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ORIGINAL ARTICLE

Correlation of serum phosphate levels and carotid intimal thickness in CKD patients

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Abstract

Background- Chronic kidney disease is a significant global health issue characterized by notable morbidity and mortality rates. Among CKD patients, cardiovascular disease stands as the primary cause of death, often accompanied by accelerated atherosclerosis. Hyperphosphatemia, characterized by elevated serum phosphate levels in CKD patients and has been implicated in the progress of vascular calcification and cardiovascular events.

Aim: To observe relationship between serum phosphate and carotid intimal thickness in individuals with CKD.

Discussion: Existing studies have presented conflicting findings, with some demonstrating a positive correlation while others reporting no significant association. Consequently, a cross-sectional study was conducted on CKD patients representing various stages of renal impairment. Serum phosphate levels were measured, and carotid intimal thickness was assessed using ultrasound imaging.

Conclusion: This study demonstrates a significant association between serum phosphate levels and carotid intimal thickness in CKD patients. Elevated serum phosphate levels were found to be correlated with increased carotid intimal thickness, suggesting a potential role of phosphate in the progression of atherosclerosis in CKD.

Keywords: Carotid intimal medial thickness, CKD, diabetes, serum phosphate.

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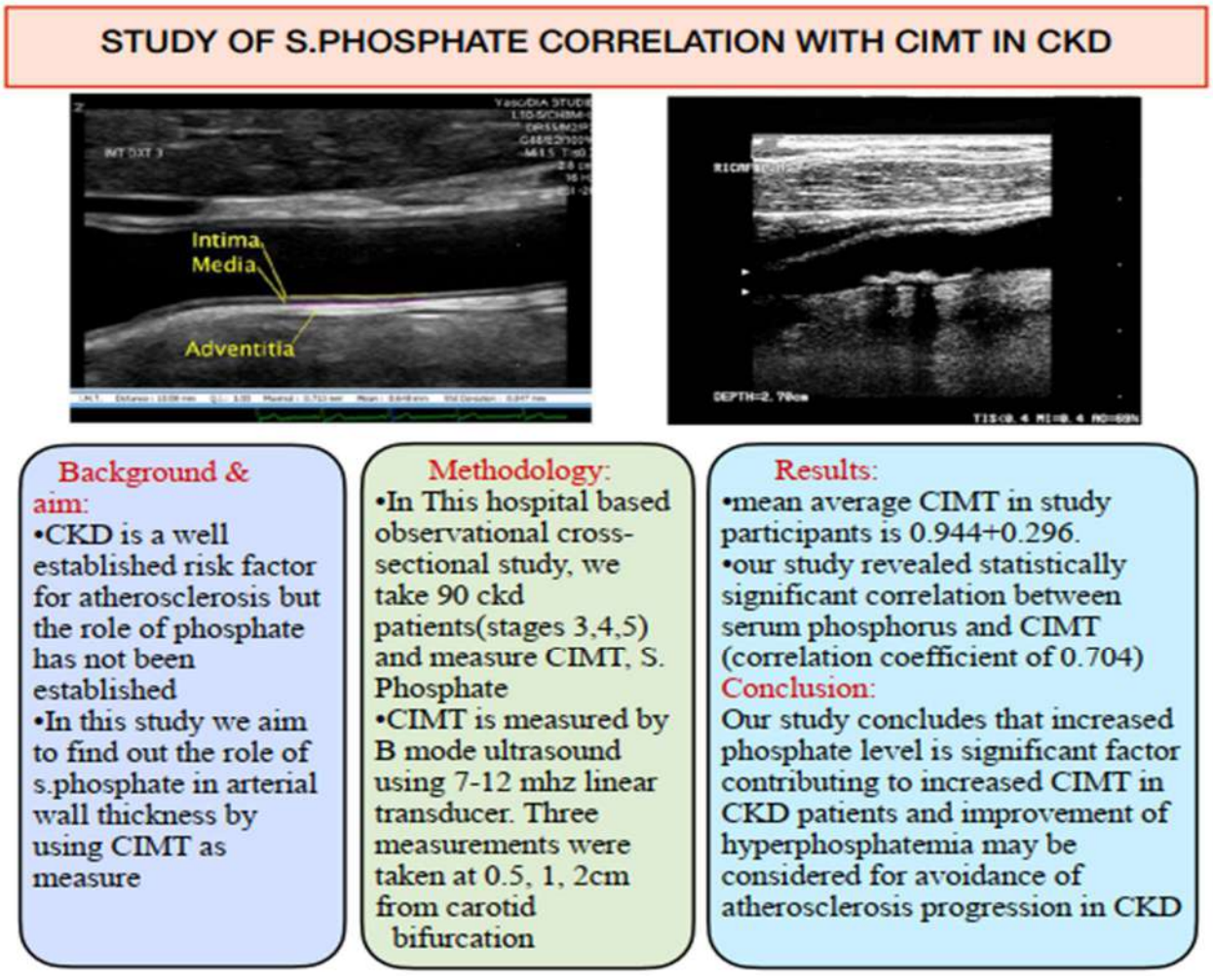
Abbreviations

