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CORRELATION OF SERUM PHOSPHATE AND CAROTID INTIMAL MEDIAL THICKNESS IN PREDIALYSIS CHRONIC KIDNEY DISEASES PATIENTS

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ABSTRACT:

BACKGROUND- The study attempted to correlate serum phosphate and carotid intimal medial thickness in pre dialysis CKD patients.

METHODS- This was a cross sectional case control study involving 70 CKD patients. They were compared with age and gender matched 30 controls. Serum phosphate and Carotid Intimal Medial thickness was done in all patients along with routine investigations.

RESULTS- Carotid intimal thickness correlated with serum phosphate. There was significant negative correlation between CIMT and eGFR. The association between serum phosphate and CIMT could be expressed as a mathematical equation.

CONCLUSIONS- serum phosphate estimation can be used as a surrogate marker to assess CIMT in CKD patients.

KEY WORDS: CKD, CIMT, eGFR, phosphate, pre-dialysis CKD patients

INTRODUCTION:

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with Implications for health (K/DOQI guidelines) (1). The prevalence of chronic renal disease (CKD) is increasing across the world. The prevalence has been estimated as 8-16% across the world. There is very high cardiovascular morbidity and mortality in CKD patients. The risk of death is 10-20 times more than age and sex matched general population.

It is well known that majority of patients of CKD will not reach end stage renal disease instead they would die prematurely due to cardiovascular events. Stage 3 CKD patients have 20 times risk of dying due to cardiovascular diseases than to progress to end stage renal disease (2, 3). The high cardiovascular morbidity and mortality cannot be explained by traditional cardiovascular risk factors alone. Newer non-traditional cardiovascular risk factors are being explored to account for very high cardiovascular deaths.

This study an attempt to explore the relationship between serum phosphate and carotid intimal medial thickness in pre dialysis CKD patients so as to devise a simple and reliable indicator to predict cardiovascular morbidity and mortality.

MATERIAL AND METHODS:

This was a cross sectional prospective study on 70 patients with chronic kidney disease as defined by K/DOQI guidelines (kidney disease outcome quality initiative group) having an estimated GFR (eGFR) <60ml/min/1.73sq meter, who did not require renal replacement therapy at the time of presentation (called as pre dialysis

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chronic kidney disease patients) attending the Nephrology clinic, General Medicine outpatients and indoor services in Safdarjung hospital,(a tertiary care hospital and college and research institute) were studied. Staging of these patients was done according to the eGFR using MDRD formula (modification of diet in renal disease). Each patient was subjected to detailed history and examinations of past records, with special emphasis on records of hypertension, chronic kidney disease, diabetes mellitus and other comorbid conditions. A thorough clinical examination was done, especially to assess malnutrition and fluid overload. Patients were divided into two groups, group a comprised of 70 patients of CKD and Group B included age and gender matched 30 healthy controls. Patients with AKI, on phosphate binders or hypolipedimic drug, prior history of cardiovascular mortality, stroke, parathyroid pathology and carotid surgery were excluded from the study group.

All cases were subjected to routine investigations (hemogram, blood urea, creatinine, eGFR, serum electrolytes, calcium, phosphate, sugar, HbA1C, USG KUB and urine R/M).

Estimated GFR (eGFR) was calculated by using MDRD (modification of diet in renal formula)- eGFR = 186 x (Creat / 88.4)-1.154 x (Age)-0.203 x (0.742 if female)

The left and right Carotid arteries were examined by using PHILIPS HDBXE high definition ultrasound system equipped with a 3-12 MHz linear array transducer. Intimal thickness was taken as the distance between leading edge of first echogenic line (lumen intimal interface) and second echogenic line (medial adventitia interface). These measurements were recorded 0.5,1 and 2 cm below bifurcation of common carotid artery on bo th sides. The arithmetic mean of these measurements on both sides was recorded. The average of intimal thickness on both sides was used for statistical purposes. All measurements were recorded by a single radiologist in a plaque free arterial segment. (The plaque was defined as focal widening relative to the adjacent segment, with protrusion into the lumen).

