NUTRITION RESEARCH 37 (2017) 58–66

Available online at www.sciencedirect.com

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Original Research

Dietary phosphorus intake is negatively associated with bone formation among women and positively associated with some bone traits among men—a cross-sectional study in middle-aged Caucasians

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ARTICLE INFO

Article history:
Received 16 August 2016
Revised 7 December 2016
Accepted 16 December 2016

Keywords:
Phosphorus
Calcium
Bone mineral density
Bone turnover markers
Peripheral quantitative computed tomography
Cross-sectional study

ABSTRACT

High dietary phosphorus (P) intake has acute negative effects on calcium (Ca) and bone metabolism, but long-term clinical data are contradictory. We hypothesized that high P intake is associated with impaired bone health as suggested by earlier short-term studies on bone metabolism. In this cross-sectional study, we investigated associations between dietary P intake, bone traits in the radius and tibia, and bone turnover in a population-based sample of 37- to 47-year-old Caucasian premenopausal women (n = 333) and men (n = 179) living in Southern Finland (60°N). We used various regression models in an "elaboration approach" to elucidate the role of P intake in bone traits and turnover. The addition of relevant covariates to the models mainly removed the significance of P intake as a determinant of bone traits. In the final regression model (P intake, weight, height, age, Ca intake, serum 25-hydroxyvitamin D, physical activity, smoking, contraceptive use in women), P intake was slightly positively associated only with bone mineral content and cross-sectional cortical bone area in the tibia of men. Among women, inclusion of Ca removed all existing significance in the crude models for any bone trait. In women P intake was negatively associated with the bone formation marker serum intact pro–collagen type I

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; aBMD, areal bone mineral density; BMC, bone mineral content; BMD, bone mineral density; Ca, calcium; S-CTX, serum collagen type 1 cross-linked C-terminal telopeptide; CV, coefficient of variation; S-iPINP, serum intact pro–collagen type I amino-terminal propeptide; P, phosphorus; PTH, parathyroid hormone; BMD, bone mineral density.

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http://dx.doi.org/10.1016/j.nutres.2016.12.009

amino-terminal propeptide, whereas no association was present between P intake and bone turnover in men. In conclusion, these findings disagree with the hypothesis; P intake was not deleteriously associated with bone traits; however, P intake may negatively contribute to bone formation among women.

1. Introduction

An estimated 15% of adults older than 50 years in Finland have osteoporosis [1]. However, during this millennium, femoral neck bone mineral density (BMD) among elderly Finnish women has been observed to increase, indicating improved bone health in this group [2]. Due to frequent dairy product consumption, calcium (Ca) intake has generally been adequate among Finns [3]. Also, vitamin D intake has increased over the last decade due to the food fortification policy [3,4]. Besides Ca, phosphorus (P) is known to be essential for bone tissue as a form of hydroxyapatite [5]. Nevertheless, there is concern about potential detrimental effects of excess dietary P intake on bone health due to a potential imbalance in Ca-P homeostasis. Short-term experimental studies in humans have shown that excess P intake together with low Ca intake is detrimentally associated with Ca and bone metabolism in terms of, for example, augmented serum parathyroid hormone (PTH) concentrations and/or impaired bone turnover [6-9]. In animals, long-term high P intake with a normal Ca intake has been shown to cause bone loss and impaired bone mineralization [10,11]. In contrast, clinical human data on the relationship between P intake and BMD and bone mineral content (BMC) are contradictory, and some studies are confounded by adequate Ca intake and small number of participants [12-18]. Concerns about high P intake and bone are relevant because P intake in Western countries exceeds 2- to 3-fold the nutritional recommendations (600-700 mg/d) [3,19-22]. Especially the increased use of food additive phosphates has augmented P intake; up to 50% of P intake may originate from additives [23], which have been suggested to be more harmful for bone metabolism than natural P [24-28].

Considering the possible deleterious role of high P intake in bone metabolism, we hypothesized that dietary P intake is negatively associated with bone health in terms of decreased bone formation and increased resorption as well as decreased bone size, BMC, and BMD. We used an "elaboration approach" to elucidate the role of P intake in radial and tibial bone structure measured by peripheral quantitative computed tomography (pQCT) and bone turnover in 37- to 47-year-old Caucasian adults in a cross-sectional design, taking into account other important *intrinsic* and *extrinsic* factors in bone health.

