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Dietary protein and skeletal health: a review of recent human research

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Abstract

Purpose of review—Both dietary calcium and vitamin D are undoubtedly beneficial to skeletal health. In contrast, despite intense investigation, the impact of dietary protein on calcium metabolism and bone balance remains controversial. A widely held view is that high intakes of animal protein result in increased bone resorption, reduced bone mineral density, and increased fractures because of its ability to generate a high fixed metabolic acid load. The purpose of this review is to present the recent or most important epidemiological and clinical trials in humans that evaluated dietary protein's impact on skeletal health.

Recent findings—Many epidemiological studies have found a significant positive relationship between protein intake and bone mass or density. Similarly, isotopic studies in humans have also demonstrated greater calcium retention and absorption by individuals consuming high-protein diets, particularly when the calcium content of the diet was limiting. High-protein intake may positively impact bone health by several mechanisms, including calcium absorption, stimulation of the secretion of insulin-like growth factor-1, and enhancement of lean body mass. The concept that an increase in dietary protein induces a large enough shift in systemic pH to increase osteoclastic bone resorption seems untenable.

Summary—Recent epidemiological, isotopic and meta-analysis studies suggest that dietary protein works synergistically with calcium to improve calcium retention and bone metabolism. The recommendation to intentionally restrict dietary protein to improve bone health is unwarranted, and potentially even dangerous to those individuals who consume inadequate protein.

Keywords

bone; dietary protein; osteoporosis

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Introduction

An estimated 75 million people in the USA, Europe and Japan are affected by osteoporosis. One in three women and one in five men over the age of 50 years will suffer from some type of osteoporotic-related fracture [1]. The etiology of osteoporosis is multifactorial; alterations in nutrition and physical activity are important in preventing osteoporosis. Calcium and vitamin D are fundamental to the acquisition and maintenance of bone throughout life. The role of dietary protein in maintaining bone health, however, is more controversial. Recent research suggests that dietary protein is an essential nutrient to bone health throughout the lifespan and may actually be beneficial, not deleterious to bone as once thought [2]. A higher protein diet increases insulin-like growth factor-1 (IGF-1), increases intestinal calcium absorption, suppresses parathyroid hormone, and improves muscle strength and mass, all of which may benefit the skeleton. This review will outline the evidence supporting the hypothesis that high dietary protein may support calcium metabolism and bone health.

Protein-induced metabolic acidosis and bone loss

Undoubtedly, an increase in dietary protein results in greater urinary calcium. What has been unclear up to this point is the source of the urinary calcium. The traditional hypothesis was that a high intake of protein, particularly from animal sources, generates a high fixed metabolic acid load because the animal proteins contain higher amounts of sulfur-containing amino acids. Should the kidneys and lungs be unable to completely handle the diet-induced acid load, a source of additional buffer would be necessary via osteoclast-activated bone resorption. The large bicarbonate reservoir of the skeleton would provide this buffer; calcium would consequently be released from bone with the carbonate. The hypothesis is supported by both cellular and animal studies [3] as well as several human intervention trials demonstrating the addition of a base, such as bicarbonate or citrate, suppresses bone resorption [4,5].

Is the endogenous acid production from a high-protein diet of sufficient magnitude to adversely impact on bone? We suspect the answer is ‘not likely’. In the healthy individual, the lungs work to regulate pH by immediately expiring carbon dioxide, a metabolic by-product. The kidneys excrete excess hydrogen ions primarily as ammonium ions and secondarily as phosphates (titratable acidity). These tightly regulated homeostatic mechanisms defend normal blood pH at 7.40 within a narrow pH range 7.38–7.42. Because food proteins are typically consumed throughout the daytime hours, acid generation occurs during the postprandial periods, thus providing ample time for neutralization during the fasting periods. The change in serum pH in response to diet is small. In a controlled human trial, when two diets (with maximal acid and alkaline generating capacities) were consumed, the predictable change in urine pH was significant and in the 1.02 range; however, the change of serum pH was only in the range of 0.014 pH units [6]. Additionally, the pH of extracellular fluid bathing cells deviates little from 7.40 and the initial activation of osteoclastic-resorption requires a decline in the systemic pH of approximately 0.2 units [3]. Thus, the small serum changes in pH in response to a maximal endogenous acid generating diet, does not appear to be of the same magnitude required by the osteoclastic cells to

activate resorption. For that reason, it seems unlikely that increasing dietary protein would lead to osteoclast-dependent bone resorption [2]. Much of the clinical and epidemiological data reviewed below are also consistent with the above notion.

