Association of Fetuin-A With Incident Diabetes Mellitus in Community-Living Older Adults

The Cardiovascular Health Study

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Background—The liver-secreted protein fetuin-A induces peripheral insulin resistance in vitro. In a pilot study, we observed that higher fetuin-A levels were associated with diabetes mellitus in older persons. However, this finding has not been confirmed in large cohorts. We sought to confirm the association of fetuin-A with incident diabetes mellitus in older persons and to determine whether the association differs by age, sex, and race and among persons with cardiovascular disease (CVD).

Methods and Results—Among 3710 community-living individuals ≥65 years of age without diabetes mellitus at baseline, fetuin-A was measured in serum collected in 1992 to 1993. Participants were followed up for 10.6 years (median) for incident diabetes mellitus. Cox regression models evaluated the association of fetuin-A with incident diabetes mellitus. Interaction terms evaluated heterogeneity by age, sex, race, and CVD. Mean age was 75 years; 60% were female; 15% were black; and 16% had CVD. Mean fetuin-A concentrations were 0.47±0.10 g/L. During follow-up, 305 incident diabetes cases occurred. Each 0.10-g/L (SD)-greater fetuin-A was associated with 19% higher risk of diabetes mellitus (hazard ratio, 1.19; 95% confidence interval, 1.06–1.33) after adjustment for demographics, lifestyle factors, albumin, kidney function, and CVD. Further adjustment for potential mediators (body mass index, waist circumference, hypertension, lipids, and C-reactive protein) moderately attenuated the association (hazard ratio, 1.13; 95% confidence interval, 1.00–1.28). Results were similar by sex, race, and CVD status but were stronger in persons <75 years old (P for interaction=0.01).

Conclusions—Higher fetuin-A is associated with incident diabetes mellitus in older persons regardless of sex, race, or prevalent CVD status. The association may be attenuated in those ≥75 years of age. (Circulation. 2012;125:2316-2322.)

Key Words: cardiovascular diseases ■ diabetes mellitus ■ alpha-2-HS-Glycoprotein ■ geriatrics ■ obesity ■ risk factors

Secular trends in diet and lifestyle have resulted in an epidemic of diabetes mellitus.1,2 Diabetes incidence and prevalence are both high in older persons,3 an ominous trend as our population ages because this age group already bears the greatest burden of cardiovascular disease (CVD). Yet, aging is associated with a redistribution of fat centrally and with sarcopenia,4,5 so standard clinical risk factors such as body mass index may become less reliable markers of diabetes risk in older age.6

Clinical Perspective on p 2322

Recent studies have identified a family of proteins secreted from adipose tissue, collectively called adipokines, that regulate glucose metabolism. Their study has provided new insights into the biology of glucose regulation in younger and older populations alike. In contrast to adipokines, which come from fat, fetuin-A (also known as α-Heremans-Schmid glycoprotein [Ahsg]) is secreted from the liver.7 In vitro, fetuin-A reversibly binds the insulin receptor tyrosine kinase in peripheral tissues, thereby inhibiting the insulin-induced intracellular signal cascade, producing peripheral insulin resistance.8–10 Consistent with this function, fetuin-A knockout mice are insulin sensitive,11,12 whereas wild-type mice treated with exogenous fetuin-A acutely develop insulin resistance.13

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Epidemiology and Prevention
To date, 2 studies have evaluated the association of serum fetuin-A levels with incident diabetes mellitus in human populations. Stefan and colleagues\textsuperscript{14} demonstrated that higher fetuin-A levels were associated with incident diabetes mellitus in 2867 middle-aged and predominantly white participants in Europe. In a pilot study, we made similar observations among 519 well-functioning 70- to 79-year-old participants in the Health Aging and Body Composition Study.\textsuperscript{15} Younger age, female sex, and white race were all strongly associated with higher fetuin-A levels in our prior study. Moreover, fetuin-A is known to inhibit arterial calcification,\textsuperscript{16} and lower levels have been associated with subclinical CVD in some\textsuperscript{17-20} but not all studies.\textsuperscript{21,22} Whether the association of fetuin-A with diabetes mellitus differs by age, sex, race, or CVD status remains unknown. The modest sample size of our pilot study did not provide sufficient statistical power to evaluate heterogeneity across these subgroups.

