Dietary protein, calcium metabolism, and skeletal homeostasis revisited

Jane E Kerstetter, Kimberly O’Brian, and Karl L Insogna

ABSTRACT High dietary protein intakes are known to increase urinary calcium excretion and, if maintained, will result in sustained hypercalciuria. To date, the majority of calcium balance studies in humans have not detected an effect of dietary protein on intestinal calcium absorption or serum parathyroid hormone. Therefore, it is commonly concluded that the source of the excess urinary calcium is increased bone resorption. Recent studies from our laboratory indicate that alterations in dietary protein can, in fact, profoundly affect intestinal calcium absorption. In short-term dietary trials in healthy adults, we fixed calcium intake at 20 mmol/d while dietary protein was increased from 0.7 to 2.1 g/kg. Increasing dietary protein induced hypercalciuria in 20 women [from 3.4 ± 0.3 (±SE) during the low-protein to 5.4 ± 0.4 mmol/d during the high-protein diet]. The increased dietary protein was accompanied by a significant increase in intestinal calcium absorption from 18.4 ± 1.3% to 26.3 ± 1.5% (as determined by dual stable isotopic methodology). Dietary protein intakes at and below 0.8 g/kg were associated with a probable reduction in intestinal calcium absorption sufficient to cause secondary hyperparathyroidism. The long-term consequences of these low-protein diet–induced changes in mineral metabolism are not known, but the diet could be detrimental to skeletal health. Of concern are several recent epidemiologic studies that demonstrate reduced bone density and increased rates of bone loss in individuals habitually consuming low-protein diets. Studies are needed to determine whether low protein intakes directly affect rates of bone resorption, bone formation, or both. Am J Clin Nutr 2003;78(suppl):584S–92S.

KEY WORDS Dietary protein, urinary calcium, parathyroid hormone, vitamin D, hypercalciuria, bone, soy

INTRODUCTION

Almost 30 million Americans are affected by osteoporosis, and women are 4 times more likely to suffer from this disease than men (1). The health problem is reaching near-epidemic proportions in the United States and worldwide. Nutrition plays an important role in both the prevention and the pathogenesis of many chronic diseases, including osteoporosis. Numerous studies have established that dietary calcium and vitamin D are critical nutrients for both accrue and maintaining skeletal mass. In contrast, our understanding of how other dietary components, such as protein, affect calcium homeostasis and skeletal metabolism is limited.

This review summarizes data from the US Department of Agriculture’s 1994–1996 Continuing Survey of Food Intakes by Individuals (CSFII) on the range of dietary protein and calcium intakes by adults in the United States. Earlier studies that focused on the role of a high-protein diet in causing hypercalciuria, a negative calcium balance, increased bone resorption, and increased fracture risk are reviewed. Finally, evidence that a low-protein diet impairs calcium absorption and could negatively impact skeletal balance is summarized.

DIETARY PROTEIN AND CALCIUM INTAKES IN THE UNITED STATES

The mean protein intake for adult men and women in the United States and the percentage of individuals consuming each level of protein is summarized in Table 1 (2). For this review, we have identified low-, medium-, high-, and very-high-protein diets in comparison to the recommended dietary allowance (RDA); these are defined in Table 1. Diets with the highest protein levels are observed in men, and protein intake tends to decline with age. Particularly noteworthy is that 15–38% of adult men and 27–41% of adult women have dietary protein intakes below the RDA.

There are limited data on protein intakes of US vegetarians, especially vegans. Studies in adult lactoovegetarians have generally reported mean protein intakes that are close to or slightly below the RDA (3). Protein intakes of adult vegetarians in the United States have rarely been reported to be more than 150% of the RDA (4–6).

The frequency of an inadequate dietary calcium intake is much higher than that for protein (Table 2). According to CSFII data, more than 70% of adult men and women in the United States have low dietary calcium intakes (2). For purposes of this review, we have identified very-low-, low-, medium-, and high-calcium diets in comparison to the 1989 RDA (defined in Table 2). These data were collected in the mid-1990s (when the RDA for calcium in adults was 800 mg) and before the most recent RDAs were established (1000–1200 mg for adults). It is important to note that these...
TABLE 1
Percentage of individuals with diets within the given ranges of protein intake in the United States.

