

Letter to the editor

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DOES SUBCLINICAL ATHEROSCLEROSIS REALLY EXIST IN SYSTEMIC SCLEROSIS? COMMENT ON THE ARTICLE BY TUIEL ET AL.

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To the Editor:

We read with interest the article by Turiel et al. recently published in *Arthritis Care & Research* (1), which suggested the presence of subclinical atherosclerosis (ATS) in patients with systemic sclerosis (SSc), as indicated by early impairment of coronary flow reserve (CFR), increased carotid artery stiffness and carotid intima-media thickness (IMT), and there are some comments we would like to make.

The recent interest on this topic is probably the consequence of improvement in overall survival of SSc patients and increase of non-SSc comorbidities which contribute to mortality (2).

Microvascular damage is considered to be a hallmark of SSc. Nevertheless, there have been conflicting reports regarding the presence and extent of macrovascular disease that might evolve due to ATS in SSc patients (3). The microvascular changes described in SSc include endothelial damage and smooth muscle cell migration in the intima, which may resemble atherosclerotic changes. Despite conflicting results of IMT in SSc patients, the most recent and largest studies of SSc patients found no difference in either plaque occurrence or IMT (4,5), while the prevalence of coronary artery and cerebrovascular disease remains unclear (6). Akram et al. found in SSc patients a similar prevalence of coronary artery disease compared to general population (based on analysis of 172 angiographic studies, which is the gold standard to evaluate CAD) (7).

Atherosclerosis and SSc seem to share some pathophysiological mechanism. Proposed mediators of the vasculopathy of SSc which have also been implicated in atherosclerosis include endothelial dysfunction, a reduced number of circulating endothelial progenitor cells, and an increased number of microparticles (8). Thus, a diagnostic method which might differentiate between the two processes is of primary importance in SSc.

In general, CFR alone cannot differentiate microcirculation dysfunction from anatomic arterial stenosis (9). Therefore, the common finding of abnormal CFR in SSc patients does not necessarily imply atherosclerotic plaque in these asymptomatic patients. In our experience, CFR impairment

was not sustained by epicardial coronary stenosis, as confirmed by cardiac MDCT, but seemed related to microcirculation involvement in SSc patients (10). As result, it can be concluded that abnormal CFR in SSc patients is most probably not caused by coronary ATS.

The role of plasma ADMA levels in SSc should be better defined; in fact lack of any correlation between ADMA levels and CFR in the study by Turiel et al. seems to be related to endothelial dysfunction but not to impaired microcirculation, differently from other rheumatic disease in which it has been proposed as a surrogate marker of subclinical ATS (11).

Indeed, as a single marker may not be sufficient to determine the cardiovascular risk, a combination of different diagnostic investigations including biomarkers and imaging modalities can be utilized. In conclusion, the utility of all of these markers has not been validated in well-controlled studies in large cohorts of SSc patients, differently from other rheumatic disease such as systemic lupus erythematosus and rheumatoid arthritis in which premature and accelerated ATS has been well established (12, 13). As a result, their potential clinical implications remain still unclear.

REFERENCES

1. Turiel M, Gianturco L, Ricci C, Sarzi-Puttini P, Tomasoni L, De Gennaro Colonna V, et al. Silent cardiovascular involvement in patients with diffuse systemic sclerosis: a controlled cross-sectional study. *Arthritis Care Res* 2013;65:274-280.
2. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1997-2002. *Ann Rheum Dis* 2007;66:940-944.
3. Nussinovitch U, Schoenfeld Y. Atherosclerosis and macrovascular involvement in systemic sclerosis: myth or reality. *Autoimmun Rev* 2011;10:259-66.
4. Nordin A, Bjornadal L, Jensen-Urstad K, Svenungsson E. *ACR/ARHP 09 Scientific Meeting Philadelphia*, vol. 454;2009
5. Hetteema ME, Zhang D, de Leeuw K, Stienstra Y, Smit AJ, Kallenberg CG, et al. Early atherosclerosis in systemic sclerosis and its relation to disease or traditional risk factors. *Arthritis Res Ther* 2008;10:R49.

6. Ngian GS, Sahhar J, Wicks IP, Van Doornum S. Cardiovascular disease in systemic sclerosis – an emerging association? *Arthritis Res Ther* 2011;13:237.
7. Akram MR, Handler CE, Williams M, Carulli MT, Andron M, Black CM, et al. Angiographically proven coronary artery disease in scleroderma. *Rheumatol* 2006;45:1395-8.
8. Au K, Singh MK, Bae S, Maranian P, Ogawa R, Spiegel B, et al. Atherosclerosis in systemic sclerosis. A systematic review and meta-analysis. *Arthritis Rheum* 2011;63:20178-2090.
9. Montisci R, Vacca A, Garau P, Colonna P, Ruscazio M, Passiu G, et al. Detection of early impairment of coronary flow reserve in patients with systemic sclerosis. *Ann Rheum Dis* 2003;69:890-3.
10. Vacca A, Siotto P, Cauli A, Montisci R, Garau P, Ibba V, et al. Absence of epicardial coronary stenosis in systemic sclerosis patients with severe impairment of coronary flow reserve. *Ann Rheum Dis* 2005;65:274-75.
11. Dimitroulas T, Sandoo A, Kitas GD. Asymmetric dimethylarginine as a surrogate marker of endothelial dysfunction and cardiovascular risk in patients with systemic rheumatic diseases. *Int J Mol Sci* 2012;13:12315-12335.
12. Hak AE, Karlson EW, Feskanich D, Stampfer MJ, Costenbader KH. Systemic lupus erythematosus and the risk of cardiovascular disease: results from the nurses' health study. *Arthritis Rheum* 2009;61:1396-1402.
13. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation* 2003;107:1303-1307.