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Original

The regulation of phosphate and its association with alterations in bone and mineral metabolism

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Abstract

Introduction and objective: although high levels of serum phosphate have been related to the risk of fracture and aortic calcification, it is not known if there is any association of urinary phosphate with the incidence of osteoporotic fracture and aortic calcification.

Material and methods: 141 postmenopausal women > 50 years of age underwent dorso-lumbar radiology that was repeated 4 years later, determining general biochemical markers and bone and mineral metabolism in blood and fresh urine, clinical and anthropometric parameters were collected. The appearance of new vertebral and non-vertebral fractures and new aortic calcification was radiographically confirmed. Women with estrogen and antiresorptive treatment > 3 months were excluded.

Results: 11 new non-vertebral fractures were detected (7 Colles, 2 hip and 2 in other locations) and 10 incident vertebral fractures confirmed radiographically. Body mass index, phosphaturia, creatinuria, phosphaturia/creatinuria and estimated glomerular filtration rate (eGFR) were significantly lower and age was higher in the fractured women. Increases of 10 mg/dL in phosphaturia were associated with 29 % fewer incident fractures [OR, 0.71; 95 % CI = (0.46-0.98)], after logistic regression adjusted for age, body mass index, creatinuria and eGFR. This effect was more marked with non-vertebral incident fractures [OR, 0.50; 95 % CI = (0.10-0.91)], while in vertebral this association was lost [OR, 0.83; 95 % CI = (0.54-1.14)]. Furthermore, 17 % of the cohort had new aortic calcifications. At a multivariate level, increases of 10 mg/dL of phosphaturia were associated with a lower incidence of aortic calcification [OR, 0.80; 95 % CI = (0.64-0.97)].

Conclusions: low phosphate levels seem to be associated with a higher incidence of osteoporotic fracture and aortic calcification in women. Phosphaturia could be an indicator of hormonal and renal effects on phosphate regulation and used as a risk factor for aortic fracture and calcification.

Keywords:
Phosphaturia.
Abdominal aortic calcification.
Osteporotic fracture.

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INTRODUCTION

Osteoporotic fractures constitute a significant health and economic issue for public health systems (1) and are associated with high morbidity and mortality in the general population.

There is increasing evidence that elevated phosphate levels are linked to an increased risk of fracture (2,3). In fact, two large population cohort studies, the Rotterdam Study and the MrOS (Osteoporotic Fracture Study in Men), reported that increased serum phosphate levels were associated with fracture risk in participants without chronic kidney disease (3). Recently, this same effect has been observed in both male and female dialysis populations, suggesting that lowering serum phosphate levels may prevent fractures (4). In fact, an observational study of 13,427 dialysis patients showed that those not treated with phosphate binders had a 20 % higher risk of fracture compared to those who were treated (5). These findings are supported by evidence from animal models in which dietary phosphate increase induces bone fragility, even when circulating phosphate concentrations remain within the normal range (6).

The direct association between bone tissue deterioration and the development of arterial calcification has long been acknowledged (7,8). The role of phosphate in the development and progression of arterial calcification is well established in the presence of impaired renal function (9), but also in the general population (10).

As is well known, fragility fractures are associated with aging, but they occur more frequently in women. One of the main factors attributed to this gender difference is the estrogen deprivation that occurs in women after menopause, which leads to accelerated bone tissue loss, ultimately resulting in greater susceptibility to fragility fractures (11). Cardiovascular disease and its clinical manifestation with the onset of arterial calcification in women also begin to manifest with menopause and the loss of estrogen (12).

Postmenopausal women with estrogen depletion exhibit hyperphosphatemia due to increased proximal tubular phosphate reabsorption (13). However, no studies have ever analyzed whether there is any association between urinary phosphate levels and the presence of fractures and/or arterial calcifications. Therefore, the aim of this study was to evaluate the effect of urinary phosphate on the incidence of osteoporotic fractures and aortic calcification in women from the general population.

MATERIAL AND METHODS

We selected a random sample of 316 women over 50 years old from the municipal registry of Oviedo (Asturias, Spain). The protocol for this study included completing a questionnaire on risk factors related to osteoporosis, two lateral thoracolumbar X-rays, a densitometry study of the lumbar spine and hip, anthropometric measurements (height and weight) to calculate body mass index (BMI), a gynecological and drug history. All subjects had sufficient ambulatory capacity to climb two floors without an elevator, and 99 % lived in their own home.

After 4 years, the participants were invited to repeat the radiological study, densitometric measurements, anthropometric measurements, osteoporosis risk factor questionnaire, and a biochemical study. A total of 213 women participated in the second control, and 168 agreed to undergo the biochemical study. A total of 18 women were excluded from the analysis for having received osteoporotic or estrogenic treatment, and another 9 were excluded for still being in their menstrual periods. Data were available for 141 women at both the start and after 4 years.

