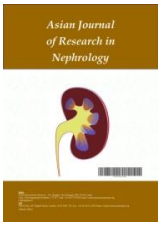

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Vascular and Valvular Calcification in Diabetic Patients with or without CKD

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Authors' contributions

This work was carried out in collaboration between the two authors. Author DKC conceptualized the study, collected data, did literature search, collaborated for statistical analysis and prepared the first draft. Author BMC re-analyzed the draft and extracted information to prepare this paper, did sample size calculation, defined sampling technique, analyzed data, prepared some graphs and charts, did literature search to include recent references, reviewed, revised and prepared manuscript for submission. Both authors read and approve the final manuscript.

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ABSTRACT

Introduction: Chronic kidney disease (CKD) is associated with atherosclerosis, heart failure, valvular heart disease, arrhythmia, cardiovascular calcification, and sudden cardiac death. The calcification of the cardiovascular system increases as CKD progresses and is associated with increased morbidity and mortality.
This study was undertaken to assess vascular calcification and its risk factors in diabetics with early CKD.
Methods: This is a prospective, observational study. Data analysis of the outcomes was done by SPSS-17 version. Patients were enrolled from the nephrology out-patient/ in-patient department at St Johns Medical College hospital, Bangalore. Patients were studied between July 2010 to July 2012 for a period of 2 years.
Study Population: The study population included 60 diabetic patientswere divided into 2 groups (Group A- diabetic patients with normal renal functions; Group B- diabetic patients with CKD) in 1:1 ratio after matching the age, duration of diabetes and history of smoking.

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Results: In this study we observed that vascular and valvular calcification were significantly higher in the Group B (diabetics with CKD) as compared to Group A (diabetics with normal renal functions). Higher serum phosphorous levels and lower mean eGFR levels showed significant correlation with vascular calcification in Group B.
A significant correlation was found between lower mean eGFR levels and vascular calcification in Group B. Also, correlation was found to be significant between vascular calcification and valvular calcification in Group B.

Keywords: Vascular calcification; cardiac valve calcification; aortic calcification; Kauppila score; chronic kidney disease; diabetes.

1. INTRODUCTION

Factors like elevated calcium–phosphorus product [Ca x P], anemia, oxidative stress, inflammation and advanced glycation end-products are associated with increased cardiovascular calcification, most notably in the coronary arteries [1-3]. Microinflammation is detected in early stages of CKD, and is associated with vascular calcification [3,4]. However, it is well recognized that calcification occurs throughout the arterial tree and in the cardiac valves (aortic and mitral) and myocardium [5].

Patients with CKD have a more than two-fold higher rate of all forms of cardiovascular calcification than patients without CKD. Vascular calcification, specifically arterial calcification, has been recognized for many years as a common complication of chronic kidney disease (CKD) [6]. Once CKD is present, there appears to be a marked acceleration in the rate and magnitude of cardiovascular calcification, thus making this change in the cardiovascular system one of the most recognized differences between those with and without CKD [7].

The diagnosis of CKD–MBD (mineral and bone disorder) includes the detection of extraosseous calcification, including arterial, valvular, and myocardial calcification. It is generally well recognized that the prevalence of calcification increases with progressively decreasing kidney function and is greater than that in the general population [8]. Cardiovascular calcification is associated with, and predictive of, adverse clinical outcomes, including cardiovascular events and death [9].

Medial calcification causes arterial stiffness, which may result in an elevated pulse pressure and increased pulse wave velocity (PWV), and may contribute to left ventricular hypertrophy, dysfunction and failure. Furthermore, an advanced calcification of the heart valves may lead to dysfunction contributing to heart failure and an increased risk of endocarditis. Cardiovascular calcifications are usually progressive, and their extent and severity are highest in patients with CKD. Recent reports suggest an increased prevalence of cardiovascular calcification in patients at early stages of CKD. Thus, a considerable percentage of CKD patients are at risk of cardiovascular events from vascular calcification [1,9,10].

In our study we compared vascular and cardiac valve calcification in diabetic patients with normal renal function and diabetic patients with chronic kidney disease.

2. METHODS

2.1 Source and Method of Collecting Data

Sixty patients attending the nephrology out-patient/ in-patient department at St Johns Medical College hospital, Bangalore, were included in the study.

2.2 Duration of Study

Patients were studied between July 2010 to July 2012 for a period of 2 years.

