ORIGINAL ARTICLE

COMPARISON OF VASCULAR CALCIFICATION AND MINERAL BONE DISEASE IN NON-DIALYSIS (CKD4/5ND) VS DIALYSIS DEPENDENT (CKD5D) PATIENTS

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Background: Chronic kidney disease (CKD) has been a highly prevalent medical condition in all parts of the world affecting the haemostasis of the body in number of ways. Epidemiological data suggest that no region of the world has been spared from this condition and both developing and developed countries equally share the burden of this disease. Objective was to compare the vascular calcification and mineral bone disease in non-dialysis vs dialysis patients suffering from chronic kidney disease at a tertiary care hospital of Pakistan. It is a Comparative study, conducted at the Department of nephrology Pak Emirates Military Hospital Rawalpindi. Four months from November 2020 to February 2021. **Methods:** A total of 310 cases were included in the study, which were diagnosed as chronic kidney disease in nephrology department by a consultant nephrologist on basis of National Kidney Foundation/Kidney Disease Outcome Quality Initiative (NKF/KDOQI) 2002. They were divided into two equal groups by block randomization. Group I had the patients who were not dependent on dialysis (CKD4/5ND) while group II had dialysis dependent patients. Abdominal aorta, mitral and tricuspid valves were assessed to look for vascular calcification. Calcium, phosphate and parathyroid hormone levels were done to assess the mineral bone profile. **Results:** Out of 310 patients, 192 (61.9%) patients were males and 118 (38.1%) were females. Ninty-eight (31.6%) had evidence of vascular calcification while 212 (68.4%) did not have vascular calcification. 147 (47.4%) had hypocalcaemia, 167 (53.8%) had hyperphosphatemia while 98 (31.6%) patients had raised Parathyroid hormone levels. Regression analysis revealed that vascular calcification and abnormal mineral bone profile was significantly present more among patients who were dependent on dialysis (p-value<0.05). **Conclusion:** Bone mineral disease and vascular calcification were consistent findings among patients suffering from chronic kidney disease. Patients who were dependent on dialysis were more prone to develop these complications as compared to those who were not dependent on dialysis.

Keywords: Bone mineral disease; Chronic kidney disease; Dialysis; Vascular calcification

Citation: Salahuddin, Azam MN, Raja KM, Mir AW, Tahir T, Khan FR, e*t al.* Comparison of vascular calcification and mineral bone disease in non-dialysis (CKD4/5ND) vs dialysis dependent (CKD5D) patients. J Ayub Med Coll Abbottabad 2022;34(1):118–21.

INTRODUCTION

Chronic kidney disease (CKD) has been a highly prevalent medical condition in all parts of the world affecting the haemostasis of the body in number of ways.[1] Epidemiological data suggest that no region of the world has been spared from this condition and both developing and developed countries equally share the burden of this disease.[2,3] Multiple options have been in use to manage this chronic debilitating condition ranging from life style changes to renal replacement therapies and transplants.[4]

Patients with chronic renal diseases have been prone to develop number of biochemical and haematological abnormalities.[5]Bone mineral disease is an umbrella term often used to cover the salt and electrolyte abnormalities encountered by these patients.[6] Various tissues of the body become sites of calcium deposition and lose their structural and functional role in the body. All the modalities used for treatment of chronic kidney disease including dialysis have role to regulate this imbalance and slow down the process of calcification.[4]

Extra renal manifestations especially pertaining to mineral bone profile and calcification of various sites have been studied extensively. Iseri *et al* published an interesting paper in 2020 regarding bone mineral density and mortality associated with these parameters among patients suffering from chronic kidney disease. They concluded that patients with end stage renal disease had significant metabolic alterations that affected essentially all organ of the body including the bones. There was increased risk of fractures, vascular calcification, arteriosclerosis and increased mortality among these patients.[7] Peeters *et al.* conducted an interesting study in 2017 and used X ray to look for abdominal aortic calcification among

patients suffering from non-dialysis dependent chronic kidney disease. They revealed that more than 70% of patients had some level of aortic calcification and old age, previous CVS abnormalities and other metabolic abnormalities predicted the presence of aortic calcification among the study population.[8] Leskinen *et al*. in 2009 studied valvular calcification and its relationship with presence of atherosclerosis among patients suffering from chronic renal disease. Their findings were that 31% pre-dialysis and 50% of dialysis patients had findings of either mitral or aortic valve calcification on echocardiography. Duration of dialysis and presence of diabetes mellitus were independent risk factors for valvular calcification in their study participants.