INCIDENCE OF OSTEOPOROTIC FRACTURE

For the diagnosis of new vertebral fractures, the baseline radiographs were compared with the follow-up X-rays by two independent readers who performed a qualitative radiological evaluation without knowing the clinical conditions of the evaluated subjects. A new or incident fracture was defined as a reduction, visible to the naked eye, in any of the vertebral body heights vs the baseline X-ray, following the Genant method (14). If there was no agreement between the 2 readers, the fracture was defined by consensus after joint review. The interobserver reproducibility (Cohen's kappa coefficient) of the 2 readers in defining incident fractures was 0.82, indicating good reproducibility. All non-vertebral osteoporotic fractures, excluding those of the skull and extremities, were confirmed by X-ray.

EVALUATION OF INCIDENT VASCULAR CALCIFICATION

The presence of new aortic calcification was determined by comparing the baseline X-rays with those taken 4 years later.

Abdominal aortic calcification was evaluated by 2 independent investigators and categorized as grade 0 (absent), grade 1 (mild-moderate), and grade 2 (severe). Isolated punctate calcifications, a linear calcification visible in < 2 vertebral bodies, or a dense calcified plaque were defined as mild-moderate calcification (15). The presence of a linear calcification visible along at least two vertebral bodies and/or the presence of > 2 dense calcified plaques was defined as severe calcification. The intra- and interobserver

reproducibility (Cohen's kappa coefficient) for analyzing the radiographs to define incident aortic calcification was 0.78 and 0.73, respectively, indicating good reproducibility (15).

DENSITOMETRIC EVALUATION

Bone mineral density (BMD) was measured using a Hologic® QDR-1000 DXA densitometer (Hologic Inc., Waltham, MA, USA). In all cases, antero-posterior lumbar spine (L2-L4) and right femur BMD were analyzed. The coefficient of variation (CV) was 1.2 % and 1.9 %, respectively (15). Quality control and precision were performed daily with a lumbar spine phantom, which yielded a CV of 0.0 ± 0.1 %. In the fourth year, BMD was determined in the same areas used in the first study, and the percentage change between both measurements was used to assess changes in BMD.

BIOCHEMICAL ANALYSIS

No biochemical analysis was performed at baseline. After 4 years, blood and fresh urine samples were collected from each participant in a fasting state. Once the serum and urine were separated, they were stored at -80 °C until quantification. Creatinine serum levels, estimated glomerular filtration rate, calcium, phosphorus, albumin, total alkaline phosphatase, acid phosphatase, and tartrate-resistant acid phosphatase were measured. In urine, creatinine, phosphorus, and calcium levels were determined. Both serum and urine were analyzed using an autoanalyzer (Hitachi Mod. 717, Ratigen, Germany).

Serum levels of calcidiol (25OHD) were measured by prior extraction with acetonitrile (IDS, Ltd., Bolton, UK), with intra- and inter-assay CVs of 5.2 % and 8.2 %, respectively. Levels of 1,25-dihydroxyvitamin D were measured by radioimmunoassay (IDS, Ltd.); intra- and inter-assay CVs were 6.5 % and 9 %, respectively. Intact PTH levels were measured by radioimmunoassay (Nichols Institute, San Juan Capistrano, CA, USA), with intra- and inter-assay CVs of 2.6 % and 5.8 %, respectively.

All studies were conducted in accordance with the principles outlined in the Helsinki Declaration and were formally approved by the Clinical Trials Committee of the Principality of Asturias.

STATISTICAL ANALYSIS

Data analysis was performed using SPSS version 17.0 for Windows. Quantitative variables were analyzed using Student's t-test. Qualitative variables were analyzed using chi-square tests. Pearson correlations were performed between quantitative variables.

To analyze, at a multivariate level, the effect of phosphaturia on the incidence of vertebral and non-vertebral osteoporotic fractures, as well as on the incidence of aortic calcification, logistic regression was used, adjusted for variables that were statistically significant in the univariate model.

RESULTS

In the 4-year follow-up period, 11 new non-vertebral fractures were detected (7 Colles fractures, 2 hip fractures, and 2 in other locations), along with 10 incident vertebral fractures. All fractures were confirmed radiographically.

Table I shows the demographic, anthropometric, and biochemical variables at 4 years from the start of the study in women with incident vertebral and non-vertebral fractures. Women with incident fractures had significantly lower BMI, phosphaturia, creatinuria, and estimated glomerular filtration rate (eGFR), while their age was significantly higher.

Considering that women with incident fractures were associated with significantly lower phosphaturia levels at a univariate level, a logistic regression model was conducted using incident osteoporotic fracture as the dependent variable and phosphaturia as the independent variable, adjusted for age, BMI, creatinuria, and eGFR. Increases of 10 mg/dL in phosphaturia were associated with 29 % fewer incident fractures [odds ratio (OR, 0.71; 95 %CI, 0.46-0.98)].

Table II shows the demographic, anthropometric, and biochemical variables at 4 years from the start of the study, separated by women with and without incident non-vertebral fractures. Women with fractures had significantly lower BMI, phosphaturia, and creatinuria. The logistic regression analysis, adjusted for BMI and creatinuria, showed that increases of 10 mg/dL in phosphaturia were associated with 50 % fewer incident fractures [OR, 0.50; 95 %CI, 0.10-0.91)].

