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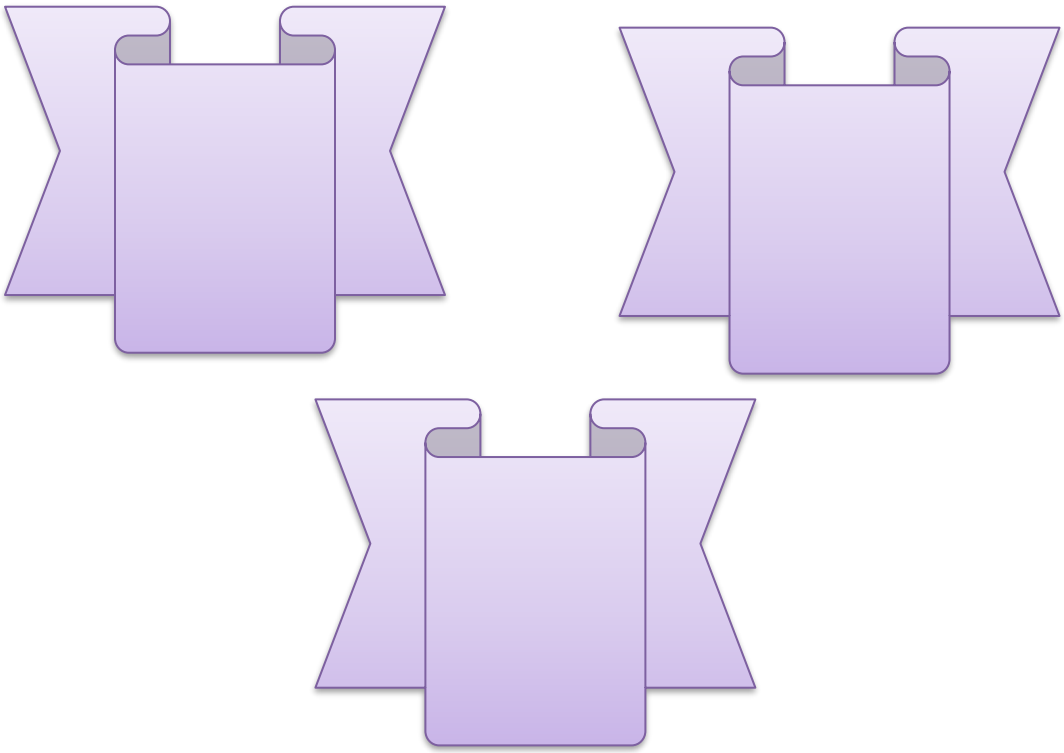

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Original Article

Study of The Relation between Fetuin-A and Abdominal Aorta Calcification in Chronic Hemodialysis Patients

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ABSTRACT

Background: Patients with chronic renal disease, particularly those on frequent hemodialysis, exhibit distinct mineral and endocrine changes. Extra-osseous bone formation promoters and inhibitors are out of balance, which results in vascular calcification, a dynamic process controlled by bone kidney disease.

Aim of the work: To determine if hemodialysis patients' fetuin-A levels correlate with their risk of abdominal aortic calcification.

Patients and Methods: Sixty Hemodialysis patients [30 cases and 30 controls] from Ain shams University Hospitals were enrolled in this comparative cross-sectional study. All the patients have signed an informed consent and underwent laboratory and radiological investigations, including a pelviabdominal x-ray examination. Multislice CT abdomen was done for the cases only.

Results: In the group with aortic calcification, the mean serum fetuin-A concentration was 302.51±68.46 ng/ml [range: 201.3 – 414.6 ng/ml], while in the group without aortic calcification, it was 564.53±135.55 ng/ml [range: 284.3 – 793.2 ng/ml]. Regarding the relation between fetuin-A and aortic calcium score, there was a non-significant negative correlation [p-value = 0.376] [r = - 0.168] in the studied population.

