

# Vascular Calcification in Maintenance Hemodialysis Patients in Pakistan: A single centre Cross-sectional study

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## ABSTRACT

### Background:

Cardiovascular disease is the most common cause of death in patients with chronic kidney disease (CKD), including dialysis-dependent CKD. The high cardiovascular risk may be due in part to excess vascular calcification. Our study aimed to determine the frequency of vascular calcification in maintenance hemodialysis patients.

### Material and Method:

The study was conducted in the Department of adult Nephrology, Indus Hospital, Karachi. This was a cross-sectional study. All patients had a lateral abdominal x-ray performed and reported according to the Kauppila score to reach the outcome i-e frequency of vascular calcification.

### Results:

A total of 104 patients comprised our participants, of which 56(53.8%) were males while 48 (46.2%) were females. The mean age was  $45.7 \pm 14.2$ , with the minimum age being 20 years and the maximum 73 years. Most of our patients belonged to the middle socioeconomic group 96 (66.3%). The most prevalent cause of ESKD was DM in our patients 24 (23.1%), and almost all patients had AVF101 (97.1%) for HD access. Abdominal aortic calcification was present in 27 (26%) patients while ECHO revealed calcification in 10 (9.6%) patients. The degree of calcification according to the Kauppila score was mild to moderate in 17(16.4%) and severe in 10(9.6%), while 77(74%) showed no calcification. The majority of patients were using calcium carbonate and calcium supplements 73 (70.2%).

### Conclusion:

In conclusion, the frequency of vascular calcification in maintenance hemodialysis patients was low, it increases with the increase in age and no gender predominance was noted.

**Keywords:** vascular calcification, hemodialysis, hyperparathyroidism, calcium, phosphorus, echocardiogram, End stage kidney disease, Kauppila score.

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## Introduction:

Chronic kidney disease (CKD) is a highly prevalent condition with increasing incidence in recent years. A recent study on CKD, which included twelve low-income to middle-income countries in six regions of the world,

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reported a CKD prevalence of 14.3% in the general population, and 36.1% in the high-risk population.<sup>1</sup> In Pakistan, Ashar et al found an overall prevalence of 16.6% of CKD in a community-based cohort in the cosmopolitan city of Karachi.<sup>2</sup> Patients with CKD have high morbidity and mortality rates compared to a matched general population due to cardiovascular diseases (CVD).<sup>3</sup> End-stage kidney disease (ESKD) patients have a high prevalence of vascular calcification (VC), because of multiple risk factors that induce the phenotypic transformation of vascular smooth muscle cells (VSMCs), into osteoblast-like cells capable of inducing tissue mineralization. VC has been associated with numerous traditional cardiovascular risk factors, including advanced age, hypertension, diabetes, and dyslipidemia, as well as with non-traditional cardiovascular risk factors, such as hyperphosphatemia, hyperparathyroidism, and excessive calcium intake.<sup>4</sup>

Calcification stiffens vessels and valves and reducing compliance, thus contributing to left ventricular hypertrophy and increasing all-cause mortality risk. Abdominal aortic calcification is independently associated with cardiovascular events in dialysis patients and the general population.<sup>5</sup> VC is common in patients with CKD including ESKD.<sup>6</sup> Its prevalence is reportedly different in different populations. In a multicentre, international cross-sectional observational study conducted in the western population, Kraus et al found the prevalence of echocardiographic valvular calcification (at  $\geq 1$  of the 3 sites) was 100% and that of radiographic aortic calcification was 77.8%.<sup>7</sup> On the other hand, Al Ghonaem et al in a multi-centric study conducted in the Kingdom of Saudi Arabia found the prevalence of VC to be around 40.3%.<sup>8</sup>

According to US Renal Data System (US Renal Data System, 1998), up to 40-50% of patients with ESKD die of CVD reflecting their rapidly progressing atherosclerotic burden and heavy arterial calcification. Cardiovascular disease in the Pakistani population is highly prevalent, and the trends are different compared to other populations. For example, in a case-control study, Liaquat et al found in a population of 835 patients, a high propensity of CVD risk factors at a younger age with a female preponderance.<sup>9</sup> They also found a high prevalence of hypertension and dyslipidemia as the most prominent risk factors.