In this study, we measured serum fetuin-A concentrations among a large sample of community-living individuals who participated in the Cardiovascular Health Study (CHS) and were followed up for 10.6 years (median) for incident diabetes mellitus. We aimed to confirm the association of fetuin-A with incident diabetes mellitus in a larger sample of older individuals and secondarily to evaluate for heterogeneity in this association by age, sex, race, and prevalent CVD status.

Methods

Participants

The CHS is a community-based study of older adults designed to evaluate risk factors for development and progression of CVD. The study design and protocols have been described previously.\textsuperscript{23,24} In brief, eligibility required age $\geq$65 years, expectation to remain in the area for 3 years after recruitment, no active cancer treatment, and the ability to provide consent. Between 1989 and 1990, 5201 participants were recruited from 4 communities through the use of Medicare eligibility lists in each area (Sacramento, CA; Forsyth County, North Carolina; Washington County, Maryland; and Allegheny County, Pennsylvania). An additional 687 predominantly black participants were recruited in 1992 to 1993. We considered the 1992 to 1993 visit the baseline visit for this analysis. Among 5265 individuals who participated at this visit, we excluded individuals with missing or insufficient blood specimens for fetuin-A measurement (n = 551), those with prevalent diabetes mellitus at baseline (n = 708), those with missing information on diabetes status at baseline (n = 81), individuals with no follow-up information on diabetes status after the baseline visit (n = 124), and those missing covariate data (n = 91), resulting in a final analytic sample of 3710 participants for this analysis. All participants provided written informed consent, and the study was approved by the investigational review boards of the 4 clinical sites, the Data Coordinating Center at the University of Washington, and the lead investigator’s institution at the University of California San Diego.

Measurements

Fetuin-A

Serum was collected at the 1992 to 1993 study visit and stored at $-70^\circ$C until 2010, when it was thawed and measured for fetuin-A with an ELISA kit (Epitope Diagnostics, San Diego, CA). The assay uses a 2-site “sandwich” technique with polyclonal antibodies that bind different epitopes of human fetuin-A. Serum samples were measured twice in each participant, and results were averaged. We observed coefficients of variation between 3.3% and 9.1%.

Incident Diabetes Mellitus

Glucose was measured on fasting blood samples obtained during the annual clinic examinations in 1992 to 1993, 1996 to 1997, 1998 to 1999, and 2005 to 2006 and on nonfasting blood samples in 1994 to 1995. Medication use was assessed at baseline and annually thereafter by medication inventory through 2007.\textsuperscript{25} We classified participants as having diabetes mellitus if fasting glucose was $\geq$126 mg/dL, casual glucose was $\geq$200 mg/dL, or individuals used insulin or oral hypoglycemic agents. Participants with diabetes mellitus at baseline were excluded from further analysis, and those who did not have diabetes mellitus by this definition but developed it during follow-up were classified as incident diabetes cases.