Conclusion: We found a statistically significant difference between the two groups in terms of serum fetuin-A levels. However, there was no significant association between fetuin-A and aortic calcium score. The duration of dialysis and Ca x P Product were the most critical two parameters affecting the fetuin-A level.

Keywords: Dialysis; Fetuin-A; Abdominal aortic calcification.

INTRODUCTION

Dialysis patients with chronic kidney disease [CKD] require frequent hemodialysis and are affected by particular mineral and endocrine imbalances [1]. Numerous factors, including renal bone disease and an imbalance between bone-forming promoters and bone-blocking inhibitors, contribute to arterial calcification. The accumulation of calcium salts in tissues is known as calcification. In contrast to calcification, mineralization is characterized by the deposition of any mineral [2].

Major arteries, such as the aorta, particularly the aortic arch, are more likely to calcify than smaller vessels, and the increased stiffness of large vessels does not appear to contribute to hypertension. Instead, smaller diameter arterioles play crucial roles in the development of hypertension due to increased smooth muscle tone and endothelial and possibly fibroblast dysfunction play essential roles in the development of hypertension [3].

As a liver-derived plasma glycoprotein that generates calcium and phosphate soluble complexes, Fetuin-A has been demonstrated to be an effective inhibitor of vascular calcification, which explains why low levels of fetuin in the serum have been associated with elevated vascular calcification levels [4].

Multi-slice computed tomography [CT], lateral abdominal radiography [KDIGO 2009 guidelines], or mammography, a sensitive method for determining micro-calcification, are used to diagnose vascular calcification [5].

Fetuin-A may be a vital marker for metabolic syndrome, in which case this will lead to deep insight in early diagnosis, identification of new biomarkers, and acquiring unique landscape for pharmacological interventions [6].

Fetuin-A is a multidimensional plasma glycoprotein with a molecular weight of approximately 60 kDa and half-life of seven days. During fetal development, multiple tissues are responsible for its production, however later in life, the liver is the organ that mainly responsible for that. Fetuin-A is a natural blocker of insulin receptor tyrosine kinase, and insulin resistance and frank diabetes mellitus are commonly long-term sequel of its increase [7].

Higher levels of fetuin-A and fetuin-B are commonly observed in non-alcoholic fatty liver disease NAFLD. Thus, fetuin-A and fetuin-B might be involved in the pathogenesis of the occurrence of NAFLD. Furthermore, fetuin-A may play a vital mission in the pathophysiological transformation of NAFL to non-alcoholic steatohepatitis NASH [8].

Epicardial adipose tissue [EAT] volume and annexin-A2/fetuin-A signalling are independent risk factors that had direct impact on coronary calcium score [CCS], suggesting that EAT might control pro-calcifying status in the later stages of ischemic heart disease [9].

Fetuin-A/adiponectin ratio [F/A ratio] is a more reliable biomarker for evaluating metabolic syndrome than either fetuin-A or adiponectin alone. Further well-structured clinical studies with larger number of cases are needed to confirm recent medical data [10].

PATIENTS AND METHODS

It was a comparative cross-sectional study conducted at the hemodialysis unit of Ain Shams University involving 60 prevalent hemodialysis patients who received thrice-weekly, four-hour hemodialysis sessions with bicarbonate-containing dialysate and heparin-based anticoagulation. Prior to the study, all patients provided their informed consent.

Exclusion criteria: Patients with an active infection, malignancy, and chronic inflammatory disease chronic liver and pulmonary diseases.

Each patient was subjected full history [age, sex, particular habits such as smoking, duration of dialysis, history of previous fractures, etiology of CKD and drug history], thorough clinical examination [anthropometric measures including body weight [in kg] and patient height [in square meter] and assessment of body mass index].