CKD	:	Chronic Kidney Disease
RAAS	:	Renin Angiotensin Aldosterone System
mTOR	:	Mammalian Target of Rapamycin
ESRD	:	End Stage Renal Disease
IL-6	:	Interleukin-6
AGEs	:	Advanced Glycation End Products
TNF-α	:	Tumor Necrosis Factor Alpha
CIMT	:	Carotid Intimal Medial Thickness
TGF-β	:	Transforming Growth Factor Beta
eGFR	:	estimated Glomerular Filtration Rate

Graphical Abstract



Introduction

CKD is a significant global health issue characterized by notable morbidity and mortality rates. Diabetes mellitus, particularly type 2 diabetes, is a leading cause of CKD worldwide. Persistent hyperglycemia, the hallmark of diabetes, plays a central role in the development and progression of diabetic CKD [1].

Among CKD patients, cardiovascular disease stands as the primary cause of death, often accompanied by accelerated atherosclerosis. Hyperphosphatemia, characterized by elevated serum phosphate level in CKD patients and has been implicated in progress of vascular calcification and cardiovascular events [2].

However, the precise relationship between serum phosphate levels and carotid intimal thickness, a recognized indicator of subclinical atherosclerosis, in CKD patients remains unclear. Existing studies have presented conflicting findings, with some demonstrating a positive correlation between serum phosphate levels and carotid intimal thickness, while others reporting no significant association.

CKD Pathophysiology

The pathophysiology of diabetic CKD is multifaceted and involves numerous interconnected mechanisms.

One of the primary mechanisms is the activation of the RAAS. Increased glucose levels promote the production of angiotensin II, a potent vasoconstrictor that causes renal arteriolar constriction and promotes inflammation and fibrosis. Angiotensin II also stimulates the release of aldosterone, which contributes to sodium and water retention, further increasing intraglomerular pressure and renal damage [3]. Another imperative factor in pathophysiology of diabetic CKD is accumulation of AGEs. These toxic metabolites form as a result of prolonged exposure to high glucose levels and contribute to oxidative stress, inflammation, and endothelial dysfunction in the kidneys. AGEs also interact with specific receptors, such as the receptor for AGEs, leading to further inflammatory responses and tissue injury [4].

Hyperglycemia stimulates the release of pro-inflammatory cytokines, like IL-6 and TNF-α, promoting recruitment and activation of immune cells in the renal tissue [5]. TGF-β is a key mediator that promotes the accumulation of extracellular matrix proteins, leading to glomerulosclerosis and tubulointerstitial fibrosis. Additionally, aberrant activation of intracellular signaling pathways, such as protein kinase C and mTOR, contributes to abnormal cell proliferation, apoptosis, and hypertrophy, further worsening renal damage [6].

CKD and Cardiovascular effects

CKD is associated with a significantly increased risk of CVD, making it a major contributor to morbidity and mortality in CKD patients. The pathophysiology of CKD-related cardiovascular effects is multifactorial and involves a complex interplay of various mechanisms [7].

