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Study of Correlation of Serum Phosphorus with Carotid Intima Media Thickness in Chronic Kidney Disease

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Abstract
Background: *Serum phosphorous is a significant risk factor for raised carotid intima media thickness (CIMT) with the conventional risk factors. Kidney dysfunction may also affect the clearance of phosphorus, which could be responsible for the calcification of major arteries.*
Aim: *To correlate serum phosphorus with carotid intima media thickness in chronic kidney disease.*
Material and Methods: *In this prospective observational study 190 cases of Chronic Kidney Disease were studied for carotid intima media thickness (CIMT). CIMT was measured using by B-mode ultrasonography using a 5 MHz transducer.Three measurements taken 0.5, 1, 2 cm below carotid bifurcation of common carotid artery on each side. IMT of both sides was calculated and average of those two values is used for statistical analysis.*
Results: *When serum phosphorous was correlated with CIMT in all four stages of CKD, it was found to have no statistical significance (p value 0.503). However, when compared in each group, serum phosphorous was found to be lowest in stage Vd (4.5±1.18mg/dl) and highest in stage III (4.5±1.18mg/dl).*
Conclusion: *Carotid intima media thickness showed significantly positive correlation with serum phosphorous in the complete cohort. Correction of hyperphosphatemia may be emphasized for the prevention of progression of arteriosclerosis and to prevent vascular calcification in CKD.*
Keywords: *Chronic kidney disease,serum phosphorous, carotid intima media thickness,arteriosclerosis*

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I. Introduction

Chronic kidney disease (CKD) is evolving as a major chronic disease worldwide1. In India, the age adjusted incidence rate of End stage kidney disease (ESRD) has been estimated to be about 229 per million populations.[1]

Kidney dysfunction alters the lumen of blood vessels by inhibiting the cross-linking of collagen, making them atherogenic (narrows the lumen of the vessels).[2] Kidney dysfunction may also affect the clearance of calcium and phosphorus, which could be responsible for the calcification of major arteries such as coronary arteries.[2]

Raised serum phosphorus concentration is an important risk factor for vascular calcification.Hyperphosphataemia leads to alterations of calcium hemostatsis with a predisposition to metastatic calcifications of arterial wall, development and progression of secondary hyperparathyroidism.[3] Reduction of serum phosphorous level by using phosphate binders helps to prevent vascular calcification.[3]

It has been found that serum phosphorous is a significant risk factor for raised carotid intima media thickness (CIMT) with the conventional risk factors such as blood sugar, age and Body Mass Index (BMI).[3]The present study was conducted to correlate serum phosphorus with carotid intima media thickness in chronic kidney disease.

II. Material And Methods

This prospective observational study was conducted on 190 cases of Chronic Kidney Disease visiting Medicine outpatient department of a tertiary care hospital.

Inclusion criteria:

- All patients of Chronic Kidney Disease stage III, IV, Vnd, Vd.
- Age >18 years

Exclusion criteria:

- All patients of Acute kidney injury (as defined by RIFLE criteria)
- History of carotid surgery
- Pregnancy

Methodology

Carotid intima media thickness (CIMT) was measured using by B-mode ultrasonography using a 5 MHz transducer. Intima media thickness (IMT) is defined as a distance between the leading edge of first echogenic line (lumen-intima interface) and second echogenic line (media-adventitia interface) of far wall. Three measurements taken 0.5, 1, 2 cm below carotid bifurcation of common carotid artery on each side. IMT of both sides was calculated and average of those two values is used for statistical analysis.

B-mode Doppler ultrasound measurement of the CIMT was carried out following these steps:

(1) Patient lied in the supine position comfortably with his/her neck well exposed with no clothes covering his neck.

(2) Neck was slightly hyperextended and rotated 45° away from the side being examined. Patient was comfortable and excessive extension of the neck was avoided.

(3) Some patients were not able to lie supine. They were examined adequately in a sitting position. The examiner sat beside the patient's thorax and scanned the neck from this position, or sat at the patient's head and scanned the neck from that location.

(4) A high frequency linear superficial transducer (5–12 MHz) is ideal for intima–media CIMT measurements and plaque morphology assessment.

(5) The examination starts with a transverse scan of the carotid artery from as low in the neck as possible (common carotid artery) to as high in the neck as possible behind the angle of the mandible. This approach allows a better orientation and demonstration of the relationship between common carotid artery, internal jugular vein, thyroid, and trachea, and sternomastoid muscle. It helps in taking a general idea of the depth and course of the vessels, together with the level of the bifurcation and the orientation of its branches. In addition, areas of major disease could be identified and noted for further assessment.