Fetuin-A plasma level was measured using the following technique: Microplate wells were pre-coated with polyclonal anti-human fetuin-A antibodies for the Human Fetuin A ELISA. After an incubation and washing period of 60 minutes, a polyclonal anti-human fetuin antibody was detected. Antibody conjugated with horseradish peroxidase [HRP] was added to the wells and treated for 60 minutes with the

collected fetuin-A. Following the second washing step, the substrate solution [TMB] was reacted with the residual HRP conjugate. The reaction was stopped with an acidic solution yielding a yellow product for analysis. Fetuin-A concentration was proportional to absorbance, whereas the known sample concentrations were determined by graphing absorbance values against standard concentrations to create a standard curve.

The sample was collected at 1:00 p.m. and sequestered at 80 °C for further analysis. Fetuin-A was tested in two separate tests. Fetuin-A ELISA kit, is appropriately diluted. The recombinant fetuin-A spike recovery in a sample buffer was 97-107 percent. Two goat anti-human fetuin-A polyclonal antibodies were used to bind to separate epitopes of human fetuin-A using the sandwich technique. At 5 ng/mL, the upper limit of detection is [concentration directly measurable]. The coefficients of variation for both intra- and inter-assays are less than 10 %.

Radiological investigation

Pelvi-abdominal x-ray survey was performed to reach the target cases with abdominal aortic calcification [30 cases]. Target cases are those with any degree of calcification [calcific deposits] on lateral pelviabdominal x ray according to **Honkanen *et al.*** [11].

A multi-slice CT abdomen for those with any degree of calcification on X ray. The abdominal aorta calcification score was calculated using a Toshiba Medical Systems Corp. The scanner included a built-in ECG monitor and the necessary software to test and evaluate the Agatston score. Three-millimeter-thick scanning layers were used for the scans [for the aorta starting scanning 3 cm proximal to the bifurcation of the aorta]. Images were then transferred to a VITREA 2 [Vital Images, Inc.] workstation with an Agatston score calculator. After the radiologist determined that the artery wall was calcified in the images, the calculations were performed automatically. The outcomes were shown on a computer monitor. Quantification of calcification is performed on stand-alone workstations after image acquisition implementing one of three scores: the Agatston score, the volume score, or the mass score [12].

The plaque's peak density [also known as attenuation] and area [total surface of calcification] were used to determine the Agatston score. Consequently, it included information regarding the plaque's size and calcium concentration. For a volume score, at least 130 Hounsfield units per square inch are required [a CT measure of density]. According to the authors' classification, AAC severity was categorized as mild [1-100], moderate [101-1000], and severe [>1000].

Statistical analysis: Data were collected, revised, coded, and entered into the Statistical Package for Social Science [IBM SPSS] version 23. The quantitative data were presented as mean, standard deviations, and ranges. In addition, qualitative variables were presented as numbers and percentages. The comparison between groups with qualitative data was made using the Chi-square test and Fisher exact test instead of the Chi-square only when the expected count in any cell was less than 5.The comparison between two groups with quantitative data and parametric distribution was made by using the independent t-test. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. The confidence interval was set to 95%, and the accepted error margin was set to 5%. Therefore, $P < 0.05$ is considered significant. Receiver operating characteristic curve [ROC] was used to assess the best cut off point with its sensitivity, specificity, positive predictive value, negative predictive value and area under curve [AUC] of the studied marker [fetuin A]. Uni-variate and Multi-variate logistic regression analysis was used to assess predictors of aortic calcification.

RESULTS

Our study revealed that 52.6% of our HD patients had abdominal aorta calcification. Fetuin A was much lower significantly in the aortic calcification group. Age, BMI, dialysis duration, PTH, and Ca x P product, all had negative correlation with fetuin A. Multivariate linear regression analysis of the correlated parameters revealed that the duration of dialysis and Ca x P Product were the two most influential parameters affecting the fetuin-A level. The cutoff value of serum fetuin-A to differentiate between the two groups was [≤414.6 ng/ml].