Hypertension, in particular, is commonly observed in CKD and plays a central role in promoting vascular remodeling, endothelial dysfunction, and atherosclerosis [8]. The dysregulation of

mineral and bone metabolism in CKD, characterized by elevated phosphate levels and deranged calcium-phosphate balance, also plays a significant role in cardiovascular complications. Hyperphosphatemia promotes vascular calcification, a process similar to atherosclerosis, leading to arterial stiffening and increased cardiovascular risk [9]. Elevated parathyroid hormone levels in CKD contribute to vascular calcification and left ventricular hypertrophy, further exacerbating cardiovascular effects [10].

Carotid Intimal Medial Thickness

Carotid intimal-medial thickness is a valuable indicator of atherosclerotic vascular disease, providing a comprehensive representation of arterial wall alterations resulting from numerous cardiovascular risk factors over time [11]. Arteries and veins consist of three layers, with the middle layer being thicker in arteries compared to veins. CIMT specifically refers to the combined thickness of the intimal and medial layers of the vessel wall. It serves as a direct marker of atherosclerosis and has predictive value for cardiovascular mortality. The non-invasive nature, cost-effectiveness, and accessibility of CIMT measurement make it an attractive alternative to invasive methods like angiography for detecting atherosclerosis [12]. Ultrasound imaging using B-mode with a frequency range of 7-12 Hz can be performed on easily accessible large vessels such as the carotid, radial, brachial, and femoral arteries. Among these, the carotid artery is the preferred site for CIMT measurement. The procedure involves locating the best site for measurement using a transverse view while the patient is in a supine position [13]. Calipers are used to measure CIMT, with readings taken on each side and an average value calculated. A CIMT measurement exceeding 1 mm is considered significant. The focus on studying the intimal layer of the artery stems from the fact that atherosclerosis primarily affects this region. The accessibility of the carotid arteries makes them suitable for measuring intimal-medial thickness due to their superficial location [14].

Serum Phosphate level in CKD

Elevated serum phosphate levels are commonly observed in patients with CKD due to impaired kidney function. The kidneys play a vital role in regulating serum phosphate, and the loss of this regulatory function leads to a propensity for phosphate retention [15]. In early stages of CKD, the filtered phosphate load is reduced, leading to an imbalance in serum phosphorus levels. Normal serum phosphorus levels typically range from 2.5 mg/dl to 4.5 mg/dl [16]. However, as the eGFR falls below 25 to 40 mL/min/1.73 m^2, overt hyperphosphatemia develops [17]. Serum phosphorus levels continue to rise as CKD progresses to ESRD [18]. Hyperphosphatemia has been linked to raised morbidity and death rate in CKD patients. Specifically, it has been independently linked to the calcification of large arteries e.g. aorta and small arteries e.g. coronary arteries, left ventricular hypertrophy in individuals with ESRD. These findings highlight the importance of managing serum phosphate levels in CKD patients to mitigate the adverse cardiovascular effects associated with hyperphosphatemia [19].

Material and Methods

Biochemical assay

A venous blood sample was collected to measure the levels of serum phosphate (inorganic). The samples were processed using a fully automated biochemistry analyzer (XL-1000). The test utilized the principle of U.V. Molybdate, where serum phosphate reacts with Ammonium molybdate to form reduced phosphomolybdate in presence of strong acids. The reduced phosphomolybdate level was measured, which is directly proportional to the concentration of inorganic phosphorus in the sample. Additional tests including serum albumin, serum creatinine, hemoglobin, C-reactive protein, serum calcium and serum lipid profile were measured using the XL-1000 analyzer.

Carotid intimal medial thickness

CIMT was assessed using B-mode ultrasound with a Siemens Acuson x 300 machine equipped with a 7 to 12MHz linear transducer. CIMT is determined by measuring the distance between the leading edge of the first echogenic line (Lumen-Intima interface) and the second echogenic line (Media-Adventitia interface) on the far wall of the carotid artery. Measurements were taken at three locations i.e., 0.5 cm, 1 cm, and 2 cm below the common carotid bifurcation on each side, referred to as the upper, middle, and lower CIMT, respectively. The average of these measurements was calculated. The CIMT values from both left and right sides were obtained, and its average was used. A single radiologist performed the CIMT measurements in plaque-free arterial segments. Plaques were identified as areas of localized enlargement compared to the neighboring segment, characterized by protrusion into the lumen.

