Low calcium:phosphorus ratio in habitual diets affects serum parathyroid hormone concentration and calcium metabolism in healthy women with adequate calcium intake

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Excessive dietary P intake alone can be deleterious to bone through increased parathyroid hormone (PTH) secretion, but adverse effects on bone increase when dietary Ca intake is low. In many countries, P intake is abundant, whereas Ca intake fails to meet recommendations; an optimal dietary Ca:P ratio is therefore difficult to achieve. Our objective was to investigate how habitual dietary Ca:P ratio affects serum PTH (S-PTH) concentration and other Ca metabolism markers in a population with generally adequate Ca intake. In this cross-sectional analysis of 147 healthy women aged 31–43 years, fasting blood samples and three separate 24-h urinary samples were collected. Participants kept a 4-d food record and were divided into quartiles according to their dietary Ca:P ratios. The 1st quartile with Ca:P molar ratio ≤0.50 differed significantly from the 2nd (Ca:P molar ratio 0.51–0.57), 3rd (Ca:P molar ratio 0.58–0.64) and 4th (Ca:P molar ratio ≥0.65) quartiles by interfering with Ca metabolism. In the 1st quartile, mean S-PTH concentration (P=0.021) and mean urinary Ca (U-Ca) excretion were higher (P=0.051) than in all other quartiles. These findings suggest that in habitual diets low Ca:P ratios may interfere with homoeostasis of Ca metabolism and increase bone resorption, as indicated by higher S-PTH and U-Ca levels. Because low habitual dietary Ca:P ratios are common in Western diets, more attention should be focused on decreasing excessively high dietary P intake and increasing Ca intake to the recommended level.

Ca:P ratio: Parathyroid hormone: Ca metabolism: P intake: Ca intake

Osteoporosis is a major public health problem and a costly disease worldwide. From a nutritional point of view, the importance of adequate vitamin D and Ca intake for bone health is well established¹–³. Nevertheless, less consensus exists about whether the intake of Ca and P, the main bone-forming minerals, must exist in a certain ratio in adult diets to ensure optimal bone health. Based on calculations of recommended dietary Ca and P intakes, the optimal dietary Ca:P molar ratio is suggested to be 1.3⁴–⁷, corresponding to a Ca:P weight ratio of 1.3. However, in many countries, dietary P intake is two- to threefold higher than recommended levels⁸–¹¹, while total dietary Ca intake remains below nutritional recommendations¹¹–¹⁶. These dietary habits lead to the lower dietary Ca:P ratios observed in various countries in recent years⁸,¹¹,¹³–¹⁹.

The hypothesis of adverse effects of diets with a low Ca:P ratio originated from animal model studies, where animals fed a low Ca:P ratio diet manifested secondary hyperparathyroidism, loss of bone and osteopenia¹⁰. In addition, a high Ca:P ratio due to low P intake was found to be favourable for bone mineralisation in adult rats, as it increased Ca absorption¹⁰. Relative to the number and quality of animal studies, the effects of dietary Ca:P ratios on Ca and bone metabolism in human subjects have been investigated little. Furthermore, whether the dietary Ca:P ratio is clinically significant in adult human subjects has been debated²¹,²². Some earlier findings in young females have supported the importance of a sufficient dietary Ca:P ratio in bone health in epidemiological²³,²⁴, intervention²⁵ or short-term controlled studies²⁶,²⁷.

Parathyroid hormone (PTH) is a major regulator of Ca, P and bone metabolism. Ca and P have opposite effects on serum PTH (S-PTH) concentration, as dietary P has been found to increase S-PTH concentrations²²,²⁶ by decreasing serum-ionised Ca (S-iCa) concentration²⁸ and by directly affecting PTH secretion²⁹, probably through the Na-phosphate co-transporter in the parathyroid gland³⁰, while Ca administration has been demonstrated to decrease S-PTH³¹,³² through

Abbreviations: ANCOVA, analysis of covariance; LSD, least significant difference method; PTH, parathyroid hormone; S-Ca, serum Ca; S-iCa, serum-ionised Ca; S-Pi, serum phosphate; S-PTH, serum PTH; S-25(OH)D, serum 25-hydroxy vitamin D; U-Ca, urinary Ca; U-Pi, urinary phosphate.
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an increase in S-iCa(28). Intermittent administration of PTH stimulates bone formation(33) and increases trabecular bone mass(34), while continuous excessive PTH secretion increases bone turnover(35,36) and releases Ca and P from bone.