Table [1]: Demographic data of the studied groups

History		With aortic calcification [n=30]	Without aortic calcification [n=30]	Test value	P-value
Sex	Female Male	18 [60.0%] 12 [40.0%]	16 [53.3%] 14 [46.7%]	0.271*	0.602
Age [years]	Mean ± SD Range	61.70 ± 7.66 49 – 74	50.53 ± 6.87 38 – 63	5.945•	**< 0.001**
Duration of dialysis [months]	Mean ± SD Range	72.43 ± 11.48 50 – 90	41.77 ± 8.29 22 – 54	11.860•	**< 0.001**
Smoking	No Yes	20 [66.7%] 10 [33.3%]	22 [73.3%] 8 [26.7%]	0.317*	0.573
Body mass Index [kg/m^2]	Mean ± SD Range Yes	27.09 ± 2.91 21.4 – 32.7 7 [23.3%]	21.16 ± 3.33 16.4 – 28.9 4 [13.3%]	7.354•	**< 0.001**
Etiology of CKD	Unknown	3 [10.0%]	3 [10.0%]	0.593	0.988
	DM	9 [30.0%]	9 [30.0%]		
	HTN	9 [30.0%]	7 [23.3%]		
	GN	4 [13.3%]	4 [13.3%]		
	PKD	2 [6.7%]	3 [10.0%]		
	Nephrolithiasis	3 [10.0%]	4 [13.3%]		

*: Chi-square test; •: Independent t-test

Table [2]: Laboratory data of the studied groups

Investigations		With aortic calcification	Without aortic calcification	Test value•	P-value
		No. = 30	**No. = 30**		
Fetuin A [ng/ml]	Mean ± SD Range	302.51 ± 68.46 201.3 – 414.6	564.53 ± 135.55 284.3 – 793.2	-9.451	**< 0.001**
Serum albumin [g/dl]	Mean ± SD Range	3.35 ± 0.23 3.11 – 3.92	3.81 ± 0.20 3.45 – 4.2	-8.248	**< 0.001**
Corrected calcium [mg/dl]	Mean ± SD Range	10.12 ± 0.22 9.7 – 10.5	9.21 ± 0.37 8.5 – 9.9	11.521	**< 0.001**
Serum phosphorus [mg/dl]	Mean ± SD Range	5.59 ± 0.20 5.23 – 5.92	4.90 ± 0.44 4.27 – 5.76	7.907	**< 0.001**
Ca x P [mg^2/dl^2]	Mean ± SD Range	56.63 ± 2.36 51.31 – 61.84	45.08 ± 3.92 37.49 – 51.25	13.839	**< 0.001**
PTH [mg/dl]	Mean ± SD Range	673.21 ± 82.21 524.3 – 801.5	384.27 ± 108.75 189.6 – 561.7	11.609	**< 0.001**
Vitamin D [Pg/ml]	Mean ± SD Range	18.39 ± 4.44 12.4 – 26.3	16.54 ± 4.12 10.7 – 27.5	1.673	**0.100**
Aortic calcium score	Mean ± SD Range	478.06 ± 242.58 78.8 – 924.2	-- --	--	--

Table [3]: Correlation between fetuin-A and laboratory data of the studied groups

	Fetuin-A [ng/ml]	
	Correlation coefficient	**P-value**
Age [year]	**-0.390****	**0.002**
Duration of Dialysis	**-0.660****	**< 0.001**
Body mass Index [kg/m ^{2}]	**-0.539****	**< 0.001**
Serum albumin	**0.563****	**< 0.001**
Corrected calcium [mg/dl]	**-0.615****	**< 0.001**
Serum phosphorus [mg/dl]	**-0.554****	**< 0.001**
Ca x P [mg2/dl2]	**-0.656****	**< 0.001**
PTH [mg/dl]	**-0.545****	**< 0.001**
Vitamin D [Pg/ml]	-0.253	0.051
Aortic calcium score	-0.168	0.376

Table [4]: Multivariate linear regression analysis using the backward method for parameters affecting the level of fetuin-A

