Original Paper

Kidney & Blood Pressure Research

Kidney Blood Press Res 2011;34:328–333
DOI: 10.1159/000327848

Received: October 25, 2010
Accepted: March 27, 2011
Published online: May 26, 2011

Fetuin-A Pretransplant Serum Levels, Kidney Allograft Function and Rejection Episodes: A 3-Year Posttransplantation Follow-Up

Marcel Roos[a] Falko M. Heinemann[b] Monika Lindemann[b] Peter A. Horn[b] Jens Lutz[a] Konrad Stock[a] Klaus Thürmel[a] Marcus Baumann[a] Oliver Witzke[c] Uwe Heemann[a]

[a]Department of Nephrology, Technische Universität München, Munich, and [b]Institute for Transfusion Medicine and [c]Department of Nephrology, University Hospital Essen, Essen, Germany

Key Words
Fetuin-A · Kidney transplantation · Graft failure · Rejection

Abstract
Background: Fetuin-A is a negative acute-phase protein, which acts as a potent calcification inhibitor and an antagonist of transforming growth factor-β. Thus, fetuin-A levels are influenced by chronic inflammation and actively affect fibrosis and calcification processes, respectively. Graft rejection, interstitial fibrosis and tubular atrophy, chronic inflammation and calcification are common causes for kidney allograft loss. This study evaluated whether pretransplant fetuin-A levels predict long-term graft survival and rejection episodes in patients after kidney transplantation. ***Methods:*** In 206 renal transplant recipients pretransplant fetuin-A levels were measured in serum by ELISA. During the 36 months' active follow-up (median 1,249 days) 13 patients died (94% patient survival) and renal allograft failure was reported in 18 patients (91% graft survival). ***Results:*** Pretransplant fetuin-A levels did not differ among patients with incident graft failures as compared to patients with functional graft after long-term follow-up or rejection episodes (fetuin-A: 393.6 ± 46 vs. 384.4 ± 69 vs. 405 ± 27.4 μg/ml). In logistic regression analysis, pretransplant fetuin-A levels did not correlate with graft failure after 3 years' follow-up ($p = 0.895$). In COX regression analysis, fetuin-A levels were not associated with the time to graft loss. Moreover, fetuin-A levels correlated neither with renal and metabolic parameters nor with cellular or humoral rejection episodes. ***Conclusion:*** Pretransplant levels of fetuin-A are not a predictor for renal allograft loss or rejection episodes after 36 months' follow-up in transplant recipients.

Introduction

Kidney transplantation is the best therapy available for most patients with end-stage renal disease. However, the length of kidney allograft survival is frequently shorter than that of the recipient. Several causes for kidney allograft failure have been identified, e.g. graft rejection, interstitial fibrosis and tubular atrophy (IF/TA), chronic inflammation, in some cases also calcification of the allograft [1–4]. Thus, efforts should be made towards improvements in long-term allograft survival [5, 6]. Innovative risk-identifying strategies are still an unmet medical need in order to improve pretransplant risk evaluation and subsequent efforts to prevent allograft loss.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1420–4096/11/0345–0328$38.00/0

Accessible online at:
www.karger.com/kbr

Dr. med. Marcel Roos
Department of Nephrology, Klinikum rechts der Isar
Ismaninger Strasse 22
DE–81675 München (Germany)
Tel. +49 89 4140 2231, E-Mail marphiro@hotmail.com

Fetuin-A is a liver-derived negative acute-phase protein present in all extracellular fluids [7]. Owing to its high affinity for calcium phosphates, fetuin-A accumulates in the mineralized bone matrix, in atherosclerotic plaques, and in pathologically mineralized tissues [8, 9]. Fetuin-A binds to multiple ligands, including the fibrogenic growth factor TGF-β, thus acting as a soluble receptor-like antagonist of TGF-β actions [10]. It could be demonstrated that incubation of fetuin-A with hepatic stellate cells significantly inhibited collagen synthesis in hepatic stellate cells, potentially linking fetuin-A as an antifibrotic agent and cytokine antagonist [10, 11].

