

Serum Fetuin-A in Chronic Kidney Disease: A Promising Biomarker to Predict Cardiovascular Risk

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Abstract

Introduction: Chronic kidney disease (CKD) is associated with adverse sequelae of cardiovascular disease, renal failure, and premature death. The key factors that could contribute to the development of cardiovascular disease in patients with CKD include inflammation and vascular calcification. Serum fetuin-A, a α_2 -glycoprotein is a systemically acting inhibitor of extraskelatal calcification and is down regulated following inflammation.

Purpose: To estimate serum fetuin-A levels in patients with CKD and to analyze its relationship with inflammatory biomarkers and calcium-phosphorus levels.

Materials and Methods: A total of 80 patients with CKD and 80 healthy, age and gender matched controls were enrolled in the study. Serum levels of fetuin-A, high-sensitivity C-reactive protein (hsCRP), calcium, phosphorus, albumin, lipid profile, glucose, urea, and creatinine were measured.

Results: A significant reduction of serum fetuin-A levels were observed in patients with CKD (mean = 0.4416 ± 0.17 g/L) when compared to controls (mean = 0.7527 ± 0.18 g/L; $P = 0.001$). Serum fetuin-A levels also showed a significant negative correlation with creatinine clearance, hsCRP and calcium-phosphorus product and a significant positive correlation with albumin levels ($P < 0.01$).

Conclusion: In CKD, progressive reduction of serum fetuin-A levels occur along with the gradual decline in renal function. The reduced production and increased consumption of serum fetuin-A in CKD could promote vascular calcification and contribute to the cardiovascular disease. Hence, in patients with CKD, measurement of serum fetuin-A could be a promising biomarker to prognosticate cardiovascular risk.

Key words: Chronic kidney disease, Fetuin-A, High-sensitivity C-reactive protein, Inflammation, Vascular calcification

INTRODUCTION

Chronic kidney disease (CKD) refers to an irreversible progressive deterioration in renal function.¹ It is a worldwide, chronic, noncommunicable disease epidemic with a prevalence of 0.79% in India.² CKD is frequently complicated by accelerated cardiovascular disease.

Over 80-90% of patients with CKD die primarily of cardiovascular disease before reaching the need for dialysis.³ This emphasizes the importance of early detection of cardiovascular disease in CKD.

Alteration of mineral metabolism occurs in CKD and promotes vascular calcification which poses an increased risk of cardiovascular and all-cause mortality in patients with CKD.⁴ CKD is also associated with chronic inflammation, which promotes endothelial dysfunction, vascular remodeling, and progression of atherosclerosis. Hence, an active interplay occurs between atherosclerosis, vascular calcification, and inflammation against a background of severe calcium-phosphorus disturbances in CKD, contributing to the development of cardiovascular disease.

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The serum protein fetuin was initially identified as the major globulin in calf and fetal serum by Pedersen in 1944. The human homolog was named fetuin-A/ α_2 -heremans-schmid glycoprotein, after the two codiscoverers, Heremans and Schmid. During fetal development, fetuin-A is expressed in most organs including liver, kidney, gastrointestinal tract, skin, and brain. In adults, it is produced primarily by the hepatic parenchymal cells.⁵ The human gene was mapped to the region 3q21-29 of chromosome 3.⁶ It is a 59 kDa glycoprotein belonging to the cystatin superfamily of cysteine protease inhibitors. It has a binding site for calcium-phosphate near the N-terminus.⁷ The serum fetuin-A concentration of adult humans ranges from 0.5 to 1 g/L.^{8,9}

Fetuin-A is an anti-inflammatory protein that can attenuate the inflammatory responses. However, the expression of fetuin-A is negatively regulated by several pro-inflammatory cytokines which produces downregulation of its synthesis during inflammation; hence fetuin-A is regarded as a “negative acute phase reactant.”¹⁰ Fetuin-A is also a systemic inhibitor of calcification and is present throughout the extracellular space. Approximately, 50% of calcification inhibitory capacity of the human plasma is contributed by fetuin-A. In the serum, fetuin-A stabilizes calcium and phosphate and prevents their precipitation by binding basic calcium phosphate (BCP).^{11,12} Surface binding of calcium is mediated by the negative charges on the extended β sheet of the D1 domain of fetuin-A resulting in high affinity binding despite its relatively low serum concentration. Fetuin-A thus acts as a systemic inhibitor of pathological mineralization which complement the local inhibitors such as matrix-Gla protein and pyrophosphate that act in a cell/tissue-restricted fashion.¹³

