Correlation of serum phosphate with carotid intimal-medial thickness in chronic kidney disease patients

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ABSTRACT

While increased serum phosphate concentration is a significant risk factor for vascular calcification, it is unclear whether serum phosphate is also a risk factor for increased arterial wall thickness in chronic kidney disease (CKD) patients. Using B-mode ultrasonography, we examined carotid intimal-medial thickness (CIMT) of CKD patients and analyzed risk factors for increased IMT with regard to the effect of serum phosphate. One hundred patients were enrolled (73 patients without diabetes, 27 patients with diabetes; 57 men, 43 women; age, 46.2 ± 15.3 years). CIMT of patients with diabetes was significantly greater than that of patients without diabetes (0.78 ± 0.250 versus 0.66 ± 0.178 mm; $P < 0.0001$). For the group of all patients, CIMT correlated strongly and significantly with serum phosphate ($r = 0.911$; $P < 0.001$). In multiple regression analysis serum phosphate level (β = 0.356; <0.0001) was found to be a significant independent risk factor for increased CIMT, in addition to other independent risk factors, including advanced age, higher systolic blood pressure, urinary albumin and the presence of diabetes ($R^2 = 0.956$; $P < 0.00001$). In conclusion, high serum phosphate level is a significant and independent factor associated with advanced arteriosclerosis in CKD patients with and without diabetes in addition to advanced age.

Key words: Carotid intimal-medial thickness, chronic kidney disease, diabetes, phosphate

Introduction

Chronic kidney disease (CKD) is a significant predictor of cardiovascular disease.[1-3] Cardiovascular disease and stroke are the leading causes of death in patients with end-stage renal disease, who have a risk for death 10 to 20 times that of age- and sex-matched general population.[4-6] It has been recently reported that arteriosclerosis, assessed by means of the arterial wall thickness and stiffness, is advanced in patients with the chronic renal failure.[7,8] In the general population, advanced age, hypertension, cigarette smoking and hyperlipidemia are the most significant risk factors for advanced arteriosclerosis,[9] In uremic patients, it is unclear whether risk factors for arteriosclerosis are similar to those in the non-uremic population; it is also unclear whether there is a difference in risk factors for advance arteriosclerosis between uremic patients without and with diabetes. Although increased serum phosphate concentration is a significant risk factor for vascular calcification,[10] which is an advanced form of atherosclerosis, it is unclear whether serum phosphate concentration is associated with arterial wall thickness in CKD. In the present study, using a non-invasive method of B-mode ultrasonography, we examined carotid arterial thickness of a 100 CKD patients and explored risk factors for an increase in the arterial wall thickness. We focus on risk factors for arteriosclerosis of CKD patients without and with diabetes, separately, and examined whether serum phosphate level is associated with carotid arterial thickness.

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Materials and Methods

Patients

A total of 124 patients with diagnosis of CKD meeting the inclusion and exclusion criteria were enrolled for study in medicine/nephrology Department of Hamidia Hospital Bhopal from 1 December 2011 to 30 October 2012. This study was approved by the Gandhi Medical College and Hamidia Hospital Bhopal. Patient having diagnosed as acute kidney injury, history of carotid

surgery, patient having previous history of ischemic heart disease, myocardial infarction and stroke were excluded.

Of these, 116 patients CKD patients gave informed consent to participate in the study, and 100 patients could complete the requisite battery of investigation and their clinical data were analyzed. Of these patients, 27 patients had type 2 diabetes, 13 men and 14 women aged 30 to 75 years (mean, 53.93 ± 12.40 years), 12 receiving dialysis and 15 not receiving dialysis and 73 patients did not have diabetes consisting of 44 men and 29 women with an age range of 14 to 80 years (mean, 44.04 ± 16.80 years), 40 were on dialysis and 33 were not on dialysis. Glomerular filtration rate (GFR) was calculated using Cockcroft-Gault formula. Maximum 77 patients were in CKD stage 5, 18 were in stage 4 and 5 were in CKD stage 3. The percentage of patients with diabetes (27%) is similar to that for the population of patients with CKD in India at the end of 2011 (28.1%).

Blood pressure was recorded with standard mercury sphygmomanometer with cuff adapted to arm circumference without arteriovenous fistula, after the subject had rested in the supine position for 15 minutes. The systolic and diastolic blood pressure levels were taken as the points of appearance and disappearance of Korotkoff sounds respectively. Three measurements were taken with 10 min break and average of measurements was taken as the final value of blood pressure. Body mass index (BMI) was calculated using the formula: BMI = Weight (Kg)/Height^2 (m^2).

