Association of serum phosphate with valvular and vascular calcification in patients with end-stage renal disease

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Aim
This study aims to evaluate the calcifying effect of phosphorus on vascular smooth muscle by detecting the association between serum phosphorus and valvular and vascular calcification.

Patients and methods
The study included 40 patients who were diagnosed to have end-stage renal disease within the last 5 years with their age ranging from 18 to 40 years. The patients were divided into two groups according to the duration of dialysis: group I included patients on regular hemodialysis for less than 1 year and group II included patients on regular hemodialysis for 1–5 years duration. All patients were subjected to full history taking and clinical examination: laboratory investigations (urea, creatinine, parathyroid hormone (PTH), calcium, phosphorus, liver function test, sodium, potassium level), measurement of coronary artery calcification by multi-slice computed tomography (MSCT) coronary calcium scoring, vavular calcification by echocardiography, and carotid intima media thickness by gray scale ultrasound.

Results
Coronary calcium score, valvular calcification, and carotid intima media thickness had insignificant correlation with age, duration of dialysis, serum calcium, and parathormone hormone; however, all of them had positive moderate significant correlation with serum phosphorous level.

Conclusion
Hyperphosphatemia has an effective role in the progression of valvular and vascular calcification; so, good control of hyperphosphatemia may participate in preventing and delaying the progress of cardiovascular calcification and subsequently decrease cardiovascular morbidity and mortality in end-stage renal disease.

Keywords:
carotid intima media thickness, coronary calcification, end-stage renal disease, hemodialysis, phosphorus, valvular calcification

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Introduction

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are dramatically increasing diseases causing major socioeconomic burden in industrialized countries [1].

Cardiovascular diseases are still the leading cause of death in CKD patients. It is estimated that ESRD patients are 5–20 times more likely to die because of cardiovascular causes than the general population. Cardiac calcification and left ventricular hypertrophy are common causes for cardiac mortality in those patients [2].

A number of factors have been associated with progression of vascular calcification (VC) in dialysis patients such as age, duration of dialysis, diabetes mellitus, abnormalities of mineral metabolism as well as use and dose of calcium-based phosphate binders [3].

CKD-Mineral and Bone Disorder (MBD) is a risk factor for cardiac disease, it is routinely based on ectopic calcification, especially of coronary arteries [4], aortic [5], and heart valvular [6] calcifications. They are strong predictors of a poor prognosis in CKD patients. The severity of these calcifications plays a role in the progression of ischemic heart disease or cardiomyopathy directly or indirectly.

Hyperphosphatemia is a common problem among patients with ESRD [7]. It is a part of the signaling cascade that triggers VC and it aggravates the effects of coronary atherosclerosis through increased VC and smooth muscle proliferation.

Also, as a consequence of hyperphosphatemia, it has been suggested that myocardial calcification may alter microcirculatory hemodynamics through increased extravascular resistance and further compromise myocardial perfusion [7].

In addition to that there is a correlation between coronary artery calcification and a number of dialysis-related factors, such as duration of dialysis, hyperphosphatemia, high Ca × P product, and vitamin D therapy [8].

A number of noninvasive imaging techniques are now available to detect and quantify VC. These include plain radiographs of the abdomen and extremities to identify macroscopic calcifications of the aorta and peripheral arteries, echocardiography for assessment of valvular calcification, gray scale ultrasound for calcification of carotid arteries, femoral arteries and aorta and multi-slice computed tomography (MSCT) coronary calcium scoring for detection and quantification of coronary calcification [9].

Aim

This study aims to evaluate the calcifying effect of phosphorus on vascular smooth muscle by detecting the association between serum phosphorus and valvular and VC.

Patients and methods

This is a cross-sectional study performed at the Nephrology Unit of Internal Medicine Department and Diagnostic Radiology Department of Assiut University Hospitals in the period between May 2017 and May 2018. The study included 40 patients with ESRD within the last 5 years with patient mean age of 26.10 years (±6.29).

The patients were divided into two groups according to the duration of dialysis: group I included patients with dialysis duration of less than 1 year and group II included patients with a duration of dialysis of 1–5 years.

The patients were subjected to the following:
(1) Full history taking and clinical examination
(2) Laboratory investigations (urea, creatinine, parathyroid hormone (PTH), calcium, phosphorus, liver function test, sodium, potassium level, alkaline phosphatase)
(3) Measurement of coronary artery calcification by MSCT coronary calcium scoring (using Siemens SOMATOM Definition AS 128 Slice computed tomography (CT Scanner), Munich, Germany).

