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Original Article

Internal Medicine Section

The Correlation of Carotid Intima-media Thickness with Calcium-phosphorus Product in Patients Undergoing Maintenance Haemodialysis: A Cross-sectional Study

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ABSTRACT

Introduction: The risk of Cardiovascular Disease (CVD) morbidity and mortality remains high in all stages of Chronic Kidney Disease (CKD). Elevated calcium and phosphorus have direct effects on vascular smooth muscle cells, promoting vascular calcification and arteriosclerosis. Carotid Artery Intima-Media Thickness (CIMT) is a well-established index of systemic atherosclerosis and correlates with the incidence of coronary artery disease and stroke in the CKD population.

Aim: To study levels of Serum Calcium-Phosphorus product (S. CaxP) and CIMT in patients undergoing Maintenance Haemodialysis (MHD) and to correlate CIMT with S. CaxP.

Materials and Methods: This was a cross-sectional study conducted at the Department of General Medicine, K.R. Hospital (Krishna Rajendra Hospital), Mysore Medical College and Research Institute (MMCRI), Irwin Road, Mysuru, Karnataka, India over a period of one and a half years between January 2020 and July 2021. Data were collected from patients visiting the Outpatient Department (OPD) or those admitted for MHD, as well as through the medical records of stage 5 CKD patients who were admitted to the hospital for MHD. Subjects' serum calcium, serum potassium, S. CaxP, and CIMT were evaluated. The Student's t-test and the Chi-square test were employed to assess the significance between the groups. A p-value <0.05 was considered statistically significant.

Results: Of the 76 individuals included in the study, 27 were females with mean age 44.07 years and 49 were males with a mean age 43.81 years. The mean CIMT among the study population was 1.2108±0.28966 mm, and the mean S. CaxP was 46.9237 mg^2/dL^2. There was a positive correlation between CIMT values, S. Calcium, S. phosphorus, S. CaxP, and the duration of MHD. High S. CaxP is a significant and independent risk factor associated with advanced arteriosclerosis in CKD patients, independent of age, gender, Diabetes Mellitus (DM), Hypertension (HTN), and hyperlipidemia.

Conclusion: Patients with CKD have a high risk of CVD. Although these patients share many cardiovascular risk factors with the general population, additional factors, such as abnormal calcium/phosphorus metabolism, elevate their risk for CVD. The present study concludes that there is a positive correlation between serum calcium-phosphorus product levels and CIMT, as well as with the duration of maintenance haemodialysis.

Keywords: Atherosclerosis, Cardiovascular disease morbidity, Vascular calcification

INTRODUCTION

Chronic Kidney Disease (CKD) includes a spectrum of pathophysiological processes associated with abnormal kidney function and a progressive decline in Glomerular Filtration Rate (GFR). End-Stage Renal Disease (ESRD) represents a stage of CKD in which the accumulation of toxins, fluids, and electrolytes that the kidneys usually excrete can lead to death without renal replacement therapy, dialysis, or kidney transplantation [1]. CVD is the leading cause of morbidity and mortality in patients at every stage of CKD [2]. Between 30 and 45% of those patients who reach stage 5 CKD experience advanced cardiovascular complications [1]. An assosciation between change in some serum chemical biomarkers, such as serum phosphorus, calcium, and their product (Ca-P product) and increased cardiovascular morbidity and mortality in ESRD patients undergoing chronic dialysis has been described [3].

Kidney dysfunction alters lumen of blood vessels by inhibiting the cross-linking of collagen, making them atherogenic (narrowing the lumen of the vessels). Kidney dysfunction may also affect the clearance of calcium and phosphorus, which could be responsible for the calcification of major arteries [4]. The prevalence of vascular and cardiac complications in CKD accounts for approximately 16.2% [5]. Dysregulation of calcium and phosphorus metabolism is common in CKD patients [6]. Elevated calcium and phosphorus have direct effects on vascular smooth muscle cells that promote vascular calcification and arteriosclerosis [7]. Arterial stiffness increases afterload and can precipitate left ventricular heart failure [8]. Elevated calcium promotes apoptosis of vascular smooth muscle cells and vesicle release. Calcium and phosphoruact synergistically to promote vascular calcification and arteriosclerosis [9]. Aortic and Mitral Valve Calcification (AVC and MVC, respectively) are critical indicators of CVD and all-cause mortality in CKD patients [10].