Table III shows the demographic, anthropometric, and biochemical variables at 4 years from the start of the study, separated by women with and without incident vertebral fractures. In women with fractures, significantly lower phosphaturia and creatinuria levels were observed. However, in the logistic regression analysis adjusted for creatinuria, phosphaturia (increases of 10 mg/dL) was not associated with the incidence of vertebral fractures [OR, 0.83; 95 %CI, 0.54-1.14)].

In light of the previous results and considering that phosphaturia had a greater effect on non-vertebral fractures than on vertebral fractures, the percentage changes in bone mineral density at the lumbar level and femoral neck were analyzed between the 2 cross-sectional time points.

Table I. Demographic, anthropometric, and serum and urinary markers of general and bone and mineral metabolism in women with and without incident vertebral and non-vertebral fractures

Variables	Fractured (*n* = 17)	Non-fractured (*n* = 124)	*p-value*
Age (years)	67.8 ± 8.1	63.6 ± 7.9	*0.044*
BMI (kg/m^2)	26.2 ± 2.4	29.0 ± 4.7	*0.001*
Creatinine (mg/dL)	0.95 ± 0.19	0.92 ± 0.11	0.481
Estimated glomerular filtration rate (eGFR) (mL/min)	52.9 ± 10.9	66.8 ± 16.9	*< 0.001*
Serum phosphorus (mg/dL)	3.51 ± 0.47	3.62 ± 0,.41	0.304
Serum calcium (mg/dL)	9.34 ± 0.16	9.40 ± 0.33	0.181
Calcidiol (ng/mL)	14.3 ± 7.2	14.9 ± 8.9	0.774
Calcitriol (pg/mL)	36.0 ± 10.1	38.1 ± 12.8	0.531
Total alkaline phosphatase (U/L)	181 ± 59	186 ± 88	0.821
PTH (pg/mL)	63.7 ± 37.4	54.8 ± 21.4	0.360
Acid phosphatase (U/L)	2.79 ± 0.65	2.83 ± 0.92	0.839
Tartrate-resistant acid phosphatase (TRAP) (U/L)	2.26 ± 0.62	2.16 ± 0.70	0.567
Serum albumin (g/L)	44.6 ± 2.3	45.3 ± 2.1	0.228
Urinary phosphorus (mg/dl)	47.8 ± 15.0	73.8 ± 33.8	*< 0.001*
Urinary calcium (mg/dl)	12.7 ± 6.4	14.1 ± 8.4	0.509
Urinary creatinine (mg/dL)	63.6 ± 26.8	79.9 ± 37.6	*0.034*
Tubular phosphate reabsorption (TPR)	0.78 ± 0.08	0.76 ± 0.07	0.258

Table II. Demographic, anthropometric, and serum and urinary markers of general and bone and mineral metabolism in women with and without incident non-vertebral fractures

Variables	Fractured (*n* = 9)	Non-fractured (*n* = 132)	*p-value*
Age (years)	67.3 ± 8.8	63.9 ± 7.9	*0.214*
BMI (kg/m^2)	26.7 ± 2.3	28.9 ± 4.6	*0.033*
Creatinine (mg/dL)	0.99 ± 0.22	0.92 ± 0.11	0.352
Estimated glomerular filtration rate (eGFR) (mL/min)	54.2 ± 12.3	66.0 ± 16.9	*0.054*
Serum phosphorus (mg/dL)	3.43 ± 0.42	3.62 ± 0.41	0.195
Serum calcium (mg/dL)	9.32 ± 0.17	9.40 ± 0.33	0.500
Calcidiol (ng/mL)	14.0 ± 7.6	14.9 ± 8.8	0.780
Calcitriol (pg/mL)	38.0 ± 10.1	37.8 ± 12.7	0.972
Total alkaline phosphatase (U/L)	166 ± 71	187 ± 85	0.465
PTH (pg/mL)	76.1 ± 48,.7	54.5 ± 21.1	0.212
Acid phosphatase (U/L)	2.80 ± 0.79	2.83 ± 0.90	0.923
Tartrate-resistant acid phosphatase (TRAP) (U/L)	2.26 ± 0.72	2.16 ± 0.69	0.698
Serum albumin (g/L)	44.46 ± 18	45.3 ± 2.1	0.253
Urinary phosphorus (mg/dL)	42.2 ± 12.2	72.6 ± 33.3	*< 0.001*
Urinary calcium (mg/dL)	11.7 ± 6.5	14.1 ± 8.3	0.396
Urinary creatinine (mg/dL)	58.2 ± 19.1	79.3 ± 37.3	*0.012*
Tubular phosphate reabsorption (TPR)	0.78 ± 0.07	0.76 ± 0.07	0.345

Table III. Demographic, anthropometric, and serum and urinary markers of general and bone and mineral metabolism in women with and without incident vertebral fractures

