Association of Fetuin-A With Mitral Annular Calcification and Aortic Stenosis Among Persons With Coronary Heart Disease
Data From the Heart and Soul Study
Joachim H. Ix, MD; Glenn M. Chertow, MD, MPH; Michael G. Shlipak, MD, MPH; Vincent M. Brandenburg, MD; Markus Ketteler, MD; Mary A. Whooley, MD

Background—Fetuin-A is a multifunctional hepatic secretory protein that inhibits dystrophic vascular and valvular calcification. Lower serum fetuin-A concentrations are associated with valvular calcification in persons with end-stage renal disease. Whether fetuin-A is associated with valvular calcification in other patient populations is unknown.

Methods and Results—We evaluated the associations among serum fetuin-A concentrations, mitral annular calcification, and aortic stenosis in 970 ambulatory persons with coronary heart disease and without severe kidney disease. The presence or absence of mitral annular calcification and aortic stenosis was determined by transthoracic echocardiography. The subjects’ mean age was 66 years; 81% were men; 189 (20%) had mitral annular calcification; and 79 (8%) had aortic stenosis. Participants were categorized by tertiles of fetuin-A concentrations. Those within the highest fetuin-A tertile had significantly lower odds of mitral annular calcification compared with the lowest tertile (adjusted odds ratio, 0.47; 95% confidence interval, 0.29 to 0.77; \( P = 0.002 \)); this association was similar regardless of diabetes status (\( P \) for interaction = 0.34). In contrast, the association of fetuin-A with aortic stenosis was modified by the presence or absence of diabetes mellitus (\( P \) for interaction = 0.03). Among participants without diabetes, the highest fetuin-A tertile had a significantly lower odds of aortic stenosis compared with the lowest tertile (adjusted odds ratio, 0.37; 95% confidence interval, 0.15 to 0.92; \( P = 0.03 \)), whereas among participants with diabetes, no statistically significant association was observed between fetuin-A and aortic stenosis (adjusted odds ratio, 1.49; 95% confidence interval, 0.48 to 4.63; \( P = 0.49 \)).

Conclusions—Among persons with coronary heart disease, we observed an inverse association of fetuin-A and mitral annular calcification. An inverse association also was observed between fetuin-A and aortic annular calcification. An inverse association also was observed between fetuin-A and aortic stenosis among participants without diabetes mellitus. Fetuin-A may represent an important inhibitor of dystrophic calcification in persons with coronary heart disease. (Circulation. 2007;115:2533-2539.)

Key Words: alpha2HS-glycoprotein ■ calcium ■ diabetes mellitus ■ fetuin-A, human ■ valves

Significant advancements have taken place in the understanding of the basic mechanisms of dystrophic vascular calcification in which the response of the vascular smooth muscle cell to a variety of metabolic perturbations has been elegantly elucidated.\(^1\)\(^2\) However, studies that have examined the mechanisms of valvular calcification have focused predominantly on the microenvironment within valvular tissues,\(^3\)\(^-\)\(^6\) where proteins expressed locally may either inhibit or promote dystrophic calcification. The role of circulating proteins as systemic regulators of dystrophic calcification is largely unknown.

Received December 5, 2006; accepted February 16, 2007.

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Circulation is available at http://www.circulationaha.org

DOI: 10.1161/CIRCULATIONAHA.106.682450

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calcium and phosphorus and increases their solubility in a manner reminiscent of the means by which apolipoproteins solubilize lipids. Incubation of fetuin-A with calcium and phosphorus at physiological pH prevents crystallization for >9 days, whereas the minerals crystallized within hours in its absence. Similar effects have been demonstrated in human serum. Moreover, fetuin-A knockout mice develop widespread soft tissue and valvular calcification when challenged with a phosphorus/vitamin D–enriched diet.

Among persons with end-stage renal disease, lower fetuin-A concentrations are associated with more extensive vascular and valvular calcification in cross-sectional analyses and with increased cardiovascular events and all-cause mortality longitudinally. Whether serum fetuin-A concentrations are associated with dystrophic calcification among other populations is unknown. To that end, we evaluated the hypothesis that lower serum fetuin-A concentrations would be associated with higher prevalence of mitral annular calcification (MAC) and aortic stenosis (AS) among persons with coronary heart disease.

Methods

Study Participants
The Heart and Soul Study is a prospective cohort study designed to investigate the influence of psychosocial factors on the progression of coronary heart disease. Methods have been described previously. Briefly, participants were recruited from outpatient clinics in the San Francisco Bay (Calif) area if they met one of the following inclusion criteria: history of myocardial infarction, angiographic evidence of >50% stenosis in ≥1 coronary vessels, evidence of exercise-induced ischemia by treadmill or nuclear testing, or history of coronary revascularization. Participants were excluded if they were not able to walk 1 block, had a myocardial infarction within the past 6 months, or were likely to move out of the area within 3 years.