Serum phosphate was measured by using Roche Hitachi 912 auto analyser. The reagent components were ammonium molybdate, sulphuric acid and detergent. The principle behind this procedure was that in acid medium phosphate reacts with ammonium molybdate to form a yellow phosphorous molybdate complex. The complex absorption was maximum at 340 nm. Absorption is proportional to the concentration of inorganic phosphate in the sample. Thus the concentration of phosphate in a given sample could be calculated by comparing the absorption of the sample with that of the standard against the reagent blank.

Serum/Plasma Phosphate (mg/dl) =Serum/Plasma: ΔA Sample * x Conc. of Std/Cal (mg/dl) ΔA Std/Cal Normal serum phosphate level in adults is 2.6-4.5mg/dl. Serum phosphate was analysed as a categorical variable.

STATISTICAL ANALYSIS

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected, then non parametric test was used.

Statistical tests were applied as follows-

1. Quantitative variables were compared using Unpaired t-test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups.

2. Qualitative variables were correlated using Chi-Square test /Fisher's exact test.

3. Pearson correlation coefficient and Linear regression was used to assess the association of S. phosphate and CIMT.

A p value of <0.05 was considered statistically significant.

RESULT:

The study is a cross sectional study comprising of 70 randomly selected CKD patients and 30 cases

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of age and sex matched controls conducted in VMMC and Safdarjung hospital, Delhi. Patients with eGFR<60 ml/min/1.73m^2 who were not on dialysis were included in our study group. Carotid intimal medial thickness and serum Phosphate levels were measured in both groups. Comparison was done between the cases and control groups in respect to the serum phosphate levels and the carotid medial intimal medial thickness and their correlation was analysed. Intimal medial thickness was measured in various stage of CKD and compared.

After using appropriate statistical methods for both continuous and categorical variables the following results were obtained.

Table 1: compares the clinical profile of both study and the control group.

	MRD(n=70)	Normal(n=30)	P value
Age			.4
Mean ± Stdev	45 ± 15.11	42.17 ± 15.94	
Median	44	45	
Min-Max	16-78	18-78	
Inter quartile Range	35 – 56	30 - 55	
B.urea			<.0005
Mean ± Stdev	106.02 ± 44.07	31.6 ± 9.45	
Median	99	29	
Min-Max	40-232	16-54	
Inter quartile Range	77 – 122	25 - 38	
S.creatinine			<.0005
Mean ± Stdev	5.31 ± 2.13	0.72 ± 0.24	
Median	5.05	0.7	
Min-Max	1.9-12	0.4-1.4	
Inter quartile Range	3.700 - 6.300	0.500 - 0.900	
S.calcium			.831
Mean ± Stdev	8.73 ± 1.05	8.69 ± 0.82	
Median	8.8	8.7	
Min-Max	6.8-11	6.8-10.8	
Inter quartile Range	7.900 - 9.500	8.100 - 9.100	
S.phosphate			<.0005
Mean ± Stdev	5.69 ± 0.93	4.39 ± 0.74	
Median	5.8	4.55	
Min-Max	3.2-7.7	2.8-6	
Inter quartile Range	5 - 6.400	3.800 - 4.800	
Hb			.046
Mean ± Stdev	8.95 ± 1.67	9.73 ± 1.57	
Median	9.1	9.95	
Min-Max	4.1-12.4	6.3-12.4	
Inter quartile Range	8 – 10	8.400 - 10.900	
S.Sodium			.701
Mean ± Stdev	141.24 ± 6.21	141.63 ± 5.83	
Median	142	141.5	

