J Renal Inj Prev. 2022; 11(1): e06.

http://journalrip.com doi: 10.34172/jrip.2022.06

Journal of Renal Injury Prevention

Serum fetuin-A levels and its relationship with biochemical parameters in hemodialysis patients

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ARTICLE INFO

Article Type:
Original

Article History:
Received: 7 February 2021
Accepted: 14 April 2021
ePublished: 18 May 2021

Keywords:
Hemodialysis
Fetuin A
Chronic kidney disease
End-stage renal disease

ABSTRACT

Introduction: Cardiovascular events are the most important complications of end-stage renal disease (ESRD). The role of fetuin-A and vascular calcification inhibitors in cardiovascular complications, dysregulated biochemical markers, and mortality is uncertain in patients under hemodialysis.

Objectives: The aim of this study was to investigate the relationship of fetuin-A with cardiovascular complications and biochemical markers in hemodialysis patients.

Patients and Methods: In this cross-sectional study, 65 patients undergoing hemodialysis were enrolled. Blood samples were taken at pre-dialysis to determine serum fetuin-A, calcium, phosphorus, intact parathyroid hormone (iPTH), C-reactive protein (CRP), albumin, triglyceride, total cholesterol, as well as blood hemoglobin, and hematocrit. The data was analyzed considering the statistical significance level of 0.05.

Results: Out of 65 patients, seven patients died during the study, and 58 patients were finally evaluated. Mean (±SD) serum fetuin-A level was 1268.71 ± 1229.4 µg/mL. There was no significant difference in the mean fetuin-A level between genders ($P=0.904$). There were no significant correlations between the serum level of fetuin-A and age, duration of dialysis, heart diseases, serum levels of calcium, phosphorus, PTH, albumin, CRP, cholesterol and finally blood hemoglobin. However, significant relationships were found between fetuin-A level and serum triglyceride (TG) level ($P=0.019$) and body mass index (BMI) ($P=0.024$).

Conclusion: Fetuin-A level was significantly associated with serum TG level and BMI. Regarding the links of obesity and hypertriglyceridemia with cardiovascular diseases (CVDs), controlling serum TG level and body weight can reduce the risk of vascular atherosclerosis in patients undergoing dialysis.

Original

Implication for health policy/practice/research/medical education:
End-stage renal disease (ESRD) is often associated with several complications. An important matter in these patients is early diagnosis of complications and prevention of their progression. Given the possible relationship between fetuin-A in hemodialysis patients with inhibitors of vascular calcification, atherosclerosis and biochemical markers and the pathogenesis factors involved in atherosclerosis, by confirming the relationship between biochemical markers and fetuin-A and the effect on vascular calcification it may be possible to reduce complications in hemodialysis patients.

Please cite this paper as: Abbasi Jamaati B, Ghorbani R, Zahmatkesh M, Tamadon MR. Serum fetuin-A levels and its relationship with biochemical parameters in hemodialysis patients. J Renal Inj Prev. 2022; 11(1): e06. doi: 10.34172/jrip.2022.06.

Introduction

End-stage renal disease (ESRD) is the final stage of kidney failure presenting with uremic syndrome as accumulation and precipitation of uremic toxicants and hemostatic disorder as severe dysregulation of water and electrolytes (1). Dialysis and kidney transplantation are major and important treatments for patients with ESRD.

Hemodialysis is a procedure encompassing a wide range of renal therapies (2). Dialysis is associated with systemic and local complications including oral lesions and altered content and flow rate of the saliva (3,4). On the other hand, salivary functions such as lytic and buffering properties are important to maintain tooth integrity, oral antimicrobial activity, and taste. Alternations in saliva content can further lead to abnormal food digestion (4).

Patients with ESRD are at risk of cardiovascular diseases

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(CVDs) and complications (5,6). Mortality rates are higher among dialysis patients than that of the general population, and CVDs constitute the most common causes of mortality in patients undergoing dialysis (7). Vascular calcification is an important pathologic process predisposing ESRD patients to atherosclerosis and CVDs (6,7).