The study protocol was approved by the following Institutional Review boards: the University of California San Francisco Committee on Human Research, the Research and Development Committee at the San Francisco VA Medical Center, the Medical Human Subjects Committee at Stanford University, the Human Subjects Committee at the VA Palo Alto Health Care System, and the Data Governance Board of the Community Health Network of San Francisco. All participants provided written informed consent.

Between September 2000 and December 2002, a total of 1024 participants enrolled and underwent a daylong baseline study appointment that included a medical history interview, physical examination, rest echocardiogram, and comprehensive health status questionnaire. Fasting (12-hour) serum samples were obtained and frozen at −70°C. Subjects for whom frozen serum was not available were excluded, resulting in a study sample of 970 subjects for this analysis.

Serum Fetuin-A
Serum fetuin-A was measured with a BNII nephelometric assay (Dade Behring, Newark, Del) as previously described. Serum samples were centrifuged (60 minutes at 15 000g) and diluted 4-fold with PBS (400 μL) (N Diluent, Dade Behring Holdings) and exposed to a polyclonal rabbit anti–human fetuin-A antibody. Particles agglutinated to increase the intensity of scattered light proportionally to the amount of fetuin-A in the sample and were compared to standardized curves. The assay was evaluated in side-by-side comparison with immunoblot analyses to exclude cross-reactivity of the antibodies with other serum proteins and proteolytic fragments of fetuin-A. The assay does not cross-react with fetuin-B. The intra-assay and interassay coefficients of variation are 7.7% and 8.1%. The assay range is from 0.05 to 3.5 g/L.

MAC and AS
All study participants underwent echocardiograms at rest with an Acuson Sequoia ultrasound system using a 3.5-MHz transducer at a core laboratory at the San Francisco VA Medical Center. Complete 2-dimensional echocardiograms, including Doppler images, were obtained in all standard views. Echocardiograms were read by a single experienced cardiologist who was blinded to participants’ clinical information.

MAC was defined by an echo-dense structure located at the junction of the atrioventricular groove and the posterior mitral leaflet on the parasternal long-axis, apical 4-chamber, or parasternal short-axis view. Peak and mean aortic-valve pressure gradients were calculated by the Bernoulli equation; aortic valve area was calculated by the continuity equation. AS was defined by a peak velocity of >2.0 m/s, a peak gradient of >15 mm Hg, and a valve area of <2.0 cm².

Other Patient Characteristics and Laboratory Measurements

Self-reported age and medical history were determined by questionnaire. Study participants underwent a complete physical examination that included blood pressure determination by trained study personnel using a calibrated sphygmomanometer. Participants were weighed and measured without shoes, and body mass index (kg/m²) was calculated. Kidney function was determined by the abbreviated (4-variable) Modification Diet and Renal Disease study formula: estimated glomerular filtration rate = 186 × (serum creatinine)⁻¹ · (age)⁻₀·₂₀·₃ · (0.742 if female) × (1.21 if black). Fasting serum samples were used to measure total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels. Low-density lipoprotein cholesterol concentrations were estimated by the Friedewald equation. High-sensitivity C-reactive protein was measured with the Roche Integra Assay and Beckman Extended Range Assay as previously described.

Statistical Analysis

Participants were categorized into fetuin-A tertiles. Baseline differences in participant characteristics were compared across fetuin-A tertiles by ANOVA or Kruskal-Wallis test for continuous variables and the χ² test or Fisher exact test for categorical variables. Logistic regression analysis evaluated the bivariate and multivariable associations of fetuin-A tertiles with the presence or absence of MAC and AS. Candidate covariates for adjustment represent those presented in Table 1. Each candidate covariate was added individually to the model. When addition of a covariate changed the β coefficient of the association of fetuin-A with each valvular lesion by ≥5%, the covariate was retained in final models. Multiplicative interaction terms were created to evaluate for effect modification by diabetes and age, which were selected a priori on the basis of prior research. Analyses were performed with Stata Statistical Software, version 9 (Stata Corp, College Station, Tex).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Among the 970 participant study sample, the mean age was 66 years, 81% were men, 60% were white, 16% were black, and 23% were categorized as “other race.” The mean fetuin-A concentration was 0.65 ± 0.14 g/L and was normally distributed in the study sample. Baseline characteristics by tertiles of fetuin-A are shown in Table 1. Compared with participants in the lowest tertile, participants with higher fetuin-A concentrations were younger, more frequently women, and more likely to have diabetes mellitus; had higher body mass index, low-density lipoprotein cholesterol, and serum triglyceride concentrations; and had lower high-density lipoprotein cho-
Serum fetuin-A concentrations. Kidney function did not differ across groups. Participants with higher fetuin-A concentrations also had higher C-reactive protein, albumin, and calcium concentrations.