Measurement of serum fetuin-A levels could, therefore, have potential value to predict vascular calcification and hence the cardiovascular risk in CKD. Hence, in this study, the serum levels of fetuin-A were estimated in patients with CKD and its relationship between inflammation and abnormalities in calcium-phosphorus levels were analyzed.

MATERIALS AND METHODS

The study was conducted at a tertiary care hospital in South India after getting approval from the ethical committee. 80 patients (55 males and 25 females) were selected as cases from the outpatients and ward of the Department of Nephrology. 80 age and gender matched individuals from the general population without any history or clinical evidence of CKD were taken as the control group.

Inclusion Criteria

1. Patients with established diagnosis of CKD
2. Age more than 18 years.

Exclusion Criteria

Patients with acute or chronic inflammatory diseases, previous history of cerebrovascular diseases, acute kidney injury, nephrotic syndrome, malignancy, those who underwent renal transplant, and those on lipid lowering drugs, calcium/phosphate binders and on immunotherapy or immunosuppressive treatment were excluded from the study.

Informed consent was obtained from all subjects before the study. Blood samples were collected from them after an overnight fasting of 12 h. Under aseptic precautions, 5 ml of venous blood sample was collected and centrifuged. An aliquot of the serum (0.5 ml) was taken for the estimation of fetuin-A and stored at -20°C in the deep freezer. The remaining serum was used for the estimation of glucose, urea, creatinine, calcium, phosphorus, high-sensitivity C-reactive protein (hsCRP), albumin, total cholesterol (TC), triglycerides (TGLs), and high-density lipoprotein (HDL).

Serum fetuin-A was estimated by enzyme immunoassay using the kit obtained from R & D systems, USA. Serum hsCRP was estimated by turbidimetric immunoassay. Serum glucose was estimated by glucose-oxidase/peroxidase method, urea by urease method, creatinine by modified Jaffe's method, albumin by bromocresol green dye binding method, calcium by Arsenazo method, phosphorus by ultra-violet molybdate method, TC by cholesterol-oxidase - PAP method, TGLs by GPO - PAP method, and HDL-cholesterol by phosphotungstate/magnesium precipitation method in XL 300 auto analyzer. Low-density lipoprotein (LDL) was calculated using Friedwald's formula. Creatinine clearance (CrCl) was calculated using Cockcroft-Gault formula.

Statistical Analysis

Statistical analysis was done using SPSS software. The data were expressed in terms of mean and standard deviation. Student's *t*-test and Chi-square test were employed for the analysis of data. $P < 0.05$ was taken as the significant value. Correlation between the measured parameters was assessed using Pearson's correlation coefficient.

RESULTS

A total of 160 subjects were selected as the study group for this study. This included 80 cases with CKD and 80 healthy controls.

The mean values of serum fetuin-A and other estimated parameters of the study group are given in Table 1. Table 2 shows the gender matched comparison of serum fetuin-A levels in the study group which was statistically not significant. Table 3 shows the comparison of serum fetuin-A levels in various age groups in the study subjects. Serum fetuin-A levels were significantly lower in the cases than controls in all the included age groups. We further compared the parameters of CKD case group with CrCl values. Figures 1 and 2 show a gradual decline in Fetuin-A and CaxP levels, respectively, as the CrCl decreases. Figure 3 shows a gradual increase in hsCRP levels with the decrease in CrCl.

Table 4 shows the Pearson's coefficient of correlation between serum fetuin-A and the other studied biochemical parameters in the cases. There is a highly significant negative correlation of fetuin-A with hsCRP and CaxP ($P < 0.01$) and a highly significant positive correlation of fetuin-A with CrCl and albumin ($P < 0.01$) (Figures 4-7).

