Original Research Paper

Nephrology

SERUM PHOSPHATE LEVELS AND ITS CORRELATION WITH CAROTID INTIMA MEDIA THICKNESS IN CHRONIC KIDNEY DISEASE

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ABSTRACT This is a hospital based observational study done over a span of 6 months, wherein the various factors that influence atherosclerosis in CKD patients were studied. Among the factors that were studied apart from traditional risk factors like age, smoking, diabetes, hypertension, phosphorus, calcium phosphorus product, newer markers of atherosclerosis namely non HDL cholesterol and non HDL cholesterol phosphorus product were also compared. Due to confounding effects of various interlinked risk factors, multivariate analysis was done. Patients with AKI, previous stroke, coronary artery disease, carotid surgery or trauma were excluded from study.
Among the various parameters, smoking, phosphorus, calcium- phosphorus product, phosphorus-non HDL cholesterol correlated significantly with CAIMT and hence atherosclerosis. Serum phosphorus is a significant independent risk factor for atherosclerosis in CKD patients. Phosphorus non HDL product, Calcium-Phosphorus product, smoking also correlated strongly with CAIMT. Non HDL cholesterol independently didn't influence CAIMT significantly in this study, but the product of Phosphorus and non HDL cholesterol correlated significantly with CAIMT.

KEYWORDS :

Introduction:
Chronic kidney disease patients are at increased risk for atherosclerosis and cardiovascular mortality. Leading morality cause in CKD is CVD and stroke, who have a risk for death 10 to 20 times that of general population. Atherosclerosis can be measured by means of arterial wall thickness and stiffness by carotid artery intima media thickness.

In the general population, advanced age, hypertension, cigarette smoking and dyslipidaemia are the most significant risk factors for advanced arteriosclerosis. In uremic patients, it is not clear whether risk factors for arteriosclerosis are similar to those in the non-uremic population.

Although increased serum phosphate concentration is a significant risk factor for vascular calcification, which is an advanced form of atherosclerosis, whether serum phosphate concentration is associated with arterial wall thickness in CKD is not clear.

In this study using B mode ultrasound of carotid artery, the carotid intima media thickness (which is a direct marker of atherosclerosis) is compared with serum phosphate levels in CKD patients and the effects of various factors – smoking, diabetes, dyslipidaemia, non HDL cholesterol, systolic BP are also studied.

Subjects and Methods:
Patients admitted in Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 diagnosed to have CKD, fulfilling the inclusion and exclusion criteria were included in the study group. 100 such patients were taken up for this study. It is a hospital based Observational study over a period of 6 months.

Patients with chronic kidney disease were included and **p**atients with acute kidney injury, previous stroke, coronary artery disease, carotid artery trauma or surgery were excluded from study. Patients were subjected with following investigations: haemogram, renal function tests, serum albumin, serum calcium, phosphorus, fasting lipid profile, carotid artery doppler.Statistics was analyzed using Epi Info and SPSS 20. The variables with p <0.05 were considered significant.

Results:
This study was conducted in CKD patients of stage 3, 4, 5 and 5D to analyze the various factors affecting CAIMT which is a marker of atherosclerosis in patients. CAIMT is a surrogate marker of coronary artery disease risk. In non CKD patients the various factors influencing atherosclerosis are age, smoking, physical inactivity, presence of diabetes, dyslipidemia. Whether the same risk factors apply to CKD or other markers (Phosphorus, C-P product, non HDL cholesterol, P- non HDL cholesterol product) predominate as atherosclerosis marker is analyzed in this study.

In this study, 9 CKD 3, 25 CKD 4 and 66 CKD 5 patients were studied.

Of which 7 were on HD and 22 on PD. 50 were diabetic CKD patients and 72 were Hypertensive.17 patients were smokers and 83 nonsmokers.46 females and 54 males were included.

The average age of patients included was 53.32 years, average systolic BP was 149.6 mm Hg, average e GFR was 14.09 ml/ min/ 1.73 m^2 .Average phosphorus was 4.777 mg/dl which was higher than the normal range. Average calcium was 8.5904, average C-P product 41.1393, average non HDL cholesterol 137.26, average total cholesterol 172.9, average serum creatinine 5.659 mg/dl. The mean CAIMT was 1.2455 ± 0.3523 mm which was higher than the population cut off of 1 mm.

