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Atherosclerosis: An Extra Articular Manifestation of Rheumatoid Arthritis

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Abstract

The theme of the review article is to highlight the link between Rheumatoid Arthritis and atherosclerosis with emphasis on inflammation as the root cause for both the diseases. The article therefore stresses on the aggressive treatment of inflammation in RA patients and get the patients in remission to slower down the progress of atherosclerosis which is the main cause of mortality in RA patients due to cardiovascular disease (CVD) events.

Keywords: Atherosclerosis; Rheumatoid Arthritis; Inflammation

Introduction

Rheumatoid Arthritis (RA) is an inflammatory articular disease of autoimmune origin [1]. RA is complicated by atherosclerosis, which could be considered an extraarticular manifestation accelerated atherosclerosis subsequently leads to cardiovascular events. Globally, the prevalence of RA is from 0.4% to 1.3% and cardiovascular disease (CVD) are considered as the MCC of mortality in patients with RA [2-4].

RA is both a chronic inflammatory disease with systemic inflammatory state involving several organs [5]. Inflammation is considered as an independent risk factor for the development of atherosclerosis [6]. Chronic inflammation with immune dysregulation plays important role in atheroma development. The major complication of RA is the atherosclerosis [7]. This warrants close surveillance of CVD in RA patients.

We would discuss the link between RA and atherosclerosis with emphasis on inflammation as the root cause for both the diseases. We would also highlight the pathogenesis of atherosclerosis. Pathogenesis of atherosclerosis has evolved in many decades and its true understanding is important to design new therapeutic modalities for its treatment.

Discussion

RA and atherosclerosis are both of inflammatory origin. Atherosclerotic plaque and synovial lesion share the same pathological appearance. RA is a joint disease with cardiovascular diseases as a major cause of mortality. Atherosclerosis is itself an inflammatory disorder and a extraarticular manifestation of RA. This links RA with atherosclerosis. Inflammation plays key role in this relationship. Atherosclerosis is accelerated in RA and subsequently leads to CVD risk. Baseline CRP can be used as independent predictors of CVD related events. Systemic inflammation leads to atherosclerosis even before affecting the joints. So, the risk of CVD events pops up even before RA is diagnosed. This emphasizes screening of RA patients for CVD risk factors right at the first visit the longer the duration of the disease, the more the risk of CVD events. Chronic systemic inflammation in RA increases CVD risk. This warrants early therapeutic intervention in RA patients. Pro-inflammatory cytokines TNF-Alpha, IL-6 are independently predictive of CVD events in these patients [8]. These cytokines are released into the systemic circulation and have effect on the endothelium. Inflammatory mediators lead to proatherogenic profile that is typical of RA [9].

Microcirculation disorders account for myocardial ischemia in RA patients. Endothelial dysfunction is an early indicator of CVD. Microvascular abnormalities lead to myocardial ischemia. Small resistance vessels function is disturbed and so myocardial perfusion is affected.

Atherosclerosis begins with endothelial dysfunction, associated with increased expression of adhesion molecules, proinflammatory cytokines, oxidative stress. Endothelial dysfunction is the early step in the atherogenesis process. Microvascular endothelial function is a better predictor of CV outcome. Vasculogenesis is also linked to atherosclerosis. In RA, (CRP) level is an independent predictor of CVD events. Suppression of inflammation reduces CVD mortality. Inflammatory conditions with raised CRP levels lead to atherogenesis. Inflammation is the key role player for atherogenesis [10].

Pathomechanisms involved in development of atherosclerosis in RA are well illustrated in **Figure 1**. All possible factors that lead to endothelial dysfunction are-systemic inflammation, hormones, oxidative stress, smoking, proinflammatory cytokines, altered action of endothelial progenitor cells, expression of adhesion molecules, immune dysregulation, genetic background and other traditional risk factors e.g. metabolic syndrome, impaired physical activity,

type-2 Diabetes Mellitus (T2DM), hypertension (HTN), hyperlipidemia, increased basal metabolic index (BMI) [11-15]. These all factors lead to micro vascular dysfunction.