Ca and P metabolism is tightly bound together, which is reflected in, for instance, the S-PTH-mediated regulation of urinary Ca (U-Ca) and urinary phosphate (U-Pi) excretions. In normal physiological conditions, an increase in S-PTH concentration results in lower U-Ca and higher U-Pi excretion. Understandably, as both dietary Ca and P intakes affect S-PTH, an increase in dietary Ca intake elevates U-Ca excretion(27,37), while high P intake per se (5,38) or together with low Ca intake (26,27) decreases U-Ca excretion. Decreased S-PTH concentration, in turn, leads to higher U-Ca and lower U-Pi excretion. U-Pi excretion diminishes, as decreased S-PTH inhibits the activity of Na-phosphate co-transporters in kidneys(39).

Our objective here was to examine how habitual dietary Ca:P ratio affects S-PTH concentration and other Ca metabolism markers in healthy premenopausal women. We hypothesised that low dietary Ca:P ratios have a more deleterious impact than high Ca:P ratios on Ca metabolism. Since dietary Ca intake in Scandinavian countries generally meets nutritional recommendations, we were able to determine whether the optimal dietary Ca:P molar ratio of 1 is achieved among participants whose habitual dietary Ca intake is at the recommended level (≥ 800 mg/d)(49).

Participants and methods
Participants
Our participants represent a subgroup of randomly selected 31- to 43-year-old Finnish women. Details about these cross-sectional study participants have been provided elsewhere(49). Only women with no illnesses or medications affecting Ca metabolism were included. Women with no or irregular menstruation as well as those with incomplete 4-d food records were excluded. Our final study group comprised 147 healthy premenopausal women, whose oestrogen status was presumed to be reasonable normal due to regular menstruation. Before the study, each participant gave her informed consent to the procedures, which were conducted in accordance with the Helsinki Declaration. The Helsinki University Ethics Committee approved the study protocol.

Questionnaire and dietary assessment
A questionnaire was used to collect information on weight, height, smoking habits and alcohol consumption of participants. In addition, the questionnaire requested information on age, age at menarche, past medical history (e.g. contraceptives used) and menstruation cycle.

To gather data on habitual energy and nutrient intakes, participants were instructed on how to keep a 4-d food record, which included three weekdays and 1 d of the weekend. Participants were advised to maintain their habitual food intakes during this period and to record all foods and beverages immediately after consumption. A nutritionist together with the participant checked the 4-d food record. We calculated participants’ habitual dietary intakes with a computer-based program, the Unilever Dietary Analysis Program (Becel Palvelu Paasivaara Oy, Finland, 1989), based on the food composition database (Fineli) of the Finnish National Public Health Institute.

Study design
Participants’ dietary Ca:P ratios were calculated based on the information of Ca (mg/d) and P (mg/d) intakes provided in the 4-d food record. Weight Ca:P ratios were converted into molar ratios by using molecular weight of Ca (40.08 g/mol) and P (30.97 g/mol). Both molar and weight ratios of each Ca:P quartile are presented in Table 1. To examine the effects of different dietary Ca:P ratios on S-PTH and Ca metabolism markers, we divided participants into quartiles according to their dietary Ca:P molar ratios. Characteristics of quartiles are presented in Table 1. In addition, since we found that the 1st quartile differed from all other quartiles in effects on S-PTH and several other Ca metabolism markers and the 2nd, 3rd, and 4th quartiles had similar effects, we also compared the 1st quartile to the combined group of the other quartiles.

