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Original Research Article

A Study on the Association between Serum Phosphorus and Carotid Intima-Media Thickness in Chronic Kidney Disease Patients

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Abstract:

Background: Elevated serum phosphorus emerges as a notable risk factor for increased carotid intima media thickness (CIMT), alongside established conventional risk factors. Renal impairment may further influence the elimination of phosphorus, potentially contributing to the calcification of major arteries.

Aim: To establish the association between serum phosphorus levels and carotid intima-media thickness in individuals with chronic kidney disease.

Material and Methods: In this prospective observational study, we studied 400 cases of chronic kidney disease to analyze carotid intima-media thickness (CIMT). Utilizing B-mode ultrasonography with a 5 MHz transducer, CIMT measurements were performed at 0.5, 1, and 2 cm below the carotid bifurcation of the common carotid artery on each side. The carotid intima-media thickness (CIMT) for both sides was computed, and statistical analysis was conducted using the average of these two values.

Results: The correlation analysis between serum phosphorus and carotid intima-media thickness (CIMT) across all four stages of chronic kidney disease (CKD) yielded no statistically significant findings (p-value 0.503). However, when comparing different groups, it was found that serum phosphorus levels were the highest in stage III (4.5±1.18 mg/dl) and the lowest in stage Vd (4.5±1.18 mg/dl).

Conclusion: A significant positive correlation was seen between carotid intima-media thickness and serum phosphorus levels in the overall sample. Emphasizing the correction of hyperphosphatemia may play a crucial role in preventing the progression of arteriosclerosis and mitigating vascular calcification in individuals with chronic kidney disease (CKD).

Keywords: serum phosphorus, carotid intima-media thickness, chronic kidney disease (CKD), hyperphosphatemia, arteriosclerosis.

Introduction

Chronic kidney disease (CKD) is emerging as a prevalent chronic condition on a global scale. The estimated age-adjusted incidence rate of End-stage renal disease (ESRD) in India is approximately 229 cases per million populations. [1]

The dysfunction of the kidneys induces changes in the blood vessels, impeding the cross-linking of collagen and rendering them atherogenic, thereby narrowing the vessel lumen. [2]

Additionally, and kidney dysfunction can impact the clearance of calcium and phosphorus, potentially leading to the calcification of major arteries, including coronary arteries. [2] An increased level of phosphorus in the blood is a notable risk factor for the development of vascular calcification. Hyperphosphatemia disturbs the balance of calcium in the body, making the artery wall more prone to developing calcifications and contributing to the advancement of secondary hyperparathyroidism. [3] Lowering serum phosphorus levels by using phosphate binders has been recognized as a prophylactic strategy for vascular calcification. [3] Research has shown that increased levels of phosphorus in the blood are a significant contributing factor to the thickening of the carotid artery wall, known as carotid intima-media thickness (CIMT). This risk is in addition to other well-known variables such as advancing age, diabetes, and a high Body Mass Index (BMI). [3] The purpose of this study was to examine the relationship between the levels of phosphorus in the blood and the thickness of the carotid artery wall in persons who had chronic kidney disease.

Material and Methods

This prospective observational study was conducted on 400 cases of chronic kidney disease visiting Nephrology department of four tertiary care hospitals.

Inclusion criteria

1. Patients diagnosed with CKD in stages III, IV, VnD (stage V not on dialysis), and Vd (Stage V on dialysis).
2. Age exceeding 18 years.
3. Patients on regular follow-up at the outpatient department.
4. Participants providing informed consent for their involvement in the study, adhering to ethical guidelines.
5. Availability for follow-up assessments as per the study protocol.
6. Stable medical condition to ensure the safety and well-being of the participant during the study.

Exclusion criteria

1. Patients with Acute Kidney Injury, as defined by the RIFLE criteria.
2. Individuals unwilling to provide informed consent for participation in the study.
3. Patients with a prognosis of short expected survival (less than 3 months).
4. Pregnancy.
5. Any history of carotid surgery in the past.

Methodology

Carotid intima-media thickness (CIMT) was measured using B-mode ultrasonography with a 5 MHz transducer. CIMT is defined as the measurement from the front edge of the first echogenic line (the interface between the lumen and intima) to the second echogenic line (the interface between the media and adventitia) on the far wall.