Hemodialysis patients have lower levels of fetuin-A than age- and sex-matched controls and lower fetuin-A concentrations are associated with increased vascular calcifications and enhanced mortality from cardiovascular disease in patients with end-stage renal disease [12, 13]. However, little data exist on fetuin-A in kidney transplant recipients. Recently, it was demonstrated that fetuin-A levels increased after kidney transplantation along with the improvement of endothelial functions [14]. A small study (n = 30) did not demonstrate an association between fetuin-A levels and allograft rejection [15]. The effect of pretransplant fetuin-A serum levels on allograft outcome, rejection episodes and long-term follow-up has not been elucidated in a large patient cohort. Regarding the various features of fetuin-A in terms of being downregulated during inflammation [16], inhibiting calcification and fibrosis [4, 10, 11], it may be speculated that pretransplant fetuin-A serum levels predict allograft outcome and rejection episodes. Therefore we investigated the relationship between fetuin-A levels prior to kidney transplantation and outcome 3 years after transplantation in 206 patients.

Patients and Methods

Patients. Two hundred and six patients were enrolled in this study as previously described [17]. Briefly, all patients were transplanted with kidney (n = 194) or kidney/pancreas (n = 12) allografts in a consecutive series from May 2001 to June 2004 in the University Hospital Essen, Germany, of whom 174 (84%) were transplanted with a kidney from a deceased donor and 32 (16%) patients received an allograft from a living donor. Pediatric transplantations and combined kidney/liver transplantations were excluded. Primary kidney diseases of the patients enrolled were glomerulonephritis (n = 75), cystic kidney disease (n = 29), diabetes mellitus type I and II (n = 20), intestinal nephritis (n = 20), renal vascular disease (n = 13), and other diseases (n = 49). Sixty-three patients were treated with cyclosporine (CsA, 100–150 ng/ml whole blood through level, tested by FPIA Abbott TDx monoclonal assay; Abbott Laboratories Ltd., Wiesbaden, Germany) and 136 patients with tacrolimus (4–10 ng/ml whole blood through level, tested by Abbott Imx tacrolimus assay). A total of 109 patients received MMF in combination with tacrolimus and 56 patients in combination with CsA. Additionally, all but 4 patients received prednisone prior to transplantation; antithymocyte globulin was given to 8 patients, combined with tacrolimus or MMF. Renal function after transplantation was estimated by measuring serum creatinine on days 10, 90, 180, 360 and 720. To correct renal function for differences in patient age and weight, the creatinine clearance was calculated using the Cockcroft and Gault [18] formula. HLA typing of patients and donors was performed by serology or polymerase chain reaction using sequence-specific primers for the HLA-A, HLA-B, DR, and DQ loci as previously described.

Rejection. Occurrence of rejection episodes and the loss of allograft function were recorded. In total, 13 patients died within 3 years after transplantation. Patients who died with a functioning allograft (n = 9) were excluded from survival analysis. Clinically manifested rejections were observed in 47 patients, of whom 10 patients developed two or more rejection episodes. Rejections were confirmed by renal biopsies in 43 patients. The biopsies revealed humoral rejections in 12 patients and cellular rejections were diagnosed in 31 patients, of whom 5 patients had cellular vascular and 26 patients had cellular interstitial rejections. Only biopsy-proven rejections were included in the correlation and survival analyses. The loss of allograft function was generally histologically diagnosed in all patients concerned.

Clinical Chemistry. Fetuin-A levels were measured with ELISA according to the manufacturer's instructions (BioVendor). The intra- and interassay coefficients of variation were both <5.0%.

Statistics. The correlation between isolated parameters was estimated by Spearman's correlation coefficient. The Mann-Whitney U test was used to compare two groups. Data are expressed as means ± SD, $p < 0.05$ was considered significant. Statistical analyses were performed with SPSS software version 15.0 (SPSS Inc., Chicago, Ill., USA).

Results

Pretransplant clinical and demographic characteristics of the patients are presented in table 1. In total, 206 patients were included in this study and active follow-up was conducted for a median of 1,249 days (interquartile range 1,020–1,445 days). The follow-up data revealed a 94% patient survival (13 patients died). Nine patients died with a functioning allograft and were therefore excluded from the survival analysis. In the remaining group of 197 patients, 18 patients (9%) experienced graft failure within 2 years after transplantation: 12 patients failed due to rejections, failure due to allograft venous thrombosis occurred in 2 cases, and donor-associated problems led to failure in another 2 patients. Finally, 2 patients failed due to technical problems. Total fetuin-A level was 404 (375–426) μg/ml. Pretransplant fetuin-A levels did not differ among patients with incident graft failures as compared