Recently, the beneficial role of vascular calcification inhibitors has been reported in patients undergoing hemodialysis (6). Prolonged dialysis, advanced age, as well as elevated PTH, C-reactive protein (CRP), dyslipidemia, hyperhomocysteinemia and hypoalbuminemia have been among risk factors of vascular calcification. Other contributors to vascular calcification in patients with ESRD include hyperphosphatemia, hypercalcemia, as well as elevated serum calcium phosphate (8). The roles of tumor necrosis factor-α, transforming growth factor 23, osteocalcin, osteonectin, core-binding factor-α1, alkaline phosphatase, and bone morphogenetic protein 24, a bone metabolic cytokine, have been suggested in the formation of vascular lesions in studies on smooth muscle and endothelial cells (9-12). Recent findings also indicate that inflammation contributes to the calcification process (13). Inflammation is a multifactorial pathogenic process in ESRD (13). CRP is an inflammatory marker that independent of other mediators is increased in acute inflammation and CVD (14,15). Other studies have also shown that calcification is associated with malnutrition, inflammation, atherosclerosis, as well as increased serum fibrinogen, hypoalbuminemia, and elevated CRP level (16-18).

Fetuin-A, also known as α2-Hermans-Schmid glycoprotein, is a blood circulating protein produced by the liver. During fetal life, the level of this protein is higher than that of albumin. Fetuin-A is a calcium-bonded glycoprotein inhibiting vascular calcification. Other inhibitors of calcification include matrix Gla protein, osteoprotegerin, and osteopontin. (19-21). The prognostic role of fetuin-A has been indicated in dialysis patients.

Large vascular lesions predispose to small-peripheral arterial disease and may subsequently lead to sudden death in ESRD patients undergoing dialysis. Therefore, early diagnosis of atherosclerosis and vascular diseases is essential in these patients. Currently, pulse rate measurement, cardio-ankle vascular index, ankle-brachial index, toe-brachial index, and aortic calcification measurement deliver rapid and simple methods for diagnosis of vascular calcification (22,23). Patients with ESRD undergoing hemodialysis variably show vascular calcification as some patients represent with severe disease while others with similar uremia intensity may present no evidence of this pathological condition (24).

A possible role has been suggested for vascular calcification inhibitors including fetuin-A in managing atherosclerosis and its risk factors. In this regard, fetuin-A may be a potential factor to predict vascular calcification and subsequently prevent hemodialysis complications in ESRD patients. Patients with ESRD undergoing dialysis are susceptible to cardiovascular complications, which are the most important causes of death in this condition. Accordingly, fetuin-A may help to identify patients at risk of cardiovascular events and reduce the morbidity and mortality rates.

Objectives

We aimed to investigate the relationship of fetuin-A with biochemical markers, as well as cardiovascular complications in ESRD patients undergoing dialysis.

Patients and Methods

Study design

In this cross-sectional study, 65 patients referred to the dialysis clinic of the Kosar hospital of Semnan were included. During follow up, seven patients died and therefore the data of 58 patients were finally analyzed.

A checklist was used to record patients' height, weight, blood pressure, and biochemical parameters. Blood samples were taken at pre-dialysis phase to determine serum levels of fetuin-A, calcium, phosphorus, intact parathormone (iPTH), CRP, albumin, triglyceride, total cholesterol, as well as blood hemoglobin, and hematocrit.

Data analysis

Data were analyzed by SPSS 23 software. Pearson and Spearman's correlation coefficients, Shapiro-Wilk test, and student *t* test were used to analyze the data. The statistical significance level was considered as $P<0.05$.

Results

In this study, 65 patients undergoing hemodialysis were studied. In the course of the study, seven patients died, and the data of 58 remaining patients were finally analyzed. Table 1 shows the comparison of mean fetuin-A levels based on demographic data and levels of blood biochemical indicators.