Sampling and biochemical measurements
On the study days, blood samples were taken anaerobically between 07.30 hours and 09.15 hours after a 12-h overnight fast. In addition, 24-h urine was collected three times during the study. The urine and separated serum samples were stored at −20°C until analysed. The S-iCa concentration was analysed with an ion-selective analyser (Microlyte 6, Thermo Electron Corporation, Vantaa, Finland). The intra-assay CV was 1.6 % for S-iCa. The serum-intact PTH concentration was measured using an immunoradiometric assay (Nichols Institute, Juan San Capistrano, CA, USA), with 10–65 ng/l as the reference range. Intra- and interassay CV for serum-intact PTH were 3.7 and 1 %, respectively. The serum 25-hydroxy vitamin D (S-25(OH)D) concentration was measured by routine laboratory methods using an Elan Automatic Analyser (Eppendorf–Netheler–Hinz GmbH, Hamburg, Germany). CV % for S-Ca and S-Pi was 1.0 ± 1.6 %. The intra- and interassay CV were 10.1 and 14.9 %, respectively. Serum Ca (S-Ca) and phosphate (S-Pi), and U-Ca and phosphate (U-Pi) concentrations were measured by routine laboratory methods using an Elan Automatic Analyser (Eppendorf–Netheler–Hinz GmbH, Hamburg, Germany). CV % for S-Ca and U-Ca was 1.20 ± 1.60 %, and for S-Pi and U-Pi it was 2.90 %. To calculate U-Ca and U-Pi values, the averages of three separate urine collections, corrected with urinary creatinine excretion, were used.

Statistical analysis
Statistical approaches. Power calculation based on S-PTH concentration (expected difference between quartiles in mean S-PTH concentration 12 ng/l), assuming 90 % power with α = 0.05, indicated that a sample size of eleven in each group was adequate(41). Subject characteristics between quartiles were compared by ANOVA. The differences in the averages of the dependent variables between the Ca:P quartiles were compared with ANOVA and analysis of covariance (ANCOVA). ANCOVA was used because it enables inclusion of both categorical (e.g. use of contraceptives) and continuous...
Table 1. Basic characteristics of all study participants (n 147) and of participants in each dietary molar Ca:P quartile
(Mean values of daily nutrient intakes with their standard errors)

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n 147)</th>
<th>1st Quartile* (n 38)</th>
<th>2nd Quartile† (n 36)</th>
<th>3rd Quartile‡ (n 39)</th>
<th>4th Quartile§ (n 34)</th>
<th>P (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37.7 0·27</td>
<td>37·4 0·51</td>
<td>37·6 0·53</td>
<td>38·5 0·54</td>
<td>37·3 0·58</td>
<td>0·37 (NS)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23·3 0·28</td>
<td>23·3 0·61</td>
<td>23·1 0·50</td>
<td>23·4 0·51</td>
<td>23·3 0·62</td>
<td>0·97 (NS)</td>
</tr>
<tr>
<td>Contraceptive users (%)</td>
<td>26·5</td>
<td>26·3 19·4</td>
<td>9·0</td>
<td>18·5 0·42</td>
<td>8·0 0·33</td>
<td>0·34 (NS)</td>
</tr>
<tr>
<td>Dietary energy intake (MJ/d)</td>
<td>7·9 0·19</td>
<td>7·7 0·42</td>
<td>7·5 0·32</td>
<td>8·5 0·42</td>
<td>8·0 0·33</td>
<td>0·34 (NS)</td>
</tr>
<tr>
<td>Dietary protein intake (g/d)</td>
<td>73·3 1·60</td>
<td>73·9 3·5</td>
<td>66·2 2·6</td>
<td>77·9 2·7</td>
<td>74·6 3·7</td>
<td>0·062 (NS)</td>
</tr>
<tr>
<td>Dietary Na intake (g/d)</td>
<td>1·62 0·09</td>
<td>1·87 0·18</td>
<td>1·37 0·15</td>
<td>1·46 0·16</td>
<td>1·82 0·19</td>
<td>0·084 (NS)</td>
</tr>
<tr>
<td>Dietary Ca intake (mg/d)</td>
<td>1056 33·6</td>
<td>742 41·0</td>
<td>908 40·5</td>
<td>1253 45·3</td>
<td>1339 84·6</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Dietary P intake (mg/d)</td>
<td>1411 32·7</td>
<td>1319 61·9</td>
<td>1299 56·5</td>
<td>1582 54·2</td>
<td>1438 80·7</td>
<td>0·005</td>
</tr>
<tr>
<td>Dietary P intake from milk and cheese (mg/d)</td>
<td>414·8 19·9</td>
<td>312·1 51·2</td>
<td>358·4 29·9</td>
<td>508·5 28·1</td>
<td>483·4 40·7</td>
<td>0·0005</td>
</tr>
<tr>
<td>Dietary Ca:P (mg:mg)</td>
<td>0·74 0·01</td>
<td>0·56 0·014</td>
<td>0·70 0·004</td>
<td>0·79 0·004</td>
<td>0·92 0·013</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Serum 25-OH vitamin D (nmol/l)</td>
<td>47·7 3·0</td>
<td>44·0 5·0</td>
<td>47·0 5·4</td>
<td>43·2 4·5</td>
<td>57·6 8·6</td>
<td>0·31 (NS)</td>
</tr>
</tbody>
</table>