2. Methods and materials

2.1. Participants

The population-based study carried out in January to May 2010 comprised recruitment of 37- to 47-year-old Caucasian women and men in the Helsinki area (60°N). Recruitment of the participants and the study protocol are described in detail elsewhere [29]. Pregnant women were excluded from the study. The total number of recruited participants for the first phase of the study was 678. Of these, 653 participated in the second phase where bone measurements were carried out. In the final analysis of this substudy, 141 participants were not included due to incomplete data or exclusion criteria (menopause, earlier history of eating disorder, medication affecting Ca or bone metabolism, or moderate renal dysfunction, ie, estimated glomerulus filtration rate <60 mL/min [30]), resulting in 179 men and 333 premenopausal women, for whom full nutrition, pQCT, background, and biomarker data were available. This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Helsinki Uusimaa Hospital District Ethics Committees. Written informed consent was obtained from all participants.

2.2. Bone assessments

Distal (4% and 5% site) and shaft sites (30%) of the radius and tibia were measured with pQCT (XCT 2000R; Stratec Medizintechnik Gmbh, Pforzheim, Germany). The radius of the nondominant side and the left tibia were scanned, except for participants who had previous fractures or metal implants in the scan site; their contralateral site was measured. The pQCT scanning and the analysis protocol, earlier used in the GENDI Study [31], were based on well-established protocols [32]. Total BMC (mg), total bone cross-sectional area (mm^2), cortical bone area (mm^2), trabecular bone density (mg/cm^3), and cortical bone density (mg/cm^3) were assessed. In vivo coefficients of variation (CVs%) for the radius were 2.5% for distal total area and 3.9% for shaft site, 4.4% for cortical area at distal site and 1.1% at shaft site, 1.6% for trabecular density at distal site, and 0.5% for cortical density at shaft site. For the tibia, the corresponding values were 1.3%, 1.2%, 2.6%, 1.2%, 0.5%, and 0.6%. The long-term stability of the scanner was assessed by daily phantom scans, which showed constant density levels over the study period.

2.3. Dietary intake data

Habitual dietary intake data of participants were collected by 3-day food records, which included 2 weekdays and 1 weekend day. The participants were instructed to maintain their normal food habits during the recording period and to record all foods, beverages, and dietary supplements immediately after consumption. Nutrient intake was calculated using a computer-based program (Diet 32 version 1.4.6.2; Aivo2000, Turku, Finland), which is obtained from the Finnish food composition database Fineli®, developed and continuously updated by the Finnish National Institution of Health

and Welfare (www.fineli.fi). The background data questionnaire included a question about the use of vitamin and mineral supplements, allowing for more accurate calculations of total Ca and vitamin D intakes.

2.4. Bone biomarkers

Twelve-hour fasting blood samples were collected between 7:30 AM and 9:15 AM. Serum was extracted from blood by centrifugation and stored immediately after sampling at –20 °C or –70 °C until analysis. Serum phosphate (S-Pi), serum creatinine (S-Krea), serum 25-hydroxyvitamin D (S-25[OH]D), and serum PTH (S-PTH) concentrations were analyzed at the Department of Food and Environmental Sciences, University of Helsinki, in 2010. S-Pi was analyzed by a spectrophotometric molybdate method using a Konelab20 automatic analyzer (Thermo Clinical Labsystems Oy, Espoo, Finland) [33]. S-Krea was analyzed by Jaffe method using Konelab20 [34]. Interassay and intra-assay CVs% for S-Pi and S-Krea were less than 4.6%. S-25(OH)D concentrations were analyzed by enzyme immunoassay with IDS EIA Kit (Immunodiagnostics Systems Ltd, Bolton, UK) [35]. Interassay and intra-assay CVs% were 2.7% and 3.2%, respectively, based on the provided controls measured in the laboratory. At the time that the samples were analyzed, the laboratory was in the process of achieving the Vitamin D External Quality Assessment Scheme certificate, DEQAS (deqas.kpmd.co.uk/), for ensuring reproducibility of analyses. The laboratory received the DEQAS proficiency certificate for this method in 2012. S-PTH concentrations were analyzed by a 2-site chemiluminescent enzyme-labeled immunometric assay by Immulite1000 (Siemens Healthcare Diagnostics, Tarrytown, NY, USA) [36]. Interassay and intra-assay CVs% were 7.6% and 1.0% for the low control sample and 7.9% and 5.4% for the high control sample, respectively. Serum intact pro–collagen type I amino-terminal propeptide (S-iPINP) and serum collagen type 1 cross-linked C-terminal telopeptide (S-CTX) were analyzed by chemiluminescence immunoassay using an IDS-iSYS Multidiscipline Automated Analyzer (Immunodiagnostic Systems Ltd, Bolton, UK) at the NordLab Oulu, and at the Department of Clinical Chemistry of the University of Oulu in 2012 [37,38]. For both assays, intra-CV% was less than 5.3% and inter-CV% was less than 2.9%.

