

Original Research

Calcium Effects on Phosphorus Absorption: Implications for the Prevention and Co-Therapy of Osteoporosis

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Key words: calcium intake, phosphorus absorption, osteoporosis, osteoporosis therapy, calcium supplements, calcium carbonate, calcium phosphate

Objective: To evaluate the effect of calcium intake on absorption of dietary phosphorus, with special reference to typical calcium intakes and to those likely to be encountered in prevention and treatment of osteoporosis.

Setting: Two academic health sciences centers; inpatient metabolic research unit.

Methods: Evaluation of calcium and phosphorus balance data obtained in two data sets, the first, 543 studies of healthy women aged 35–65, and the second, 93 men and women aged 19–78; development of multiple regression models predicting fecal phosphorus (the complement of net absorbed phosphorus); data from the two centers analyzed separately as a check on the consistency of the findings.

Results: Mean net absorption of phosphorus was 60.3% (± 18.1) for data set 1 and 53.0% (± 9.4) for data set 2. Just two variables, fecal calcium and diet phosphorus, were positively and independently associated with fecal phosphorus. These variables explained 73% of the variance in fecal phosphorus in data set 1 and 33% in data set 2. Fecal calcium alone explained the lion's share of the relationship. The coefficients of the fecal calcium term in the models fitted to the data were 0.332 ± 0.022 and 0.155 ± 0.039 , for data sets 1 and 2, respectively. Adjusting for the relationship between fecal calcium and calcium intake and using the parameters of the larger data set, it follows that each increase in calcium intake of 0.5 g (12.5 mmol) decreases phosphorus absorption by 0.166 g (5.4 mmol).

Conclusions: As calcium intake increases without a corresponding increase in phosphorus intake, phosphorus absorption falls and the risk of phosphorus insufficiency rises. Intakes with high Ca:P ratios can occur with use of supplements or food fortificants consisting of non-phosphate calcium salts. Older patients with osteoporosis treated with current generation bone active agents should receive at least some of their calcium co-therapy in the form of a calcium phosphate preparation.

INTRODUCTION

In recent years two calcium salts (carbonate and acetate), used in large doses, have largely replaced aluminum hydroxide preparations for control of phosphorus absorption in patients with end-stage renal disease. The effect, as with the aluminum compounds, is based on the fact that calcium complexes with phosphate in the intestinal lumen and thereby reduces its absorption. The interaction has not been well quantified even at the high doses used in renal failure patients, nor is its

importance or magnitude clear for the substantially lower dose calcium supplementation employed as co-therapy for osteoporosis.

Two facts suggest that it may be important to examine calcium's effects on phosphorus absorption under these circumstances. First is the emergence of therapies for osteoporosis that require high dose co-therapy with calcium in order to achieve their potential increase in bone mineral density [1–3], and, second, such therapies are often concentrated in elderly patients who tend to have the lowest food phosphorus intakes

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[4]. Reduction of absorption of diet phosphorus in such individuals could produce a lowering of serum phosphate concentration that would both augment osteoclastic bone resorption [5] and interfere with osteoblast work efficiency [6].

To evaluate this potential for an unintended harmful effect of calcium co-therapy, we turned to our respective databases of calcium and phosphorus balance measurements in an attempt to quantify the extent to which luminal calcium affects phosphorus absorption in the range of normal intakes and to develop the parameters of any such relationship so as to estimate the risk in patients being treated with current generation bone active agents.

METHODS

Subjects

Subjects in data set 1 were 191 Roman Catholic nuns studied from 1967 through 1992 as inpatients on a metabolic research unit. Their ages ranged from 35 to 65 at the time of study. Most were studied several times at five-year intervals. Together they contributed 470 measurement sets to this analysis. The subjects have been extensively characterized elsewhere [7]. When routine work-up revealed concurrent medical conditions that might interfere with calcium metabolism during a particular study, the data for such a study were eliminated from this analysis. The subjects each gave written consent to the project, and the Creighton University IRB approved the project after it came into existence (well after the inauguration of this study).

Subjects in data set 2 were a mixed group of 88 women and five men, studied in Leeds, U.K. They, too, have been described elsewhere [8, 9]. Many of the women in data set 2 were taking calcium supplements during their balance measurements, some with meals, but many at bedtime, while virtually none of the subjects in data set 1 received supplements.

