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Preliminary Report

Association of hyperphosphataemia with haemodynamic disturbances in end-stage renal disease

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Abstract

Background. Because recent data demonstrated that the shortened survival and excess cardiovascular death of end-stage renal disease (ESRD) patients are predicted by hyperphosphataemia, we examined the haemodynamic alterations associated with high serum phosphorus levels in ESRD patients on haemodialysis.

Methods. Sixty-six ESRD patients were studied. Patients were separated arbitrarily into two groups, i.e. with predialysis serum phosphate <2 mmol/l ('normal' phosphate) and, serum phosphate >2 mmol/l ('high' phosphate). Cardiac and arterial function and structure were analysed by computer-assisted ultrasonography.

Results. Hyperphosphataemic patients were characterized by higher diastolic and mean blood pressures ($P<0.05$), and higher cardiac index ($P<0.001$) caused by an increased stroke index ($P<0.05$) and higher heart rate ($P<0.01$). The cardiac work index was significantly increased in patients with higher phosphate levels ($P<0.01$). Hyperphosphataemic patients tended to have a higher common carotid artery diameter ($P=0.07$), but similar carotid artery intima-media thickness, and lower carotid wall-to-lumen ratio ($P<0.05$) than patients with 'normal' serum phosphorus. As a result of lower wall-to-lumen ratio in the presence of higher mean blood pressure, the carotid tensile stress was higher in hyperphosphataemic ESRD patients ($P<0.05$).

Conclusion These findings suggest that, in stable ESRD patients, hyperphosphataemia is associated with increased BP, hyperkinetic circulation, increased cardiac work, and high arterial tensile stress. These haemodynamic abnormalities could favour the development of cardiovascualr complications and contribute to high cardiovascular morbidity and mortality.

Key words: arteriosclerosis; cardiac output; cardiac work; end-stage renal disease; hyperphosphataemia; hypertension

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Introduction

Cardiovascular disease is a major cause of morbidity and mortality in patients with end-stage renal disease (ESRD) [1,2]. Epidemiological and clinical studies have shown that damage of large conduit arteries is a major contributing factor. Macrovascular disease develops rapidly in ESRD patients and is responsible for the high incidence of congestive heart failure, left ventricular hypertrophy (LVH), ischaemic heart disease, sudden death, strokes, and peripheral artery disease [3]. The most frequent underlying causes of these complications are occlusive lesions due to atheromatous plaques, and arterial stiffening due to arteriosclerosis characterized by dilation and hypertrophy of large capacitive and conduit arteries [4]. A recent study demonstrated that the shortened survival and excess cardiovascular death in ESRD patients could be predicted by hyperphosphataemia [5]. In ESRD patients, the consequences of hyperphosphataemia include alterations of calcium homeostasis with a predisposition to metastatic calcifications of arterial walls, and the development and progression of secondary hyperparathyroidism, both conditions that can contribute to alterations of cardiovascular function and homeostasis [6–9]. However, the increased mortality risk associated with hyperphosphataemia was independent of parathyroid hormone (PTH) [5] and the mechanism(s) associating high serum phosphorus levels and death is unknown. The aim of the present study was to analyse the relationships between serum phosphorus levels and cardiac and arterial characteristics in stable ESRD patients on haemodialysis.

Methods

Subjects

Sixty-six stable, non-diabetic ESRD patients under 60 years of age were studied. Patients were on haemodialysis for 97 ± 113 months (range 12–324 months). On the basis of clinical reports and complementary paraclinical investigations (echocardiography, ECG, echoDoppler examination) patients with a history of acute myocardial infarction,

valvular heart disease, cerebral vascular disease, common carotid artery (CCA) stenosis, and heart failure were excluded. Forty patients were being regularly treated with recombinant human erythropoietin. Twenty-four patients were on antihypertensive therapy, which was stopped 4 weeks prior to the study. Patients were dialysed with an AN69 membrane (Hospal, Meyzieu, France), the duration of dialysis was individually tailored (4–6 h thrice weekly) to control body fluids and to achieve a $Kt/V > 1.2$. Each subject gave informed written consent for the study, which was approved by our institutional review board.