Inclusion criteria

- Age ≥ 18 years
- CKD stage ≥ 3

Exclusion criteria

- History of carotid surgery
- AKI
- H/o IHD, MI, CVA
- Pregnancy

Observation and Results

The relationship between CIMT average and different clinical parameters was examined in a study involving 90 patients. The mean age of the study participants was 57.2 ± 14.4 years, with maximum participants of age between 51-60 years, followed by 41-50 years. Males constituted 57.8% of the study population, while females accounted for 42.2%. The mean body mass index was observed to be 25.1 ± 3.15 kg/m^2, indicating that most patients fell into the obese category. Hypertension was prevalent among the majority of patients, with a mean SBP of 143.98 ± 21.67 mmHg and a mean DBP of 84.44 ± 14.85 mmHg. Furthermore, the study revealed that a significant number of participants tested positive for C-reactive protein, indicating inflammation. Mean hemoglobin, GFR, and serum albumin levels were found to be low, while parameters such as creatinine, blood urea, random blood sugar, serum triglycerides, and urine albumin were high. Distribution of lab investigations are as shown in Table 1.

Table 1. Laboratory investigations statistics

Parameter	Mean	Median	Std. Dev.	Minimum	Maximum
Hb (g/dl)	8.54	8.1	2.37	5.7	16.1
S. Creat. (mg/dl)	5.22	4.28	3.35	1.4	16.1
B. Urea (mg/dl)	131.42	114	74.97	38.6	399
GFR (ml/min)	21.67	17	16.26	5	123
RBS (mg/dl)	232.88	201	157.01	83	793
S. Albumin (g/dl)	2.79	2.6	0.63	1.9	4.5
Urine Albumin	1.48	1	0.5	1	2
S. Calcium(mg/dl)	7.98	8.2	1.96	4	14.12
S. HDL (mg/dl)	35.92	28.2	16.28	6	106
S. LDL (mg/dl)	69.74	64	40.79	15	187
S. TC (mg/dl)	140.14	128	63.3	48	319
S. TG (mg/dl)	173.64	157	95.11	67	491

The mean right sided CIMT in upper, middle, and lower portion was measured 0.99 mm, 0.87 mm and 0.87 mm respectively as shown in Table 2 while mean left sided CIMT in upper, middle and lower portion was measured 1.17mm, 0.91 mm, and 0.86 mm respectively as shown in Table 3. Mean average CIMT was 0.944 ± 0.296.

Table 2. Right CIMT statistics on carotid doppler

Right CIMT				
	Upper	Middle	Lower	AVERAGE RIGHT CIMT
Mean	.9889	.8711	.87333	.91111
Median	.9000	.9000	.80000	.90000
Std. Deviation	.50201	.21107	.295585	.293202
Minimum	.30	.60	.400	.467
Maximum	2.70	1.40	2.700	1.867

Table 3. Left CIMT statistics on carotid doppler

Left CIMT				
	Upper	Middle	Lower	AVERAGE LEFT CIMT
Mean	1.166	.909	.858	.977
Median	1.100	.800	.900	.967
Std. Deviation	.561	.286	.259	.330
Minimum	.500	.500	.400	.500
Maximum	3.000	2.000	2.000	1.933