Vascular and valvular calcification is highly prevalent in the hemodialysis population. CKD population has a higher incidence of heart disease as compared to the general population and vascular calcification is one of the leading causes of heart disease. Therefore, there is an obligation to investigate the prevalence or frequency of vascular calcification in the Pakistani hemodialysis population who are at a substantial risk already, and study results will help us in modifying treatment strategies in our high-risk population at our dialysis centers.

### Material and method:

This Cross-sectional study was conducted at The Indus hospital Korangi and Indus hospital dialysis center, Peer Ilahi Bux colony Karachi for a period of six months from Jan 2020 to June 2020 through non-probability consecutive sampling. The inclusion criteria comprised all patients more than 18 years of age to 85 years of age and with ESKD on maintenance dialysis for more than three months due to any cause, three times per week. We excluded patients with acute kidney injury, non-consenting patients, and patients with dialysis duration of fewer than three months.

Written informed consent was obtained from all the eligible patients. Socio-demographic information like age, gender, and clinical history from the patient and co-morbid like diabetes, hypertension, ischemic heart disease, and the cause of ESKD were collected on a pre-designed Performa. Calcification was assessed through lateral abdominal x-ray for Aortic calcification (as described below). X-ray reported according to Kauppila score: A lateral abdominal x-ray was performed that includes from the T-10 vertebra to the first S-2 vertebra. The aorta was identified as a tubular structure in front of the vertebral column. Only the segments of the abdominal aorta in front of the first 4 lumbar vertebrae (L1-L4) were analyzed. The Score was assigned from 0 to 3 [0: No

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calcification, 1: small calcification (1/3 the vertebra length), 2: moderate (2/3), 3: Large (affects more than 2/3 of the vertebrae length)] according to the length of each detected plaque. Both anterior and posterior parts of the aorta were considered, relating them with the location according to where they are located in front of the L1, L2, L3, or L4 vertebrae. With this scoring, a final score was reached between 0 to 24 points. For example:

*L1 = anterior aortic wall calcification 0-3, Posterior aortic wall calcification 0-3, total score for L1, 0-6*

*L2 = anterior aortic wall calcification 0-3, Posterior aortic wall calcification 0-3, total score for L2, 0-6*

*L3 = anterior aortic wall calcification 0-3, Posterior aortic wall calcification 0-3, total score for L3, 0-6*

*L4 = anterior aortic wall calcification 0-3, Posterior aortic wall calcification 0-3, total score for L4, 0-6*

All patients undergo a routine echocardiogram at 6 months to a year intervals and we used these reports to evaluate for the presence of vascular calcification.

### Statistical analysis:

Data was entered in Statistical Package for Social Sciences (SPSS) IBM version 21. Cleaning and coding were done before the evaluation of the data. Mean $\pm$  SD/median, IQR was obtained for continuous variables like age, lab parameter, calcification score, and duration on hemodialysis, while the frequency with percentage was calculated for categorical variables like gender, and co-morbid conditions. All continuous variables were categorized before analysis.

To observe the association of variables, which had a p-value of less than 0.001 was kept in binary logistic regression analysis, odds ratio with 95% CI was calculated and a p-value of <0.005 was considered significant.

### Results:

There was a total of 104 patients in our study, of which 56(53.8%) were males. The mean age was 45.7 $\pm$  14.2 (20-73) years. Most of our patients belonged to the middle socioeconomic group 96 (66.3%). The most prevalent cause of ESKD was DM in our patients 24 (23.1%), and almost all patients had AVF, n=101 (97.1%) for HD access. Abdominal aortic calcification was present in 27 (26%) patients while ECHO revealed calcification in 10 (9.6%) patients. The degree of calcification according to the Kauppila score is mentioned in Figure no 1. The majority of patients were using calcium carbonate and calcium supplements, n=73 (70.2%), Table 1. All laboratory parameters are shown in Table 2.

