Symposium: Nutritional Advances in Human Bone Metabolism

Changing Phosphorus Content of the U.S. Diet: Potential for Adverse Effects on Bone[1]

MONA S. CALVO[2] AND YOUNGMEE K. PARK

Office of Special Nutritionals, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC 20204

ABSTRACT The dietary intake of phosphorus in the United States is high relative to calcium. Intake estimates from the 1989–1991 Continuing Surveys of Food Intakes by Individuals conducted by the U.S. Department of Agriculture show that for both men and women, median calcium intakes do not meet the 1989 Recommended Dietary Allowances (RDAs) for most age groups over 10 y of age, whereas phosphorus intakes exceed the RDAs for most age groups. The use of phosphorus-containing food additives in the processing of foods contributes substantially to the daily phosphorus intake, and their use is increasing. Because much of the phosphorus through food additive use is not reflected in the estimates of phosphorus intakes derived from national food consumption surveys, these estimates underestimate true dietary intakes of phosphorus. High phosphorus intake has been shown to cause secondary hyperparathyroidism and bone loss in several animal models. High phosphorus, low calcium consumption consistent with current observed intake levels resulted in changes in calcium-regulating hormones that were not conducive to optimizing peak bone mass in young women. Evidence that such high phosphorus intakes may impair synthesis of the active metabolite of vitamin D and disrupt calcium homeostasis particularly in older women are discussed. J. Nutr. 126: 1168S–1180S, 1996.

INDEXING KEY WORDS:

- *dietary phosphorus* • *dietary calcium*
- *calcitriol* • *osteoporosis*

Elaborate hormonal mechanisms have evolved to finely regulate plasma calcium concentrations, maintaining it within very narrow limits to avoid serious disruption of neurologic and neuromuscular functions that occur with hypo- and hypercalcemia (Broadus 1993). Although plasma phosphorus also occurs over a narrow plasma concentration, it is less rigidly maintained than calcium. Abrupt changes in phosphorus concentration beyond the normal range will not directly stimulate parathyroid hormone (iPTH)[3] or calcitonin (Ct) release. However, elevated phosphorus concentrations can stimulate iPTH release indirectly by lowering calcium levels (Broadus 1993, Lemann 1993a). Plasma phosphorus concentration is largely regulated by the kidney under the influence of the calcitropic hormones that stimulate change in renal phosphorus clearance. Unlike calcium, phosphorus is readily and efficiently absorbed at all levels of dietary intake (Anderson 1991, Lemann 1993b); consequently, plasma phosphorus concentrations are more commonly disrupted by oral ingestion in normal individuals.

Because such elevations in serum phosphorus have physiological consequences that could be harmful if sustained over time, we need to give some consideration to the increasing phosphorus content of the U.S. diet and to high phosphorus intakes by some subgroups of the U.S. population, particularly those whose calcium intakes are low. This review focuses on the current dietary intake of phosphorus in relation to calcium intake in the United States and explores the scientific evidence suggesting that an excessive intake may adversely affect bone health.

Calcium and phosphorus intakes of the U.S. population

Data from the second National Health and Nutrition Examination Survey (NHANES) conducted in 1976–

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[2] To whom correspondence should be addressed.

[3] Abbreviations used: Ct, calcitonin; CSFIIs, Continuing Surveys of Food Intakes by Individuals; 2^0HPT, secondary hyperparathyroidism; iPTH, parathyroid hormone.

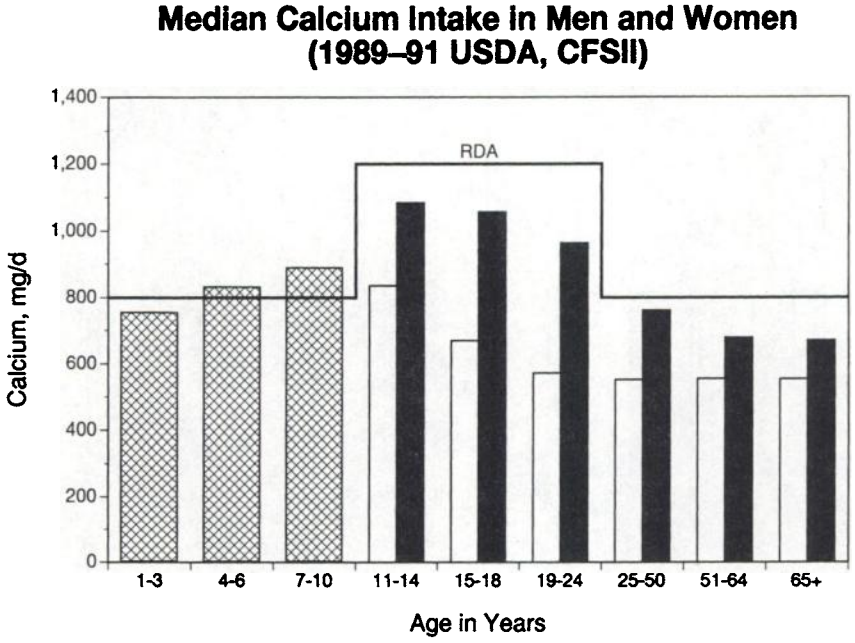

FIGURE 1 Median intakes of calcium by age and sex for persons having 3-d dietary intake data from the 1989–1991 Continuing Surveys of Food Intakes by Individuals conducted by U.S. Department of Agriculture (U.S. Department of Agriculture 1993a, 1993b, 1994). All values were weighted by the weighting factors provided in the database to represent the U.S. population estimates. Children's data ■; women's data □; men's data ■. Recommended Dietary Allowances (RDAs) for calcium for various age and sex groups are presented by the horizontal line.

1980 showed a general low intake of calcium relative to recommended daily intake guidelines and relative to phosphorus intake (Calvo 1993). Using data from more recent national food consumption surveys by U.S. Department of Agriculture (USDA), i.e., the 1989–1991 Continuing Surveys of Food Intakes by Individuals (CSFIIs) conducted in 1989–1991, we have estimated current intakes of calcium and phosphorus by U.S. population groups. This database contained 3-d dietary intake data (one 24-h recall and 2 dietary records) by ~12,000 people of all ages and both sexes who were selected by a multistage area probability sample drawn from the 48 conterminous states and Washington, D.C. to provide the U.S. population estimates. The results of these newer surveys agree with earlier findings. **Figure 1** shows estimates of the median intakes of calcium from the 1989–1991 CSFIIs. Median calcium intakes by children under 11 y of age essentially met the 1989 Recommended Dietary Allowances (RDAs) (National Academy of Sciences 1989). Median calcium intakes of women, particularly adolescent girls and young women, were far short of the RDA with the values representing 56 and 48% of the 1989 RDA. Although somewhat lower than the RDAs, median calcium intakes of men were much closer to the RDAs with the values ranging from 80 to 95% of the RDA.