Protocol

Data set 1 was a longitudinal, observational, cohort design and data set 2, cross-sectional. In data set 1, subjects completed seven-day diet diaries prior to each admission to the metabolic unit, and controlled diets were prepared for the eight-day inpatient stay to match the self-selected intakes of nitrogen, phosphorus and calcium of the subjects prior to admission. The diet was constant throughout the stay, and all excreta were collected and analyzed. Stool collections were timed and demarcated by the use of a nonabsorbable intake marker (polyethylene glycol through most of the project duration), ingested with each meal.

During the inpatient study, subjects maintained their usual intake of medications, vitamin and mineral supplements, health food preparations, etc. Each such product was analyzed for its

calcium and phosphorus content, and those values were included in the total intake of the nutrients concerned.

The methods for data set 2 were similar except that each balance study extended over two weeks, the first week for equilibration, and the second week for daily fecal collections. The diets were the same every day during this two-week period, and polyethylene glycol was fed from day 1 and used as a non-absorbable fecal marker.

Analytical Methods and Statistical Analysis

The analytical methods have all been described in detail elsewhere [7–10]. Data were characterized by standard descriptive statistics using a variety of packages [SPSS for Windows (SPSS, Chicago, IL) and Excel (Microsoft, Redmond, WA)]. Multiple linear regression models were developed using SPSS. Some of the subjects in both sets were studied more than once over the 25-year period involved (mean 2.4 times in data set 1), and their data are treated in this analysis as if they were independent observations. This approach is justified by the fact that there was substantial within-subject drift in dietary intake patterns, absorption efficiencies and hormonal status over the period of the several studies, and the within-individual variance was not appreciably different from the between-individual variance with respect to the variables of interest. Data set 2 was used mainly to test whether the relationships observed in data set 1 could be confirmed in an independently studied group of individuals.

RESULTS

Table 1 sets forth the descriptive statistics with respect to the relevant intake and output variables by data set. The mean intakes of calcium and phosphorus in the women of data set 1 [0.696 and 1.101 g/day (17.4 and 35.5 mmol)] were very similar to the NHANES-III median values for women 50–59 years of age. In data set 2, phosphorus intake was about the same, but calcium intake was ~50% higher than in data set 1, largely because of the use of non-phosphate calcium supplements as a part of study protocols. The slope of fecal calcium on calcium intake in these studies was 0.896 in data set 1 and 0.851 in data set 2 (weighted average: 0.890), indicating net absorption of incremental calcium intakes in the range of 11%.

It is the unabsorbed calcium that would interact with phosphorus in the chyme, and its interference with phosphorus absorption was explored with various multivariate models employing the variables listed in Table 1 (as well as several others, not shown). The statistically best model, and the one that was physiologically the most straightforward, related fecal phosphorus to fecal calcium and phosphorus intake. (Net absorbed phosphorus, by definition, is given as phosphorus intake minus fecal phosphorus). The parameters of the linear regression equations are set forth in Table 2 for the two data sets separately.

Table 1. Intake and Output Values for Calcium and Phosphorus*

	Data Set 1		Data Set 2	
	Mean	S.D.	Mean	S.D.
Calcium intake	0.696 (17.4)	0.306 (7.65)	1.142 (28.6)	0.224 (5.6)
Phosphorus intake	1.101 (35.5)	0.301 (9.7)	1.116 (36.0)	0.133 (4.3)
Diet Ca:P (mol:mol)	0.482	0.136	0.806	0.190
Net absorption calcium	0.111 (2.78)	0.079 (2.0)	0.137 (3.4)	0.121 (3.0)
Net absorption phosphorus	0.663 (21.4)	0.199 (6.4)	0.592 (19.1)	0.127 (4.1)
Fecal calcium	0.585 (14.6)	0.284 (7.1)	1.006 (25.2)	0.236 (5.9)
Fecal phosphorus	0.439 (14.2)	0.170 (5.5)	0.524 (16.9)	0.106 (3.4)
Fecal Ca:P (mol:mol)	1.022	0.273	1.523	0.378

* N = 470 for all variables in Data Set 1 and 93 for Data Set 2; except for ratios, values are g/day (mmol/day).