(6) Longitudinal scan was then performed. Longitudinal views of the layers of the normal carotid wall demonstrate two nearly parallel echogenic lines separated by a hypoechoic to anechoic region; the distance between these lines represents the combined thickness of the intima and media (I–M complex).

We measured serum iPTHlevel by Fully Automated ChemiluminescentImmuno Assay method. We did quantitative determination of calcium in human serum, plasma on COBAS INTEGRA System by BAPTA method.

We did quantitative determination of phosphorus concentration in human serum, plasma on COBAS INTEGRA systems by Molybdate method.

Statistical analysis:

Continuous variables are described as mean±standard deviation (SD). Linear regression was done to determine the association and correlation of serum phosphorus with carotid intima- media thickness in chronic kidney disease patients. SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA)was used for analysis. The analysis of variance (ANOVA) [for quantitative data within three groups] with post hoc Bonferroni test (to make more intra-groups comparison) was used for quantitative data comparison of all clinical indicators. Chi-square test used for qualitative data whenever two or more than two groups were used to compare. Multivariate analysis pearson's correlation and regression were used. Level of significance was set at $p \leq 0.05$.

III. Results

Total 190 patients of CKD were included in study. Out of those, 100 patients were on maintenance hemodialysis (MHD). Rest 90 patients were on conservative management (30 each in stage III, IV, Vnd). Study population of stage Vd group were on MHD schedule at our center. There was statistically significant correlation between intact PTH and CIMT. When serum iron studies were compared in all stages of CKD, only serum ferritin was found to have statistical significance in stage Vd.

CKD stage Vd (on MHD) patients were studied based on their demographic and laboratory parameters. Average age of this group was 42.9+13.18 years.

In current study, males were predominant in each of the stage (73.33%, 73.33%, 76.67%, 76% in stage III, IV, Vnd, Vd respectively).

Among stage Vd group, average HD vintage was 11.44+12.15 months, median was 6.5 months. Inter-quartile range was 3.25- 18 months. Patients in stage Vd were compared as per their HD access. Out of 100, 51

patients had cuffed tunneled catheter as HD access, followed by arterio-venous fistula (AVF) in 36 patients and temporary catheter (uncuffed non-tunneld) in 13 patients. 60% patients on MHD were on twice a week schedule while rest 40% patients were on thrice a week schedule.

Among the stage Vd group, 95% patients were hypertensive. 28% cases had Diabetes Mellitus and 12% had Ischemic heart disease (IHD).

Demographic and laboratory parameters in stages III, IV and Vnd were compared. Except serum urea, serum creatinine and eGFR none of the metabolic parameters showed significance across CKD stages.