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	SE	Beta		
[Constant]	1206.270	126.261		9.554	0.000
Duration of Dialysis	-3.217	1.163	-0.348	-2.766	**0.008**
Ca x P [mg2/dl2]	-11.584	3.216	-0.454	-3.602	**0.001**

Table [5]: Receiver operating characteristic curve [ROC] between patients' group and control group regarding the fetuin-A level

Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
≤ 414.6	0.934	100.00	86.67	88.2	100.0

DISCUSSION

The incidence and severity of aortic calcification as well as risk factors were analyzed. A number of studies have shown that fetuin-A is important. Data from these studies could not be pooled due to discrepancies in data presentation and outcome measures. Instead, we present the results of other studies according to the quality of the main study [13].

Regarding the prevalence of abdominal aorta calcification in hemodialysis patients, our study revealed that 52.6% of the studied population by abdominal x-ray had abdominal aorta calcification, which is a low prevalence compared to the previous studies. **Pencak *et al.*** [14] revealed that calcification of the abdominal aorta was prevalent among hemodialysis patients [81 %].

Surana *et al.* [15] explained the low prevalence of abdominal aorta calcification in our study and the high prevalence in other studies. They suggested that the prevalence of vascular calcification varies considerably. The characteristics of the sample have a significant impact on the variations tested, the location of the examination, and the diagnostic procedure used to detect calcification. In detecting calcification, the lateral lumber X-ray is less sensitive than multislice CT.

Regarding age, our findings demonstrated that, the mean age is higher in the group with aortic calcification than that without. Similarly, **Chen et al.** [16] demonstrated that the mean age of the vascular calcification group was 64 ± 11 years, while the mean age of the group without vascular calcification was 53 ± 12 years, with a P value of < 0.001. In addition, **Pencak *et al.*** [14] demonstrated that abdominal aortic calcification could be detected at the age of 25. The mean age of Group A is 48 years, while the mean age of Group B is 31 years, and the severity of calcification increases with age. These finding can be explained by **kuller *et al.*** [13] who illustrated that the presence and severity of abdominal aortic calcification are likely to be influenced by a person's age [the more one's age, the greater one's risk of abdominal aortic calcification].

Regarding gender, our study showed that 56.7% of the studied cases were females, while 43.3% were males. In a study by **Kiel *et al.*** [17], the Framingham Heart Study cohort of men and women was evaluated for 25 years for signs of aortic calcification using a less sensitive imaging method. There were no significant differences in calcification rates between the sexes. However, in women, bone loss and the aorta calcification rate were strongly linked. This finding can be attributed to a large proportion of adipose tissue in females compared to males contributing to the hypo perfusion of the skin and subcutaneous tissue [tensile stress on septa connecting skin to the deep fascia] arterioles resulting in ischemic necrosis [18].

Regarding smoking, our study showed that 30% of the studied population was smokers, with a low prevalence of smoking in both groups. Similarly, there was no correlation between smoking or dyslipidemia and the development of calcification [14]. Furthermore, **Fedak *et al.*** [19] showed that 15 [21%] of the studied population are smokers.

Regarding dialysis duration, our findings revealed that the mean duration of dialysis in the studied population was 57.10 ± 18.38 months, with a minimum duration of 22 months

and a maximum duration of 90 months. The aortic calcification group has a longer duration of dialysis than that without calcification, with a p-value of < 0.001. A higher risk of calciphylaxis has been associated with a dialysis history of more than 6-7 years. Patients with a considerably shorter dialysis history have been reported to develop calciphylaxis. As with other risk variables associated with calciphylaxis, this association has been inconsistent across studies [3].

Consistent with our findings, **Oh *et al.*** [18] illustrated that patients with CKD who receive renal replacement therapy for an extended period are at a higher risk for developing calciphylaxis because their exposure to risk factors increases over time. People on long-term hemodialysis are consequently more likely to develop vascular calcification [the longer the duration of hemodialysis, the greater the prevalence of vascular calcification]. Therefore, the BMI is higher in the group with aortic calcification than that without, with a p-value of < 0.001, indicating a significant difference between the two studied groups regarding BMI.