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Min-Max	128-155	131-152	
Inter quartile Range	136 - 146	137 - 146	
S.Potassium			.882
Mean ± Stdev	4.5 ± 0.59	4.49 ± 0.36	
Median	4.4	4.5	
Min-Max	3.4-6.1	3.8-5.3	
Inter quartile Range	4.100 - 4.800	4.200 - 4.800	
Blood pressure systole			0.009
Mean ± Stdev	138.2 ± 16.5	129.2 ± 12.7	
Median	138	128	
Min-Max	110-180	100-154	
Inter quartile Range	126 - 146	120 - 140	
Blood pressure diastole			.026
Mean ± Stdev	86.57 ± 9.99	81.13 ± 7.66	
Median	84	82	
Min-Max	72-120	68-94	
Inter quartile Range	80 – 92	76 - 86	
blood sugar fasting			.839
Mean ± Stdev	127.23 ± 41.08	119.6 ± 26.92	
Median	111	115	
Min-Max	77-222	75-224	
Inter quartile Range	96 – 156	104 - 130	
Cholesterol			<.0005
Mean ± Stdev	249.47 ± 71.73	173.63 ± 33.05	
Median	244	165.5	
Min-Max	139-458	140-301	
Inter quartile Range	198 - 289	150 – 188	
LDL			.001
Mean ± Stdev	105.66 ± 27.57	90.97 ± 18.53	
Median	99	85.5	
Min-Max	68-202	70-160	
Inter quartile Range	89 – 111	80 - 96	
urine pus			.158
Mean ± Stdev	2.09 ± 6.3	0.2 ± 0.48	
Median	0	0	
Min-Max	0-36	0-2	
Inter quartile Range	0 – 1	0 - 0	
urine protein			.158
Mean ± Stdev	0.46 ± 0.88	0.2 ± 0.55	
Median	0	0	
Min-Max	0-3	0-2	
Inter quartile Range	0 – 1	0 - 0	
urine blood			.083
Mean ± Stdev	0.59 ± 1.77	0.07 ± 0.25	

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Median	0	0	
Min-Max	0-11	0-1	
Inter quartile Range	0 – 0	0 - 0	
TLC			.892
Mean ± Stdev	7548.57 ± 2104.36	7616.67 ± 2695.47	
Median	7400	7900	
Min-Max	4300-11600	3100-13000	
Inter quartile Range	5800 - 9300	4800 – 9800	
eGFR			<.0005
Mean ± Stdev	17.9 ± 8.97	115.22 ± 35.45	
Median	15.78	106.25	
Min-Max	5.79-50.66	72.41-196.67	
Inter quartile Range	10.807 - 22.109	89.583 - 132.506	

The mean phosphate level in CKD patients was 5.69± 0.93 as compared to 4.39± 0.74 in control group ($p<0.0005$). Serum Phosphate levels correlated well with the severity of CKD. Average phosphate levels rose from 4.46 ± 0.86 in stage 3 CKD to 5.79 ± 0.73 in stage 4 and 5.91 ± 0.9 in stage 5 CKD. ($p<0.0001$). On applying the tests for significance, it was seen that the p- value was highly significant on comparing stage 3 and stage 4, and also stage 3 and stage 5 (p-value <0.0005). But on comparing stage 4 and stage 5, the data was not significant and thus similar. (p value = 0.561). (Table 1)

Table 2: Correlation of serum phosphate with different stages of CKD

Phosphate (mg/dl)	Stage 3	Stage 4	Stage 5	Stage 3 vs Stage 4 (P value)	Stage 3 vs Stage 5 (P value)	Stage 4 vs Stage 5 (P value)
Sample size	8	30	32	<0.0005	<0.0005	0.561
Mean ± SD	4.46 ± 0.86	5.79 ± 0.73	5.91 ± 0.9			
Median	4.4	5.85	5.9			
Min-Max	3.2-6.1	4.4-7.1	4-7.7			
Inter quartile Range	3.950 - 4.850	5.000 - 6.400	5.100 - 6.700			

The mean Carotid Intimal Medial Thickness in study group was 0.74 ± 0.21 as compared with0.64 ± 0.16 in control group (p=0.034).

Similarly, Carotid intimal Medial Thickness values on right and left side were significantly higher in CKD patients as compared with controls($p<0.05$). Carotid Intimal Medial Thickness values were comparable on either side.