Older age was significantly associated with calcification, and the patients > 60 years of age had a maximum proportion of calcification of 11 (57.9%) out of 19 patients, as compared to the patients with < 40 years of age in whom only 2 (5.3%) patients had evidence of calcification out of 38 patients. The presence of comorbid conditions like DM, HTN, and IHD further predisposed the patients to the development of calcification [16 (51.6%), 26 (30.2%), and 8 (53.3%)] respectively and compared to the patients who did not have these comorbid [11 (15.1%), 1 (5.6%) and 19 (21.3%)] respectively. Patients with normal levels of serum calcium were more susceptible to calcification as compared to the low calcium 19 (33.8%) vs 8 (29.6%), although statistically insignificant. Likewise, the patients who were using calcium carbonate were more vulnerable to developing calcification than non-users [22 (30.1%) vs 5 (6.1%)]. All other variables had manifested no association with abdominal calcification.

The variables that were found to have some association with calcification were further analyzed in logistic regression analysis to find their amount of effect. The patients with an age of < 40 years were taken as the referent category, and it was observed that patients from 40 to 60 years of age were 7.6 times more likely to develop calcifications as compared to patients with an age of < 40 years. Similarly, patients > 60 years of age were 24.8 times more prone to the development of calcifications as compared to < 40 years. Hypertensive patients were 7.4 times more prone to calcifications compared to normotensives. Same as diabetic patients, who had 6 times more

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**Table:1 Demographic and clinical characteristics of 104 maintenance hemodialysis patients.**

Demographic and clinical characteristics of patients n= 104		n (%) Mean± SD/ Median (IQR)
Gender	Male/Female	56(53.8)/48(46.2)
Age		45.7± 14.2 /46 (21.8)
Socioeconomic status	Low	35(33.9)
	Middle	96(66.3)
Comorbid	HTN	86(82.7)
	DM	31(29.8)
	IHD	15(14.4)
	Thyroid disorder	1(1)
	MM	1(1)
Causes of ESKD	Unknown	42(40.4)
	DM	24(23.1)
	Stone disease	12(11.5)
	GN	11(10.6)
	HTN	6(5.8)
	Reflux disease	4(3.8)
	ADPKD	4(3.80)
Access of HD	MM	1(1)
	AVF	101(97.1)
Calcification	AVG	3(2.9)
	Abdominal Aortic evidence	27(26)
Medicine use	Echocardiographic evidence	10(9.6)
	Calcium carbonate	73(70.2)
	Calcitriol	81(77.9)
	Cinacalcet	4(3.8)
	Erythropoietin	92(88.5)
	Iron sucrose	89(85.6)
Duration of HD	Sevelamer	12(11.5)
		6.4 ± 4.5/ 5 (6.4)
Mean Kappouli score		4.3 ± 7.8/ 0 (8)

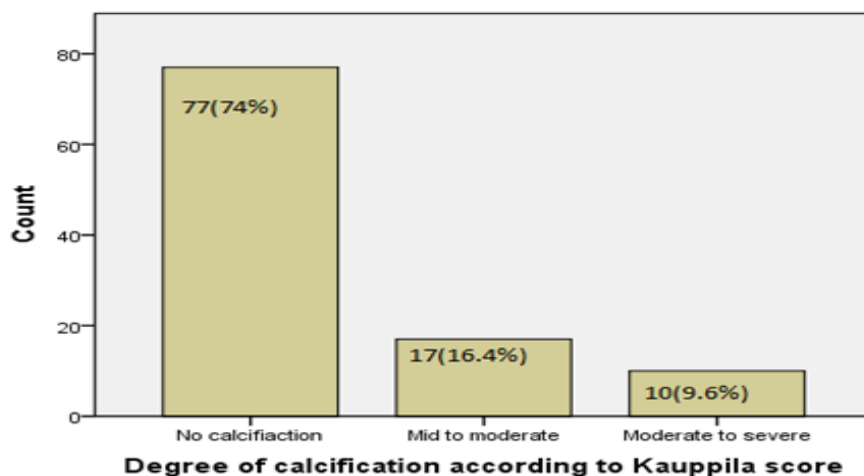
calcification than non-diabetics. In the same way, patients with IHD were 4.2 times more predisposed to the development of calcification as compared to those without IHD, and lastly, the patients who had low levels of serum calcium 59% developed less calcification as compared to patients with normal levels of calcium Table 3. Older age was significantly associated with calcification and the patients > 60 years of age had the maximum proportion of calcification 11 (57.9%) out of 19 patients as compared to the patients with < 40 years of age in whom only 2 (5.3%) patients had evidence of calcification out of 38 patients. Similarly, the presence of comorbid