TABLE 1: Demographic& Laboratory parameters in all CKD stages

Parameters	**CKD stage III**	**CKD stage IV**	**CKD stage Vd**	**CKD stage VnD**
Age	42.53+10.91	41.13+11.06	42.9+13.18	40.96+11.05
Male	22(73.33%)	22(73.33%)	76 (76%)	23(76.67%)
Female	8(2.64%)	8(2.64%)	24 (24%)	7(2.33%)
HTN	27(90%)	26(86.67%)	95 (95%)	30(100%)
DM	4(13.33%)	6(20%)	28 (28%)	8(2.64%)
IHD	2(6.67%)	1(3.33%)	12 (12%)	2(6.67%)
BMI Kg/m2	19.56+4.14	21.23+4.35	19.6+ 3.97	19.5+4.01
SC mg/dl	2.18+0.26	3.75+0.43	7.83+1.93	6.62+1.12
Urea mg/dl	76.53+13.28	73+12.91	87.86+18.35	84.73+19.83
Hbgm/dl	9.10+1	8.45+1.37	7.9+1.16	8.55+1.16
Sodium mmol/l	137.16+2.92	136.13+3.07	135.98+3.65	136.16+2.94
Potassium mmol/l	4.57+0.46	4.42+0.55	4.44+0.54	4.39+0.56
Calcium mg/dl	8.47+0.4	8.49+0.38	8.4+0.4	8.63+0.59
Phosphorous mg/dl	4.96+1.29	4.86+1.23	4.5+1.18	4.77+1.1
Uric acid mg/dl	5.15+1.61	4.82+1.56	5.68+1.71	5.82+1.78
Albumin gm/dl	3.27+0.29	3.29+0.44	3.19+0.4	3.4+0.77
Bicarbonate meq/	20.83+2.47	20.75+2.32	20.56+2.08	20.7+2.42
Cholesterol mg/dl	194.03+22.09	181.63+46.56	193.72+34.42	192.8+26.13
TG mg/dl	148.4+17.31	148.66+17.25	144.47+21.56	151.16+20.47
LDL mg/dl	43.63+13.23	41.86+8.25	31.5+7.56	37.83+7.83
Sr. iron µg/dl	122.06+23.75	119.46+22.81	126.6+23.3	130.9+21.01
Sr. ferritin µg/dl	163.93+42.27	179.96+54.56	150.34+52.93	178.4+42.7
Sr. TIBC µg/dl	264.56+81.15	262.43+82.61	254.06+89.7	227.6+68.58
Transferrin sat %	31.63+8.6	32.5+7.78	32.2+7.83	29.4+5.86
Intact PTH pg/ml	174.9+92.05	169.2+82.11	177.71+84.77	195.5+92.94
hs CRP mg/L	1.28+1.18	1.63+1.59	24.81+28.73	1.2+0.66
HbA1C	5.77+0.57	5.74+0.67	6.02+0.99	5.91+0.76
UPCR	1.14+0.58	1+0.52	1.2+0.68	1+0.61
eGFR ml/min/1.73 m2	33.6+3.32	17.73+2.66	7.83+2.8	9.33+2.27

Comparison of demographic and laboratory parameters in four stages of CKD done. Some parameters like hemoglobin, serum calcium, serum phosphorous, serum albumin, serum bicarbonate, serum triglycerides, serum LDL, serum ferritin, CIMT mean and calcium-phosphorous product were found to be on lower side in stage Vd as compared to conservative CKD stages(III, IV, Vnd) though no statistical significance was found. While hs CRP, HbA1C and UPCR were found to be on higher side in stage Vd as compared to conservative CKD stages, but again no statistical significance was found.

CIMT (mean) when compared across those four stages, found to be minimum in stage Vd with mean 0.69±0.109mm (Range 0.35-0.95mm). It was found to be highest in stage III with mean 0.74 ±0.079mm (Range 0.60-0.85mm). However, it was found to have no statistical significance across four stages of CKD.

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

Side	Stage	N	Mean±SD
CIMT right side	Stage Vd	100	0.661±0.12
	Stage VnD	30	0.7±0.11
	Stage IV	30	0.71±0.098
	Stage III	30	0.73±0.102
	Total	190	0.68±0.116
CIMT left side	Stage Vd	100	0.72±0.121
	Stage VnD	30	0.71±0.095
	Stage IV	30	0.75±0.086
	Stage III	30	0.75±0.097
	Total	190	0.73±0.109

When serum phosphorous was correlated with CIMT in all four stages of CKD, it was found to have no statistical significance (p value 0.503). However, when compared in each group, serum phosphorous was found to be lowest in stage Vd (4.5±1.18mg/dl) and highest in stage III (4.5±1.18mg/dl).

TABLE 3: Correlation of serum Phosphorous with CIMT

		CIMT right	CIMT left	CIMT Mean
Stage Vd (NS)				
Serum phosphorous	Pearson Correlation	0.024	-0.009	0.008
	p value	0.81	0.92	0.93
Stage Vnd (NS)				
Serum phosphorous	Pearson Correlation	0.030	0.090	0.072
	p value	0.875	0.635	0.707
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

When CKD Vd group was compared to conservative CKD groups (stage III, IV and Vnd), serum phosphorous (p value 0.01)was found to have statistical significance with mean CIMT.

