Published in final edited form as:
Am J Cardiol. 2009 January 1; 103(1): 46–49. doi:10.1016/j.amjcard.2008.08.032.

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

Sijie Zheng, MD, PhD[a], **Lisa de las Fuentes, MD**[b], **Andrew Bierhals, MD**[c], **Rachel Ash-Bernal, MD**[b], **Karen Spence, MS**[b], **Eduardo Slatopolsky, MD**[a], **Victor G. Davila-Roman, MD**[b], and **James Delmez, MD**[a]

a*Division of Nephrology, Washington University School of Medicine, St. Louis, Missouri 63110*

b*Cardiovascular Imaging and Clinical Research Core Laboratory, Cardiovascular Division, Washington University School of Medicine, St. Louis, Missouri 63110*

c*Department of Medicine, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri 63110*

Abstract

Vascular calcium deposition in end-stage renal disease occurs commonly, however its relationship to cardiovascular risk factors and fetuin-A levels in African-Americans is not known. Compliant African-American HD patients (n=17) agreed to undergo a 64-slice multidetector computed tomography for the assessment of coronary artery calcium score (CACS). The relationship between traditional cardiovascular risk factors (i.e., age, gender, dialysis vintage, history of diabetes, means of the previous 3 years of the weekly pre-dialysis blood pressure and hemoglobin, means of monthly values of calcium, phosphorus, alkaline phosphatase, uric acid and albumin, and means of quarterly measures of parathyroid hormone and lipids), and fetuin-A levels and CACS was explored by univariate analyses. Serum phosphorus levels over the previous 3 years were well controlled. The CACS range was 0-3,877 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 limits [CL]: -18.09, -3.62], p=0.006). There was no association between age and fetuin-A level (standardized $\beta = -0.02$ [95%CL: -0.10, 0.23]). In conclusion, African-American patients on long-term HD and with good phosphorus control exhibit a strong inverse correlation between fetuin-A levels and CACS which is independent of age.

Keywords

Fetuin-A; Hemodialysis; Coronary artery calcium score; African-American

Cardiovascular disease is the most common cause of morbidity and mortality in end-stage renal disease patients on hemodialysis (HD). Major risk factors for cardiovascular disease in this population include high calcium intake, age, dialysis vintage, high levels of phosphorus, C-reactive protein, and osteoprotegerin. (1-10) Other studies have identified a coronary artery

Address for correspondence: James Delmez, MD, Washington University School of Medicine, Campus Box 8129, 660 S. Euclid Ave., St. Louis, Missouri, 63110, Tel: 314-362-7207; fax: 314-747-3743, e-mail: jdelmez@wustl.edu.

The authors report no conflict of interest related to this work

calcium score (CACS) >400 and low serum levels of the calcification inhibitor fetuin-A as risk factors for cardiovascular disease in Caucasian HD patients, but this association has not been shown in African-American HD patients. (11-15) The hypothesis of this study was that CACS would exhibit an inverse relationship with serum fetuin-A levels in African-American patients undergoing long-term HD.

METHODS

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

Exclusion criteria included age <18 years, active infection, mental incompetence, pregnancy, atrial fibrillation, and weight >350 pounds. 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 or more of ergocalciferol monthly to maintain their 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 one patient was receiving paricalcitol at the time of testing. All patients maintained a Kt/V of >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 digitized records. The blood pressure measurements represent the average of weekly pre-dialysis 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-row multidetector computed tomography (MDCT) scanner (Somatom Sensation 64, Siemens, Forchheim, Germany) was used for measurement of CACS; testing was performed on a non-dialysis day. MDCT was acquired with 190mAs, 120kV, reconstructed at 60% of R-R interval, and 3mm thickness. The MDCT CACS were determined by 3 independent observers by use of commercially available software (Vitrea®, Vital Images, Inc., Minnetonka, MN); the intraobserver (2 independent readings by the same observers) and interobserver (3 independent observers) interclass correlation coefficients for CACS was 0.99 (considered excellent).

Routine laboratory measurements were performed by Spectra Laboratories, Rockleigh, NJ. Blood for fetuin-A (Epitope, Inc. San Diego, CA) measurements were obtained before a dialysis treatment within a week of the MDCT study; levels were measured in duplicate and reported values represent the average.