One hundred eighty-nine study participants (20%) had MAC. The prevalence of MAC was greatest among participants within the lowest fetuin-A tertile (Figure 1). Compared with the lowest tertile, participants in the highest tertile had approximately one-half the odds of MAC, an association that persisted and was minimally attenuated in fully adjusted models (Table 2). We found no evidence of effect modification in the association of fetuin-A and MAC by diabetes status (P for interaction=0.34) or age (P for interaction=0.62).

Seventy-nine participants (8%) had AS. The association of fetuin-A and AS differed significantly among participants with or without diabetes mellitus (P for interaction=0.03). Among participants without diabetes mellitus, the prevalence of AS was greatest in the lowest fetuin-A tertile, whereas among participants with diabetes, the prevalence was similar across groups (Figure 2). In the nondiabetic stratum, the highest fetuin-A tertile had roughly one-third the odds of AS compared with the lowest tertile after multivariate adjustment (Table 3). Among nondiabetic participants, the odds of AS were not statistically different across fetuin-A tertiles (Table 3). We found no evidence of effect modification by age (P for interaction=0.73).

**Discussion**

In the present study, we demonstrate an inverse association of serum fetuin-A concentrations with MAC among a cohort with coronary heart disease and without severe kidney disease. A similar association was observed between fetuin-A and AS but was limited to participants without diabetes mellitus. These associations were moderately strong and were essentially unaltered after extensive statistical adjustment for traditional risk factors for cardiovascular disease and dystrophic calcification. These findings are consistent with the hypothesis that fetuin-A may be an inhibitor of dystrophic valvular calcification among persons with coronary heart disease and, in the context of prior research, suggest a novel mechanism for the regulation of dystrophic mineralization.

**Table 1. Baseline Characteristics by Tertiles of Fetuin-A**

<table>
<thead>
<tr>
<th>Fetuin-A Tertiles</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range, g/L</td>
<td>0.59</td>
<td>0.60 to 0.70</td>
<td>&gt;0.70</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>324</td>
<td>325</td>
<td>321</td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>69±11</td>
<td>67±11</td>
<td>64±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>274 (85)</td>
<td>268 (82)</td>
<td>246 (77)</td>
<td>0.03</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td>196 (60)</td>
<td>195 (60)</td>
<td>193 (60)</td>
<td>0.56</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td>70 (22)</td>
<td>72 (22)</td>
<td>113 (35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>70 (22)</td>
<td>72 (22)</td>
<td>113 (35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>236 (73)</td>
<td>225 (69)</td>
<td>226 (71)</td>
<td>0.51</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>65 (20)</td>
<td>58 (18)</td>
<td>68 (21)</td>
<td>0.53</td>
</tr>
<tr>
<td>Calcium channel blocker use</td>
<td>82 (25)</td>
<td>81 (25)</td>
<td>73 (23)</td>
<td>0.72</td>
</tr>
<tr>
<td>Multivitamin use</td>
<td>72 (22)</td>
<td>65 (20)</td>
<td>52 (16)</td>
<td>0.15</td>
</tr>
<tr>
<td>Measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27±5</td>
<td>28±5</td>
<td>29±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estimated GFR, mL · min⁻¹ · 1.73 m²⁻²</td>
<td>77±25</td>
<td>76±23</td>
<td>75±21</td>
<td>0.31</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>95±28</td>
<td>105±33</td>
<td>113±38</td>
<td>0.05</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>49±15</td>
<td>46±14</td>
<td>43±12</td>
<td>0.07</td>
</tr>
<tr>
<td>Triglycerides, mg/dL, median (interquartile range)</td>
<td>80 (61–199)</td>
<td>110 (76–155)</td>
<td>144 (102–248)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL, median (interquartile range)</td>
<td>1.9 (0.6–3.9)</td>
<td>2.4 (1.0–5.5)</td>
<td>2.4 (1.0–4.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.8±0.4</td>
<td>3.9±0.3</td>
<td>4.0±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium, mg/dL</td>
<td>9.4±0.5</td>
<td>9.5±0.5</td>
<td>9.6±0.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Phosphorus, mg/dL</td>
<td>3.6±0.6</td>
<td>3.7±0.6</td>
<td>3.7±0.6</td>
<td>0.12</td>
</tr>
</tbody>
</table>

GFR indicates glomerular filtration rate; LDL, low-density lipoprotein; and HDL, high-density lipoprotein. Values are mean±SD unless otherwise indicated.

