Association of Low Serum Fetuin A Levels With Poor Arteriovenous Access Patency in Patients Undergoing Maintenance Hemodialysis

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Background: Fetuin A, a predictor of mortality in dialysis patients, is associated with vascular calcification and atherosclerosis in hemodialysis (HD) patients. Whether it predicts arteriovenous (AV) access patency is unknown. This study aimed to investigate the association between fetuin A and AV access patency in HD patients.

Study Design: Prospective observational study.

Setting & Participants: 238 prevalent HD patients (127 women and 111 men; mean age, 60 ± 12 years) were followed up for AV access patency for 32 months.

Predictors: Tertiles of baseline circulating fetuin A levels, corresponding to 0.15-0.25, 0.26-0.32, and 0.33-0.51 g/L.

Outcome: The major outcome was loss of unassisted AV access patency, defined as AV access thrombosis or need for intervention.

Measurements: Fetuin A and other markers of inflammation.

Results: 100 patients had loss of AV access patency (42%) on follow-up. Patients in the lowest fetuin A tertile had the worst AV access patency (log-rank test, $\chi^2 = 8.68$; $P = 0.01$). Using Cox proportional hazards regression with patients in the lowest fetuin A tertile as reference, patients in the intermediate tertile had an HR of 0.49 (95% CI, 0.29-0.82), whereas those in the highest fetuin A tertile had an HR of 0.43 (95% CI, 0.25-0.75) for loss of AV access patency. Similarly, considering patients using AV fistulas or grafts separately, patients in the highest fetuin A tertile had less risk of losing AV access patency than patients in the other tertiles (HR, 0.40 [95% CI, 0.19-0.84] for patients with AV fistulas and HR, 0.25 [95% CI, 0.10-0.65] for patients with AV grafts).

Limitations: Focus on the patency of prevalent rather than new AV access in maintenance hemodialysis patients.

Conclusions: Fetuin A deficiency is associated with a higher risk of loss of AV access patency in either native AV fistulas or AV grafts in HD patients.

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INDEX WORDS: Fetuin A; arteriovenous access patency; atherosclerosis; tumor necrosis factor α (TNF-α); hemodialysis.

Arteriovenous (AV) access dysfunction is a major complication that has high mortality and hospitalization rates in prevalent hemodialysis (HD) patients.[1-3] For patients with an AV fistula or AV polytetrafluoroethylene (PTFE) graft, the 1- or 2-year patency rate of AV access is poor.[4,5] Some investigations propose that venous neointimal hyperplasia leads to AV graft and late AV fistula stenosis.[6,7] The proliferation of myofibroblasts and migration of smooth muscle cells are coordinated by inflammatory mediators, such as tumor necrosis factor α (TNF-α), fibroblast growth factor, and vasoactive and adhesion molecules, promoting a process like atherosclerosis leading to AV access stenosis and thrombosis.[8-10] Nevertheless, the detailed pathogenesis of AV access dysfunction is still being investigated, and several medical or interventional treatments have been developed to maintain AV access function, with limited success.[11-13]

Fetuin A is a protein secreted by hepatocytes and a circulating inhibitor of calcium phosphate precipitation that links to cardiovascular (CV) calcification and predicts CV and non-CV mortality in dialysis patients.[14] In regard to the process

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of atherosclerosis, fetuin A acts as a potent inhibitor of calcification.[15] It also is a negative acute-phase reactant that is downregulated in the inflammatory process during atherosclerosis.[16-19] In addition, fetuin A is associated closely with dyslipidemia, especially hypertriglyceridemia, in HD patients without diabetes mellitus (DM), which is another precipitating factor of atherosclerosis.[20]

Because atherosclerosis and inflammation contribute to AV access dysfunction, it is hypothesized that fetuin A may be associated with AV access failure in HD patients. Therefore, this prospective observational study was conducted to investigate whether serum fetuin A concentration influences AV access patency in prevalent HD patients.