2.3 Inclusion Criteria

1. Diabetics (type 1 or type 2) with early CKD.
2. Diabetics with normal renal functions.

2.4 Exclusion Criteria

1. Patients with acute renal failure.
2. Patients receiving maintenance dialysis.
3. Renal transplant recipients.
4. Patients who currently are taking or who within the last five years had been taking medication known to influence bone mineral metabolism [such as corticosteroids, other immunosuppressive agents, hormone replacement therapy (HRT), vitamin D analogs, calcium

supplements, phosphate binders, anticoagulants or lithium].
5. Prolonged bedridden patients.
6. Patients with age less than 18 years and more than 60 years.
7. Other causes of vascular calcification like tuberculosis, sarcoidosis, multiple myeloma.

2.5 Criteria for CKD Diagnosis

Abnormalities of kidney structure or kidney function (as assessed by markers of kidney damage and/or eGFR of less than 60 ml/min/1.73m2) present for more than 3 months.

Markers of kidney disease: albuminuria (albumin creatinine ratio > 3 mg/mmol), hematuria (confirmed renal origin), electrolyte abnormalities due to tubular disorders, renal histological abnormalities, structural abnormalities detected by imaging (e.g. polycystic kidneys, reflux nephropathy) or a history of kidney transplantation.

Stages of CKD are given in Table1.

2.6 Study Design

It was a prospective, observational study. Data analysis of the outcomes was done by SPSS-17 version.

2.7 Participants

Sixty diabetics were studied for vascular calcification and were divided into 2 groups after matching the age, duration of diabetes and history of smoking.

Thirty diabetics with normal renal functions were assigned as Group A.

Thirty diabetics with early CKD (stage 2 to 3) were assigned as Group B.

2.8 Procedures

- Vascular calcification detected in lateral abdominal X-ray was compared with valvular calcification by 2D echo only in Group B.
- Vascular calcification was detected by lateral abdominal X-ray and scored using Kauppila scoring system.

To calculate the *Kauppila score*, a lateral lumbar spine X-ray was taken for each patient. A semiquantitative scoring system was used to assess the calcifications in the anterior and posterior aortic walls by observing the four segments corresponding to the areas in front of each of the first four lumbar vertebrae. Each segment was assigned a score for anterior wall calcifications and a score for posterior wall calcifications. Scores ranged between 0 and 3 (0 = no calcification, 1 = irregular punctate calcifications, 2 = localized linear calcifications, 3 = linear calcifications spanning the length of the vertebra). The total score of a patient was calculated as the addition of the partial scores and ranged from 0 to 24.

2.9 Statistical Analysis

2.9.1 Statistical test used

Mean of the continuous data were compared with the student t test and multivariable data were compared with multivariate analysis.

Null Hypothesis:was used when there was no significant difference in the mean value between two groups i.e. $\mu1=\mu2$

Alternate Hypothesis:was used when there was a significant difference in the mean value between two groups i.e. $\mu1\neq\mu2$

Level of Significance:$\alpha=0.05$

Decision Criterion:P-Value was compared with the level of significance. If $P < 0.05$, null hypothesis was rejected, and the alternate hypothesis was accepted. If $P \geq 0.05$, null hypothesis was accepted.

Spearman's Rank Correlationwas used to compare eGFR with vascular calcification scores.

Table 1. CKD stages

CKD Stage	Description
CKD stage 1	Kidney damage with normal renal function, eGFR ≥ 90 ml/min/1.73m^2
CKD stage 2	Mild loss of kidney function as shown by abnormal biochemical markers, eGFR 60-89 ml/min/1.73m^2
CKD stage 3	Moderate loss of renal function, eGFR 30-59 ml/min/1.73m^2
CKD stage 4	Severe loss of renal function, eGFR 15-29 ml/min/1.73m^2
CKD stage 5	End stage renal disease (ESRD), eGFR less than 15 ml/min/1.73m^2

3. RESULTS

Vascular calcification in diabetics with normal renal function (Group A) and diabetics with early CKD (Group B) were assessed and compared.

The study groups consisted of predominantly males (80% in group A, and 63% in group B). The gender and age distribution of patients in the two groups is shown in Tables 2 and 3.

Table 2. Gender distribution of patients in group A and group B

Group	Male		Female		Total of n
	n	%	n	%	
Group A	24	80	6	20	30
Group B	19	63	11	37	30
Total	43	72	17	28	60

n: number. %: percentage. Group A: diabetics with normal renal function. Group B: diabetics with chronic kidney disease

Most of the patients in the two groups (A and B) were non-smokers. The numbers are shown in Table 4.