Table 1. Patient characteristics and demographics

Parameter	Total	Patients with graft failure	Patients without graft failure	p value	Patients without rejection	Patients with rejection	p value
Patients, n	206 (100)	18 (8.7)	188 (91.3)		163 (79.2)	43 (20.8)	
Age, years[a]	48 (31–65)	47.5 (36–65)	48 (37–60)	0.60	50 (39–61)	44 (31–54)	0.014
Male, n	130 (63.1)	12 (5.8)	118 (57.3)		105 (51)	25 (12.1)	
Female, n	76 (36.9)	6 (2.9)	70 (34)		58 (28.2)	18 (8.7)	
Fetuin-A, μg/ml[a]	404 (375–426)	401 (375–425)	404 (386–417)	0.92	404 (385–417)	404.6 (394–426)	0.13
Cold ischemic time, h[a]	15 (10–21)	15 (14–20.25)	16 (10–20)	0.23	16 (10–20)	15 (8.25–21)	0.87
Donor age, years[a]	48 (37–70)	58.5 (46–70)	48 (37–58)	0.013	48 (38–59)	53 (40–59)	0.38
Kidney transplantation, n	194 (94.2)	18 (8.7)	176 (83.5)		151 (73.3)	43 (20.9)	
Kidney and pancreas, n	12 (5.8)	–	12 (5.8)		12 (5.8)	–	
First transplantation, n	164 (79.6)	8 (3.9)	156 (75.7)		130 (63.1)	34 (16.5)	
Retransplantation, n	42 (20.4)	10 (4.9)	32 (15.6)		33 (26.1)	9 (4.4)	
Transplantation from living donor, n	32 (15.5)	–	32 (15.5)		23 (11.2)	9 (4.4)	
Transplantation from deceased donor, n	174 (84.5)	18 (8.7)	156 (75.8)		140 (68)	34 (16.5)	
Patients with HLA-MM cadaveric, n	107 (52)	7 (3.4)	100 (48.5)		103 (50)	24 (11.7)	
Patients with HLA-MM living, n	21 (10.2)	1 (0.5)	20 (9.7)		18 (8.7)	3 (1.4)	
PRA <5%, n	186 (90.3)	15 (7.3)	171 (83.0)		148 (71.9)	38 (18.4)	
PRA ≥5%, n	20 (9.7)	3 (1.4)	17 (8.3)		15 (7.2)	5 (2.5)	
Immunosuppression							
CsA + MMF, n	56 (100)	4 (7)	52 (93)		52 (93)	4 (7)	
CsA, n	7 (100)	1 (14.3)	6 (85.7)		6 (85.7)	1 (14.3)	
Tacrolimus + MMF, n	109 (100)	6 (5.5)	103 (94.5)		103 (94.5)	6 (5.5)	
Tacrolimus, n	27 (100)	5 (18.5)	22 (81.5)		22 (81.5)	5 (18.5)	
Other, n	7 (100)	2 (28.6)	5 (71.4)		5 (71.4)	2 (28.6)	
Patient's death within 2 years posttransplant, n	13 (100)	4 (30.8)	9 (69.2)		9 (69.2)	4 (30.8)	

Figures in parentheses are percentages. [a] Data are presented as median (interquartile range).

to patients with a functional graft after long-term follow-up, 401 (375–425) versus 404 (386–417) μg/ml, or rejection episodes versus without rejection episodes, 404 (385–417) versus 404.6 (394–426) μg/ml (p = n.s.). Patients with graft failure received their organs from older donors compared to patients without graft failure (p = 0.013). Moreover, patients without rejections were significantly older than patients with a rejection episode (p = 0.014).

In logistic regression analysis, pretransplant fetuin-A levels did not significantly predict graft failure after 3 years' follow-up (p = 0.895). We further investigated in COX regression analysis whether fetuin-A levels were associated with the time point (in days) of allograft loss. For the total study population the results were not significant (p = 0.89, HR 0.999, CI 0.992–1.007), nor when stratified for sex (men: p = 0.74, HR 1.002, CI 0.990–1.014, women: p = 0.48, HR 0.997, CI 0.998–1.006).

In order to evaluate pretransplant associations between fetuin-A levels and metabolic and renal parameters, analysis with Spearman correlation coefficients was performed (table 2). In this study population, pretransplant serum fetuin-A levels did not significantly correlate with metabolic markers such as HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides, fasting glucose, adiponectin and the body mass index. Moreover, glomerular filtration rate (GFR) on days 90, 180 and 360 after transplantation, respectively, did not correlate significantly with pretransplant fetuin-A values. Moreover, there was neither a clinically relevant nor a statistically significant correlation between delta GFR (90–720) and fetuin-A levels (r = 0.016, p = 0.84).