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Table 3: Comparison of carotid intimal medial thickness amongst cases and controls

	CASES	CONTROLS	P-VALUE
CIMT Left Avg (mm)			.042
Mean ± SD	0.73 ± 0.22	0.63 ± 0.18	
Median	0.72	0.63	
Min-Max	0.33-1.3	0.33-1.07	
Inter quartile Range	0.567 - 0.867	0.500 - 0.767	
CIMT Right Avg (mm)			0.039
Mean ± SD	0.74 ± 0.21	0.65 ± 0.16	
Median	0.73	0.68	
Min-Max	0.4-1.27	0.4-1.03	
Inter quartile Range	0.533 - 0.867	0.467 - 0.767	
CIMT Average (mm)			0.034
Mean ± SD	0.74 ± 0.21	0.64 ± 0.16	
Median	0.72	0.67	
Min-Max	0.38-1.28	0.37-0.95	
Inter quartile Range	0.550 - 0.867	0.517 - 0.750	

Carotid Intimal Medial Thickness values of stage 5 CKD patients were significantly higher than stage 3($p<0.0001$). But the difference between stage 4 and 5 was not significant ($p=0.16$). Similarly, CIMT of stage 4 were higher than stage 3($p=0.02$). (Table 3)

Table 4: Comparison of CIMT amongst controls and different stages of CKD and between different stages of CKD amongst themselves

	Control	**Stage 3**	**Stage 4**	**Stage 5**	**P value Control vs Stage 3**	**P value Control vs Stage 4**	**P value Control vs Stage 5**	**P value Stage 3 vs 4**	**P value Stage 3 vs 5**	**P value Stage 4 vs 5**
CIMT Average(mm)					0.127	0.095	0.003	0.02	<.0001	0.16
Sample size	30	8	30	32						
Mean ± SD	0.64 ± 0.16	0.55 ± 0.09	0.72 ± 0.19	0.8 ± 0.23						
Median	0.67	0.5	0.73	0.8						
Min-Max	0.37-0.95	0.47-0.7	0.38-1.28	0.43-1.23						
Inter quartile Range	0.517 - 0.750	0.492 - 0.617	0.567 - 0.850	0.642 - 0.992						

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CIMT Left Avg (mm)										
Sample size	30	8	30	32						
Mean ± SD	0.63 ± 0.18	0.53 ± 0.09	0.71 ± 0.2	0.79 ± 0.22	0.118	0.12	0.004	0.02	<.0001	0.156
Median	0.63	0.48	0.72	0.8						
Min-Max	0.33-1.07	0.43-0.67	0.33-1.3	0.4-1.23						
Inter quartile Range	0.500 - 0.767	0.467 - 0.617	0.567 - 0.833	0.650 - 0.933						
CIMT Right Avg (mm)										
Sample size	30	8	30	32						
Mean ± SD	0.65 ± 0.16	0.57 ± 0.09	0.73 ± 0.19	0.8 ± 0.23	0.167	0.089	0.004	0.025	<.0001	0.177
Median	0.68	0.53	0.73	0.82						
Min-Max	0.4-1.03	0.5-0.73	0.4-1.27	0.4-1.23						
Inter quartile Range	0.467 - 0.767	0.500 - 0.617	0.600 - 0.867	0.633 - 1.000						

Relationship between serum phosphate and CIMT (table 5)

Correlation co-efficient **r** was calculated to test the strength of association between Carotid Intimal Medial Thickness and serum phosphate levels. Correlation co-efficient (**r**) between mean Carotid Intimal Medial Thickness and phosphate level was +0.4259(p=0.0002). **r** value on right and left side was +0.3921 and +0.4476 respectively (p=0.0008 & 0.0001). Hence, there was a significant association between Carotid Intimal Medial Thickness and serum phosphate level.

Table 5: Correlation between serum phosphate and Carotid intimal medial thickness

	Correlation coefficient r	**P value**	**95% Confidence interval for r**
CIMT Right Avg	0.3921	0.0008	0.1730 to 0.5741
CIMT Left Avg	0.4476	0.0001	0.2376 to 0.6176
CIMT Avg	0.4259	0.0002	0.2121 to 0.6007