2.5. Background data collection

Data on background variables (such as physical activity, disease history and medication, smoking, menopausal status) were collected by a self-administered questionnaire that included completion instructions. The questionnaire was checked by researchers at the research unit, and lacking information was requested if needed. Smoking was classified as current/former smoker or never smoker. In the present analyses of women, only those reporting regular menstruation were included. Physical activity was expressed as a frequency, and duration of exercise or exercise training was calculated as minute/week. Body mass index (kg/m^2) was calculated based on height and weight measured in light clothing with a standard stadiometer (to the nearest half cm) and scale (to the nearest 100 g) at the research unit.

2.6. Statistical analyses

The final number of participants was intended to be 800 persons (400 women, 400 men). The sample size is based on a statistical power of 80% (α = .05) to find a 4% difference (SD = 0.050 g/cm^3) in distal radius trabecular density between the highest and lowest P intake tertiles by analysis of variance, and takes into account an initial dropout of 40% (based on 1200 participants).

Statistical analysis was performed using SPSS Statistics version 21 (IBM, Armonk, NY, USA). The normality and homogeneity of the data were verified and log-transformed to improve normality if needed. Statistically significant data were determined for a *P* value less than .05. Data are shown as means and SDs. Differences between sexes concerning background variables were analyzed by the Mann-Whitney *U* test. Associations between P intake, pQCT data, bone turnover markers, and potential covariates were assessed by Spearman correlation coefficients (data not shown). After the initial observation that P intake was not a strong determinant of bone traits, whereas it was very sensitive to other relevant explanatory variables in the regression model, we chose to use the so-called elaboration approach [39].

To evaluate the role of P intake in bone health, we used the elaboration technique, which has been widely used in social sciences to understand the composite effect and the dependency structure of several determinants [39]. Our approach is modified as it sets the focus on the effect magnitudes instead of partial correlations. Thus, we compared the resulting regression coefficients among several models [39]. In the elaboration approach, the best-fit model is not sought; rather the aim is to observe and compare the effect of P intake on bone characteristics across various models, that is, in different contexts determined by other factors known to modulate the bone characteristics. The rationale of this approach is to regard multicollinearity more as a source of information than as a nuisance. Elaboration looks for the interplay between the different explanatory variables on the importance of P intake.

Hence, the data were analyzed using several regression models with different combinations of determinants (explanatory variables) of bone traits/turnover. The starting model always had P intake as the only explanatory variable. After this, the other relevant explanatory variables were added to the model and the resulting β coefficients, that is, slopes, of P intake were compared. Based on changes in the slopes, the role of P intake among bone variables was interpreted. We chose to study the following determinants of bone traits/turnover mainly for their contextual relevance based on earlier literature: weight, height, age, Ca intake, contraceptive use among women, smoking, S-25(OH)D, and physical activity [40-42]. The logic of inclusion order was to start with variables that have an established, *intrinsic* effect on bone characteristics, that is, height, weight, and age. After this, *smaller-scale, extrinsic* variables were added (first: Ca intake, then: contraceptive use (not in men), smoking, S-25(OH)D concentration, and physical activity). This logic resulted in 5 different models (Table 1). We also created models with S-PTH, but because its effect was negligible, the results of these models are not reported.

Table 1 – Inclusion order of the explanatory variables of bone traits and turnover markers to the models

Starting model	Variables added to previous model			
Model 1	Model 2	Model 3	Model 4	Model 5
Phosphorus intake	Weight Height	Age	Calcium intake	Serum 25-hydroxyvitamin D Physical activity Smoking Contraceptive use [a]

[a] Not in the models for men.