Baseline characteristics of the 147 participants are displayed in Table 1. The baseline characteristics of study participants in each dietary molar Ca:P quartile are presented in Table 1. The baseline characteristics of all study participants (n 147) and of participants in each dietary molar Ca:P quartile (Mean values of daily nutrient intakes with their standard errors).

Results

Baseline characteristics of the 147 participants are displayed in Table 1. The baseline characteristics of study participants in each dietary molar Ca:P quartile are presented in Table 1. The baseline characteristics of all study participants (n 147) and of participants in each dietary molar Ca:P quartile (Mean values of daily nutrient intakes with their standard errors).
5th percentile intake was 0·38 (weight ratio 0·49) and at the 95th percentile intake was 0·74 (weight ratio 0·96).

Effect of dietary calcium:phosphorus ratios on serum parathyroid hormone. The mean S-PTH concentration differed significantly between the Ca:P quartiles ($P=0·014$, ANOVA), being higher in the 1st quartile than in the others. To exclude the possibility that these differences are not due to differences in relevant covariates, we adjusted the S-PTH means for the following variables (S-iCa and S-25(OH)D concentrations and use of contraceptives). After these adjustments, the S-PTH differences remained practically the same, as did their statistical significance ($P=0·021$, ANCOVA).

The mean S-PTH values and the statistical differences of the 2nd, 3rd and 4th quartiles from the 1st quartile are shown in Fig. 3. The mean S-PTH concentration was 30 % higher in the 1st quartile than in the combined group of the 2nd, 3rd and 4th quartiles ($P=0·002$). No differences in the mean S-PTH concentrations were present among the 2nd, 3rd and 4th quartiles, and the smallest $P$-value among quartiles in the ANCOVA model was only 0·88.

Effect of dietary calcium:phosphorus ratios on urinary excretion of calcium and phosphate. The dietary Ca:P ratio significantly affected the 24-h U-Ca excretion ($P=0·047$, ANOVA). The mean U-Ca excretion in the 1st quartile was significantly higher than the combined group of the 2nd, 3rd and 4th quartiles ($P=0·002$). No differences in the mean U-P excretion were present among the 2nd, 3rd and 4th quartiles, and the smallest $P$-value among quartiles was 0·16.

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higher than in the other quartiles. After adjusting the U-Ca means for the following relevant covariates (dietary Na and protein intakes, S-PTH and S-25(OH)D concentrations, and use of contraceptives), similar effects remained in the U-Ca differences and in their statistical significance ($P=0.051$, ANCOVA). The mean U-Ca values are shown in Fig. 4. When comparing the 2nd, 3rd and 4th quartiles as a combined group with the 1st quartile, the mean U-Ca excretion was about 30% higher in the latter ($P=0.006$, ANCOVA). In addition, the mean U-Ca excretion did not vary between the 2nd, 3rd and 4th quartiles (ANCOVA; $P=0.58–0.90$).