Variables	Fractured (*n* = 10)	Non-fractured (*n* = 131)	*p-value*
Age (years)	68.5 ± 7.2	63.8 ± 8.0	*0.072*
BMI (kg/m^2)	25.7 ± 2.5	28.9 ± 4.6	*0.053*
Creatinine (mg/dL)	0.90 ± 0.12	0.92 ± 0.12	0.586
Estimated glomerular filtration rate (eGFR) (mL/min)	53.0 ± 9.9	66.1 ± 17.0	*0.007*
Serum phosphorus (mg/dL)	3.63 ± 0.47	3.60 ± 0.41	0.829
Serum calcium (mg/dL)	9.34 ± 0.15	9.40 ± 0.33	0.615
Calcidiol (ng/mL)	13.7 ± 7.1	14.9 ± 8.8	0.675
Calcitriol (pg/mL)	32.9 ± 10.2	38.2 ± 12.7	0.198
Total alkaline phosphatase (U/L)	213 ± 47	184 ± 87	0.289
PTH (pg/mL)	57.9 ± 25.6	55.6 ± 23.9	0.771
Acid phosphatase (U/L)	2.87 ± 0.64	2.83 ± 0.91	0.879
Tartrate-resistant acid phosphatase (TRAP) (U/L)	2.35 ± 0.68	2.16 ± 0.69	0.398
Serum albumin (g/L)	44.7 ± 2.7	45.3 ± 2.1	0.407
Urinary phosphorus (mg/dL)	50.1 ± 16.5	71.8 ± 33.5	*0.002*
Urinary calcium (mg/dL)	12.7 ± 6.2	14.0 ± 8.3	0.649
Urinary creatinine (mg/dL)	65.7 ± 31.0	78.6 ± 37.1	*0.286*
Tubular phosphate reabsorption (TPR)	0.79 ± 0.08	0.76 ± 0.07	0.188

None of the three bone segments analyzed correlated with phosphaturia: lumbar spine: r = -0.077, p = 0.431; femoral neck: r = -0.66, p = 0.482; total hip: r = 0.028, p = 0.764.

However, when associations between urinary phosphate and bone mineral density in the three segments were analyzed, only in the second cross-sectional analysis was no correlation found between lumbar BMD and urinary phosphate (r = 0.118, p = 0.229), but a correlation was found between femoral neck BMD and urinary phosphate (r = 0.239, p = 0.004), and between total hip BMD and urinary phosphate (r = 0.232, p = 0.006) (Fig. 1).

A total of 23 women (17.1 %) developed new aortic calcifications during the 4-year follow-up period. Table IV presents the demographic, anthropometric, and biochemical variables at 4 years from the start of the study, separated by women with and without incident aortic calcification, considering the presence of new calcification not seen on the baseline X-rays. Women with incident aortic calcification had significantly lower serum albumin and phosphaturia levels. Logistic regression analysis, adjusted for serum albumin, showed that increases of 10 mg/dL in phosphaturia were associated with a lower incidence of aortic calcification [OR, 0.80; 95 %CI, 0.64-0.97)]. It was also notable that increases of 1 mg/dL in serum albumin reduced the incidence of aortic calcification by 31 % [OR, 0.69; 95 %CI, 0.54-0.88)].

DISCUSSION

The results of this study present, for the first time in the literature, an association between decreases in phosphaturia and an increase in the incidence of osteoporotic fractures and aortic calcification. In fact, increases of 10 mg/dL in phosphaturia in postmenopausal women decreased the incidence of both vertebral and non-vertebral fractures by 29 %, with a much stronger effect observed in non-vertebral fractures, which occur in bones with a more cortical content, as shown by the significant correlation between phosphaturia and BMD in the femoral neck and total hip. This effect was not observed in lumbar BMD, which has a more trabecular content. On the other hand, increases of

Table IV. Demographic, anthropometric variables, and general serum and urinary markers of bone and mineral metabolism in women with and without incident aortic calcifications

Variables	Calcification (*n* = 23)	No Calcification (*n* = 110)	*p-value*
Age (years)	69.6 ± 6.1	68.0 ± 8.3	*0.296*
BMI (kg/m^2)	29.7 ± 4.4	28.6 ± 4.6	*0.314*
Creatinine (mg/dL)	0.90 ± 0.11	0.93 ± 0.13	0.296
Estimated glomerular filtration rate (eGFR) (mL/min)	67.1 ± 14.6	65.0 ± 17.4	*0.596*
Serum phosphorus (mg/dL)	3.64 ± 0.48	3.61 ± 0.39	0.775
Serum calcium (mg/dL)	9.34 ± 0.24	9.40 ± 0.33	0.390
Calcidiol (ng/mL)	14.6 ± 7.2	14.7 ± 8.6	0.976
Calcitriol (pg/mL)	40.3 ± 14.2	37.0 ± 11.3	0.223
Total alkaline phosphatase (U/L)	214 ± 169	180 ± 55	0.347
PTH (pg/mL)	60.7 ± 27.0	55.1 ± 33.8	0.320
Acid phosphatase (U/L)	2.70 ± 0.89	2.87 ± 0.90	0.436
Tartrate-resistant acid phosphatase (TRAP) (U/L)	2.08 ± 0.82	2.19 ± 0.67	0.495
Serum albumin (g/L)	44.1 ± 2.3	45.5 ± 2.1	0.004
Urinary phosphorus (mg/dL)	59.1 ± 26.9	73.8 ± 34.5	*0.047*
Urinary calcium (mg/dL)	13.0 ± 8.7	14.0 ± 8.2	0.591
Urinary creatinine (mg/dL)	69.6 ± 35.0	80.2 ± 37.8	*0.219*
Tubular phosphate reabsorption (TPR)	0.78 ± 0.06	0.75 ± 0.07	0.148

10 mg/dL in phosphaturia in this same cohort reduced the incidence of aortic calcification by 20 %.