Figure 2 presents estimates of the median intakes of phosphorus from the 1989–1991 CSFIIs. Unlike calcium, median phosphorus intakes were at or above the RDA for all age and sex groups except for adolescent girls and young women < 25 y of age. Although lower than the RDA values, phosphorus intakes of the adolescent girls and young women were 86 and 79% of the RDA, respectively, compared with 56 and 48% of the RDA for calcium.

Estimates of calcium and phosphorus intakes presented in Figures 1 and 2 are likely to be an underestimation of the true intakes for several reasons. First, these estimates were not adjusted for potential underreporting of food intakes. National food consumption surveys such as NHANES and CSFIIs are self-reported surveys. Many studies have reported evidence of underreporting of energy intakes, and thus food intakes, in self-reported food consumption surveys compared with the energy intake determined to maintain weight or total energy expenditure measured by a doubly labeled water method (Black et al. 1993, Forbes 1991, Lichtman et al. 1992, Mertz et al. 1991, Schoeller 1990). Because these studies were conducted using a relatively small number of individuals who were not nationally representative, the extent of underreporting in national food consumption surveys remains unclear (Glinsmann and Park 1995). However, comparison of the mean energy intakes from the 1989-91 CSFIIs with the 1989 RDAs for energy showed that the survey estimates were ~20% (age and sex group range, 7–29%) lower than the RDAs (Glinsmann and Park 1995). The RDAs for energy represent the average energy needs of individuals engaged in light-to-moderate physical activity with no safety margin. On the other hand, there is a prevalence of overweight in the United States, and this prevalence is increasing (Federation of American Societies

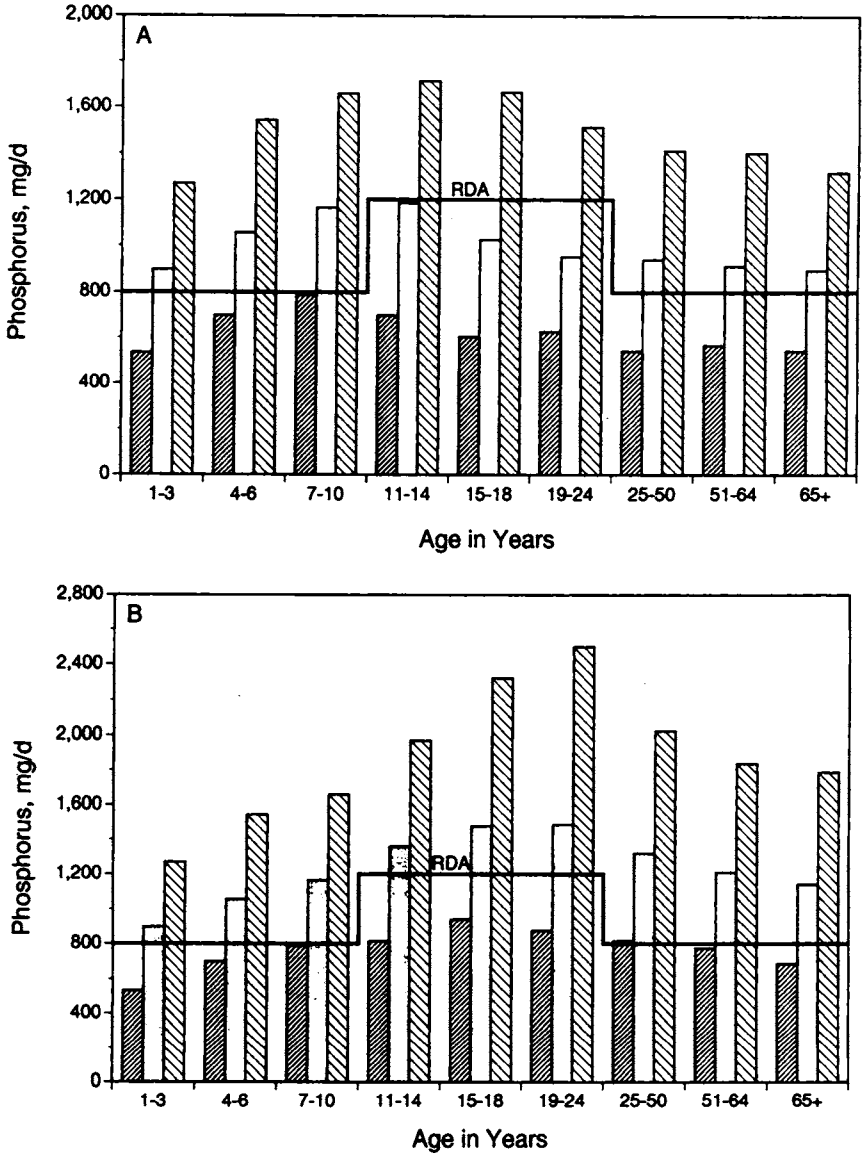

FIGURE 2 Tenth, fiftieth and ninetieth percentile intakes of phosphorus by age and sex for persons having 3-d dietary intake data from the 1989–1991 Continuing Surveys of Food Intakes by Individuals conducted by U.S. Department of Agriculture (U.S. Department of Agriculture 1993a, 1993b, 1994). All values were weighted by the weighting factors provided in the database to represent the U.S. population estimates. (***A***) women's data; (***B***) men's data; data for 1–10 y of age in ***A*** and ***B*** include both boys and girls. Recommended Dietary Allowances (RDAs) for calcium for various age and sex groups are presented by the horizontal line.

for Experimental Biology 1995). This suggests that underreporting is likely to occur in national food consumption surveys.

Second, the intake estimates presented in Figures 1 and 2 represent intakes only from food and beverages and do not include calcium or phosphorus intakes from vitamin or mineral supplements. Calcium supplements are used commonly by some segments of the U.S. population such as older women. Although there appear to be no supplements specifically intended to raise the phosphorus intake per se, phosphorus compounds are used in the supplement for other nutrients such as calcium (Park et al. 1991). Third, although nutrient intake estimates from the CSFIIs include minerals from the water used to prepare foods, they do not include minerals from drinking water. Exclusion of drinking water is likely to underestimate mineral intakes such as calcium of people in hard water areas.