We then correlated fetuin-A levels with the occurrence of rejection episodes (p = n.s.). The average fetuin-A level in nonrejectors was 392.9 μg/ml and in patients with rejection 404 μg/ml (p = 0.13). No significant correlation was observed for the association of fetuin-A levels and the general occurrence of rejection episodes, as well as for cellular and humoral rejection episodes, respectively (p = n.s.). No association was found when rejection-associated graft loss was correlated with pretransplant fetuin-A serum levels (p = n.s.).

Table 2. Associations of fetuin-A with metabolic and renal parameters

Parameters		Serum fetuin-A	
		r	p
CRP, mg/dl	0.83 ± 1.13	0.019	0.82
HDL cholesterol, mg/dl	41.96 ± 11.86	0.186	0.40
LDL cholesterol, mg/dl	112.52 ± 26.19	–0.318	0.16
Total cholesterol, mg/dl	181.24 ± 37.84	0.066	0.67
Triglycerides, mg/dl	176.93 ± 105.02	0.061	0.70
Fasting glucose, mg/dl	111.70 ± 50.72	0.150	0.13
Adiponectin, U/ml	47.70 ± 40.95	0.122	0.08
Body mass index	24.4 ± 3.8	0.019	0.79
Kidney survival, days	1,140 ± 375	0.122	0.09
GFR after 10 days, ml/min	43.5 ± 26.5	–0.087	0.23
GFR after 90 days, ml/min	58.1 ± 21.9	–0.007	0.92
GFR after 180 days, ml/min	57.1 ± 21.1	–0.034	0.65
GFR after 360 days, ml/min	56.6 ± 19.7	–0.017	0.82
GFR after 720 days, ml/min	55.0 ± 19.0	0.043	0.57

All values are means ± SD unless indicated otherwise.

Discussion

To the best of our knowledge, this is the first study to evaluate the influence of pretransplant serum fetuin-A levels on kidney allograft outcome and rejection (including cellular and humoral) episodes in a large study population of 206 kidney transplant recipients and a long-term follow-up of 3 years. This study demonstrates that pretransplant fetuin-A levels are not a predictor for long-term graft survival in renal transplant recipients. Moreover, fetuin-A serum levels were not associated with biopsy-proven rejection episodes in our study population.

In general, renal allograft loss is the consequence of cumulative damage from a series of time-dependent stressors and factors [19] and there is considerable evidence that IF/TA, chronic inflammation and calcification processes are crucial risk factors for allograft failure [1–4].

Over the last decade fetuin-A has emerged as one of the most potent calcification inhibitors in serum [20]. Low fetuin-A levels were found to be related to increased vascular calcifications in dialysis patients and to calcific uremic arteriolopathy [20, 21], leading to higher overall cardiovascular mortality. One part of the relation between low fetuin-A levels and increased mortality appeared to be explained by the potential down-regulation of fetuin-A in inflammatory states [22]. Recently, a negative association between serum fetuin-A levels and concentration of the inflammatory cytokines IL-1β, IL-6 and tumor necrosis factor-α in chronic kidney disease and hemodialysis patients could be demonstrated [23]. This supports the hypothesis of inflammation-dependent down-regulation of fetuin-A expression. Moreover, it could be shown that fetuin-A administration inhibits the synthesis of tumor necrosis factor-α in a model of acute inflammation [24], and inflammation is an independent predictor of renal allograft loss [25, 26].

Surprisingly, our results could not prove an association between pretransplant fetuin-A serum levels and renal allograft failure after a 36-month follow-up. From the multifactorial actions of fetuin-A in terms of being involved in inflammatory and fibrotic processes, we would have expected lower fetuin-A levels in patients with graft failure and also rejection episodes.

One possible explanation for our findings could be the fact that fetuin-A levels may decrease after a single hemodialysis session [27]. Blood samples for this study were collected without taking into account the time points of dialysis treatment. Hence, possible dialysis sessions could have manipulated fetuin-A levels in this study, which might also explain the lack of an association between pretransplant serum fetuin-A and C-reactive protein (CRP) levels (table 2), as a marker for chronic inflammation. Moreover, fetuin-A levels are known to respond to pharmacological interventions, e.g. treatment with the phosphate binder sevelamer increased fetuin-A levels [28]. No data were available for the time point of phosphate binder intake, so that we, here again, cannot exclude possible confounders like calcium-phosphate medication in influencing fetuin-A levels.