<table>
<thead>
<tr>
<th>Sex and age</th>
<th>Mean protein intake</th>
<th>Low-protein diets</th>
<th>Medium-protein diets</th>
<th>High-protein diets</th>
<th>Very-high-protein diets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g</td>
<td>% (&lt;100% RDA)</td>
<td>% (100–150% RDA)</td>
<td>% (150–200% RDA)</td>
<td>% (≥200% RDA)</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–29 y</td>
<td>104</td>
<td>15.3</td>
<td>31.2</td>
<td>28.3</td>
<td>25.2</td>
</tr>
<tr>
<td>30–39 y</td>
<td>103</td>
<td>15.8</td>
<td>30.1</td>
<td>30.2</td>
<td>23.9</td>
</tr>
<tr>
<td>40–49 y</td>
<td>95</td>
<td>17.2</td>
<td>39.5</td>
<td>25.0</td>
<td>18.3</td>
</tr>
<tr>
<td>50–59 y</td>
<td>90</td>
<td>21.8</td>
<td>38.2</td>
<td>25.3</td>
<td>14.7</td>
</tr>
<tr>
<td>60–69 y</td>
<td>84</td>
<td>24.1</td>
<td>46.4</td>
<td>22.1</td>
<td>7.4</td>
</tr>
<tr>
<td>&gt;70 y</td>
<td>73</td>
<td>37.7</td>
<td>46.0</td>
<td>13.8</td>
<td>2.5</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–29 y</td>
<td>66</td>
<td>27.2</td>
<td>44.8</td>
<td>18.1</td>
<td>9.9</td>
</tr>
<tr>
<td>30–39 y</td>
<td>65</td>
<td>29.4</td>
<td>44.3</td>
<td>17.7</td>
<td>8.6</td>
</tr>
<tr>
<td>40–49 y</td>
<td>64</td>
<td>29.0</td>
<td>45.8</td>
<td>18.8</td>
<td>6.4</td>
</tr>
<tr>
<td>50–59 y</td>
<td>64</td>
<td>29.9</td>
<td>45.8</td>
<td>19.2</td>
<td>5.1</td>
</tr>
<tr>
<td>60–69 y</td>
<td>60</td>
<td>31.8</td>
<td>46.9</td>
<td>17.5</td>
<td>3.8</td>
</tr>
<tr>
<td>&gt;70 y</td>
<td>57</td>
<td>41.1</td>
<td>41.6</td>
<td>13.5</td>
<td>3.8</td>
</tr>
</tbody>
</table>

1 Adapted from reference 2.

CSFII data do not contain the calcium obtained from nutritional supplements or from foods fortified with calcium. Therefore, they will naturally underestimate total calcium intake. On the other hand, if considered in light of the recent higher RDAs, then the data in Table 2 underestimate the prevalence of dietary calcium “deficiency” in the United States. Thus, when considering the impact of dietary protein on calcium metabolism, the relatively poor calcium intake of most Americans should be kept in mind.

DIETARY PROTEIN CALCIUM HOMEOSTASIS AND SKELETAL METABOLISM: A HISTORICAL OVERVIEW

Dietary protein and urinary calcium

There is no question that increasing dietary protein increases urinary calcium. We have reviewed data from over 20 clinical intervention trials in adult humans where the diet was controlled, dietary protein was manipulated, and urinary calcium was measured (7). Despite varied experimental designs, sources of protein, and study periods ranging from 4 to 60 d, almost all studies have reported a positive relationship between protein intake and urinary calcium. On average, for every 50 g increase in dietary protein, there is approximately a 1.6 mmol increase in 24-h urinary calcium excretion (7). Indeed, some investigators have concluded that dietary protein is a more important regulator of urinary calcium than dietary calcium intake (8, 9).