3. Results

Background, nutrient intake, and biochemical data of the study participants are shown in Table 2. β Coefficients, that is, slopes, of P intake in the regression models are presented in Table 3. In each bone variable, the model with the highest adjusted coefficient of determination (r^2) is indicated in boldface in Table 3 (adjusted r^2 values are given in Table 4). In the Results section, we have concentrated on those variables where relevant changes in coefficients (ie, slopes) of P intake were observed. Cortical and trabecular bone mineral densities are only reported in the tables because P intake was not significant in any model of cortical or trabecular density for either sex. Bone trait data of the study participants are presented in Table 5.

Table 2 – Background, dietary, and biomarker characteristics of the study participants

	Women (n = 333)	Men (n = 179)
Age (y)	41.9 ± 2.6	42.1 ± 3
Height (m) *	1.65 ± 0.06	1.79 ± 0.06
Weight (kg) *	72.7 ± 14.3	87.4 ± 13.5
Body mass index (kg/m^2) *	26.4 ± 5.2	27.2 ± 4
Physical activity (min/wk) *,[a]	514 ± 393	390 ± 322
Current or former smokers (%)	46	56
Contraceptive use (%)	34	–
Energy intake (kJ/d) *	7984 ± 1775	9147 ± 1974
Phosphorus intake (mg/d) *	1538 ± 383	1812 ± 466
Calcium intake (mg/d) [b]	1202 ± 430	1217 ± 482
S-iPINP (ng/mL) *,[c]	35.4 ± 13.2	40.3 ± 13.3
S-CTX (ng/mL) *,[c]	0.34 ± 0.15	0.48 ± 0.18
Serum parathyroid hormone (ng/mL) *	57.4 ± 25.3	50.8 ± 22.9
Serum 25-hydroxyvitamin D (nmol/L)	55.9 ± 19.8	53.1 ± 18.2
Serum phosphate (mmol/L)	1.13 ± 0.15	1.12 ± 0.17
Estimated glomerulus filtration rate (mL/min) *	85.5 ± 18.9	103.9 ± 18.9

Values are means ± SD.
Abbreviations: S-CTX, serum collagen type 1 cross-linked C-terminal telopeptide; S-iPINP, serum intact pro–collagen type I amino-terminal propeptide.
[a] Leisure activity or regular exercise.
[b] From food and supplements.
[c] For women n = 332.
* P values <.05 for difference between women and men in the Mann-Whitney U test.

3.1. Bone turnover markers

Adjusted R^2 values in the different bone turnover marker models ranged from 0.020 to 0.091 among women and from 0.000 to 0.096 among men (Table 4). Among women, the slope of P intake was negative in all models of S-iPINP (Table 3); ie, P intake was a negative determinant of bone formation. After adding Ca (model 4), the slope of P intake became more negative and remained significant. In the models of S-CTX, P intake was a significantly negative determinant until Ca intake was introduced to the model. However, concerning both S-iPINP and S-CTX, adjusted R^2 increased significantly only after introducing weight and height to the model. Among men, P intake was not a significant determinant of bone turnover markers, nor did the additional determinants affect the slope.

3.2. Bone mineral content

Adjusted R^2 values in the models of BMC ranged from 0.025 to 0.328 among women and from 0.004 to 0.253 among men (Table 4). P intake was a significant positive determinant of distal tibia (women and men), tibial shaft (women), and distal radius (women) until Ca intake was added to the model (Table 3). The role of P attenuated when other explanatory variables were introduced to the model. Significance of P intake as a positive determinant of tibial shaft BMC was present in all models among men. Introducing height and weight attenuated the association; the inclusion of Ca, however, reversed this effect. In radial shaft BMC, P intake was a significant positive determinant only in model 1 among women, and no significance was found among men. An increase in the total adjusted R^2 values was observed when height and weight were introduced to the models among both sexes.