Table 1 Parameters and Means

	MEAN	STANDARD DEVIATION
AGE	53.32	13.5861
SYSTOLIC BP	149.6	23.4809
e GFR	14.9016	10.9791
PHOSPHORUS	4.777	1.4319
CALCIUM	8.5904	1.0424
HDL	37.52	10.3528
NON HDL	137.26	43.6237
P- NON HDL PRODUCT	672.347	310.4387
C-P PRODUCT	41.1393	12.6078
CAIMT	1.2455	0.3523
HB	8.653	2.2098
BMI	23.2411	3.2255
T.CHOLESTEROL	172.9	42.015
S. CREATININE	5.659	3.3601

CKD STAGE AND VARIOUS PARAMETERS

Table 2 CKD Stage and Various Parameters

CKD Stage	PHOSPHORUS	CALCIUM	C-P Product	NON HDL	P-NON HDL Product	m CAIMT
3	3.7444	9.1222	34.1133	161.1111	627.9889	0.9278
4	4.2440	8.3832	35.64	134.96	581.268	1.222
5	5.1197	8.5964	44.1805	134.8788	712.8955	1.2977
P Value	0.0020	0.1900	0.0027	0.2141	0.1780	0.0105

Mean serum phosphorus levels increased according to CKD stage ; 3.7444 in CKD 3, 4.2440 in CKD 4, 5.1197 in CKD 5 with p value 0.0020. m CAIMT increased with CKD stage ; 0.9278 mm in CKD 3, 1.222 in CKD 4, 1.2977 in CKD 5 with p value 0.0105.

Calcium- Phosphorus product also increased according to CKD stage; 34.1133 in CKD 3, 35.64 in CKD 4, 44.1805 in CKD 5 with p value of

0.0027. Mean Calcium values decreased with CKD stage, mean non HDL cholesterol level also decreased with CKD stage, but were not statistically significant.
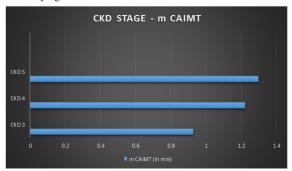

Figure 1 CKD Stage m CAIMT

GENDER DISTRIBUTION OF PARAMETERS
Mean CAIMT was higher in male CKD 1.2843 mm against 1.2000 in females, mean Phosphorus values were higher in female CKD 4.8087 mg/dl against 4.7500 in male CKD. Mean calcium was lower in male CKD patients 8.5300, mean phosphorus non HDL product was higher in male CKD 686.7370 whereas it was 655.4543 in female CKD patients.

DISTRIBUTION OF PARAMETERS IN DIABETES
Mean phosphorus in DM 4.6780 was lower than non DM patient 4.8760 with p value 0.0129. Mean C-P Product was also lower in DM patient 40.5462 than non DM patients 41.7324 with p value 0.0129.However the rest of parameters studied were not statistically significant in this study.

CORRELATION OF VARIOUS PARAMETERS WITH CAIMT
In this study systolic BP, e GFR, hemoglobin values, phosphorus, C-P product, P- non HDL cholesterol correlated significantly with CAIMT with p values <0.05, whereas age, non HDL cholesterol, total cholesterol didn't correlate with CAIMT significantly. Serum phosphorus correlated strongly with CAIMT with Pearson correlation coefficient of 0.4308. C-P product also correlated strongly with CAIMT with Pearson correlation coefficient of 0.3239. e GFR and Hemoglobin values had significant negative correlation with CAIMT with Pearson correlation coefficients of -0.2866 and -0.2795 respectively implying that fall in e GFR and hemoglobin correlated with CAIMT significantly. While non HDL cholesterol didn't have significant correlation with CAIMT independently, phosphorus-non HDL cholesterol did significantly correlate with CAIMT with Pearson correlation coefficient of 0.2597.

Hence serum Phosphorus is an independent significant risk factor for increased CAIMT and hence atherosclerosis.
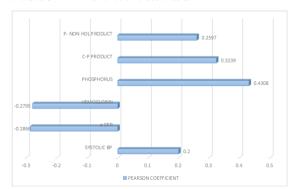

Figure 2 Correlation of Various Parameters with CAIMT

Conclusion:
• The mean CAIMT in CKD patients was higher than population cut off. (1.2455 ± 0.3523)
• The mean phosphorus, C-P product, mean CAIMT increased with CKD stage progression.
• The mean phosphorus and C-P product were lower in DM patients than non DM patients.