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conditions like DM, HTN, and IHD predisposed the patients to the development of calcification [16 (51.6%), 26 (30.2%), and 8 (53.3%)] respectively, compared to the patients who did not have these comorbid [11 (15.1%), 1 (5.6%) and 19 (21.3%)] respectively. Similar was the case with the patients who had normal levels of serum calcium, who were then more susceptible to calcification as compared to the patients with low calcium 19 (33.8%) vs 8 (29.6%), although the p-value is marginally non-significant. Likewise, the patients who were using calcium carbonate had more vulnerability to developing calcification than non-users [22 (30.1%) vs 5 (6.1%)]. All other variables had manifested no association with abdominal calcification.

**Table 2:** Laboratory parameters of 114 maintenance hemodialysis patients at the time of inclusion.

Laboratory parameters	Mean $\pm$ STD	Median, IQR	Minimum	Maximum
Hemoglobin	11.1 $\pm$ 2.1	10.9, 2.8	7.7	18.8
Calcium	8.5 $\pm$ 0.8	8.5, 1.1	6.5	11
Phosphorus	4.1 $\pm$ 1.7	3.9, 2.6	0.7	8.2
Parathyroid hormone	463 $\pm$ 373	429, 457	17	2259
Vitamin D	31.3 $\pm$ 15.1	29.7, 15.7	8.8	92.3
Albumin	3.9 $\pm$ 0.5	4, 0.6	1.9	5
Alkaline phosphatase	167 $\pm$ 109.5	134.5, 85.3	47	754
Calcium Phosphorus product (CaXPO <sub>4</sub> )	35 $\pm$ 14.9	33.1, 21.5	5.5	72.6



**Figure 1.** Degree of calcification as calculated by Kauppila Score

The variables which were found to have some association with calcification were further analyzed in logistic regression analysis to find their amount of effect. The patients with an age of < 40 years were taken as referent category and observed that the patients from 40 to 60 years of age had 7.6 times more developed calcification as compared to patients with an age of < 40 years. Similarly, the patients > 60 years of age had 24.8 times more developed calcifications as compared to < 40 years. Hypertensive patients were 7.4 times more prone to calcifications compared to normotensives. Same as diabetic patients had 6 times more calcification than non-diabetics. In the same way, patients with IHD were 4.2 times more predisposed to the development of calcification as compared to those without IHD, and lastly, the patients who had low levels of serum calcium 59% developed less calcification as compared to patients with normal levels of calcium Table 3.

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After observing the individual effect of all the variables, we ran a multivariate logistic regression analysis and found that the effect of age on calcification was low, as the patients in the age group of 40 to 60 years had 3.9 times more calcification as compared to patients of age <40 years. However, this effect became insignificant when adjusted with other variables. Similarly, the odds ratio of patients of more than 60 years also decreased to 12.1 times but remained significantly the same as the effect of all comorbid conditions decreased when adjusted in multivariable analysis and the p-value became insignificant Table 4.