Cardiac measurements

Echocardiographic studies were performed using a Hewlett-Packard Sonos 100 device equipped with a 2.25 MHz probe allowing M-mode, two-dimensional, and pulsed Doppler measurements. Measurements were performed blindly by two physicians according to the recommendations of the American Society of Echocardiography [10]. M-mode measurements included LV posterior wall thickness (PWT), interventricular septal thickness (IVS), LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD). LV mass was calculated according to the Penn convention [11], and LV mean wall thickness as $(IVS + PWT)/2$. Interobserver and intraobserver reproducibilities were reported previously [12]. Stroke volume was calculated from LV outflow velocity integral (cm/beat, i.e. stroke distance) and aortic outflow diameter, and cardiac output as the product of stroke volume × heart rate. LV outflow and aortic velocities were taken from the apical position. Cardiac work was calculated as the product of stroke volume and mean aortic systolic pressure determined by applanation tonometry of CCA. Haemodynamic parameters were indexed to body surface area.

Blood pressure (BP) and arterial measurements

Brachial BP was measured with a mercury sphygmomanometer after 15 min of recumbency. Phases I and V of the Korotkoff sounds were taken as the systolic BP (SBP) and diastolic BP (DBP). The mean BP (MBP) was calculated as: $MBP = DBP + (SBP - DBP/3)$.

Common carotid artery (CCA) measurements

The CCA pressure wave was recorded non-invasively with a pencil-type probe incorporating a high-fidelity Millar strain gauge transducer (SPT-301, Millar Instruments, Houston, Tx). The CCA pressure waveform and amplitude were analysed by applanation tonometry using a sphygmocardiograph and generalized transfer function for aortic and carotid pressure wave amplitude determinations. A detailed description of this system was published previously [4,13]. CCA diastolic diameter (CCADD) was measured with a high-resolution B-mode (7.5 MHz transducer) echotracking system (Wall-Track System, Maastricht). A complete detailed description of this system and the reproducibility of the measurements were published previously [4,14]. The accuracy of the system is ± 30 μm for CCADD. The repeatability coefficient of the measurements was ± 0.273 mm for CCADD. Measurements were made on the right CCA, 2 cm below the bifurcation. CCA intima-media thickness (IMT) was measured on the far wall at the same level as the diameter measurements with computer-assisted acquisition, processing and storage. The computing equipment was linked to an 80386/16 MHz processor and an imaging card providing real-time digitizing of the video analogue signal from the echo recording (processing corresponding to 256 levels of grey). The IMT was automatically analysed from changes of density on the section perpendicular to the vessel wall with specific software (Eurequa, TSA, Meudon, France) [4,15]. The repeatability coefficient of the IMT measurement was ± 60 μm [4]. The CCA intima-media cross-sectional area (IMCSA) was calculated as $\pi(CCADD/2 + IMT)^2 - \pi(CCADD/2)^2$. CCA compliance and CCA distensibility were determined from changes of the CCAD during systole ($Ds - Dd$; where Ds is CCA diameter at the end of systole and Dd diameter at the end of diastole) and simultaneously measured CCA pulse pressure (ΔP) according to following formulas: CCA compliance $= [\pi Dd(Ds - Dd)/2]/\Delta P (m^2 \times kPa^{-1} \times 10^{-7})$; CCA distensibility $= 2[(Ds - Dd)/Dd]/\Delta P\ (kPa^{-1} \times 10^{-3})$ [4,14]. The repeatability coefficients of the measurement were $\pm 1\ kPa^{-1} \times 10^{-3}$ for CCA distensibility and $0.52\ m^2 \times kPa^{-1} \times 10^{-7}$ for CCA compliance. While distensibility provides information about 'elasticity' of the artery as a hollow structure, the incremental modulus of elasticity (E*inc*) provides information on the properties of the wall material, independent of the geometry. E*inc* was calculated as follows: $3(1 + LCSA/IMCSA) \times 1/CCAdistensibility$ [4], where LCSA is CCA luminal cross sectional area and IMCSA (intima-media cross-sectional area).