Males constituted 39 (60%) patients. Mean (±SD) serum fetuin-A level was 1268.71 ± 1229.4 μg/mL. There was no significant difference comparing serum fetuin-A between men and women ($P=0.904$). The patients' mean and median ages were 63.4 ± 6 and 66 years old respectively (the range of 27 to 88 years). There was no significant correlation between age and fetuin-A level (r = -0.21, $P=0.113$).

The mean patients' body mass index (BMI) was 24.8 ± 4.7 kg/m^2. Overall, 34.5% and 10.3% of the patients were overweight and obese respectively. There was a positive and significant correlation between fetuin-A level and BMI (r = 0.297, $P=0.024$).

The mean and median values of dialysis duration were 4.52 ± 3.51 and 3 years respectively (the range of 1 to

Table 1. Comparison of mean fetuin-A levels based on demographic and blood biochemical indicators

Parameters		No (%)	Fetuin-A				Correlation coefficient	*P* value
			Mean	SD	Median	Interquartile range		
Gender	Male	26 (40)	1110.9	971.3	809.0	569	--	0.904
	Female	39 (60)	1347.8	1375.8	675.0	675		
Age	< 60	20(34.4)	1601.8	1472.8	739.5	2433	-0.210	0.113
	60-69	17 (29.3)	1129.2	1181.8	829	530		
	>70	21 (36.2)	1064.3	979.2	610	520		
BMI	<25	32 (55.2)	1102.2	1075.2	663.5	574	0.297	0.024
	25-29.9	20 (34.5)	1142.7	1110.4	762.0	561		
	>30	6 (10.0)	2577.0	1756.4	2841.5	3363		
Dialysis duration (y)	<5	36 (62.1)	1192.0	1282.8	636.5	660	0.124	0.353
	5-9	13 (22.4)	1135.4	995.5	829	476		
	>10	9 (15.5)	1768.1	1322.2	1105	2337		
Calcium	<8.5	17 (26.2)	1254.2	1209.8	751	313	0.059	0.842
	8.5-10.2	48 (73.8)	1252.6	1246.0	675	727		
Phosphorus	2.5-4.5	18 (27.7)	1298.9	1319.0	729	627	-0.004	0.974
	>4.5	47 (72.3)	1235.5	1204.6	675	566		
PTH	≤ 65	11 (16.9)	1641.2	1582.0	811	3428	0.096	0.446
	>65	54 (83.1)	1174.0	1144.0	675	691		
Hemoglobin	Normal	50 (76.9)	1293.6	1232.2	734.5	739	-0.095	0.454
	Abnormal	15 (23.1)	1117.9	1243.1	663	312		
Albumin	> 3.5	14 (24.1)	1701.2	1653.9	703.5	3549	-0.227	0.086
	3.5-5.5	44 (75.9)	1131.1	1104.7	729	648		
TG	< 200	53 (81.5)	1142.2	1103.8	675	550	0.307	0.019
	≥ 200	12 (18.5)	1742.8	1637.5	806	3276		
Cholesterol	< 200	62 (95.4)	1223.4	1230.1	675	569	0.131	0.299
	≥ 200	3 (4.6)	1867.3	1203.2	1541	--		
CRP	Negative	39 (60)	1261.5	1239.4	675	482	0.035	0.783
	+1	5 (7.7)	1080.6	721.1	845	1200		
	+2	7 (10.8)	1652.4	1413.4	1105	2472		
	+3	14 (21.5)	1216.9	1320.2	665.5	638		

PTH, parathyroid hormone; TG, triglyceride; BMI, body mass index; CRP, C-reactive protein.

16 years). No significant correlation was found between the duration of dialysis and fetuin-A level (r = 0.124, $P = 0.353$).

Mean and median values of serum calcium level were 8.7 ± 0.8 and 8.8 mg/dL respectively (the range of 8.5-10.2 mg/dL). Hypocalcemia (i.e. serum calcium <8.5) was observed in 26.2% of the patients while 73.8% had normal calcium level (8.5-10.2 mg/dL). No patient showed serum calcium level higher than normal. There was no significant correlation between serum calcium level and Fetuin-A level (r = 0.059, $P = 0.642$). However, there was a significant correlation between serum calcium level and heart diseases ($P = 0.049$).