The mean 24-h U-Pi excretion did not differ between the Ca:P quartiles ($P=0.33$, ANOVA). However, after adjustment for relevant covariates (dietary Na intake, S-PTH and S-25(OH)D concentrations, and use of contraceptives), the mean U-Pi excretion tended to be different between the quartiles ($P=0.13$, ANCOVA). In the 1st quartile, U-Pi excretion was 6–17% higher than in the 2nd, 3rd and 4th quartiles. Furthermore, when comparing the 2nd, 3rd and 4th quartiles as one group with the 1st quartile, the mean U-Pi excretion was about 13% higher in the 1st quartile ($P=0.055$, ANCOVA).

**Effect of dietary calcium:phosphorus ratios on serum ionised calcium, calcium and phosphate.** The mean S-iCa concentration differed significantly between the quartiles ($P=0.027$, ANOVA), being the highest in the 4th quartile. S-iCa concentration in the 4th quartile differed significantly from all other quartiles ($P=0.050$, $P=0.006$ and $P=0.013$ in the 2nd, 3rd and 4th quartiles, respectively, Fisher’s LSD comparisons, ANOVA). After adjusting the S-iCa means for the relevant variables (S-PTH, S-25(OH)D and S-Pi concentrations, and use of contraceptives), the S-iCa differences remained practically the same, as did their statistical significance ($P=0.040$, ANCOVA; Table 2). However, the 1st quartile did not differ significantly from the 4th quartile ($P=0.242$, Fisher’s LSD comparisons, ANCOVA), although the 2nd ($P=0.010$, Fisher’s LSD comparisons, ANCOVA) and 3rd ($P=0.022$, Fisher’s LSD comparisons, ANCOVA) quartiles did (Table 2).

While no differences existed in S-Ca concentration between the Ca:P quartiles by ANOVA ($P=0.27$), S-Ca concentration tended to differ between quartiles ($P=0.061$, ANCOVA) after adjustment for relevant covariates (S-PTH, S-25(OH)D and S-Pi concentrations, and use of contraceptives; Table 2).

The mean S-Pi concentration did not differ between the quartiles ($P=0.85$, ANOVA). After adjusting the S-Pi means for relevant covariates (S-PTH, S-25(OH)D and S-iCa concentrations, and use of contraceptives), no differences between the quartiles were found ($P=0.87$, ANCOVA; Table 2).

**Fig. 2.** The mean molar dietary calcium:phosphorus ratios (y-axis) in each calcium (x-axis) and phosphorus (z-axis) intake quartile. Dietary calcium intake in calcium quartiles was $< 770$, $771–997$, $998–1251$ and $> 1251$ mg/d in the 1st, 2nd, 3rd and 4th quartiles, respectively. Dietary phosphorus intake in phosphorus quartiles was $< 1122$, $1122–1347$, $1348–1643$ and $> 1643$ mg/d in the 1st, 2nd, 3rd and 4th quartiles, respectively.

**Fig. 3.** Effects of calcium:phosphorus ratios on serum parathyroid hormone (S-PTH) concentration (means with their standard errors) in the different quartiles. The covariates included serum 25-hydroxyvitamin D and ionised calcium concentrations, and use of contraceptives. Analysis of covariance (ANCOVA) was performed. Mean value was significantly different from that of the 1st quartile: *$P = 0.014$, †$P = 0.07$*, ‡$P = 0.017$ (Fisher’s least significant difference comparison, ANCOVA). ■ 1st quartile; □ 2nd quartile; △ 3rd quartile; □ 4th quartile.