DISCUSSION

Cardiovascular disease is the most frequent cause of death among people with CKD. The overall mortality rate in CKD from cardiovascular disease has been found to be about 30 times greater than that of general population.¹⁴ The nontraditional risk factors of cardiovascular disease such as inflammation and vascular calcification accelerate the onset of cardiovascular complications in CKD.

Serum fetuin-A is regarded as a negative acute phase reactant which is down regulated following inflammation.

Table 1: Descriptive statistics of the study group

Parameters	Mean±SD	
	Controls (n=80)	Cases (n=80)
Age (years)	47.85±10.552	50.40±11.895
BMI (kg/m ²)	24.561±2.700	21.942±4.163
Fetuin-A (g/L)	0.752±0.176	0.4416±0.170
Glucose (mg/dl)	91.05±9.657	103.67±23.098
Urea (mg/dl)	22.92±3.244	99.95±27.731
Creatinine (mg/dl)	0.841±0.082	3.068±2.153
CrCl (ml/min)	96.476±8.409	32.994±21.241
hsCRP (mg/L)	0.568±0.232	4.618±3.037
Calcium (mg/dl)	9.905±0.497	9.542±0.675
Phosphorus (mg/dl)	3.410±0.367	4.539±1.105
CaxP (mg ² /dl ²)	33.711±3.285	42.844±8.718
Albumin (g/dl)	4.005±0.332	3.208±0.432
TC (mg/dl)	173.575±14.501	175.375±16.343
TGL (mg/dl)	133.96±16.363	182.50±26.576
HDL (mg/dl)	41.72±3.368	38.03±5.202
VLDL (mg/dl)	26.792±3.272	36.500±5.315
LDL (mg/dl)	105.057±14.74	101.065±18.089

BMI: Body mass index, CrCl: Creatinine clearance, hsCRP: High sensitive C-reactive protein, CaxP: Calcium-phosphorus product, TC: Total cholesterol, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein, LDL: Low-density lipoprotein, SD: Standard deviation

Further, fetuin-A has also been identified as a potent circulating inhibitor of systemic calcification by inhibition of calcium-phosphate precipitation. In this study, we estimated the levels of serum fetuin-A in patients with CKD and analyzed its relationship with inflammation and altered mineral metabolism.

Serum fetuin-A concentrations were found to be significantly decreased in patients with CKD (Mean = 0.4416 ± 0.17 g/L) when compared to the control group (mean = 0.7527 ± 0.18 g/L; $P = 0.001$). Further, fetuin-A levels were found to be progressively decreased from Stage 2 (CrCl = 60-90 ml/min) to Stage 5 (CrCl <15 ml/min) of CKD. This shows that reduction in serum fetuin-A levels develop relatively in the early stages of CKD. These findings conform to those of the study of Caglar *et al.*, which reported a decrease in serum fetuin-A levels in all stages of CKD, except Stage 1.¹⁵ Lower levels of serum fetuin-A were also reported in hemodialysis patients in the previous studies.^{16,17}

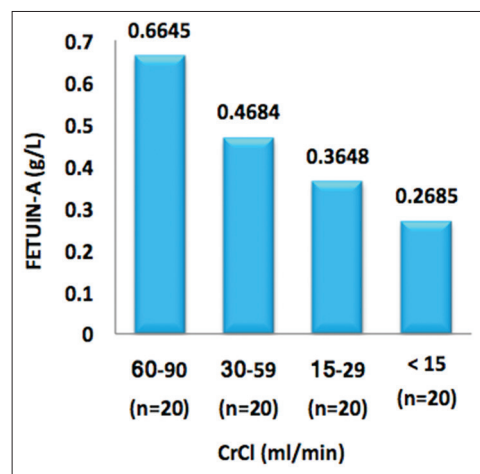


Figure 1: Comparison of serum fetuin-A levels in chronic kidney disease cases in relation to creatinine clearance

