Subclinical Vasculitis as a Potential Mechanism to Explain the Heightened Cardiovascular Risk in Rheumatoid Arthritis

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One decade ago, James Rudd, who also coauthored the present article, published the results of the first prospective trial investigating 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) for imaging of inflammatory changes in carotid artery disease in Circulation.1 Since that time, FDG-PET has emerged as a powerful noninvasive technique to measure vascular inflammation due to atherosclerosis.1–10

Over time, several prospective and retrospective studies evaluated the diagnostic impact of vascular FDG-PET not only in the clinical, but also in the animal setting. Today, there is emerging evidence indicating that noninvasive PET imaging shows a significant correlation with established clinical cardiovascular risk factors such as obesity, smoking, older age, male sex, hypercholesterolemia, Framingham risk score, diabetes mellitus, insulin resistance, C-reactive protein, and matrix metalloproteinases, and plaque high-risk morphological features.14–19 Furthermore, it was also shown that FDG-PET is able to serve as a predictive marker for emerging cardiovascular events.20 Most interestingly, inflammatory vascular changes as depicted by FDG-PET emerged as primary end point measures in several well-designed prospective multicenter trials investigating the effect of different newly developed or established medical treatment approaches in atherosclerosis.21–23

The FDG uptake in the inflamed arterial wall or in inflamed vascular plaques is thought to depict macrophage activity, which by itself might be driven by hypoxia.11–13

In this context, the current study by Mäki-Petäjä and colleagues24 represents 1 further step for establishing vascular FDG-PET in routine clinical care. It is not only that this highly renowned group from Cambridge provided first insights into the vascular changes in patients experiencing rheumatoid arthritis (RA) and the effect of anti-tumor necrosis factor α (TNF-α) therapy on inflammation in the vasculature in those patients, they mainly, once again, provided a well-designed, prospective, vascular-tailored study about vascular PET imaging covering a new topic of noninvasive evaluation of vascular inflammation. The importance of performing those well-designed clinical trials cannot be overemphasized, because they are clearly needed to flatten the way of PET to enter into routine clinical care in patients with vascular disease. Furthermore, they provided a broad spectrum of FDG-uptake parameters such as the standardized uptake value, the target to background ratio, and the most diseased segment. Based on these analyses, they were able to show that patients with RA have an increased aortic FDG uptake even in comparison with patients with stable cardiovascular disease (CVD). Furthermore, they provided data indicating that TNF-α therapy is likely able to reduce aortic inflammation in those patients. In general, this study emphasizes the importance of FDG-PET imaging not only for identifying patients at risk for vascular inflammation and, consequently, for CVD, but also for serving as an end point for treatment evaluation.

It is also important to emphasize the background population of this study. Although it is now well recognized that inflammation plays an important role in plaque vulnerability in the general population, the role of RA-related inflammation, and perhaps, more importantly, autoimmunity, as a driver of heightened CVD risk in the RA population remains incompletely understood. In fact, the interpretation of the study results by the authors as “subclinical vasculitis” is particularly intriguing to the rheumatology community, given the established role of autoantibodies and autoimmunity in a subset of vasculitides. From a clinical perspective, aortic vasculitis has previously been described in the RA population by Gravallese et al25 in an autopsy-based case series, linked to coronary arthritis and myocardial infarction in a subset of RA-related aortitis cases. Thus, it is plausible that aortic vasculitis may be linked to a more generalized vasculitis that includes the coronary arteries and could contribute to the heightened CVD risk observed in the RA population.

The study by Mäki-Petäjä and colleagues24 is an important contribution to the rheumatology community for another
reason. Although it has been observed in multiple studies that anti-TNF biologics reduce the risk of incident CVD events in RA patients, the underlying mechanism(s) have been widely debated. The current study adds diminution of localized vascular inflammation to the growing list of potential mechanisms by which anti-TNF biologics may reduce CVD risk. One important limitation of this study is that it is not clear whether other immunomodulator biological drug classes, or even methotrexate, can reduce vascular inflammation in a comparable manner. For RA-related outcomes, including joint counts, patient-reported outcomes, and achievement of clinical remission, there is a growing literature that nonbiological RA drugs such as methotrexate, in particular, prescribed as combination therapy, can frequently achieve clinical outcomes comparable to targeted biological therapies, including anti-TNF drugs.

The work by Miiki-Petäjä and colleagues raises a number of additional intriguing questions. An important question is whether or not the extent of aortic vascular inflammation detected by PET can actually predict clinical CVD events in the RA population. Moreover, if vascular inflammation by PET does indeed predict incident CVD events, are there surrogate biomarkers that can be applied to clinical practice more easily and in a more cost-effective manner? Specifically, what is the relationship between circulating inflammatory biomarkers and vascular inflammation? And finally, to what extent can short-term changes in such biomarkers predict changes in vascular inflammation and CVD risk? In many respects, this study raises several interesting questions that need to be answered in the future, and yet it can be viewed as a landmark study that pushes forward our understanding of a potential mechanism underlying the heightened CVD risk in the RA population.

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Disclosures
None.

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