The presence of cardiovascular complication was evaluated by means of clinical information on patient charts regarding past and present history of coronary (myocardial infarction, angina pectoris), cerebral (stroke), and peripheral (amputation, angiographically shown arteriosclerosis obliterans) artery diseases. Information for cardiovascular medications, including antihypertensives and nitrites were collected from patient charts.

Measurements of carotid artery intimal-medial thickness

Carotid intima media thickness was measured by B mode ultrasound using a 3.5MHz transducer. Intima Media Thickness is defined as distance between the leading edge of first echogenic line (Lumen–Intima interface) and second echogenic line (Media– Adventitia interface) of far wall. Three measurements were taken 0.5, 1 and 2 cm below carotid bifurcation of common carotid artery on each side. The arithmetical averages of these were taken. The IMT of both sides (right and left) was calculated and averages of these two values were used for statistical analysis. Carotid intimal-medial thickness (CIMT) measurement was always performed by single radiologist in plaque free arterial segments. Plaques are defined as focal widening relative to the adjacent segment, with protrusion into the lumen. For different parameters, mean and standard deviation was calculated. The values of P which are ($P < 0.05$) were treated as significant.

Biochemical assays

Blood was drawn after 8 hour of overnight fasting to measure serum parameters such as albumin, creatinine, hemoglobin, C-reactive protein (CRP), calcium, phosphate, total cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride. Morning urine sample was taken for estimation of urinary albumin. Measurements were performed using routine laboratory methods. Corrected calcium was calculated by using formula: Corrected calcium = 0.8 (4-serum albumin) + serum calcium (mg/dL).

Statistical analysis

All values were expressed as mean ± SD. Unpaired Student's *t*-test and Chi-square test were performed for comparison of CKD patients without and with diabetes. Correlation and multiple linear regression analysis were performed to examine relationships between IMT and clinical variables. Multiple regression analysis was performed to assess the combined effects of clinical variables on CIMT. Dummy variables were used for sex (1 for male, 2 for female), diabetes (1 for no diabetes, 2 for diabetes) modality of treatment (1 for Dialysis, 2 for not on dialysis). $P < 0.05$ was considered statistically significant. All statistical analyses were performed by using the SPSS Version 17.0.

Results

Table 1 lists clinical characteristics of CKD patients without and with diabetes. Age, BMI, Systolic blood pressure, CRP, urinary albumin, serum phosphate and calcium phosphate product of CKD patient were significantly higher with diabetes than those of non-diabetes. Other clinical parameter did not different significantly between the two groups. The patient in CKD group without diabetes had higher values of serum albumin, GFR, corrected serum calcium whereas values were more for BMI, systemic blood pressure, diastolic blood pressure, hemoglobin, serum creatinine, high-density lipoprotein, low-density lipoprotein and total cholesterol in the diabetic group.

Relationship between carotid intimal-medial thickness and clinical parameters

Relationship between CIMT and clinical parameters were examined for the groups for all patients, patients

without diabetes and CKD patients with diabetes separately by mean of correlation analysis [Table 2]. In the group of all CKD patients, significant high positive correlation were found between mean carotid intimal-medial thickness (mCIMT) and age, BMI, systolic blood pressure, Corrected serum calcium, serum phosphorous and calcium phosphate product. The correlation was strong with Age, BMI, systemic blood pressure, urinary albumin and serum phosphate but is only mildly correlated with corrected calcium. There was mild negative correlation mCIMT with GFR, which is also significant statistically. There was a negative correlation with serum albumin in group of all patients, but it is not significant statistically.

Similar results were found in the CKD patients without and with diabetes but the correlation were moderate for systolic blood pressure, BMI, calcium phosphate product in both groups with significant difference. The correlation was weak for urinary albumin, corrected calcium, but with statistically significant difference. There was weak negative correction with GFR in both non-diabetic and diabetic group with significant statistical difference. However, no significant correlation could be established with diastolic blood pressure, CRP, HDL, Triglyceride, Total cholesterol in any of the group under study. There was direct correlation of mCIMT and CKD stage ($P \leq 0.0001$). As the stage of CKD increases the mCIMT increases but in our study more increase is noted between stage 3 and stage 4 and little increment between stage 4 and stage 5 as depicted in Table 3.

