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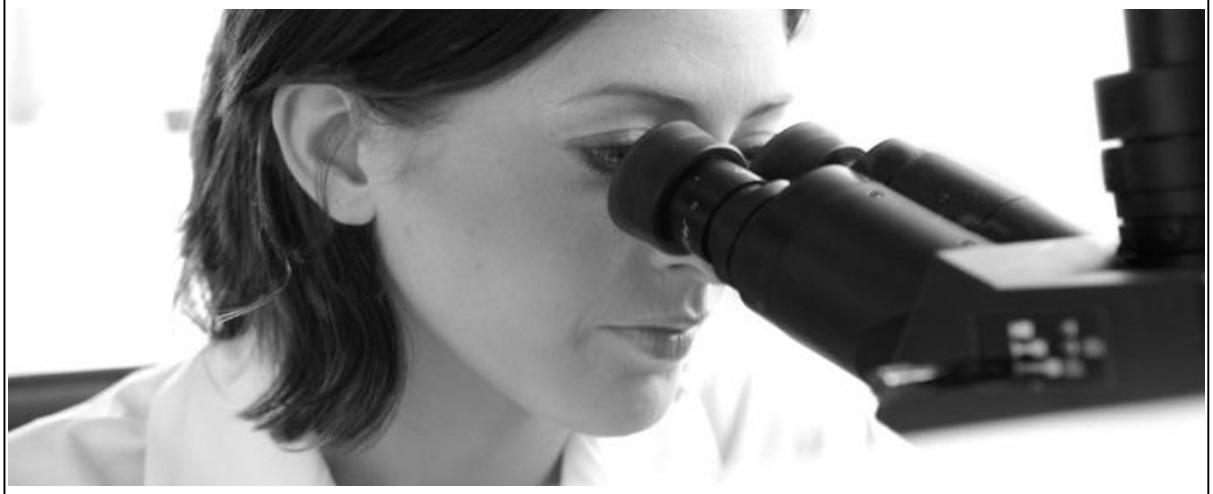

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RESEARCH ARTICLE

VASCULAR AND VALVULAR CALCIFICATION IN DIALYSIS PATIENTS: THE ROLE OF FETUIN-A

Magdy M.Sharqawy*., Khaled A.Seif., Abdul Baset S.Abdul Azim., Essam N.Dein., Sherif H. Maroof and Adel E.Gazzar

Department of Internal Medicine-Nephrology Division-Faculty of Medicine-Ain Shams University, Egypt

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ABSTRACT

Background: Vascular calcifications (VC) are important predictors of cardiovascular mortality in end-stage renal disease patients (ESRD). Fetuin-A is a negative acute phase glycoprotein that plays a pivotal role in the (CalciumXPhosphorus) precipitation along with its multifunctional effects on vascular smooth muscle cells and fibroblasts. **Objectives**: Study the association of serum Fetuin-A with vascular and valvular calcifications in dialysis patients. **Patients and methods:** Study was conducted on 119 patients [75 males (63%) and 44 females (37%)] with ESRD on dialysis [91 patients on hemodialysis (HD) and 28 patients on peritoneal dialysis (PD) with matching controls. All participants were evaluated by (serum creatinine, blood urea nitrogen, sodium, potassium, serum calcium, phosphorus and calculated [CaXP]), Serum Parathyroid hormone and serum Fetuin-A, as well as Echocardiography, lateral view lumbar spine plain x-ray lateral view in standing position. **Results:** Valvular calcification was present in 52 patients (43.7%) and was prevalent more among HD patients {n=40(44%)} than among (PD) patients {n=12(42.9%)}. VC was prevalent in 99 patients (83.2%) and it was found to be more among HD patients (n=76)(83.5%) than among PD patients(n=23)(82.1%).Calcium X Phosphorus by product was significantly higher among patients with valvular calcification than those without(Pv < 0.05).Serum Fetuin A levels were lower in patients with valvular calcification (16.2 ± 6.8) than those without (20.3±7.1) which was statistically highly significant (Pv < 0.01).The same goes towards Fetuin-A levels in participants with vascular calcification, as Fetuin-A levels were lower in a highly significant manner (Pv < 0.01).
Conclusion: The role of Fetuin-A is probably not only linked to active prevention of calcium phosphate precipitation but also reflects the severity of inflammation.