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tion, including diabetes mellitus, body mass index, low-density lipoprotein cholesterol, triglycerides, and calcium concentrations. These results suggest that fetuin-A may involve a regulatory mechanism of dystrophic valvular calcification that is independent of previously recognized mechanisms. Future research evaluating fetuin-A among persons with coronary heart disease may therefore provide novel insights into the biology of valvular heart disease.

The association between fetuin-A and MAC was evident regardless of diabetes status, whereas the association between fetuin-A and AS was limited to persons without diabetes mellitus. The mechanisms responsible for these disparate findings are uncertain; however, other risk factors for dystrophic calcification have previously been demonstrated to have differential associations with aortic and mitral valve calcification.21,27,28 Whereas prior research has consistently demonstrated a strong association between diabetes mellitus and MAC,29–31 diabetes and AS have not been strongly linked.21,28 Whether fetuin-A or other molecular promoters or inhibitors of dystrophic calcification may explain these disparate observations should be evaluated in future studies.

Separate from its function as an inhibitor of dystrophic calcification, fetuin-A also appears to promote insulin resistance by binding to the extracellular domain of insulin receptor tyrosine kinase in peripheral tissues and decreases the rate of autophosphorylation and subsequent downstream intracellular signaling cascades.32,33 Despite their extensive calcification, fetuin-A knockout mice are characterized by resistance to weight gain, lower free fatty acid and triglyceride concentrations, and improved insulin sensitivity.34 We previously demonstrated that higher fetuin-A concentrations are associated with the metabolic syndrome and an atherogenic lipid profile in humans.19 This dual role of fetuin-A may explain the differential relationship between fetuin-A and AS among the diabetic and nondiabetic participants. In line with this hypothesis, prior epidemiological studies in populations primarily without diabetes mellitus have demonstrated an inverse correlation of fetuin-A with vascular calcification14,15 but a direct correlation in diabetic cohorts.35 The cross-sectional study design does not allow us to investigate the longitudinal relationship of these associations; however, we hypothesize that factors promoting an insulin-resistant phenotype might result in higher serum fetuin-A concentrations, which may be protective in this setting by limiting the amount of dystrophic calcification conferred by an insulin-resistant state.36,37

Prior epidemiological studies evaluating the associations of fetuin-A with dystrophic calcification have largely been limited to populations with end-stage renal disease in which lower fetuin-A concentrations are associated with vascular14 and valvular calcification15 and mortality.11,15 Here, we demonstrate an inverse association of fetuin-A with dystrophic valvular calcification among a population without severe kidney disease. We have previously demonstrated that fetuin-A concentrations are similar across the spectrum from normal to moderate kidney dysfunction.8 Together, these data suggest that fetuin-A may function as an inhibitor of dystrophic calcification among other populations and is not limited

### TABLE 2. Odds of Mitral Annular Calcification by Fetuin-A Tertiles

<table>
<thead>
<tr>
<th>Fetuin-A Tertiles</th>
<th>Proportion, % (n/N)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (&lt;0.59 g/L)</td>
<td>25 (82/323)</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>II (0.60 to 0.70 g/L)</td>
<td>20 (63/323)</td>
<td>0.71 (0.49 to 1.03)</td>
<td>0.71 (0.48 to 1.06)</td>
</tr>
<tr>
<td>III (&gt;0.70 g/L)</td>
<td>14 (44/319)</td>
<td>0.47 (0.31 to 0.71)</td>
<td>0.47 (0.29 to 0.77)</td>
</tr>
</tbody>
</table>

P for Trend = 0.001

OR indicates odds ratio; CI, confidence interval.
*Adjusted for age, gender, race/ethnicity, diabetes mellitus, low-density lipoprotein cholesterol, triglycerides, and albumin.
to persons with end-stage renal disease. However, all participants in the present study had coronary heart disease. Future studies are required to evaluate whether these observations are generalizable to the general population.