TABLE 4: Serum phosphorus

		CIMT right	CIMT left	CIMT mean	S ph
Dialysis (n=100)	Mean±SD	0.66±0.12	0.72±0.12	0.69±0.109	4.58±1.18
Non-Dialysis (n=90)	Mean±SD	0.71±0.108	0.73±0.094	0.72±0.08	4.86±1.206
Total (n=190)	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

IV. Discussion

CKD, with its high prevalence, morbidity and mortality, is an important public health problem.[1] With 3% of land mass, India hosts 17% of the Earth's population.Large numbers of patients below the poverty line, low gross domestic product, and low monetary allocations for health care have led to suboptimal outcomes[1]
A characteristic feature of arterial disease in CKD is thickening and calcification of the medial arterial layer, known as arteriosclerosis. In its purest form, media calcification is concentric and does not extend into the arterial lumen.[4]

In present study, carotid intima media thickness showed significantly positive correlation with serum phosphorous ($p<0.05$). In a study by Sharma VK et al, mCIMTin CKD stage 3, 4, 5 were 0.375±0.125 mm, 0.608±0.193 mm, 0.6171±0.236 mm respectively. Faster change is noted between stage 3 and stage 4 CKD as compared to stage 4 and stage 5. In the analysis of the group of all CKD patients, serum phosphate level was a significant risk factor for increased CIMT independent of other confounding factors. There was very strong correlation between mCIMT and serum phosphate in their study group.[5]
Ruan et al study demonstrates that increasing levels of serum phosphorus, even within the normal range, are positively and independently related to subclinical atherosclerosis, measured as carotid IMT.[6]

Experimental data have shown that phosphorus is involved in the whole process of vascular calcification leading to a new consensus that has renamed the old term of renal osteodystrophy with CKD mineral bone disorder (CKD-MBD) and emphasizes the almost neglected role of the skeleton in these pathological states.[7]
In CKD patients, hyperphosphatemia has been reported to be a significant risk factor for vascular calcification and phosphate level reduction by means of phosphate binders has been reported to attenuate vascular calcification.[8,9]

V. Conclusion

Carotid intima media thickness showed significantly positive correlation with serum phosphorous in the complete cohort. Correction of hyperphosphatemia may be emphasized for the prevention of progression of arteriosclerosis and to prevent vascular calcification, in CKD.

Limitation of the study:

Limitation of our study was the smaller study population. We recommend larger study with more sample size, longitudinal study to assess progression of Atherosclerosis in CKD, interventional longitudinal study to see whether rigid control of hyperphosphatemia and hyperparathyroidism would be helpful in

decreasing Atherosclerosis and study of various other parameters responsible for atherosclerosis like Apoliporotein-A would be of help.

References

[1]. Singh AK, Farag YM, Mittal BV, Subramanian KK, Reddy SR, Acharya VN, Almeida AF, Channakeshavamurthy A, Ballal HS, Gaccione P, Issacs R. Epidemiology and risk factors of chronic kidney disease in India–results from the SEEK (Screening and Early Evaluation of Kidney Disease) study. BMC nephrology. 2013 Dec;14(1):114.

[2]. Vadakedath S, Kandi V. Dialysis: a review of the mechanisms underlying complications in the management of chronic renal failure. Cureus. 2017 Aug;9(8).

[3]. Kalantar-Zadeh K, Gutekunst L, Mehrotra R, Kovesdy CP, Bross R, Shinaberger CS, Noori N, Hirschberg R, Benner D, Nissenson AR, Kopple JD. Understanding sources of dietary phosphorus in the treatment of patients with chronic kidney disease. Clinical Journal of the American Society of Nephrology. 2010 Mar 1;5(3):519-30.

[4]. Souberbielle JC, Roth H, Fouque DP. Parathyroid hormone measurement in CKD. Kidney international. 2010 Jan 2;77(2):93-100.

[5]. Sharma VK, Dwivedi P, Dubey AK. Correlation of serum phosphate with carotid intimal-medial thickness in chronic kidney disease patients. Indian journal of nephrology. 2014 Jan;24(1):15.

[6]. Ruan L, Chen W, Srinivasan SR, Xu J, Toprak A, Berenson GS. Relation of serum phosphorus levels to carotid intima–media thickness in asymptomatic young adults (from the Bogalusa Heart Study). The American journal of cardiology. 2010 Sep 15;106(6):793-7.

[7]. Spradling KD, Glenn JP, Garcia R, Shade RE, Cox LA. The baboon kidney transcriptome: analysis of transcript sequence, splice variants, and abundance. PloS one. 2013 Apr 23;8(4):e57563.

[8]. Cozzolino M, Dusso AS, Slatopolsky E. Role of calcium-phosphate product and bone-associated proteins on vascular calcification in renal failure. Journal of the American Society of Nephrology. 2001 Nov 1;12(11):2511-6.

[9]. Chertow GM, Burke SK, Raggi P, Treat to Goal Working Group. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney international. 2002 Jul 1;62(1):245-52.

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