In the case of phosphorus, there is yet another reason for underestimation. Phosphorus-containing food additives are used extensively in the processing of foods (Dziezak 1990), but much of the phosphorus from the food additives is not included in phosphorus intakes derived from national food consumption surveys. Currently, ≥45 phosphorus-containing compounds are approved for use in food processing as nutrients, dietary supplements or for functional purposes such as to preserve moisture or color and an emulsifier or a seques-

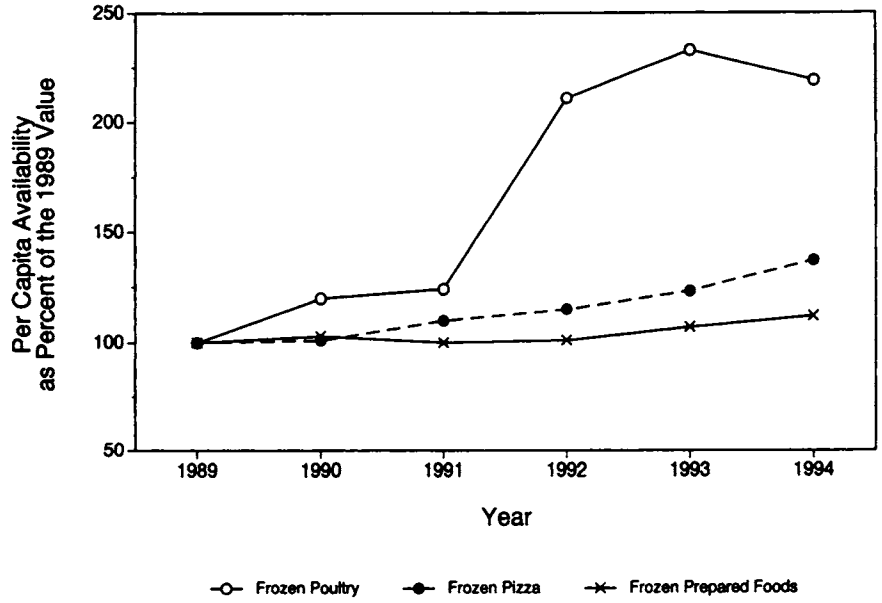

FIGURE 3 Per capita availability of selected commercial food commodities from 1989 to 1994 expressed as percent of the 1989 value. Annual quantities of grocery store sales in the United States used to calculate estimates of per capita availability came from the A.C. Nielsen Scantrack database. The sales data (proprietary, not available to the public) were provided by Thomas B. O'Brien, Office of Food Labeling, FDA after the approval from the A.C. Nielsen Company.

trant (Office of Federal Register 1995). Modified food starches are used commonly in processed foods. Because of their excellent freeze-thaw stability, phosphate esters of starch are used in frozen foods (Whistler and Daniel 1985). Currently, six phosphate-containing modified starches are approved by the FDA (Office of Federal Register 1995). Ingredient lists of products show that modified food starches are used in many frozen foods such as gravy, cream pies and prepared entrees and meal-type products. About 70 phosphorus-containing compounds are approved for use as indirect food additives for various purposes such as for the use as components of packaging materials, adjuvants, production acids or sanitizers (Office of Federal Register 1995). Some of the phosphate in the indirect additives may migrate or enter into food. However, amounts of phosphorus from indirect additives are small and are not likely to contribute significantly to the daily phosphorus intake.

Phosphorus-containing food additives contribute >30% of the adult phosphorus intake (Greger and Krystofiak 1982). However, nutrient composition tables do not always reflect the current practices of food additive uses in food processing; therefore, actual intakes of phosphorus may be higher than reported (Oenning et al. 1988). We examined the methodology used to estimate nutrient contents of foods in the CSFIIs to see if it reflects the food additive use. The current methodology reflects the food additive use if commercially prepared foods are listed separately in the database and nutrient contents of commercially prepared foods were used. Current national food consumption databases contain only limited number of separate listings of commercially prepared foods. Most of the foods in national food consumption surveys (survey foods) including the CSFIIs are recipe-type foods, i.e., they are prepared from two or more ingredients excluding water. These recipe-type foods do not have a separate listing for commercially prepared foods, and their nutrient contents are calculated from nutrient contents of ingredients. Ingredients of these recipe-type foods do not include food additives. Therefore, the current system for estimating nutrient contents of survey foods is not capable of capturing phosphorus from food additives, resulting in an underestimation of phosphorus intakes.

Changing phosphorus contents of the U.S. diet

Phosphorus contents of the U.S. diet are increasing as a result of the increasing use of phosphorus-containing food additives and an increasing consumption of processed foods containing these additives. We reported that the use of phosphorus-containing food additives have increased by ~17% over the last decade (Calvo 1993). As explained above, much of the phosphorus from food additives is not included in phosphorus intake estimates derived from national food consumption surveys. Therefore, national food consumption survey estimates of phosphorus intakes over time do not show increasing trends in phosphorus intakes. Food and nutrient disappearance data published by the Economic Research Service of the USDA (Putnam and Allshouse 1994) are often used to examine trends in the consumption of food and nutrients. These disappearance data also do not include nutrients from food

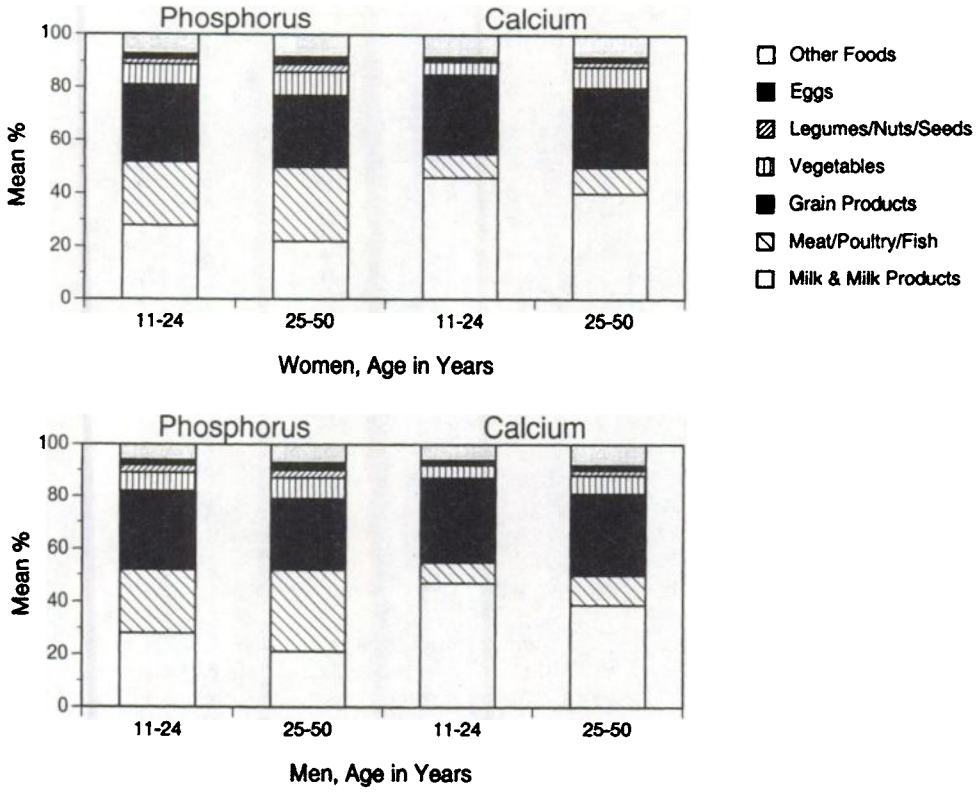

FIGURE 4 Food sources of calcium (right) and phosphorus (left) for selected U.S. population groups. Food consumption data source: 1989–1991 Continuing Surveys of Food Intakes by Individuals conducted by U.S. Department of Agriculture (U.S. Department of Agriculture 1993a, 1993b, 1994). All values were weighted by the weighting factors provided in the database to represent the U.S. population estimates. (Top) women's data; (Bottom) men's data.