Mean duration of diabetes mellitus in group A was 6.2 years, and in group B was 7.5 years. The duration of diabetes in the two groups was comparable.

Vascular calcification was found to be significantly higher in the Group B as compared to Group A (P=0.001), as shown in Table 5, and Fig 1.

A significant number of patients in Group B (diabetics with chronic kidney disease) had cardiac valvular calcification as compared to Group A (diabetics with normal renal function) (P=0.04), as depicted in Table 6 and Fig. 2.

Mean corrected calcium levels were lower in patients with vascular calcification, however the correlation between these two was not significant (Fig. 3).

A significant correlation was found between higher serum phosphorous levels and vascular calcification in Group B (diabetic CKD group) (P<0.01) (Fig. 4).

A significant correlation was found between lower mean eGFR levels and vascular calcification in Group B (diabetic CKD) (P<0.01) (Fig. 5).

Table 3. Age distribution of patients in group A and B

Group	Gender	Count	Mean*	Median*	Minimum*	Maximum*
Group A	Male	24	46.67	47	41	50
	Female	6	44	43.5	41	48
Group B	Male	19	46.16	46	41	50
	Female	11	46	47	41	50

** Age in years. Group A: diabetics with normal renal function. Group B: diabetics with chronic kidney disease*

Table 4. Distribution of smokers and non-smokers in the two groups

Group	Group A		Group B		Total of n
	n	%	n	%	
Non-smokers	25	83	23	77	48
Smokers	5	17	7	23	12
Total	30	100	30	100	60

n: number. %: percentage. Group A: diabetics with normal renal function. Group B: diabetics with chronic kidney disease

Table 5. Vascular calcifications seen on lateral abdominal X-rays of patients in group A and group B

Group	Group A		Group B		Total of n	χ^2	P value
	n	%	n	%			
Group A	1	3	29	97	30	10.417	0.001
Group B	11	37	19	63	30		
Total	12	20	48	80	60		

n: number. %: percentage. VC: vascular calcification. Group A: diabetics with normal renal function. Group B: diabetics with chronic kidney disease

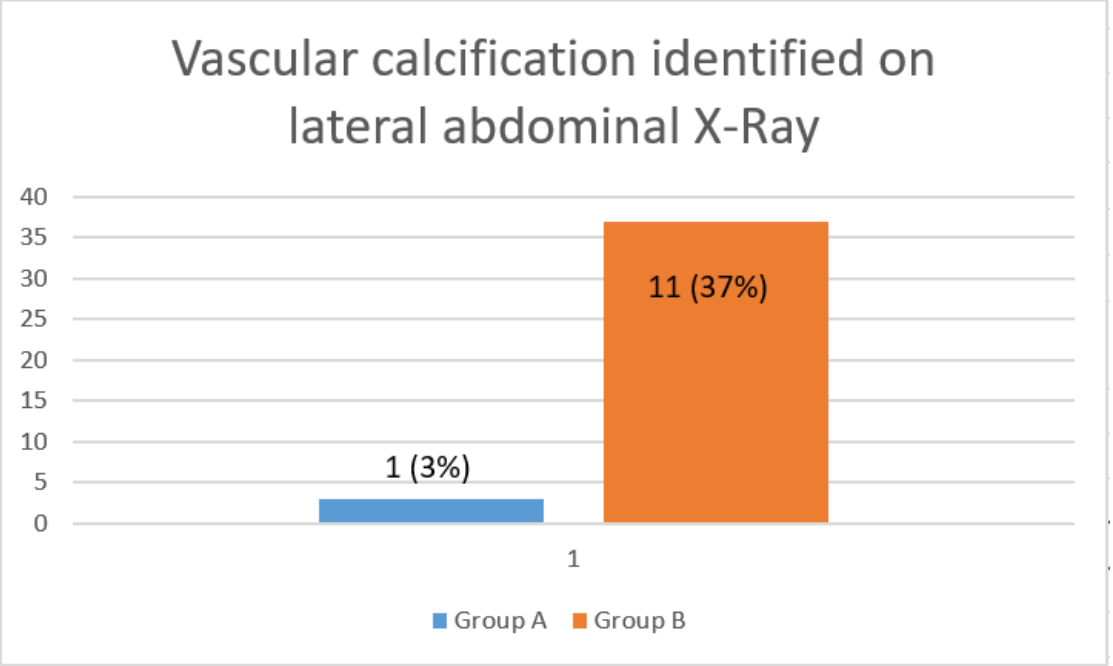

Fig. 1. Vascular calcification in group A (diabetic, normal renal functions) and group B (diabetic CKD)