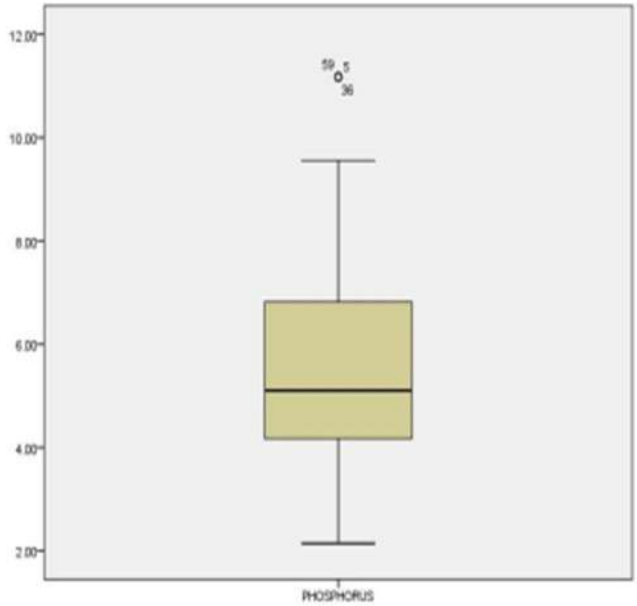


Figure 1. Box whisker plot and table of S. phosphate levels depicting its statistics.

Table 4. Statistics of S. phosphate levels

Parameter	Mean	Median	Std. Dev.	Minimum	Maximum
S. Phosphate (meq/L)	5.5290	5.1000	2.0062	2.14	11.18

Serum phosphate being the central core of the study was plotted on a box whisker plot as shown in Figure 1 with the help of its statistical values as shown in Table 4, to evaluate its distribution among the patients.

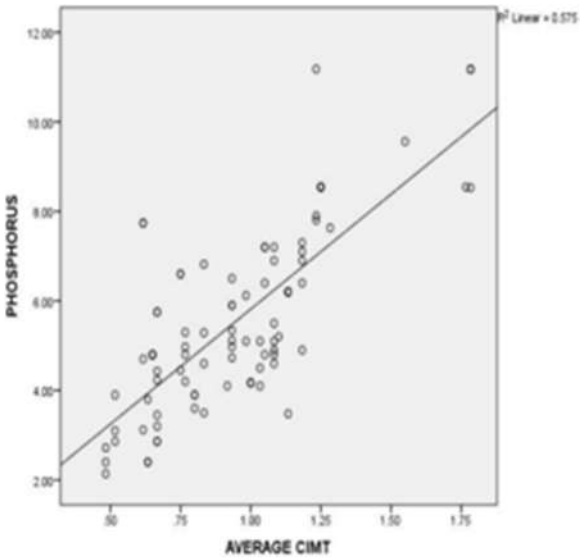


Figure 2. Correlation between average CIMT and S. phosphate levels

To assess the correlation between CIMT and various parameters, scatter plots were created, plotting the average CIMT value against serum phosphate, age, RBS, BMI, serum triglycerides and hemoglobin individually. In this study, a significant positive correlation was observed between serum phosphate levels and CIMT as shown in Figure 2, with a correlation coefficient (ρ) of 0.704. Also, justifying the monitoring and management of S. phosphate levels to mitigate cardiovascular risk. Affirmative correlation is also seen with age as shown in Figure 3.