INTRODUCTION

Background

Cardiovascular disease (CVD) is the most frequent cause of morbidity and mortality in patients with ESRD. Accelerated calcifying atherosclerosis, medial calcification, and valvular calcification are hallmarks of CVD in the dialysis population (1). Hemodialysis patients are affected by a chronic inflammatory state, represented by higher concentrations of positive acute phase proteins, as C-reactive protein (CRP), IL-6, lower levels of albumin and negative acute phase molecules as Fetuin-A. New insights in the calcification process have revealed that vascular cells play an active, not only a passive role, as they stimulate osteoblastic calcification differentiation of the vascular walls. A number of inhibitors of this stimulation have been identified, including osteopontin, matrix Gla-protein and Fetuin-A (2). Fetuin-A/ α 2-Heremans-Schmid glycoprotein (AHSG) is a liver-derived negative acute phase glycoprotein present in all extracellular fluids. Owing to its high affinity for calcium phosphate, Fetuin-A accumulates in the mineralized bone matrix, in atherosclerotic plaques, and in pathologically mineralized issues. Chemically, Fetuin-A acts as an inhibitor of spontaneous calcium phosphate precipitation by forming soluble colloidal calciprotein particles that contain Fetuin, calcium, and phosphate. On the cellular level Fetuin-A accumulates in mineralization-competent matrix vesicles associated with vascular smooth muscle cells, thus attenuating apoptosis and dystrophic calcification (3, 4).

Participants and methods

A total of 119 patients with ESRD on maintenance dialysis have been enrolled in this retrospective cross sectional study conducted in the nephrology department at Ain Shams University hospitals. All patients included in this study were on dialysis for > 3 months and regarding their modality of renal replacement therapy; 91 patients (76.47%) were on

*Corresponding author: **Magdy M.Sharqawy**
Department of Internal Medicine-Nephrology Division-Faculty of Medicine-Ain Shams, University, Egypt

hemodialysis, 28 patients (23.52%) on peritoneal dialysis with an age range of (32-71 years) with a mean of 50.7±11.5 (75 males {63%} and 44 females {37%}).Amongst the commonest co-morbidities, HTN was present in 76 patients (63.9%) and DM in 27 patients (22.7%). A written consent was signed by all participants.

Analytic procedures

All participants in this study were subjected to the following; clinical examination, laboratory investigations including (complete blood picture, renal panel, serum electrolytes, lipid profile blood sugar, serum uric acid, alkaline phosphatase, Parathyroid hormone by Enzyme Linked Immunosorbent Assay (ELISA),C-reactive protein, serum Ca, P, and calculated (Ca × P) product and serum Fetuin-A (ELISA).

Radiologically; Echocardiography by (M-mode-2D Doppler-Colored Doppler) was done to detect valvular calcifications which were defined as bright echoes > 1mm on one or more cusps of the aortic or mitral valves or the annulus, Lumbar Spine plain X-ray: lateral view in standing position was performed for all participants and abdominal aorta calcification score was implemented (AACS) *(Kauppila et al., 1997)* (5). Lesions were graded as follows: 0, no aortic calcific deposits; 1, small scattered calcific deposits filling less than 1/3 of the longitudinal wall of the aorta; 2, 1/3 or more, but less than 2/3 of the longitudinal wall of the aorta calcified; calcifications in front of L3 and L4 vertebrae. 3, two thirds or more of the longitudinal wall of the aorta calcified (Figure 1).

Assessment of aortic calcifications segmentally from lateral lumbar radiograph, scoring 0 for aortic calcifications (both posterior and anterior) in front of L1 vertebra, 2 for calcification in the posterior wall, 1 for anterior wall in front of L2 vertebra and 3 for calcifications in front of L3 and L4 vertebrae.