METHODS

Participants

In March 2007 at the Far Eastern Memorial Hospital (Taipei, Taiwan), 321 patients received maintenance HD. After excluding 83 patients, 238 patients older than 18 years (mean age, 60 ± 12 years; 127 women) were enrolled. Exclusion criteria were: (1) active infection, (2) recent hospitalization or unstable hemodynamic status within the preceding 3 months, (3) active malignancy, (4) receiving HD through a functioning AV access for less than 6 months, (5) recent AV access event (thrombosis, infection, or intervention in the 6 months before recruitment), and (6) patient refusal.

Study patients received 3.5-5 hours of HD 3 times weekly with a blood flow rate of 250-300 mL/min and dialysate flow of 500 mL/min. They used bicarbonate dialysate and reverse-osmosis–purified water. In 73% of patients, a high-flux polysulfone membrane was used as dialyzer, whereas in the remaining 27%, a synthetic membrane low-flux dialyzer was used. Mean duration of HD therapy before recruitment was 3.6 years (range, 0.8-18.0 years). The hospital's Institutional Review Board approved the study, and all participants provided written informed consent.

Baseline Demographic and Clinical Data and Laboratory Parameters

Baseline data, including sex, age, type of AV access, body weight and height, body mass index, presence of hypertension or DM, underlying kidney disease, HD regimen, duration of HD therapy, erythropoiesis-stimulating agent dosage, and concurrent medications of each patient, such as antiplatelets (aspirin, dipyridamole, pentoxifylline, and clopidogrel), anticoagulant (warfarin), and HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors (statins) were recorded.

Venous blood samples were obtained in the morning after an overnight fast more than 8 hours before the patient's midweek dialysis treatment. All laboratory tests were performed by the hospital's central laboratory. Biochemistry data were determined using a Hitachi 747 autoanalyzer (Hitachi Ltd, www.hitachi.com). Kt/V_{urea} and normalized protein catabolic rate were calculated using a single-compartment model.

Total cholesterol and triglycerides were measured enzymatically, whereas high-density lipoprotein (HDL) cholesterol was measured after precipitating apolipoprotein B–containing lipoproteins with dextran sulfate and magnesium chloride. Low-density lipoprotein cholesterol level was calculated using the Friedewald formula, with non–HDL-cholesterol equal to total cholesterol minus HDL cholesterol.

High-sensitivity C-reactive protein (hs-CRP) was assayed using an image autoanalyzer with the nephelometric method (Beckman Coulter Inc, www.beckmancoulter.com), whereas serum TNF-α was measured using an enzyme-linked immunosorbent assay (BioSource [now DIAsource ImmunoAssays], www.diasource-diagnostics.com). Blood samples for measurement of TNF-α were centrifuged immediately and stored at −70°C until assay.

Measurement of Serum Fetuin A

Serum fetuin A was measured using a highly sensitive 2-site enzyme-linked immunoassay (GenWay Biotech Inc, www.genwaybio.com). Nephelometry for fetuin A used the same high-specificity antibody as the enzyme-linked immunosorbent assay and established reproducible standard curves after testing for appropriate dilution. This was evaluated in a side-by-side comparison with immunoblot analysis to exclude cross-reactivity of the antibodies with other serum proteins and proteolytic fragments of fetuin A. The intra-assay coefficient of variation was 5.5%, and the inter-assay coefficient of variation was 6.2%. The assay linear measurement range of human fetuin A was 0.05-3.5 g/L. Blood samples for measurement of fetuin A were sampled on recruitment and immediately centrifuged and stored at −70°C until assay.

Outcome

The outcome was loss of the primary unassisted AV access patency, defined as the first occurrence of AV access thrombosis, an access procedure performed to correct stenosis ≥50% of diameter, or other surgical modifications of the AV access (eg, for infection). Patients were referred for angiography if blood flow rate at the access site decreased by >25% from baseline or venous pressure at the access site was >200 mm Hg.

