Summary

Rheumatoid arthritis as a vascular disease
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Accelerated atherosclerosis and increased cardiovascular risk have become major factors of mortality in rheumatoid arthritis (RA). RA-associated atherosclerosis cannot be solely explained by Framingham risk factors, the inflammatory mechanisms underlying RA may be crucial for early atherosclerosis and cardiovascular disease development.

In our cross sectional controlled study we assessed brachial artery flow mediated dilation (FMD) as indicator of endothelial dysfunction, common carotid intima-media thickness (ccIMT), an early marker of atherosclerosis, as well as laboratory markers of inflammation, autoimmunity and accelerated atherosclerosis in RA and control population. Patients with RA and controls were normalized for traditional risk factors for atherosclerosis.

FMD was significantly lower, ccIMT was significantly higher in comparison to controls in Hungarian population with RA. We observed negative correlation between FMD and disease duration (as a disease related factor) independently of age. Interestingly, FMD was positively correlated with a Th1 type cytokine, serum interferon-γ levels, and inversely correlated with total leukocyte counts. ccIMT showed significant positive correlation with age and total serum cholesterol levels, and an apparent inverse correlation with serum IL-1 levels. Anti-dsDNA levels also showed strong positive correlation with ccIMT without pathological elevation of anti-dsDNA levels.

Patients with impaired FMD (<5%) were older, and had longer disease duration and presented significantly lower serum interferone-γ levels. Higher ccIMT values (>0,65 mm) were associated with elevated age, decreased IL-1 and interferone-γ levels, elevated anti-dsDNA levels were measured in these subpopulation.

After the influence of traditional risk factors (cigarette smoking, hypertension, diabetes, dyslipidemia, obesity) was excluded we still found endothelial dysfunction and progressive atherosclerosis in RA patient indicating the potential role of inflammation in the atherosclerotic process. Our results and several other studies demonstrate that the pathogenesis of RA and atherosclerosis may overlap. Although RA-associated atherosclerosis also involves traditional Framingham risk factors, such as cigarette smoking, hypertension, diabetes, dyslipidemia, or obesity, these do not fully account for the development of vascular damage in RA.

Experimental data suggest that the inflammation in atherosclerosis is based on stem from results from a Th1 type immune mechanisms. Interestingly, the typical Th1 type cytokines such as IL-1 and interferone-γ were inversely associated with early signs of atherosclerosis that support the need of further studies to shed light on the details of the molecular mechanisms of inflammation associated with atherosclerosis.

Several reports indicated, that TNF-α blockers may exert favourable but transient effects on FMD of the brachial artery and ccIMT in RA. In our first pilot study we investigated the vascular effects of adalimumab (a humanized TNF-α blocker) on disease activity in recent onset RA. Adalimumab therapy considerably improved arthritis as it decreased CRP levels and disease activity (DAS28), and resulted in a significant increase in FMD by as early as week 2. Significantly, these effects were sustained until week 12. Furthermore, the production of von Willebrand factor, a marker of endothelial activation was also decreased. Regarding

carotid atherosclerosis, after 24 weeks adalimumab treatment a significant improvement in ccIMT was observed.

In conclusion, blocking the typical Th1 type cytokine (TNF-α) with adalimumab improved endothelial function and postponed the development of atherosclerosis in strong correlation with disease activity in early RA.

In our second pilot study we assessed the effects of rituximab (anti-CD20 antibody blocking the B cell function) on FMD, ccIMT and lipid profile during a 16 weeks follow up. Rituximab treatment resulted in a rapid and sustained improvement in FMD, but only a mild, non-significant decrease in ccIMT. Rituximab exerted early and sustained favorable effects on plasma total cholesterol and HDL-C levels.

Our results suggest that effective inhibition of inflammatory process carried out both with TNF-α blocking agents or with B cell depletion seems to be beneficial for endothelial function to delay early atherosclerosis. These effects affected the metabolic homeostasis and partially were dependent on direct anti-inflammatory mechanisms.

Key words: rheumatoid arthritis, atherosclerosis, endothelial function

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