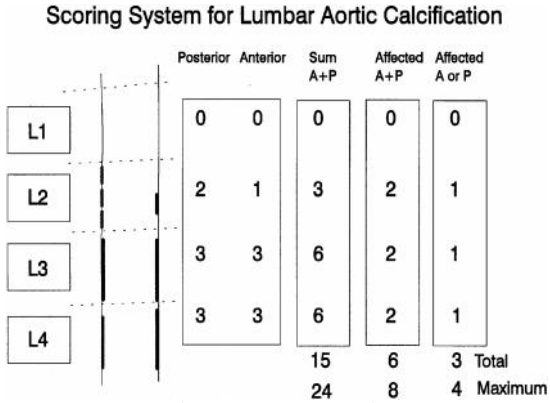

Figure 2 Scoring system for lumbar aortic calcifications. Scores based on findings in (Figure 1).

In the affected segments a score (0–4) is applied and the number of individual aortic segments which showed any calcification were calculated. If anterior and posterior aortic segments are affected a score (0–8) is applied, the number of individual aortic segments, both anterior and posterior, which showed any calcification were summed. In the antro–posterior severity score (0–24), the scores of individual aortic segments both for the posterior and anterior wall were summed.

STATISTICAL METHODOLOGY

Analysis of the data was done using SPSS (statistical program for social science) version 10 under the platform of Microsoft Windows XP Professional Edition. Data were expressed in the form of mean ± SD. Student t-test of One Way and ANOVA, Chi-square test. Relation between variables was done using Pearson's correlation coefficient and P value expressed as follows; P value>0.05 (NS=non significant), P value <0.05 (S=significant), P value<0.01 (HS=highly significant).

RESULTS

Table 1 Laboratory parameters of the studied population (n=119)

Type of dialysis	**Hemodialysis**	**91 (76.5 %)**
	Peritoneal dialysis	28 (23.5 %)
Duration of dialysis (months)	Range	36.0 – 90.0
	Mean ± SD	64.1 ± 16.7
Kt/V	Range	1.08 – 1.44
	Mean ± SD	1.25 ± 0.1
URR	Range	40.0 – 70.0
	Mean ± SD	56.9 ± 6.8
Creatinine	Range	6.9 – 19.3
	Mean ± SD	13.0 ± 2.9
BUN	Range	85.0 – 252.0
	Mean ± SD	152.4 ± 37.1
Ca (mg/dl)	Range	6.8 – 10.2
	Mean ± SD	8.2 ± 0.8
Po4(mg/dl)	Range	2.9 – 8.4
	Mean ± SD	5.3± 1.3
CaXP product	Range	23.2 – 83.6
	Mean ± SD	44.1± 12.4
Na(mEq/L)	Range	121 – 150
	Mean ± SD	139.5± 6.1
K(mEq/L)	Range	3.2– 7.5
	Mean ± SD	5.3± 1.0
Albumin	Range	2.5– 4.5
	Mean ± SD	3.5±0.6
CRP	Range	4.0 – 21.0
	Mean ± SD	10.3± 4.7
Parathyroid hormone(pg/ml)	Range	6.6 – 2586
	Mean ± SD	775.3± 622.6
Fetuin-A (g/L)	Range	5.5 – 30.9
	Mean ± SD	18.5± 7.2

Valvular calcification was present in 52 patients of the studied population (43.7%) and was prevalent more among HD patients {n=40(44%)} than among (PD) patients {n=12(42.9%)}.

Among those patients, calcification of aortic valve was present in 32 patients (61.5%) while mitral valve calcification was present in 15 patients (28.9%) and finally combined aortic and mitral valve calcification was present in 5 patients (9.6%). Vascular calcification was prevalent in 99 patients from the studied population (83.2%) and it was found to be more among HD patients {(n=76) (83.5%)} than among PD patients {(n=23)(82.1%)}.