Measurements were taken at 0.5, 1, and 2 centimeters below the carotid bifurcation of the common carotid artery on both sides. The CIMT values for each side were computed, and the statistical analysis utilized the average of these two values.

The B-mode Doppler ultrasound measurement of carotid intima-media thickness (CIMT) involved the following procedural steps:

1. The patient assumed a comfortable supine position with the neck well exposed and free from any clothing covering the neck.

2. The neck was slightly hyperextended, and a 45° rotation away from the side being examined was applied, ensuring the patient's comfort and avoiding excessive neck extension.

3. In cases where patients couldn't lie supine, a seated position was adopted. The examiner either sat beside the patient's thorax and conducted the neck scan or sat at the patient's head and performed the scan from that location.

4. Utilization of a high-frequency linear superficial transducer (5–12 MHz) was deemed ideal for CIMT measurements and assessment of plaque morphology.

5. The examination commenced with a transverse scan of the carotid artery, spanning from the lowest point in the neck (common carotid artery) to the highest point behind the angle of the mandible. This approach facilitated better orientation, illustrating the relationships between the common carotid artery, internal jugular vein, thyroid, trachea, and sternomastoid muscle. It provided a preliminary understanding of vessel depth, course, bifurcation level, and branch orientation. Additionally, regions of significant pathology were identified and marked for further evaluation.

6. Subsequently, a longitudinal scan was conducted. Longitudinal views of the normal carotid wall depicted two nearly parallel echogenic lines separated by a hypoechoic to anechoic region. The distance between these lines represented the combined thickness of the intima and media (I–M complex).

Fully Automated Chemiluminescent Immune Assay method is used for measuring serum intact parathyroid hormone (iPTH) levels. For the quantitative determination of calcium in human serum and plasma, we employed the BAPTA method on the COBAS INTEGRA System. Additionally, the quantitative determination of phosphorus concentration in human serum and plasma was carried out on COBAS INTEGRA systems using the Molybdate method.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD). Linear regression analysis was employed to determine the association and correlation between serum phosphorus and carotid intima-media thickness in patients with chronic kidney disease.

The statistical software SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) was utilized for the analysis.

Quantitative data comparison of clinical indicators within three groups was conducted using analysis of variance (ANOVA), with post hoc Bonferroni test for additional intra-group comparisons. For qualitative data involving two or more groups, the Chi-square test was applied. Multivariate analysis, including Pearson's correlation and regression, was employed to explore complex relationships among

variables. The level of significance was set at $p \leq 0.05$ to determine statistically meaningful associations.

Results

The study encompassed a total of 400 chronic kidney disease (CKD) patients, with 200 undergoing maintenance hemodialysis (MHD) and the remaining 200 managed conservatively. The stage Vd subgroup on MHD received scrutiny across four tertiary care centers, revealing a statistically significant correlation between intact parathyroid hormone (PTH) and carotid intima-media thickness (CIMT). In the overall CKD population, serum iron studies were compared, highlighting statistical significance only for serum ferritin in stage Vd.

Within the CKD stage Vd (MHD) group, the study focused on demographic and laboratory parameters. The average age for this subgroup was 42.9 ± 13.18 years. Across all CKD stages, males predominated (73.33%, 73.33%, 76.67%, 76% in stages III, IV, VnD, Vd, respectively). Specifically, within the stage Vd group, the average hemodialysis (HD) vintage was 11.44 ± 12.15 months, with a median of 6.5 months and an interquartile range of 3.25-18 months. HD access in stage Vd patients was categorized, with 102 patients having cuffed tunneled catheters, 72 using arterio-venous fistula (AVF), and 26 utilizing temporary catheters (uncuffed non-tunneled). Among those on MHD, 60% followed a twice-weekly schedule, while the remaining 40% opted for a thrice-weekly schedule. Within the stage Vd group, 95% of patients were hypertensive, 28% had Diabetes Mellitus, and 12% had ischemic heart disease (IHD). Demographic and laboratory parameters were compared across stages III, IV, and VnD, revealing significance only for serum urea, serum creatinine, and estimated glomerular filtration rate (eGFR).