Variables are expressed as mean ± standard deviation. Variables not normally distributed and were logarithmically transformed for analyses (CACS, triglycerides, and alkaline phosphatase). Univariate analyses were performed to determine the relationship between the variables and CACS; reported values include the standardized β coefficient with the 95% confidence limits. Statistical analysis was performed using SAS (v. 9.1, SAS Institute, Cary, NC). All tests were 2-tailed; a p-value <0.05 was considered significant.

RESULTS

The characteristics of the study population are shown 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). There was a history of myocardial infarction, stroke, or peripheral vascular disease in 13 (76%); 2 were active smokers. The mean values of blood pressure, lipids, calcium, phosphorus, and albumin levels 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 relationships between the variables of interest and CAC scores showed that only fetuin-A was significantly associated with CACS (F=10.2, p=.006); age was not associated with fetuin-A levels (Table 2).

DISCUSSION

Results of the present study show that African-American patients on long-term HD and good phosphorus control exhibit 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 homogeneous 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 prior to imaging. (16-17) Although several studies have evaluated the association of low fetuin-A levels with increased mortality in dialysis patients, in all studies the predominantly race was Caucasian or Asian. (13-15,18-19)

Fetuin-A, a 62-kilodalton glycoprotein secreted in abundance by the liver, appears to have diverse biological 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) Expression of circulating fetuin-A is down-regulated 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 one key circulating inhibitor of soft tissue calcification. (23-25) Clinical studies of fetuin-A are hampered, however, by levels which have been shown to be affected by inflammation and by genetic polymorphisms. (15)

Compared to patients with normal kidney function, in HD patients coronary artery calcification occurs at an earlier age, is more prevalent, and also 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.

Acknowledgements

This study was supported in part by the Research in Renal Diseases Fund, Washington University, the Barnes-Jewish Hospital Foundation to the Cardiovascular Imaging and Clinical Research Core Laboratory (VGD-R), and National Institute of Health grants UO1 DK58978-01 (JD) and KL2RR024994 and K1244023249 (LdlF).

References

1. Collins AJ, Foley R, Herzog C, Chavers B, Gilbertson D, Ishani A, Kasiske B, Liu J, Mau LW, McBean M, Murray A, St Peter W, Xue J, Fan Q, Guo H, Li Q, Li S, Peng Y, Qiu Y, Roberts T, Skeans M, Snyder J, Solid C, Wang C, Weinhandl E, Zaun D, Zhang R, Arko C, Chen SC, Dalleska F, Daniels

F, Dunning S, Ebben J, Frazier E, Hanzlik C, Johnson R, Sheets D, Wang X, Forrest B, Constantini E, Everson S, Eggers P, Agadoa L. Excerpts from the United States Renal Data System 2007 annual data report. Am J Kidney Dis 2008;51:S1–320.

2. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, Elashoff RM, Salusky IB. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 2000;342:1478–1483. [PubMed: 10816185]
3. London GM, Guerin AP, Marchais SJ, Metivier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant 2003;18:1731–1740. [PubMed: 12937218]
4. Raggi P, Boulay A, Chasan-Taber S, Amin N, Dillon M, Burke SK, Chertow GM. Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? J Am Coll Cardiol 2002;39:695–701. [PubMed: 11849871]
5. Oh J, Wunsch R, Turzer M, Bahner M, Raggi P, Querfeld U, Mehls O, Schaefer F. Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. Circulation 2002;106:100–105. [PubMed: 12093777]
6. Guerin AP, London GM, Marchais SJ, Metivier F. Arterial stiffening and vascular calcifications in end-stage renal disease. Nephrol Dial Transplant 2000;15:1014–1021. [PubMed: 10862640]
7. Stompor T, Pasowicz M, Sullowicz W, Dembinska-Kiec A, Janda K, Wojcik K, Tracz W, Zdzienicka A, Klimeczek P, Janusz-Grzybowska E. An association between coronary artery calcification score, lipid profile, and selected markers of chronic inflammation in ESRD patients treated with peritoneal dialysis. Am J Kidney Dis 2003;41:203–211. [PubMed: 12500238]
8. Block GA, Spiegel DM, Ehrlich J, Mehta R, Lindbergh J, Dreisbach A, Raggi P. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney Int 2005;68:1815–1824. [PubMed: 16164659]
9. Barreto DV, Barreto FC, Carvalho AB, Cuppari L, Cendoroglo M, Draibe SA, Moyses RM, Neves KR, Jorgetti V, Blair A, Guiberteau R, Fernandes Canziani ME. Coronary calcification in hemodialysis patients: the contribution of traditional and uremia-related risk factors. Kidney Int 2005;67:1576–1582. [PubMed: 15780114]
10. Nitta K, Akiba T, Uchida K, Kawashima A, Yumura W, Kabaya T, Nihei H. The progression of vascular calcification and serum osteoprotegerin levels in patients on long-term hemodialysis. Am J Kidney Dis 2003;42:303–309. [PubMed: 12900812]
11. Moe SM, Reslerova M, Ketteler M, O'Neill K, Duan D, Koczman J, Westenfeld R, Jahnen-Dechent W, Chen NX. Role of calcification inhibitors in the pathogenesis of vascular calcification in chronic kidney disease (CKD). Kidney Int 2005;67:2295–2304. [PubMed: 15882271]
12. Coen G, Manni M, Agnoli A, Balducci A, Dessi M, De Angelis S, Jankovic L, Mantella D, Morosetti M, Naticchia A, Nofroni I, Romagnoli A, Gallucci MT, Tomassini M, Simonetti G, Splendiani G. Cardiac calcifications: Fetuin-A and other risk factors in hemodialysis patients. Asaio J 2006;52:150–156. [PubMed: 16557100]
13. Hermans MM, Brandenburg V, Ketteler M, Kooman JP, van der Sande FM, Boeschoten EW, Leunissen KM, Krediet RT, Dekker FW. Association of serum fetuin-A levels with mortality in dialysis patients. Kidney Int 2007;72:202–207. [PubMed: 17342178]
14. Ketteler M, Bongartz P, Westenfeld R, Wildberger JE, Mahnken AH, Bohm R, Metzger T, Wanner C, Jahnen-Dechent W, Floege J. Association of low fetuin-A (AHSG) concentrations in serum with cardiovascular mortality in patients on dialysis: a cross-sectional study. Lancet 2003;361:827–833. [PubMed: 12642050]
15. Stenvinkel P, Wang K, Qureshi AR, Axelsson J, Pecoits-Filho R, Gao P, Barany P, Lindholm B, Jogestrand T, Heimburger O, Holmes C, Schalling M, Nordfors L. Low fetuin-A levels are associated with cardiovascular death: Impact of variations in the gene encoding fetuin. Kidney Int 2005;67:2383–2392. [PubMed: 15882283]
16. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003;42:S1–S201. [PubMed: 14520607]
17. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis 2005;45:S1–S153.

18. Wang AY, Woo J, Lam CW, Wang M, Chan IH, Gao P, Lui SF, Li PK, Sanderson JE. Associations of serum fetuin-A with malnutrition, inflammation, atherosclerosis and valvular calcification syndrome and outcome in peritoneal dialysis patients. Nephrol Dial Transplant 2005;20:1676–1685. [PubMed: 15899935]

19. Honda H, Qureshi AR, Heimburger O, Barany P, Wang K, Pecoits-Filho R, Stenvinkel P, Lindholm B. Serum albumin, C-reactive protein, interleukin 6, and fetuin a as predictors of malnutrition, cardiovascular disease, and mortality in patients with ESRD. Am J Kidney Dis 2006;47:139–148. [PubMed: 16377395]

20. Heiss A, DuChesne A, Denecke B, Grotzinger J, Yamamoto K, Renne T, Jahnen-Dechent W. Structural basis of calcification inhibition by alpha 2-HS glycoprotein/fetuin-A. Formation of colloidal calciprotein particles. J Biol Chem 2003;278:13333–13341. [PubMed: 12556469]

21. Reynolds JL, Skepper JN, McNair R, Kasama T, Gupta K, Weissberg PL, Jahnen-Dechent W, Shanahan CM. Multifunctional roles for serum protein fetuin-a in inhibition of human vascular smooth muscle cell calcification. J Am Soc Nephrol 2005;16:2920–2930. [PubMed: 16093453]