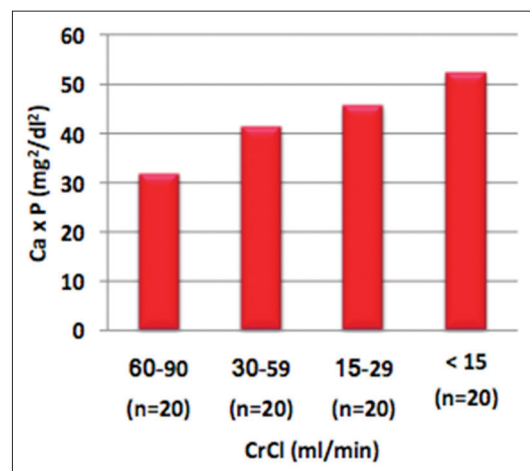


Figure 2: Comparison of serum CaxP levels in chronic kidney disease cases in relation to creatinine clearance

Table 2: Gender matched comparison of serum fetuin-A levels (g/L) in the study group

Control			Study		
Male n=55	Female n=25	P value	Male n=55	Female n=25	P value
0.7112±0.16	0.8441±0.19	0.886*	0.4293±0.16	0.4686±0.19	0.661*

*P>0.05 - Not significant

Table 3: Age matched analysis of serum fetuin-A levels in the study group

Age	Serum fetuin-A (g/L)			P value
	Groups	n	Mean±SD	
<30 years	Controls	3	0.7390±0.2211	P=0.007*
	Cases	3	0.6440±0.1187	
31-40 years	Controls	17	0.7532±0.1938	P=0.0001**
	Cases	17	0.4648±0.1518	
41-50 years	Controls	23	0.7932±0.1694	P=0.0001**
	Cases	23	0.4893±0.1871	
51-60 years	Controls	19	0.7598±0.1816	P=0.0001**
	Cases	19	0.3936±0.1187	
>60 years	Controls	18	0.6916±0.1618	P=0.0001**
	Cases	18	0.3667±0.1525	

*P<0.05 - Significant, **P<0.001 - Highly significant, SD: Standard deviation

Table 4: Pearson's correlation coefficient between fetuin-A and other biochemical parameters in cases

Parameters	Correlation value	P value
Urea	-0.691**	P<0.01*
Creatinine	-0.595**	P<0.01*
CrCl	0.855**	P<0.01*
hsCRP	-0.756**	P<0.01*
Calcium	0.464**	P<0.01*
Phosphorus	-0.819(**)	P<0.01*
CaxP	-0.818**	P<0.01*
Albumin	0.616**	P<0.01*
TC	-0.078	P>0.05**
TGL	-0.366**	P<0.01*
HDL	0.443**	P<0.01*
VLDL	-0.366**	P<0.01*
LDL	-0.086	P>0.05†

**Correlation is significant at P<0.01 level; *P<0.05 - Significant; †P>0.05 - Not significant

The mean level of serum fetuin-A in CKD cases in this study is 0.4416 ± 0.17 g/L. This finding is fairly concordant with that of Cottone *et al.*, where the mean fetuin-A concentration was 0.53 ± 0.17 g/L in patients with CKD.⁹ We also observed that serum fetuin-A levels were significantly lower in all age groups and in both genders when compared to controls, which indicates that age and gender does not have an impact on serum fetuin-A levels.

CKD is a state of chronic persistent low-grade inflammation in which there is a chronic systemic elevation of pro-inflammatory markers. The prototypic marker of inflammation in the clinical setting is hsCRP, a positive acute phase reactant and a higher level of this inflammatory biomarker is associated with cardiovascular

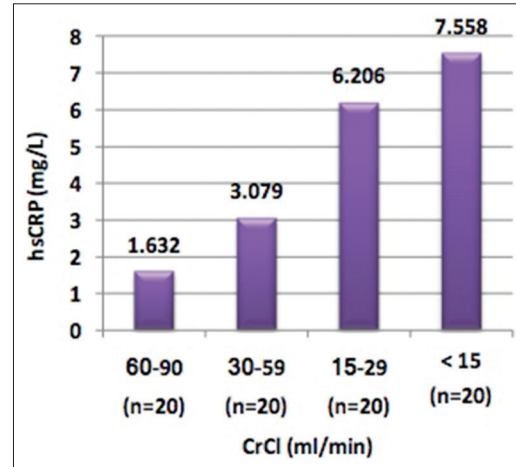


Figure 3: Comparison of serum high-sensitivity C-reactive protein levels in chronic kidney disease cases in relation to creatinine clearance