Dietary protein and intestinal calcium absorption

More than 80 years ago, Sherman (10) first observed that feeding an all-meat diet to humans increased urinary calcium, a finding later confirmed by McCance et al (11). McCance et al (11) also found that when 5 adult subjects consumed a diet low in protein (45–70 g/d), their intestinal calcium absorption was < 20% lower than when they consumed a high-protein diet (145–170 g/d).

TABLE 2
Percentage of individuals with diets within the given ranges of calcium intake in the United States.

<table>
<thead>
<tr>
<th>Sex and age</th>
<th>Mean calcium intake</th>
<th>Very-low-calcium diets</th>
<th>Low-calcium diets</th>
<th>Medium-calcium diets</th>
<th>High-calcium diets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg</td>
<td>% (&lt;50% RDA)</td>
<td>% (50–100% RDA)</td>
<td>% (100–150% RDA)</td>
<td>% (≥150% RDA)</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–29 y</td>
<td>990</td>
<td>20.0</td>
<td>40.7</td>
<td>24.6</td>
<td>14.7</td>
</tr>
<tr>
<td>30–39 y</td>
<td>951</td>
<td>9.1</td>
<td>39.0</td>
<td>27.0</td>
<td>24.9</td>
</tr>
<tr>
<td>40–49 y</td>
<td>876</td>
<td>11.9</td>
<td>39.3</td>
<td>29.4</td>
<td>19.4</td>
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<tr>
<td>50–59 y</td>
<td>791</td>
<td>14.5</td>
<td>46.3</td>
<td>25.9</td>
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<tr>
<td>60–69 y</td>
<td>796</td>
<td>13.4</td>
<td>43.5</td>
<td>30.1</td>
<td>13.0</td>
</tr>
<tr>
<td>&gt;70 y</td>
<td>746</td>
<td>15.7</td>
<td>45.5</td>
<td>26.2</td>
<td>12.6</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–29 y</td>
<td>701</td>
<td>34.4</td>
<td>48.7</td>
<td>13.6</td>
<td>3.3</td>
</tr>
<tr>
<td>30–39 y</td>
<td>661</td>
<td>24.0</td>
<td>50.7</td>
<td>19.0</td>
<td>6.3</td>
</tr>
<tr>
<td>40–49 y</td>
<td>634</td>
<td>29.1</td>
<td>47.0</td>
<td>18.9</td>
<td>5.0</td>
</tr>
<tr>
<td>50–59 y</td>
<td>630</td>
<td>26.2</td>
<td>50.5</td>
<td>18.5</td>
<td>4.8</td>
</tr>
<tr>
<td>60–69 y</td>
<td>604</td>
<td>30.4</td>
<td>48.9</td>
<td>17.1</td>
<td>3.6</td>
</tr>
<tr>
<td>&gt;70 y</td>
<td>584</td>
<td>29.1</td>
<td>50.1</td>
<td>17.2</td>
<td>3.6</td>
</tr>
</tbody>
</table>

1 Adapted from reference 2.
In 1942, McCance noted: “It is remarkable that the relationship between protein intake and calcium absorption has not been appreciated before. Very little calcium would be absorbed if the diet contained no protein or amino acids” (11).

Six subsequent studies published between 1932 and 1974 documented that high-protein diets resulted in a rise in intestinal calcium absorption and hypercalcuria [cited in (12)]. Because the increase in urinary calcium could largely be explained by the increase in intestinal calcium absorption, there was little concern that high-protein diets would adversely affect skeletal health (12). However, beginning in the mid-1970s, most balance studies in humans (8, 13–20) were unable to demonstrate an effect of dietary protein on intestinal calcium absorption, although there were 3 reports to the contrary (21–23).

Two recent studies have also found no relationship between dietary protein intake and calcium absorption (24, 25). Heaney (24) recently reported to the contrary (21–23). Heaney (24) recently reported that high-protein diets would adversely affect skeletal health (12). However, beginning in the mid-1970s, most balance studies in humans (8, 13–20) were unable to demonstrate an effect of dietary protein on intestinal calcium absorption, although there were 3 reports to the contrary (21–23).