Table 6. Calcified cardiac valves found on 2D Echocardiography in groups A (diabetics with normal renal function) and B (diabetics with chronic kidney disease)

Group	Calcified Cardiac Valve		No calcification		Total of n	
	n	%	n	%		
Group A	5	17	25	83	30	P value: 0.04
Group B	14	47	16	53	30	
Total	19	31.7	41	68.3	60	

n: number. %: percentage

Correlation was found to be significant between vascular calcification on X-Ray and valvular calcification on 2D Echo in Group B (diabetic CKD) (P=0.003).

4. DISCUSSION

There are various methods of screening vascular and valvular calcifications such as ultrasonography, ECHO, electron beam computed tomography, multi slice computed tomography and plain X ray. These methods vary in sensitivity and specificity as well as in their capacity to differentiate the type of calcification [1].

Agatston score (popularly called calcium score) for coronary artery calcification, Kauppila index for aortic calcification in abdomen, and Adragao score for lower abdominal aorta and peripheral arteries are commonly used in research for quantitative assessment of vascular calcification and risk stratification [1].

We used semi quantitative assessment of vascular calcifications with plain X-ray as it has the advantages of being the simple, cheap and applicable in daily clinical practice, which has been validated in several studies. We used Kauppila score for assessing aortic calcification in abdomen.

There are many studies which have assessed vascular calcification in advanced chronic kidney disease (CKD). However, very few studies have assessed vascular calcification in early CKD.

As diabetics without complications are also more prone for vascular calcification, we subdivided the study group into diabetics without CKD (group A) and diabetics with early CKD (group B).

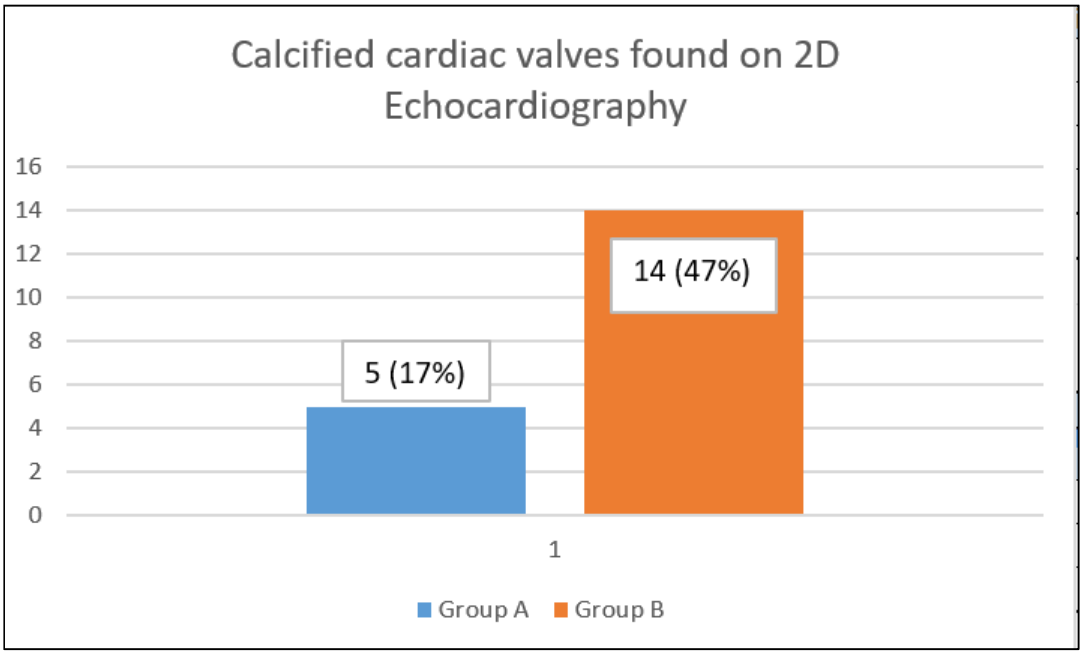

Fig. 2. Calcified cardiac valves found on 2D Echocardiography in groups A (diabetics with normal renal function) and B (diabetics with chronic kidney disease)