**Table:3** Association of variables with abdominal aortic calcification among 114 maintenance hemodialysis patients.

Variables		Abdominal Aortic Calcification			P value
		Yes n (%)	No n (%)	Total n (%)	
Age	<40 years	2 (5.3)	36(94.7)	38(36.5)	<0.001
	40-60 years	14(29.9)	33(70.2)	47(45.2)	
	>60 years	11(57.9)	8(42.1)	19(18.3)	
Gender	Male	13(23.2)	43(76.8)	56(53.8)	0.49
	Female	14(29.2)	34(70.8)	48(46.2)	
Duration of HD	<10 years	22(27.2)	59(72.8)	81(77.9)	0.601
	≥ 10 years	5(21.7)	18(78.3)	23(22.1)	
DM	No	11(15.1)	62(84.9)	73(70.2)	<0.001
	Yes	16(51.6)	15(48.4)	31(29.8)	
HTN	No	1(5.6)	17(94.4)	18(17.3)	0.03
	Yes	26(30.2)	60(77.9)	86(82.7)	
IHD	No	19(21.3)	70(75.7)	89(85.6)	0.001
	Yes	8(53.3)	7(46.7)	15(14.4)	
Calcium	Normal	19(33.8)	38(66.7)	57(54.8)	0.059
	Low	8(29.6)	39(50.6)	47(45.2)	
Phosphorus	Normal	14(27.5)	37(72.5)	51(49)	0.877
	Low	7(22.8)	24(77.4)	31(29.8)	
	High	6(27.3)	16(72.7)	22(21.2)	
PTH	Normal	6(27.3)	16(72.7)	22(21.2)	0.439
	Low	7(36.8)	12(63.2)	19(18.3)	
	High	14(22.2)	49(77.8)	63(60.6)	
CaPO4 product	Normal	24(25.8)	69(74.2)	93(88.5)	0.916
	High	3(27.3)	8(72.7)	11(10.6)	
Sevelamer use	No	25(27.2)	67(72.8)	92(88.5)	0.435
	Yes	2(16.7)	10(83.3)	12(11.5)	
Calcitriol use	No	4(14.7)	19(82.6)	23(22.1)	0.288
	Yes	23(28.4)	58(71.6)	81(77.9)	
Cinacalcet use	No	26(26)	74(74)	100(96.2)	0.964
	Yes	1(25)	3(75)	4(3.8)	
Ca carbonate use	No	5(16.1)	26(83.9)	31(29.8)	0.136
	Yes	22(30.1)	51(69.9)	73(70.2)	

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### Discussion:

This is the first study that evaluates vascular calcification in HD patients in the Pakistani population. Overall, 26% of our hemodialysis population has shown abdominal aortic wall calcification, while 9.6% of the patients have echocardiographic findings suggestive of valvular calcification. This is quite different from the reports published in other countries.

**Table:4** Amount of effect of variables on the development of calcification among 114 maintenance hemodialysis patients.

Clinical parameters		Univariate logistic regression			Multivariate logistic regression		
		Odds ratio	95% CI lower-Upper	P value	Odds ratio	95% CI lower-Upper	P value
Age	40-60 years	7.6	1.6 - 36.2	0.01	3.9	0.74 - 20.6	0.101
	>60 years	24.8	4.6 - 134.2	<0.001	12.1	1.9 - 76.6	0.008
Hypertension		7.4	0.93 - 58.3	0.058	6.2	0.67 - 57.7	0.109
Diabetes mellitus		6	2.3 - 15.6	<0.001	2.2	0.68 - 7.4	0.183
Ischemic heart disease		4.2	1.4 - 13.1	0.013	2.5	0.6 - 10.1	0.214
Serum Calcium		0.41	0.16 - 1.1	0.063	0.46	0.15 - 1.4	0.179

The prevalence of abdominal aortic calcification (AAC) is reported to be 70.7% (70.8% among dialysis patients) in a recent study. This multicentric, cross-sectional study was primarily aimed to determine the prevalence of AAC detected by plain lateral abdominal radiograph and secondarily aimed to assess predictive factors for AAC. Lumlertgul and Kantachavesiri et al evaluated 1500 patients, aged 18 – 70 years, with CKD stages 3 – 5D for  $\geq 3$  months prior to the evaluation, and were enrolled at 24 study centers in Thailand; 54.3% were non-dialysis patients. The prevalence of AAC was 70.6% and 70.8% in non-dialysis and dialysis patients, respectively.<sup>10</sup> Using the same calcification evaluation, Toussaint et al. reported 94.4% prevalence in Australian hemodialysis patients (mean age 69 years, maximal age 90 years). They performed the lateral lumbar X-ray of the abdominal aorta to determine AAC, which is related to the severity of calcific deposits at lumbar vertebral segments L1 to L4.<sup>11</sup> Honkanen et al. as well reported a prevalence of 81% AAC in 933 dialysis patients (mean age 61.4 years). In a cross-sectional study conducted in 47 centers in six European countries with a population of 93 patients, they concluded that AAC detected by lateral lumbar radiograph was associated with several risk factors of uremic calcification. They suggested that this semi-quantitative method is more widely available and less expensive than the current procedures for studying calcification and could form part of a pre-transplant workup and cardiovascular risk stratification.<sup>12</sup> In another recent study of a Japanese cohort of 347 patients not on dialysis (mean age  $67.4 \pm 12.3$  years), with a more advanced measurement method of non-contrast CT scan, Tatami et al, reported an AAC prevalence of 86.3%.<sup>13</sup> Factors for these discrepancies in prevalence remain unknown but are likely attributable to the difference in the study population's age and ethnicity. Another speculation is the dietary difference. WHO Food Cluster Diets reports remarkable differences in milk- and processed food consumption, which may contain different calcification-inducing and/or suppressing factors, among the Caucasian and Asian clusters.<sup>14</sup> It can be worth discussing another noticeable point of the current data showing a significant sagging down of prevalence data among the CKD5-ND (CKD5 not on dialysis) population.