Other Measurements

Age, sex, race, smoking status, physical activity, and alcohol consumption were based on self-report. Cystatin C concentrations were measured with a BN II nephelometer (Siemens; www.siemens.com) as described previously.\textsuperscript{26} The interassay and intra-assay coefficients of variation were <2.9% and <3.2%, respectively. Estimated glomerular filtration rate (eGFR) was calculated with the following equation: eGFR = 76.7 $\times$ cystatin C (mg/L)$^{-1.19}$\textsuperscript{27} Participants with a history of myocardial infarction, revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery), stroke, or transient ischemic attack were classified as having prevalent CVD. Anthropometric measurements were made by trained personnel using standardized protocols. Participants wore lightweight examination suits and no shoes. Standing height was measured with a stadiometer calibrated in centimeters. Body weight was measured with a balance-beam scale calibrated in kilograms. Body mass index was calculated (kilograms body weight divided by height in meters squared). Waist circumference was measured at the level of the umbilicus. After 5 minutes at rest, seated blood pressure was determined 3 times with standard mercury sphygmomanometers (Hawksley & Sons Ltd, Sussex, UK). The second and third measurements were averaged. Hypertension was defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or antihypertensive medication use and a physician diagnosis of hypertension. The Olympus Demand System (Olympus, Lake Success, NY) was used to measure serum triglyceride and high-density lipoprotein cholesterol concentrations. C-reactive protein was determined by ultrasensitive ELISA as described elsewhere.\textsuperscript{28} Insulin was measured with a competitive radioimmunoassay\textsuperscript{29} and was combined with fasting glucose measurements to calculate homeostasis model assessment of insulin resistance (HOMA-IR).\textsuperscript{30}

Statistical Analysis

We categorized participants into quartiles based on the distribution of fetuin-A concentrations in the study sample, and we evaluated the distribution of demographics and diabetes risk factors across fetuin-A categories. Tests for trend across ordered categories were performed with linear regression or a nonparametric test for trend\textsuperscript{31} as appropriate. Differences in the distribution of categories of alcohol consumption and smoking status across quartiles of fetuin-A were tested with $\chi^2$ tests. Next, Kaplan–Meier curves and the log-rank test were used to evaluate the unadjusted association of fetuin-A categories with time to incident diabetes mellitus. To allow adjustment for potential confounders, we fit multivariable models using Cox regression, allowing the lowest fetuin-A quartile to serve as the reference category. Because the functional form of the association of fetuin-A with incident diabetes mellitus was fairly linear across quartiles, we also evaluated fetuin-A as a continuous predictor variable (per 1 SD greater) to maximize statistical power. Sequential models were developed. An initial model adjusted for age, sex, race, and field center site. A subsequent model additionally adjusted for lifestyle factors and variables that we considered potential confounders of the association (physical activity, smoking [current, former, never], and alcohol use [0, 0–7, $>7$ drinks per week], serum albumin, eGFR, and prevalent CVD). Fetuin-A has been associated with obesity, hyperlipidemia, and inflammation in prior studies,\textsuperscript{11,32,33} but the directions of these associations remain uncertain. Thus, we constructed a final model that additionally
Participants were followed up for a median of 10.6 years (interquartile range, 5.9–14.0 years), during which time 305 cases of incident diabetes mellitus were ascertained. In unadjusted analysis, we observed a graded increase in the rate of diabetes mellitus with higher fetuin-A quartiles (log-rank \( P=0.02 \); the Figure). Table 2 shows the association of fetuin-A with incident diabetes mellitus in a series of adjusted models. After adjustment for age, sex, race, and field center

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The mean age of the 3710-person study sample was 74.8 ± 5.2 years; 60% (n = 2239) were female; and 14.5% (n = 537) were black. The mean fetuin-A concentration was 0.47 ± 0.10 g/L, and the distribution was approximately normal within the study sample.

Table 1 shows the distribution of demographics and diabetes risk factors by fetuin-A quartiles. Compared with participants in the lowest quartile, those with higher fetuin-A concentrations were younger, more frequently female and white, were less likely to drink alcohol, had lower eGFR, and had greater body mass index, waist circumference, triglycerides, C-reactive protein concentrations, serum albumin, and HOMA-IR, whereas high-density lipoprotein cholesterol concentrations were lower in the highest quartile.
whereas no association was observed in those in the highest quartile were at 84% greater risk, and in those aged 75 years of age, compared with the lowest fetuin-A quartile, subjects in the highest quartile were at 69% higher risk of incident diabetes mellitus, and each 1-SD-greater fetuin-A level was associated with a 23% greater risk. This association was modestly attenuated with additional adjustment for lifestyle factors, eGFR, and prevalent CVD (model 2). Next, we adjusted for additional factors which could function as either mediators or confounders in the pathway between fetuin-A and incident diabetes mellitus (body mass index, waist circumference, triglycerides, high-density lipoprotein, serum albumin, and C-reactive protein). In this model, each 1-SD-higher fetuin-A level remained associated with a 13% higher risk of diabetes mellitus (body mass index, waist circumference, hypertension, triglycerides, high-density lipoprotein, serum albumin, and C-reactive protein).