Extra-renal manifestations are very important to be assessed and addressed in order to manage the patients of CKD and improve their overall quality of life. A local study published in 2019 regarding abnormalities related to serum calcium, phosphorus, calcium phosphorus product and PTH levels among patients undergoing maintenance haemodialysis concluded that majority of patients undergoing maintenance haemodialysis did not have these parameters in target range. Limited work has been done to compare the dialysis and pre-dialysis patients for bone mineral disease and vascular calcification in Pakistan. We therefore planned this study with the rationale to compare the vascular calcification and mineral bone disease in non-dialysis vs dialysis patients suffering from chronic kidney disease in our hospital.

MATERIAL AND METHODS

This comparative study was conducted at the department of nephrology in Pak Emirate Military Hospital Rawalpindi from November 2020 to February 2021. Sample size was calculated by WHO Sample Size Calculator with population prevalence proportion of abdominal aortic calcification as 73%.[11] Non probability Consecutive sampling technique was used to gather the sample. All patients of CKD IV and V who were either dependent or not dependent on dialysis between the age of 18 and 65 were included in the study. Diagnosis and staging of CKD were done as per National Kidney Foundation/Kidney Disease Outcome Quality Initiative (NKF/KDOQI) 2002.[12] Exclusion criteria were the patients with any valvular and vascular disease prior to diagnosis of CKD, malignancies (solid or haematological), severe infection or any organ failure other than kidneys in past six months. Patients who had any autoimmune disorder or those who had dialysis secondary to any illness other than CKD or those having rickets or osteomalacia were also not included in the study. Patients with other comorbid diseases causing derangement of calcium, magnesium, phosphate, Vitamin D, PTH or ALP were also excluded from the study. Ethical review board committee of the hospital was approached to get the ethical approval for this study via letter no (A/28/EC/214/2020). Written informed consent was taken from all the potential participants of this study before the start of study after complete description of the study. CKD patients fulfilling the above-mentioned inclusion and exclusion criteria managed at nephrology department of our hospital were included in the study. Venous blood was taken from the participants between 9 and 11 a.m. Serum calcium, phosphate and PTH levels were measured according to the standard methods at hospital laboratory. Reference ranges were as follows:[13]

Ionized Calcium (iCa): 1.15–1.33 mmol/L
Phosphate (PO4): 0.8–1.62 mmol/L
PTH (Parathyroid hormone): 0.8–6 pmol/L

X ray abdomen was performed by consultant radiologist to assess the presence of calcification. A semi-quantitative scoring system, as described by Kauppila *et al*.[14] was used ranging from 0 to 24 points. Score of >4 was used to identify presence of aortic calcification among our study participants. Echocardiography was performed by consultant cardiologist to look for calcification of aortic, mitral or tricuspid valve in study participants. Characteristics of participants were described by using the descriptive statistics. Chi-square was applied to look for the statistically significant difference for hypocalcaemia, hyperphosphatemia, raised PTH and presence of vascular calcification in the two study groups. Once it was established then extent was determined by the binary logistic regression analysis. All statistical analysis was performed using Statistics Package for Social Sciences version 24.0 (SPSS-24.0). Differences between groups were considered significant if *p*-values were less than or equal to 0.05.

RESULTS

Target population was all the dialysis and non-dialysis dependent CKD patients but after the application of inclusion and exclusion criteria and consent of the individuals 310 patients were finally recruited in the study from whom data could be collected and analysed. Out of 310 patients 192 (61.9%) patients were males and 118 (38.1%) were females. Mean age of the study participants was 44.51±7.442 years and mean duration of CKD was 4.47±2.366 years. 98 (31.6%) had evidence of vascular calcification while 212 (68.4%) did not have vascular calcification. 147 (47.4%) had hypocalcaemia, 167 (53.8%) had hyperphosphatemia

while 98 (31.6%) patients had raised Parathyroid hormone levels. Table-1 shows that after application of chi-square analysis, vascular calcification and abnormal mineral bone profile was significantly present more among patients who were dependent on dialysis (p-value<0.05). Table-2 shows that binary logistic regression analysis confirmed the statistics generated by chi-square analysis.

