the proof of the importance of physical exercise in suppressing disease activity and optimizing disease outcomes, routine physical activity should be incorporated into the basic treatment of patients with chronic ARDs. Even so, further research is needed to examine and analyze the effects of physical exercise and muscle fitness on CV outcomes in these patients [20].

The Mediterranean diet or plant-based diets, rich in whole grains, fruits and vegetables, and low in saturated fats and sodium, might help reduce symptoms associated with rheumatoid arthritis. There is a strong scientific rationale for the use of dietary n-3 fatty acid supplementation to modulate inflammation [21]. A recent review revealed a significant reverse association between fish consumption and risk of RA [22].

2.3. Pharmacological Interventions

2.3.1. Lipid-Lowering Drug Treatment

Chronic ARD patients have an altered pro-atherogenic lipid profile distinguished by low HDL-c levels and elevated LDL-c, total cholesterol (TC), and triglyceride levels. Furthermore, higher levels of oxLDL and lower levels of small dense LDL-c were found in untreated active RA patients, which is a potential CV risk factor associated with an increased risk of ATS [23]. Numerous laboratory trials have conclusively shown that lipid-lowering medications have

anti-inflammatory and immunomodulatory effects [18]. Statins are capable of inducing apoptosis in RA synoviocytes, and they inhibit the synthesis of T helper 1 cytokine in inflamed joints, especially IL-2 and interferon-α. After treatment with statins, endothelial cells produce more eNOS and less endothelin, resulting in less endothelial cell activation, which is an early phase in atherogenesis. Furthermore, statins lower the level of circulating CRP and other pro-inflammatory molecules, inhibit inflammatory cytokine production, and have a plaque-stabilizing effect. Recent studies examined the impact of statins in patients with chronic ARDs, especially RA [24].

Patients with high blood lipid levels, who were controlled with lipid-lowering drugs, had less of a chance of developing RA than subjects who were not handled with statins, implying that this class of drugs may play a protective role against RA progression in subjects with impaired lipid profiles. Evidence for the beneficial impact of statins on disease progression is rising; this evidence is being supported by the immunomodulatory process. In RA patients, the use of simvastatin and atorvastatin has been shown to change indirect measures of subclinical ATS. Following a brief duration of statin administration, some RA cohorts showed a substantial improvement in systemic arterial stiffness and endothelium-dependent vasodilation, and these are all considered to be indirect indicators of yet reversible endothelial dysfunction [25]. A thorough assessment of the risk-to-benefit ratio of long-term statin treatment should always be taken into account. Furthermore, prior to statin administration, patients' age and consequent CV risk factors, clinical activity, concurrent medications, comorbidity, and long-term prognosis should be adequately assessed [26].

2.3.2. NSAIDs and Cyclooxygenase-2 Inhibitors

While the advancement of synthetic and biologic DMARDs has resulted in significant reductions in the use of COXIBs and NSAIDs in the treatment of ARDs, these agents continue to play important roles in disease control. Nevertheless, in the general population, the use of COXIBs and NSAIDs is linked to an increased risk of CVD. Following the use of rofecoxib and valdecoxib, a subgroup study classified RA patients as being a CV risk group, and this eventually led to the withdrawal of these drugs from the market. CV risk in ARD patients following treatment with rofecoxib on their own was observed in a study that was published in 2015. Notably, therapy with NSAIDs and COXIBs may be effective in many RA patients, as it may improve physical activity and reduce inflammation [27].

2.3.3. Glucocorticosteroids

Although glucocorticosteroids have a confusing and controversial association with CV risk, they are one of the most commonly prescribed drugs for the rapid management of inflammation. They are, indeed, very successful in reducing inflammation, which is linked to an increased risk of CV disease, but, on the other hand, they can trigger hypertension, raise insulin resistance from baseline values, cause metabolic syndrome, and alter lipid profiles, all of which simultaneously increase CV risk [28]. Higher incidence of arterial stiffness, endothelial dysfunction, plaque formation, and high mortality rates were correlated with RA patients who used high-doses of glucocorticosteroids for a long-term (a dose of >7.5 mg prednisolone equivalent a day), but the net CV impact of glucocorticosteroid exposure remains uncertain [29].