Two recent studies have also found no relationship between dietary protein intake and calcium absorption (24, 25). Heaney (24) recently reported that in 191 Roman Catholic nuns aged 48.7 ± 7.0 y who were studied over more than a 20-y period, there was no relationship between intestinal calcium absorption (as assessed by dual isotopic methods) and dietary protein. The mean protein intake in his study was 62 g (≈ 1 g/kg), and their calcium intake averaged 17.6 mmol/d, comparable to the mean calcium intake observed for adult women in the CSFII database. Likewise, Dawson-Hughes and Harris (25) found that in men and women over the age of 65 y, there was no association between usual protein intake and intestinal calcium absorption. Protein intakes in these subjects averaged ≈ 82 g/d (≈ 1 g/kg), and calcium and vitamin D intakes were controlled. It should be noted that both of these studies were observational and characterized associations between protein intake and intestinal calcium absorption in subjects consuming their typical diets. Both studies were retrospective examinations of previous data from studies designed to answer other questions.

As a consequence, the prevailing view that emerged in the early 1980s and that is widely held is that dietary protein does not significantly alter intestinal calcium absorption, and therefore absorption does not explain protein-induced hypercalcemia (12).

**Dietary protein and bone**

In the 1990s, the investigative focus shifted to bone as the source of the extra urinary calcium excreted during a high-protein diet. As noted, increasing dietary protein from 75 to 125 g/d results in an increase in urinary calcium by an average of 1.6 mmol/d (7). If the additional calcium lost is entirely from bone, it would result in a 1–2% increase in urinary calcium by an average of 1.6 mmol/d (7). If the additional calcium lost is entirely from bone, it would result in a 1–2% increase in urinary calcium by an average of 1.6 mmol/d (7).

One mechanism by which high dietary protein could induce bone loss may be related to the metabolic acid load engendered by such a diet. Meat and fish, which are high in sulfur-containing amino acids, generate appreciable fixed metabolic acid loads, whereas fruits and vegetables generate little acid and, in fact, may under certain circumstances generate more base than acid. While renal metabolism represents the principal mechanism by which fixed metabolic acid loads are handled by the body, renal buffering may be incomplete, particularly with aging. Under those circumstances, the skeleton may be called on to act as a buffer to neutralize acid generated from high-protein diets. Liberation of buffer from bone comes at the expense of mineral dissolution and ultimately bone loss [cited in (26)]. Consistent with this hypothesis is the finding that the magnitude of urinary calcium excretion during a high-protein diet is dependent, to a large extent, on the sulfur amino acid content of the diet (29–31).

In 1986, Hegsted reported in a cross-cultural study that as dietary protein intake increased, so did hip fracture rates (32). Subsequently, Abelow et al found a similar positive correlation between animal protein intake and cross-cultural age-adjusted hip fracture rates (33). Three subsequent epidemiologic studies have reached the same conclusion (34–36). In contrast, Munger et al reported higher fracture rates at low-dietary-protein intakes (37).

**BACK TO THE FUTURE**

Our ability to accurately measure changes in mineral homeostasis has improved considerably in the past 2 decades. We now have better ways to noninvasively assess rates of skeletal formation and resorption, to quantify bone mass, and to measure parathyroid activity. Using these tools, a more complex picture of protein’s effect on calcium metabolism and skeletal homeostasis, particularly during low-dietary-protein conditions, is beginning to emerge.

**Medium-protein diets and calcium homeostasis**

There is uniform agreement that at medium levels of protein intake (roughly 100–150% of the RDA or 1.0–1.5 g protein/kg), measures of calcium and skeletal metabolism are normal (14, 19, 24, 25, 38). About 30–50% of US adults have protein intakes that are considered medium. Using a 4-d experimental model in which nutrients were controlled, we have also documented normal calcium homeostasis when healthy adults consumed a diet containing 1.0 g protein/kg and 20 mmol calcium (38). Measures of the parathyroid hormone-1-α-hydroxylase axis (PTH-1-α-hydroxylase axis) and urinary calcium excretion were within the normal ranges under these moderate conditions.