However, **Chen *et al.*** [16] demonstrated that the mean BMI of the vascular calcification group was 23.3 ± 4, while the mean BMI of the group without vascular calcification was 22.9 ± 3.7, with a p-value of 0.2. Similarly, **Janigan et al.** [20] suggested that obesity has been linked to proximal calciphylaxis, according to research [involving the trunk, thighs, and breasts], but theories as to why adipose tissues are more likely to be involved in the disease remain. Arterioles in the dermis are supported by the fibroelastic septa that connect the skin to the rest of the body. Obese dialysis patients were subjected to a larger level of tensile stress on these septa and arterioles due to the expansion of the subcutaneous compartment by fat.

Regarding the etiology of CKD, our study revealed that diabetic nephropathy is the most common cause [30.0%]; hypertension is the second most common cause [26.7%]. There was no significant difference between the two studied groups regarding the etiology of CKD [P value = 0.988]. In line with our findings, **Ulutas *et al.*** [21] showed that of the 93 patients studied, 30 [32.3 %] had diabetes, 26 [28.8 %] had hypertension, 16 [17.2 %] had chronic glomerulonephritis, and 11 [11.8 %] had chronic idiopathic kidney disease [10.8%].

Regarding corrected serum calcium, it was higher in the group with aortic calcification than that without, with a P value of < 0.001. In contrast to our findings, **Chen *et al.*** [16] demonstrated that the mean corrected calcium of the vascular calcification group was 9.2 0.8 mg/dl, while the mean corrected calcium of the control group was 9.2 ± 0.7 mg/dl, with a P value of 0.5.

Serum phosphorus was higher in the group with aortic calcification than in the group without calcification, with a p-value of 0.001. Likewise, **Karamanidou *et al.*** [21] suggested that the high serum phosphorous concentration in significantly older patients with vascular calcification can be explained by the more frequent non-adherence of these patients to phosphorous binding drugs and diet recommendations.

Our study revealed that the mean calcium-phosphorus product was higher in the group with aortic calcification with a p-value of < 0.001. Regarding measured parathyroid hormone, it was higher in the group with aortic calcification than that without, with a P-value of < 0.001. In agreement with the current study findings, **Fedak *et al.*** [19], in a study of the relation between fetuin-A and carotid arteries calcification, demonstrated that the mean PTH of the studied population was 378 [132-1035] pg/ml, with a p-value of 0.02 [higher in the calcified carotid group]. In contrast, **Chen *et al.*** [16] illustrated that the mean PTH of the vascular calcification group was 235 pg/ml, while the mean PTH of the group without vascular calcification was 289 pg/ml, with a P value of 0.06.

Our study revealed that serum albumin was significantly higher in the group without aortic calcification [P= 0.001]. Consistent with our findings, **Chen *et al.*** [16] demonstrated that the mean serum albumin of the vascular calcification group was 4.0 ± 0.4 g/dl, while the mean serum albumin of the group without vascular calcification was 4.1 ± 0.4 g/dl, with a P value of 0.02.

In addition, a previously established association exists between low serum albumin levels and an increased risk of calciphylaxis in patients. According to **Bleyer *et al.*** [23], there was a 17-fold increase in calciphylaxis for each lg/dL drop in albumin. **Coates *et al.*** [24] found that 7 out of 16 patients in their series had lost

10% of their body weight prior to being diagnosed with calciphylaxis, which supports this finding.

Oh *et al.* [17] suggested that low albumin is associated with poor wound healing and an increased risk of infection, implying that low albumin may predispose patients to calciphylaxis. Dialysis patients may experience hypoalbuminemia due to poor diet or inflammation. Dialysis patients with calciphylaxis have lower albumin levels than dialysis patients without calciphylaxis. It is difficult to determine whether hypoalbuminemia is caused by calciphylaxis, as these studies have methodological limitations, which makes it difficult to make definitive conclusions [25].