3.3. Cross-sectional total and cortical bone area

Adjusted R^2 values in the models of cross-sectional bone area ranged from 0.004 to 0.356 among women and from 0.000 to 0.326 among men (Table 4). P intake was a positive determinant of total bone area among women until height and weight were introduced to the model, after which the significances weakened (Table 3). Among both sexes, P intake was a significant positive determinant of total bone area of distal tibia until Ca was added to the model. In total bone area of radial shaft, also among men, the inclusion of weight and height removed the significance of P intake. Furthermore, in cortical bone area of radial and tibial shaft, as well as distal tibia among women, P intake was significant. In distal tibia, this significance was present only in the first model, and in the shaft sites, the significance disappeared after adding Ca. Among men, P intake was a significant positive determinant of cortical bone area of distal tibia and tibial shaft in the 3 first models, and the inclusion of Ca removed the significance. Moreover, P intake was significant in model 5 of tibial shaft among men, but not in model 4. In total bone and cortical area, increases in R^2 values occurred after introducing height and weight to the models.

Table 3 – β Coefficients for phosphorus intake in regression models for bone turnover markers and bone traits among women and men

	Women (n = 333) [a]					Men (n = 179)				
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 1	Model 2	Model 3	Model 4	Model 5
Bone turnover markers										
S-CTX	−0.151 *	−0.160 *	**−0.155** *	−0.111	−0.119	0.001	0.005	−0.007	−0.007	**−0.010**
S-iPINP	−0.202 **	**−0.224** **	−0.224 **	−0.284 *	−0.272 *	0.117	0.124	0.105	0.115	**0.107**
Bone traits										
Bone mineral content										
Distal radius	0.168 *	**0.101** *	0.102 *	0.082	0.080	0.056	0.030	**0.023**	0.039	0.031
Radial shaft	0.170 *	**0.090**	0.090	0.108	0.126	0.067	0.045	**0.042**	0.041	0.042
Distal tibia	0.232 **	0.154 *	0.157 *	0.097	**0.074**	0.115 *	0.081 *	**0.077** *	0.046	0.045
Tibial shaft	0.215 **	**0.121** *	0.122 *	0.077	0.065	0.122 **	0.096 *	0.094 *	0.116 *	**0.119** *
Total bone area										
Distal radius	0.129 *	**0.054**	0.054	0.026	0.018	0.090	**0.064**	0.063	0.146	0.145
Radial shaft	0.172 *	**0.094**	0.095	0.128	0.141	0.086 *	**0.059**	0.059	0.048	0.049
Distal tibia	0.177 *	**0.094** *	0.094	0.049	0.031	0.157	**0.138**	0.122	0.061	0.053
Tibial shaft	0.156 *	**0.055**	0.056	0.005	−0.013	0.118 *	**0.090** *	0.088 *	0.108	0.112
Cortical bone area										
Distal radius	0.083	**0.036**	0.037	0.013	0.009	0.021	−0.001	**−0.009**	0.018	0.008
Radial shaft	0.184 *	**0.102** *	0.103 *	0.104	0.114	0.074	**0.053**	0.050	0.049	0.052
Distal tibia	0.125 *	0.081	0.083	0.028	**0.017**	0.157 *	0.138 *	0.122 *	0.061	**0.053**
Tibial shaft	0.206 **	0.108 *	0.109 *	0.048	**0.033**	0.118 *	**0.090** *	0.088 *	0.108	0.112 *
Bone mineral density										
Trabecular, distal radius	0.076	0.079	0.080	0.070	**0.074**	0.033	0.034	0.027	−0.024	**−0.032**
Cortical, radial shaft	−0.087	−0.063	−0.066	−0.012	**0.017**	−0.007	**−0.008**	−0.008	−0.009	−0.010
Trabecular, distal tibia	0.101	0.094	**0.098**	0.084	**0.071**	0.039	0.030	0.024	−0.002	**−0.008**
Cortical, tibial shaft	0.010	**0.045**	0.044	0.128	0.143	0.004	**0.006**	0.006	0.008	0.007

Models are described in Table 1. Values are β coefficients for phosphorus intake. Biggest adjusted R^2 values among models are in **boldface**. All continuous variables in the models were log-transformed to improve normality; contraceptive use was not used in the models for men. Abbreviations: S-CTX, serum collagen type 1 cross-linked C-terminal telopeptide; S-iPINP, serum intact pro–collagen type I amino-terminal propeptide.

[a] For bone traits, n = 333; for bone turnover markers, n = 332.

* $P < .05$.