**Low protein intake: the acute impact**

Because a high-protein diet was felt to be potentially detrimental to bone, it was assumed that a moderately low-protein diet would either have no effect or be beneficial to bone health. In 3 studies conducted over the past 5 y, we (38–40) have examined the impact of moderately low-protein diets on mineral and skeletal metabolism in healthy adults. These data describe a hitherto underappreciated perturbation in calcium homeostasis induced by an acute reduction in dietary protein intake.

In 1997, we reported the short-term effect of 3 levels of dietary protein [low (0.7 g/kg), medium (1.0 g/kg), and high (2.1 g/kg)] on mineral metabolism in 16 healthy women (age 26.7 ± 1.3 y) (38). The study consisted of 3 interventions, each of which included 2 wk of a well-balanced adjustment diet (moderate calcium, sodium, and protein) followed by an experimental period of 4 d (or 14 d in 7 subjects). During the experimental period, all diets contained 40 mmol calcium and 100 mEq sodium. Alcohol was not permitted, and caffeinated beverages were limited to one a day. All foods on the experimental diet were weighed to the 0.1 g in the General Clinical Research Center kitchen, and subjects consumed all of the experimental diet. All subjects consumed all 3 diets in random order.

As expected, the rise in urinary calcium excretion mirrored the rise in dietary protein intake (Table 3). The most surprising finding in the first study was that by day 4 of the low-protein diet, striking elevations in serum PTH and circulating concentrations of 1,25-dihydroxyvitamin D (calcitriol) developed in all subjects (Figure 1). In fact, concentrations of these calcitropic hormones exceeded the upper limits of normal in most cases. Serum PTH was increased 1.5–2.4-fold by day 4 and 1.6–2.7-fold by day 14 over values seen in subjects consuming a moderate (1.0 g/kg) protein intake. The rise in PTH was accompanied by significant increases in both nephrogenous cyclic AMP (NcAMP, a sensitive
### TABLE 3
Urinary calcium excretion in 16 young women as they consumed 4 and 14 d of 3 levels of dietary protein

<table>
<thead>
<tr>
<th>Protein intake</th>
<th>Urinary calcium mmol/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0.7 g/kg)</td>
<td>Baseline 3.35 ± 0.42</td>
</tr>
<tr>
<td></td>
<td>Day 4 2.70 ± 0.35</td>
</tr>
<tr>
<td>Medium (1.0 g/kg)</td>
<td>3.27 ± 0.40</td>
</tr>
<tr>
<td></td>
<td>Day 14 2.56 ± 0.58</td>
</tr>
<tr>
<td>High (2.1 g/kg)</td>
<td>3.22 ± 0.38</td>
</tr>
<tr>
<td></td>
<td>Day 14 4.20 ± 0.89</td>
</tr>
</tbody>
</table>

1 ± SEM. Baseline and day 4, n = 16 subjects; day 14, n = 7. Data from Kerstetter et al (38).

2,3 Significantly different from the medium-protein diet on the same day: 2 P < 0.05, 3 P < 0.0001.

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and specific indicator of PTH bioactivity) and serum calcitriol. Thus, healthy young women abruptly developed secondary hyperparathyroidism (secondary HPT) within 4 d of ingesting a moderately low-protein diet that was otherwise balanced in all other nutrients. The secondary HPT persisted during 2 wk of a low-protein diet and, in preliminary studies, for 4 wk (Kerstetter, unpublished observations, 2002). Secondary hyperparathyroidism is the appropriate rise in circulating concentrations of PTH in response to a hypocalcemic challenge. It results, most often, from a decrease in intestinal calcium absorption, a decrease in calcium efflux from bone, or an increase in renal calcium losses.