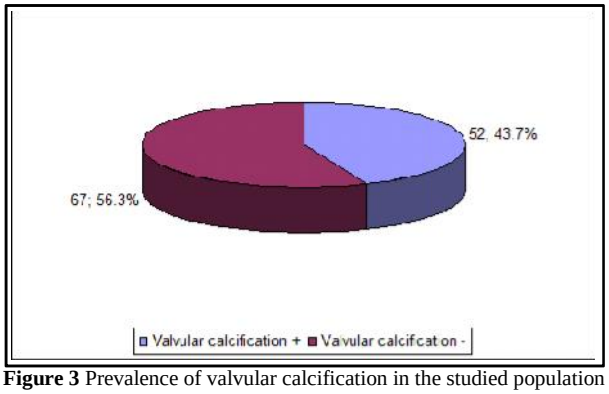

Figure 3 Prevalence of valvular calcification in the studied population (n=119).

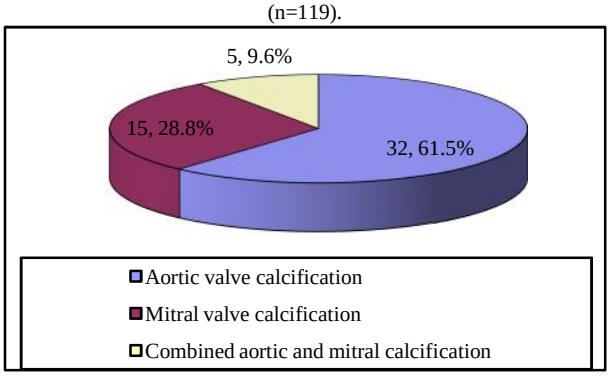

Figure 4 Pattern of valvular calcification in the studied population (n=52).

Calcium X Phosphorus by product was significantly higher among patients with valvular calcification than those without (Pv < 0.05).

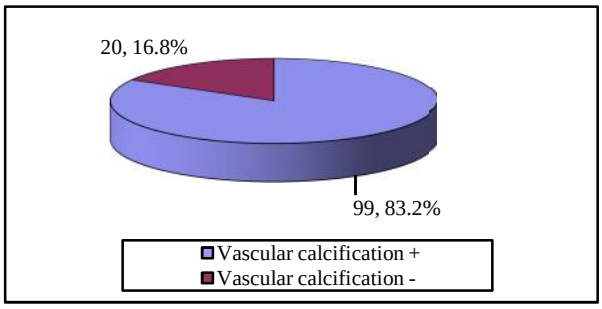

Figure 5 Prevalence of vascular calcification in the studied patients.

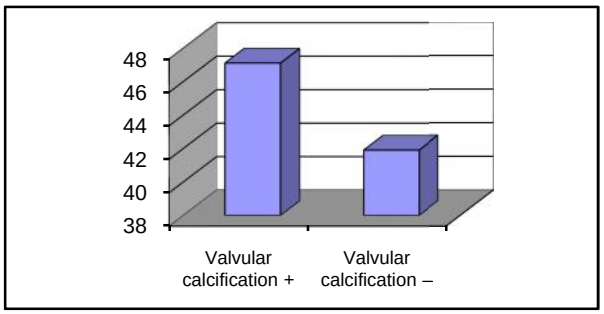

Figure 6 Valvular calcification and Ca × P by product.

No statistically significant differences were found in this study between patients with valvular calcification and patients without regarding the lipid profile, nor hematological parameters or serum electrolytes except for serum phosphorus levels which were higher in those patients with valvular calcification than those without in a statistically significant manner (Pv <0.05). Moreover, in this study, patients with valvular calcification had highly significant lower serum albumin and Fetuin A levels(Pv < 0.01) along with a significant higher CRP levels(Pv < 0.05)**(Figures 7 & 8)**respectively.