Epidemiological studies

Beasley *et al.* [7] recently reported in a group of young women that bone mineral density (BMD) did not vary with protein intake, whereas Zhang *et al.* [8] found a negative relationship in prepubertal girls with very low-calcium intakes. However, the vast majority of population studies examined older adults and found the data generally support a positive association between protein intake and bone health. For example, Hannan and colleagues [9] evaluated the relationship between baseline protein intake and 4-year change in BMD in 615 study participants with a mean age of 75 years. When percentage protein intake was divided into quartiles, the group with the lowest protein intake (ranging from 0.21 to 0.71 g protein/kg) demonstrated the greatest loss in BMD. The highest quartile consumed 1.24–2.78 g/kg protein and demonstrated the least loss in BMD over the 4-year period [9]. This change in BMD translated to lower fracture risk. The same investigators [10•] found in almost a 1000 older men and women (mean age of 75 years) in the Framingham Osteoporosis Study that protein intakes in the higher quartiles were associated with a significantly lower risk for hip fracture. Perhaps even more intriguing is the interaction of dietary protein with calcium in a younger cohort. In a group of 55-year old participants, who had the lowest calcium intake (<800 mg), the highest protein consumers had 2.8 times more hip fractures of the lowest protein consumers [11•]. However, in the high-calcium group (>800 mg), the association was reversed: highest protein consumers had 85% reduction in hip fracture risk than the lowest protein consumers.

In a 5-year cohort study of 862 elderly women, food frequency questionnaires and dual energy X-ray absorptiometry (DXA) scans were used to examine the relationship between dietary protein at baseline and body composition 5 years later [12•]. After 5 years, there was greater bone mineral content (BMC) in those consuming the highest amount of protein (>87 g/day) than in those consuming moderate (66–87 g/day)-protein or low (<66 g/day)-protein diets. Whole body BMC and appendicular BMC were 5.3 and 6.0% greater in the highest versus lowest tertile of protein intake, respectively. Participants consuming the highest amount of protein also had significantly higher whole body lean muscle mass than those consuming the moderate or low levels of protein. These data support the hypothesis that protein intake positively impacts bone and muscle, while also suggesting that the greater BMC may be due in part to an interaction between muscle and bone [12•].

Isotopic studies

Several recent short-term feeding studies used calcium isotopes (generally considered the most sensitive and specific method) to evaluate calcium metabolism with different levels of dietary protein in humans. In a randomized crossover study of 15 healthy postmenopausal women [13], participants were assigned to a low (12% of energy)-meat protein and high (20% of energy)-meat protein diet each containing 600 mg calcium for 8-week periods. After a 4-week adjustment period on each diet, 2-day diets were labeled with ^{47}Ca and

whole body scintillation counting was performed over the subsequent 28 days. If the traditional hypotheses were correct, one would expect to see lower calcium retention among the group consuming the higher protein level. However, no significant difference was seen in calcium retention between the groups. Rather, a trend toward better calcium retention was observed on the higher protein diet. The high-meat protein and low-meat protein diets also did not adversely affect biochemical markers of bone turnover [13].

In a follow-up randomized, controlled feeding study conducted by this same team of investigators, 27 postmenopausal women were assigned to either a low (675 mg Ca/day)-calcium or high (1510 mg Ca/day)-calcium diet. Participants consumed low (10% of energy)-protein and high (20% of energy)-protein diets containing their assigned calcium level for 7 weeks each with a 3-week washout period in between. On the lower calcium diet, fractional calcium absorption increased with the higher protein diet (in comparison to the low-protein diet); however on the higher calcium diet this effect was not seen. The higher protein diet significantly increased serum IGF-1, an anabolic hormone that is beneficial to bone. The higher protein diet also reduced urinary deoxypyridinoline, a marker of bone collagen breakdown [14••].

In a final study, dual stable isotopes were used to evaluate the effect of a 10-day dietary intervention containing a moderate (1.0 g/kg)-protein or high (2.1 g/kg)-protein diet during a low intake of calcium (800 mg) in healthy women [15]. The high-protein diet resulted in a significant, 42% relative, increase (7.7% raw) in intestinal calcium absorption and a significant increase in calcium excretion. No significant differences were seen in kinetic measures of bone turnover. However, the higher protein diet caused a significantly lower urinary fraction of calcium from bone origin. These data suggest that, at least acutely, hypercalcuria secondary to increased dietary protein is, in fact, the result of increased intestinal calcium absorption. Further, although not significant, there was a trend toward lower bone turnover in the high-protein group, which may positively impact bone [15]. In all of the above isotopic studies [13,14••,15] in which dietary protein had a positive effect on calcium and bone, dietary calcium was limited to 600–800 mg. At higher calcium intakes, the impact is less evident.