** $P < .001$ for phosphorus intake in the model.

4. Discussion

We examined the association of the effect of P intake on several bone variables in a middle-aged Finnish population of women and men. Of interest were bone traits in the radius and tibia, measured by pQCT, indicating long-term bone health, as well as bone turnover markers, reflecting acute bone metabolism. The elaboration approach was used to statistically elucidate the role of P intake, among other various intrinsic and extrinsic factors, in bone health. With regard to bone turnover markers, significant results were observed only in women. Dietary P intake was negatively associated with S-iPINP, a bone collagen formation marker, possibly indicating impaired bone formation with higher P intake. P intake was also negatively related to S-CTX, indicating decreased collagen degradation with increasing P intake among women. However, when Ca was introduced to the model, the association disappeared. Among men, significant associations between P intake and bone turnover were not observed. Concerning the bone traits, significant results were mainly seen in tibial bone for men.

The results about bone traits were contradictory to both our hypothesis and the evidence from short-term studies on bone metabolism [6-9]; associations between P intake and bone traits were positive. The observed β coefficients (slopes) of P intake and adjusted coefficients of determination in different regression models indicate that dietary P intake overall is not a strong determinant of BMC, bone cross-sectional area, and cortical or trabecular density. Furthermore, the significance of P intake as a determinant attenuated when Ca intake was introduced to the models, but inclusion of Ca did not improve coefficients of determination, that is, the explanatory power of the models. Ca somehow compensated the effect of P intake as a weak determinant in bone traits. Based on the results, the role of P intake as a determinant of bone traits does not seem to be clinically relevant.

Differences emerged in the associations between dietary P and bone traits among the sexes. Ca seemed to be a stronger modulator of bone among women than among men. An earlier study showed that some differences exist between the sexes in maintaining Ca homeostasis; women may be more vulnerable to high P intake, especially through Ca and PTH metabolism [43]. Earlier short-term randomized controlled trials carried out on younger women have revealed that high P intake increases S-PTH concentrations when Ca intake is low, and decreases bone formation; this may result in persistently elevated S-PTH concentrations [6-9]. In our cross-sectional study, we observed a similar association with

Table 4 – Adjusted coefficients of determination (R^2) or regression models, and significant *P* values in bone variables among women and men

	Women (n = 333) [a]					Men (n = 179)				
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 1	Model 2	Model 3	Model 4	Model 5
Bone turnover markers										
S-CTX	0.020 *	0.083 *	**0.091** *	0.089	0.082	0	0.037	0.088	0.083	**0.096**
S-iPINP	0.038 **	**0.089** **	0.087 **	0.086 *	0.088 *	0.003	0.021	0.036	0.031	**0.033**
Bone traits										
Bone mineral content										
Distal radius	0.025 *	**0.168** *	0.166 *	0.164	0.166	0.004	0.137	**0.144**	0.14	0.118
Radial shaft	0.026 *	**0.231**	0.229	0.227	0.228	0.015	0.155	**0.157**	0.152	0.123
Distal tibia	0.051 *	0.258 *	0.262 *	0.262	**0.279**	0.035 *	0.221 *	**0.229** *	0.226	0.222
Tibial shaft	0.043 *	**0.328** *	0.327 *	0.326	0.327	0.065 **	0.25 *	0.248 *	0.244 *	**0.253** *
Total bone area										
Distal radius	0.014 *	**0.212**	0.209	0.207	0.205	0.015	**0.132**	0.127	0.13	0.116
Radial shaft	0.027 *	**0.223**	0.222	0.220	0.214	0.019 *	**0.172**	0.167	0.163	0.135
Distal tibia	0.028 *	**0.278** *	0.276	0.275	0.271	0.011	**0.234**	0.231	0.226	0.205
Tibial shaft	0.021 *	**0.348**	0.346	0.346	0.345	0.052 *	**0.326** *	0.322 *	0.319	0.322
Cortical bone area										
Distal radius	0.004	**0.075**	0.073	0.070	0.063	0	0.054	**0.062**	0.057	0.059
Radial shaft	0.031 *	**0.240** *	0.238 *	0.235	0.234	0.016	**0.158**	0.157	0.152	0.128
Distal tibia	0.013 *	0.141	0.141	0.14	**0.163**	0.029 *	0.102 *	0.127 *	0.124	**0.166**
Tibial shaft	0.040 **	0.355 *	0.354 *	0.354	**0.356**	0.055 *	**0.277** *	0.275 *	0.272	0.273 *
Bone mineral density										
Trabecular, distal radius	0.003	0.047	0.045	0.042	**0.051**	0	0	0.018	0.018	**0.019**
Cortical, radial shaft	0.005	0.057	0.057	0.056	**0.069**	0	**0.067**	0.064	0.059	0.064
Trabecular, distal tibia	0.007	0.056	**0.062**	0.059	**0.062**	0.001	0.015	0.024	0.020	**0.035**
Cortical, tibial shaft	–0.003	**0.051**	0.048	0.049	0.047	0	**0.094**	0.089	0.084	0.070