additives, and thus they are not useful to assess trends in phosphorus intakes of the U.S. population.

Using estimates of annual quantities of grocery store sales in the United States reported in the A.C. Nielsen Scantrack database, we examined trends in the per capita availability of several food categories that include recipe-type foods, but their phosphorus contents in the national food consumption surveys do not include phosphorus from food additive use. The food categories include frozen pizza, frozen poultry and frozen prepared foods. Many products in these food categories contain phosphorus-containing food additives for various purposes. The per capita availability of foods was calculated by dividing estimates of the annual quantities of foods in each food category by U.S. population estimates reported by the Bureau of the Census of the U.S. Department of Commerce. The results are shown in **Figure 3.** Because the absolute amounts differ greatly for different categories, the data are expressed as percent of the base year to include all data in one figure. The data show a trend of increasing consumption of commercially prepared foods containing phosphorus.

Another evidence that supports increasing phosphorus contents of the U.S. diet is the increasing consumption of fast foods. Between 1977–1978 and 1987–1988, the percentage of total food expenditures spent on foods away from home increased across all racial groups, income classes, and regions of the country (Federation of American Societies for Experimental Biology 1995). Examination of the ingredients of foods sold at a major fast food restaurant in the United States showed that phosphate compounds are used in some entrees such as fish fillet and chicken patties or fillets to retain moisture or as anticaking agents. However, phosphorus from phosphate compounds used in these fast foods is not reflected in the phosphorus contents of these foods in national food consumption surveys.

Imbalance of calcium and phosphorus in the U.S. diet

One reason for the imbalance between calcium and phosphorus intake is attributed to the fact that phosphorus is more ubiquitous in the food supply than calcium. This makes it easier to obtain phosphorus than calcium. Using the 1989–1991 CSFIIs, we examined food sources of calcium and phosphorus. For this purpose, all foods in the food consumption database were divided into nine major food groups according to the major ingredients of the food following the USDA's food-grouping classification system. The nine major food groups were as follows: milk and milk products; meat, poultry and fish; eggs and egg products; legumes,

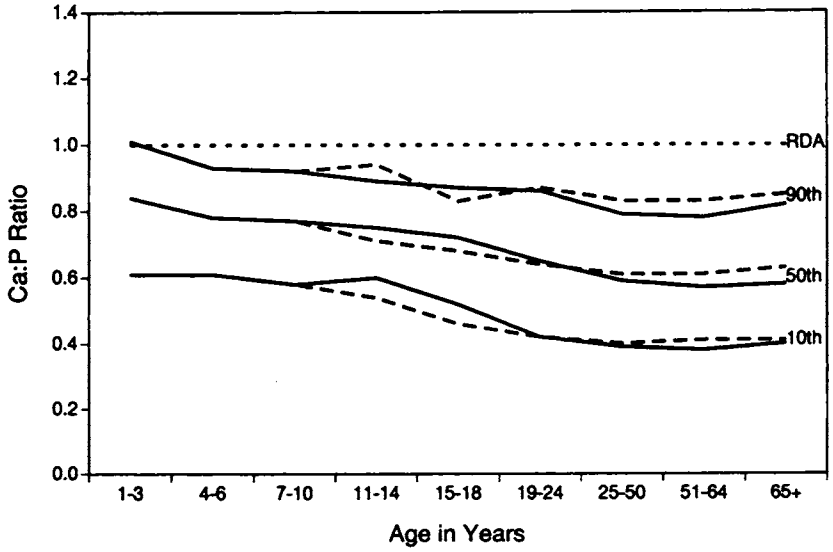

FIGURE 5 Calcium to phosphorus ratios in the diets of men (—) and women (---) having 3-d dietary intake data from the 1989–1991 Continuing Surveys of Food Intakes by Individuals conducted by U.S. Department of Agriculture (U.S. Department of Agriculture 1993a, 1993b, 1994). All values were weighted by the weighting factors provided in the database to represent the U.S. population estimates.

nuts and seeds; grain products; fruits; vegetables; fats, oils and salad dressings; and sugars, sweets and beverages. To estimate the percent contribution of each food group to the total daily calcium and phosphorus intake, the average daily intake of calcium and phosphorus from each of the nine major food groups was divided by the total average daily intake of calcium and phosphorus for each individual in the database and then multiplied by 100. Using the SAS procedures (SAS Institute 1990), the mean percent contribution of each food group was estimated for various age/sex groups. The results are presented in **Figure 4** for selected age and sex groups. Milk and milk products were the primary source of calcium in the diets of all age and sex groups, accounting for ~40–50% of the total daily intake of most age and sex groups. Grain products were another major contributor of calcium in the U.S. diet, accounting for ~20–30% of the daily intake. Milk and milk products and grain products were also major sources of phosphorus in the diets of all age and sex groups, each accounting for ~20–30% of the daily intake of most age and sex groups. Unlike calcium, meat, poultry and fish were an equally important source of phosphorus, accounting for another 20–30% of the daily intake. This food group contributed only ~5–10% to the daily calcium intake. Because contributions of three food groups (fruits; fats, oils and salad dressings; and sugars, sweets and beverages) were small, they are presented together as other foods in Figure 4.

The imbalance between calcium and phosphorus intake is best shown by plotting the average daily intake of calcium and phosphorus as a ratio (Ca:P). **Figure 5** presents estimates of the 10th, 50th and 90th percentile values of Ca:P ratio from the 1989–1991 CSFIIs as a function of age. The desired Ca:P intake ratio is 1 (1:1) (National Academy of Sciences 1989) except for infants; the ratios for infants are 1.3 for up to 6 mo of age and 1.2 for 6–12 mo. The data in Figure 5 show that the actual ratio for the majority of individuals in the United States is well below this level. For all percentiles of intake, both men and women show an overall trend toward a lower ratio or greater imbalance between calcium and phosphorus intake with increasing age.