Table-1: Study parameters in both groups

Factors studied	Non-dialysis dependent patients	Dialysis dependent patients	*p*-value
Hypocalcaemia			
No	95 (61.2%)	68 (43.8%)	0.002
Yes	60 (38.8%)	87 (56.2%)	
Hyperphosphatemia			
No	89 (57.4%)	54 (34.8%)	<0.001
Yes	66 (42.6%)	101 (65.2%)	
Vascular calcification			
No	120 (77.4%)	92 (59.3%)	0.001
Yes	35 (22.6%)	63 (40.7%)	
PTH levels			
Within limit	108 (69.7%)	104 (67.1%)	0.625
Deranged	47 (30.3%)	51 (32.9%)	

Table-2: Difference in dialysis and non-dialysis patients of chronic kidney disease regarding vascular calcification and mineral bone density: The binary logistic regression analysis

	p-value	Odds ratio	95% Confidence interval	
			lower	Upper
Hypocalcaemia (ref. was normal levels)	0.004	1.986	1.238	3.187
Hyperphosphatemia (reference was normal phosphate levels)	0.000	2.455	1.523	3.959
Vascular calcification (ref. was no evidence of calcification)	0.002	2.225	1.331	3.720
Deranged PTH (ref. was normal PTH levels)	0.400	1.246	0.746	2.083

DISCUSSION

Patients suffering from chronic renal disease pass through a lot of phases as the stage of the disease advances. Dietary management, medical treatment, dialysis and renal transplant are the modes of treatment which could cater for many aspects of this debilitating illness but still a lot of aspects remain unaddressed and quality of life of the CKD patient remains compromised in one way or another.[4] Extra-renal manifestations may be seen in almost all the patients in advanced CKD and timely diagnosis and management is the key in process of management of such patients. Biochemical abnormalities especially bone mineral profile has been area of keen interest for clinicians and researchers. Secondary calcification of vital organs of the body has also been a common phenomenon among these patients. We designed this study with an aim to compare the vascular calcification and mineral bone disease in non-dialysis vs dialysis patients suffering from chronic kidney disease at a tertiary care hospital of Pakistan. Slouma *et al*. in their study published in 2020 on 90 patients of CKD undergoing haemodialysis concluded that osteoporosis and fracture are common in dialysis patients. The reduced BMD was associated with advanced age and elevated levels of PTH.[17] Our study was a bit different in design from that of Slouma *et al*. as we studied biochemical parameters for bone profile while they studied bone mineral density with the help of dual-energy x-ray absorptiometry. Results of our study were in line with results of Slouma *et al*. as bone mineral disease was a common finding in our analysis as well.

Brandenburg *et al*.[16] published an interesting paper in 2019 regarding valvular calcification found in patients of chronic renal disease. They revealed that calcific aortic stenosis was the most prevalent valvular heart disease in western part of the world. Valvular calcification was particularly prevalent in patients with underlying CKD or ESRD. Our findings supported their findings and more than 30% of our study participants had vascular calcification. Patients with CKD on dialysis were more at risk of having vascular calcification as compared to those who were not on dialysis.

A systemic review published by Hsu *et al*.[17] in 2020 came up with the findings that bone mineral diseases associated with CKD include abnormalities of calcium, phosphorus, PTH, and/or vitamin D. In such patients, fracture risk should be considered. Biomarkers such as ALP and iPTH may assist to assess bone turnover. We found out that hypocalcaemia and hyperphosphatemia were common findings among patients suffering from CKD especially among those dependent on dialysis.

Reiss *et al*.[18] in 2018 studied inter-relationships and controversies related to chronic renal disease, arterial calcification and bone health.

They concluded that altered phosphorus levels and calcium-phosphorus product promote vascular calcification. Controlling mineral disturbances was considered among the current strategies for treatment of vascular calcification in CKD patients. Phosphorous and calcium levels were significantly deranged in our study participants as well along with considerable number of patients having evidence of vascular calcification.

Bone mineral profile and vascular calcification status of study participants was not studied before the compromise of kidney functions and dependence on renal replacement therapy therefore it cannot be concluded that these changes were consequence of renal compromise. Better results could be generated with better study design and large sample size.

CONCLUSION

Bone mineral disease and vascular calcification were consistent findings among patients suffering from chronic kidney disease. Patients who were dependent on dialysis were more prone to develop these complications as compared to those who were not dependent on dialysis.

Conflict of interest
None
Acknowledgement
None

AUTHORS' CONTRIBUTION

MNAK: Literature search, proof reading. KMR: Proof reading, study design. ARA: Study design, data analysis. BB, Wahaj: data interpretation. FRK, Salahuddin: Write-up. AWM, TT, Ahsan, Salahuddin: Data collection.

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Submitted: March 30, 2021	*Revised: May 23, 2021*	*Accepted: May 30, 2021*

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