Table 1: Patient clinical characteristics according to presence of diabetes

	Patients without diabetes	Patients with diabetes	*P*
Sex (male/female)	44/29	13/14	0.162
Age (yrs)	44.04±16.80	53.93±12.40	0.006
Body mass index	18.55±2.14	19.67±1.89	0.018
Systolic blood pressure (mmHg)	163.29±21.44	165.33±18.68	0.662
Diastolic blood pressure (mmHg)	97.64±13.80	98.59±10.15	0.745
Hemoglobin (mg/dl)	8.42±2.10	8.85±1.71	0.341
C-reactive protein (Absent/Present)	31/42	6/21	0.009
Serum creatinine (mg/dl)	6.99±3.76	8.19±3.84	0.163
GFR	11.72±7.24	10.31±6.85	0.068
eGFR	12.19±7.10	10.74±6.54	0.064
Serum albumin (mg/dl)	2.99±0 0.64	2.82±0 0.68	0.236
Urinary albumin (Absent/Present)	26/47	6/21	0.000
Corrected calcium (mg/dl)	10.23±1.70	9.96±1.27	0.455
Serum phosphate (mg/dl)	5.15±1.31	6.84±1.51	0.000
Calcium×Phosphate (mg^2/dl^2)	53.46±19.22	68.31±19.51	0.001
HDL (mg/dl)	33.31±7.69	34.40±10.69	0.574
Triglyceride (mg/dl)	121.42±65.86	136.59±62.04	0.302
Total cholestrol (mg/dl)	149.73±43.14	159.82±45.35	0.308
CIMT	0.54±0.22	0.78±0.17	0.000
Treatment modality (ND/D)	33/40	15/12	0.689

GFR: Glomerular filtration rate, HDL: High density lipoprotein, CIMT: Carotid intima media thickness, ND: Not on dialysis, D: On dialysis

Risk factors for increased CIMT

To examine the combined effect of factors affecting CIMT, multiple regression analysis was performed separately

Table 3: Distribution of mCIMT and number of patients as per CKD staging by Cockcroft-Gault formula

CKD stage	mCIMT	SD	Number of patients
Stage 3	0.375	0.125	05
Stage 4	0.608	0.193	18
Stage 5	0.6171	0.236	77

CKD: Chronic kidney disease, mCIMT: Mean carotid intimal-medial thickness, SD: Standard deviation

Table 2: Clinical characteristics of all patients without and with diabetes

	All patients (*N*=100)		Patients without diabetes (*N*=73)		Patients with diabetes (*N*=27)	
	r	*P*	r	*P*	r	*P*
Gender	0.074	0.463	0.023	0.845	0.037	0.854
Age	0.940	<0.0001	0.966	<0.0001	0.916	<0.0001
Body mass index	0.875	0.000	0.776	0.016	0.539	0.025
Systolic blood pressure	0.789	0.000	0.453	<0.0001	0.469	<0.0001
Diastolic blood pressure	0.158	0.116	0.174	0.140	0.102	0.613
Blood sugar	0.415	<0.0001	-	-	-	-
Hemoglobin	0.180	0.073	0.170	0.152	0.086	0.670
C-reactive protein	0.133	0.187	0.001	0.998	0.267	0.178
Serum creatinine	0.053	0.601	–0.089	0.453	0.238	0.232
GFR	–0.225	0.024	–0.349	0.009	–0.505	0.007
Serum albumin	–0.132	0.190	–0.154	0.193	0.130	0.519
Urinary albumin	0.605	0.000	0.268	0.022	0.283	0.024
Corrected calcium	0.398	0.000	0.372	0.001	0.384	0.001
Serum phosphate	0.911	<0.0001	0.745	<0.0001	0.790	<0.0001
Calcium×phosphate	0.768	<0.0001	0.710	<0.0001	0.719	<0.0001
HDL	0.030	0.777	–0.111	0.351	0.046	0.819
Triglyceride	0.037	0.714	–0.069	0.565	0.190	0.342
Total cholestrol	–0.030	0.765	–0.141	0.235	0.077	0.702

GFR: Glomerular filtration rate, HDL: High density lipoprotein

for the group of all patients, patients without and with diabetes [Table 4]. Independent variables were selected based on results of correlation analysis performed on the group in the study separately. Results were similar in the study groups and it was found that serum phosphate was significant and independent risk factor for increased CIMT in addition to the conventional risk factor such as blood sugar, age, BMI, Systolic blood pressure and urinary albumin. The relationship between CIMT and serum phosphate level in the group of all CKD patients is shown in Figure 1.

Discussion

CIMT, which can be measured noninvasively using B-mode ultrasonography, has been reported be an early marker of atherosclerosis and predictor of vascular events. By examining 100 CKD patients in the present study, we showed that arteriosclerosis, assessed by means of CIMT of CKD patients with diabetes, was significantly advanced compared with that of CKD patients without diabetes. Furthermore, analyses of factors associated with advanced arteriosclerosis showed that increased serum phosphate level was one of the significant and independent factors associated with increased IMT of the carotid artery, not only for the group of all patients, but also for CKD patients with and without diabetes, in addition to advanced age and other conventional risk factors.