We tested for heterogeneity by age, sex, race, and prevalent CVD status. The association of fetuin-A with incident diabetes mellitus was similar in men and women, blacks and whites, and those with and without prevalent CVD (P for interactions >0.10 for all). However, the association was stronger in individuals <75 years of age compared with those who were older (P for interaction=0.01). In participants <75 years of age, compared with the lowest fetuin-A quartile, those in the highest quartile were at 84% greater risk, and each 1-SD-greater fetuin-A was associated with a 23% greater risk of diabetes mellitus in the final adjusted model, whereas no association was observed in those ≥75 years of age (Table 3).

### Table 2. Association of Fetuin-A With Incident Diabetes Mellitus in the Cardiovascular Health Study

<table>
<thead>
<tr>
<th>Range, g/L</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/person-years at risk</td>
<td>56/8811</td>
<td>71/8913</td>
<td>93/8989</td>
<td>85/8670</td>
</tr>
</tbody>
</table>

**Hazard ratio (95% confidence interval)**

- Model 1* 1.00 (Reference) 1.31 (0.92–1.87) 1.75 (1.25–2.45) 1.69 (1.20–2.40) 1.23 (1.09–1.38) 0.001
- Model 2† 1.00 (Reference) 1.27 (0.89–1.80) 1.72 (1.23–2.41) 1.56 (1.10–2.21) 1.19 (1.06–1.34) 0.003
- Model 3‡ 1.00 (Reference) 1.16 (0.81–1.65) 1.52 (1.08–2.13) 1.37 (0.95–1.96) 1.13 (1.00–1.28) 0.05

*Model 1 is adjusted for age, sex, race, and field center site.†Model 2 is adjusted for model 1 variables plus physical activity, smoking, alcohol use, estimated glomerular filtration rate, and prevalent cardiovascular disease.‡Model 3 is adjusted for model 2 variables plus body mass index, waist circumference, hypertension, triglycerides, high-density lipoprotein, serum albumin, and C-reactive protein.

In secondary analysis, we investigated whether the age interaction might reflect different relationships of fetuin-A with insulin resistance between the 2 age groups by analyzing the cross-sectional relationship of fetuin-A with HOMA-IR at the baseline study visit. In the fully adjusted model, fetuin-A was associated with higher HOMA-IR in both age groups, but the association was again stronger in persons <75 years of age (β per 1-SD-higher fetuin-A, 0.27 [95% confidence interval, 0.20–0.34] in persons <75 years of age and 0.16 [95% confidence interval, 0.07–0.24] in persons ≥75 years; P for interaction=0.02).

### Table 3. Age-Stratified Association of Fetuin-A With Incident Diabetes Mellitus in the Cardiovascular Health Study*

<table>
<thead>
<tr>
<th>Range, g/L</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/person-years at risk</td>
<td>29/5170</td>
<td>44/5367</td>
<td>62/5587</td>
<td>65/5619</td>
</tr>
</tbody>
</table>

**Adjusted hazard ratio (95% confidence interval)**

- Age <75 y
  - 1.00 (Reference) 1.36 (0.84–2.19) 1.74 (1.10–2.74) 1.84 (1.15–2.95)
  - 1.23 (1.06–1.43) 0.006
- Age ≥75 y
  - 1.00 (Reference) 0.95 (0.55–1.64) 1.26 (0.74–2.15) 0.85 (0.46–1.57)
  - 0.96 (0.78–1.19) 0.73

*P value for interaction=0.01.
†Adjusted for age, sex, race, field center site, physical activity, smoking, alcohol use, estimated glomerular filtration rate, prevalent cardiovascular disease, body mass index, waist circumference, hypertension, triglycerides, high-density lipoprotein, serum albumin, and C-reactive protein.

