Reply to the comment on: Carotid artery ultrasonography and shear wave elastography in Takayasu's arteritis: a comparative analysis with diabetes mellitus

Sirs,

We appreciate the interest shown by Çağlar *et al*. (1) in our recent study (2). However, based on their comments, it appears they may not have fully understood the main objective of the study, which represents the final step of a continuum project. We therefore welcome the opportunity to clarify the overall aim of our work, summarise our previous contributions to the understanding of atherosclerosis in Takayasu's arteritis (TAK) (3-5), and respond to the specific issues raised.

We first demonstrated in a controlled study using ultrasonography (US) that TAK patients have distinctly elevated carotid intima-media thickness (IMT) compared to patients with systemic lupus erythematosus (SLE) and healthy controls (3). This thickness was homogeneous, concentric, and particularly prominent at the proximal portion of the common carotids, a defining feature of large-vessel vasculitis. We also discovered that TAK patients had significantly increased atherosclerotic plaques at a rate comparable to that observed in SLE (3). Building on this, we utilised multi-detector CT to reveal distinctive calcification patterns in TAK, notably circumferential thoracic aortic calcification, which was unique to TAK and disproportionate to coronary calcification (4). This finding further supported the concept that local inflammation drives atherosclerosis at sites of vasculitic involvement. We then sought to describe morphological changes and evaluate arterial stiffness in the carotids using shear-wave elastography (SWE) and US, this time employing a more sophisticated machine with higher spatial resolution and more advanced image-processing capabilities (5). We demonstrated that TAK patients had significantly elevated carotid IMT, outer diameter and SWE stiffness values compared to both SLE patients and HCs. Notably, disease activity (ITAS2010) correlated with SWE but not IMT. These results suggested that arterial stiffness occurs independently from atherosclerosis and correlates with arterial wall thickening and disease activity. Most recently, we applied the same methodology to compare TAK with type 2 diabetes mellitus (T2DM) as a prototype of advanced atherosclerosis (2). The study revealed that despite having lower cardiovascular risk factors, TAK patients exhibited greater IMT, arterial diameter, and stiffness than diabetic patients, with distinct atherosclerotic patterns. In light of the whole project (2-5), we concluded that TAK itself confers excess risk for accelerated atherosclerosis, likely driven by local vascular inflammation, increased wall thickness, arterial stiffness, and hypertension.

Specifically, Çağlar *et al*. argue that the study failed to control for treatment-related confounders that could independently affect arterial stiffness and IMT. We did not control for medications, and this was a deliberate choice for several reasons. First, our goal was to compare authentic populations as they present in clinical practice. Second, this would be in any case impossible because TAK patients by necessity require immunosuppressive and anti-hypertensive therapy throughout their lives; these medications are integral to the disease state itself. Attempting to control for them would create a highly selected, non-representative sample, other than impossible given that TAK is a rare disease. Lastly, the claim that glucocorticoids and biological immunosuppressive drugs can each alter vascular inflammation and elasticity (1) remains largely hypothetical, as there has been no solid evidence indicating this thus far.

Regarding disease activity, ITAS2010 was assessed but not included in regression models. This was intentional as our primary aim was to compare vascular characteristics between TAK and T2DM cohorts. To note, we have previously demonstrated that disease activity correlated with SWE in earlier work (5).

We did not formally assess intra- and inter-observer variability because we had recently validated this technique using identical equipment and operator (5). As stated in detail previously (2-5), both our SWE protocol and IMT measurements followed standard protocols. Furthermore, the authors cite a 2025 publication which seems to be published after our study as the gold standard for methodology.

Finally, the authors contend that without histopathologic correlation or adjunctive imaging, it remains uncertain whether elevated SWE values represent fibrotic remodelling or ongoing subclinical inflammation. Their concern is frankly unrealistic for a clinical comparative study. Are the authors suggesting we should have performed carotid artery biopsies? We would like to remind again, our purpose in this study was not to discern these features but to compare vascular changes in TAK with plain atherosclerosis. Whether SWE can distinguish active inflammation from chronic fibrotic changes remains an intriguing question for future investigation.

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Competing interests: none declared.

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