Models are described in Table 1. Values are adjusted coefficients of determination (R^2) for each model.
Biggest adjusted R^2 values among models are in **boldface**. All continuous variables in the models were log-transformed to improve normality; contraceptive use was not used in the models for men.
Abbreviations: S-CTX, serum collagen type 1 cross-linked C-terminal telopeptide; S-iPINP, serum intact pro–collagen type I amino-terminal propeptide.
[a] For bone traits, n = 333; for bone turnover markers, n = 332.
* $P < .05$.
** $P < .001$ for phosphorus intake in the model.

the bone formation in women, but not in men, possibly strengthening the evidence of sex-specific differences in effects of P intake on bone turnover. However, S-PTH did not seem to be a mediator of the effects of P because adding it to the models did not change the results. The cross-sectional design here may be one explanation for not finding an effect of S-PTH.

Earlier data on P intake and bone, excluding bone turnover and Ca metabolism markers, in Western countries are scarce, and due to the dual-energy x-ray absorptiometry measurements, comprise only areal BMD (aBMD) and not volumetric BMD data like pQCT [14,15,17,18]. A small cross-sectional study of 24- to 28-year-old women showed a negative association between P intake and radial aBMD [15]. In women aged 18 to 31 years, dietary P intake was positively correlated with radial aBMD and spine aBMD and BMC [17]. Whiting et al [18] found out that P intake positively predicted total body and lumbar spine aBMD in middle-aged men, but no effect on hip aBMD was observed. A recent study of the National Health and Nutrition Examination Survey data showed that high P intake was positively associated with femoral BMC in teenage girls and with femoral BMC and aBMD in adults [14]. Our new data suggest significant positive associations between P intake and weight-bearing tibial sites, especially among men; however, no association between P intake and volumetric BMD was found. All of these above-mentioned observations were made under circumstances in which Ca intake was at least satisfactory—this confounding effect cannot be excluded. Furthermore, the measured bone sites differ between these studies and the results are conflicting, complicating the drawing of conclusions about the role of P intake in bone health.

The associations between P intake and BMC, bone cross-sectional area, and cortical and trabecular density are influenced by many factors. Our study showed that BMC and bone cross-sectional area are especially related to height but also to some extent to weight, because persons with larger body size have larger bones. Thus, the small but positive association between P intake and BMC and bone cross-sectional area in men may be due to men, as generally taller and larger persons, eating more and thus getting more P from the diet. However, we did not adjust the data for energy intake because we aimed to observe the effect of absolute P intake on bone variables using models that also included other factors known to play a role in bone structure and metabolism. Because vitamin D plays a role in bone homeostasis [43], we also have to point out that the fairly satisfactory S-25(OH)D concentrations (mean, >50 nmol/L, defined as the cutoff level