Laboratory methods

Arteriovenous fistula blood was obtained immediately before haemodynamic investigations after an overnight fast. The plasma was separated immediately at 4°C in a refrigerated centrifuge, and stored at −20°C until plasma determinations were performed. Routine biochemical parameters were evaluated using standard methods, and serum albumin and plasma fibrinogen were measured nephelometrically. Total homocysteine was determined in plasma by means of a fluorometric HPLC method originally described by Fortin and Genest as previously reported [16]. PTH (1–84) was assessed by radioimmunoassay. All these assays were done once weekly and reported values are the averages of all the values measured during the month preceding the haemodynamic investigations, i.e. average of four measurements. Interdialytic body weight changes (ΔBW), and BP measurements are the average value of all predialysis measurements made during the same period.

Statistical analysis

Data are expressed as means ± SD. Patients were arbitrarily separated in two groups, those with serum phosphates < 2 mmol/l and those with plasma phosphates > 2 mmol/l. Student's *t*-test was used to compare the two groups of ESRD patients. Univariate and multivariate stepwise regression analyses were used to assess the correlations between serum phosphorus and cardiovascular parameters or risk factors. Regression analyses were conducted on the entire population. A $P < 0.05$ was considered significant.

Results

Patients clinical characteristics (Table 1)

The two groups were comparable for all parameters except younger age ($P < 0.05$), higher interdialytic body weight changes (ΔBW) ($P < 0.05$), lower predialysis

Table 1. Clinical characteristics and blood chemistry values for the two ESRD groups as a function of serum phosphorus

Parameter	Normal phosphates $n=32$	High phosphates $n=34$
Clinical characteristics		
Age (years)	46±11	40±12[a]
M/F ratio	1.35	1.30
Body surface area (m^2)	1.65±0.22	1.71±0.25
Body mass index (kg/m^2)	22.6±4.4	22.8±3.4
Time on dialysis (months)	95±76	96±86
Smoking (pack/year)	10.0±12.0	7.5±12.0
Duration of dialysis session (h)	4.20±0.10	4.35±0.10
Interdialytic body weight changes (kg)	2.30±0.75	2.65±0.55[a]
Kt/V	1.38±0.10	1.38±0.12
Blood chemistry		
Serum phosphorus (mmol/l)	1.65±0.28	2.30±0.38[b]
Serum calcium (mmol/l)	2.38±0.11	2.30±0.13[a]
Haematocrit (%)	31.7±1.7	32.3±3.1
Serum albumin (g/l)	40.0±2.6	39.5±2.4
Calcium × phosphorus product	3.86±0.70	5.27±1.00[b]
PTH (pg/ml)	206±144	493±290[b]
Plasma fibrinogen (g/l)	4.60±0.95	4.30±0.85
Homocysteine (μmol/l)	41.0±18.0	34.0±8.5
Total cholesterol (mmol/l)	4.90±0.80	5.00±1.18
HDL cholesterol (mmol/l)	1.17±0.54	1.04±0.44
Triglycerides (mmol/l)	1.83±0.90	1.84±0.81

[a]$P<0.05$; [b]$P<0.001$.

calcium ($P<0.05$), higher phosphate ($P<0.001$), and calcium × phosphate product ($P<0.001$), and higher PTH ($P<0.001$) in hyperphosphataemic group.