High phosphate levels have been observed in patients with end-stage renal failure, and it is a common issue [11]. These elevated phosphate levels are believed to initiate chain reactions that lead to secondary hyperparathyroidism, calcification of soft-tissues, and other processes contributing to cutaneous calciphylaxis [12]. High phosphate levels are independently associated with increased mortality rates in haemodialysis patients. It has also been indicated that higher amounts of CA × P may raise the mortality rate [2]. In this respect, CKD mimics an accelerated ageing of the cardiovascular system [13].

The CIMT is a well-established index of systemic atherosclerosis and correlates with the incidence of coronary artery disease and stroke in the CKD population [14]. CIMT is a measure of atherosclerotic vascular disease. It is considered a comprehensive indicator of all alterations caused by multiple cardiovascular risk

factors over time on the arterial walls [15]. CIMT specifically refers to the combined thickness of the intimal and medial layers of the vessel wall. CIMT is measured between the intimal-luminal and medial-adventitial interfaces of the carotid artery wall, represented as a double-line density on an ultrasound image [16]. It serves as a direct marker of atherosclerosis and has predictive value for cardiovascular mortality [17]. The usefulness of the Ca-P product index as a determinant of systemic atherosclerosis has been questioned. The present study aimed to correlate CIMT with the calcium-phosphorus product in patients undergoing maintenance haemodialysis.

MATERIALS AND METHODS

This was a hospital-based cross-sectional study done Outpatient Department (OPD) of General Medicine, K.R. Hospital (Krishna Rajendra Hospital), Mysore Medical College and Research Institute (MMCRI), Irwin Road, Mysuru, Karnataka, India from January 2020 to July 2021. After obtaining Institutional Ethical Committee approval for the study (ECR/134/inst/KA/2013/RR-16), written informed consent was obtained from the subjects.

Sample size calculation: The sample size (n) was calculated using the formula

$n = z^2pq/d^2$ for a level of confidence of 95%.

Where, z = desired confidence level = 1.96,p = estimated proportion of an attribute in the population = 5%, q = (100-p) = 95%,d = desired level of precision = 5%.

$n=(1.96x1.96)(5)(95)/5^2$

The calculated sample size is 76.

Inclusion criteria: Patients with CKD on maintenance haemodialysis, aged 18-60 years.

Exclusion criteria: Previous history of coronary artery disease, previous history of cerebrovascular disease, patients on calcium and phosphorus supplementation, pregnancy, History of carotid artery surgery, Patients who refused to give informed written consent for the study

Study Procedure

The present study was conducted using clinical and biochemical parameters of patients visiting the OPD or those admitted to the hospital with CKD. All patients included in the study underwent a detailed clinical evaluation, which recorded demographic characteristics, history of lower limb swelling, decreased urine output, changes in appetite, bony pain, co-morbidities, smoking status, and alcohol intake. Physical examinations, including anthropometric measurements, pulse rate, blood pressure, a head-to-toe examination, and assessment of bone tenderness, were performed. A blood sample was collected from each patient, and laboratory tests were conducted at KR Hospital, Mysuru. The collected data were entered into a pre-structured proforma and analysed.

Collection of a Blood Sample

Under aseptic precautions, 5 mL of venous blood was collected using a syringe and transferred into plain sterile vacutainer tubes. It was allowed to clot at 37°C and then centrifuged at 3000 rpm for 10 minutes to separate the serum. The separated serum was transferred to plain bullet vials and immediately used for analysis.

Analysis of a Blood Sample

Separated serum was introduced into fully or semi-automated closed-system analysers (Cobas Integra 400 Plus from Roche and an electrolyte analyser from Roche), which were utilised for the analysis of minerals as mentioned below.

- Calcium: Modified Ortho-Cresolpthalein Complex by Cobas Integra 400 Plus, Roche Diagnostics.
- Phosphorus: Modified phosphomolybdate by Cobas Integra 400 Plus, Roche Diagnostics.

The reference value for S. calcium is 8.6 to 10.3 mg/dL [18].