Follow-up was censored on the date of loss of primary unassisted AV access patency, the end of the study (November 1, 2009), or at the time of death, whichever came first. Because cutoff values for fetuin A for predicting outcomes in HD patients were inconclusive,[16-18,21,22] a plot of fetuin A concentration and hazard ratio (HR) of outcome with Lowess function was performed initially. Results showed their nonlinear relationship and suggested stratifying patients into tertiles according to fetuin A level for outcome analysis (Fig 1).

Statistical Analysis

Normally distributed continuous variables are presented as mean ± standard deviation, and non–normally distributed continuous variables are presented as median with 25th and 75th percentiles. Categorical data are presented as percentages. Participants were divided into tertiles based on serum

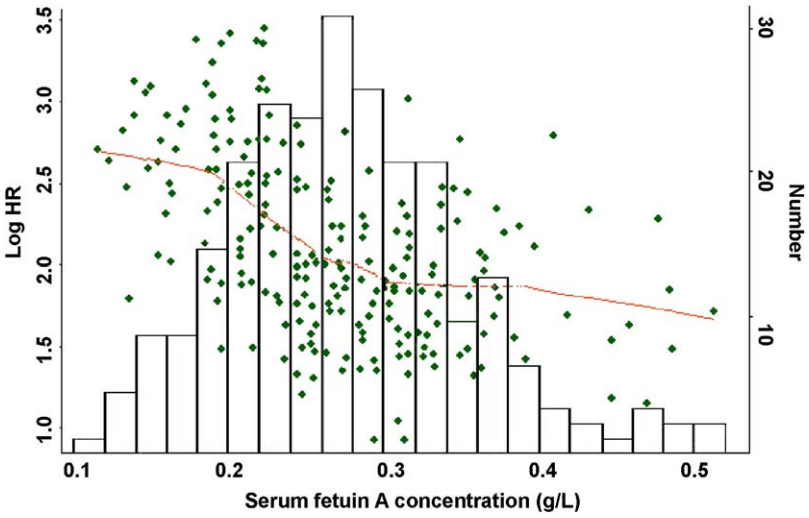

Figure 1. Distribution of fetuin A concentrations in hemodialysis patients in the study (n = 238). The histogram represents the number of patients (right axis) at different fetuin A concentrations, on which is superimposed a scatter plot of log hazard ratio (HR; left axis) of loss of arteriovenous access patency versus fetuin A concentration with Lowess smoothed function. The plot suggested nonlinear relationships; we therefore categorized patients into tertiles by fetuin A concentration for outcome analyses.

fetuin A concentrations, with tertile 1 representing the lowest concentrations (tertile 1, 0.15-0.25; tertile 2, 0.26-0.32; and tertile 3, 0.33-0.51 g/L). Differences in baseline characteristics and biochemical parameters were compared using analysis of variance for continuous variables and χ^2 test for categorical variables, whereas nonparametric Kruskal-Wallis test was used for non–normally distributed continuous variables.

The Kaplan-Meier method (log-rank test) and Cox proportional hazards regression model were used to assess differences in patients' AV access patency by fetuin A tertiles. In the Cox proportional hazards model, covariates for multivariable adjustment included fetuin A tertile and factors selected based on their reported association with AV access patency in prevalent HD patients (ie, age, sex, type of AV access, HD vintage, presence of DM, body mass index, use of erythropoiesis-stimulating agents, use of antiplatelet agents, and levels of hemoglobin, calcium-phosphorus product, hs-CRP, TNF-α, intact parathyroid hormone, low-density lipoprotein cholesterol, and triglycerides).[2,10,13,23]

Cox analyses of the outcomes also were performed in predefined subgroups, which were defined according to median values or values divided into thirds or based on their medical condition (eg, type of AV access). *P* values for the interaction between subgroup and fetuin A tertiles were reported. All statistical analyses were performed using SPSS software, version 15.0 (SPSS Inc, www.spss.com), and $P < 0.05$ is considered statistically significant.