### Discussion

In a large biracial and geographically diverse cohort of community-living older persons and with a median follow-up time of >10 years, we demonstrate that higher serum fetuin-A levels are associated with an increased risk of diabetes mellitus. This study confirms findings in a middle-aged white population and our findings in a pilot study of older persons. In secondary analysis, we demonstrate that fetuin-A remains associated with incident diabetes mellitus in men, blacks, and individuals with prevalent CVD, although...
the association was limited primarily to individuals <75 years of age.

Recent studies have elucidated mechanisms through which fat-derived adipokines influence insulin resistance. Fetuin-A differs in that, to the best of our knowledge, it is the only factor that is produced and secreted by the liver that directly influences peripheral insulin resistance.7 Recent work has demonstrated that fetuin-A binds the β subunit of the insulin receptor; thus, it does not compete with insulin binding.34 To date, only 2 proteins are known to bind the ectodomain of the insulin receptor, insulin and fetuin-A; the former stimulates signal transduction and the later inhibits it.34 In addition to binding and inhibiting the insulin receptor, recent in vitro and in vivo studies in mice suggest that fetuin-A stimulates the production of inflammatory cytokines and suppresses the production of the adipokine adiponectin.13 Other studies demonstrate that free fatty acids promote the generation of fetuin-A in hepatocytes, a process that is more efficient in the presences of inflammatory stress.35 Collectively, these studies suggest that fetuin-A may provide a mechanism for the liver to regulate glucose metabolism in other organs. Thus, the findings reported here provide evidence that 1 or more of these pathways may be important to the development of incident diabetes mellitus not only in middle-aged individuals but also in older persons, at least until 75 years of age.

The identification of mechanisms leading to incident diabetes mellitus in older persons is important to public health. Rates of incident diabetes mellitus are high in older persons, and incident diabetes mellitus is strongly associated with all-cause and CVD mortality in this age group.36 Current population trends show marked increases in the prevalence of obesity, and simultaneously, our population is aging.1 These factors suggest that rates of diabetes mellitus in older persons are likely to increase in future years, which might fuel higher rates of CVD, kidney disease, visual impairment, and other established consequences of diabetes mellitus. Yet, because body composition and glucose regulation change with age, biological mechanisms and risk factors for incident diabetes mellitus may differ in older individuals. Stefan and colleagues14 reported that fetuin-A is associated with incident diabetes mellitus in a middle-aged European cohort (mean age, 49 years). Whether this association differed by age was not reported. In our pilot study, fetuin-A was associated with incident diabetes mellitus in a separate sample of well-functioning persons 70 to 79 years of age,15 but the limited number of participants and narrow age range in this study limited the ability to test for heterogeneity by age. Here, we observed that the association of fetuin-A with diabetes mellitus was observed only in those <75 years of age. Moreover, the association of fetuin-A with HOMA-IR was also stronger in the <75-year-old age group.

The mechanisms responsible for these findings are uncertain. One possibility is that fetuin-A may become a less important regulator of peripheral insulin resistance in the oldest old. Another possibility is that participants who lived to ≥75 years and remained healthy enough to participate in this study differed systematically from the younger participants. Finally, there were fewer cases of diabetes mellitus in the ≥75-year-old age group (n=105 versus 200 in the <75-year-old group), and we tested multiple interactions. Although the P value for interaction was statistically significant (P=0.01) and similar findings were confirmed evaluating HOMA-IR in a cross-sectional analysis, it is possible that these were chance findings. Thus, we believe these findings require confirmation in other settings.