The reference value for S. phosphorus is 2.8 to 4.5 mg/dL [18].

The reference value for the Ca-P product is <55 mg^2/dL^2 [18].

The presence and severity of valvular heart disease were determined using M-mode 2D echocardiography. CIMT was assessed with B-mode ultrasonography. While the patient was lying in the supine position, a transverse view was initially used to locate the optimal site for measuring CIMT. CIMT was measured with callipers in ultrasound from the beginning of the first white line to the end of the second white line. Three readings were taken, and their average was calculated. A CIMT of more than 1 mm was considered significant [19].

STATISTICAL ANALYSIS

The data is presented as descriptive statistics in the form of frequencies, tables, figures, and graphs. Results were expressed as mean±SD. The Student's t-test and the Chi-square test were used to assess the significant differences between the groups. A p-value <0.05 was considered statistically significant. The data was analysed using the Statistical Package for Social Sciences (SPSS) software version 22.0.

RESULTS

In the present study, 76 patients undergoing maintenance haemodialysis had their S. CaxP levels and CIMT assessed. The findings are summarised as follows:

Of the 76 individuals 27 were females and 49 were males. The mean age was 43.81 years for males and 44.07 years for for females. The majority of patients were older than 40 years [Table/Fig-1].

Age group (years)	Male n (%)	Female n (%)
< 30	7 (14.3%)	2 (7.4%)
31-40	13 (26.5%)	8 (29.6%)
41-50	12 (24.5%)	11 (40.7%)
51-60	17 (34.7%)	6 (22.3%)
Total	49 (100%)	27 (100%)

[Table/Fig-1]: Age and gender-wise distribution.

Among of the 76 individuals studied, 37 (48.7%) had DM and 40 (52.6%) had HTN. The mean values for High-Density Lipoprotein, (HDL) Low-Density Lipoprotein,(LDL) and Very Low-Density Lipoprotein(VLDL), Fasting Trigycricides (FTG), and total cholesterol in the study population were 45.1944 mg/dL, 117.6389 mg/dL, 28.4028 mg/dL, 136.0833 mg/dL, and 178.5 mg/dL, respectively [Table/Fig-2].

Lipid profile	Mean values (mg/dL)
HDL	45.19
LDL	117.63
VLDL	28.40
FTG	136.08
Total cholesterol	178.5

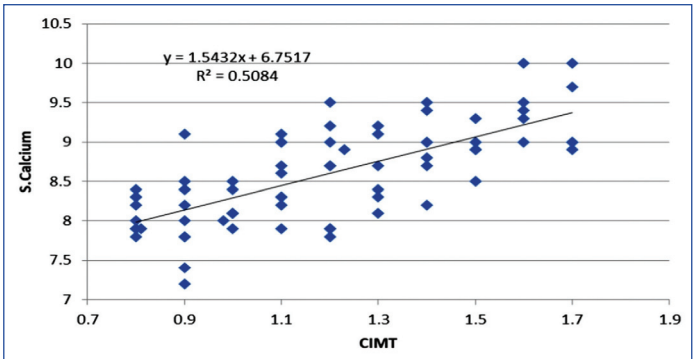
[Table/Fig-2]: Lipid profile parameters of subjects.

The mean CIMT was 1.2108 mm [Table/Fig-3].

The study population's mean S.Ca value was 8.6145 mg/dL. The levels of S.Ca and CIMT had a positive correlation. The p-value was less than 0.001 which was statistically significant [Table/Fig-4].

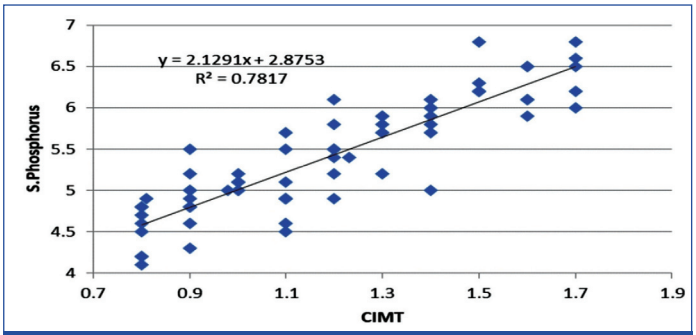
Mean CIMT (Right-side)	Mean CIMT (Left-side)	Mean CIMT (Mean of Right-side + Left-side)
1.2188 mm	1.2028 mm	1.2108 mm

[Table/Fig-3]: Mean CIMT on the right and left-sides.



