

Accelerated Atherosclerosis in Rheumatoid Arthritis: Rationale for Mannose-binding Lectins?



Rheumatoid arthritis (RA) is characterized by chronic inflammation involving connective tissues throughout the body, particularly diarthrodial joints, eventually leading to joint destruction and physical disability¹. In parallel with erosive arthritis, other extraarticular manifestations have been described in the disease, representing systemic activation of the immune system¹, which is generally associated with excess mortality². Atherosclerosis, among others, is considered an extraarticular manifestation of RA³. Well established RA reduces median life expectancy, compared to that of healthy subjects^{4,5}. Overall, about 40% excess mortality has been shown in RA⁶. In addition to infections and gastrointestinal hemorrhage due to nonsteroidal anti-inflammatory drugs (NSAID), cardiovascular (CV) mortality is increased in RA. Besides CV diseases, the leading causes of death in RA are infection and malignancies, which also contribute to increased mortality^{7,8}.

Accelerated atherosclerosis in RA is signified by increased CV morbidity and mortality⁸⁻¹². Generally, in patients with RA, CV diseases reduce life expectancy by 5 to 10 years on average¹³⁻¹⁵. In both RA and atherosclerosis, inflammatory immune-mediated processes play central roles, and the 2 diseases share several common pathogenic mechanisms^{14,16,17}. Besides the common inflammatory pathways, RA itself has been considered as an independent risk factor for accelerated CV disease^{18,19}. In a large prospective cohort of women, based on over 100,000 subjects, participants with RA had a significantly increased risk of myocardial infarction compared to those without RA¹⁹.

Traditional CV risk factors, including age, hypertension, smoking, and disorders of the lipid profile, all contribute to the propagation of atherosclerosis, and consequently poorer CV outcomes in patients with RA²⁰⁻²². Yet these traditional Framingham risk factors only partially explain the increased risk for accelerated atherosclerosis in RA. Recent findings support the idea that immune-inflammatory processes associated with RA contribute to the increased risk of ischemic CV disease^{11,23,24}. Inflammatory cytokines that are pro-

duced in excess in RA (e.g., tumor necrosis factor- α , platelet-derived growth factor) activate endothelial and subendothelial myofibroblasts that might lead to the accumulation of immunocompetent cells in atherosclerotic plaques¹. Classical Framingham as well as other potential risk factors for accelerated atherosclerosis in RA are summarized in Table 1^{5,11}.

Mannose-binding lectins (MBL) play an important role in the innate immune system, having the ability to bind to various sugar motifs, and activating the complement system via MBL-associated serine proteases. MBL, as a Toll-like receptor co-receptor, increases microbial uptake as an opsonin, but have the ability to coordinate, amplify, and synchronize innate immune defense mechanisms²⁵. Relatively high amounts of assorted molecular forms of MBL (both homozygous and heterozygous carrier forms) and varying plasma levels of MBL have been described. Polymorphisms in the promoter region of the human *MBL2* gene have been shown to give rise to varying plasma levels of MBL²⁶. Among various immune-mediated diseases, MBL polymorphisms have been associated with RA progression; some studies have described an association of MBL polymorphisms with erosive joint destruction, yet other studies could not verify these findings²⁷⁻²⁹. In a recent study, Jacobsen, *et al* found that *MBL* gene polymorphisms were associated with disease activity and physical disability in anti-cyclic citrullinated peptide (CCP)-positive patients with untreated early RA³⁰. The study showed a dose-dependent association between *MBL2* expression potential and disease activity as well as physical disability in anti-CCP-positive RA patients before initiation of disease-modifying antirheumatic drug treatment³⁰. Importantly, this study reported that high serum levels of MBL increased the risk of ischemic heart disease in patients with RA.

The followup study of these findings by Troelsen, *et al*³¹ is published in this issue of *The Journal*. The authors describe mortality in a cohort of 229 Danish RA patients and assess whether reported factors and MBL influence risk

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Table 1. Risk factors for accelerated atherosclerosis in patients with RA.