Table 1: Demographic and laboratory data across all stages of chronic kidney disease

Parameters	CKD stage Vd	CKD stage VnD	CKD stage IV	CKD stage III
Age	42.9+13.18	40.96+11.05	41.13+11.06	42.53+10.91
Male	152 (76%)	46 (76.67%)	44 (73.33%)	44 (73.33%)
Female	48 (24%)	14 (23.3%)	16 (26.4%)	16 (26.4%)
BMI Kg/m2	19.6+ 3.97	19.5+4.01	21.23+4.35	19.56+4.14
HTN	190 (95%)	60 (100%)	52 (86.67%)	54 (90%)
DM	56 (28%)	16 (26.4%)	16 (20%)	8 (13.33%)
IHD	24 (12%)	4 (6.67%)	3 (3.33%)	4 (6.67%)
Sr. Creatinine mg/dl	7.83+1.93	6.62+1.12	3.75+0.43	2.18+0.26
Urea mg/dl	87.86+18.35	84.73+19.83	73+12.91	76.53+13.28
eGFR ml/min/1.73 m2	7.83+2.8	9.33+2.27	17.73+2.66	33.6+3.32
UPCR	1.2+0.68	1+0.61	1+0.52	1.14+0.58
Intact PTH pg/ml	177.71+84.77	195.5+92.94	169.2+82.11	174.9+92.05
HbA_1c	6.02+0.99	5.91+0.76	5.74+0.67	5.77+0.57
Hb gm/dl	7.9+1.16	8.55+1.16	8.45+1.37	9.10+1
Sodium mmol/l	135.98+3.65	136.16+2.94	136.13+3.07	137.16+2.92
Potassium mmol/l	4.44+0.54	4.39+0.56	4.42+0.55	4.57+0.46
Calcium mg/dl	8.4+0.4	8.63+0.59	8.49+0.38	8.47+0.4
Phosphorus mg/dl	4.5+1.18	4.77+1.1	4.86+1.23	4.96+1.29
Uric acid mg/dl	5.68+1.71	5.82+1.78	4.82+1.56	5.15+1.61
Albumin gm/dl	3.19+0.4	3.4+0.77	3.29+0.44	3.27+0.29
Bicarbonate mEq/l	20.56+2.08	20.7+2.42	20.75+2.32	20.83+2.47
Sr. Iron µg/dl	126.6+23.3	130.9+21.01	119.46+22.81	122.06+23.75
Sr. Ferritin µg/dl	150.34+52.93	178.4+42.7	179.96+54.56	163.93+42.27
Sr. TIBC µg/dl	254.06+89.7	227.6+68.58	262.43+82.61	264.56+81.15
Transferrin sat %	32.2+7.83	29.4+5.86	32.5+7.78	31.63+8.6
Cholesterol mg/dl	193.72+34.42	192.8+26.13	181.63+46.56	194.03+22.09
TG mg/dl	144.47+21.56	151.16+20.47	148.66+17.25	148.4+17.31
LDL mg/dl	31.5+7.56	37.83+7.83	41.86+8.25	43.63+13.23
CRP mg/L	24.81+28.73	1.2+0.66	1.63+1.59	1.28+1.18

The comparison of demographic and laboratory parameters across the four stages of chronic kidney disease (CKD) revealed interesting trends. Although no statistical significance was observed, certain parameters such as hemoglobin, serum calcium, serum phosphorus, serum albumin, serum bicarbonate, serum triglycerides, serum LDL, serum ferritin, carotid intima-media thickness

(CIMT) mean, and calcium-phosphorus product was found to be lower in stage Vd compared to conservative CKD stages (III, IV, VnD). Certain parameters like high-sensitivity C-reactive protein (hs CRP), glycated hemoglobin (HbA1C), and urinary protein-to-creatinine ratio (UPCR) were noted to be higher in stage Vd compared to conservative CKD stages, although again, no statistical significance was observed. When analyzing the mean of CIMT across the four stages of CKD, the values were highest in stage III (mean 0.74 ± 0.079 mm, Range 0.60-0.85 mm) and lowest in stage Vd (mean 0.69 ± 0.109 mm, Range 0.35-0.95 mm). However, these disparities did not demonstrate statistical significance throughout the four phases of CKD.