RESULTS

Patient Characteristics

In the study population, 163 patients had a native AV fistula and 75 had an AV PTFE graft. Baseline characteristics of patients by tertile of fetuin A concentration are listed in Table 1. Fetuin A concentrations were normally distributed among participants (mean, 0.28 ± 0.08 g/L; Fig 1). Patients in the third tertile were younger ($P < 0.001$), fewer had DM ($P < 0.002$), were less likely to use an AV graft ($P = 0.03$), and had higher albumin ($P < 0.001$) and lower hs-CRP ($P = 0.001$) levels.

Outcomes

Overall, 100 of 238 patients (42%) reached the outcome during the 32-month (960-day) follow-up. AV access patency of patients in tertiles were significantly different ($\chi^2 = 8.68$; $P = 0.01$, log-rank test) using the Kaplan-Meier method (Fig 2).

Using the Cox proportional hazard model with multicovariate adjustments and the first tertile as the reference group, the second tertile had an HR of 0.49 (95% confidence interval [CI], 0.29-0.82; $P = 0.007$) and the third tertile had an HR of 0.43 (95% CI, 0.25-0.75; $P = 0.003$) for loss of primary unassisted AV access patency in all patients using either an AV fistula or AV graft. Moreover, 52 (31.9%) patients with an AV fistula and 48 (64%) with an AV graft experienced loss of unassisted patency during follow-up.

In patients with an AV fistula, patients in the second (HR, 0.41; 95% CI, 0.18-0.90; $P = 0.03$) and third tertiles (HR, 0.40; 95% CI, 0.19-0.84; $P = 0.02$) experienced less loss of unassisted patency than patients in the first tertile. In patients with an AV graft, those in the second (HR, 0.33; 95% CI, 0.14-0.78; $P = 0.01$) and third tertiles (HR, 0.25; 95% CI, 0.10-0.65; $P = 0.004$) experienced less loss of unassisted patency than those in the first tertile (Table 2).

Table 1. Baseline Characteristics of Patients by Tertile of Fetuin A Concentration

	All Patients (N = 238)	Fetuin A Tertile (g/L)			*P* for Trend
		0.15-0.25 (n = 80)	0.26-0.32 (n = 79)	0.33-0.51 (n = 79)	
Age (y)	60 ± 12	64 ± 11	59 ± 11	56 ± 12	<0.001
Women (%)	54	55	48	57	0.8
Diabetes mellitus (%)	42	55	43	28	<0.001
AV graft (%)	32	36	37	22	0.03
Dialysis vintage (y)	3.6 ± 4.1	3.3 ± 3.9	3.9 ± 4.4	3.6 ± 4.0	0.7
Kt/V_{urea}	1.54 (1.41, 1.70)	1.51 (1.37, 1.73)	1.56 (1.44, 1.71)	1.58 (1.44, 1.75)	0.5
Systolic BP (mm Hg)	148 ± 32	147 ± 28	150 ± 33	148 ± 27	0.5
Diastolic BP (mm Hg)	84 ± 17	80 ± 13	85 ± 19	84 ± 22	0.5
Pulse BP (mm Hg)	71 ± 23	70 ± 17	72 ± 14	70 ± 22	0.8
BMI (kg/m^2)	22.8 ± 3.8	22.1 ± 3.8	23.4 ± 3.8	22.8 ± 3.7	0.2
History of AV access failure (%)	55	58	53	56	0.9
No. of previous AV access failures	1.6 ± 2.1	1.9 ± 2.5	1.5 ± 2.2	1.7 ± 1.9	0.3
AV access flow (mL/min)	278 ± 76	278 ± 64	281 ± 70	276 ± 54	0.5
Ultrafiltration (kg/dialysis session)	2.7 ± 1.1	2.5 ± 1.0	2.9 ± 1.2	2.6 ± 1.1	0.6
Laboratory data					
Hemoglobin (g/dL)	10.8 ± 1.4	10.8 ± 1.5	10.9 ± 1.4	10.8 ± 1.4	0.8
Platelets ($\times 10^3/\mu L$)	200 ± 65	199 ± 68	202 ± 70	199 ± 58	0.9
Potassium (mmol/L)	4.6 ± 0.7	4.5 ± 0.7	4.6 ± 0.6	4.7 ± 0.7	0.1
Calcium (mg/dL)	9.2 (8.8, 9.6)	9.2 (8.8, 9.7)	9.2 (8.9, 9.5)	9.2 (8.9, 9.7)	0.7
Phosphorus (mg/dL)	5.0 (4.2, 6.1)	5.2 (4.2, 6.1)	5.0 (4.3, 6.8)	5.0 (4.2, 5.9)	0.9
Ca × P	45 (39, 57)	47 (37, 56)	46 (40, 61)	47 (40, 56)	0.9
LDL-C (mg/dL)	80 (60, 104)	79 (59, 103)	76 (61, 98)	87 (60, 109)	0.8
Triglycerides (mg/dL)	147 (95, 232)	157 (95, 243)	147 (94, 235)	149 (100, 243)	0.5
iPTH (pg/mL)	245 (120, 428)	178 (104, 415)	263 (139, 465)	245 (134, 411)	0.6
hs-CRP (mg/L)	3.3 (1.1, 7.9)	4.9 (1.4, 14.6)	4.0 (1.2, 9.2)	2.4 (0.9, 5.8)	0.001
TNF-α (ng/mL)	7.83 (6.27, 9.21)	7.34 (6.0, 9.37)	7.56 (6.36, 9.58)	6.99 (6.14, 8.62)	0.3
Albumin (g/L)	4.1 ± 0.4	3.9 ± 0.4	4.1 ± 0.3	4.2 ± 0.3	<0.001
nPCR (g/kg/d)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	1.1 (1.0, 1.3)	0.4
Medications (%)					
ESAs	99	99	100	99	0.7
Vitamin D_3	27	25	27	28	0.3
Statins	14	10	13	20	0.1
Antihypertensive agents	48	44	51	48	0.8
Aspirin/antiplatelet agents	41	48	35	39	0.3