Haemodynamic and cardiovascular characteristics (Table 2)

Hyperphosphataemic patients were characterized by significantly higher DBP and MBP ($P<0.05$), in association with higher cardiac output and cardiac index ($P<0.001$) and lower total peripheral resistance ($P<0.05$). This elevated cardiac index reflected increased stroke volume index ($P<0.05$) and higher heart rate ($P<0.01$). As a consequence of higher BP and cardiac index the cardiac work and work index were significantly increased in patients with higher serum phosphate levels ($P<0.01$). Both groups were characterized by similar LV mass, and similar and normal systolic and diastolic LV functions. The hyperphosphataemic group tended to have higher CCADD ($P=0.07$) but similar CCA IMT, distensibility and E*inc*. However, the CCA wall-to-lumen ratio was significantly lower in hyperphosphataemic patients ($P<0.05$), and in conjunction with higher arterial BP the CCA tensile stress was significantly higher in hyperphosphataemic ESRD patients ($P<0.05$).

Relationships between the serum phosphorus and clinical or cardiovascular characteristics

Univariate correlations. Negative correlations were observed between patients' age and serum phosphorus ($r=-0.340$; ($P<0.01$), or PTH ($r=-0.446$; $P<0.001$), while a significant positive correlation was noted between patients' ΔBW and phosphate levels ($r=0.393$; $P<0.01$), and serum phosphorus and PTH ($P<0.01$).

The DBP ($r=0.401$; $P<0.001$) or MBP (Figure 1) ($r=0.440$; $P<0.001$) were positively correlated with serum phosphorus. A positive correlation was observed between serum phosphorus and stroke volume ($r=0.417$; $P<0.001$), heart rate ($r=0.308$; $P=0.01$), cardiac index (Figure 2) ($r=0.470$; $P<0.0001$), and cardiac work index ($r=0.340$; $P<0.01$). SBP and MBP were correlated with ΔBW ($r=0.366$; $P<0.01$ and $r=0.380$; $P<0.01$ respectively). Cardiac index was positively correlated with ΔBW ($r=0.440$; $P<0.001$) and negatively with blood haemoglobin or haematocrit ($r=-0.314$; $P<0.01$). LVr mass was inversely correlated with haemoglobin level ($r=-0.270$; $P<0.05$) and positively related to ΔBW ($r=0.520$; $P<0.001$). No correlations were observed between LV parameters and serum phosphorus. CCA diameter was positively correlated with ΔBW ($r=0.450$; $P<0.001$), serum phosphorus ($r=0.402$; $P<0.01$), and negatively correlated with the haemoglobin level ($r=-0.315$; $P<0.01$). Serum phosphorus was negatively correlated with CCA wall-to-lumen ratio ($r=-0.320$; $P<0.01$) (Figure 3), and positively with CCa tensile stress ($r=0.440$; $P<0.001$) (Figure 4).

Multiple regression analysis. Because serum phosphorus correlated with several parameters, which by themselves, interacted with haemodynamic and cardiovascular parameters (age, ΔBW, PTH, haemoglobin, etc.) a multiple stepwise regression analysis was undertaken to identify the independence of correlations linking serum phosphorus to cardiovascular alterations. After adjustment for all confounding variables, hyperphosphataemia was positively associated to MBP

Table 2. Haemodynamic and cardiovascular parameters in the two ESRD groups as a function of serum phosphorus

Parameter	Normal phosphates	High phosphates
Haemodynamic		
SBP (mmHg)	141.0±23.8	151.0±25.8
DBP (mmHg)	81.8±13.4	88.8±13.3[a]
MBP (mmHg)	101.4±15.7	110.7±15.7[a]
Stroke volume index (ml/beat/m^2)	37.1±10.4	43.7±12.5[a]
Heart rate (beats/min)	67±10	75±15[b]
Cardiac index (ml/min/m^2)	2350±600	3130±820[c]
Total peripheral resistance (dynes/s/cm^5/m^2)	3750±1400	3040±1070[a]
Cardiac work (kg/m/min/m^2)	4.34±1.47	5.35±1.55[b]
Cardiovascular		
LV mass index (g/m^2)	164±46	153±44
% LV shortening	33.7±7.2	35.4±4.5
LV end-diastolic diameter (cm)	5.40±0.66	5.38±0.51
LV mean wall thickness (cm)	1.03±0.20	1.05±0.28
E/A ratio	1.05±0.42	1.05±0.28
CCA diameter (mm)	5.90±0.77	6.24±0.77
CCA IMT thickness (μm)	760±109	742±115
Carotid wall/lumen ratio	0.256±0.030	0.238±0.029[a]
CCA distensibility (kPa^{-1}/10^3)	21±9	19.7±8.7
CCA E_{inc} (kPa/10^3)	0.48±0.24	0.56±0.36
CCA tensile stress (dynes/10^3/cm^2)	92±19	105±23[a]