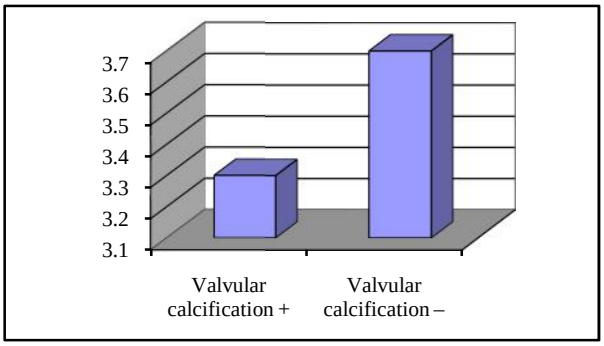

Figure 7 Valvular calcification and serum albumin.

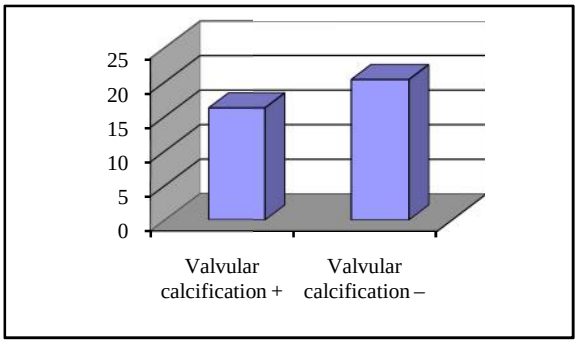

Figure 8 Valvular calcification and serum Fetuin-A.

Infact serum Fetuin-A levels were lower in patients with valvular calcification (16.2 ± 6.8) than those without (20.3±7.1) which was statistically highly significant (Pv < 0.01).The same goes towards Fetuin-A levels in participants with vascular calcification in this study, as Fetuin-A levels were lower in a highly significant manner (Pv < 0.01), while CRP was higher in a significant manner (Pv < 0.05).

Within the same study, participants with valvular calcification (n=52) had higher frequency of vascular calcification (100%) when compared to those participants without which were 47 out of 67 participants (70%) which proved to be highly significant (Pv < 0.01).Moreover, DM proved to be prevalent in a significant manner among those patients with vascular calcification (Pv < 0.05), while HTN proved to be marginally higher in patients with vascular calcification in comparison to those without.

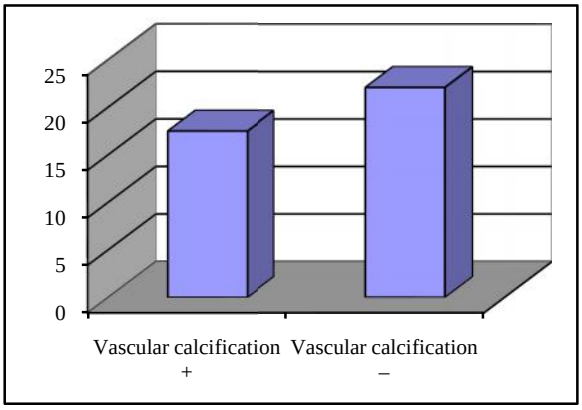

Figure 9 Vascular calcification and serum Fetuin-A.

Table 2 Relation of Fetuin-A levels to different laboratory findings.

Laboratory parameter	Fetuin-A	
	r	p
Uric acid	0.01	0.83
Ca	0.02	0.8
P	0.11	0.21
Ca X P	0.12	0.18
Albumin	0.25	0.005
Parathyroid hormone	0.14	0.1
CRP	-0.27	0.002
Na	0.16	0.07
K	0.13	0.13

This study showed a positive correlation between serum Fetuin-A and serum albumin and a negative correlation with CRP in the studied population both of which were highly significant (PV < 0.01), yet serum Fetuin-A showed no correlation of any statistical significance with any of serum calcium, phosphorus not their by product.