Examination of Ca:P ratios by calcium intake status showed that Ca:P ratios in the diets of people whose calcium intake ranked lower are worse than the ratios in the diets of people whose calcium intakes ranked higher. **Table 1** compares selected percentile values of Ca:P ratios for lower calcium consumers with the values for the higher calcium consumers. Lower calcium consumers are defined as persons who consumed <50% of the RDA for calcium; higher calcium consumers are defined as persons who consumed ≥50% of the RDA for calcium. The data show that Ca:P ratios of lower calcium consumers are considerably lower than those of higher calcium consumers. For example, the median ratio of the lower calcium consumers was ~30% lower than the median ratio of the higher calcium consumers.

The concept of an ideal Ca:P ratio for the human diet was not introduced until the 1968 edition of the RDA, which was the first edition to establish intake guidelines for phosphorus (National Academy of Sciences 1968). Guidelines for the nutrient intake requirement of laboratory and domestic animals have traditionally set these minerals at intake levels relative to each other and provided specific guidelines for the Ca:P ratio of the diet (Draper 1994). The National Research Council nutrient requirement guidelines for calcium

TABLE 1

Median Ca:P ratios in lower vs. higher Ca intake[1,2]

Age and sex group	Lower intake		Higher intake	
	n	Ratio	*n*	Ratio
Children, *y*				
1–3	82	0.6	583	0.9
4–10	92	0.6	1295	0.8
Women, *y*				
11–24	502	0.6	728	0.8
25–50	709	0.5	1672	0.7
51–64	262	0.5	547	0.7
≥65	332	0.5	811	0.7
Men, *y*				
11–24	201	0.5	828	0.7
25–50	226	0.4	1573	0.6
51–64	104	0.4	494	0.6
≥65	108	0.5	556	0.6
Total sample ≥ 1	2616	0.5	9087	0.7

[1] Lower Ca intake group includes people whose Ca intake was <50% of the RDA. Higher Ca intake group includes people whose Ca intake was ≥50% of the RDA.

[2] Includes persons having 3-d dietary intake data and excludes breast-fed children.

and phosphorus intake for the majority of species set the Ca:P ratio at ≥1. The ratio can differ with age of the animal, with higher ratios for the weanling than for adult, which is also true for humans. As mentioned earlier, infants are the only age group for which the RDA for Ca is higher than that for phosphorus.

A sound rationale for the higher Ca:P ratio in infants exists. Feeding standard high phosphorus milk-based infant formulas with Ca:P molar ratios of ~1:1 has been associated with hypocalcemia, convulsions and apparent secondary hyperparathyroidism within the first weeks of age (Venkataraman et al. 1985). More recently, Specker (1991) reported that feeding milk-based formulas having Ca:P molar ratios closer to human milk in the early neonatal period increased serum phosphorus, decreased serum ionized calcium and increased iPTH levels compared with feeding human milk. They speculate that the observed differences in indices of calcium homeostasis were related to the high phosphorus content of the formulas relative to human milk rather than the absolute Ca:P ratio.

Effects of high phosphorus intakes in animals

Concern about the relatively high levels of phosphorus in the adult U.S. diet and its role in the development of osteoporosis stems from animal studies. High phosphorus intake, even with adequate calcium intake, has been shown to cause secondary hyperparathyroidism (2°HPT), bone loss and osteopenia in a variety of animal models (Calvo 1994, Draper and Bell 1979, Lutwak 1975). Studies in rodents were instrumental in establishing that high phosphorus intakes, independent of calcium intake, increase bone resorption and reduce bone mass. This is illustrated in **Figure 6** showing the percent ash weight from the femur, vertebra and mandible of rats fed diets containing adequate calcium (0.6%) and increasing levels of phosphorus (0.3, 0.6, 1.2 and 1.8%). Rats fed diets containing excess phosphorus (≥1.2% P) had significantly reduced mineral ash weight of the femur, vertebra and mandible (Draper et al. 1972). Shah et al. (1967) demonstrated that the effect of the Ca:P ratio in the diet was independent of the absolute intake of both elements in adult mice fed diets containing varying levels of Ca (0.1, 0.3, 0.6 and 1.2%) at two ratios of phosphorus intake. Mouse femoral bone mass was depressed by either a low calcium intake or a high phosphorus intake (1.2%).

The mechanism through which excess phosphorus intake induces increased bone resorption was determined using radiocalcium techniques and deep labeling of rat bone with ^{45}Ca (Sie et al. 1974). The rapid and efficient absorption of excess phosphorus relative to the less efficient absorption of calcium from the diet raises plasma phosphorus concentrations, causing a decrease in plasma calcium (Clark 1969, Sie et al. 1974). The decrease in plasma calcium in turn stimulates iPTH secretion and phosphaturic action in the kidneys, which serves to correct the elevated serum phosphorus. Prolonged stimulation of iPTH secretion stimulates a marked increase in bone resorption with little to no change in bone formation. This effect of chronic high phosphorus diets was prevented by parathyroidectomy in rodents (Anderson and Draper 1972) and was shown to diminish with age in senescent rodents (Draper et al. 1980).

Feeding excess dietary phosphorus has similar effects in other species including rabbits, pigs, dogs, cats, horses and primates (Calvo 1994). Some of these studies have been criticized as not being relevant to humans based on differences in the sensitivity of the animal models used, gross calcium inadequacy of the diets fed and/or the exaggerated concentration of dietary phosphorus fed. **Table 2** presents results of those studies carried out in dogs, an animal model that is considered relevant to changes in human bone (Kimmel and Jee 1982) and illustrates the validity of some of this criticism. Significant reduction in bone mass was demonstrated in adult dogs in a relatively short period of time by feeding diets deficient in calcium but with extremely high phosphorus concentrations, Ca:P ratios of 1:10 (Cook et al. 1983, Krook et al. 1971, Saville and Krook 1969). A hierarchy was demonstrated in the degree these bones were affected, with those containing the greatest trabecular bone showing the lowest ash content. LaFlamme and Jowsey (1972) showed hyperparathyroidism and increased bone resorption and decreased bone mass feeding a diet that more closely approximated human phosphorus intake. Some question exists, however, about the adequacy of calcium and other nutrients in this diet. In contrast, Harris et al.