Note: Values are expressed as mean ± standard deviation, median (25th, 75th percentiles), or percentage. Conversion factors for units: hemoglobin in g/dL to g/L, ×10; calcium in mg/dL to mmol/L, ×0.2495; phosphorus in mg/dL to mmol/L, ×0.3229; LDL-C in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L, ×0.01129; albumin in g/dL to g/L, ×10. No conversion necessary for platelet count in $\times 10^3/\mu L$ and $\times 10^9/L$; iPTH in pg/mL and ng/L; potassium in mEq/L and mmol/L.

Abbreviations and definitions: AV, arteriovenous; BP, blood pressure; BMI, body mass index; Ca × P, calcium-phosphorus product; ESA, erythropoiesis-stimulating agent; hs-CRP, high-sensitivity C-reactive protein; iPTH, intact parathyroid hormone; LDL-C, low-density lipoprotein cholesterol; nPCR, normalized protein catabolic rate; TNF-α, tumor necrosis factor α; statins, HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors.

In the predefined subgroup analyses (Table 3; n = 238), fetuin A deficiency was associated with worse AV access patency in patients younger than 65 years and those using antiplatelet agents. Regarding inflammatory markers, fetuin A deficiency was linked to a higher risk of loss of AV access patency in only the subgroup with lower hs-CRP and medium TNF-α concentrations.

Using Cox proportional hazards regression with multivariable adjustment, several factors also were associated significantly with loss of primary unassisted AV access patency in 238 patients. Patients