Table 2. Parameters of the Regression Models for the Various Data Sets*†

Data Set	N	Constant	Coefficient of Fecal Ca Term	Coefficient of Diet P Term	R ²
1	470	0.023 (-0.011; +0.055)	0.332 (0.288; 0.376)	0.201 (0.159; 0.243)	0.733
2	96	-0.053 (-0.229; +0.123)	0.155 (0.079; 0.232)	0.377 (0.241; 0.512)	0.326

* Mean (upper and lower bounds of 95% confidence interval); all values in grams.

† The equation to which the data were fitted is as follows:

$$\text{Fecal P} = \text{Constant} + C_f * \text{FecalCa} + C_p * \text{DietP},$$

where C_f and C_p are the coefficients of the fecal Ca and diet P terms, respectively.

The strongest predictor of fecal phosphorus was not diet phosphorus, as might have been expected, but unabsorbed diet calcium (i.e., fecal calcium). Before including diet phosphorus in the model in data set 1, for example, fecal calcium alone gave a value for R^2 of 0.682. The data themselves in data set 1, plus the plane defined by the least-squares regression model, are presented in Fig. 1. The fit of the full model to the data was extremely good ($R^2 = 0.733$). The fit of the data to a similar model was less good for data set 2, although still highly significant. This concordance serves as confirmation of the general correctness of the model of data set 1.

Holding phosphorus intake constant and converting fecal calcium to the corresponding intake value, one can calculate, using the fecal calcium coefficient for data set 1, that each 0.5 g (12.5 mmol) increment in calcium intake increased fecal phosphorus (and therefore decreased phosphorus absorption) by 0.166 g (5.4 mmol). Several worked examples of the predicted interference in phosphorus absorption by calcium using the parameters of data set 1, for various intakes of calcium and phosphorus, are displayed in Table 3. However, given the different intake Ca:P ratios of the two data sets, contrasting their phosphorus absorption values shows this same effect directly. Despite a slightly higher mean phosphorus intake in the individuals of data set 2, as Table 1 displays, the subjects of data set 2 absorbed an average of 0.071 g (2.3 mmol) less phosphorus ($p < 0.01$). According to the models of Table 2, this is best explained by their higher mean calcium intake [i.e., 446 mg (11.1 mmol) higher].

Because the standard error of the coefficient of the fecal calcium term for the model describing data set 1 is small

(0.022), the upper confidence limit for the amount of phosphorus bound is only 210 mg (6.8 mmol) phosphorus per 500 mg (12.5 mmol) calcium. Using this extreme value, the highest plausible therapeutic calcium intake (e.g., 2.5 g/day–62.5 mmol) will bind up to 1.05 g (34 mmol) phosphorus. Conversely, the least amount plausibly bound at this high calcium intake would be 0.61 g (19.7 mmol).

As can be seen in Table 3, at the 0.5 g (16 mmol) phosphorus intake level, net absorption is predicted to be negative at calcium intakes above 1.0 g (25 mmol)/day, and would be close to zero at the highest calcium intakes for even the 1.0 g (32 mmol) phosphorus intake. Such calculated negative absorption figures for diets with high Ca:P ratios may not mean that phosphorus is literally pulled out of the body. Rather they indicate excess capacity to bind additional food phosphorus, should it be ingested.

DISCUSSION

Phosphorus is not usually considered a problem nutrient. If anything, it has been argued, there is an excess of phosphorus in the food supply, at least in the U.S. [11–14]. The facts, however, are not so clearly supportive of this conclusion [15]. In comparison with laboratory animals, in which the potential harm of high phosphorus intakes has been mainly studied, human phosphorus intake is low. Primate chows have a phosphorus density of ~5 mmol/100 kCal, rat chows range from 4–6 mmol/100 kCal, and dog chows contain ~9 mmol/100 kCal. By contrast, median phosphorus density in the U.S. diet

