COMMENTS AND RESPONSES

Association of Lower Plasma Fetuin-A Levels With Peripheral Arterial Disease in Type 2 Diabetes

Response to Stefan et al.

We acknowledge the comments made by Stefan et al. (1) and appreciate the opportunity to address them further while clarifying some points. The Penn Diabetes Heart Study (PDHS) is not a retrospective study but a prospective community-based cohort focusing on subclinical atherosclerosis in patients with type 2 diabetes. Notably, PDHS participants are recruited specifically to exclude clinical cardiovascular disease (CVD) or moderate-to-severe chronic kidney disease (CKD). However, the substantial burden of subclinical coronary atherosclerosis observed in PDHS participants (2) suggests an increased long-term cardiovascular risk. Therefore, the PDHS provides the opportunity to study subclinical peripheral atherosclerosis in patients with type 2 diabetes without the confounding and possible reverse causation associated with clinical CVD and established CKD while also minimizing the potential for selection and survival biases often found in more convenient type 2 diabetes samples.

In this context, we performed a cross-sectional analysis of plasma fetuin-A association with PAD parameters at the time of enrollment. The crude prevalence of obstructive PAD (ankle brachial index <0.9) was relatively low (5.6%) in our sample, and we acknowledged clearly in our article (3) the need for replication of our findings in larger studies. It is noteworthy that the inverse association between PAD and fetuin-A in the PDHS was relatively strong for a single biomarker (odds ratio [OR] of PAD for one SD decrease in fetuin-A; 1.6 [95% CI 1.05–2.5], $P = 0.03$), consistent in the fetuin-A stratified analysis (OR of PAD for lowest tertile of fetuin-A; 3.2 [1.2–8.5], $P = 0.01$), and in fact one the strongest for PAD in our analysis of traditional and novel CVD risk factors (manuscript in preparation). We recognize that medial arterial calcification, microvascular disease, or even aortic valvular disease are possible confounding factors of the association observed.

We point to the recent publication by Emoto et al. (4) that demonstrates a negative correlation between plasma fetuin-A and carotid- and femoral-calcified atherosclerotic plaques in type 2 diabetic patients without kidney disease. These findings in a similar study population are remarkably consistent with ours and provide strong support for our findings. Ultimately, prospective data with longitudinal outcomes in large cohorts will provide definitive answers.

Emerging data argue against a homogenous association of fetuin-A with vascular disease traits across different vascular territories and in all pathophysiological states but rather modifying effects depending on the pathobiologic milieu in which this glycoprotein interacts (5). This theory is supported by a recent fetuin-A gene manipulation study (6) showing increased intimal atherosclerotic calcification in Apo-E–deficient mice only in the setting of fetuin deficiency, hyperphosphatemia, and kidney disease. We hypothesize that fetuin-A in type 2 diabetic patients inhibits calcification of atherosclerotic plaques, but that CKD and dialysis may modify or confound the relationship.

In summary, our study highlights the importance of further large prospective studies and animal model systems to evaluate the role of serum fetuin-A in the early development and progression of complex vascular phenotypes in subjects with type 2 diabetes. Careful examination of the impact of modifying environmental, host-genetic, and other pathophysiological factors is required to determine causality and human clinical and therapeutic relevance.

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