The finding that low-protein diets induce secondary HPT was unanticipated. However, subsequently Giannini et al (41) reported observations similar to our own. He studied 18 patients (10 men and 8 women aged 45.6 ± 12.3 y) with idiopathic hypercalciuria and renal calculi as they consumed a diet containing 0.8 g protein/kg and 24 mmol calcium. Urinary calcium excretion fell and serum PTH rose within 15 d of restricting protein intake (41).

What induces the elevation in serum PTH when protein intake is limited? The answer could be a change in intestinal, skeletal, or renal calcium handling. Because dietary calcium was kept constant and adequate (20–24 mmol) in both our study (38) and that of Giannini et al (41), dietary calcium insufficiency seems an unlikely explanation. This leaves open the possibility that intestinal, skeletal, or renal handling of calcium is altered under low-protein conditions.

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**FIGURE 1.** Mean (± SEM) calcitropic hormones in 16 young women consuming low- (○), medium- (□), and high- (△) protein diets. The upper limit of normal is designated by the dashed lines. PTH, parathyroid hormone; NcAMP, nephrogenous cyclic AMP; GF, glomerular filtrate. * *, **, ***Significantly different from the medium-protein diet on the same day: * P < 0.05, ** P < 0.005, *** P < 0.0001. Reprinted with permission from reference 38.
Although calcium balance studies failed to find an effect of dietary protein on intestinal calcium absorption, we were concerned that balance studies are not sufficiently sensitive to detect an effect. Furthermore, given the earlier work of Sherman (10) and McCance et al (11), we decided to revisit the question by employing dual stable calcium isotopes to directly measure intestinal calcium absorption at different levels of dietary protein.

In the absorption studies, we used the same diet protocol used in the first experiment except that we measured intestinal calcium absorption at day 4 using dual stable calcium isotopes. Seven young women completed the study while consuming high- (2.1 g protein/kg) and low-protein (0.7 g protein/kg) diets, and the results were reported (39). Since then, using the same protocol, we have studied 13 additional healthy women (10 young and 3 postmenopausal), so that data for a total of 20 women are summarized in Figure 2. These studies reveal 2 noteworthy findings. First, there is very large natural interindividual variability in both urinary calcium and intestinal calcium absorption. Despite the homogenous population and the well-controlled 2-wk lead-in diet, the variability is quite large. To control for this, we used a paired study design in which each subject serves as her own control. Every subject ingested both the low- and high-protein diets in random order, and change within a single subject was measured. Calcium absorption during the low-protein diet averaged 18.4 ± 1.3%, significantly lower than during the high-protein diet: 26.3 ± 1.5% ($P = 0.00003$, paired $t$ test). These data provide direct evidence that impaired intestinal calcium absorption explains, in part, the secondary HPT and hypocalciuria observed when dietary protein is restricted (39).

In these studies, a protein intake of 0.7 g/kg led to impaired intestinal calcium absorption and secondary HPT, while subjects consuming 1.0 g/kg demonstrated little change in calcium homeostasis. Because the range of dietary protein between 0.7 and 1.0 g/kg encompasses the RDA for this nutrient (0.8 g/kg), we next undertook a dose-response study to examine the effect of graded levels of dietary protein (0.7, 0.8, 0.9, and 1.0 g protein/kg) on calcium homeostasis (40). Following our standard 4-d experimental model, all 4 diets were administered randomly to 8 healthy young women; the principal findings are summarized in Table 4.

Baseline urinary calcium and calcitropic hormones were within normal limits and identical between all interventions (not shown). Serum PTH rose by day 4 in all subjects consuming the 0.7 and 0.8 g protein/kg diets, while during the 0.9 and 1.0 g protein/kg diets, concentrations of calcitropic hormones remained normal. A parallel response was seen in calcitriol and NcAMP. The secondary HPT observed during 0.8 g/kg diets is likely due to impaired intestinal calcium absorption, judging from the findings at the 0.7 g/kg level of protein intake (39).