Table 5 – Bone trait characteristics of the study participants

	Women (n = 333)	Men (n = 179)
Bone mineral content (mg)		
Distal radius	193.6 ± 27.0 (116.4-281.0)	290.4 ± 44.8 (192.0-444.0)
Radial shaft	189.0 ± 21.2 (125.4-262.2)	260.6 ± 32.3 (182.3-415.0)
Distal tibia	517.1 ± 68.4 (313.1-738.0)	694.3 ± 102.4 (459.9-971.8)
Tibial shaft	623.9 ± 72.7 (418.5-852.2)	785.6 ± 93.2 (560.0-1033.1)
Total bone area (mm^2)		
Distal radius	315.5 ± 47.6 (183.3-496.0)	418.2 ± 66.9 (261.0-600.0)
Radial shaft	96.3 ± 14.1 (60.0-149.0)	137.0 ± 19.8 (99.0-215.0)
Distal tibia	807.2 ± 111.3 (502.5-1274.0)	981.3 ± 127.3 (683.0-1359.5)
Tibial shaft	355.6 ± 46.7 (254.5-531.3)	445.5 ± 51.6 (325.3-580.0)
Cortical bone area (mm^2)		
Distal radius	77.6 ± 11.6 (50.8-122.3)	112.7 ± 20.5 (74.8-187.3)
Radial shaft	83.1 ± 10.0 (55.0-117.8)	116.8 ± 15.7 (80.5-188.0)
Distal tibia	172.4 ± 29.8 (87.0-269.8)	248.3 ± 55.2 (115.8-427.5)
Tibial shaft	282.6 ± 34.2 (187.8-418.8)	359.6 ± 44.7 (257.8-489.3)
Bone mineral density (mg/cm^3)		
Trabecular, distal radius	196.8 ± 28.5 (128.6-281.0)	227.5 ± 25.8 (163.0-285.0)
Cortical, radial shaft	1138.1 ± 38.2 (998.6-1252.4)	1117.5 ± 36.4 (999.3-1210.8)
Trabecular, distal tibia	215.9 ± 27.2 (129.3-290.6)	235.8 ± 27.4 (159.9-302.1)
Cortical, tibial shaft	1104.7 ± 27.4 (992.2-1162.2)	1093.3 ± 28.3 (1002.2-1151.0)

Values are means ± SD (ranges).

for sufficient vitamin D status by the Institute of Medicine [41]) among our study participants may have masked the potentially harmful associations between P and bone.

Strengths of our study are the large population-based sample consisting of both women and men (albeit less men than women), assessment of several bone traits with pQCT in 2 functionally different bones (radius and tibia) and sites (distal site and diaphysis), analysis of relevant biomarkers, and extensive background data. Our study population is representative of nutrient intakes in the same-aged Finnish FINDIET Study population in the Helsinki area; Ca, P, and energy intakes were similar, and their body mass indexes were concordant [3]. Moreover, in contrast to commonly used dual-energy x-ray absorptiometry, providing ambiguous aBMD values [44], pQCT provides relevant data for trabecular and cortical densities as well as bone geometry, size, and mass [32]. All of these traits are relevant to bone strength and may be differently associated with nutrient intakes, as the present results indicated. A limitation of this study is its cross-sectional design; we were unable to take into account the earlier diet of the participants such as earlier exposure to high P intake. Thus, the associations with bone turnover may be more relevant than the associations with bone traits. We also did not specifically evaluate the confounding influence of bone-loading activity on bone traits or take the history of physical activity into account. Moreover, we did not consider the potential influence of genetic factors [45]. We also did not distinguish P intake from different sources. It would have been interesting to see how food additive phosphates contribute to bone health. The statistical analysis design did not allow the use of scoring technique for food additive P intake that was used in our earlier study on the same population [29].

In conclusion, in the present sample of a middle-aged Finnish population with adequate Ca intake, we found that P intake was generally not a determinant of bone traits measured by pQCT. The weak positive association between P intake and tibial BMC and bone cross-sectional area in men may be due to men, as larger persons, eating more and, thus, getting more P from their diet. However, no associations were observed between P intake and bone turnover among men, whereas among women, P intake was associated with reduced bone turnover. Overall, adding Ca as a determinant to the models seemed to attenuate the association between P intake and bone traits, and this effect was stronger among women. Prospective studies on the association between high P intake, especially in the form of highly absorbable food additive phosphate, and potential bone deterioration are needed, particularly among people with low Ca intake.

Conflicts of interest

JR has a patent for the PINP assessment method, but the royalty period has expired. STI, HJR, EMS, VEK, HJK, MUMK, MHP, EKAL, HS, MKK, and CJLA have no conflicts of interest to report.

Acknowledgment

The authors thank technician Anu Heiman-Lindh for laboratory analyses in Helsinki. This work was supported by the Academy of Finland (Grant No. 127536), Juho Vainio Foundation, Raisio PLC Research Foundation, Finnish Cultural Foundation, Maud Kuistila Memorial Foundation, Emil Aaltonen Foundation, Medicinska Understödsföreningen Liv Och Hälsa, and National Doctoral Programme of Musculoskeletal Disorders and Biomaterials (TBDP). The funders had no role in the design, analysis, or the writing of this article.

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