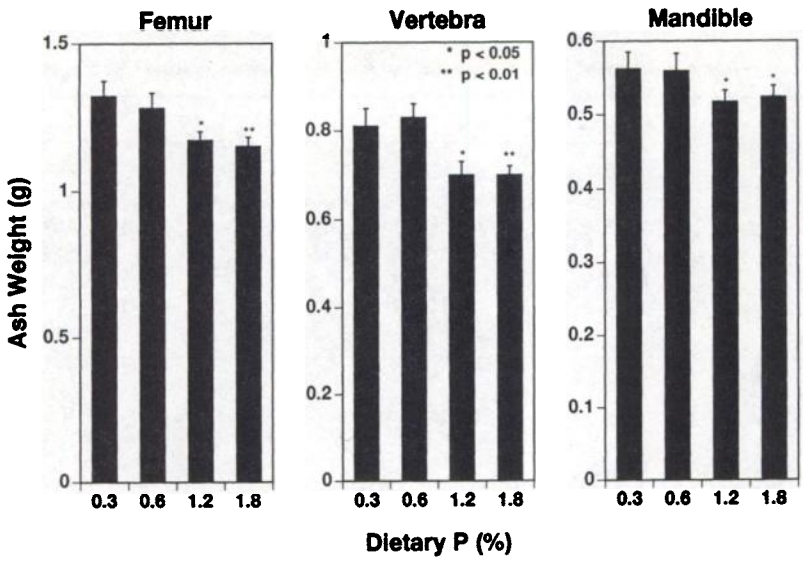

FIGURE 6 Effects of adequate calcium, high phosphorus diets on ash content of rodent femur, vertebra and mandible. Figure was drawn from data presented by Draper et al. 1972.

(1976) demonstrated an increase in cortical bone accretion after only 12 wk of feeding a calcium adequate, phosphorus-supplemented diet (1.2%). Harris and coworkers only examined cortical bone, the least sensitive type of bone; with prolonged feeding they may have observed changes in predominantly trabecular bone such as the vertebra. All of the studies shown in Table 2 showed evidence of increased soft tissue calcification, notably in the kidneys, with high phosphorus feeding.

The most frequently cited criticism of animal studies showing potentially harmful effects of excess phosphorus is that the 2^0HPT and bone resorption is due to the limited calcium content of the diet, particularly for immature animals. Two more recent studies in young baboons and young female beagles address this point and demonstrate that the physiological response to low calcium differs from the response to high phosphorus, low calcium intake. At least in animal models, the presence of excess phosphorus appears to have a more harmful effect on bone. Pettifor et al. (1984) studied the effect of feeding diets varying in calcium and phosphorus content on calcium metabolism, bone histomorphometry and femoral ash content of young vitamin D-replete baboons fed these diets for >16 mo. The phosphorus content of three of the experimental diets was adequate and constant, whereas the calcium content was high, medium or low. The fourth dietary group was fed a diet that was low (inadequate) for both calcium and phosphorus. After 8 mo, baboons fed the low calcium, normal phosphorus diet were hyperphosphatemic and hypocalcemic, whereas those fed the diet low in both minerals showed no changes in serum mineral levels at 8 mo. Both low calcium groups showed histologic evidence of osteomalacia at 8 mo, hyperosteoidosis, but no differences in osteoclast number or osteoclast resorptive surface. After 16 mo, the baboons fed the low calcium, normal phosphorus diet showed histologic evidence of 2^0HPT (increased osteoclast number and resorptive surface), whereas those fed the low calcium, low phosphorus diet showed only histologic features of osteomalacia (**Table 3**). The mean femoral ash content was lower in baboons fed the low calcium, normal phosphorus diet (Table 3); however, this difference was not statistically significant.

Pettifor et al. (1984) make an interesting comparison between their findings in young baboons and South African children with calcium-deficient rickets. The

TABLE 2

Results of studies of excess dietary phosphorus in dogs

Study	% Dietary P % Dietary Ca	Physiologic response
Saville and Krook 1969	1.2% P 0.12% Ca 12 mo	↓ ash content: vertebra, femur, humerus
Krook et al. 1971	1.2% P 0.12% Ca 42 wk	↓ ash content: vertebra (31%) humerus (11%) femur (14%) of control
Laflamme and Jowsey 1972	0.3, .9, 1% P 0.3% Ca 360 d	Evidence of HPT ↑ bone resorption ↓ bone mass ↑ soft tissue Ca
Harris et al. 1976	~1.2% P ~0.6% Ca 12 wk	↑ cortical bone ↑ accretion (^{47}Ca) ↑ renal Ca
Cook et al. 1983	1.2% P 0.12% Ca 10–20 wk	↑ iPTH 10, 20 wk ↓ cancellous bone of femoral head

P = phosphorus; Ca = calcium; HPT = hyperparathyroidism; iPTH = parathyroid hormone.

TABLE 3

16-mo iliac crest histomorphometry and femur composition[1]

	High Ca	Medium Ca	Low Ca	Low Ca/low P
n	7	7	7	7
Ca:P (wt:wt)	1.29	0.45	0.13	0.44
Growth plate thickness, *mm*	0.276 ± 0.3	0.357 ± 0.035	0.410 ± 0.044	0.333 ± 0.033*
Osteoid volume, *% relative bone*	11.2 ± 2.1	14.6 ± 2.9	14.5 ± 2.9	15.9 ± 4.9
Osteoblastic surface, *% total bone*	20.6 ± 7.3	26.3 ± 5.2	26.3 ± 5.4	22.4 ± 7.8
Osteoclast, *number/mm²*	4.6 ± 1.5	6.8 ± 2.1	8.3 ± 1.6	4.4 ± 1.7*
Femur ash, *g/100 g dry fat free bone*	56.3 ± 1.9	57.3 ± 1.4	55.1 ± 1.0	56.2 ± 1.5

[1] Values are means ± SD.
* Significant effect of reducing dietary P content ($P \leq 0.001$). Source: Pettifor et al. (1984) Calcif. Tissue Int. 36: 668.

early hyperosteoidosis at 8 mo and later 2°HPT at 16 mo are similar to the histologic changes observed in children with calcium deficiency rickets who first develop osteomalacia and later histologic evidence of 2°HPT. The usual diet of these children is inadequate in calcium but contains adequate concentrations of phosphorus and vitamin D (Marie et al. 1982).

The second study demonstrating 2°HPT induced by excess phosphorus fed moderately low but adequate calcium (0.5%), high phosphorus (1.4%) diets to 6-mo-old female beagles (Calvo et al. 1987). The minimum daily calcium requirement for adult dogs is 119 mg/kg body weight (National Academy of Sciences 1985). This translates to ~1.25 g Ca/d (equivalent to 31 mmol) in 6-mo-old beagles, which was the concentration fed in the high phosphorus group. The Ca:P ratio of the test diet was ~1:3 (0.33), a concentration close to the Ca:P ratio (0.37 for persons 1 y of age or older) in the diets of ~5% of the U.S. population. Three groups of dogs were fed special diets for 14 mo. The control group was fed a 1% Ca, 0.8% P diet, which are considered standard concentrations for dog rations (National Academy of Sciences 1985). The experimental group was fed the high phosphorus, lower calcium or test diet, and a third group was fed the test diet for 7 mo and then switched to a calcium-fortified control diet (1.2% Ca, 0.8% P). The third group was designed to determine the reversibility of any harmful effects of the high phosphorus, lower calcium diet.