The dose-dependent effect of dietary protein on the PTH-1-a-hydroxylase axis is important for 2 reasons (40). First, it demonstrates that the response to a progressive reduction in dietary protein intake is not a graded phenomenon but rather a threshold effect, with the abrupt appearance of disordered mineral homeostasis observed at levels of protein intake below 0.9 g/kg. Second, it suggests that in healthy young women consuming a well-balanced, calcium-sufficient diet (20 mmol), the current RDA for protein (0.8 g/kg) results, in at least the short term, in altered calcium homeostasis.

It is important to recall that the current daily reference intake (DRI) for calcium for adult women is 25 mmol (1000 mg) (42), a level slightly higher than the 20 mmol (800 mg) used in our experiments. However, the average calcium intake for adult women is in the 15–18 mmol range (600–720 mg) (43), slightly less than the 20 mmol used in the experiments. It would be important to know whether the current higher DRI for calcium would ameliorate the secondary HPT induced by the low-protein diet. Likewise, we do not know whether the secondary HPT is exacerbated when calcium intake is lower than 20 mmol, which would be the case for almost 80% of adult women in the United States (2).

Low protein intake: the chronic impact

Do the acute changes in calcium metabolism induced by a low-protein diet have a long-term impact on bone health? The answer,
at present, is not known. There are no well-controlled intervention studies conducted over a sufficient length of time to answer the question. As we have observed, acute restriction in dietary protein lowers calcium absorption, resulting in a compensatory rise in serum PTH. If these changes persisted, then a new steady state for calcium metabolism would be established. The persistent elevation in PTH would lead to an increase in circulating concentrations of calcitriol that would eventually increase intestinal calcium absorption. This would tend to ameliorate the secondary HPT but could not completely correct it. In the new steady state, subtle elevations in serum PTH and calcitriol would persist, although absolute values might remain within normal limits. Such subtle changes in calcium metabolism would be difficult to detect without rigorously controlled experimental conditions. Although difficult to undertake, long-term carefully controlled intervention studies need to be designed to test this hypothesis.

Epidemiologic studies, taken as a whole, do not satisfactorily describe the chronic impact of low-protein diets. When bone mineral density (BMD) is the primary outcome, most (44–53) but not all (54–58) epidemiologic studies show a positive relationship between protein intake and BMD. Stated another way, most of the epidemiologic evidence shows that when other known dietary factors are controlled, individuals who consume low-protein diets have lower BMD. Using the NHANCES III database, we found that in 1882 non-Hispanic white women 50-y-old and older, after adjusting for age and body weight, a low protein intake was associated with a significantly lower hip BMD (53). Similarly, Hannan et al (52) studied 615 participants in the Framingham Osteoporosis Study over a 4-y period and found that lower levels of protein intake were associated with significantly higher rates of bone loss at the hip and spine. Persons in the lowest quartile of protein intake showed the greatest rates of bone loss. These findings are consistent with earlier work of Freudenheim et al, who reported that a low protein intake (animal or vegetable) and BMD. Almost all of them report findings addressing the relationship between source of protein intake (animal or vegetable) and BMD. Final results of these studies need to be designed to test this hypothesis.

High protein intakes

The data summarized in Figure 2 force a reconsideration of the hypothesis that the high-protein diet-induced increase in urinary calcium is of skeletal origin. In the data from 20 women summarized in Figure 2, the increase in intestinal calcium absorption (from 18.4% to 26.3%) accounts for the majority of the observed increase in 24-h urinary calcium excretion (from 3.4 to 5.4 mmol/d). Given that the diet contained 20 mmol of calcium, the 8% absolute change in intestinal calcium absorption accounts for 1.6 mmol of the 2.0 mmol increment in urinary calcium excretion. Thus, 80% of the urinary calcium increment is due to augmented intestinal calcium absorption. This, of course, leaves unexplained 20% of the increment that might have a skeletal origin, a possibility currently under investigation.