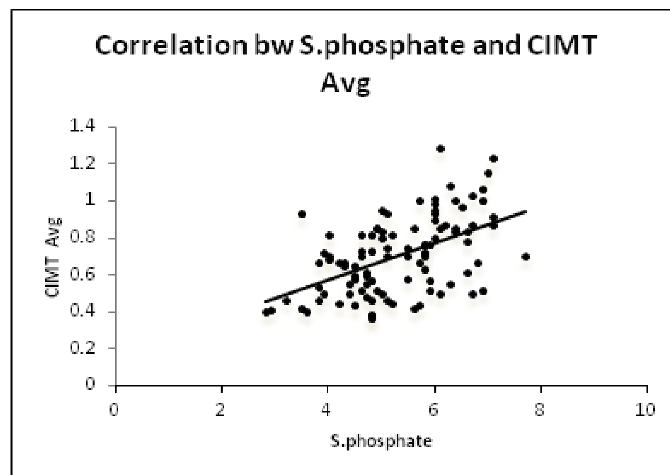

Figure 1: correlation between serum phosphate and cimt average

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A formula predicting CIMT value from serum phosphate level was calculated by using y intercept and slope of the graph (y=mx +c). The formula is as follows-

CIMT = 0.1808 + 0.09746x S. Phosphate.

Standard error for this formula is 0.025 and the standard deviation is 0.209 with a 95% confidence limit of 0.047 to 0.148

DISCUSSION:

Cardiovascular disease is a major concern in persons with chronic kidney disease. There continues to be a substantial cardiovascular risk factor burden among adults with chronic kidney disease stage 3 to 5 and to a lesser extent, adults with chronic kidney disease with chronic kidney disease stage 1 and 2 as compared to adults without chronic kidney disease.

The patients with chronic kidney disease are more likely to die of cardiovascular disease than to reach end stage disease. Stage 3 chronic kidney disease patients have 20 times risk of dying due to the cardiovascular disease than to progress to end stage renal disease. [2, 3]

Several large prospective population studies have shown that even mild chronic kidney disease is an independent risk factor for cardiovascular disease, independent of hypertension, diabetes and albuminuria and similar in magnitude to diabetes and hypertension [4, 5]

Now it is recognized that these metabolic disturbances also lead to vascular calcification and may be responsible for accelerated cardiovascular disease and excess mortality seen in chronic kidney disease populations. These metabolic disturbances include hyperphosphatemia and hyperparathyroidism.

Hyperphosphatemia has now been recognised as predictor of cardiovascular disease [6-8].

Phosphate levels rise with progression of chronic renal disease. In the present study, serum phosphate levels were significantly higher in patients of chronic kidney disease as compared to the control group ($p<0.001$) Moreover, serum phosphate levels were found to be well correlated with degree of chronic kidney disease. Phosphate levels in stage 3 chronic kidney disease were 4.46 ± 0.86. Similar trends have been observed in various scientific studies [9]. There was a regular increase in phosphate levels to 5.79 ± 0.73 in chronic kidney disease stage 4 and 5.91 ± 0.9 in stage 5 chronic kidney disease. The difference in value of serum phosphate with chronic kidney disease stage3 and stage 4 was statistically significant ($p<0.0005$). However, the difference between stage 4 and stage 5 was not significant (p value = 0.561).

The mean carotid intimal medial thickness in the present study was 0.74 ± 0.21 (chronic kidney disease patients) as compared with 0.64 ± 0.16 in the control group (p=0.034).

Similarly, carotid intimal medial thickness values on right and left side were significantly higher in chronic kidney disease patients as compared with controls($p<0.05$) . Carotid intimal medial thickness values were comparable on either side.

In present study, there was some correlation between carotid intimal medial thickness and stage of chronic kidney disease. Carotid intimal medial thickness values of stage 5 chronic kidney disease patients were significantly higher than stage 3($p<0.0001$). But the difference between stage 4 and 5 was not significant (p=0.16). Similarly, carotid intimal medial thickness of stage 4 were higher than stage 3 (p=0.02). Such correlation of carotid intimal medial thickness and stage of chronic kidney disease was not found in various studies reported in literature [10, 11].

Since carotid intimal medial thickness is correlated with stage of chronic kidney disease and cardiovascular morbidity and mortality independently, degree of chronic kidney disease can be used directly to assess the cardiovascular risk. There are reports in the literature which directly link cardiovascular morbidity and mortality [12].