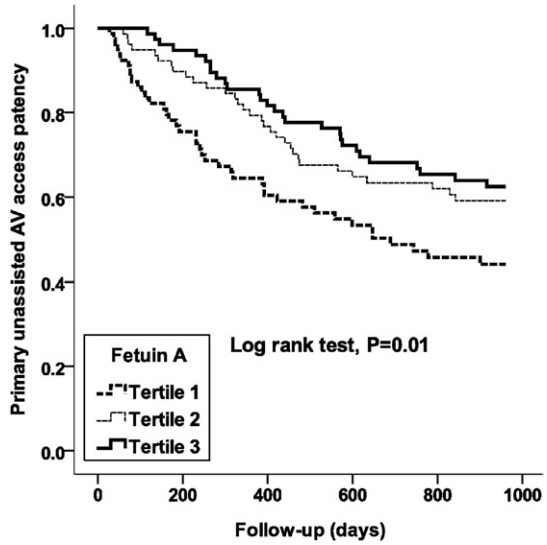

Figure 2. Kaplan-Meier analysis of arteriovenous (AV) access patency. Patients in tertiles of fetuin A concentrations were significantly different ($\chi^2 = 8.68$; $P = 0.01$, log-rank test).

with an AV graft had an HR of 3.15 (95% CI, 2.01-4.92; $P < 0.001$) for loss of AV access patency compared with those with an AV fistula. In addition, age (HR per 10-year increase, 1.05; 95% CI, 1.001-1.026; $P = 0.05$), use of antiplatelet agents (HR, 0.51; 95% CI, 0.37-0.82; $P = 0.04$), and triglyceride level (HR per 100-mg/dL increase, 1.02; 95% CI, 1.02-1.04; $P = 0.004$) had an impact on AV access patency.

In patients with an AV fistula (n = 163), only fetuin A tertile (Table 2; $P = 0.03$) and TNF-α level (HR, 1.15; 95% CI, 1.03-1.28; $P = 0.02$) were associated with poor AV fistula unassisted patency. In patients with an AV graft, fetuin A tertile (Table 2; $P = 0.009$), HD vintage (HR, 0.9; 95% CI, 0.81-0.99; $P = 0.001$), and triglyceride level (HR per 100-mg/dL increase, 1.03; 95% CI, 1.01-1.06; $P = 0.02$) predicted AV graft failure.

DISCUSSION

The present investigation mainly shows that lower fetuin A concentrations in prevalent HD patients independently predict worse primary unassisted AV access patency regardless of the use of an AV fistula or AV graft. Furthermore, higher TNF-α and triglyceride levels are linked

Table 2. Outcomes of Patients by Tertile of Fetuin A Concentration

Fetuin A Tertile	Loss of Primary Unassisted Patency (no.)	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)[a]	*P*	Adjusted HR (95% CI)[b]	*P*
Patients Used Either AV Fistula or AV Graft (n = 238)							
All			0.02[c]		0.003[c]		0.004[c]
1	43	1.0 (ref)	—	1.0 (ref)	—	1.0 (ref)	—
2	33	0.61 (0.38-0.97)	0.04	0.52 (0.28-0.86)	0.002	0.49 (0.29-0.82)	0.007
3	24	0.52 (0.32-0.84)	0.007	0.49 (0.29-0.81)	0.005	0.43 (0.25-0.75)	0.003
Patients Used AV Fistula (n = 163)							
All			0.07[c]		0.04[c]		0.03[c]
1	22	1.0 (ref)	—	1.0 (ref)	—	1.0 (ref)	—
2	16	0.56 (0.29-1.09)	0.09	0.51 (0.27-1.10)	0.06	0.41 (0.18-0.90)	0.03
3	14	0.51 (0.27-0.98)	0.04	0.48 (0.27-0.97)	0.04	0.40 (0.19-0.84)	0.02
Patients Used AV Graft (n = 75)							
All			0.05[c]		0.009[c]		0.009[c]
1	21	1.0 (ref)	—	1.0 (ref)	—	1.0 (ref)	—
2	17	0.51 (0.26-0.99)	0.05	0.29 (0.13-0.65)	0.02	0.33 (0.14-0.78)	0.01
3	10	0.50 (0.29-0.99)	0.04	0.37 (0.16-0.89)	0.03	0.25 (0.10-0.65)	0.004

Abbreviations: AV, arteriovenous; CI, confidence interval; HR, hazard ratio; ref, reference.

[a]Adjusted for age, type of AV access (only in analysis of all patients), hemodialysis vintage, presence of diabetes, use of antiplatelet agent, and body mass index.