At the biochemical level, PTH was not able to explain this effect. Serum PTH levels were found to be slightly, but not significantly, higher in women with either incident fracture or incident aortic calcification. This slight increase should have contributed to an increase in urinary phosphate excretion, something that not only did not happen, but even went in the opposite direction.

There are several mechanisms that could explain how phosphate might affect bone quality and strength. Regarding bone formation, inorganic phosphate can stimulate several regulatory molecules (phos antigen 1, osteopontin, insulin-like growth factor I, and sclerostin), which would inhibit Wnt/beta-catenin and osteoblast proliferation (16,17). Inorganic phosphate also affects bone resorption by limiting the survival and differentiation of osteoclasts, inducing changes in the expression of RANKL, miR-223, and osteoprotegerin (18-22).

However, in our study, we did not observe higher serum phosphate levels in the group of women with fractures, with urinary phosphate levels being the factor that marked the observed differences. The fact that we did not see any effect of serum phosphate on fracture incidence in women has been previously described in other epidemiological studies. In an elderly population study, the upper decile (D10) of serum phosphate in men had a 78 % higher risk of incident fracture (HR, 1.78; 95 %CI, 1.25-2.54), a relationship not found in women (HR, 1.09; 95 %CI, 0.83-1.44) (2). These results are similar to those of other studies where the association between high serum phosphate levels and incident fractures was substantially stronger in men than in women (3). The disparity between men and women could reflect a difference in sensitivity to high serum phosphate levels, keeping in mind that, in general, women have higher serum phosphate levels than men of similar age.

Unlike what has been described by other authors (23-25), we did not find any associations between serum phosphate levels and the incidence of aortic calcification.

Since the main biochemical regulators of phosphorus metabolism do not allow us to discern why we found this association between urinary phosphate and the

