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Atherosclerotic cardiovascular disease in rheumatoid arthritis: aspects of pathogenesis and risk

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Abstract

Patients with rheumatoid arthritis (RA) have an increased prevalence and severity of atherosclerosis, and a corresponding increased risk of cardiovascular disease. The mechanisms causing this are not well elucidated, but both traditional cardiovascular risk factors and RA-associated factors have been associated with atherosclerosis and increased risk of cardiovascular events in patients with RA. Cardiovascular risk estimation based on traditional cardiovascular risk factors, often underestimates the risk in patients with RA. The aims of this thesis were to examine factors and biomarkers associated with atherosclerosis in patients with RA, and to evaluate an algorithm for cardiovascular risk estimation in patients with RA.

Methods Patients with early RA in the four northernmost counties of Sweden have since 1995 been included in a prospective study of both the progress of RA and comorbidities. Besides clinical data, radiographs, genetic markers and autoantibodies are registered. Paper I includes 665 patients aged 40-80 years from that cohort, in whom the 10-year risk of a first cardiovascular event was estimated with both Expanded Cardiovascular Risk Prediction Score in Rheumatoid Arthritis (ERS-RA), and the general population based ACC/AHA algorithm. The estimations were then compared to the actual outcomes. Paper II examines factors associated with coronary artery calcification (CAC) in 22 patients with long-standing RA. Papers III and IV use data from a cohort of patients <60 years of age at diagnosis of RA (n=79), in whom development of atherosclerosis has been prospectively followed since diagnosis of RA. This is a subset of patients from the larger cohort in paper I. Controls matched for age and sex (n=44) are examined as well. In paper III, phenotypes of T-cells and IgG-antibodies against cytomegalovirus (CMV) are analysed in relation to carotid intima-media thickness (IMT). In paper IV, bone mineral density and markers and regulators of bone metabolism are analysed in relation to IMT.

Results Cardiovascular risk estimation with the RA-specific algorithm ERS-RA is not superior to estimation with the ACC/AHA algorithm. Both algorithms underestimate the risk in patients with a high grade of inflammation and in patients with an estimated moderate risk. In patients with long-standing RA, presence of CAC is associated with inflammatory activity, both at time of examination and in earlier stages of RA. Presence of anti-CMV IgG antibodies and altered T-cells (both CD4+ and CD8+) lacking the co-stimulatory molecule CD28 (CD28null) are associated with a higher IMT, and patients IgG-positive for CMV have a rapid increase in IMT after onset of RA. Regulators of bone metabolism (sclerostin, osteoprotegerin and osteocalcin) are associated with a higher IMT in patients with RA.

Conclusion Cardiovascular risk estimation in patients with RA still needs to be improved. The fact that CMV-positivity, altered populations of T-cells and IMT all are associated, and that also regulators of bone metabolism reflect IMT, suggests that the pathogenesis of atherosclerosis in patients with RA is multifactorial. This thesis provides knowledge of the accelerated development of atherosclerosis in RA and could possibly be relevant also in other chronic inflammatory diseases, where markers of accelerated atherosclerosis and increased cardiovascular risk are lacking.

Keywords

Rheumatoid arthritis, inflammation, atherosclerosis, cardiovascular disease, risk estimation, cytomegalovirus, T-cells, bone turnover, osteoprotegerin, osteocalcin

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