ANIMAL VERSUS PLANT-BASED PROTEINS

It is relatively well established that dietary animal protein induces a greater increase in urinary calcium excretion than does vegetable protein, perhaps, in part, because of the higher sulfur amino acid content of the former diet. One might therefore hypothesize that animal protein–based diets might affect skeletal homeostasis to a greater extent than vegetable-based diets.

A review of available epidemiologic literature where BMD is the outcome does not clearly support the notion that vegetable-based proteins are healthier for the skeleton. There are at least 15 reports addressing the relationship between source of protein intake (animal or vegetable) and BMD. Almost all of them report no differences in BMD between vegetarians and nonvegetarians (4, 60–64). A few studies report less bone loss after age 50 y in lactoovovegetarians (65, 66) in comparison to omnivores. On the other hand, in a community-based study of 76 Buddhist vegetarian
women (aged 70–89 y), BMD at the hip was lower in these women in comparison to omnivorous control subjects (50), which could mean that vegetarians have a higher fracture risk (49).

An epidemiologic approach is limited by the heterogeneity in vegetarian and omnivorous groups and the differences in health and lifestyle factors that are not easily quantified or controlled. For example, Inuits (67, 68), who consume very high amounts of animal protein (< 200 g/d) and a very-low-calcium diet, lose bone faster over the age of 50 y than do whites living in the mainland United States. However, it is difficult to separate the effect of high dietary protein from that of low dietary calcium or vitamin D status in these studies.

Ball and Maughan (69) conducted a direct comparison of the acid-base status of a small group of premenopausal omnivorous women to that of vegetarian women, with both groups consuming their typical diets. The vegetarian women naturally consumed less protein, excreted less urinary calcium, and excreted less urinary titratable acid (69). Furthermore, intervention studies by Sebastian et al (70) support the notion that the acid-generating potential of a diet is related to bone health. They found that potassium bicarbonate supplementation for 18 d led to a reduction in urinary hydroxyproline excretion (a marker of bone resorption) in 18 postmenopausal women, suggesting that neutralization of dietary fixed acid may improve bone balance.

When hip fracture is the primary outcome variable, the epidemiologic data consistently suggest that hip fractures rates are positively associated with animal protein intake (33–35). Frassetto et al (36) showed that the incidence of hip fractures in elderly women was positively associated with animal protein intake and negatively associated with vegetable protein intake. Based on the consistency of the fracture data, one would predict that animal protein would be negatively associated with BMD and vegetable protein would be positively associated with BMD. But, as is the case with studies examining total dietary protein, BMD studies and fracture studies are discordant vis à vis source of protein. Most recently, Promislow et al (51) showed in the Rancho Bernardo study population that animal protein intake is positively associated with BMD while vegetable protein is negatively associated with BMD.

**SUMMARY AND CONCLUSIONS**

There is agreement that diets moderate in protein (in the approximate range of 1.0–1.5 g protein/kg) are associated with normal calcium metabolism and presumably do not alter skeletal homeostasis. Less than 30–50% of US adults consume dietary protein that could be considered moderate. At low protein intakes, intestinal calcium absorption is reduced, resulting in increases in serum PTH and calcitriol that persist, at least for 2 wk. The long-term implications of these findings are unknown, but recent epidemiologic data suggest increased rates of bone loss in individuals consuming such diets. Individuals consuming high protein intakes, particularly from omnivorous sources, develop sustained hypercalciuria that is due for the most part to an increase in intestinal calcium absorption. Whether an increase in bone resorption contributes to the hypercalciuria and in the long term results in higher fracture rates remains uncertain.

Bone is complex tissue that changes slowly. As such, it is difficult to design and conduct well-controlled nutrition studies in humans to quantify the effect of one nutrient on bone. However, given the increasing prevalence of osteoporosis and the clear impact dietary protein has on calcium metabolism, it is imperative that we gain a better understanding of the complex interplay between dietary protein and skeletal health. Toward that end, longer-term physiologic studies and eventually dietary intervention studies will be required to provide better-informed dietary protein guidelines for optimal skeletal health.

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**REFERENCES**


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