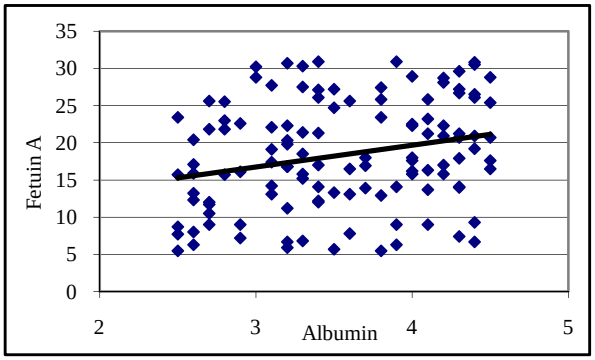

Figure 10 Correlation between serum albumin and serum Fetuin-A levels.

DISCUSSION

The most common cause of death in dialysis patients is cardiovascular disease (CVD). When compared with general population, CVD in (ESRD) is 10-20 times higher despite recent developments in renal replacement therapies (RRT) (6). This can be attributed to many factors including endothelial dysfunction (ED), hypertension, anemia, hyperparathyroidism, chronic inflammation, diabetes, and its macro-and microvascular complications, and vascular calcification (VC)(7). With respect to (VC), there appears to be two relevant effects of Fetuin-A: it prevents the precipitation of Ca and P in addition to being an important mediator of insulin resistance. Augmenting these defenses may have important therapeutic potentials in preventing the devastating effects of (VC) observed in patients with chronic kidney disease(8).Within this study, aortic valve calcification was present in 32 patients (61.5 %) followed by mitral valve calcification in 15 patients (28.9 %) and combined aortic and mitral calcification were present in 5 patients (9.6 %). This was in concordance with Ikee *et al*., (9) who noted that aortic valve calcification was the most common type of valvular calcification in their study. Raggi *et al*., (10) also noted that (38.2%) of patients had mitral valve calcification and (44.4%) had aortic valve calcification on echocardiography which were similar to findings of this study. Among other studies with similar findings, were those of Honkanen *et al*.,(11) who reported prevalence of aortic vascular calcification in (81.0 %) of dialysis patients, Wang *et al*.,(12) who found aortic vascular calcification in (90.9 %) of patients and Toussaint *et al*., (13)who reported abdominal aortic calcification in (94.4 %) of patients. This study also revealed that patients with valvular calcification had significantly higher phosphorous levels and Ca × P product when compared with patients without. Yet no significant differences were noted between participants regarding levels of Na, K and Ca. These findings were in agreement with those of Rufino *et al*., (14). Patients with valvular calcification in this study had significantly lower serum albumin levels when compared to patients without, which was in agreement with Ikee *et al*., (15) who showed valvular calcification in dialysis patients to be associated with lower serum albumin levels. Furthermore, this study revealed that participants with valvular calcification had significantly lower levels of Fetuin & A when compared to those without, which was similarly revealed in the study of Wang *et al*., (16) who concluded that serum Fetuin & A showed important associations with valvular calcification in peritoneal dialysis patients as well as El-Shehaby *et al*., (17**)** who reached similar conclusions in HD patients. Other laboratory findings included higher CRP levels in patients with VC when compared to those without along with lower serum Fetuin - A levels in patients with VC when compared to those without. These findings were in concordance with Tsushima *et al*., (18) as patients with VC had significantly higher CRP levels in comparison to those without, and Wang *et al*., (19) found that patients with VC had significantly lower Fetuin - A levels when compared to those without. Even though some studies suggested higher Fetuin-A levels in PD patients than HD patients (20), lower serum Fetuin-A levels were linked to an increased risk of all-cause mortality and cardiovascular death in both HD (21) and PD patients (16).Results of this study accord with findings of Honda *et al*., (22) regarding a positive correlation between serum Fetuin-A and serum albumin. In the study by Stenvikel *et al*., (23), Fetuin-A deficiency strongly correlated with hypoalbuminemia, and since serum albumin levels decrease in presence of systemic inflammation, they may not reflect nutritional state but are predictive of vascular morbidity (24). Elevated CRP levels are a well known predictor of mortality and CV deaths in dialysis patients (25), these findings are confirmed in this study with a negative correlation between serum Fetuin-A levels and CRP levels, which are also similar to the published data by Wang *et al*., (16), although the study by La Clair *et al*., (26) found no correlation. Finally, in the study including 238 PD patients by Wang *et al*., (16), important associations were found between serum Fetuin-A and cardiac valvular calcification, atherosclerosis, inflammation, malnutrition, and Fetuin-A was linked to mortality and CV events in PD patients.