Table 2: CIMT (mean) inter-comparison of groups

Side	CKD Stage	Number	Mean±SD
CIMT right side	Stage III	60	0.73±0.102
	Stage IV	80	0.71±0.098
	Stage Vd	200	0.661±0.12
	Stage VnD	60	0.7±0.11
	Total	400	0.68±0.116
CIMT left side	Stage III	60	0.75±0.097
	Stage IV	80	0.75±0.086
	Stage Vd	200	0.72±0.121
	Stage VnD	60	0.71±0.095
	Total	400	0.73±0.109

The correlation analysis between serum phosphorus and carotid intima-media thickness (CIMT) across all four stages of chronic kidney disease (CKD) revealed no statistical significance (p-value 0.503). Nevertheless, upon individual group comparisons, it was observed that serum phosphorus levels were lowest in stage Vd (4.5 ± 1.18 mg/dl) and highest in stage III (4.5 ± 1.18 mg/dl).

Table 3: Correlation of serum Phosphorus with CIMT

		CIMT right	CIMT left	CIMT Mean
Stage III (NS)				
Serum phosphorous	Pearson Correlation	0.088	0.104	0.119
	p-value	0.64	0.58	0.53
Stage IV (NS)				
Serum phosphorous	Pearson Correlation	0.082	0.087	0.106
	p-value	0.66	0.64	0.57
Stage VnD (NS)				
Serum phosphorous	Pearson Correlation	0.030	0.090	0.072
	p-value	0.875	0.635	0.707
Stage Vd (NS)				
Serum phosphorous	Pearson Correlation	0.024	-0.009	0.008
	p-value	0.81	0.92	0.93

In the comparison between the CKD Vd group and conservative CKD groups (stage III, IV, and Vnd), a statistically significant association was identified between serum phosphorus (p value 0.01) and the mean carotid intima-media thickness (CIMT).

Table 4: Serum phosphorus

		CIMT right	CIMT left	CIMT mean	Sr. Phosphorus
Non-Dialysis (n=200)	Mean±SD	0.71±0.108	0.73±0.094	0.72±0.08	4.86±1.206
Dialysis (n=200)	Mean±SD	0.66±0.12	0.72±0.12	0.69±0.109	4.58±1.18
Total (n=400)	Mean±SD	0.68±0.11	0.73±0.109	0.708±0.09	4.71±1.201
p value		0.001 (S)	0.29	0.01 (S)	0.11

Discussion

In India, where 17% of the world's population resides on a mere 2.4% of the landmass, healthcare disparities are exacerbated by a significant portion of the population living below the poverty line and limited financial allocations for healthcare. This economic reality is reflected in the suboptimal outcomes of chronic kidney disease (CKD) within the country. Arterial disease in CKD is marked by

arteriosclerosis, characterized by the thickening and calcification of the medial arterial layer, with media calcification often exhibiting a concentric pattern.

Individuals with Chronic Kidney Disease (CKD) face an elevated risk of premature death, often occurring before reaching end-stage kidney disease (ESKD), and are intricately linked to an increased susceptibility to cardiovascular disease (CVD) correlated with the severity of their kidney condition. [4] The global surge in cardiovascular mortality, coupled with the recognition of kidney disease as a cardiovascular risk factor, has intensified the investigation into the interplay between obesity and kidney disease. [4] A mounting body of evidence consistently establishes the correlation between adult obesity and an augmented risk of kidney disease. Obesity is associated with conditions such as hypertension, diabetes mellitus, and heart failure, collectively contributing to about 25% of CKD cases in Western populations. [4]

Traditional cardiovascular disease (CVD) risk factors like hypertension, hyperlipidemia, and diabetes are compounded by nontraditional factors in Chronic Kidney Disease (CKD) patients, including anemia, volume overload, dyslipidemia, hyperparathyroidism, hyperhomocysteinemia, microalbuminuria, hyperuricemia, and chronic inflammation. [5] This interplay significantly increases the risk of cardiovascular mortality, with around 40% of CKD patients experiencing cardiovascular disease even before progressing to end-stage renal disease (ESRD). [11] Conventional risk factors like smoking, hypertension, diabetes, and dyslipidemia may underestimate cardiovascular risk in CKD patients, emphasizing the importance of considering nontraditional factors, and reflecting the need for a comprehensive approach in risk assessment and management in this population. [6]

Our study delves into the intricate associations within CKD, focusing on the correlation between carotid intima-media thickness (CIMT) and serum phosphorus. Carotid intima-media thickness (IMT) serves as a non-invasive, precise, and sensitive quantitative assessment of subclinical coronary atherosclerosis. Prospective studies highlight its ability to predict clinical cardiovascular events autonomously from conventional risk factors.