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; LV, left ventricular; CCA, common carotid artery; IMT, intima media thickness; E_{inc}, elastic incremental modulus.
[a]$P<0.05$; [b]$P<0.01$; [c]$P<0.001$.

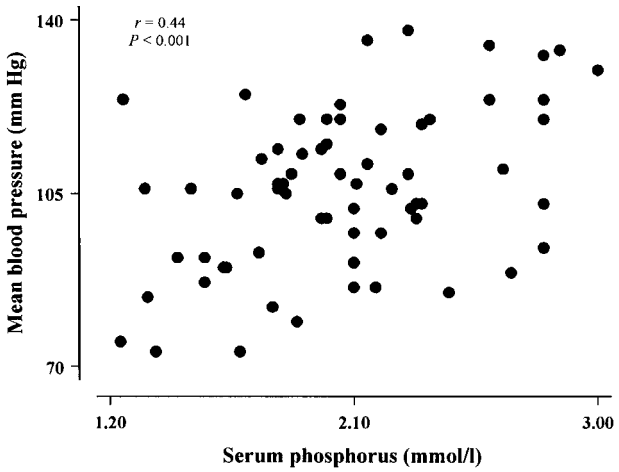

Fig. 1. Scatterplot showing the correlation between serum phosphorus and mean blood pressure in ESRD patients.

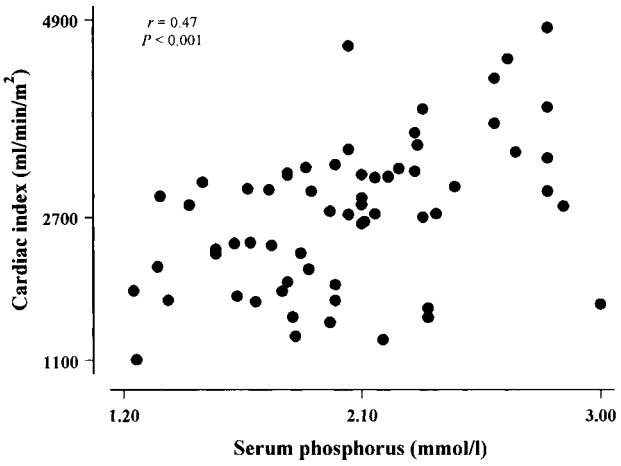

Fig. 2. Scatterplot showing the correlation between serum phosphorus and catdiac index in ESRD patients.

(r=0.340; $P<0.01$), cardiac index and cardiac work index ($r=0.428$; $P<0.001$ and $r=0.417$; $P<0.01$ respectively). A negative significant correlation was observed between serum phosphorus and CCA wall-to-lumen ratio ($r=-0.324$; $P<0.01$) while phosphataemia was positively correlated with CCA tensile stress ($r=0.318$; $P<0.05$).

Discussion

The results of the present study indicate that, in haemodialysed ESRD patients, hyperphosphataemia is associated with a hyperkinetic circulation characterized by increased MBP associated with high cardiac output but decreased peripheral resistance. The increased cardiac output is due to increased stroke volume and increased heart rate. The hyperkinetic circulation, in turn, induces increased cardiac work. In parallel with central haemodynamic changes, hyperposphataemia was associated with elevated tensile stress of the CCA.