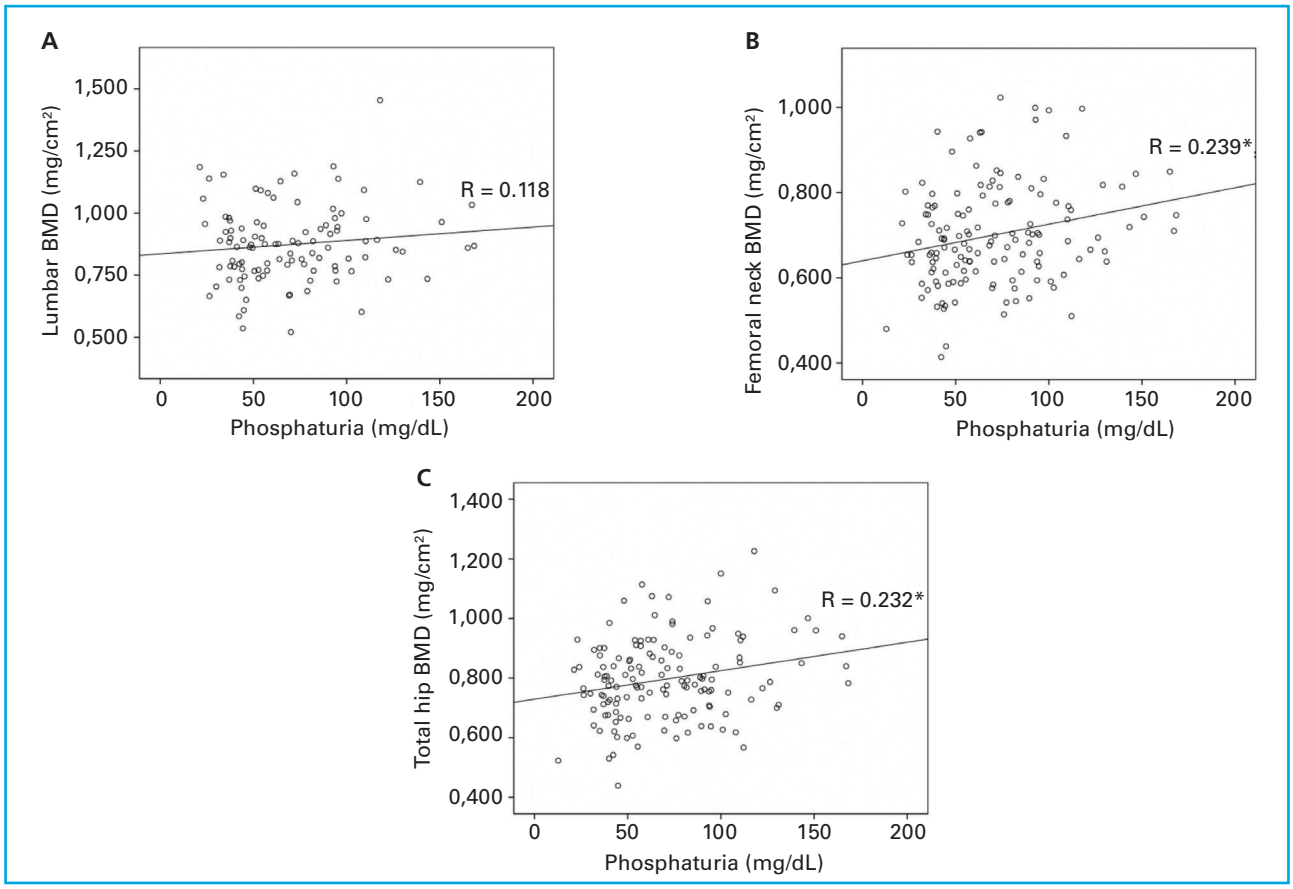

Figure 1. Correlations between phosphaturia and bone mineral density (BMD) in the second cross-sectional cut in lumbar spine (A); femoral neck (B); total hip (C). *$p < 0.05$.

incidence of fractures and/or aortic calcification, we need to consider other regulatory mechanisms. In this cohort of postmenopausal women, there is an estrogen deficit. It is known that estrogens are an important physiological regulator involved in the functional modulation of several hormones, suggesting that the mechanisms by which estrogens regulate mineral metabolism could be complex and involve both direct and indirect effects.

We should highlight the hypophosphatemic and hyperphosphaturic effects of estrogens in different clinical studies. Several studies have observed that estrogen administration in postmenopausal women is associated with hypophosphatemia, which in some cases is due to reduced phosphate reabsorption in the proximal tubule (26-28) and the negative regulation of NaPi-IIa in the proximal tubule (29). In contrast, decreases in estrogen levels are associated with an increase in serum phosphate (hyperphosphatemia) and an increase in tubular phosphate reabsorption in the proximal tubule with a decrease in urinary phosphate excretion (hypophosphaturia). Therefore, in the context of former studies, these data suggest that estrogens may directly or indirectly induce phosphaturia in humans (30).

There is strong evidence indicating that estrogens can exert a rapid, non-genomic effect in certain target tissues (31,32). It remains to be determined whether these pathways contribute to the phosphaturic effect of estrogens (33).

After menopause, the main estrogen of reproductive years, 17β-estradiol, decreases significantly, and estrone becomes the primary estrogen in tissues and circulation. Estrone is produced through the conversion of adrenal androstenedione by aromatase, primarily in adipose tissue. Estrone increases almost 2 times in obesity due to its greater aromatization in adipose tissue (34).

Serum levels of 17β-estradiol and estrone are more than double in obese individuals vs lean postmenopausal women (35). Therefore, we could hypothesize the existence of fat-induced estrogen production, which could contribute to women with overweight having extra estrogen secretion increasing phosphaturia compared to what happens in the typical osteoporotic woman who is thin and fragile. In fact, when analyzing the incidence of vertebral and non-vertebral fractures in the univariate analysis, BMI was significantly lower in those women with fractures.

The effect of phosphaturia on the incidence of aortic calcification, similar to that observed for incident fractures, is both interesting and surprising. However, we cannot ignore that both alterations are associated with age, which may be related to the possibility that in response to calcifying stimuli, vascular smooth muscle cells dedifferentiate into osteoblast-like cells capable of synthesizing osteogenic markers (36). It is also worth noting how decreases in serum albumin contribute to the increase in calcification, a phenomenon described by other authors (37).

We cannot rule out the existence of limitations in this study. First, we do not have serum estrogen levels that could explain these differences in phosphaturia. Second, we do not have serum FGF23 levels, which could provide additional value, but when the study was conducted, we did not have this serum marker and unfortunately, there is no sample available for testing. Third, phosphaturia was only measured in the second cross-sectional cut, limiting the associations found. Finally, we must not forget that the sample size is somewhat limited.

Nevertheless, despite acknowledging the limitations, this study also has strengths, such as being a prospective study with a follow-up participation rate above 50 %, at a time when epidemiological studies were not very common in our country. The prospective, rather than cross-sectional, nature of the study strengthens the validity of the results and their greater degree of association.

We can conclude that low phosphaturia seems to be associated with a higher incidence of osteoporotic fractures and aortic calcification in postmenopausal women. Regarding osteoporotic fractures, the effect seems more marked in bones with higher cortical than trabecular content. Whether serum estrogen levels contribute to this effect is something that should be confirmed in future studies. Based on these results, in elderly women, phosphaturia could be an indicator of hormonal and renal effects on phosphate regulation and could be used as another risk factor for osteoporotic fractures and aortic calcification.