A mere increase of 0.1 mm in IMT correlates with a heightened risk of cardiovascular mortality ranging from 24% to 31% in dialysis patients. [6] Among healthy middle-aged adults, carotid intima-media thickness (CIMT) readings within the range of 0.6 to 0.7 mm are deemed normal, whereas a CIMT measuring 1 mm or higher is linked to a substantial risk of coronary heart disease. [7] In the case of healthy Indian adults, the average reported CIMT values were 0.67 mm, with a maximum value of 0.70 mm. [7] Notably, our findings align with existing research, emphasizing serum phosphate as a crucial independent risk factor for increased CIMT. The progression of CIMT, particularly in its response to stages 3, 4, and 5 CKD, has been documented in literatures, with our study contributing to this body of knowledge. Interestingly, we observed a faster change in CIMT between stages 3 and 4 compared to the transition from stage 4 to stage 5, highlighting the dynamic nature of atherosclerotic changes in CKD. Drawing upon supporting evidence, our study reinforces the notion that increasing serum phosphorus levels, even within the normal range, are positively and independently related to subclinical atherosclerosis, measured through CIMT. The intricate involvement of phosphorus in vascular calcification, leading to the coining of the term chronic kidney disease-Mineral Bone Disorder (CKD-MBD), underscores the often-overlooked role of the skeleton in these pathological states. In the context of CKD, hyperphosphatemia emerges as a significant risk factor for vascular calcification. Interventions such as phosphate binders, aimed at reducing phosphate levels, have shown promise in attenuating vascular calcification, providing potential therapeutic avenues. This aligns with broader experimental data that underscore the role of phosphorus in the entire process of vascular calcification, emphasizing the need for a holistic approach to managing CKD-MBD.

Shifting our focus to our investigation into CKD stage Vd patients undergoing maintenance hemodialysis (MHD), we meticulously scrutinized demographic and laboratory parameters. The study cohort, with an average age of 42.9 ± 13.18 years, exhibited a notable male predominance across CKD stages. The prevalence of hypertension was strikingly high at 95% among stage Vd patients, and comorbidities such as Diabetes Mellitus and Ischemic Heart Disease were also observed. Despite the relatively low average BMI in stage Vd patients, no statistical significance was observed between BMI and HD vintage.

Our comparative analysis of demographic and laboratory parameters across CKD stages revealed significant variations in specific metabolic markers. However, several parameters, including hemoglobin, serum calcium, serum phosphorus, serum albumin, serum bicarbonate, serum triglycerides, serum LDL, serum ferritin, carotid intima-media thickness (CIMT) mean, and calcium-phosphorous product, showed no statistical significance.

Particularly noteworthy was the minimal CIMT mean observed in stage Vd (0.69 ± 0.109 mm), with no statistical significance across the four CKD stages. Correlation analyses provided further insights, indicating significant associations between

CIMT and estimated glomerular filtration rate (eGFR) and serum intact parathyroid hormone (PTH), highlighting their potential roles in CKD-related atherosclerotic changes. Serum high-sensitivity CRP levels demonstrated significance in stage Vd, with the highest levels observed in this group (24.81 ± 28.73 mg/l). Additionally, serum ferritin levels exhibited intra-group significance in stage Vd compared to stage VnD and stage IV. However, serum albumin correlation with CIMT showed no statistical significance.

Conclusion

In the entire study cohort, a notable positive correlation was observed between serum phosphorus levels and carotid intima-media thickness (CIMT). In the context of chronic kidney disease (CKD), managing hyperphosphatemia emerges as a crucial intervention, potentially playing a significant role in impeding the advancement of arteriosclerosis and alleviating vascular calcification.

Limitations of the study

Our longitudinal study, examining the progression of atherosclerosis in CKD, confronts limitations inherent in such an approach. The interventional aspect of our research, focusing on the strict control of hyperphosphatemia and hyperparathyroidism to mitigate atherosclerosis, encounters challenges in establishing definitive causation due to potential confounding variables. Additionally, while we delve into various parameters associated with atherosclerosis, such as Apolipoprotein-A, it is essential to recognize that the intricate nature of this condition may not be fully captured by our study's scope.

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