CONCLUSION

The role of Fetuin-A is probably not only linked to active prevention of calcium phosphate precipitation but also is a sign of severity of inflammation. Assessment of both cardiac calcification, whether coronary or valvular and serum levels of Fetuin-A may be of value to identify those subjects at higher risk of development and progression of cardiovascular lesions. Furthermore, the potential role of Fetuin-A as a target of preventive strategies for cardiac calcification needs more investigations.

References

1. Ivanovski O, Nikolov IG, Drueke BT, Massy AZ., 2007. Atherosclerosis and vascular calcification in uraemia - a new experimental model. Prilozi. Dec;28(2):11-24.
2. Amal M. El-shehab, Abir Zakaria, Mohamed El-Khatib& Naglaa Mostafa., 2010. Association of fetuin-A and cardiac calcification and inflammation levels in hemodialysis patients. Scandinavian Journal of Clinical & Laboratory Investigation; 70: 575–582.
3. Reynolds JL, Joannides AJ, Skepper JN, McNair R, Schurgers LJ, Proudfoot D, Jahnen-Dechent W, Weissberg PL, Shanahan CM, 2004. Human vascular smooth muscle cells undergo vesicle-mediated calcification in response to changes in extracellular calcium and phosphate concentrations: a potential mechanism for accelerated vascular calcification in ESRD. J Am Soc Nephrol; 15:2857 – 67.
4. Kuźniar J, Porazko T, Klinger M., 2008. Relationship between Fetuin-A concentration, elevated levels of inflammatory markers, and arterial wall stiffness in end-stage kidney disease. J Ren Nutr. Jan; 18(1):83-6.
5. Kauppila LI, Polak JF, Cupples LA *et al*., 1997. New indices to classify location, severity and progression of calcific lesions in the abdominal aorta: a 25-year follow-up study. Atherosclerosis; 132: 245–250.
6. Collins AJ**.**2003. Cardiovascular mortality in end-stage renal disease. Am J Med Sci.; 325:163–7.
7. London GM, Guérin AP, Marchais SJ, Métivier F, Pannier B, Adda H**.**2003. Arterial medial calcification in end-stage renal disease: Impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant; 18:1731–40.
8. Moe MS, Reslerova M, Ketteler M, O'Neill K, Duan D, Koczman J.2005.Role of calcification inhibitors in the pathogenesis of vascular calcification in chronic kidney disease. Kidney Int 67: 2295–304.
9. Ikee R, Honda K, Ishioka K, Oka M, Maesato K, Moriya H, Hidaka S, Ohtake T, Kobayashi S.2010.Differences in associated factors between aortic and mitral valve calcification in hemodialysis. Hypertens Res. Jun; 33(6):622-6.
10. Raggi P, Bellasi A, Gamboa C, Ferramosca E, Ratti C, Block GA, Muntner P. 2011 . All-cause mortality in hemodialysis patients with heart valve calcification. Clin J Am Soc Nephrol.Aug; 6(8):1990-5.
11. Honkanen E, Kauppila L, Wikström B, Rensma PL, Krzesinski JM, Aasarod K, Verbeke F, Jensen PB, Mattelaer P, Volck B; CORD study group 2008. Abdominal aortic calcification in dialysis patients: results of the CORD study. Nephrol Dial Transplant. Dec; 23(12):4009-15.
12. Wang M, Wang M, Gan LY, Li SJ, Hong N, Zhang M. 2009. Vascular calcification in maintenance hemodialysis patients. Blood Purif.; 28(1):15-20.