For measuring coronary artery calcification, Agatston score had been used. This is a semiautomated tool to calculate a score based on the extent of coronary artery calcification detected by an unenhanced low-dose CT scan.

Grading of coronary artery disease based on total calcium score:
(1) No evidence of coronary artery disease: 0 calcium score.
(2) Minimal: 1–10.
(3) Mild: 11–100.
(4) Moderate: 101–400.
(5) Severe: more than 400.
    (a) Measurement of cardiac valvular calcification by echocardiography.
    (b) Measurement of carotid intima media thickness by gray scale ultrasound.

Inclusion criteria

(1) ESRD patients on regular hemodialysis within the last 5 years with their age 18–40 years.
(2) Patients on calcium carbonate as medical treatment for mineral bone disease.

Exclusion criteria

(1) Patients with other causes of hypercalcemia as Addison's disease, malignancy, sarcoidosis, multiple myeloma, vitamin D toxicity, thiazide diuretics, and immobilization.
(2) Patients on phosphate binders or combined therapy with calcium carbonate and vitamin D analogs.
(3) Diabetic patients.
(4) Patients with hyperlipidemia.
(5) Patients known to have ischemic heart disease before starting dialysis.
(6) Rheumatic heart disease patients.

Statistical analysis

Data were collected and analyzed using SPSS Inc., Chicago, USA. Continuous data were expressed in the form of mean ± SD or median (range), while nominal data were expressed in the form of frequency (percentage).

χ^2-Test was used to compare the nominal data of different groups in the study, while Student's *t*-test was used to compare the mean of two different groups. Spearman's correlation was used to determine the correlation between different continuous variables in this study. *P* value was significant if less than 0.05.

Results

In this study, 40 patients with ESRD within the last 5 years have been examined. In group I (20 patients on regular hemodialysis for <1 year duration), the mean age was 26.10 ± 6.29 years and the age ranged between 18 and 35 years. Out of this group, 11 (55%) patients were men, five (25%) patients were smokers,

and majority (70%) of patients came from rural area. In group II (20 patients on regular hemodialysis for a duration between 1 and 5 years), the mean age was 30.50 ± 5.35 years with a range between 18 and 38 years. It was noticed that majority (60%) of them were men, six (30%) were smokers, and 13 (65%) of them came from rural area (Table 1).

Demographic data had no significant differences between both groups with exception of age that was significantly higher in group II (P = 0.02; Fig. 1).

It was noticed that there were no significant differences between both groups as regards laboratory data with exception of serum calcium and phosphorous that was significantly higher in group II in comparison to group I (Table 2 and Figs. 2 and 3).

Lipid profile had no significant difference between both groups but PTH was significantly higher in group II (P = 0.00; Fig. 4).

It was noticed that valvular calcification, coronary calcification, and carotid intima media thickness had no significant differences between both studied groups (P = 0.48 for each item; Table 3).

It was noticed that coronary calcification and carotid intima media thickness had insignificant correlation with age, duration of dialysis, serum calcium, and parathormone hormone and both of them had positive significant moderate correlation with serum phosphorous (Table 4 and Figs. 5 and 6).

Discussion

Regarding demographic data in our study and the difference between the two studied groups we found that demographic data had no significant differences between both groups with exception of age that

Table 1 Demographic data of the studied patients

	Group I (n=20)	Group II (n=20)	P
Age (range) (years)	26.10±6.29 (18-35)	30.50±5.35 (18-38)	**0.02**
Sex			
Male	11 (55)	12 (60)	0.20
Female	9 (45)	8 (40)	
Smoking	5 (25)	6 (30)	0.21
Residence			
Rural	14 (70)	13 (65)	0.51
Urban	6 (30)	7 (35)	

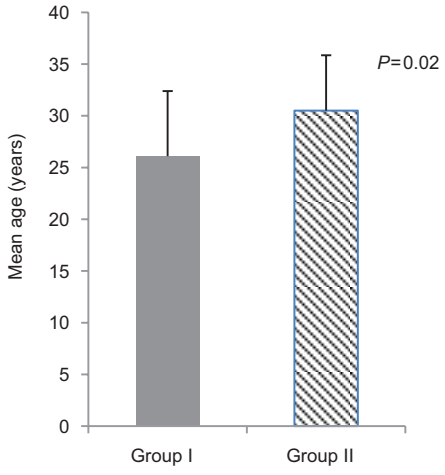
Data were expressed in the form of mean±SD and frequency (percentage). P<0.05, significant. Group I, patients who are on regular dialysis for a duration of less than 1 year; group II, patients who are on regular dialysis for a duration between 1 and 5 years.

