Review Article - Role of Systemic Inflammation in CVD Events in Rheumatoid Arthritis

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Abstract— The review highlights the role of inflammation in Rheumatoid Arthritis(RA) patients in promoting atherogenesis and subsequently CVD events It also discusses the implication of long term suppression of the systemic inflammatory response in RA could be effective in reducing risk of coronary heart disease.

Index Terms— Rheumatoid, Arthritis, Systemic Inflammation, Atheromatous, Rheumatoid, Coronary artery, Disease.

1. INTRODUCTION

Rheumatoid Arthritis (RA) is an inflammatory arthritis .[1]Inflammation interacts with traditional risk factors to promote atheromatous lesions.There is a linear correlation between degree of inflammation and risk of developing cardiovascular disease .[2-3]Systemic inflammatory response plays a key role in development of accelerated atherogenesis .By implication,suppression of inflammatory response in RA should be effective in reducing risk of coronary artery disease .There is considerable evidence for development of coronary artery disease in RA patients.[4-6]

2. INFLAMMATORY PATHWAY LEADING TO CVD,A SEQUALE

Systemic markers of inflammation in RA could independently predict CHD events in both Men and Women.[7]Levels of cytokines and inflammatory mediators play important role in the prediction of CVD events in RA.The main focus of this review is to highlight the concept of inflammatory driven atherogenesis .This concept is well supported by the similar appearance of plaque composition of unstable coronary lesions and inflammatory synovitis in RA.In RA most powerful measure of synovial inflammation is CRP and levels of CRP can be used as a guiding tool to judge the clinical response to therapy. [8-9]Elevated systemic cytokine levels and acute phase reactants, inflammatory mediators closely correlate to lipid levels..Thus ,altered circulating cytokines not only arise from liver but from the inflamed joints .Cytokines are known to induce metabolic effects like,alterations in lipids molecular chemistry .and peripheral insulin resistance .However chronic elevations in cytokine levels promotes accelerated atherogenesis via aggravation of lipid metabolism and insulin resistance .Of significance are leptin and IL-6 levels .[10-12]

3. INFLAMMATORY MEDIATORS AND ITS ROLE INATHEROGENESIS

In RA the site of inflammation is the synovial tissue from which cytokines are released into the systemic circulation .Levels of inflammatory mediators are linearly correlated to the grade of inflammation .TNF-ALPHA,IL-1 beta and IL-6 are at higher levels when inflammation are at the peaks .[13-14]These circulating cytokines have systemic effects on distant tissues ,including adipose,skeletalmucle ,liver and vascular endothelium,leading to proatherogenic changes like,insulin resistance ,dyslipidemia,prothrombotic effects ,pro-oxidative stress and endothelial dysfunction .These lead to accelerated atherogenesis .Magnitude of systemic inflammatory response in RA correlates to CVD events .So primarily comorbid condition ,cardiovascular disease is related to the number of inflamed joints .[15-17]

4. INSULIN RESISTANCE & ITS ROLE IN ATHEROGENESIS

Insulin resistance and hyperinsulinemia also correlate well to the degree of inflammation .Steroids subside inflammation and cause improvement in insulin sensitivity implicating inflammatory pathway as the main causal pathway .IL-6 and TNF-Alpha cause elevated levels of fatty acids and play important role in insulin resistance .[18]This highlights useful role of TNF-Alpha blockade on insulin sensitivity in RA subjects

5. Role of DyslipidemicProfile

RA patients demonstrate low levels of HDL and high levels of LDL.There is inverse association between inflammatory markers (CRP or ESR)and HDL .Antiinflammatory agents cause reduction in CRP and ESR and lead to elevation of HDL levels .Serum LDL correlate positively with the degree of inflammation and levels of inflammatory mediators .The dyslipidemic pattern in RA is highly atherogenic .Serum LDL are the prime predictors of CVD events .Inflammatory activity in RA leads to elevations in lipid parameters ,supporting role in atherogenesis .[19]