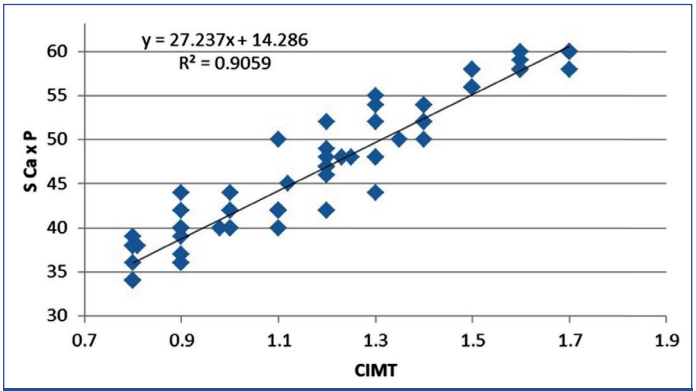
[Table/Fig-4]: Correlation between CIMT and serum calcium.

The study population's mean S.P level was 5.4289 mg/dL. The levels of phosphorus and CIMT showed a positive correlation, with a p-value of less than 0.001, demonstrating statistical significance [Table/Fig-5].



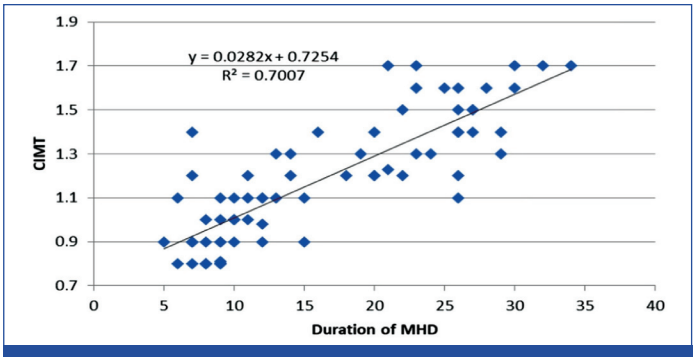
[Table/Fig-5]: Correlation between CIMT and serum phosphorus.

The mean S. CaxP value of the study population was 46.9237 mg²/dL². S. CaxP and CIMT showed a positive correlation, with a p-value less than 0.001, indicating statistical significance [Table/Fig-6].



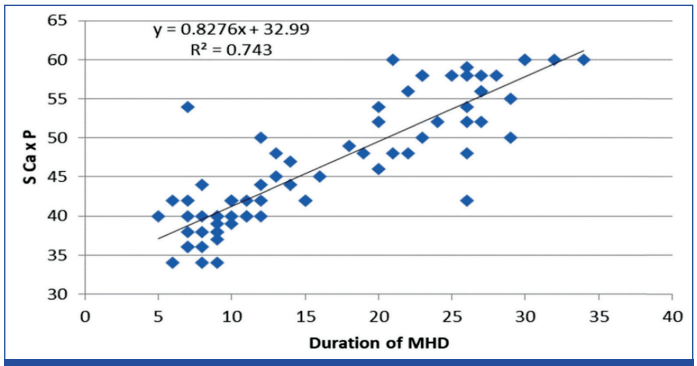
[Table/Fig-6]: Correlation of S. CaxP levels with CIMT

The mean duration of MHD in the study population was 16.1579 months. A positive correlation was found between MHD duration and CIMT. The p-value was less than 0.001, indicating statistical significance [Table/Fig-7].



[Table/Fig-7]: Correlation of CIMT with the duration of MHD.

The study population's mean MHD duration was 16.1579 months. There was a positive correlation between S. CaxP and the duration of MHD, with a p-value less than 0.001, indicating a statistically significant association [Table/Fig-8].



[Table/Fig-8]: Correlation of S. CaxP with the duration of MHD.

DISCUSSION

This cross-sectional study was conducted to correlate the calcium-phosphorus product and CIMT in patients with CKD at a tertiary care hospital in Mysuru.