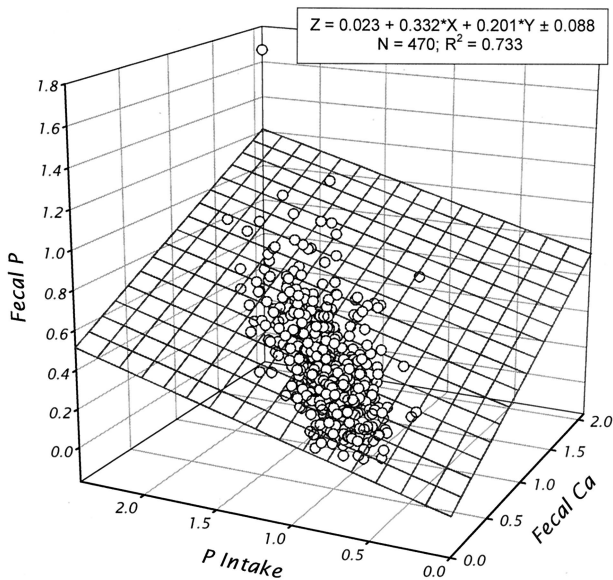


Fig. 1. Three dimensional plot of fecal phosphorus as a function of diet phosphorus and fecal calcium for the 470 balances of data set 1. The diagonal plane through the data is the least squares fit according to the parameters set forth in Table 2. In the equation inset, Z = fecal P, X = fecal Ca, and Y = diet P. (Copyright Robert P. Heaney, 2002. Used with permission.)

is on the order of only 2 mmol/100 kCal [4]. And the most recent adult RDA for phosphorus is 700 mg/day, which, for a 2200 kCal energy intake, is only ~1 mmol/100 kCal [15].

The data of NHANES-III show that appreciable numbers of individuals ingest less than 70% of even the adult RDA on any given day [4], i.e., less than 490 mg/day. Thus the 0.5 g phosphorus intake column in Table 3 is applicable to an appreciable number of individuals. Table 4 lists the percentile distribution of phosphorus intakes from NHANES-III, by age group, for non-Hispanic, white U.S. women. As is clearly evident, phosphorus intake is not normally distributed, and low phosphorus intakes, while found at all ages, are concentrated in the elderly. 15% of those 80 years and older and 10% of those 60 to 80 ingest less than 70% of the adult RDA on any given day.

But it is not certain that the adult RDA is the correct referent for patients receiving current generation anti-osteoporosis therapies. Bone active agents such as teriparatide (recombinant

human parathyroid hormone 1–34) have the capacity to increase central skeletal bone mineral density at a linear rate of 10% to 15% a year [1, 3]. This degree of bone building is the largest an individual will have experienced since the adolescent growth spurt, a life-stage when the phosphorus RDA in the U.S. is 1250 mg (40 mmol/day), not the adult 700 mg figure. If one takes 70% of the growth RDA as the critical intake value (i.e., 1250 × 0.7 = 875), one sees from Table 4 that more than half of women over 80 years have intakes below this level, and between 25 and 50% of women aged 60 to 80 years also have phosphorus intakes that may be suboptimal for current anti-osteoporosis agents.

Under such circumstances, absorbed phosphorus may be too low to support both soft tissue phosphorus needs and new bone mineralization (which consumes mineral at a Ca:P molar ratio of ~1.6:1). Any induced phosphorus insufficiency under these circumstances, expressed as a lowering of serum inorganic phosphorus concentration, would not only limit bone gain, but enhance osteoclastic bone resorption [5]—precisely opposite to the direction toward which current anti-osteoporosis therapy is pointed. Moreover, teriparatide, specifically, exerting its inherent parathyroid hormone activity, would itself lower the renal phosphorus threshold, thereby compounding the problem by lowering serum inorganic phosphorus levels still further.

In the past, the principal source of calcium in the diet has been dairy foods, which contain phosphorus as well as calcium. Thus phosphorus intake tended to vary with calcium, and high calcium intakes would not have affected phosphorus nutriture adversely. However, increased awareness of the importance of calcium, and the corresponding increase in supplement use, coupled with widespread food fortification with calcium (mostly as non-phosphate calcium salts), have combined to change the calcium intake distribution in adults appreciably, without much effect on phosphorus intakes. Although precise quantification of the current distribution of total calcium intakes remains to be done (e.g., in the next NHANES), it is virtually certain that supplements and fortification have raised Ca:P intake ratios for the older age strata over the past few years.