In a recent pilot feeding study, however, Ceglia *et al.* [16] observed no increase in intestinal calcium absorption on a high (1.5 g/kg)-protein versus low (0.5 g/kg)-protein diet using dual-tracer stable isotopes. This intervention did not keep phosphorous constant. The high dietary phosphorus load that naturally accompanies a high dietary protein diet may blunt any change in intestinal calcium absorption [16]. In addition, these participants also received 1200 mg elemental calcium which could have masked any effect of a change in dietary protein, as it did in the study by Hunt and colleagues [14••].

The strength of design of the feeding studies, with each participant serving as his/her own control, and the methods used to measure calcium metabolism make these findings an important addition to the epidemiological data supporting a positive relationship between long-term higher protein intake and bone health. However, the dietary feeding studies are limited by their short-term nature and small sample sizes.

If experimental diets contain high levels of calcium, the impact of protein on absorption may not be evident [14••,16]. On the contrary, when dietary calcium is limited [14••,15] the effect of protein on calcium absorption is revealed. Because dietary calcium is inadequate in many older individuals, inadequate dietary protein may compound the problem of calcium bioavailability while increasing protein may help to rectify it.

Meta-analyses of clinical and epidemiological data

A systematic review and meta-analysis of protein intake and bone health was recently reported by Darling *et al.* [17••]. These investigators initially collected more than 2000 potential studies of which 61 met the inclusion criteria for their systematic review. Overall, the authors could find little support for a negative relationship between dietary protein and bone. The pooled *r* values from the cross-sectional surveys did not identify any negative association between protein intake and BMD/BMC at the clinically important skeletal sites. If anything, a slight positive association showed that protein was able to account for 1–2% of BMD measurements. Darling's group further studied 19 randomized, placebo-controlled trials and found an overall slightly positive impact of protein supplementation (from all different sources) on lumbar BMD. These small changes in bone, however, did not translate to a beneficial association between dietary protein and fracture rates. In other words, no significant association (either positive or negative) of protein intake with fracture incidence was found in either the qualitative review or the meta-analysis. This meta-analysis does not support the contention that higher dietary protein is detrimental to bone, but it does suggest that a small yet potentially important positive effect may result from a higher protein intake.

Fenton *et al.* [18••] recently evaluated the relationship between the acid generating capacity of the diet and urinary calcium, calcium balance, and markers of bone resorption. Five studies were selected based on preset methodological criteria. Although a significant positive relationship between net acid excretion (NAE) and urinary calcium was predictably observed, NAE was not associated with calcium balance or markers of bone resorption. The findings of this meta-analysis suggest that the increased acid-generating capacity of a high-protein diet may lead to increased urinary calcium loss but this loss does not necessarily translate to negative calcium balance or bone loss.

Potential mechanisms

Several potential mechanisms might explain how increasing the amount of protein in the diet could potentially benefit calcium retention and bone homeostasis, including improved calcium absorption [14••,15], suppression of parathyroid hormone [16,19], increased production of IGF-1 [14••,20], and a gain in lean body mass [21]. These potential mechanisms probably overlap and are not mutually exclusive.

An important mechanism involves IGF-1, a key mediator of bone growth that is regulated by dietary protein [22]. In two studies employing high-protein intakes, significantly greater levels of IGF-1 were found in participants consuming the higher protein diets [14••,20]. The anabolic effect of IGF-1 on muscle, rather than bone, may help further explain the positive relationship, though indirect, between dietary protein and bone. Thus, protein-induced increases in IGF-1 may indirectly benefit bone because of a direct enhancing action on

muscle tissue and strength, which also increases bone strength. A frequently overlooked fact is that changes in bone mass and muscle strength tend to track together over the lifespan [21].

Conclusion

Many epidemiological studies have found a significant positive relationship between protein intake and bone mass or density. Similarly, isotopic studies have also demonstrated greater calcium retention and absorption by individuals consuming high-protein diets, particularly when the calcium content of the diet was limiting. High-protein intake may positively impact bone health by several mechanisms, including calcium absorption, stimulation of the secretion of IGF-1, and enhancement of lean body mass. Clearly, long-term clinical intervention trials in which dietary protein is increased in healthy and well-nourished older individuals should be conducted in order to assess changes in muscle, bone, and fracture risk. Meanwhile, limiting the protein in the diets of older individuals in order to improve bone health does not appear to be scientifically warranted.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 63).

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Key points

- The traditional view that a high protein diet increases bone loss and osteoporotic fractures is currently called into question.
- Many epidemiological studies have found a significant positive relationship between protein intake and BMD.
- Protein intake has also been inversely associated with hip fracture in postmenopausal women.
- Isotopic studies have demonstrated greater calcium retention and absorption among individuals consuming higher protein diets in comparison to lower protein diets.
- There are potential mechanisms by which increasing the amount of protein in the diet could potentially benefit calcium retention and bone homeostasis.