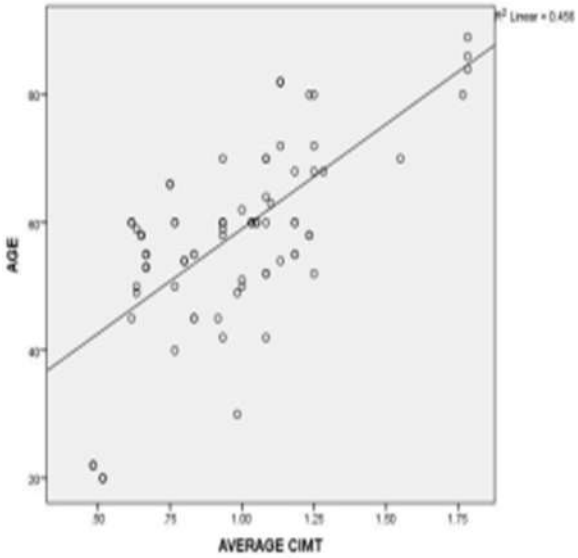


Figure 3. Correlation between average CIMT and Age

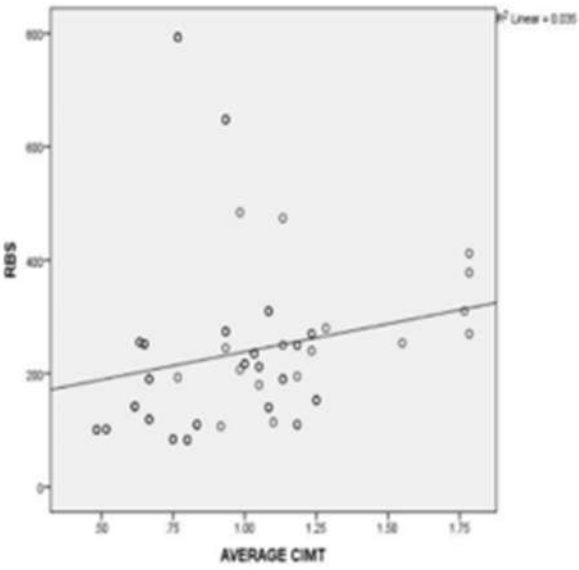


Figure 4. Correlation between average CIMT and Random blood sugar levels

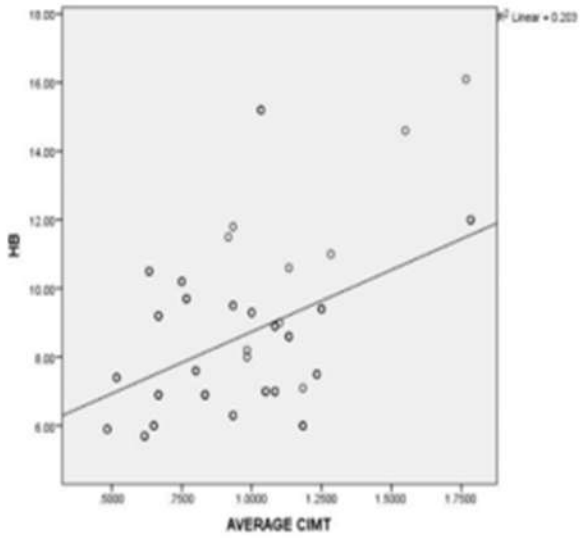


Figure 5: Correlation between average CIMT and BMI

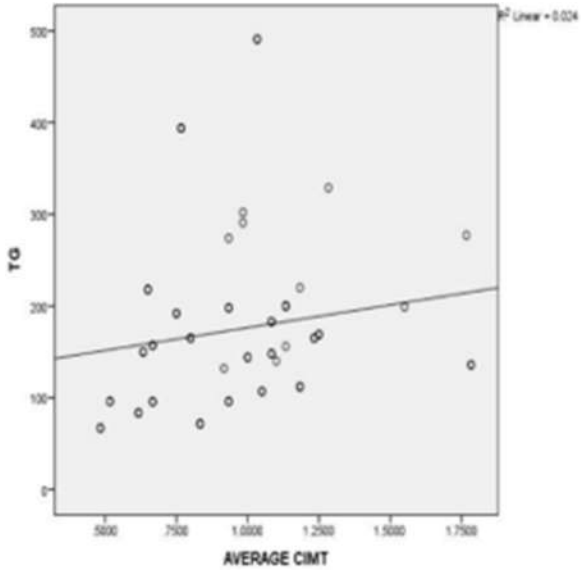


Figure 6: Correlation between average CIMT and S. Triglyceride levels

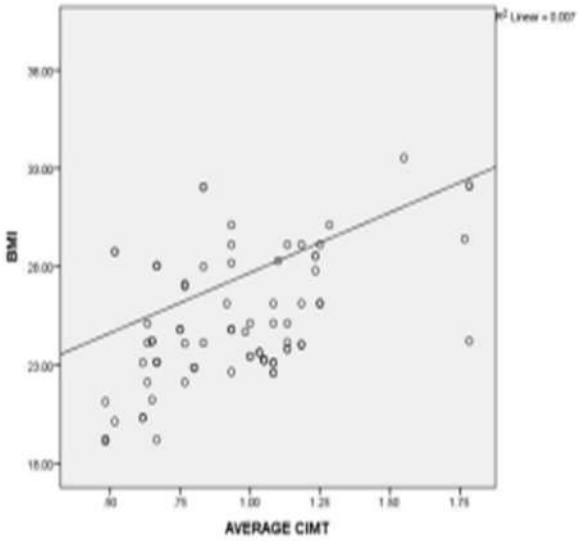


Figure 7: Correlation between average CIMT and Hemoglobin

Positive scatter plot between RBS and CIMT average as well as BMI and CIMT average highlighting its correlation are depicted in Figure 4 and 5 respectively.

