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COMMENTARY

Is fetuin-A a biomarker of preclinical atherosclerosis in essential hypertension?

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In this issue of the Journal, Guarneri and coworkers[1] report the results of a cross-sectional study aimed at assessing the relationship of fetuin-A, a circulating calcium-regulatory glycoprotein that inhibits vascular calcification, and common carotid intima–media thickness (CIMT) in a cohort of untreated hypertensive subjects free from overt cardiovascular disease. Before addressing this issue in detail, some general considerations about the clinical and prognostic value of CIMT may be useful.

CIMT is a well-recognized marker of atherosclerosis; it has been associated with traditional cardiovascular risk factors and prevalent/incident cardiovascular disease. As the pioneering studies by Pignoli *et al.*,[2] who demonstrated that CIMT provides a reliable measurement of the arterial wall size based on both histological and anatomic comparisons, hundreds of cross-sectional studies using high-definition ultrasound scanning of carotid arteries have consistently shown a direct, independent relationship between CIMT and established risk factors such as age, blood pressure, diabetes, dyslipidemia and smoking. Further studies have provided a clear evidence of an association between CIMT and preclinical cardiac and extracardiac alterations, including left ventricular hypertrophy, coronary calcifications, cerebral white matter lesions, peripheral arterial atherosclerosis and microalbuminuria. More importantly, a number of prospective trials, including the Atherosclerotic Risk in Communities (ARIC), the Rotterdam Study, the Cardiovascular Health Study (CHS), the European Lacidipine Study on Atherosclerosis (ELSA) and the Carotid Atherosclerosis Progression Study (CAPS) have reported that CIMT and/or plaques are strong predictors of coronary events and stroke. For instance, in the ARIC study the relation of CIMT with the incidence of coronary heart disease was assessed over a 4–7 years follow-up in 12 841 participants aged 45–64 years. In sex-specific Cox proportional hazards models, the hazard ratio of incident events for IMT values $\geqslant 1$ *vs.* <1 mm was 5.07 in women (95% confidence interval, 3.08–8.36) and 1.85 in men (95% confidence interval, 1.28–2.69). Among the 5858 elderly subjects enrolled in the CHS, the incidence of cardiovascular events (acute myocardial infarction or stroke) was highly correlated with CIMT ($P<0.001$). In particular, the relative risk of myocardial infarction or stroke adjusted for age and sex in the highest CIMT quintile as compared with the lowest one was 3.87 (95% confidence interval, 2.72 −5.51). On the basis of the documented value of CIMT as a measure of atherosclerotic burden and predictor of both prevalent and incident cardiovascular disease, Guarneri *et al.*[1] examined the link between this vascular phenotype and fetuin-A, an emerging nontraditional risk factor.

Human fetuin-A, (α_2-Heremans Schmid glycoprotein ASHG) is a liver-derived plasma protein member of the cystatin superfamily.[3] Fetuin-A is a potent inhibitor of ectopic calcification accounting for ~50% of serum capacity to prevent calcium and phosphate precipitation. Circulating fetuin-A is reduced in inflammatory states in patients on hemodialysis and is inversely related to C-reactive protein levels, meaning that it is a negative acute phase protein. Anti-inflammatory properties of fetuin-A have been consistently reported in animal models; this view, however, has recently been challenged by experimental data showing that fetuin-A promotes inflammatory cytokines and that a major mediator of inflammatory cytokine action, NF-kB, upregulates hepatic fetuin-A synthesis.

The adverse impact of fetuin-A deficiency on cardiovascular system is mainly supported by experimental studies in mouse and mice and in hemodialysis patients. Diffuse extraosseous calcifications (including vessels and cardiac valves) have been detected in fetuin-A knockout mice. In dialysis patients, low fetuin-A levels have been related to increased vascular calcification, to calcific uremic arteriolopathy and to cardiovascular mortality. The first report focusing on the relationship between serum fetuin-A levels and mortality was provided by Ketteler *et al.*[4] In a cohort of 312 patients on hemodialysis, the lowest tertile of serum fetuin-A levels was associated with increased all-cause and cardiovascular mortality ($+23$ and $+12\%$ *vs.* the highest tertile, respectively, $P=0.05$ for both). In patients with pathologically low fetuin-A concentrations, the circulating levels of C-reactive protein were significantly increased and the inverse relationship between these compounds was highly significant.