13. Toussaint ND, Pedagogos E, Lau KK, Heinze S, Becker GJ, Beavis J, Polkinghorne KR, Damasiewicz MJ, Kerr PG.2011. Lateral lumbar X-ray assessment of abdominal aortic calcification in Australian haemodialysis patients. Nephrology (Carlton). May; 16(4):389-95.
14. Rufino M, García S, Jiménez A, Alvarez A, Miquel R, Delgado P, Marrero D, Torres A, Hernández D, Lorenzo V. 2003. Heart valve calcification and calcium x phosphorus product in hemodialysis patients: analysis of optimum values for its prevention. Kidney Int Suppl. Jun; (85):S115-8.
15. Ikee R, Honda K, Oka M, Maesato K, Mano T, Moriya H, Ohtake T, Kobayashi S. 2008. Association of heart valve calcification with malnutrition-inflammation complex syndrome, beta-microglobulin, and carotid intima media thickness in patients on hemodialysis. Ther Apher Dial. Dec; 12(6):464-8.
16. Wang AY, Woo J, Lam CW, Wang M, Chan IH, Gao P, Lui SF, Li PK, Sanderson JE. 2005. Associations of serum Fetuin-A with malnutrition, inflammation, atherosclerosis and valvular calcification syndrome and outcome in peritoneal dialysis patients. Nephrol Dial Transplant. Aug; 20(8):1676-85.
17. El-Shehaby AM, Zakaria A, El-Khatib M, Mostafa N 2010. Association of Fetuin-A and cardiac calcification and inflammation levels in hemodialysis patients. Scand J Clin Lab Invest. Dec; 70(8):575-82.
18. Tsushima M, Terayama Y, Momose A, Funyu T, Ohyama C, Hada R. 2008 .Carotid intima media thickness and aortic calcification index closely relate to cerebral and cardiovascular disorders in hemodialysis patients. Int J Urol. Jan; 15(1):48-51.
19. Wang M, Wang M, Gan LY, Li SJ, Hong N, Zhang M. 2009. Vascular calcification in maintenance hemodialysis patients. Blood Purif.; 28(1):15-20.
20. Hermans MM, Brandenburg V, Ketteler M, Kooman JP, van der Sande FM, Boeschoten EW, Leunissen KM, Krediet RT, Dekker FW. 2007. Netherlands cooperative study on the adequacy of Dialysis (NECOSAD). Association of serum fetuin-A levels with mortality in dialysis patients. Kidney Int. Jul; 72(2):202-7.
21. Ketteler M, Bongartz P, Westenfeld R, Wildberger JE, Mahnken AH, Boem R, *et al*., 2003. Association of low Fetuin-A (AHSG) concentrations in serum with cardiovascular mortality in patients on dialysis: a cross-sectional study. Lancet 361: 827–33.
22. Honda H, Quereshi AR, Heimbuerger O, Barany P, Wang K, Pecoits-Filho R, *et al*.,2006. Serum albumin, C-reactive protein, interleukin-6, and fetuin A as predictors of malnutrition, cardiovascular disease, and mortality in patients with ESRD. Am J Kidney Dis 47: 139–48
23. Stenvinkel P, Wang K, Quereshi AR, Axelsson J, Pecoits-Filho R, Gao P, *et al* .,2005. Low fetuin-A levels are associated with cardiovascular death: impact of variations in the gene encoding fetuin. Kidney Int 67: 2383–92.
24. Cooper BA, Penne EL, Bartlett LH, Pollock CA.2004. Protein malnutrition and hypoalbuminemia as predictors of vascular events and mortality in ESRD. Am J Kidney Dis 43: 61–6.
25. Kalpakian MA, Mehrotra R: 2007.Vascular calcification and disordered mineral metabolism in dialysis patients. Seminars in dialysis 20:139-43,
26. La Clair R, O'Neal K, Ofner S, Sosa MJ, Labarrere CA, *et al*.,2008.Precision of biomarkers to define chronic inflammation in CKD. Am J Nephrol 28: 808–12

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