22. Szweras M, Liu D, Partridge EA, Pawling J, Sukhu B, Clokie C, Jahnen-Dechent W, Tenenbaum HC, Swallow CJ, Grynpas MD, Dennis JW. alpha 2-HS glycoprotein/fetuin, a transforming growth factor-beta/bone morphogenetic protein antagonist, regulates postnatal bone growth and remodeling. J Biol Chem 2002;277:19991–19997. [PubMed: 11901155]

23. Schafer C, Heiss A, Schwarz A, Westenfeld R, Ketteler M, Floege J, Muller-Esterl W, Schinke T, Jahnen-Dechent W. The serum protein alpha 2-Heremans-Schmid glycoprotein/fetuin-A is a systemically acting inhibitor of ectopic calcification. J Clin Invest 2003;112:357–366. [PubMed: 12897203]

24. Price PA, Lim JE. The inhibition of calcium phosphate precipitation by fetuin is accompanied by the formation of a fetuin-mineral complex. J Biol Chem 2003;278:22144–152. [PubMed: 12676929]

25. Price PA, Williamson MK, Minh Thi Nguyen T, Than TN. Serum levels of the fetuin-mineral complex correlate with artery calcification in the rat. J Biol Chem 2004;279:1594–1600. [PubMed: 14578360]

26. Kronmal RA, McClelland RL, Detrano R, Shea S, Lima JA, Cushman M, Bild DE, Burke GL. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2007;115:2722–2730. [PubMed: 17502571]

Abbreviations

CACS

coronary artery calcium score

HD

hemodialysis

Table 1

Characteristics of study population

Age (yr)	Vintage (yr)	Sex	SBP (mmHg)	DBP (mmHg)	LDL (mg/dL)	HDL (mg/dL)	Trig (mg/dL)	Alb (g/dL)	Ca (mg/dL)	Phos (mg/dL)	IPTH (pg/mL)	Alk Phos (IU/L)	Uric Acid (mg/dL)	Fetuin-A (g/L)
64	3	F	149	86	100	31	124	4.1	9.6	5.1	329	61	8.3	0.8
48	3	M	178	79	57	44	158	3.6	8.9	4.5	139	57	7.9	0.8
60	3	F	137	90	43	31	187	3.7	8.5	4.2	79	54	6.1	0.4
38	4	F	123	63	105	57	69	4.0	9.3	4.9	306	62	5.9	0.5
58	5	M	142	84	76	44	134	3.4	8.7	5.7	162	61	5.9	0.8
42	5	M	163	89	96	41	174	3.8	9.0	5.0	409	145	6.0	0.4
52	6	F	116	69	43	24	303	4.4	8.9	5.4	243	88	6.2	0.4
64	7	M	177	83	93	54	69	3.9	8.7	5.4	575	79	6.3	0.7
73	7	F	171	91	54	33	143	4.2	9.1	5.1	405	91	6.7	1.0
64	7	M	145	79	98	67	109	3.8	9.4	5.9	666	64	5.3	0.8
79	7	M	119	77	124	56	108	4.0	8.6	4.4	229	100	4.6	0.5
71	8	F	150	60	83	54	69	4.0	8.8	4.4	220	62	6.5	0.4
52	9	M	137	81	86	41	91	3.8	9.1	5.6	384	101	5.4	0.6
55	9	M	126	79	92	31	140	4.3	9.1	4.4	125	127	7.5	0.8
61	10	M	132	67	73	51	86	3.6	8.1	4.6	106	112	6.3	1.0
68	10	F	147	79	78	56	104	3.6	9.1	4.4	310	98	5.9	0.7
50	**26**	**F**	81	57	70	25	122	4.1	9.2	5.0	266	80	5.7	0.8
59±11	**8±5**		**141±25**	**77±10**	**81±22**	**44±13**	**129±57**	**3.9±0.3**	**8.9±0.4**	**5.0±0.5**	**291±162**	**85±27**	**6.3±0.9**	**0.7±0.2**

Values in bold represent means ± standard deviations. Alb, albumin; Alk Phos, alkaline phosphatase; Ca, calcium; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; iPTH, intact parathyroid hormone; LDL, low-density lipoprotein cholesterol; M, mean; Phos, phosphorous; SBP, systolic blood pressure; SD, standard deviation; Trig, triglycerides.

Table 2

Standardized Estimates and 95% Confidence Limits

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

* p = 0.006