Regarding measured serum fetuin-A, our study showed that it was lower in the group with aortic calcification than without aortic calcification, with a p-value of < 0.001. Similarly, **Chen *et al.*** [16] demonstrated that the mean serum fetuin-A of the vascular calcification group was 0.4 [0.27 - 0.64] g/l, while the mean serum fetuin-A of the group without vascular calcification was 0.62 [0.37-0.82] g/l, with a p-value of < 0.001.

With respect to the levels of fetuin-A and its correlation with aortic calcification score and biochemical parameters of calciphylaxis: Our study revealed negative significant correlation with age, duration of dialysis, body mass index, calcium phosphorus product, and parathyroid hormone, in the studied population. Multivariate linear regression analysis of the correlated parameters revealed that the duration of dialysis and Ca x P Product were the two most influential parameters affecting the fetuin-A level.

This was in contrast with **Maréchal *et al.*** [26] that found after a stepwise linear regression analysis of all determinants affecting fetuin A level, the lower level of cholesterol, the AHSG rs4918 G allele, and a history of smoking were the most ones in renal transplanted recipients.

Concerning the correlation between fetuin-A and measured serum albumin, there was a significant positive correlation [p-value < 0.001] [r = 0.563] in the studied population. This is in concordance with **Chen *et al.*** [27] that found higher albumin level in the group of high quartiles fetuin A level [P<0.001].

In the population studied, there was a non-significant negative correlation between fetuin-A and aortic calcium score. In contrast, **Muzasti and Loesnihari** [27] found a strong inverse correlation between fetuin-A levels and the abdominal aortic calcification score [P < 0.001]. In addition, lower fetuin-A levels have been found to be associated with higher abdominal aortic calcification scores. The value r = - 0.60 indicates a moderate correlation between the two variables [29]. Furthermore, fetuin-A has a negative correlation with vascular calcification and is significantly low in hemodialysis patients, accounting for the high calcification prevalence in this population [30].

Regarding the diagnostic accuracy of serum fetuin-A as a predictor and a diagnostic marker for aortic calcification in ESRD patients, we analyzed the receiver operator characteristic curve [ROC] and showed that the cutoff value of serum fetuin-A to differentiate between cases and the control group was [≤414.6 ng/ml], with 100.00% sensitivity, 86.67% specificity, positive predictive value [PPV] 88.2 % and area under the curve [AUC] of 93.4%. This cut off point is different from that was declared by **Mohamed *et al.*** [31], to differentiate between the apparently normal population and those who already had an established coronary artery disease] 520.3 ng/ml].

Conclusion

There was a significant difference between the two study groups in serum fetuin-A [serum fetuin-A levels were lower in patients with aortic calcification at the cutoff point ≤414.6 ng/mL]. However, there was a non-significant negative correlation between fetuin-A and aortic calcium scores. The most influential parameters affecting fetal A levels were dialysis duration and CaxP product.

Limitation

Our research has a number of limitations. First, study participants differed in terms of their underlying medical conditions, age, and dialysis duration. Prior to a diagnosis of CKD, we only considered smoking as a lifestyle risk. Despite the fact that CT imaging provides an accurate and quantitative assessment of the cardiovascular calcification burden in CKD patients, this technique has inherent limitations. In addition to the high cost of equipment and the patient's exposure to radiation, the inability to

perform imaging in situ and the need for advanced image training are the primary limitations. Although desirable, these methods cannot differentiate between intimal [atherosclerotic] and medial calcification. Consequently, other methods have been used to evaluate vascular damage in CKD, and some simple tools have been compared favorably to CT in terms of their ability to detect calcification and predict the outcome. Fetuin-A gene variants have not been investigated in Egyptian populations, which is a glaring omission. Our cross-sectional investigation, which only measured fetuin-A levels once, may have overlooked variations in serum levels.

Conflict of Interest and Financial Disclosure: None.

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