The present results concern patients under 60 years. Older patients were not included for following reasons: (i) the effects of ageing on cardiovascular function and structure overcome many factors including those associated with uraemia; (ii) many older patients suffered from various cardiovascular alterations for a long-time before ESRD and in many cases the cardiovascular disease was responsible for renal failure; (iii) age and serum phosphate are negatively correlated (as are age

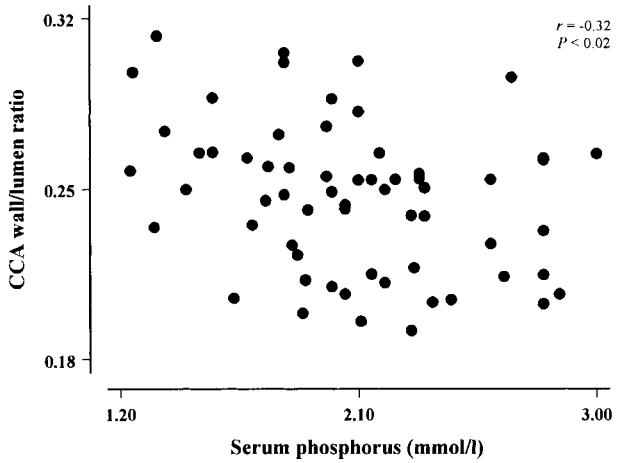

Fig. 3. Scatterplot showing the correlation between serum phosphorus and common carotid artery (CCA) wall-to-lumen ratio.

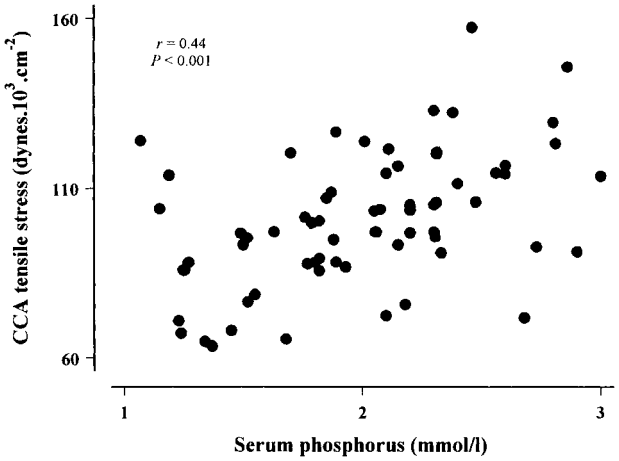

Fig. 4. Scatterplot showing the correlation between serum phosphorus and CCA tensile stress in ESRD patients.

and PTH levels), most probably because of lower dietary phosphate intake and common protein malnutrition in the elderly.

In the absence of excess catabolism, high serum phosphorus is due to phosphate accumulation from (i) high dietary intake, (ii) decreased elimination due to inadequate dialysis, (iii) poor compliance with the use of phosphate binders, and (iv) bone mobilization due hyperparathyroidism [17]. In the present study, a role for dietary intake was suggested by the positive correlation between the change in body weight in the interdialytic interval (ΔBW) and serum phosphate. These findings could be interpreted as the result of poor compliance with dietary prescriptions in hyperphosphataemic patients. Poor dialysis efficacy is less likely since the Kt/V were similar for the two groups of patients and not correlated to serum phosphate.

Increased serum phosphate was associated with higher SBP and MBP. Their relationships are difficult to interpret. High BP is frequently caused by volume overload and overhydration in ESRD patients [18]. The finding of an association between high phosphate concentration and greater inter dialysate body weight changes (ΔBW) would suggest that the correlation between phosphate levels and BP is simply the consequence of greater volume overload in less compliant patients. This possibility seems unlikely for two reasons: first, the ΔBW was not correlated to BP and, secondly in the multiple regression analysis, the correlation between serum phosphate and BP was independent of ΔBW. The multiple regression analysis also showed that the relationship between serum phosphate and central haemodynamics was independent of the haemoglobin levels.