The scatter plots of CIMT vs Triglycerides and Hb are positively correlated but not strongly linked to each other as shown in Figures 6 and 7.

Figure 8 shows that CIMT has increased with worsening of CKD stages indicating that atherosclerosis intensifies with CKD.

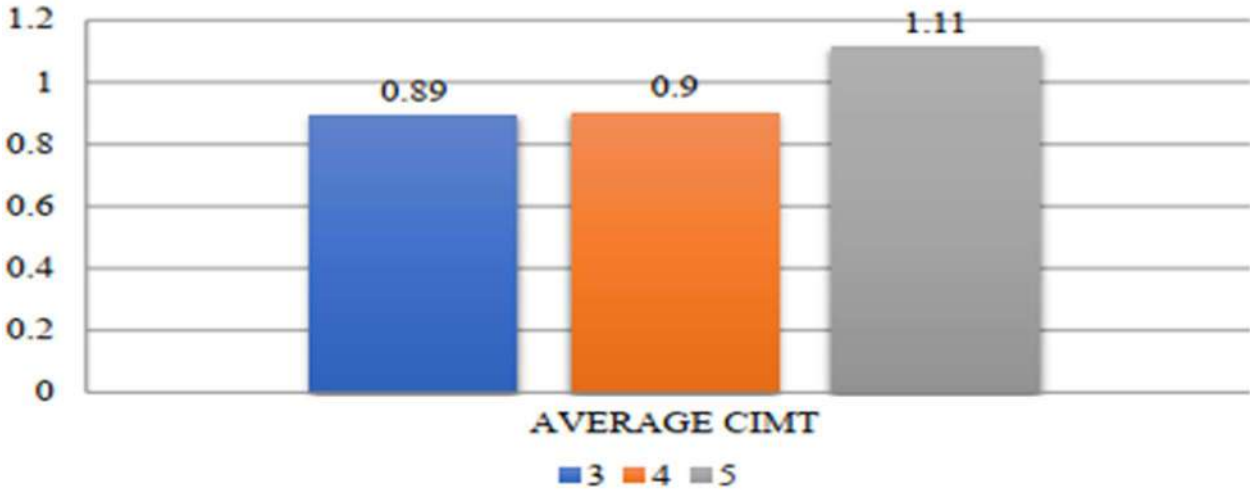


Figure 8. Variation of average CIMT with stages 3, 4 and 5 of CKD

Conclusion

The examination of CIMT in patients with CKD led to the observation that elevated serum phosphate levels were a notable factor associated with increased CIMT. Alongside this finding, other factors such as advanced age, higher levels of Hemoglobin (Hb), Body Mass Index (BMI), Serum Triglycerides (TG), and Random Blood Sugar (RBS), were also linked to increased CIMT. Addressing hyperphosphatemia could be considered as a potential measure to prevent the progression of arteriosclerosis in CKD patients.

Future Scope

The association between serum phosphate and average CIMT in CKD patients is a topic that holds promise for further exploration and research. Longitudinal studies can be conducted to establish a cause-and-effect relationship. Furthermore, it would be beneficial to investigate the impact of interventions targeting serum phosphate levels on carotid intimal thickness and cardiovascular outcomes in CKD patients. This could involve evaluating the effectiveness of phosphate-lowering therapies, such as dietary modifications, phosphate binders, or novel pharmacological agents. Incorporating advanced imaging techniques and biomarkers related to vascular calcification and atherosclerosis could enhance the understanding of the underlying mechanisms. Exploring genetic and molecular factors that influence phosphate metabolism and vascular health may also provide valuable insights.

Ethics declarations

Funding This study did not receive any funding.

Conflict of interest

The authors declare that they have no competing interests.

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability

Not applicable.

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