6. ROLE OF OXIDATIVE STRESS

Cytokines can directly promote oxidative modification ofLDL ,So high levels of oxidized lipidsare found in RA .Enhanced oxidative activity is found in RA and is positively correlated with acute phase reactants .Antioxidant levels of vitamin Aand E are low in RA patients .High oxidant stress titers and low antioxidant levels also lead to atherogenic profile in RA .[20]

7. HEMOSTATIC CHANGES IN RA

Raised levels of TNF-alpha and IL-6 ,lead to elevated fibrinogen ,von Willbrand factor ,fibrin D dimer and tissue plasminogen activator antigen concentration ,thrombocytosis leading to hypercoagulable state in RA .There is a significant graded relationship between cytokine levels and Hypercoagulable state also with blood pressure .[21]

8. HOMOCYSTEINE LEVELS AND CORRELATION TO INFLAMMATION

Homocysteine levels are inversely correlated to markers of inflammation (CRP,ESR)[23]

Chronic systemic inflammation leads to spectrum of metabolic defects in RA including insulin resistance ,Low HDL levels ,endothelial dysfunction .These metabolic defects correlate with the degree of inflammatory activity in these disease processes .Immune dysregulation and metabolic dysfunction play interlinked role in RA.[24]

New Approach to treatment modality –Long term suppression of the systemic inflammatory response in RA should reduce CVD risk .MTX treatment, most effective DMARD reduces mortality by reducing CHD mortality.Vitamin D is a sunshine vitamin and is key player in Bone diseases (like Osteoporosis,Osterarthritis,Rheumatoid Arthritis),Autoimmune diseases,Chronic diseases like Diabetes Mellitus,Hypertension,CardiovascularDiseases,Metabolic Syndromes and Cystic fibrosis Calcium ,Magnesium and Phosphorus are the key ions whose interplay is closely linked to each other in positive bone metabolism and Vitamin D is the regulator of this process.Hence in RA patients Vitamin D levels should be monitored and adequate supplementation should be provided .[25,27,28]

9. REFERENCES

[1] Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation.* 2002; **105**: 1135–1143.

[2] Gabriel SE, Crowson CS, Kremers HM, et al. Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. Arthritis Rheum. 2003 Jan;48(1):54–58. [PubMed]

[3] Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation.* 2003;**107**: 499–511.

[4] Pasceri V, Yeh ET. A tale of two diseases: atherosclerosis and rheumatoid arthritis. *Circulation.* 1999;**100**: 2124–2126.

[5] Book C, Saxne T, Jacobsson LT. Prediction of mortality in rheumatoid arthritis based on disease activity markers. J Rheumatol. 2005 Mar;32(3):430–434.

[6] McInnes IB. Rheumatoid arthritis: from bench to bedside. *Rheum Dis Clin North Am.* 2001; **27**: 373–387.

[7] Jacobsson LT, Knowler WC, Pillemer S, et al. Rheumatoid arthritis and mortality. A longitudinal study in Pima Indians. Arthritis Rheum. 1993 Aug;36(8):1045–1053.