Higher phosphate concentrations were associated with increased serum PTH concentrations. Experimental studies have shown that PTH acts on the heart cells *in vitro*, generating positive chronotropic and inotropic effects [6–8]. PTH significantly influences vascular tone. Whereas acute infusion of PTH results in vascular relaxation caused by activation of adenyl cyclase in vascular smooth muscle cells [19,20], prolonged hormone exposure induces receptor desensitization and the sustained effect of PTH has been implicated in the maintenance of hypertension [19,20]. On the other hand, an association between serum PTH level and a hyperkinetic circulation was also observed in haemodialysed patients, principally in conjunction with increased heart rates [9]. However, studies in humans showed that parathyroidectomy (PTX) in haemodialysed patients did not significantly modify heart function [21–23] but decreased the resting heart rate [22]. Whether the haemodynamic alterations associated with hyperphosphataemia could be exerted through the influence of PTH is difficult to analyse. Nevertheless, at least from a statistical point of view, the relationships are independent of PTH levels, and according to our univariate analysis, the PTH concentrations were not correlated with BP and/or cardiac output. However, the serum PTH concentration at one single point in time is not necessarily a precise index of the effect of PTH exerted on its target tissues.

The cardiac status of the present population of ESRD patients was characterized by moderate left ventricular (LV) hypertrophy with normal systolic and diastolic functions of the LV. The LV hypertrophy was due to a moderate enlargement of the LV in association with the lower haemoglobin levels and ΔBW. Serum phosphate was not associated with changes in LV geometry. In both groups of ESRD patients, we observed moderate enlargement of the CCA diameter and mild intima-media hypertrophy. The internal dimensions of the CCA were not-significantly greater in the hyperphosphataemic group, whose principal geometric characteristic consisted of a significantly lower CCA wall-to-lumen ratio. This finding is unexpected in view of the higher BP recorded for this group. In non-uraemic normotensive and hypertensive subjects, the arterial wall-to-lumen ration increases with increasing BP. This can be interpreted as a mechanism to maintain arterial tensile stress within the physiological limits [24]. In the absence of such compensation, as observed in the hyperphosphataemic group of ESRD patients, arterial wall tensile stress

increases, leading to an abnormal mechanical load and fatigue of biomaterials. The mechanism(s) responsible for the association between serum phosphate and lower wall-to-lumen ratio is not clear. Hyperphosphataemia could interfere with arterial wall hypertrophy by metastatic calcifications of the arterial media or through its association with high PTH levels which favour the activations of fibroblasts and development of interstitial fibrosis rather than hypertrophy of vascular smooth muscle cells [25].

The present study has several limitations and shortcomings and potential sources of error: the first is its cross-sectional design and observational nature; the second is its purely statistical approach not based on an experimental and interventional design. This latter point is important because it remains unclear whether the haemodynamic alterations observed are the consequence of phosphate levels *per se* or whether the effect is indirect, mediated by another mechanism(s). In conclusion, the observations presented herein indicate that, in stable ESRD patients, increased serum phosphate is associated with increased BP, hyperkinetic circulation, increased cardiac work, and high arterial wall tensile stress. The elevated tensile stress is the consequence of higher BP and an 'inadequate' increase of arterial wall thickness characterized by a low arterial wall-to-lumen ratio. These haemodynamic abnormalities are factors which, over the long-term, could favour the development of cardiovascular complications and high cardiovascular morbidity and mortality especially in patients with pre-existing cardiovascular alterations. Although the mechanism(s) are not clearly established, the finding that hyperphosphataemia is an independent risk factor argues for rigourous monitoring and control of serum phosphate levels in ESRD patients.

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Editor's note

Please see also *Editorial Comment* by Amann *et al.* (pp. 2085–2087 in this issue).