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REFERENCES

1. Kanis JA, Norton N, Harvey NC, Jacobson T, Johansson H, Lorentzon M, et al. SCOPE 2021: a new scorecard for osteoporosis in Europe. Arch Osteoporos 2021;16:82. DOI: 10.1007/s11657-020-00871-9
2. Hussain SM, Seeman E, Schneider HG, Ebeling PR, Barker AL, Polkinghorne K, et al. Association of serum phosphate, calcium and alkaline phosphatase with risk of incident fractures in healthy older adults. J Clin Endocrinol Metab 2024;109(12):e2188-e2195. DOI: 10.1210/clinem/dgae099
3. Campos-Obando N, Koek WNH, Hooker ER, van der Eerden BC, Pols HA, Hofman A, et al. Serum phosphate is associated with fracture risk: the Rotterdam Study and MrOS. J Bone Miner Res 2017;32(6):1182-93. DOI: 10.1002/jbmr.3094
4. Barrera-Baena P, Rodríguez-García M, Rodríguez-Rubio E, González-Llorente L, Ortiz A, Zoccali C, et al. Serum phosphate is associated with increased risk of bone fragility fractures in haemodialysis patients. Nephrol Dial Transplant 2024;39:618-26. DOI: 10.1093/ndt/gfad190
5. Kwon YE, Choi HY, Kim S, Ryu DR, Oh HJ; ESRD Registry Committee of the Korean Society of Nephrology. Fracture risk in chronic kidney disease: a Korean population-based cohort study. Kidney Res Clin Pract 2019;38:220-8. DOI: 10.23876/j.krcp.18.0099
6. Roberts JL, Yu M, Viggeswarapu M, Arnst JL, Pacifici R, Beck GR Jr. Dietary phosphorus consumption alters T cell populations, cytokine production, and bone volume in mice. JCI Insight 2023;8(10):e154729. DOI: 10.1172/jci.insight.154729
7. Szulc P, Blackwell T, Kiel DP, Schousboe JT, Cauley J, Hillier T, et al. Abdominal aortic calcification and risk of fracture among older women - The SOF study. Bone 2015;81:16-23. DOI: 10.1016/j.bone.2015.06.019
8. Mazziotti G, Tupputi U, Ferrante G, Guglielmi G. Abdominal aortic calcification as a marker of relationship between atherosclerosis and skeletal fragility. J Clin Densitom 2020;23(4):539-42. DOI: 10.1016/j.jocd.2020.05.001
9. Zhang R, Lu Y, Ye L, Yuan B, Yu S, Qin C, et al. Unique roles of phosphorus in endochondral bone formation and osteocyte maturation. J Bone Miner Res 2011;26:1047-56. DOI: 10.1002/jbmr.294
10. Khurrami L, Møller JE, Lindholt JS, Urbonaviciene G, Steffensen FH, Lambrechtsen J, et al. Cross-sectional study of aortic valve calcification and cardiovascular risk factors in older Danish men. Heart 2021;107(19):1536-43. DOI: 10.1136/heartjnl-2021-319023
11. Armas LA, Recker RR. Pathophysiology of osteoporosis: new mechanistic insights. Endocrinol Metab Clin North Am 2012;41(3):475-86. DOI: 10.1016/j.ecl.2012.04.006
12. Davezac M, Buscato M, Zahreddine R, Lacolley P, Henrion D, Lenfant F, et al. Estrogen receptor and vascular aging. Front Aging 2021;2:27380. DOI: 10.3389/fragi.2021.727380

