Relation of Serum Fetuin-A Levels to Coronary Artery Calcium in African-American Patients on Chronic Hemodialysis

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Vascular calcium deposition in end-stage renal disease occurs commonly, but its relation to cardiovascular risk factors and fetuin-A levels in African Americans is not known. Compliant African American patients who were undergoing hemodialysis (HD; n = 17) agreed to undergo 64-slice multidetector computed tomography for the assessment of coronary artery calcium score (CACS). The relation between traditional cardiovascular risk factors (i.e., age; gender; dialysis vintage; history of diabetes; means of the previous 3 years of weekly predialysis blood pressure values and hemoglobin levels; means of monthly values of calcium, phosphorus, alkaline phosphatase, uric acid; and albumin; and means of quarterly measurements of parathyroid hormone and lipids) and fetuin-A levels and CACS was explored using univariate analyses. Serum phosphorus levels over the previous 3 years were well controlled. The CACS range was 0 to 3,877 Agatston units (mean 996, median 196). Among the tested variables, only fetuin-A was significantly and inversely associated with CACS (standardized $\beta = -0.64$, 95% confidence interval −18.09 to −3.62, $p = 0.006$). There was no association between age and fetuin-A level (standardized $\beta = -0.02$, 95% confidence interval −0.10 to 0.23). In conclusion, African-American patients who were undergoing long-term hemodialysis and with good phosphorus control exhibited a strong inverse correlation between fetuin-A level and CACS that was independent of age. © 2009 Elsevier Inc. (Am J Cardiol 2009;103:46–49)

Cardiovascular disease is the most common cause of morbidity and mortality in patients with end-stage renal disease who are undergoing hemodialysis (HD). Major risk factors for cardiovascular disease in this population include high calcium intake, age, dialysis vintage, and high levels of phosphorus, C-reactive protein, and osteoprotegerin.[1–10] Other studies have identified a coronary artery calcium score (CACS) >400 Agatston units and low serum levels of the calcification inhibitor fetuin-A as risk factors for cardiovascular disease in Caucasian patients who are undergoing HD, but this association has not been shown in African-American patients who are undergoing HD.[11–15] The hypothesis of this study was that CACS would exhibit an inverse relation with serum fetuin-A levels in African American patients who were undergoing long-term HD.

Methods

The study population consisted of 17 consecutive clinically stable, ambulatory African American patients who were undergoing HD, whose selection was based on a history of good compliance with the medical regimen as subjectively assessed by nursing, dietary, and medical staff members at the Chromalloy American Kidney Center, a 34-station HD unit at Barnes-Jewish Hospital, Washington University Medical Center (St. Louis, Missouri). Informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

Exclusion criteria included age <18 years, active infection, mental incompetence, pregnancy, atrial fibrillation, and weight >350 lb. No patient had received corticosteroid therapy. Sevelamer hydrochloride was the primary phosphorus binder beginning in 2001, with the goal of maintaining phosphorus levels <6.0 mg/dl. The total amount of elemental calcium prescribed, in the form of calcium carbonate, did not exceed 1.5 g/day. All patients received ≥50,000 IU of ergocalciferol monthly to maintain 25-hydroxy vitamin D levels >30 ng/ml. Paricalcitol was prescribed for those patients whose intact parathyroid hormone levels were persistently >300 pg/ml. All but 1 patient were receiving paricalcitol at the time of testing. All patients maintained Kt/V values >1.3 and had been treated with high-flux dialyzers since 2002; the dialysate calcium was 2.5 mEq/L.

Data on demography, primary renal disease, vital signs, medications, and routine laboratory values were obtained at the time of testing from electronic medical records. The

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Table 1
Characteristics of the study population

Age (yrs)	Vintage (yrs)	Gender	SBP (mm Hg)	DBP (mm Hg)	LDL-C (mg/dl)	HDL-C (mg/dl)	Triglycerides (mg/dl)
64	3	F	149	86	100	31	124
48	3	M	178	79	57	44	158
60	3	F	137	90	43	31	187
38	4	F	123	63	105	57	69
58	5	M	142	84	76	44	134
42	5	M	163	89	96	41	174
52	6	F	116	69	43	24	303
64	7	M	177	83	93	54	69
73	7	F	171	91	54	33	143
64	7	M	145	79	98	67	109
79	7	M	119	77	124	56	108
71	8	F	150	60	83	54	69
52	9	M	137	81	86	41	91
55	9	M	126	79	92	31	140
61	10	M	132	67	73	51	86
68	10	F	147	79	78	56	104
50	26	F	81	57	70	25	122
59 ± 11	8 ± 5		141 ± 25	77 ± 10	81 ± 22	44 ± 13	129 ± 57

Values in the bottom row are means ± SDs.
DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; iPTH = intact parathyroid hormone; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure.

blood pressure measurements represent the averages of weekly predialysis values; calcium, phosphorus, albumin, and alkaline phosphatase levels were collected monthly; parathyroid hormone and fasting lipid levels quarterly; and uric acid yearly. All values from the previous 3 years were averaged for each patient.

A 64-slice multidetector computed tomographic scanner (Somatom Sensation 64; Siemens Medical Systems, Forchheim, Germany) was used for the measurement of CACS; testing was performed on a nondialysis day. Multidetector computed tomography was performed at 190 mAs and 120 kV, reconstructed at 60% of the RR interval, and 3-mm thickness. CACS on multidetector computed tomography were determined by 3 independent observers using commercially available software (Vitrea; Vital Images, Inc., Minnetonka, Minnesota); the intraobserver (2 independent readings by the same observer) and interobserver (3 independent observers) interclass correlation coefficients for CACS were 0.99 (considered excellent).