The degree of interference reported here (~166 mg phosphorus for every 500 mg ingested calcium—0.4 mmol phosphorus for every mmol calcium) is substantially less than might have been predicted from simple stoichiometry. A 1:1 molar

Table 3. Calculated Net Phosphorus Absorption for Various Calcium and Phosphorus Intakes*

Ca intake	0.5 g P/day (16 mmol)		1.0 g P/day (32 mmol)		1.5 g P/day (48 mmol)	
	Fecal P	NetAbsP†	Fecal P	NetAbsP†	Fecal P	NetAbsP†
0.5 (12.5)	0.271 (8.81)	0.229 (7.39)	0.372 (12.0)	0.628 (20.3)	0.472 (15.2)	1.028 (33.2)
1.0 (25)	0.419 (13.5)	0.081 (2.61)	0.519 (16.7)	0.481 (15.5)	0.620 (20.0)	0.880 (28.4)
1.5 (37.5)	0.567 (18.3)	-0.067 (-2.16)	0.667 (21.5)	0.333 (10.7)	0.768 (24.8)	0.732 (23.6)
2.0 (50)	0.714 (23.0)	-0.214 (-6.90)	0.815 (26.3)	0.185 (5.97)	0.915 (29.5)	0.585 (18.9)
2.5 (62.5)	0.862 (27.8)	-0.362 (-11.7)	0.963 (31.1)	0.037 (1.19)	1.063 (34.3)	0.437 (14.1)

* Using fecal Ca = 0.89 (diet Ca); all values are from the parameters of the model for data set 1; all units are g (mmol).

† Net absorption of phosphorus, i.e., phosphorus intake minus fecal phosphorus.

Table 4. Distribution of Phosphorus Intakes* in the U.S.†

Ages (years)	5th	10th	15th	25th	50th	75th	85th	90th	95th
30–39	434‡	581	677	761	1111	1457	1637	1804	2092
40–49	486‡	575	634	764	1027	1341	1564	1650	1797
50–59	451‡	525	596	739	976	1214	1375	1565	1892
60–69	399‡	482‡	586	727	998	1299	1497	1735	2183
70–79	415‡	478‡	550	679	902	1224	1397	1500	1748
80+	353‡	431‡	486‡	581	833	1157	1286	1435	1686

* mg P/day.

† Non-Hispanic, white women from NHANES-III (4).

‡ Less than 70% adult RDA.

ratio for CaHPO_4 would predict binding of 388 mg phosphorus by 500 mg calcium and, for $\text{Ca}_3(\text{PO}_4)_2$ at a Ca:P molar ratio of 1.5:1.0, 258 mg phosphorus would be bound per 500 mg calcium. A molar ratio of 1:1 seems more likely at digestate pH values below 7.0. Even at the upper end of the confidence interval for the regression model—210 mg (6.8 mmol)—binding would still be substantially less than the lowest stoichiometric prediction. This discrepancy may be partly due to rapid absorption of phosphorus in the duodenum well before calcium and phosphorus complexes can form in the chyme. In any event it undoubtedly reflects the complexity and multiplicity of the interactions within the digestive residue.

The data assembled in Fig. 1, derived from individuals ingesting mainly unfortified, food-based diets, can be seen to tend to cluster along a diagonal, with calcium and phosphorus intakes varying together. 95% of the subjects had dietary Ca:P molar ratios below 0.75:1.0 in data set 1 and below 1:1 in data set 2. Accordingly, the data analyzed here provide only limited information about phosphorus absorption at intakes with Ca:P molar ratios substantially above 1:1. However, there are other sources of information that bear on this high Ca:P region of the intake space. One is the experience in patients with end-stage renal disease, where high calcium intakes (as the carbonate or acetate salts) do demonstrably block absorption of phosphorus from diets with normal to low phosphorus contents. Nordin, in his extensive review of nutritional phosphorus metabolism several years ago [16], noted then that unabsorbed food calcium lowers phosphorus absorption in normal subjects. And Spencer *et al.* [17], in a series of metabolic balance studies, described a 25% reduction in phosphorus absorption in healthy individuals with typical phosphorus intakes when calcium intake was increased from 216 mg (5.4 mmol)/day to 2028 mg (50.7 mmol)/day. Schiller *et al.* [18] reported ~60% reduction in net phosphorus absorption in normal individuals when a test meal was coadministered with 25 mmol (1000 mg) calcium as the acetate salt. The Ca:P intake ratio achieved by Spencer *et al.* was ~2:1 (mol:mol) and by Schiller *et al.*, ~2.5:1 (mol:mol), much higher than one could achieve using foods alone, but in a range likely to be encountered as a part of current osteoporosis therapy.