Table 2 Baseline laboratory data of the studied groups

	Group I (n=20)	Group II (n=20)	P
Liver function tests			
Bilirubin (mg/dl)	0.98±0.21	1.08±0.11	0.67
Albumin (g/dl)	34.56±7.09	32.09±8.22	0.34
Protein (g/dl)	76.01±11.98	78.11±10.21	0.31
AST (U/l)	45.98±10.23	46.02±9.21	0.53
ALT (U/l)	44.12±12.21	41.02±10.22	0.51
Kidney function tests			
Serum creatinine (µmol/l)	989.7±171.37	1013.1±373.59	0.06
Blood urea nitrogen (mmo/l)	23.96±8.32	34.97±6.74	0.080
Serum electrolytes			
Sodium (mmol/l)	130.23±3.09	129.11±2.23	0.23
Potassium (mmol/l)	5.01±1.02	4.87±1.22	0.11
Calcium (mg/dl)	7.56±1.40	9.39±0.54	**0.00**
Phosphorus (mmol/l)	5.32±2.32	6.26±1.51	**0.01**
Parathormone hormone (ng/dl)	277.4±67.89	566.8±122	**0.00**

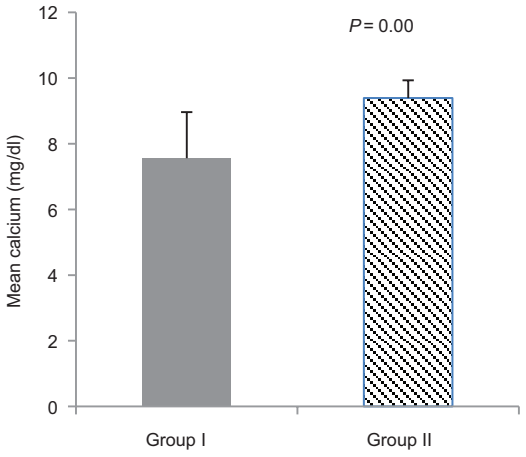
Data were expressed in the form of mean±SD and frequency (percentage). P<0.05, significant. Group I, patients who are on regular dialysis for a duration of less than 1 year; group II, patients who are on regular dialysis for a duration between 1 and 5 years, The bold values are statistically significant values.

Figure 1



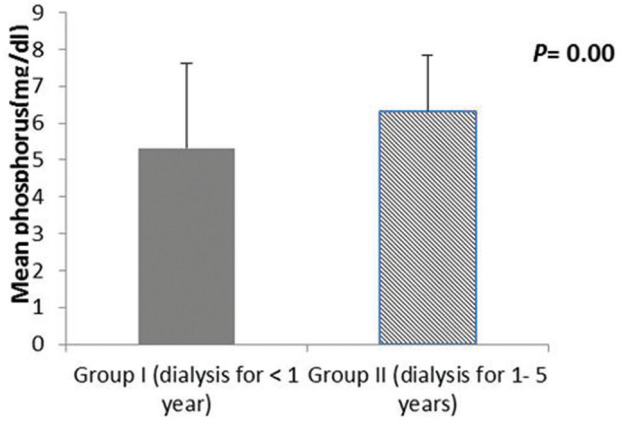
Mean age in both the studied groups.

Figure 2



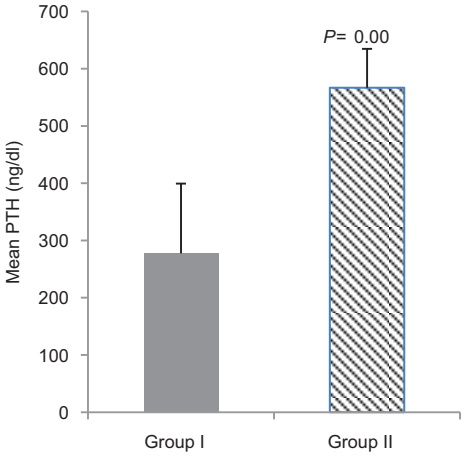
Serum calcium level in both the studied groups.