13. Adami S, Gatti D, Bertoldo F, Rossini M, Fratta-Pasini A, Zamberlan N, et al. The effects of menopause and estrogen replacement therapy on the renal handling of calcium. Osteoporos Int 1992;2(4):180-5. DOI: 10.1007/BF01623924
14. Genant HK, Wu CY, Van Kujik C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993;8:1137-48. DOI: 10.1002/jbmr.5650080915
15. Naves M, Rodríguez-García M, Díaz-López JB, Gómez-Alonso C, Cannata-Andía JB. Progression of vascular calcifications is associated with greater bone loss and increased bone fractures. Osteoporos Int 2008;19(8):1161-6. DOI: 10.1007/s00198-007-0539-1
16. Kanatani M, Sugimoto T, Kano J, Chihara K. IGF-I mediates the stimulatory effect of high phosphate concentration on osteoblastic cell proliferation. J Cell Physiol 2002;190:306-12. DOI: 10.1002/jcp.10067
17. Beck GR, Zerler B, Moran E. Phosphate is a specific signal for induction of osteopontin gene expression. Proc Natl Acad Sci USA 2000;97:8352-7. DOI: 10.1073/pnas.140021997
18. Gupta A, Guo XL, Alvarez UM, Hruska KA. Regulation of sodiumdependent phosphate transport in osteoclasts. J Clin Invest 1997;100:538-49. DOI: 10.1172/JCI119563
19. Kanatani M, Sugimoto T, Kano J, Kanzawa M, Chihara K. Effect of high phosphate concentration on osteoclast differentiation as well as bone resorbing activity. J Cell Physiol 2003;196:180-9. DOI: 10.1002/jcp.10270
20. Koyama Y, Rittling SR, Tsuji K, Hino K, Salincarnboriboon R, Yano T, et al. Osteopontin deficiency suppresses high phosphate load-induced bone loss via specific modulation of osteoclasts. Endocrinology 2006;147:3040-9. DOI: 10.1210/en.2005-0671
21. Yates AJ, Oreffo ROC, Mayor K, Mundy GR. Inhibition of bone resorption by inorganic phosphate is mediated by both reduced osteoclast formation and decreased activity of mature osteoclasts. J Bone Miner Res 1991;6:473-8. DOI: 10.1002/jbmr.5650060508
22. M'Baya-Moutoula E, Louvet L, Metzinger-Le Meuth V, Massy ZA, Metzinger L. High inorganic phosphate concentration inhibits osteoclastogenesis by modulating miR-223. Biochim Biophys Acta 2015;1852:2202-12. DOI: 10.1016/j.bbadis.2015.08.003
23. Linefsky JP, O'Brien KD, Katz R, de Boer IH, Barasch E, Jenny NS, et al. Association of serum phosphate levels with aortic valve sclerosis and annular calcification: the cardiovascular health study. J Am Coll Cardiol 2011;58(3):291-7. DOI: 10.1016/j.jacc.2010.11.073
24. Linefsky JP, O'Brien KD, Sachs M, Katz R, Eng J, Michos ED, et al. Serum phosphate is associated with aortic valve calcification in the Multi-ethnic Study of Atherosclerosis (MESA). Atherosclerosis 2014;233(2):331-7. DOI: 10.1016/j.atherosclerosis.2013.12.051
25. Kinugasa M, Mori S, Takaya T, Ito T, Tanaka H, Satomi-Kobayashi S, et al. Serum phosphate is an independent predictor of the total aortic calcification volume in non-hemodialysis patients undergoing cardiovascular surgery. J Cardiol 2016;68(4):308-15. DOI: 10.1016/j.jjcc.2015.10.005
26. Citrin DL, Elson P, Kies MS, et al. Decreased serum phosphate levels after high-dose estrogens in metastatic prostate cancer. Possible implications. Am J Med 1984;76:787-93. DOI: 10.1016/0002-9343(84)90987-2
27. Stock JL, Coderre JA, Mallette LE. Effects of a short course of estrogen on mineral metabolism in postmenopausal women. J Clin Endocrinol Metab 1985;61:595-600. DOI: 10.1210/jcem-61-4-595
28. Uemura H, Irahara M, Yoneda N, Yasui T, Genjida K, Miyamoto KI, et al. Close correlation between estrogen treatment and renal phosphate reabsorption capacity. J Clin Endocrinol Metab 2000;85:1215-9. DOI: 10.1210/jcem.85.3.6456
29. Faroqui S, Levi M, Soleimani M, Amlal H. Estrogen downregulates the proximal tubule type IIa sodium phosphate cotransporter causing phosphate wasting and hypophosphatemia. Kidney Int 2008;73(10):1141-50. DOI: 10.1038/ki.2008.33
30. Meng J, Ohlsson C, Laughlin GA, Chonchol M, Wssel CL, Ljunggren O, et al. Sex hormones and serum phosphorus in older men: The Osteoporotic Fractures in Men (MrOs) Study. Kidney Int 2010;78(4):415-22. DOI: 10.1038/ki.2010.161
31. Funakoshi T, Yanai A, Shinoda K, Kawano MM, Mizukami Y. G protein-coupled receptor 30 is an estrogen receptor in the plasma membrane. Biochem Biophys Res Commun 2006;346:904-10. DOI: 10.1016/j.bbrc.2006.05.191
32. Filardo EJ, Quinn JA, Frackelton AR Jr, Bland KI. Estrogen action via the G protein-coupled receptor, GPR30: stimulation of adenylyl cyclase and cAMP-mediated attenuation of the epidermal growth factor receptor-to-MAPK signaling axis. Mol Endocrinol 2002;16:70-84. DOI: 10.1210/mend.16.1.0758
33. Björnström L, Sjöberg M. Mechanisms of estrogen receptor signaling: convergence of genomic and nongenomic actions on target genes. Mol Endocrinol 2005;19:833-42. DOI: 10.1210/me.2004-0486
34. Qureshi R, Picon Ruiz M, Aurrekoetxea-Rodriguez I, Nunes de Paiva V, D'Amico M, Yoon H, et al. The major pre- and post-menopausal estrogens play opposing roles in obesity driven mammary inflammation and breast cancer development. Cell Metabolism 2020;31(6):1154-72. DOI: 10.1016/j.cmet.2020.05.008
35. Key TJ, Appleby PN, Reeves GK, Travis RC, Brinton LA, Helzlsouer KJ, et al. Steroid hormone measurements from different types of assays in relation to body mass index and breast cancer risk in postmenopausal women: Reanalysis of eighteen prospective studies. Steroids 2015;99(Pt A):49-55. DOI: 10.1016/j.steroids.2014.09.001
36. Fernández-Villabrille S, Martín-Carro B, Martín-Vírgala J, Alonso-Montes C, Fernández-Fernández A, Martínez-Salgado C, et al. Phosphorus may induce phenotypic transdifferentiation of vascular smooth muscle cells through the reduction of microRNA-145. Nutrients 2023;27;15(13):2918. DOI: 10.3390/nu15132918
37. Manolis AA, Manolis TA, Melita H, Mikhailidis DP, Manolis AS. Low serum albumin: A neglected predictor in patients with cardiovascular disease. Eur J Intern Med 2022;102:24-39. DOI: 10.1016/j.ejim.2022.05.004