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The mean age of our population is  $45\pm 14.2$  while the median age is 46 years. The age of our population is younger as compared with the other population reported. For example, in a cohort of 101 adult Japanese pre-dialysis patients, Honada and Ando reported the median age of their cohort to be  $66.6\pm 13.3$  years.<sup>15</sup> Similarly, in a prospective observational study at the University of Kangnam Sacred Hospital Korea, the mean age of their cohort was  $58.2\pm 17$  years.<sup>16</sup> In the same way, the average age of HD patients in North America is 64 years.<sup>17</sup> According to the Pakistan Bureau of Statistics, the average age of the Pakistani population is 22.8 years.<sup>18</sup> The low average of our cohort reflects the overall low mean age of the population. There is a dwindling number of patients aged more than 60 years in our study population.

There is a slight predominance of male patients in our study which is similar to another reports.<sup>11-13</sup> The majority of our patients belong to the middle and low socioeconomic groups, possibly due to the philanthropic nature of our hospital, which runs on religious donations and funds.

Comorbid conditions like DM and HTN are reported to be associated with increased vascular calcification. We also found the same effect of increased calcification in those who had DM, but on multivariate analysis, this significance is lost. DM as we know has long been known for its association with arteriosclerotic disorder presenting with calcification, so-called Mönckeberg's arteriosclerosis.<sup>19</sup> Significantly higher AAC prevalence in the DM sub-group in the current study, as compared with its non-DM counterpart (84.7% vs. 58.8%) strongly supports this notion, far advancing into the CKD population. In accordance, several published reports have documented vascular calcification percentages within a range of 54% – 93% among DM patients, versus 25% – 54% among non-DM counterparts, who were either at early-or late-stage CKD.<sup>20-21</sup> The role of phosphorus is quite straightforward for pathological mechanisms and has further implications.<sup>22</sup> However, the role of vitamin D is still debatable as the association between vitamin D disorders and vascular calcification seems to be U-shaped in general CKD, i.e., if it is too low, it mediates pro-inflammation to which calcification is indirectly enhanced, as well as too high, whereby it directly promotes the calcification.<sup>23,24</sup> Our finding, which is focusing specifically on CKD patients with DM, is a reflection that the pro-inflammation led by vitamin D depletion is outweighed by pathological mechanisms in this group.

In our cohort, in patients with low levels of serum calcium, 59% of them developed less calcification as compared to patients with normal levels of calcium. This indicates that the patients who had normal calcium levels had a higher incidence of calcification. Lumlertgul and Kantachuesiri also reported the same.<sup>10</sup> Clinical evidence to date has not much-associated serum calcium and calcification in CKD patients; Raggi et al, reported a non-significant trend for increased carotid artery calcification in adult hemodialysis patients with higher serum calcium.<sup>25</sup> Nevertheless, similar associations have been found in some non-CKD contexts, for example, Rubin et al, described a relationship between serum calcium and increased carotid plaque thickness in a general population cohort (N = 1194).<sup>26</sup> In another study, Bolland et al used multivariate logistic regression to analyze data from 1471 postmenopausal women and identified serum calcium as a predictive factor for AAC with an odds ratio of 1.23.<sup>27</sup>

### Conclusion:

We found overall a low frequency of vascular and valvular calcification in our ESKD patients on hemodialysis, as compared with most literature reported. The higher age of the patients is the most significant factor associated with increased vascular calcification in our hemodialysis cohort. The other important outcome that we found was vascular calcification at normal calcium levels. We did not find an association of DM with increased calcification in multivariate analysis.

**Conflict of Interest:** None declared

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