2.3.4. Anti-Rheumatic Therapy

Due to the obviously strong connection between ATS, inflammation, and immune dysregulation, interest has recently shifted to the possible beneficial effects of biologic agents and conventional disease-modifying drugs on various CV risk factors, such as subclinical markers of ATS, lipid profile, and metabolic syndrome. In general, processes such as close monitoring of disease development, as well as early quick suppression of the inflammatory process, are now considered effective in CV disease risk prevention in subjects with ARDs [7].

2.3.5. Non-Biologic DMARDs

Methotrexate (MTX), the key RA treatment, has received the most attention in studies investigating the impact of non-biologic DMARDs on CV risks. Present findings suggest that MTX use is correlated with a lower risk (ranging from 40% to 70%) of CV events and deaths; this is mostly due to a lower risk of acute coronary events and hospitalization caused by HF. MTX therapy appears to decrease CV risk in RA patients in comparison to patients who do not receive MTX, but the mechanisms behind this preventative property remain unknown [27]. In terms of MTX efficacy, drug-induced suppression of systemic inflammation appears to be the most important mechanism for reducing CV morbidity and mortality in these patients. This inflammatory theory is currently being investigated by administering low doses of MTX to patients with chronically high CRP and a previous MI incidence to see whether MTX can play a role in reducing the risk of secondary CVDs [18][30].

2.3.6. Biologic DMARDs

In patients with RA, anti-TNF treatment decreases inflammation and it is linked to reduced CV risk when compared to non-biologic DMARDs. In these patients, anti-TNF treatment shifts lipid levels from baseline, increasing TC, HDL-c, triglycerides, and, probably, LDL cholesterol [27]. These modifications are most likely due to a normalization of lipid levels caused by inflammation suppression. At high doses, these medications can promote HF and decrease cardiac compliance in patients with mild to serious chronic HF [29]. Anti-TNF- agents, on the other hand, tend to improve vascular function, especially endothelial function and aortic stiffness; findings on carotid IMT improvement have been inconsistent. Furthermore, TNF blockade appears to preserve HDL cholesterol's antiatherogenic effects. Nevertheless, these beneficial effects on vascular function are temporary, reversible, and are found predominantly in anti-rheumatic therapy responders [31]. These findings indicate that, in the long run, prospective longitudinal trials are required to determine the precise role of anti-TNF-blockade in the prevention of ATS. Tocilizumab, a monoclonal antibody against the IL-6 receptor that activates the IL-6 signaling pathway, has also been linked to lipid modifications in clinical trials [18]. A meta-analysis found that, when compared to placebo, treatment with tocilizumab (also with tofacitinib) resulted in higher amounts of TC, HDL-c, and LDL-c in RA patients [7]. Tocilizumab has a stronger impact on lipid levels than other biological drugs, and this is not surprising given that IL-6 impacts serum lipid levels by fatty acid redistribution into peripheral tissues [30]. It is worth noting, however, that anti TNF- therapy seems to be capable of decreasing IR, CRP, and IL-6 while increasing HDL-c. Interestingly, anti-TNF- drugs have been shown to have a selective effect on T-cell subsets which are believed to be involved in plaque development [7]. In ATS plaques that form in unstable angina patients, CD4+ cells without the co-stimulatory receptor CD28 (CD4+ CD28null T cells) are formed and expanded in the peripheral blood of these patients as well

as a subset of RA patients. In RA, their expansion is correlated with increased cIMT, suggesting that this may be a marker of subclinical ATS. In this situation, infliximab has been shown to suppress the expansion of these potentially harmful T cells in RA peripheral blood [18].

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