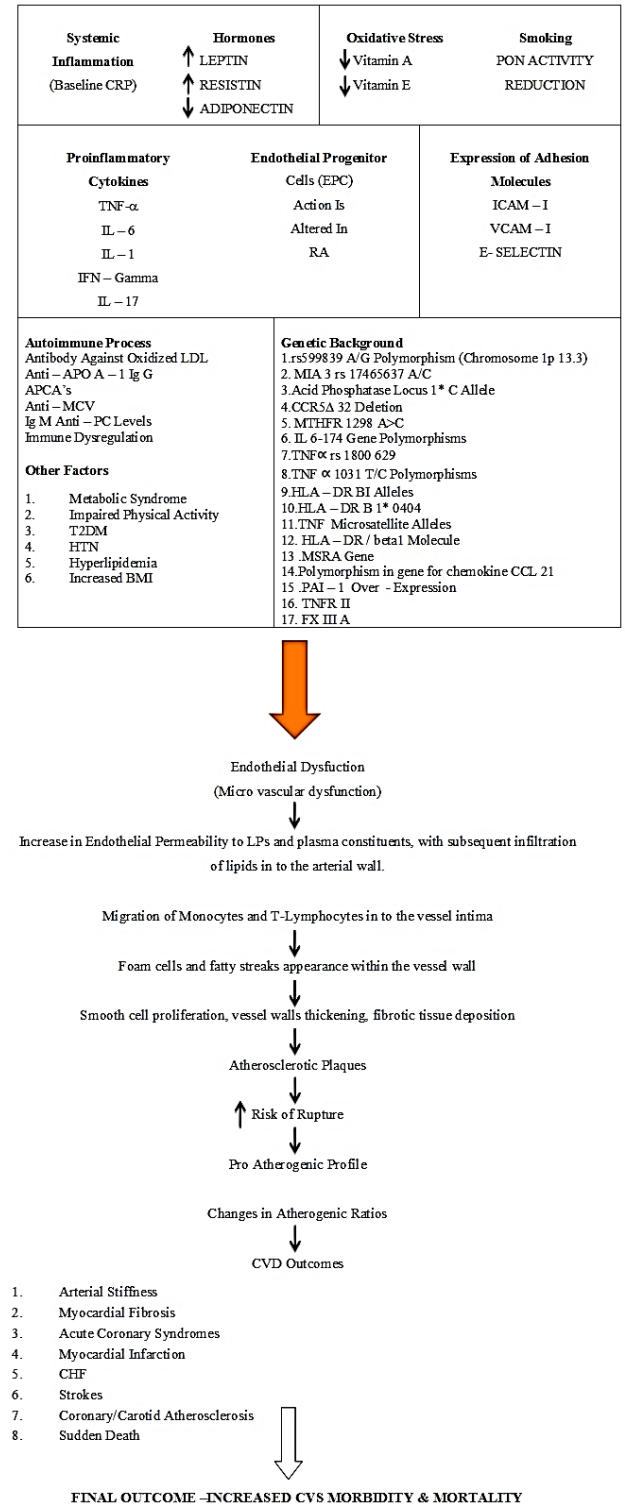

Figure 1 Pathomechanisms involved in development of atherosclerosis in RA.

Permeability of endothelium increases causing infiltration of LDL molecules. Monocytes and T-cells engulf these LDL molecules and form foam cells, which subsequently give rise to fatty streaks in the arterial wall. This is further followed by smooth muscle cell proliferation, vessel wall thickening and fibrous tissue deposition

Thus, fatty streaks get converted to fibrous plaques. Thin walled fibrous plaques with more lipid content and less smooth muscle in their composition are prone for plaque ruptures. Plaque ruptures lead to plaque complications e.g. bleeding, thrombosis and are responsible for cardiovascular events and contribute to CVD morbidity and mortality [10].

Arterial thrombosis can be prevented by preventing atherosclerosis. Reversible risk factors like hypercholesterolemia, hypertension, smoking [16], diabetes and physical inactivity, if reversed can reduce atherosclerosis complications. Glucocorticoids also affect lipid panel [17], hence judicious use of glucocorticoids is warranted in RA patients with traditional risk factors.

Genetic background, diet and physical activity decide the plasma cholesterol level. Based on the results of studies its evident there is a strong relationship between raised cholesterol levels and atherosclerosis. Familial hypercholesterolemia, LDL receptors are defective and hence it leads to premature coronary artery disease. Reduced levels of HDL are associated with CVD. Weight reduction and exercise help in raising HDL levels and reducing LDL levels and create a favorable atherogenic profile. Environmental factors such as diet have great impact on cholesterol levels. There is ample evidence [18-20] that cholesterol lowering drugs and dietary modifications reverse the progression of CVD. Modifiable risk factors such as hypertension, smoking and hypercholesterolemia when adequately controlled reduce CVD and coronary events [21,22]. Hence patients should be screened for traditional risk factors and all modifiable risk factors should be reversed to control CVD events. Aggressive lowering of serum cholesterol in post MI patents subsequently reduces the risk of surgical revascularization and deaths [23,24].

Homocysteine also plays role in dyslipidemia, growing evidences are coming up for lowering of homocysteine levels with use of folic acid, Vitamin B6 and B12 but it's still controversial [25,26]. Elevated levels of Lipoprotein have also emerged as a potential risk factor for occurrence of atherosclerosis.

Conclusion

This review has highlighted the role of systemic inflammation, proinflammatory cytokines, expression of adhesion molecules, immune dysregulation in the pathogenesis of atherosclerosis and also growing evidences are emerging for use of CRP and fibrinogen as predictors for atherosclerosis development and progression, hence role of inflammation and inflammatory mediators can be speculated, but still more large scale prospective studies are warranted to establish causal relationship between inflammatory mediators in RA patients and development and progression of atherosclerosis [27].

Recommendation

Atherosclerosis is an extraarticular manifestation of RA making CVD as a main prognostic factor. This warrants screening of CVD risk factors at the first visit of RA patients. We emphasize on cardiovascular risk management in patients with RA. CVD risk calculator should be actively used in these patients. Aggressive treatment of RA will not only control symptoms of RA but will also play role in reduction of CVD risk. Goal of RA treatment should be remission. Remission stage will also reduce CVD events in RA patients.

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