**Fig. 4.** Effects of calcium:phosphorus ratios on 24-h urinary calcium (U-Ca) excretion (means with their standard errors) in the different quartiles. The covariates included serum 25-hydroxyvitamin D and parathyroid hormone concentrations, dietary sodium and protein intakes, and use of contraceptives. Analysis of covariance (ANCOVA) was performed. Mean value was significantly different from that of the 1st quartile: *$P = 0.010$, †$P = 0.040$, ‡$P = 0.035$ (Fisher’s least significant difference comparison, ANCOVA). ■ 1st quartile; □ 2nd quartile; △ 3rd quartile; □ 4th quartile.
Discussion

In this cross-sectional study, low habitual dietary Ca:P ratios interfered with Ca metabolism in healthy women with an adequate dietary Ca intake. Interestingly, the lowest quartile (Ca:P molar ratio ≤ 0.50) differed from all other quartiles by increasing both S-PTH concentration and U-Ca excretion. In fact, quartiles other than 1st one had similar effects on increasing both S-PTH concentration and U-Ca excretion. Therefore, if the habitual diet lacks dairy products, the dietary higher proportion of the total P intake in these quartiles. 4th Ca:P quartiles indicating that dairy products represent a little Ca. Among the participants in the present study, the sources of Ca, e.g. dairy products, many others contain very high P intake. Although, some foods rich in P are also good phosphate-containing food additive, further increasing already expected to increase bone resorption, and some of the extra Ca, which has been released from bone, to be excreted in urine. Elevated U-Ca excretion might therefore reflect an increase in bone resorption.

U-Ca excretion is an important determinant of Ca retention in the healthy human body. In a controlled situation, U-Ca excretion has been strongly correlated with acute Ca intake. In a controlled short-term study, when dietary P intake was high (1850 mg/d), U-Ca excretion increased with increasing dietary Ca intake and Ca:P ratio in a dose-dependent manner in healthy women(27). In addition, 24-h U-Ca excretion was similar with P intakes of 1245 and 1995 mg/d when Ca intake was very low (250 mg/d). These findings indicate that U-Ca excretion might not diminish after a certain high P intake, which may result in an unfavourable Ca balance. Moreover, low Ca intake and high U-Ca excretion have been assumed to reduce Ca accretion in bone of young adults during growth and to have a negative impact on skeletal development. In the present study, U-Ca excretion was expected to be the highest in the 3rd and 4th quartiles, as dietary P intake was high in all of the quartiles, but dietary Ca intake was significantly higher only in the 3rd and 4th quartiles. Furthermore, in the 1st quartile, the mean Ca intake was slightly below recommended levels (≥ 800 mg/d)(4,43).
In fact, after excluding the 1st quartile, the other quartiles were highly similar in their effects on U-Ca excretion. This implies that in habitual diets with excessive dietary P intake an adequate dietary Ca intake is needed to overcome the interfering effects of low Ca:P ratios on Ca excretion.

In summary, low dietary Ca:P ratios in habitual diets of healthy women affected both S-PTH and Ca metabolism. Interestingly, the lowest Ca:P quartile differed from all other quartiles in a negative manner. The results suggested that such low Ca:P ratios (Ca:P molar ratio \( \leq 0.50 \)) in diets may disturb Ca metabolism and negatively affect bone in healthy subjects, as indicated by higher S-PTH and U-Ca levels together. However, whether it is necessary to reach a Ca:P molar ratio of 1 in diets is unknown. Even participants with a high dietary Ca intake did not achieve the suggested Ca:P ratio of 1. The present results imply that a Ca:P molar ratio higher than 0.50 is sufficient when dietary Ca intake is at the recommended level. However, higher Ca:P ratios might be needed if dietary Ca intake drops markedly below the nutritional recommendations. The present study also indicated that consumption of a large excess of dietary P is not optimal for mineral metabolism and bone health. In Western diets, low Ca:P ratios are common. Thus, more attention should be focused on decreasing excessively high P intake and increasing Ca intake to meet dietary guidelines. In Western diets, dairy products consumption will easily ensure adequate Ca intake. High dietary P intake, in turn, will be reduced by restricting the consumption of highly processed foods and increasing the consumption of raw and unprocessed foods. Nevertheless, increasing dietary Ca intake far beyond the nutritional recommendations should be avoided, as it might lead to other health risks. Identifying persons at risk of having low Ca:P ratios in their habitual diets would be useful. Also, because dietary Ca intake was generally adequate among our participants, additional studies are needed to investigate the impact of dietary Ca:P ratios in populations where low dietary Ca intake is common.

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References