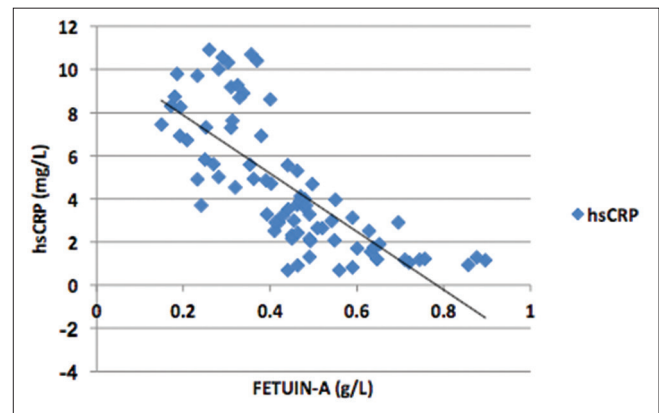


Figure 4: Scatter diagram of serum fetuin-A versus high-sensitivity C-reactive protein in chronic kidney disease cases

mortality in patients with renal insufficiency.^{18,19} In this study, we observed significantly higher levels of hsCRP in CKD cases when compared to controls (mean level: Cases - 4.618 ± 3.03 mg/L; controls - 0.567 ± 0.23 mg/L; $P = 0.001$). As the renal function declined, we observed a progressive increase in the hsCRP levels. Further, a strong inverse correlation was found between fetuin-A and hsCRP levels ($r = -0.756$; $P < 0.01$) which shows that fetuin-A is a negative acute phase reactant.

Serum albumin is regarded as one of the negative acute phase reactant and a low serum albumin level in CKD is a well-established predictor of mortality.²⁰ In this study,

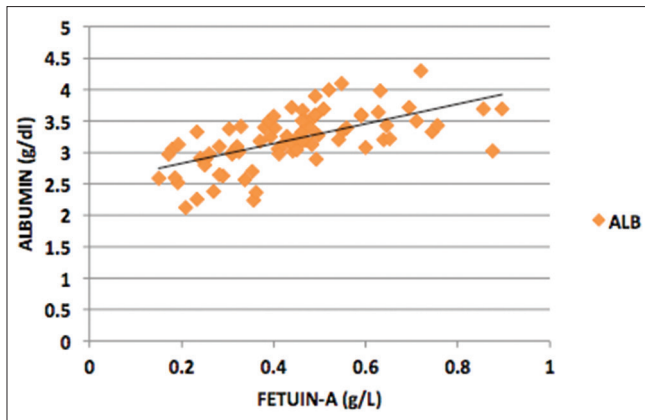


Figure 5: Scatter diagram of serum fetuin-A versus albumin in chronic kidney disease cases

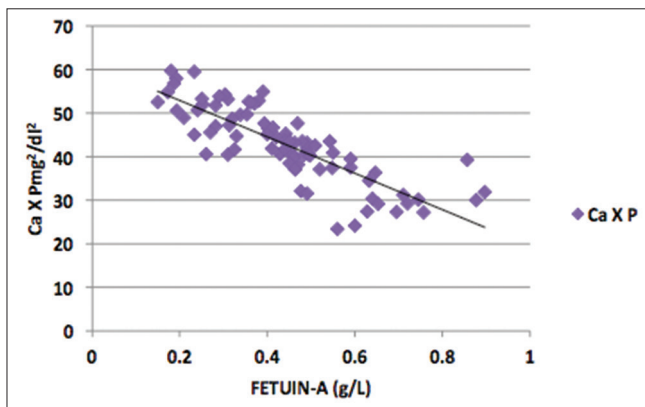


Figure 6: Scatter diagram of serum fetuin-A versus CaxP in chronic kidney disease cases