[8] de Groot L, Posthumus MD, Kallenberg CG, Bijl M Risk factors and early detection of atherosclerosis in rheumatoid arthritis. Eur J Clin Invest2010;40:835-42.
[9] Hill AG, Hill GL. Metabolic response to severe injury. *Br J Surg.* 1998; **85**: 884–890.
[10] Gonzalez A, MaraditKremers H, Crowson CS, et al. The widening mortality gap between rheumatoid arthritis patients and the general population. Arthritis Rheum. 2007 Nov;56(11):3583–3587. [PubMed]
[11] Gullick NJ, Scott DL Co-morbidities in established rheumatoid arthritis. Best Pract Res ClinRheumatol 2011;25:469-83.
[12] Banks WA, Phillips-Conroy JE, Jolly CJ, et al. Serum leptin levels in wild and captive populations of baboons (papio): implications for the ancestral role of leptin. *J ClinEndocrinolMetab.* 2001; **86**: 4315–4320.
[13] Goodson N, Symmons D. Rheumatoid arthritis in women: still associated with an increased mortality.Ann Rheum Dis. 2002 Nov;61(11):955–956.
[14] Meune C, Touze E, Trinquart L, Allanore Y High risk of clinical cardiovascular events in rheumatoid arthritis: levels of associations of myocardial infarction and stroke through a systematic review and meta-analysis. Arch Cardiovasc Dis2010;103:253-61.
[15] Ershler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. *Annu Rev Med.* 2000; **51**: 245–270.
[16] Goodson NJ, Wiles NJ, Lunt M, Barrett EM, Silman AJ, Symmons DP. Mortality in early inflammatory polyarthritis: cardiovascular mortality is increased in seropositive patients. Arthritis Rheum 2002;46:2010-9.
[17] del Rincon I, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum 2001;44:2737-45.
[18] Pincus T, Callahan LF, Sale WG, et al. Severe functional declines, work disability, and increased mortality in seventy-five rheumatoid arthritis patients studied over nine years. *Arthritis Rheum.* 1984; **27**:864–872.
[19] Solomon DH, Karlson EW, Rimm EB, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation 2003;107:1303-7.
[20] .Paolisso G, Valentini G, Giugliano D, et al. Evidence for peripheral impaired glucose handling in patients with connective tissue diseases. *Metabolism.* 1991; **40**: 902–907.
[21] Snow MH, Mikuls TR. Rheumatoid arthritis and cardiovascular disease: the role of systemic inflammation and evolving strategies of prevention. CurrOpinRheumatol 2005;17:234-41
[22] .Hallgren R, Berne C. Glucose intolerance in patients with chronic inflammatory diseases is normalized by glucocorticoids. *Acta Med Scand.* 1983; **213**: 351–355
[23] .Maradit-Kremers H, Crowson CS, Nicola PJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum 2005;52:402-11.
[24] Hotamisligil GS, Peraldi P, Budavari A, et al. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. *Science.* 1996; **271**: 665–668.
[25] Maria Aziz and Shweta Dubey (2016); Correlation between Vitamin D Deficiencyand Rheumatoid Arthritis Patients.Â Int. J. of Adv. Res.Â 4Â (7). 804-813] (ISSN 2320-5407).Â www.journalijar.com
[26] Aziz.Maria,Yadav K.S. "Pathogenesis of Atherosclerosis A Review" Medical & Clinical Reviews,2016 Vol. 2No 3 :31, 1-6
[27] Aziz.Maria, Yadav K.S. "Vitamin D Deficiency in Metabolic Syndrome Patients.International Journal of Advanced Research,(IJAR)2016,Vol. 4 Issue 7,229-241
[28] Aziz.Maria,Soni.Govind"Vitamin D- The Sunshine Vitamin Review Article" International Journal of Research and Technological Sciences 2014-2015,Vol.1 Issue Vol. 2 Issue 1, 96-103

10. CONCLUSION

Inflammation should be closely monitored in RA patients and aggressive treatment with MTX +NSAIDS + CORTICOSTEROIDS should be started as early part of treatment and every step should be taken to subside the inflammation .Simultaneous monitoring of Blood Pressure levels and serum lipid profile should be stressed .Established therapies for CHD risk reduction such as statins or ACE inhibitors should be started in RA patients with abnormal lipid profile .The anti-inflammatory properties of statins may offer particular advantage to RA patients.Systemic inflammatory response in RA is the key role player to accelerated atherogenesis .[29]This reveals that long term suppression of the systemic inflammation in RA will lessen CHD risk .Systemic inflammatory markers are better predictors of CHD risk in RA .Suppression of inflammation in RA will substantially reduce CVD events in RA patients.