The mean and median serum phosphorus level in the patients were 5 ± 0.8 and 5 mg/dL respectively (the range of 3.4-7.5). The serum phosphorus level varied from 2.5 to 4.5 mg/dL in 27.7% of the patients while the rest of them had levels >4.5 mg/dL. There was no significant correlation between serum phosphorus and fetuin-A level (r = -0. 004, $P = 0.974$).

The mean and median values of serum intact PTH were 236.2 ± 194.7 and 148 pg/mL respectively (range; 0.1-571 pg/mL). While 83.1% of the patients had iPTH level less than 65 pg/mL, 15.4% had normal serum PTH (65-100 pg/mL), and only one patient revealed iPTH level below 10 pg/mL. There was no significant correlation between serum PTH level and fetuin-A (r = 0.096, $P = 0.446$).

The mean hemoglobin 10.9 ± 1.4 g/dL (range; 7.1-13.9 g/dL) with a median value of 10.9 g/dL. Normal range hemoglobin (11-12) was observed in 23.1% while 52.3% and 24.6% of the patients had hemoglobin values of <11 and >12 g/dL respectively. There was no significant correlation between hemoglobin and fetuin-A (r = -0.095, $P = 0.454$).

The mean serum albumin level was 3.78 ± 0.43 g/dL (the range of 3-5 g/dL). The median value of albumin was also 3.75 with 75.9% of the patients had normal albumin (3.5-5.5 g/dL), and the rest showed values of <3.5. There

was no significant correlation between serum albumin and fetuin-A (r = -0 .227, $P=0.086$).

The mean serum TG level was 127.6 ± 82.9 mg/dL (30-510) with the median value of 101. Overall, 81.5% of the patients had normal (i.e. <200) and the rest had TG level >200. There was a significant correlation between serum TG and fetuin-A (r = 281, $P=0.023$).

The mean and median values of serum cholesterol were 136.7 ± 38.7 mg/dL (the range of 74-272 mg/dL) and 133 respectively. Most of the patients (95.4%) had normal cholesterol (<200), and the rest had levels greater than 200 mg/dL. No significant correlation was found between serum cholesterol level and fetuin-A (r = 0.131, $P=0.299$).

Serum CRP was negative in 60% of the patients. No significant correlation was detected between fetuin-A and serum CRP (r = 0.035, $P=0.783$).

The mean value of serum albumin was 3.78 ± 0.43 g/dL (the range of 3-5 g/dL). The median serum albumin was also 3.75 g/dL. Most of the patients (75.9%) represented normal serum albumin (3.5-5.5 g/dL) and the rest showed hypoalbuminemia. A significant inverse correlation was found between serum albumin level and the risk of heart diseases ($P=0.012$).

The mean and median values of fetuin-A were calculated as 1421.60 ± 1438.66 µg/mL and 663.50 µg/mL in patients with heart diseases and 1188.24 ± 1116.48 µg/mL in those with no heart diseases ($P=0.532$).

Discussion

In this study, from 65 patients undergoing hemodialysis, seven patients died during the study, and therefore the data of 58 patients were analyzed. The mean level of fetuin-A was not significantly different between males and females ($P=0.904$). In addition, there were no significant correlations between fetuin-A level and age, duration of dialysis, heart diseases, serum levels of calcium, phosphorus, PTH, albumin, CRP and cholesterol, or blood hemoglobin. On the other hand, significant relationships were found between fetuin-A level and serum TG ($P=0.019$) and BMI ($P=0.024$). In subgroup analyses based on gender, age, duration of dialysis, number of dialysis sessions and BMI, no significant relationships were detected between fetuin-A and other biochemical markers ($P<0.05$).

In our study, there was no significant difference in the level of fetuin-A between males and females which was contradictory to the result of Xu et al in 2011. This may be because Xu et al measured the level of fetuin-A in patients with metabolic syndrome which differed from the population evaluated in the present study (25).