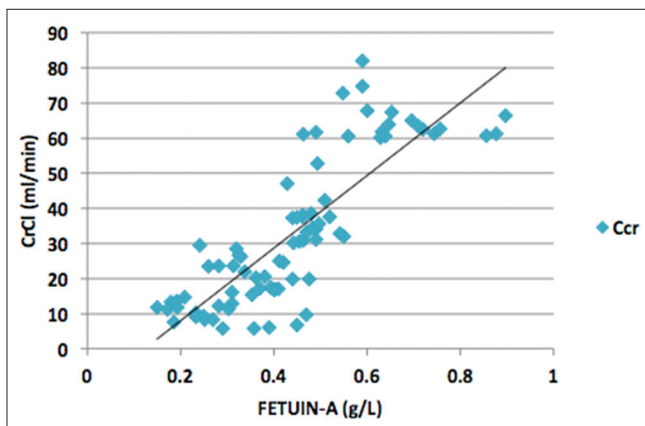


Figure 7: Scatter diagram of serum fetuin-A versus creatinine clearance in chronic kidney disease cases

serum albumin was found to be significantly reduced in CKD cases ($P = 0.001$). We also observed a progressive decrease in the serum albumin levels with declining renal function. The results also revealed a strong positive correlation of serum fetuin-A with albumin levels ($r = 0.616$; $P < 0.01$). These results are in accordance with the previous studies^{21,22} and suggest a global proatherogenic

inflammatory activation beginning from the early stages of CKD leading onto the downregulation of serum fetuin-A.

Our results also showed a highly significant increase of calcium-phosphorus product (CaxP) in CKD cases ($P = 0.001$) and a progressive increase in CaxP as the renal function declined. We also found a strong significant inverse correlation of serum fetuin-A with CaxP ($r = -0.818$; $P < 0.01$). Similar findings were observed in the previous studies.^{23,24} The mechanism accountable for this observation could be that serum fetuin-A dynamically binds to the BCP in the serum. During this process it forms transiently soluble, colloidal complexes called calciprotein particles, which are 30–150 nm in diameter. Fetuin-A coating of BCP nuclei will delay the growth of insoluble crystals and also favors mobilization and removal of the previously formed insoluble calcium salts by phagocytosis.²⁵ Fetuin-A thus acts as a “buffer” of BCP to prevent extraskeletal calcification. In CKD, increased serum levels of calcium and phosphorus devour the circulating fetuin-A and deplete its levels.

Dyslipidemia, an atherosclerotic risk factor, contributes to the initiation and progression of CKD partly by stimulating and amplifying the effect of inflammatory mechanisms.²⁶ In this study, we observed a significantly higher serum TGL and VLDL levels in cases than controls ($P = 0.001$). Serum TC and LDL were found to be within the normal reference range in our study group. We also observed a significant negative correlation of serum fetuin-A with TGL and VLDL ($r = -0.366$; $P < 0.01$) and a positive correlation with HDL ($r = 0.443$; $P < 0.01$). These findings are in accordance with the study of Zeidan *et al.*, who in addition observed elevated levels of TC and LDL.²⁷ This discordance could be explained by the fact that with concurrent inflammation and malnutrition in CKD, TC, and LDL levels might decrease.

Previous studies have demonstrated that reduced serum fetuin-A levels could be considered as a predictor of both cardiovascular and noncardiovascular mortality.^{28,29} Hermans *et al.* found that an increment of 0.1 g/L concentration of serum fetuin-A resulted in a 13% reduction in the all-cause mortality.¹⁰ Caglar *et al.* demonstrated that short-term treatment with sevelamer, a noncalcium-based phosphate binder in patients with CKD, increased serum fetuin-A concentration which in turn improved the endothelial dysfunction in these patients.³⁰

The observations from this study imply that the available circulating fetuin-A is depleted in dealing with the elevated CaxP commonly found in CKD. Further, in the chronic

inflammatory state of CKD, the synthesis of fetuin-A is down regulated.

CONCLUSION

This study shows that fetuin-A is a promising biomarker to predict cardiovascular risk in patients with CKD. Since the levels of fetuin-A begin to decline from the early stages of CKD, its estimation may facilitate early prediction of vascular calcification. However, currently, no authorized strategies are on hand to increase the serum levels of fetuin-A in CKD. Early and prompt intervention of the factors causing reduced production (inflammation) and increased consumption (elevated CaxP) of fetuin-A may increase the serum fetuin-A levels and decelerate the course of cardiovascular disease in CKD.

Our study had few potential limitations such as small sample size and lack of application of imaging techniques to evaluate the extent of vascular calcification in CKD. The association between fetuin-A levels and vascular calcification, therefore, could not be precisely investigated.

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