

Editorial

Inflammation, carotid intima-media thickness and atherosclerosis in rheumatoid arthritis

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See related research by Hannawi *et al.*, <http://arthritis-research.com/content/9/6/R116>

Abstract

Carotid intima-media thickness (cIMT) reflects early atherosclerosis and predicts cardiovascular events in the general population. An increased cIMT is present in patients with rheumatoid arthritis, compared with control individuals, from the early stages of the disease and is thought to indicate accelerated atherosclerosis, but direct evidence is not available. Whether cIMT is susceptible to rapid and potentially reversible change depending on the intensity of inflammation in states of high-grade systemic inflammation, such as rheumatoid arthritis, remains unknown. If this is the case, an increased cIMT in such disease states may not reflect structural vessel wall damage, and may not be a good predictor of future cardiovascular events in these particular populations. Prospective, long-term, longitudinal studies are needed to address these questions.

Carotid intima-media thickness (cIMT) was recently reported by Hannawi and colleagues to be higher in rheumatoid arthritis (RA) patients with recent disease onset compared with age-matched and sex-matched control individuals [1]. The noninvasive measurement of cIMT is thought to reflect structural vessel changes at relatively advanced, but still subclinical, stages of atherosclerosis. cIMT is a strong predictor for future vascular events in the general population, particularly in people with low-grade inflammation as assessed by C-reactive protein levels [2].

cIMT has previously been found to be increased in patients with longstanding RA [3]: those with long duration (>20 years) had a higher cIMT compared with patients of the same age but shorter disease duration (<7 years). Hannawi and colleagues extend these findings by reporting that an increased cIMT was already evident in RA patients as early as within 12 months of symptom onset and was determined

mainly by age and C-reactive protein [1]. Both research groups conclude that their findings support the concept that the high-grade inflammation associated with RA, in addition to causing joint disease, also accelerates the process of atherosclerosis in these patients. Hannawi and colleagues suggest explicitly that 'inflammation which precedes the onset of joint symptoms in RA promotes the development of atherosclerotic disease well before the first manifestations of joint disease ...' [1]. This would be consistent with studies showing that, compared with people who do not develop RA later in life, those who do develop the disease have elevated C-reactive protein levels many years before the diagnosis of RA [4].

Whether cIMT is a good predictor of future vascular events in patients with RA remains an open question, since no long-term studies have to date documented such an association in this particular population. Highly pertinent to this is whether studies such as those discussed above do indeed provide evidence for *accelerated* atherosclerosis in RA or reflect alternative processes. The assessment of cIMT in RA cohorts has thus far been limited almost exclusively to cross-sectional studies. These studies are only good for hypothesis generation, rather than proof of an association or its directionality. The cross-sectional association of increased cIMT with (current) C-reactive protein levels in the study of Hannawi and colleagues is a good example. Could increases in cIMT, in conditions with high-grade inflammation such as RA, simply reflect current (but quickly reversible) inflammation of the vessel wall rather than more permanent structural vessel changes? And would a single measurement of cIMT in this context be a good predictor of future vascular events in patients with RA?

cIMT = carotid intima-media thickness; RA = rheumatoid arthritis; TNF = tumour necrosis factor.

Another noninvasive technique used as a surrogate for atherosclerosis involves the assessment of vasodilatory responses: these responses are thought to reflect endothelial function alterations at the early stages of atherosclerosis. Like cIMT, endothelial dysfunction is a predictor of future cardiovascular disease in the general population [5], is present from the early stages of RA, and has also been interpreted as indicative of accelerated atherosclerosis [6]. There is, however, good evidence to suggest that the measurement of endothelial function is highly dependent upon current levels of inflammation. In healthy people, the inflammatory response elicited by vaccination is sufficient to temporarily (and reversibly) impair endothelial function [7]. Reduction of inflammation using anti-TNF therapy in RA is rapidly (although transiently) followed by improvement of the endothelial function [8]. Interestingly, high-grade systemic inflammation also associates with metabolic abnormalities, such as dyslipidaemia and insulin resistance, which normalise when inflammation is controlled [9]. Full or partial normalisation may not be exclusive to metabolic abnormalities or endothelial dysfunction, but may also occur in what are thought to be structural blood vessel changes. In patients with renal impairment – who, like RA patients, have increased cardiovascular risk – 6 months of statin therapy resulted in improvement of endothelial function, as well as in a significant reduction of cIMT; these improvements remained present, with continuation of treatment, for the full 18-month duration of the study [10]. It remains unknown whether high-grade inflammation (and its control) could have a rapid impact on the vessel wall structure as assessed by cIMT. Equally unknown remains the long-term significance of apparent, but potentially intermittent, abnormalities of vascular function and structure in RA.

It is fundamental to examine the interrelationships between the high-grade but variable systemic inflammation that characterises RA and the potentially intermittent and reversible insults to vascular function and structure – to prove whether they do indeed reflect accelerated atherosclerosis – and to assess their long-term significance in terms of hard cardiovascular outcomes specifically in the RA population. This can only be explored with lengthy, prospective, longitudinal, and, ideally, controlled studies, which are currently lacking.

Competing interests

The authors declare that they have no competing interests.

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