Routine laboratory measurements were performed by Spectra Laboratories (Rockleigh, New Jersey). Blood for fetuin-A (Epitope, Inc., San Diego, California) measurements was obtained before a dialysis treatment within 1 week of the multidetector computed tomographic study; levels were measured in duplicate, and reported values represent averages.

Variables are expressed as mean ± SD. Variables not normally distributed were logarithmically transformed for analyses (CACS, triglycerides, and alkaline phosphatase). Univariate analyses were performed to determine the relation between the variables and CACS; reported values include standardized β coefficients with 95% confidence intervals. Statistical analysis was performed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina). All tests were 2 tailed, and a p value <0.05 was considered significant.

Table 2
Standardized estimates and 95% confidence intervals

Variable	Standardized Estimate	95% Confidence Interval
Age	0.022	−0.097 to 0.228
Triglycerides	−0.023	−4.804 to 4.423
Calcium	0.111	−4.037 to 6.101
Phosphorous	0.040	−3.209 to 3.715
iPTH	0.146	−0.008 to 0.014
Alkaline phosphatase	0.000	−6.040 to 6.045
Uric acid	−0.326	−2.970 to 0.684
LDL-C	0.220	−0.047 to 0.112
Fetuin-A	−0.637*	−18.085 to −3.621
Albumin	0.373	−1.683 to 10.815

Abbreviations as in Table 1.
* p = 0.006.

Results

The characteristics of the study population are listed in Table 1. The causes of renal failure were diabetes mellitus (n = 7), hypertension (n = 6), systemic lupus erythematosus (n = 2), glomerulonephritis (n = 1), and autosomal dominant polycystic kidney disease (n = 1). Thirteen patients (76%) had histories of myocardial infarction, stroke, or peripheral vascular disease, and 2 patients were active smokers. The mean values of blood pressure, lipids, calcium, phosphorus, and albumin were well within HD guidelines.

The CACS ranged from 0 to 3,877 Agatston units (mean 996, median 196). Univariate analysis, performed to further explore the relations between the variables of interest and CACS, showed that only fetuin-A was significantly associated with CACS (F = 10.2, p = 0.006); age was not associated with fetuin-A levels (Table 2).

Table 1
(*continued*)

Albumin (g/dl)	Calcium (mg/dl)	Phosphorous (mg/dl)	iPTH (pg/ml)	Alkaline Phosphatase (IU/L)	Uric Acid (mg/dl)	Fetuin-A (g/L)
4.1	9.6	5.1	329	61	8.3	0.8
3.6	8.9	4.5	139	57	7.9	0.8
3.7	8.5	4.2	79	54	6.1	0.4
4.0	9.3	4.9	306	62	5.9	0.5
3.4	8.7	5.7	162	61	5.9	0.8
3.8	9.0	5.0	409	145	6.0	0.4
4.4	8.9	5.4	243	88	6.2	0.4
3.9	8.7	5.4	575	79	6.3	0.7
4.2	9.1	5.1	405	91	6.7	1.0
3.8	9.4	5.9	666	64	5.3	0.8
4.0	8.6	4.4	229	100	4.6	0.5
4.0	8.8	4.4	220	62	6.5	0.4
3.8	9.1	5.6	384	101	5.4	0.6
4.3	9.1	4.4	125	127	7.5	0.8
3.6	8.1	4.6	106	112	6.3	1.0
3.6	9.1	4.4	310	98	5.9	0.7
4.1	9.2	5.0	266	80	5.7	0.8
3.9 ± 0.3	8.9 ± 0.4	5.0 ± 0.5	291 ± 162	85 ± 27	6.3 ± 0.9	0.7 ± 0.2

Discussion

The results of the present study show that African American patients who were undergoing long-term HD and who had good phosphorus control exhibited a strong inverse correlation between fetuin-A levels and CACS, whereas age was not found to be significantly associated with CACS. The cohort was racially homogenous and had been treated aggressively according to current guidelines, including excellent control of blood pressure, phosphorus, lipid, albumin, lipid, and parathyroid hormone over the 3 years before imaging.[16,17] Although several studies have evaluated the association of low fetuin-A levels with increased mortality in patients who are undergoing dialysis, in all studies, the predominant race was Caucasian or Asian.[13–15,18,19]

Fetuin-A, a 62-kDa glycoprotein secreted in abundance by the liver, appears to have diverse biologic activity. In the serum, it binds calcium and phosphorus, thus acting as a buffer in states of supersaturation.[20] At the level of the vascular smooth muscle cells, intracellular fetuin-A inhibits apoptosis and vesicle-mediated calcification.[21] In addition, fetuin-A antagonizes the vascular calcifying effects of bone morphogenetic protein–2.[22] The expression of circulating fetuin-A is downregulated with inflammation, and deficiency in transgenic mice with certain murine genetic backgrounds predisposes to vascular, renal, and pulmonary calcification. Recent data suggest that fetuin-A serves as a key circulating inhibitor of soft-tissue calcification.[23–25] Clinical studies of fetuin-A are hampered, however, by levels that have been shown to be affected by inflammation and by genetic polymorphisms.[15]

Compared with patients with normal kidney function, in patients who are undergoing HD, coronary artery calcification occurs at an earlier age, is more prevalent, and is more severe.[2–4,26] Despite data showing increased mortality associated with vascular calcification, there is marked heterogeneity in vascular calcification in response to uremia and hyperphosphatemia. Fetuin-A may play a key role in cardiovascular mortality and morbidity associated with end-stage renal disease.

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