[b]Adjusted for age, type of AV access (only in analysis of all patients), hemodialysis vintage, presence of diabetes, hemoglobin level, use of antiplatelet agent, body mass index, and levels of calcium-phosphorus product, tumor necrosis factor α, high-sensitivity C-reactive protein, low-density lipoprotein cholesterol, and triglycerides.

[c]Global *P* value for fetuin A tertile.

Table 3. HRs for Loss of AV Access Patency in Predefined Subgroups

Subgroup	Fetuin A Tertile 2		Fetuin A Tertile 3		Global *P*	*P* for Interaction
	HR (95% CI)[a]	*P*	HR (95% CI)[a]	*P*		
Age (y)						0.3
<65 (n = 153)	0.38 (0.17-0.84)	0.02	0.30 (0.13-0.71)	0.006	0.01	
≥65 (n = 85)	0.59 (0.27-1.30)	0.2	0.54 (0.22-1.30)	0.2	0.3	
Use of antiplatelet agents						0.9
Yes (n = 97)	0.27 (0.11-0.65)	0.004	0.31 (0.13-0.74)	0.008	0.005	
No (n = 141)	0.64 (0.32-1.31)	0.2	0.48 (0.21-1.07)	0.07	0.2	
hs-CRP (mg/L)						0.7
<1.7 (n = 80)	0.38 (0.12-1.25)	0.1	0.19 (0.06-0.63)	0.006	0.02	
1.7-6.4 (n = 79)	0.47 (0.14-1.60)	0.2	0.88 (0.31-2.49)	0.8	0.5	
>6.5 (n = 79)	0.51 (0.23-1.14)	0.1	0.44 (0.14-1.38)	0.2	0.2	
TNF-α (mg/dL)						0.1
<6.60 (n = 80)	1.3 (0.42-4.34)	0.6	0.4 (0.10-1.70)	0.2	0.2	
6.60-8.43 (n = 79)	0.38 (0.14-1.01)	0.06	0.15 (0.05-0.42)	<0.001	0.001	
>8.43 (n = 79)	0.58 (0.22-1.40)	0.2	0.96 (0.36-2.57)	0.9	0.4	

Note: The first tertile of fetuin A level is the reference group. N = 238. Patients using either an AV fistula or AV graft.

Abbreviations: AV, arteriovenous; CI, confidence interval; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; TNF-α, tumor necrosis factor α.

[a]Covariates for multivariable adjustment included age, hemodialysis vintage, type of AV access (AV fistula or AV graft), presence of diabetes, hemoglobin level, use of antiplatelet agent, body mass index, and levels of calcium-phosphorus product, TNF-α, hs-CRP, low-density lipoprotein cholesterol, and triglycerides.

to poor AV access patency. Beyond its significant impact on coronary and valvular calcification, close links with inflammation, and potent modulation of insulin resistance, fetuin A also is associated with AV access patency in prevalent HD patients.

Late AV access dysfunction is a critical problem in prevalent HD patients. Despite wide-ranging investigations, little is known about the underlying pathogenesis. Previous small-scale investigations have suggested that interleukin 6 (IL-6), TNF-α, adhesion molecules, dyslipidemia, and insulin resistance together orchestrate neointimal hyperplasia and thereafter AV access dysfunction in HD patients without DM. Other predictors of AV access failure include type of access, presence of DM, enhanced primary or secondary homeostasis, and position of the AV access.[2,5,10]

The present results show that in patients with an AV graft, those with higher triglyceride levels and those who do not use antiplatelet agents have worse AV access patency. This confirms that these "traditional risk factors" for atherosclerosis and neointimal hyperplasia predict AV access dysfunction. Moreover, fetuin A and circulating TNF-α levels strongly predict AV access patency after various adjustments.