It should be noted, however, that fetuin-A did not maintain its significance in predicting all-cause mortality and cardiovascular mortality when C-reactive protein was entered in the model in Cox regression analyses. These data were subsequently expanded by Stenvinkel *et al.*[5] in a group of 258 patients starting renal replacement therapy. By using Kaplan–Meier survival curves, the authors assessed the association between fetuin-A concentrations and incident mortality: during the observation period of 3.5 years, all-cause and cardiovascular mortality were both

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significantly ($P<0.001$) associated with low fetuin-A levels independently of age, smoking, diabetes, serum albumin, cardiovascular disease and inflammation state (C-reactive protein $\geqslant 10\,mg\,l^{-1}$). Interestingly, a logistic regression model in a subgroup of 101 patients showed that fetuin-A was significantly ($P<0.05$) associated with the presence of carotid plaques independently of several confounders, including C-reactive protein. Finally, patients with a specific fetuin-A gene polymorphism (256 Ser allele) had lower fetuin-A levels and higher all-cause and cardiovascular mortality rate. In a cohort of 238 patients on peritoneal dialysis, low serum fetuin-A levels showed important associations with malnutrition, inflammation, atherosclerosis and valvular calcification; no independent relationship, however, was present with mortality or cardiovascular events.[6] Notably, patients having all components of malnutrition–inflammation–atherosclerosis–calcification syndrome had the lowest fetuin-A levels. This finding suggests that the assessment of fetuin-A concentration in this setting may be useful in identifying subjects at very high cardiovascular risk. A number of studies in hemodialysis patients have also focused on the association between fetuin-A and coronary calcification. In 78 patients, on hemodialysis for >6 months, serum fetuin-A levels were negatively correlated with coronary arteries calcium scores ($r=-0.30$, $P=0.009$), determined by electron-beam computed tomography; in particular, patients with extensive coronary calcification had the lowest fetuin-A concentrations. Overall, these observations support the concept that fetuin-A deficiency is a marker of vascular and cardiac calcification, a phenotype associated with unfavorable prognosis.

More controversial data about the association between fetuin-A concentrations and the extent of vascular calcification, indices of atherosclerotic involvement (that is, CIMT, arterial stiffness and ankle-brachial index) and mortality are available in patients with preserved renal function or mild-to-moderate renal impairment, as well as in individuals with Type 2 diabetes mellitus. In the Rancho Bernardo Study, a population-based prospective study of 633 men and 1025 women, the association of fetuin-A with cardiovascular mortality differed according to diabetes status.[7] Low fetuin-A levels predicted greater risk for cardiovascular mortality in subjects without diabetes, but were associated with a reduced risk of cardiovascular death in those with diabetes. The magnitude of coronary artery calcification correlated with increased rather than decreased fetuin-A levels in a group of diabetic patients with chronic kidney disease spanning stages 1–4. Finally, in 312 middle-aged subjects without known cardiovascular or inflammatory disease Rittig *et al.*[8] found a positive correlation between CIMT and fetuin-A, independently of traditional risk factors such as blood pressure or lipids.

In their paper, Guarneri and coworkers[1] examined the association between fetuin-A and subclinical atherosclerosis as assessed by common CIMT in 105 non-diabetic, untreated essential hypertensive subjects (mean age 47 ± 12 years, 66% men) with normal renal function and 55 age-matched healthy individuals (mean age 45 ± 10 years, 45% men). The main findings of the study can be summarized as follows: (1) mean plasma fetuin-A concentrations were significantly lower (-18%, $P<0.001$) in hypertensive subjects than in controls; (2) hypertensives with ticker CIMT ($\geqslant 900\,\mu m$) had lower fetuin-A levels (-11%, $P<0.001$) than their counterparts with normal CIMT (as defined according to the 2007 ESH/ESC guidelines); (3) in the whole study sample, a significant inverse correlation was found between fetuin-A and CIMT ($r=-0.40$, $P<0.001$); (4) in multiple regression analyses, older age, male gender and fetuin-A were independently correlated with CIMT ($P<0.001$ for all); this was not the case for biomarkers of oxidative stress and inflammation, such as interleukin 6, tumor necrosis factor-α and the isoprostane 8iso-PGF2α.