Figure 3



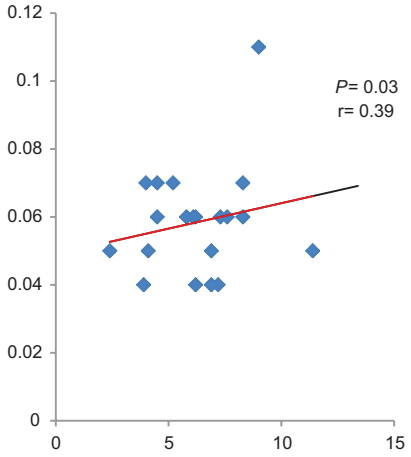
Serum phosphorus level in both the studied groups.

Figure 4



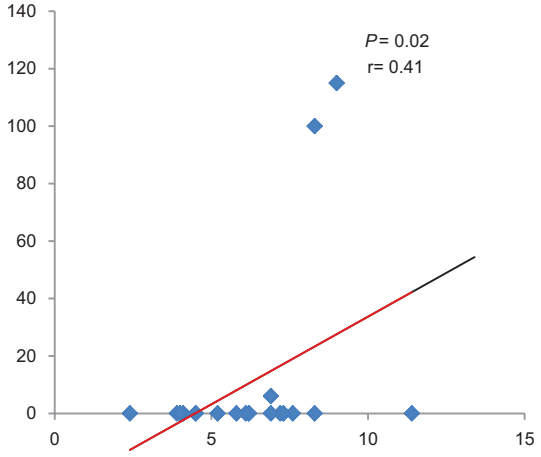
PTH level in both the studied groups.

Figure 5



Correlation carotid intima media thickness with phosphorous.

Figure 6



Correlation of coronary calcification with phosphorous.

Table 3 Valvular calcification, coronary calcification, and carotid intima media thickness in the studied groups

	Group I (*n*=20)	Group II (*n*=20)	*P*
Valvular calcification	2 (10)	0	0.48
Coronary calcification	0	2 (10)	0.48
Carotid intima media thickness	0.05±0.02	0.06±0.01	0.48

Data were expressed in the form of mean±SD and frequency (percentage). *P*<0.05, significant. Group I, patients who are on regular dialysis for a duration of less than 1 year; group II, patients who are on regular dialysis for a duration between 1 and 5 years.

Table 4 Correlation of coronary calcification and carotid intima media thickness with different parameters in the study

	Coronary calcification	Carotid intima media thickness
Age	–0.11 (0.56)	0.03 (0.83)
Duration of dialysis	–0.21 (0.55)	–0.01 (0.93)
Serum creatinine	0.02 (0.89)	0.12 (0.41)
Serum calcium	–0.19 (0.23)	–0.15 (0.33)
Serum phosphorus	**0.41 (0.02)**	**0.39 (0.03)**
Parathormone	–0.15 (0.34)	–0.12 (0.44)

Data were expressed for *r*, strength of correlation and *P*, significance of correlation, The bold values denote that there is statistically significant relation between serum phosphorus and both coronary calcification and carotid intima media thickness.

was significantly higher in those patients who were on dialysis for a duration between 1 and 5 years (P = 0.02).

It was found that there were no significant differences between both groups as regards laboratory data with exception of serum calcium and phosphorous that was significantly higher in group II, which is characterized by higher age (mean age 30.50 ± 5.35). This may be due to the protocols of treatment of CKD-MBD used in those patients and the longer duration of dialysis in that group. Incompatible to our results, a study by Nasri and Kheiri [10] shows that there was significant inverse correlation of serum phosphorus with age. However, there were no significant correlations between age and serum calcium. The mean age in that study was higher than that in our study (mean age 46 ± 18 years). The mean duration of hemodialysis for those patients was

25 ± 30 months (median: 13 months) which less than that in our study.

This study found that the PTH level was significantly lower in group I that included patients with younger age and shorter duration of dialysis. Compatible to our results, Salem *et al.*, [11] found that 50% of HD patients developed serum PTH levels more than three times normal, whereas 25% developed reduced PTH levels.

Incompatible to our results, Mehrotra *et al.* [12] in a study on 92 maintenance hemodialysis patients concluded that age was inversely correlated with both serum phosphorus and PTH, and that these relationships remained significant even when the data were adjusted for diabetic status, duration on dialysis, and diet. However, they suggested that reduced responsiveness of parathyroid glands may be more related to age-dependent accumulation of uremic toxins than to reduction in protein intake [10].

