COMMENTS AND RESPONSES

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

Response to Eraso et al.

In the article by Eraso et al. (1), circulating fetuin-A was lower in subjects with type 2 diabetes and an ankle brachial index (ABI) <0.9 compared with individuals with higher ABI. Furthermore, in an unadjusted model circulating fetuin-A correlated positively with ABI. It was concluded that low circulating fetuin-A may serve as a biomarker of peripheral arterial disease (PAD).

This conclusion is only weakly supported by the data. It is very important to know that in the study by Eraso et al. (1), subjects with any clinical evidence of cardiovascular disease (CVD) were excluded. Considering that PAD and CVD mostly occur jointly, the study design most likely resulted in a selection bias and, thus, the studied group of subjects is not representative for individuals with PAD in the general population of individuals with diabetes. This is further supported by the fact that only 38 of the 738 subjects (5%) included in the analysis had PAD according to the selected criteria ABI <0.9.

Fetuin-A has two main mechanisms of action when it comes to vascular disease. First, as discussed by Eraso et al. (1), it protects from general ectopic and vascular calcification in animals by keeping calcium and phosphorus solubilized in serum. Second, many cross-sectional studies showed associations of high fetuin-A levels with impaired glucose and lipid metabolism (2,3). There is overwhelming data providing evidence that fetuin-A induces insulin resistance and subclinical inflammation in vitro and in animals in vivo and that high circulating fetuin-A is associated with incident type 2 diabetes and CVD (3). Recently, we used a Mendelian randomization approach to demonstrate that fetuin-A may be causally related to development of CVD, yet in the opposite direction—as proposed by Eraso et al.—higher levels (and single nucleotide polymorphisms that predicted higher levels) were associated with CVD in the general population (4). In the setting of diabetes, a prior study has shown that higher fetuin-A levels are associated with greater coronary artery calcification, a sensitive marker of coronary atherosclerosis (5). Thus, the existing literature would support the hypothesis that high fetuin-A levels, rather than lower, would associate with greater risk of PAD.

Furthermore, Eraso et al. (1) suggested that low circulating fetuin-A may be a biomarker of PAD. Because of the very weak strength of association of fetuin-A levels with ABI, this statement is not sufficiently supported by the data. These data suggest that the positive predictive value of fetuin-A levels would be small.

In conclusion, caution is warranted both when the prevalence of PAD is assessed in a retrospective analysis and when fetuin-A data are interpreted in respect to their impact on vascular complications.

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