These results are in keeping with previous findings from patients on hemodialysis and patients with atherosclerotic aortic aneurysms; moreover, they extend previous observations to a sample of nondiabetic subjects with untreated hypertension, preserved renal function and free from overt cardiovascular disease. The observations by Guarneri *et al.*,[1] however, are not in line with studies carried out in a population-based sample without prevalent hypertension,[8] in subjects with nonalcoholic fatty liver disease[9] and in patients with Type 2 diabetes mellitus or with atherosclerotic vascular disease.[10] In fact, in these settings, a direct, rather than an inverse, correlation between fetuin-A levels and CIMT has been reported. These conflicting data may be related to the heterogeneity of patients examined in terms of clinical and demographic characteristics.

A few strengths and limitations of this study deserve to be mentioned. First, although cross-sectional investigations do not allow any causal inference, the paper by Guarneri *et al.*[1] offers a new piece of information by suggesting that fetuin-A downregulation is a potential pathway promoting carotid atherosclerosis in the early phases of essential hypertension. Thus, the assessment of plasma fetuin-A could identify patients with subclinical carotid atherosclerosis over and beyond traditional risk factors. It should be mentioned, however, that in this study, important variables such as blood pressure, estimated glomerular filtration rate, serum glucose, low-density lipoprotein and high-density lipoprotein cholesterol did not show any independent correlation with CIMT. Second, an important strength of the study refers to the exclusion of patients taking antihypertensive or lipid-lowering drugs that may have affected the relationship between CIMT and fetuin-A. Two additional important limitations also need to be noted. Despite the authors providing data on several variables related to oxidative stress and inflammation, C-reactive protein levels were not assessed. More importantly, no information was provided on the

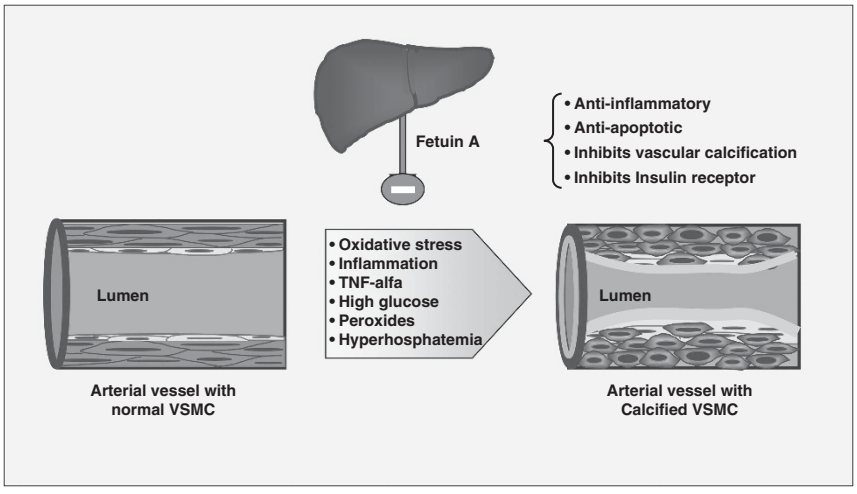

Figure 1 Major biological effects of Fetuin-A. A full color version of this figure is available at the *Hypertension Research* journal online.

carotid atherosclerotic burden in terms of carotid plaques (in particular, calcified plaques) and its relationship with fetuin-A levels.

In conclusion, the emerging role of fetuin-A in the pathophysiology of atherosclerosis and cardiovascular disease (Figure 1) needs to be further elucidated by large prospective studies in various clinical settings.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

Disclaimer: The authors alone are responsible for the content and writing of the paper.

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