Risk Factors
Age
Smoking
Inactive lifestyle/immobilization
Dyslipidemia, oxLDL, LDL \uparrow , HDL \downarrow
Hyperhomocysteinemia
Prothrombotic factors: platelets \uparrow , fibrinogen, thromboxane
Acute-phase proteins (CRP, serum amyloid A, fibrinogen)
Autoantibodies (anti-CCP, RF, anti-oxLDL, anti-HSP)
Proinflammatory cytokines
Chemokines and angiogenic growth factors
Immune complex mediated endothelial damage
Matrix metalloproteinases
Endothelial cell dysfunction induced by inflammation
Endothelial cell leukocyte adhesion molecules
Impaired apoptosis
Medications: methotrexate, corticosteroids

CCP: cyclic citrullinated peptide; CRP: C-reactive protein; HDL: high density lipoprotein; HSP: heat shock protein; LDL: low density lipoprotein; oxLDL: oxidized low density lipoprotein; RF: rheumatoid factor.

of overall mortality and mortality due to CV disease. Known predictors of RA mortality were assessed and *MBL2* extended genotypes and MBL serum levels were measured. The authors assessed the vital status and causes of death in a relatively long prospective study with a median followup of 10.3 years. At baseline, sex, age, the age at disease onset, presence of erosive arthritis based on hand and feet radiography, assessment of functional ability by Health Assessment Questionnaire (HAQ) score, and the presence of extraarticular manifestations were noted. Additionally, laboratory variables such as IgM rheumatoid factor (RF), serum C-reactive proteins (CRP), and the presence of HLA-DR1 and/or HLA-DR4 were assessed.

Concerning followup data, other known predictive factors, namely smoking, state of nutrition, and comorbidities such as hypertension and diabetes were noted. Although treatment status data for methotrexate (MTX) and anti-TNF inhibitors were retrieved from clinical charts, the use of various glucocorticosteroids, NSAID, acetylsalicylic acid, and statins was not consistently charted. Since these medications have antiinflammatory properties (in addition to anti-atherosclerotic and lipid profile-modifying effects) that can contribute to deceleration of immune-inflammatory properties of atherosclerosis, their intake can fundamentally change the course and outcome of the disease.

Troelsen, *et al* reported an overall risk of death in RA of 4.0% per year³¹. Comparing mortality in the RA cohort with mortality in an age- and sex-matched cohort based on the general Danish population, a significantly increased overall mortality rate as well as CV mortality was found, in accord with previous findings⁴⁻¹⁵. Moreover, multivariate analysis by the authors showed significant predictors of overall death were extraarticular manifestations, positive

RF, increased CRP, poor nutritional state, and high serum MBL. Predictors of CV death were HAQ score, increased CRP, poor nutritional state, and high serum MBL levels. Moreover, RA patients with *MBL2* genotypes associated with high serum levels of MBL (YA/YA, YA/XA, XA/XA) had excess overall mortality compared to patients with genotypes associated with low serum levels of MBL (YA/YO, XA/YO, YO/YO). The YA/YA genotype was associated with both highest risk of CV death and highest serum levels of MBL. Correspondingly, serum MBL was associated with significantly increased risk of both overall and CV death in RA. A genotype causing high serum MBL might contribute to the perpetuation of both RA severity/mortality and simultaneously accelerated atherosclerosis; therefore, monitoring MBL levels might be useful in diagnosis, CV risk assessment, and followup of RA.

Regarding other predictors of mortality and CV mortality such as disease duration, HAQ score, extraarticular manifestations, positive IgM RF, high CRP, and poor state of nutrition conferred significantly increased risk of overall death, while treatment with MTX and anti-TNF- α drugs contributed to significantly reduced risk of overall death. Both overall and CV mortality were increased in Danish RA patients. In this cohort, states of high MBL production and several previously reported factors contributed significantly to this increased risk of overall death and CV death. In future studies, it would be of interest to assess the objective measures of endothelial dysfunction and atherosclerosis in patients with RA (e.g., flow-mediated vasodilatation, pulse-wave velocity, intima-media thickness, and lipid variables) and correlate them with MBL levels in order to estimate the relationship between these types of lectins and probable CV complications.

This important study points out the key overall and most common CV mortality risk factors in patients with RA. The assessment of specific predictors in patients with RA, including age, sex, disease duration, and genetic factors such as the YA/YA *MBL2* genotype (associated with high serum MBL), may aid us in pinpointing high-risk patients, while thorough followup and early cardioprotective, antiplatelet therapy may lead to better clinical outcome for these patients. In addition, adequate treatment of extraarticular manifestations, changes in lifestyle affecting body mass index, reduced cigarette smoking, and proper treatment of comorbidities (e.g., diabetes and hypertension) may all prolong the life expectancy in patients with RA.

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