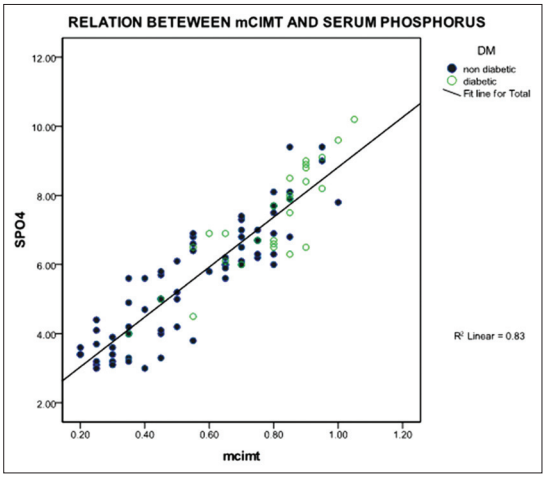

Figure 1: Scatter diagram showing relationship between mCIMT and serum Phosphorus using multiple linear regression analysis

Recently, arteriosclerosis was reported to be advanced in patients with chronic renal failure,[7] and CKD has been emphasized as a significant predictor of cardiovascular disease.[1-3] In previous studies, IMT in patients with uremia, not only those on hemodialysis therapy, but also predialysis uremic patients, was advanced compared with that in control subjects. Ishimura *et al.*, found risk factors for increased CIMT for the group of all hemodialysis patients, patients without diabetes and with diabetes.[11,12] They found that older age, higher systolic blood pressure and diabetes were significant and independent risk factors. In addition to these factors, serum phosphate level was also found to be a significant independent risk factor for increased CIMT in hemodialysis patients ($P \leq 0.001$). Oh *et al.*,[13] in an examination of 39 patients with young onset chronic renal failure, also found a significant correlation between serum phosphate level, CRP and CIMT in their study ($P \leq 0.001$). Goodman *et al.*,[14] demonstrated in children and young adults that increase due to calcium containing phosphate binder and increased calcium phosphate product causes advanced calcification and increase in carotid and coronary artery thickness. Similar results with increased calcium phosphate product with increased CIMT were noted in our study. Desbien *et al.*,[15] found decreased kidney function is associated strongly with faster change in CIMT. Similar changes were noted in our study as mCIMT in 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 our study group ($P < 0.0001$).

In CKD patients, hyperphosphatemia has been emphasized as a significant risk factor for the development of secondary

Table 4: Multiple linear regression analysis of factors associated with CIMT

	Total		Non-diabetic		Diabetic	
	B	*P*	B	*P*	B	*P*
Age	0.456	<0.0001	0.599	<0.0001	0.532	<0.0001
BMI	0.221	<0.0001	0.171	<0.0001	0.192	0.092
SBP	0.026	0.485	0.032	0.119	0.062	0.397
U. Alb.	0.055	0.045	0.014	0.275	0.052	0.464
S.Phos.	0.356	<0.0001	0.305	<0.0001	0.379	<0.0001
Ca x Ph	0.219	0.011	0.230	0.009	0.178	0.021
	R^2=0.956	<0.0001	R^2=0.961	<0.0001	R^2=0.939	<0.0001

Note: BMI: Body mass index, SBP: Systolic blood pressure, U.Alb: Urinary albumin, S.Phos: Serum phosphate, Ca x Ph: Calcium phosphate product, CIMT: Carotid intimal-medial thickness, SD: Standard deviation

hyperparathyroidism and uremic bone disease.[16,17] 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.[18,19] These studies examined vascular calcification, not the degree of arterial thickness itself. Recently, inorganic phosphate was reported to induce phenotypic change of vascular smooth muscle cells *in vitro* into osteoblast-like cells, such as inducing alkaline phosphatase and calcium-binding protein (osteocalcin and osteopontin).[20-22] Inorganic phosphate also induced by core-binding factor a 1, a key transcription factor in osteoblastic differentiation, in vascular smooth muscle cells *in vitro*.[21,22] These *in vitro* findings, suggest that hyperphosphatemia may induce osteoblastic phenotypic changes in vascular smooth muscle cells and vascular cell proliferation, possibly leading to increased arterial wall thickness in CKD patients.

In conclusion, in an examination of the CIMT of CKD patients, we found that greater serum phosphate level was one of the significant and independent factors associated with increased IMT, in addition to advance age, serum albumin, urinary albumin and calcium phosphate product. Correction of hyperphosphatemia may be emphasized for the prevention of progression of arteriosclerosis, in addition to prevention of vascular calcification, in CKD patients.

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