There are several possible explanations for the links between fetuin A deficiency and loss of AV access patency. First, fetuin A is a potent inhibitor of extraosseous calcification in dialysis patients. This extraosseous calcification causes atherosclerosis,[15] which accelerates the progression of neointimal hyperplasia until it finally reaches thrombosis.[14,17,24-26] In the present results, patients with low fetuin A concentrations had the worst AV access patency regardless of AV fistula or AV graft use (Table 2). Patients in the fetuin A tertiles had similar calcium, phosphate, intact parathyroid hormone, and calcium-phosphorus product levels, which are important precipitating factors of AV access calcification on pre-existing stenosis.[27,28] In multivariable Cox regression analysis, calcium-phosphorus product only marginally predicted AV access dysfunction after adjustment for fetuin A tertile (HR, 1.17; 95% CI, 0.98-1.39; $P = 0.09$). This suggests that fetuin A deficiency may interfere with the calcification process of AV access dysfunction in patients with a pre-existing high risk of calcification. Interestingly, in the study conducted by

Schlieper et al,[23] fetuin A concentration was not associated with vascular access calcification investigated using plain radiograph. However, precise imaging studies may be necessary to strengthen this potential association.

Second, the link between fetuin A level and inflammation in HD patients makes the former a competent determinant of AV access dysfunction. Chronic inflammation accelerates vascular calcification/atherosclerosis, and in cell culture, overexpression of inflammatory cytokines, such as IL-6 and TNF-α, on a failed AV access strengthens the inflammatory hypothesis of AV access failure.[3,8,9] Fetuin A acts as a TNF antagonist and is associated inversely with hs-CRP and IL-6 levels in HD patients.[16,22,29] Hence, the link between fetuin A level and inflammation points to the association between AV access dysfunction and fetuin A deficiency.

Study participants with lower hs-CRP levels experienced more of an impact of fetuin A deficiency on AV access patency (Table 3). On the contrary, in patients with higher hs-CRP levels (ie, those with "essential fetuin A deficiency"), the hazard of fetuin A deficiency for AV access failure became insignificant. Interestingly, TNF-α level remained a predictor of loss of AV access patency after adjusting for hs-CRP level in patients with an AV fistula. In addition, fetuin A and TNF-α levels marginally correlated (correlation coefficient $= -0.85$; $P = 0.08$) in the present study. This may occur because TNF-α has a crucial role in neointimal hyperplasia, rather than being simply a circulatory inflammatory mediator.[10,30] It can be speculated that enhanced inflammation in HD patients with low fetuin A concentrations causes high AV access complications. However, a causal relationship cannot be concluded in this observational study.

This study has some limitations. First, the study assessed the prevalence rather than incidence of the primary unassisted AV access patency. AV graft vintage influences the primary patency of AV access.[2,5] However, we made every effort to minimize this weak point by adjusting for HD vintage in multivariable analysis, which showed fetuin A level still predominately linked to AV access failure. Second, the number of patients is relatively small, and in addition, follow-up is relatively short. However, in the 32-month observation period, fetuin A deficiency maintained its critical role in predicting the loss of AV access patency compared with other reported factors. Moreover, compared with other investigations of AV access patency,[4,11-13,23] the observational period in this study is relatively long and adequate to show the influence of prespecified factors on AV access survival.

Third, fetuin A concentration may change over time in dialysis patients, and fetuin A deficiency usually worsens as dialysis vintage increases.[14,16,18,20] This study used fetuin A concentration at only a single time in the outcome analysis. However, in this study, HD vintage of patients in the fetuin A tertiles were similar (Table 1), and in previous studies, a single fetuin A level could successfully predict CV and all-cause mortality in the dialysis population.[14,16-19,22,31] Certainly, further investigations may be necessary to test whether fetuin A level measured a single time or time-dependent fetuin A levels predict AV access patency better in HD patients.

In conclusion, this prospective investigation shows that prevalent HD patients using either an AV fistula or AV graft with low fetuin A levels experience worse AV access patency. Fetuin A deficiency not only accelerates atherosclerosis and calcification of native vasculature, such as the coronary artery or aorta, but also is associated with loss of AV access patency in HD patients. Further larger scale studies are warranted to corroborate these findings.

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