Among the strengths of the present study are its relatively large sample size and the measurement of a wide spectrum of potential confounding variables. However, several limitations should be considered in the interpretation of the results. First, the cross-sectional study design does not allow evaluation of the longitudinal direction of associations. Evaluation of the longitudinal association of fetuin-A with incidence and progression of calcification among persons with and without diabetes mellitus should be evaluated in futures studies. Detailed assessment of dietary calcium and phosphorus intake and measures of calcification in other vascular tissues were not available in the study sample. Whereas MAC was determined by direct visualization of an echo-dense structure on echocardiogram, AS was determined by measurements of flow across the aortic valve. The associations of fetuin-A and AS and the effect modification by diabetes status should be confirmed in future studies with direct measures of aortic valve calcification. All participants had coronary heart disease, and the mechanisms of dystrophic calcification may differ among other populations. Because of relatively small cell counts in persons with MAC within each fetuin-A tertile, we cannot exclude that the present study missed a modest interaction in the association of fetuin-A with MAC on the basis of diabetes. Finally, the majority of participants were elderly men, and our results may not necessarily generalize to younger persons or women.

In summary, fetuin-A concentrations are inversely associated with MAC among ambulatory persons with coronary heart disease and without severe kidney disease. Fetuin-A concentrations also were inversely associated with AS among participants without diabetes mellitus. In the context of prior studies, these data are consistent with the hypothesis that fetuin-A may function as an important inhibitor of dystrophic valvular calcification among persons with coronary heart disease and that this function does not require the presence of kidney disease or other traditional cardiovascular risk factors. Future studies are required to evaluate whether fetuin-A is associated with dystrophic calcification among other vascular tissues, whether the results may generalize to persons without coronary heart disease, and whether fetuin-A concentrations may predict longitudinal progression of dystrophic calcification.

Acknowledgments

We thank Nelson B. Schiller, MD, for expert interpretation of echocardiograms and Eric Vittinghoff, PhD, for assistance in statistical consultation.
TABLE 3. Association of Fetuin-A and AS by Strata of Diabetes*

<table>
<thead>
<tr>
<th>Fetuin-A Tertiles</th>
<th></th>
<th></th>
<th></th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I (0.59 g/L)</td>
<td>II (0.60–0.70 g/L)</td>
<td>III (&gt;0.70 g/L)</td>
<td></td>
</tr>
</tbody>
</table>

**Nondiabetics (n = 683)**

<table>
<thead>
<tr>
<th>Prevalence, %</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)†</th>
<th>N</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>245 (12/238)</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
<td>4/198</td>
<td>0.005</td>
</tr>
</tbody>
</table>

**Diabetics (n = 245)**

<table>
<thead>
<tr>
<th>Prevalence, %</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)†</th>
<th>N</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>12 (6/68)</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
<td>14/109</td>
<td>0.70</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval.

*P for interaction = 0.03.
†Adjusted for age, gender, race/ethnicity, diabetes mellitus, low-density lipoprotein cholesterol, triglycerides, and albumin.

Sources of Funding

Dr Ix is funded by a grant from the American Heart Association Fellow-to-Faculty Transition Award. Dr Shlipak was funded by the American Federation for Aging Research and National Institute on Aging (Paul Beeson Scholars Program), the Robert Wood Johnson Foundation (Generalist Faculty Scholars Program), and the National Institutes of Health (R01 DK66448). The Heart and Soul Study was funded by the Department of Veterans Affairs, the American Federation for Aging Research, the Robert Wood Johnson Foundation, the National Institutes of Health (R01 HL079235), the Ischemia Research and Education Foundation, and the Nancy Kirwan Heart Research Fund. Dr Ketteler is funded by the Interdisciplinary Center of Clinical Research (IZKF BioMAT; TV B67) of the Faculty of Medicine at the RWTH Aachen.

Disclosures

Dr Shlipak has received significant research support from Roche Diagnostics. The other authors report no conflicts.

Dr Whooley has received significant research support from Roche Diagnostics. The other authors report no conflicts.

References


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**CLINICAL PERSPECTIVE**

Fetuin-A is a multifunctional hepatic secretory protein that inhibits dystrophic vascular and valvular calcification in vitro. Lower serum fetuin-A concentrations are associated with vascular and valvular calcification in persons with end-stage renal disease. Whether fetuin-A is associated with valvular calcification in other patient populations is unknown. We evaluated the association of serum fetuin-A concentrations with echocardiographically determined mitral annular calcification and aortic stenosis among 970 ambulatory persons with coronary heart disease and without severe kidney disease. We demonstrate that fetuin-A concentrations are inversely associated with mitral annular calcification independently of kidney function or traditional atherosclerotic risk factors. Fetuin-A concentrations also were inversely associated with aortic stenosis among participants without diabetes mellitus. In the context of prior studies, these data are consistent with the hypothesis that fetuin-A may function as an important inhibitor of dystrophic valvular calcification among persons with coronary heart disease and that this function is independent of the presence of kidney disease or other traditional cardiovascular risk factors.
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Circulation. 2007;115:2533-2539; originally published online May 7, 2007;
doi: 10.1161/CIRCULATIONAHA.106.682450
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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