Although multiple in vitro studies in different mammalian species,7–9 studies in knockout mice,11,12 and studies in wild-type mice treated with exogenous fetuin-A13 all suggest that it may directly induce peripheral insulin resistance, some controversy on this topic remains. Chen and colleagues37 transfected human fetuin-A into rat adipocytes and tested whether this induced insulin resistance in the adipocytes in cell culture. In contrast to the effect of fetuin-A on insulin resistance in other target tissues, these investigators failed to observe changes in insulin-stimulated glucose transport. Thus, by the design of this experiment, transfected human fetuin-A would need to interact with the rat insulin receptor. Whether such interactions occur across species subtypes of fetuin-A and the insulin receptor is unknown, which may have contributed to the null findings. However, on the basis of these findings, others have speculated that high fetuin-A may simply reflect an overfed state or mark good hepatic synthetic function, similar to serum albumin.38 To our knowledge, our study is the first to adjust for serum albumin when evaluating the association of fetuin-A with incident diabetes mellitus. Serum fetuin-A and albumin concentrations were only weakly correlated (r=0.15), and adjusting for albumin had little influence on the association of fetuin-A with diabetes mellitus in our final models. Although our epidemiological study cannot prove causality, these data suggest that higher fetuin-A levels are not merely marking hepatic synthetic function or serving as a surrogate of serum albumin. This distinction is important because if the binding of fetuin-A to the insulin receptor induces peripheral insulin resistance, then blockade of this interaction may ultimately serve as a novel target for therapy for insulin-resistant states.15

Fetuin-A measurement may also ultimately be useful in guiding therapy with established medications for diabetes mellitus. For example, recent studies have demonstrated that the peroxisome proliferator-activated receptor-γ agonist pioglitazone lowers fetuin-A levels.39 Peroxisome proliferator-activated receptor-γ agonists induce fluid retention and have been associated with increased risk of heart failure and CVD events.40,41 outcomes that are particularly common in older persons. Whether fetuin-A levels may inform the risk-to-benefit ratio of this class of medications in older persons is an important topic for future study. Short-term exercise interventions have also shown promise in lowering fetuin-A levels in young and middle-aged persons in some42,43 but not all studies.44 Future studies should investigate whether such interventions might lower fetuin-A in older persons and whether this translated into improvements in hard clinical endpoints.

Strengths of this study include its large sample size, the biracial and geographic diversity of the study participants, and the long-term follow-up for incident diabetes mellitus. The study also has important limitations. Our study included
individuals ≥65 years old, and within this age group, we observed heterogeneity in the association of fetuin-A with incident diabetes mellitus. Future studies are required to confirm this finding and to evaluate heterogeneity across a wider age spectrum. Our study sample included only whites and blacks. Results may differ in other race/ethnicities. Fetuin-A was measured at a single time point, which may not reflect long-term exposure, and precludes evaluation of whether trajectories of fetuin-A may provide information on diabetes risk above and beyond a 1-time measurement.

Conclusions
Higher serum fetuin-A levels are associated with incident diabetes mellitus in community-living older persons. Fetuin-A remains associated with diabetes risk among men, blacks, and individuals with prevalent CVD; however, the association of fetuin-A with diabetes mellitus may wane after 75 years of age. Future studies are required to confirm heterogeneity by age and to determine whether fetuin-A measurement may ultimately allow guided therapy to treat or prevent diabetes mellitus and associated complications.

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Disclosures
None.

References
Unlike adipocytokines, fetuin-A is produced in the liver. It is secreted by hepatocytes into serum, and induces peripheral insulin resistance in vitro. We sought to evaluate the association of fetuin-A with incident diabetes mellitus in older persons, and to determine if associations differ by age, sex, and race, and among persons with CVD. Among 3,710 persons aged 65 years and with 10.6 years follow-up, we observed that higher serum fetuin-A concentrations were independently associated with incident diabetes mellitus. The association was similar by sex, race, and among those with or without CVD, but appeared weaker among those aged ≥75 years at baseline. Future mechanistic studies focused on the liver-secreted protein fetuin-A may provide new insights to mechanisms leading to diabetes in older adults.
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