• Systolic BP, e GFR, hemoglobin values, phosphorus, C-P product, P- non HDL cholesterol correlated significantly with CAIMT with p values <0.05, whereas age, non HDL cholesterol, total cholesterol didn't correlate with CAIMT significantly.
• Serum phosphorus correlated strongly with CAIMT (Pearson correlation coefficient of 0.4308). C-P product also correlated strongly with CAIMT (Pearson correlation coefficient of 0.3239)
• While non HDL cholesterol didn't have significant correlation with CAIMT independently, phosphorus-non HDL cholesterol did significantly correlate with CAIMT (Pearson correlation coefficient of 0.2597).

Among the various parameters, smoking, phosphorus, calcium-phosphorus product, phosphorus-non HDL cholesterol correlated significantly with CAIMT and hence atherosclerosis.

Serum phosphorus is a significant independent risk factor for atherosclerosis in CKD patients. Phosphorus non HDL product, Calcium-Phosphorus product, smoking also correlated strongly with CAIMT. Non HDL cholesterol independently didn't influence CAIMT significantly in this study, but the product of Phosphorus and non HDL cholesterol correlated significantly with CAIMT.

Discussion:
CKD is defined as abnormality of kidney structure or function, with implications for health and CKD is classified according to cause, GFR category and albuminuria category.

Patients with CKD are at increased risk of cardiovascular diseases (CVD). CVD is leading cause of death in CKD. The various traditional and non-traditional risk factors of CVD in CKD are as follows.

Traditional CVD Risk Factors	"Nontraditional" CVD Risk Factors
Older age	Type (diagnosis) of CKD
Male gender	Decreased GFR
White race	Proteinuria
Hypertension	Renin-angiotensin system activity
Elevated LDL cholesterol	Extra-cellular fluid volume overload
Decreased HDL cholesterol	Abnormal calcium and phosphorus
Diabetes mellitus	metabolism
Tobacco use	Dyslipidemia
Physical inactivity	Anemia
Menopause	Malnutrition
Psychosocial stress	Inflammation
Family history of CVD	Infection
	Thrombogenic factors
	Oxidative stress
	Elevated homocysteine
	Advanced glycation end-products (AGEs)
	Uremic toxins

Figure 3 CVD risk Factors

FGF 23 – KLOTHO AXIS
Phosphorus is an independent risk factor of calcification in CKD. Novel marker FGF 23 and Klotho proteins have been discovered which influence calcification and atherosclerosis in CKD patients. FGF 23 causes phosphaturia by acting on Na-Pi 2a, 2c transporters in kidneys and decreases phosphorus absorption from gut by decreasing serum calcitriol levels. Net phosphorus lowering effect is seen. Klotho protein acts as catalyst for FGF23 binding to its receptors in kidney.in CKD patients there is net dysregulation of FGF 23 and Klotho leading to phosphorous accumulation and atherosclerosis.
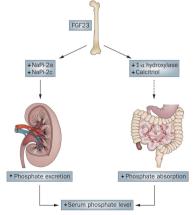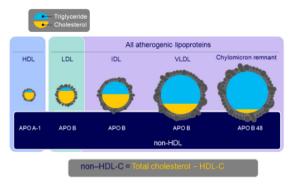

Figure 4 FGF 23 KLOTHO axis

Figure 5 non HDL cholesterol

CONCEPT OF NON HDL CHOLESTEROL

Non HDL Cholesterol represents cholesterol content of all lipids except HDL cholesterol. Non HDL cholesterol is easier to measure, non-fasting blood sample adequate for its value. Therefore treatment of non HDL cholesterol is wholesome approach to dyslipidemia management. Non HDL cholesterol is an important CVD risk factor in diabetes patients. This study verifies if it has significant role in CKD patients also.

CAROTID ARTERY INTIMA MEDIA THICKNESS (CAIMT)

CAIMT is a direct measure of atherosclerosis. It's measured using B mode ultrasound of carotid vessel. 3 methods are there for its measurement – transverse, anterolateral, posterolateral. With patient lying in supine position, initially transverse view is used to locate best site for measuring CAIMT. Then either anterolateral or posterolateral approach is used and CAIMT measured by using calipers in ultrasound from start of first white line to end of second white lines. 3 readings are taken on each side and average of them is used. Avoid measuring CAIMT in areas with plaque. A CAIMT greater than 1.0mm was considered to be an abnormal finding.
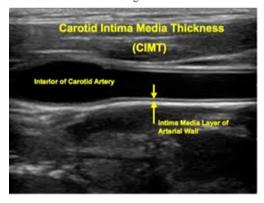

Figure 6 CAIMT

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