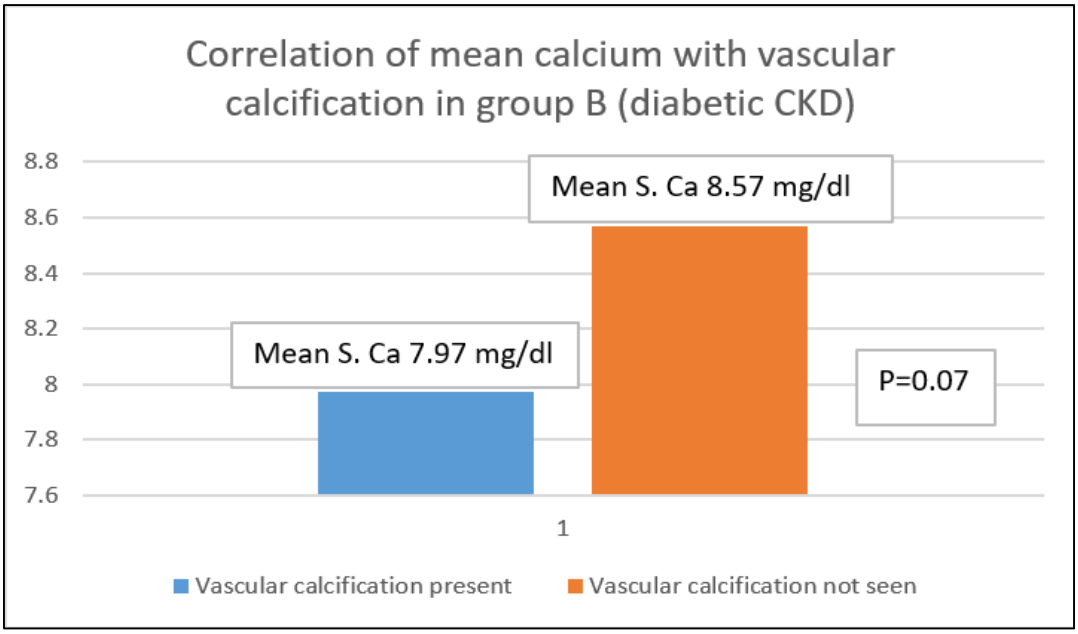

Fig. 3. Correlation of mean serum calcium level with vascular calcification in group B (diabetic CKD)

Student's' t test was used for testing the hypothesis considering difference between sample means

On comparing both the groups, the mean age and sex distribution was similar. Mean age of patients in group A was 45±2 years and in group B was 46.2±2 years. A significant male predominance was observed in both the groups with male to female ratio of (80:20) in Group A and (63:37) in Group B.

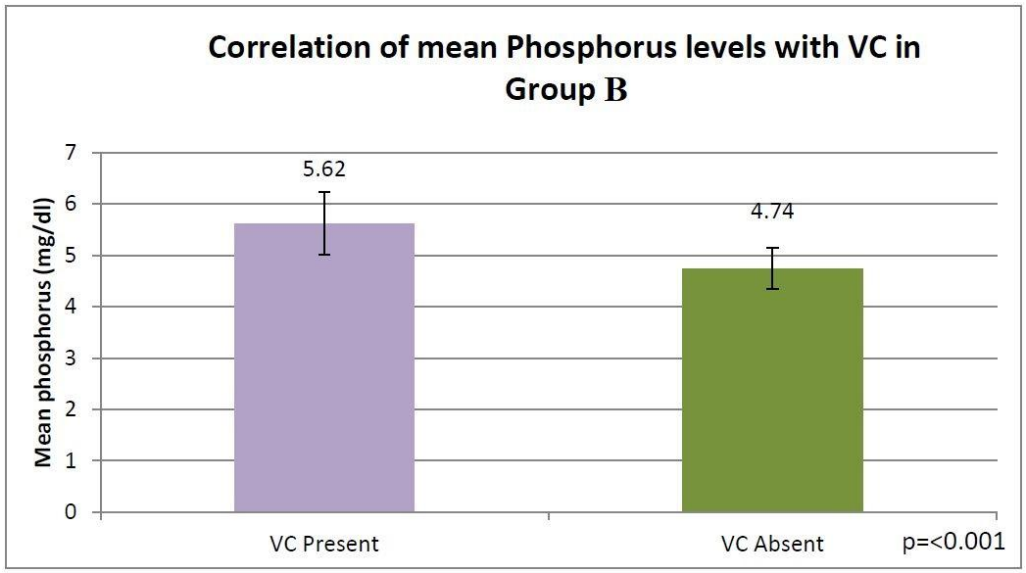

Fig. 4. Correlation of mean serum phosphorus level with vascular calcification (VC)
Student's' t test was used for testing the hypothesis considering difference between sample means