The serum phosphate level is a non- traditional cardiovascular risk factor in chronic kidney disease patients [6-8]. Higher serum phosphate concentrations are associated with mortality and cardiovascular disease events [13]. Kestenbaum et al [14] showed that serum phosphate levels were in normal range until GFR of 30ml/min was reached. The phosphate level began to rise

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beyond upper normal range inversely to the GFR thereafter. Increase serum phosphate levels have been shown to induce parathyroid hyperplasia and thus secondary hyperparathyroidism.

High intracellular phosphate is also involved in the loss of smooth muscle lineage markers and a simultaneous gain of osteogenic markers, which are important in the pathogenesis of vascular calcification and atherosclerosis (15, 16).

Reduction in serum phosphate has been shown to decrease aortic calcification in vivo through decreased expression of osteogenic markers- runx2, msx2 and osterix (17)

There was a positive correlation r = +0.4259(p=0.0002) between serum phosphate and carotid intimal medial thickness. This compares with study by V K Sharma et al (18) which reported very strong correlation (r = 0.91) between the two. However, the strength of association was weaker in our study as compared to them.

Serum phosphate levels correlate with stage of chronic kidney disease. Carotid intimal medial thickness correlates with serum phosphate level and stage of chronic kidney disease (present study). Moreover, the literature reveals strong association of carotid intimal medial thickness with degree of atherosclerosis and thus, cardiovascular risk (19-21). Hence, serum phosphate level can be used to quantify cardiovascular risk in patients of chronic kidney disease.

Since, there is paucity of good quality ultrasound machine and trained ultrasonologist in India (especially remote area) it may not be always possible to assess carotid intimal medial thickness. Therefore, it is suggested that in developing countries serum phosphate may be used as a surrogate marker of atherosclerosis and cardiovascular risk in chronic kidney disease patients.

Further, serum phosphate level can be used to calculate approximate carotid intimal medial thickness by using the formula derived mathematically in the present study. (Carotid intimal medial thickness = 0.1808 + 0.09746x s. Phosphate).

Such derivation has not been reported in literature. Such an attempt has never been made in the past. Even though the correlation (r) is not very strong as compared to the previous study (18), yet this formula can help to predict and identify the subset of chronic kidney disease patients who are high risk of cardiovascular morbidity and mortality. Such a simple, cheap, non-invasive, and modifiable risk factor is of special importance in developing country like India. Early diagnosis and subsequent intervention would go a long way to decrease the complications (mineral bone disease and atherosclerosis) in chronic kidney disease patients. This will help to improve longevity and the quality of life of these patients.

CONCLUSION:

- The average Carotid intimal medial thickness levels in CKD patients was 0.74 ± 0.21 mm as compared to 0.64 ± 0.16 mm in the control group. Carotid intimal medial thickness was significantly higher in CKD patients as compared to the control group.
- CIMT level correlated with serum phosphate. It also correlated with eGFR, haemoglobin, serum potassium, and pyuria and serum phosphate.
- CIMT levels increased with the stage of CKD progressively. Mean CIMT levels were 0.55 ± 0.09, 0.72 ± 0.19 and 0.8 ± 0.23 mm respectively in stage 3, 4 and stage 5.
- Serum phosphate levels were significantly higher in CKD patients (5.69 ± 0.93) as compared to controls (4.39 ± 0.74).
- Serum phosphate levels increased with stage of CKD. Mean serum phosphate levels were 4.46 ± 0.86, 5.79 ± 0.73 and 5.91 ± 0.9 in stage 3, stage 4 and stage 5 respectively.
- There was positive and significant correlation between serum phosphate and CIMT levels. Correlation co-efficient (**r**) between mean Carotid Intimal Medial Thickness and phosphate level was +0.4259(p=0.0002). **r** value on right and left side was +0.3921 and +0.4476 respectively (p=0.0008 & 0.0001).
- The association between serum phosphate and CIMT could be expressed mathematically as - **CIMT** (mm) = **0.1808 + 0.09746 x S. Phosphate** (mg/dl)

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- CIMT can be calculated using the above mentioned formula. One can, thus, assess cardiovascular risk directly by measuring serum phosphate, in patients of CKD.
- Hence, serum phosphate estimation can be used as a surrogate marker to assess CIMT levels in CKD patients.

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