Pre- and postprandial concentrations of iPTH increased progressively with time in dogs fed the high phosphorus, lower calcium diet compared with the control group. Parathyroid hormone concentrations were significantly suppressed when the dogs were switched to the calcium-fortified, normal phosphorus diet. Histomorphometric analyses of transiliac crest biopsies taken at 14 mo were consistent with the findings of Pettifor et al. (1984) for those dogs fed the high phosphorus, moderately low calcium diet (Calvo, M.S., unpublished data). These dogs showed increased percent osteoid and osteoid volume and greater number of osteoclasts and percent resorbing surfaces, although because of the small subject number ($n = 5$), the latter two measures were not statistically significant. However, the mean vertebral ash content of dogs fed the high phosphorus, lower calcium was significantly lower (2.5%), whereas no differences were observed between the control and calcium-fortified groups. This study demonstrates that even a modest dietary phosphorus excess with low but adequate calcium intake can result in nutritional hyperparathyroidism and lower bone mass.

Effects of high phosphorus intakes in humans

There is good evidence that phosphorus loading in humans operates through the same mechanism of nutritional or secondary hyperparathyroidism observed in animals fed excess phosphorus. Oral loads of phosphate salts administered to adults (Reiss et al. 1970) but not young adults (Calvo and Heath 1988) have been shown to depress plasma calcium and stimulate iPTH release. Reiss et al. (1970) reported a 60–125% increase in iPTH within 60 min of an oral phosphate load. Parathyroid hormone concentrations did not increase proportionately to graded oral phosphorus dosing in postmenopausal women (Brixen et al. 1992). In this study, parathyroid hormone response to repeated challenge with 1500 mg P (48 mmol) was similar in magnitude to the response to 2250 mg P (72 mmol).

Clinical studies employing chronic phosphorus supplementation were the first to show that high concentrations of phosphorus intake influence the parathyroid-vitamin D axis. Goldsmith et al. (1976) used oral phosphate therapy in postmenopausal women with osteoporosis, because in vitro studies had shown that addition of phosphorus to bone tissue cultures inhibited PTH-induced bone resorption (Raisz and Nieman 1969) and stimulated collagen synthesis (Flanagan et al. 1970). Postmenopausal women were given 1 g P (32 mmol) daily in divided doses at each meal for ≥12 mo in all but two subjects. Total daily phosphorus intake ranged from 54 to 86 mmol and calcium intake ranged from 20 to 37 mmol. Neither fasting serum concentrations of calcium nor iPTH concentrations

changed significantly during phosphorus supplementation, but serum phosphorus concentrations decreased significantly. The mean decrease in serum phosphorus at 3–4 mo was 0.3 mg/100 ml (0.096 mmol/l) and was negatively correlated with total phosphorus intake. Transiliac crest biopsies taken periodically over the duration of therapy revealed that bone-forming surfaces initially decreased in all seven patients and resorbing surfaces increased in six patients. Total phosphorus intake was positively correlated with bone-resorbing surface. No changes were observed in the density of the distal radius, although the density of the predominantly cortical bone in the midradius increased slightly in each patient.

Studies employing oral phosphate therapy were the first to demonstrate a negative association between high phosphorus intake and plasma calcitriol concentrations [the active metabolite of vitamin D or 1,25 $(OH)_2$ vitamin D]. Treatment of patients with idiopathic hypercalciuria with 2 g P/d (64 mmol) decreased urinary calcium as anticipated, slightly elevated plasma iPTH concentrations and surprisingly reduced plasma calcitriol concentrations (Van den Berg et al. 1980). In a similar vein, 1 y of oral phosphate therapy (48 mmol P/d) in patients with hyperparathyroidism significantly reduced circulating calcitriol concentrations and increased plasma iPTH (Broadus et al. 1983). Significant reductions in calcitriol concentrations in the face of elevated iPTH concentrations during long-term oral phosphate therapy were surprising findings because parathyroid hormone is generally considered the most important regulator of calcitriol synthesis.

A series of recent investigations by Portale and coworkers demonstrated that PTH regulation of calcitriol can be modified by serum phosphorus concentrations. High concentrations of dietary phosphorus (100 mmol P/d, equivalent to 3000 mg P/d, for 10 d) reduced serum calcitriol concentrations by 30% in normal men relative to concentrations observed during their usual dietary intake of 48 mmol P (1150 mg P/d) and 21.2 mmol Ca/d (850 mg Ca/d) (Portale et al. 1986). When they reduced phosphorus intake from 74 mmol P/d (2300 mg P/d) to 20 mmol/d (625 mg/d), maintaining calcium intake constant, serum calcitriol concentrations increased 58% (Portale et al. 1989). After decreasing phosphorus intake, the afternoon iPTH peak decreased by 35%, the morning serum concentration decreased 12%, but there was no change in the morning fasting concentration of phosphorus (Portale et al. 1989). However, these investigators did not observe any change in iPTH concentrations during the phosphorus supplementation. Portale et al. (1984, 1986, 1987 and 1989), therefore, concluded that dietary phosphorus finely regulates the renal production and plasma concentration of calcitriol. Dawson-Hughes et al. (1991) adds further evidence to support this conclusion with their findings from a recent study examining the association between serum ionized calcium, iPTH, phosphorus and calcitriol concentrations in a cross-sectional study of 275 healthy postmenopausal women. The relationship between iPTH and calcitriol was attenuated at high normal concentrations of phosphorus. They found that iPTH was most strongly associated with calcitriol concentrations at midnormal rather than low or high normal concentrations of phosphorus.

Failure to demonstrate elevations in iPTH in any of the phosphorus-supplemented studies conducted by Portale (1984, 1986, 1987 and 1989) or Goldsmith et al. (1976) may be attributed to the fact that these investigators measured serum iPTH only at a single time point, morning fasting sample, during phosphorus supplementation; they did not measure iPTH concentrations at several time points throughout the day. Serum iPTH follows a biphasic circadian rhythm that closely parallels that of serum phosphorus with peaks in the afternoon and late evening (Calvo et al. 1991). Changing dietary phosphorus within the normal range does not alter the general biphasic pattern of serum phosphorus, although it does alter the height of the first (afternoon) peak. An example of diet-induced changes in the circadian peak heights of phosphorus are described above (Portale et al. 1989).