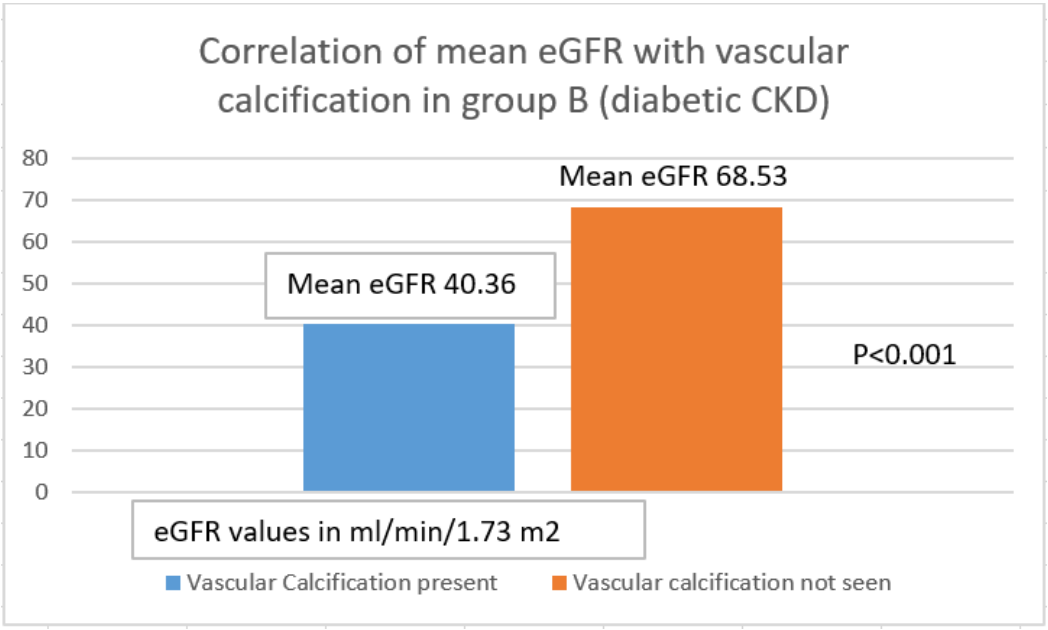

Fig. 5. Correlation of mean eGFR with vascular calcification in group B (diabetic CKD)

The prevalence of vascular calcification was found to be significantly higher in Group B (37%) as compared to Group A (3%) with (p=0.001) as determined by lateral abdominal X ray, indicating that early chronic kidney disease is an independent risk factor for vascular calcification.

Since vascular calcification can be of varying severity, a scoring system developed by Kauppila et al was adopted in our study and scoring of >7 was associated with severe vascular calcifications.

Vascular calcification was detected in 37% of patients and the Kauppila score of >7 was detected in 45% of the study group (group B, diabetic CKD).

The risk factors for vascular calcification in our study were found to be lower levels of eGFR (p=0.001) (Fig. 5) and higher mean phosphorus levels (p=<0.001) (Fig. 4).

Mean calcium (Fig. 3), vitamin D and iPTH levels did not correlate with vascular calcification in our study.

We also found patients having vascular calcification on X ray also had cardiac valvular calcification on 2D ECHO.

Aortic valve calcification was found in 17% and mitral valve calcifications was found in 16% of patients in our study (group A + group B).

5. CONCLUSION

Thirty diabetics with normal renal functions (group A) were compared with diabetics with early CKD (group B) for vascular calcification. In this study we found that vascular calcification was significantly higher in the group B. In diabetics with early CKD (group B), vascular calcification (detected on lateral abdominal X-ray) was found to be associated with the cardiac valvular calcification (detected on 2D echo).

Vascular calcifications can be detected by lateral abdominal X ray in CKD as early as stage 2 to 3, with high phosphorous levels and lower eGFR being risk factors for vascular calcification.

6. LIMITATIONS OF THE STUDY

1. While comparing Vascular Calcification in Group A and Group B, hypertension and serum lipids were not compared, as most of the patients in the study group were on treatment and this could be confounding factor.
2. Vascular Calcification Scores in Group A and Group B were not done by a single radiologist and therefore could have subjective variability.

CONSENT

Written informed consent obtained before enrolling the patient into the study.

ETHICAL APPROVAL

Hospital ethical committee clearance was obtained.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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