We also found no significant relationship between age and fetuin-A ($P=0.113$, r = -0.210) which was in line with the study of Stenvinkel et al on 258 dialysis patients in Sweden in 2005 (26). However, this finding again opposed the findings of Xu et al who reported a significant relationship between age and fetuin-A level in patients with metabolic syndrome (25). This discrepancy can also be explained by different populations studied in these reports.

There was a significant positive correlation between BMI and fetuin-A level among dialysis patients in the current study (r = 0.297, $P=0.024$). This observation was supported by the report of Xu et al (25). In another study by Brix et al on 65 obese (BMI = 45) and 21 over-weight (BMI = 26) women undergoing gastric bypass surgery, the level of fetuin-A was significantly higher in the case than the control group at 16 months post-surgery (27).

In our study, no statistically significant associations were detected between fetuin-A level and neither serum iPTH (r = 0.096, $P=0.446$) nor blood hemoglobin (r = -0.095, $P=0.454$) which correlated with the report of Oikawa et al on 40 hemodialysis patients (28).

In this study, no significant association was observed between fetuin-A level and serum albumin (r = -0.227, $P=0.086$) which was consistent with the report of Stenvinkel et al in 2005 (26). Furthermore, we found a significant inverse correlation between serum albumin level and the risk of heart diseases ($P=0.012$), and this association was exaggerated in albumin level <3.5 g/dL. Accordingly, it seems that hypoalbuminemia augments cholesterol precipitation and vascular calcification independent of serum cholesterol level.

There was no significant relationship between fetuin-A and serum CRP level (r = 0.035, $P=0.783$). This finding contradicted the reports of Oikawa et al (28). The reason for this discrepancy may be related to the methods of CRP measurement (i.e. qualitative in the recent reports and qualitative in our study). Nevertheless, our result was consistent with the study of Stenvinkel et al who described no significant association between serum CRP and fetuin-A (26).

We showed a significant positive correlation between serum TG and fetuin-A levels (r = 0.281, $P<0.023$). This finding was in line with the study of Oikawa et al (28), but it is contradicted with the report of Xu et al on patients with metabolic syndrome (25). Furthermore, we found no association between the levels of fetuin-A and cholesterol.

Moreover, no significant relationship between fetuin-A and serum calcium level was detected (r = 0.059, $P=0.842$). However, Pertosa et al noted a significant and inverse correlation between serum calcium and fetuin-A levels (36). This contradiction may be explained by the relatively low power of our study. Nevertheless, we identify a significant relationship between serum calcium level and the risk of CVDs which was consistent with the study of Pertosa et al (29).

We here investigated the association of fetuin-A with serum phosphorus (r = -0.004, $P=0.0974$) and dialysis duration (r = 0.124, $P=0.353$,). Nevertheless, neither of these indicators significantly correlated with fetuin-A level.

Conclusion

Our results showed that fetuin-A level significantly correlated with BMI and serum TG level. Although there was no significant difference in the level of fetuin-A between dialysis patients with or without CVDs, subgroup analysis revealed a significant inverse correlation between BMI and fetuin-A indicating a potential protective effect for fetuin-A against CVDs independent of obesity. The statistical power of our study was relatively low because of small sample size partly due to the death of seven patients during data collection. Studies with larger sample sizes can provide more precise and valid information.

Recommendations

It is suggested to evaluate more biochemical parameters in a comprehensive study with larger sample size to obtain more valid conclusions on the importance of fetuin-A in dialysis patients.

Limitations of the study

The main limitation of this study was the lack of a control group. The presence of the control group leads to better conclusions and comparison of the relationship between fetuin-A and other biochemical parameters in patients and healthy individuals.

Authors' contribution

MRT, BAJ and MZ were the principal investigators of the study. MRT and RG were included in preparing the concept and design. MRT and MZ revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Semnan University of Medical Sciences approved this study (IR.SEMUMS.REC.1396.127). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from M.D thesis Behzad Abbasi Jamaati at this university (Thesis #1294). Moreover, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

This study was supported by research deputy of Semnan University of Medical Sciences (Grant# 1294).

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