Despite significant reductions in total calcium concentrations, no change in circulating concentrations of iPTH was observed after the evening meal in subjects who had been consuming adequate calcium diets that were high in phosphorus due to the use of foods containing phosphate additives (Bell et al. 1977). In this study the subjects served as their own controls and first consumed a basal diet that contained no phosphate additives for 4 wk followed by a 4-wk intake of foods containing phosphate additives that were substituted for similar items in the basal diet. More than a decade later, we used this same dietary design but examined serial blood samples and employed more sensitive assays to determine if a high phosphorus, low calcium diet from the consumption of ordinary foods could provoke hormonal changes similar to those observed in animals fed high phosphorus diets (Calvo et al. 1990). Fifteen young adult women consumed a basal diet (29 mmol P/d and 20 mmol Ca/d, equivalent to 900 mg P/d and 800 mg Ca/d) for an initial 4 wk and then 10 subjects were switched to the high phosphorus, low calcium diet (58 mmol P/d and 10 mmol Ca/d, equivalent to 1700 mg P/d and 400 mg Ca/d), while the remaining five subjects continued to consume the basal diet.

Hormonal and mineral responses measured over an entire day at the end of each 4-wk dietary period were compared within individuals only. Serum iPTH concentrations increased significantly and serum ionized calcium concentrations decreased over the day after consuming the high phosphorus, low calcium diet, whereas no changes were observed in women consuming the basal diet for the entire 8-wk study. Serum phosphorus concentrations did not change as dramatically as in an earlier short-term (8-d) pilot study (Calvo

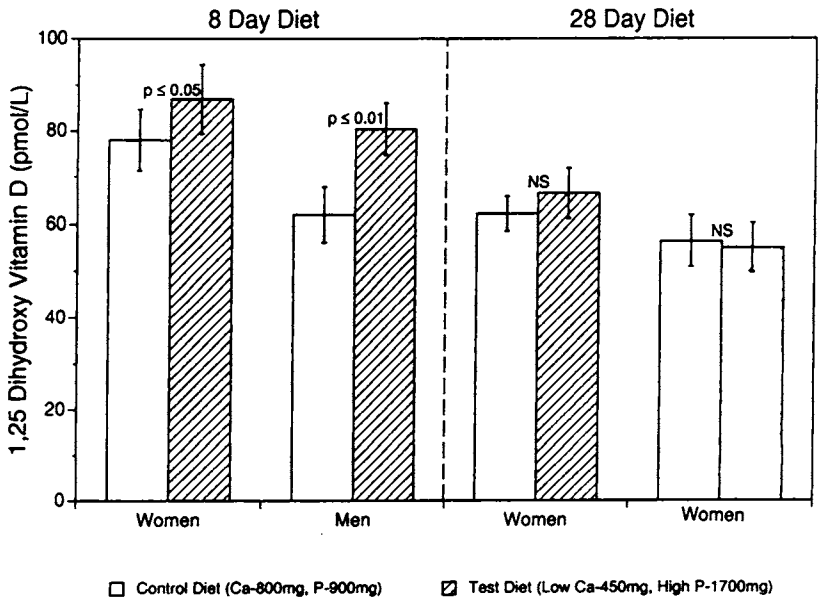

FIGURE 7 Calcitriol response in humans after short-term and long-term high phosphorus, low calcium consumption. Figure was drawn from data presented by Calvo et al. 1988 and 1990.

et al. 1988), suggesting that adaptation to high phosphorus intake occurs with prolonged intake. Indices of parathyroid hormone action in the kidney and bone were also elevated with high phosphorus, low calcium intake. However, in contrast to our earlier 8-d study, plasma calcitriol concentrations did not change in either group. As shown in **Figure 7**, there was only a modest 6% increase in plasma calcitriol concentrations with chronic high phosphorus, low calcium intake. An important adaptive response to low calcium intake that occurred in a short-term study was attenuated with longer intake. We proposed that a prolonged high phosphorus intake impaired the usual homeostatic mechanisms involved in adaptation to low calcium intake.

Women, particularly postmenopausal women, may be more sensitive than men to the modulating effects of phosphorus on serum calcitriol concentrations. We observed a greater stimulation of calcitriol concentrations in young men compared with young women after an 8-d high phosphorus, low calcium intake (Fig. 7), despite a smaller increase in iPTH in men (11% in men vs. 22% in women) (Calvo et al. 1988). Sherman et al. (1990) and others (Endres et al. 1987, Ferero et al. 1987) showed marked male-female differences in serum phosphorus across the adult age span. They observed that serum phosphorus, total and ionized calcium remain constant with age in women, but men experience a 25% fall in serum phosphorus and a 4% decline in total and ionized calcium with age (Sherman et al. 1990). The lack of age-related decline in phosphorus in women could not be explained by gender differences in vitamin D metabolites (calcidiol and calcitriol), iPTH or renal function. More recently, Prince et al. (1995) showed that plasma phosphorus concentrations did not change in women across the menopause but were significantly higher in women >10 y past menopause as were serum parathyroid hormone concentrations.

Osteoporotic women have an abnormal response to phosphorus loading relative to their age-matched normals. Acute phosphorus loading (5-d) reduced circulating concentrations of calcitriol by 50% in osteoporotic women with no changes observed in normal aged-matched controls despite an observed 250% increase in iPTH (Silverberg et al. 1989). In contrast to the significant reduction in circulating calcitriol with phosphate loading in women with osteoporosis, calcitriol concentrations in normal postmenopausal women were significantly elevated when serum phosphorus concentration was reduced (Villa et al. 1991). Villa et al. (1991) postulated that estrogen increases circulating calcitriol concentrations through a reduction in plasma phosphorus based on observations made in earlier studies (Cheema et al. 1989, Packer et al. 1990). Plasma phosphorus concentrations were lowered by feeding a phosphorus-binding antacid, aluminum hydroxide, which effectively restricted absorption of dietary phosphorus and raised plasma calcitriol without altering the concentrations of other regulators of calcitriol production (ionized calcium, total calcium and iPTH). This work provides important insight as to how phosphorus consumption may influence calcium homeostasis in postmenopausal women.

Although no clinical studies have linked high phosphorus consumption, with or without adequate calcium intake to lower bone mass or higher rates of bone loss in humans, this relationship has been demonstrated in animal models at concentrations of phosphorus and calcium consumption comparable with current human intake. The scientific evidence presented in this review clearly shows that high phosphorus, moder-

ately low calcium intake produces hormonal changes of mild secondary hyperparathyroidism in humans and with prolonged intake lower calcitriol concentrations, the body's main homeostatic mechanism for adaptation to low dietary calcium. Because of the adverse changes in parathyroid hormone and vitamin D metabolites observed in animals and humans and the resulting adverse changes observed in bone status in animals, further studies are warranted to determine the skeletal effects of high phosphorus, low calcium intakes in humans.

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