Fetuin-A has been shown to act as a soluble receptor-like antagonist of TGF-β actions [10]. Incubation of fetuin-A with hepatic stellate cells significantly inhibited collagen synthesis in hepatic stellate cells, potentially linking fetuin-A as an antifibrotic agent and cytokine antagonist [10, 11]. IF/TA are well-recognized reasons for chronic allograft failure. We have speculated to find lower fetuin-A levels in patients with allograft failure after a 36-month observation period. A possible explanation for our negative finding is the reason of the 18 graft losses in this study. The majority was due to rejection episodes (n = 12). No patient lost his graft due to histologically proven IF/TA. Thus, our study cannot exclude a possible association between fetuin-A levels and IF/TA. Further investigations are warranted potentially focusing on an association between fetuin-A levels and histological findings of chronic allograft failure and IF/TA especially.

Although fetuin-A is negatively associated with inflammatory cytokines, we could not observe an association with biopsy-proven rejection episodes. Our results are in line with a previously published study, which could not see an association between fetuin-A levels and any histological findings at 3 months [15]. Again possible confounders might have influenced fetuin-A levels, thus making it impossible to detect a significant association between rejection episodes and pretransplant fetuin-A levels.

In addition, in contrast to recent studies [12, 13], in the present study no relation was seen between serum fetuin-A concentrations and CRP. Possibly, the lower level of inflammation in our study compared with earlier studies might play a role. Moreover, the lack of a significant difference may be due to the lower sample size of our study (n = 206 vs. 312) and the fact that CRP values of each patient were not available (n = 155).

Our study has some limitations. First, parameters such as fetuin-A and CRP levels were only assessed at a single point in time instead of having time-averaged values. Second, as already mentioned above, several confounders may have potentially influenced the regulation of such an acute-phase protein as fetuin-A and therefore the outcome of this study. The magnitude of inflammation, the effect of several drugs including phosphate binders, vitamin D preparations and the severity of glomerular dysfunction may all have potential to alter fetuin-A levels. In this respect we also have to emphasize that the timing for pretransplant blood specimen collection was not scheduled specifically and is not uniform among the patient population. This addresses a strong limitation of our study, since fetuin-A levels might have varied due to shorter or longer dialysis-free periods and thus influenced our findings, especially in terms of potential correlations with kidney function (GFR) and inflammation (CRP). Third, we cannot exclude potential associations between fetuin-A levels and chronic histological changes, such as IF/TA and chronic arteriolopathy. Our observation period was potentially too short to detect graft failures due to these histological changes.

Nevertheless, our study size and long-term follow-up of 36 months has enough power to make us conclude that pretransplant fetuin-A serum levels are not a valid predictor for renal allograft outcome and rejection episodes in a large study population. Further investigations should benefit from detailed analyses of the relationship between fetuin-A serum levels and renal allograft outcome potentially focusing on IF/TA.