In this study we found that valvular calcification, coronary calcification, and carotid intima media thickness had no significant differences between both studied groups. Incompatible with that result, in a study done to evaluate the risk factors for cardiovascular calcification in hemodialysis patients Damjanovic *et al.* [13] found that the risk for cardiovascular calcification increases in older patients, patients with longer dialysis vintage. In that study the age group was higher than in ours (patients aged 59.0 ± 11.0 years) and the duration of dialysis was longer (6.39 ± 4.59 years). In concurrence with our study, Iyer *et al.* [14] found that there was no significant correlation between age and cardiovascular calcification, but they found that there was a statistically significant relation between the extent of coronary artery calcification and the duration on dialysis which is not matching with the results of our study as we found no difference between the two studied groups.

In this study valvular calcification was assessed by echocardiography and we found that there was no significant difference between the two studied groups and also valvular calcification is not significantly detected in both groups. This could be explained by the small sample size and the young age of the participating patients.

Incompatible to our study, Lee *et al.* [15], demonstrated that chronic hemodialysis patients have a high prevalence of cardiovascular calcification, with almost 90% of their subjects displaying image-documented calcification involving the arteries and or the cardiac valves. Furthermore, valvular calcification was more prevalent than peripheral artery involvement. They also found that age is an important determinant of valvular calcification.

Ellouali *et al.* [16], in their study found that the prevalence of valvular calcification was three times higher in patients on regular hemodialysis for more than 5 years than that in patients with a dialysis duration less than that and so they concluded that the longer duration of dialysis is associated with higher incidence of valvular calcification.

In this study, we found that coronary artery calcification and calcium score had positive significant moderate correlation with serum phosphorous, but it had insignificant correlation with age, duration of dialysis, serum calcium, and parathormone hormone. There was no significant difference between the two studied groups regarding the incidence of coronary artery calcification.

Concurrent with our study Raggi *et al.* [17] in their study show that higher concentrations of serum phosphorus is associated with higher incidence of coronary artery calcification. There were no significant associations among PTH and the extent of coronary artery calcification [2]. They also have found that calcification was clearly related to age (calcification in 0 of 23 patients 20 years, and 14 of 16 patients 20–30 years of age) and duration on dialysis which is not matching with the results of our study [17].

A study by Nakashima *et al.* [18] show that hyperphosphatemia showed no association with intima media thickness which is different from our results. They explained that as the serum phosphorus level is unstable in hemodialysis patients because of the effects of food intake and treatment with calcium-containing binders, these factors may make it difficult to evaluate the influence of phosphorus on carotid vascular disease.

In concurrence with our study, Hojs found that the intima media thickness of carotid arteries was not associated with the duration of hemodialysis. They failed to find a significant correlation between carotid intima media thickness and other risk factors such as hypercholesterolemia, calcium, or PTH levels.

They also established a significant positive correlation between intima media thickness of carotid arteries and age in hemodialysis patients. There was no significant correlation between serum phosphorus level and carotid intima media thickness which is not matching the results of our study [19].

In concurrence with our study, Ossareh and colleagues could not show any relationship between carotid intima media thickness and serum phosphorus level. Their study also showed a significant relationship between carotid intima media thickness and age. They

considered the natural progression of atherosclerotic progression with increasing age.

There was no relationship between carotid intima media thickness and duration of hemodialysis, serum levels of calcium and parathyroid hormone which is concurrent with our results [20].

Conclusion

This study found that coronary arteries calcification score and carotid intima media thickness had insignificant correlation with age, duration of dialysis, serum calcium, and parathormone hormone but both of them had positive significant moderate correlation with serum phosphorous.

Considering that hyperphosphatemia has an effective role in the progression of valvular and VC, good control of hyperphosphatemia may participate in preventing and delaying the progress of cardiovascular calcification and subsequently decrease cardiovascular morbidity and mortality in ESRD patients.

Recommendation

MSCT cardiograph is recommended as a screening tool for early detection of coronary VC. Phosphorus serum level is an important biomarker that can be used to expect valvular and VC in ESRD patients. Further studies with a larger sample size are required to detect the frequency of valvular and VC and its prevalence and compare it with CKD patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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