The mean calcium level in the study population is 8.6145 mg/dL, and the mean phosphorus level is 5.4289 mg/dL. The mean S. CaxP value in this population is 46.9237 mg²/dL², and the mean CIMT value is 1.2108 mm. A positive correlation was found between S.Calcium, S.Phosphorus, and CIMT. Also, S. CaxP and CIMT showed a positive correlation. A positive correlation was observed between CIMT values and S.Ca, S.Phosphorus, S. CaxP, and the duration of MHD [Table/Fig-7,8].

The gender distribution and mean age group were comparable to those of other studies conducted by Sharma VK et al., and Dighe T et al., where the mean age was 42.9±13.18 years. In the current study, the mean age was 43.9 years [19,20]. The mean calcium values among the study population were 8.6145 mg/dL, consistent with those of other studies, such as the one by Kahnooj M et al., where the calcium level was 9.16±1.31 [3]. The mean phosphorus values among the study population were 5.4289 mg/dL, similar to those reported in other studies by Kahnooj M et al., where the phosphorus level was 5.47±1.74 [3]. The mean S. CaxP value in the study population was 46.9237 mg²/dL², which was similar to the study by Rufino M et al., where the mean S. CaxP value was 46.213 mg²/dL² [21]. The mean CIMT value among the study population was 1.2108±0.28966 mm, which aligns with that reported by Adeney KL et al., where the value was 0.8±0.23 [2]. The mean duration of MHD among the study population was 16.1579 months.

In the current study, no significant correlation was found between CIMT and the age, gender, or lipid levels of the study population. High S. CaxP is a significant and independent risk factor associated with advanced arteriosclerosis in CKD patients with and without DM, older age, and hyperlipidaemia.

The mean S. CaxP of the present study is comparable to that of other studies conducted by Kahnooj M et al., [Table/Fig-9] [3,8]. The mean CIMT in the present study is higher to that of the study conducted by Adeney KL et al., and also substantially higher than that of the study carried out by Sharma VK et al., [2,19]. This difference may be attributed to the inclusion of all stages of CKD (from stage 1 to 5) in the study [Table/Fig-10] [13,2].

	Present study	Kahnooj M et al., [3]	Ayub H et al., [8]
Mean S. CaxP level in study population (mg²/dL²)	46.9237±7.94875	50.44±17.78	57.2±7.19

[Table/Fig-9]: Comparison of mean calcium phosphate product with other studies [3,8].

	Present study	Sharma VK et al., [13]	Adeney KL et al., [2]
Mean CIMT (in mm)	1.2108±0.28966	0.6171±0.236	0.8±0.23

[Table/Fig-10]: Comparison of mean CIMT with other studies [13,2].

Out of 76 people, 37 had DM (48.7%) and 40 had HTN (52.6%), which is comparable to the study done by Kahnooj M [3]. There was no significant increase in CIMT among individuals with DM or HTN in the study group. The mean values for HDL, LDL, VLDL, FTG, and total cholesterol in the study population were 45.1944 mg/dL, 117.6389 mg/dL, 28.4028 mg/dL, 136.0833 g/dL, and 178.5 mg/dL, respectively [Table/Fig-2], which are comparable to those of the study.

Limitation(s)

The present study doesn't take into account other atherosclerotic markers, such as serum lipoproteins, obesity, level of physical activity, or hypercoagulable states, including serum homocysteine levels. This is a cross-sectional study; hence, follow-up with patients was not done.

CONCLUSION(S)

Patients with CKD bear a high burden of CVD. Although individuals with CKD share many cardiovascular risk factors with the general population, additional risks exist, such as abnormal calcium and phosphorus metabolism, which further increase the risk of CVD mortality in these patients. Among those with CKD, dysregulation Dysregulation of calcium and phosphorus metabolism is common. Elevated levels of calcium and phosphorus directly impact vascular smooth muscle cells, promoting cardiovascular calcification and arteriosclerosis. The present study concludes that there is a positive correlation between S. CaxP levels and CIMT, and a positive correlation between CIMT and S. CaxP with the duration of MHD. Since CVD begins during the early stages of CKD, before ESRD, it is important to identify at-risk patients long before renal replacement therapy is needed and to address all risk factors.

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