Phosphorus binding at the highest Ca:P ratios in Spencer *et al.*'s data was ~0.09 mmol P/mmol Ca and in Schiller *et al.*'s

data, on the order of 0.2–0.24 mmol P/mmol Ca. These values are lower than the values we report here (0.4:1), but the confidence intervals of the several estimates overlap extensively, and they do not differ significantly from one another. Hence the models in Table 2 are at least directionally correct when applied to intakes with high Ca:P ratios and may be reasonably quantitative in that range as well. Moreover, the fact that both of our data sets demonstrated interference in phosphorus absorption by unabsorbed digestate calcium reinforces the finding of an effect.

The differences in the values for the coefficients in the models for our two data sets are partly what would be expected when a relationship observed in one group of data is checked in an independent group. Partly also the differences are likely due to the timing of calcium supplement use in the subjects of data set 2 (bedtime), when interference with food calcium absorption would be reduced [18]. Such timing of calcium intake would be expected to lower the value of the coefficient of the fecal calcium term, precisely as observed in Table 2. That this explanation is correct is suggested by a reanalysis of data set 2, confined to those individuals with little or no calcium supplementation. In such subjects, the coefficient of the fecal calcium term is 0.283, not significantly different from that observed in the studies of data set 1.

We hasten to stress, in conclusion, that none of this should be taken to mean that the current trends toward increasing calcium intake are harmful or that supplement use and judicious calcium fortification of foods should be curtailed. As recognized and documented at several levels over the past 20 years, calcium deficiency is perhaps the most prevalent nutrient deficiency in the industrialized nations. Moreover, increasing calcium intake, particularly in older individuals, results in prompt and clinically important skeletal benefits [e.g., 19, 20].

Thus, with both supplementation and fortification, the issue is not with the calcium itself, but with its accompanying anion. One of the more dramatically effective trials of calcium supplementation in the elderly employed tricalcium phosphate as the calcium source [19], and the authors explicitly alluded to the extra ingested phosphorus as perhaps partially responsible for the strongly positive effect they produced. This suggestion seems to have been largely ignored, both by the osteoporosis

investigative community and by calcium supplement manufacturers.

The dominant anions in the calcium supplement market today, worldwide, are carbonate and citrate. Until recently the anion probably would not have mattered. Given the calculated phosphorus absorption effects of calcium in Table 3 and the intake data of Table 4, it is likely that phosphorus intake is, in fact, sufficiently high for most adults that the accompanying anion does actually make little difference, i.e., it is calcium that is mainly deficient in their diets, and the net effect of fortification and supplementation is to bring calcium intake into relative parity with other nutrients.

However, the same may not be true for many of the older elderly nor for many of the patients requiring very high calcium intakes as osteoporosis co-therapy. It would seem, therefore, that such co-therapy should be in the form of one of the several calcium *phosphate* salts. By the same reasoning, supplements and calcium-fortified foods marketed specifically for older individuals also should contain some of their calcium as a phosphate salt, both to ensure realizing the full benefit of the additional calcium and to guard against inducing an unintended phosphorus insufficiency.

If the interference we describe here turns out to be clinically significant, it would contribute to blunted responsiveness during anti-osteoporosis therapy. The primary response variable for groups of subjects will often be change in bone density. As is generally recognized, this is an insensitive measure in individuals, and a poor response may thus be hard to detect. However, suggestive evidence of a compromised response would be low values for serum or urine phosphorus. Future studies of high potency, bone-active agents should, perhaps, incorporate provision for such measurement if they utilize a non-phosphate calcium supplement. Additionally, physicians seeking to interpret apparently weak bone density responses in individual patients might get help from these inexpensive checks on phosphorus status.

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