References

1 Matas AJ, Humar A, Gillingham KJ, et al: Five preventable causes of kidney graft loss in the 1990s: a single-center analysis. Kidney Int 2002;62:704–714.
2 El-Zoghby ZM, Stegall MD, Lager DJ, Kremers WK, Amer H, Gloor JM, Cosio FG: Identifying specific causes of kidney allograft loss. Am J Transpl 2009;9:527–535.
3 Schwarz A, Mengel M, Gwinner W, Radermacher J, Hiss M, Kreipe H, Haller H: Risk factors for chronic allograft nephropathy after renal transplantation: a protocol biopsy study. Kidney Int 2005;67:341–348.
4 Gwinner W, Suppa S, Mengel M, Hoy L, Kreipe HH, Haller H, Schwarz A: Early calcification of renal allografts detected by protocol biopsies: causes and clinical implications. Am J Transplant 2005;5:1934–1941.
5 Meier-Kriesche HU, Schold JD, Srinivas TR, Kaplan B: Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. Am J Transplant 2004;4:378–383.
6 2007 Annual Data Report. Atlas of chronic kidney disease and end-stage renal disease in the United States. Am J Kidney Dis 2008; 51:S1–S319.
7 Dziegielewska KM, Brown WM: Fetuin. Heidelberg, Springer, 1995.
8 Triffitt JT, Gebauer U, Ashton BA, Owen ME, Reynolds JJ: Origin of plasma alpha2HS-glycoprotein and its accumulation in bone. Nature 1976;262:226–227.
9 Keeley KW, Sitarz EE: Identification and quantitation of alpha 2-HS-glycoprotein in the mineralized matrix of calcified plaques of atherosclerotic human aorta. Atherosclerosis 1985;55:63–69.
10 Demetriou M, Binkert C, Sukhu B, Tenenbaum HC, Dennis JW: Fetuin/alpha2-HS glycoprotein is a transforming growth factor-beta type II receptor mimic and cytokine antagonist. J Biol Chem 1996;271:1275–1276.
11 Verma-Gandhu M, Peterson MR, Peterson TC: Effect of fetuin, a TGF beta antagonist and pentoxifylline, a cytokine antagonist on hepatic stellate cell function and fibrotic parameters in fibrosis. Eur J Pharmacol 2007; 572:220–227.
12 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.
13 Stenvinkel P, Wang K, Qureshi AR, Axelsson J, Pecoits-Filho R, Gao P, Barany P, Lindholm B, Jogestrand T, Heimbürger 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.
14 Caglar K, Yilmaz MI, Saglam M, Cakir E, Kilic S, Eyileten T, Sonmez A, Oguz Y, Oner K, Ors F, Vural A, Yenicesu M: Endothelial dysfunction and fetuin A levels before and after kidney transplantation. Transplantation 2007;83:392–397.
15 Urbanová M, Kalousová M, Zima T, Skibová J, Wohlfahrt P, Viklický O: Fetuin-A early after renal transplantation. Kidney Blood Press Res 2009;32:217–222.

16 Lebreton JP, Joisel F, Raoult JP, Lannuzel B, Rogez JP, Humbert G: Serum concentration of human alpha 2 HS glycoprotein during the inflammatory process: evidence that alpha 2 HS glycoprotein is a negative acute-phase reactant. J Clin Invest 1979;64:1118–1129.
17 Heinemann FM, Rebmann V, Witzke O, Philipp T, Broelsch CE, Grosse-Wilde H: Association of elevated pretransplant sCD30 levels with graft loss in 206 patients treated with modern immunosuppressive therapies after renal transplantation. Transplantation 2007;83:706–711.
18 Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31.
19 Nankivell BJ, Chapmann BJ: Chronic allograft nephropathy: current concepts and future directions. Transplantation 2006;81: 643–654.
20 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.
21 Moe SM, Chen NX: Inflammation and vascular calcification (review). Blood Purif 2005;23:64–71.
22 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.
23 Dervisoglu E, Kir HM, Kalender B, Caglayan C, Eraldemir C: Serum fetuin-a concentrations are inversely related to cytokine concentrations in patients with chronic renal failure. Cytokine 2008;44:323–327.
24 Abedini S, Holme I, März W, Weihrauch G, Fellström B, Jardine A, Cole E, Maes B, Neumayer HH, Grønhagen-Riska C, Ambühl P, Holdaas H, ALERT study group: Inflammation in renal transplantation. Clin J Am Soc Nephrol 2009;4:1246–1254.
25 Goldfarb-Rumyantzev AS, Naiman N: Genetic predictors of acute renal transplant rejection. Nephrol Dial Transplant 2010;25: 1039–1047.
26 Ombrellino M, Wang H, Yang H, Zhang M, Vishnubhakat J, Frazier A, Scher LA, Friedman SG, Tracey KJ: Fetuin, a negative acute phase protein, attenuates TNF synthesis and the innate inflammatory response to carrageenan. Shock 2001;15:181–185.
27 Ciaccio M, Bivona G, Di Sciacca R, Iatrino R, Di Natale E, Li Vecchi M, Bellia C: Changes in serum fetuin-A and inflammatory markers levels in end-stage renal disease (ESRD): effect of a single session haemodialysis. Clin Chem Lab Med 2008;46:212–214.
28 Caglar K, Yilmaz MI, Saglam M, Cakir E, Acikel C, Eyileten T, Yenicesu M, Oguz Y, Vural A, Carrero JJ, Axelsson J, Lindholm B, Stenvinkel P: Short-term treatment with sevelamer increases serum fetuin-a concentration and improves endothelial dysfunction in chronic kidney disease stage 4 patients. Clin J Am Soc Nephrol 2008;3:61–68.