

Dietary protein and bone: a new approach to an old question^{1,2}

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Our understanding of the role that dietary calcium and vitamin D plays in skeletal health has grown tremendously over the past several decades, and there is general consensus that both nutrients are important and beneficial. In contrast, despite intensive investigation, the effect of dietary protein on calcium metabolism and bone balance remains controversial. Further complicating the debate are the potential differences between animal and vegetable sources of protein. Diets high in protein have generally been considered to be detrimental to bone because the resultant endogenous fixed acid load (that results from amino acid metabolism) cannot be completely neutralized by the aging kidney and requires buffering in bone. This, in turn, releases calcium from the skeleton, which causes bone loss. On the other hand, increasing dietary protein increases insulin-like growth factor I, calcium absorption, and muscle strength and mass, all of which could potentially benefit the skeleton. In this issue of the Journal, Darling et al (1) provide a meta-analysis and systematic review of the dietary protein and bone literature that give us a novel and valuable perspective of the human literature.

The authors systematically searched the past 3 decades of the EMBASE and PUBMED databases for studies that evaluated dietary protein and bone health in healthy humans. Several thousand publications were initially identified; studies were then culled if they met the following exclusion criteria: reported only calcium metabolism; failed to report bone-related outcomes; or reported on subjects who were pregnant, lactating, children, or had a medical condition. Sixty-one studies were included in the final series of analyses which included 2 general approaches. An initial qualitative review included all 61 studies [31 cross-sectional surveys and ecologic and cohort studies; 19 supplementation trials examining bone mineral density (BMD), bone mineral content (BMC), or bone markers; and 11 cohort and case-control studies examining fracture risk]. Of these 61 studies, 33 trials were excluded from the second analysis because of incomplete data, which left 28 trials that underwent a quantitative meta-analysis (including 18 correlation studies, 4 fracture risk trials, and 6 pooled intervention trials).

Overall, the authors could find little support for a negative relation between dietary protein and bone. Importantly, from cross-sectional surveys, the pooled *r* values did not identify a negative association between protein intake and BMD/BMC at the clinically relevant skeletal sites. In fact, there was a slight positive association between increasing dietary protein

and BMD, such that protein was able to account for 1–2% of BMD. For an environmental factor to contribute to a complex trait such as bone mass by even that much is potentially significant. In the 19 randomized placebo-controlled trials, there was an overall slightly positive effect of protein supplementation (from all different sources) on lumbar spine BMD. Interestingly, the authors could find no significant differences between soy protein or milk basic protein on lumbar spine BMD. This small positive association between protein and bone mass, however, did not translate to decreased fracture rates. There was no significant association (either positive or negative) of protein intake with fracture incidence in either the qualitative review or the meta-analysis.

It is generally well accepted that an increase in dietary protein results in greater calcium excretion in the urine (2). The source of the extra urinary calcium is not completely clear. A widely held view is that high intakes of protein (particularly animal) create a fixed metabolic acid load due to the high sulfur amino acid content. The large carbonate reservoir of the skeleton would be called on to buffer the acid, and skeletal calcium would, in turn, be lost in the urine. The result is increased bone resorption, decreased BMD, and increased fractures. The hypothesis is supported by cellular and animal studies (*see* review in reference 3). Furthermore, the addition of a base such as potassium bicarbonate or citrate, which suppresses bone resorption (4, 5), is frequently used to justify a lower-protein diet. However, the analysis by Darling et al (1) found little evidence to support the posited pathophysiology.

Several arguments have been raised that contradict the above hypothesis that dietary protein is “bad to the bone” (6). Undoubtedly, dietary protein is a major contributor to endogenous acid production; the American diet can generate 100 mEq acid daily, primarily phosphate and sulfate (7). The pivotal question becomes: Is this endogenous acid production from a high-protein diet of sufficient magnitude to affect bone? In the healthy individual, the extra- and intracellular acid-buffering systems,

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lungs and kidneys, all have a tremendous capacity to maintain pH within a very narrow margin. As evidence, 24-h urinary net acid excretion naturally increases when dietary protein increases (8). This normal homeostatic response contributes to the maintenance of constant blood pH (6). It is difficult to imagine that a high-protein diet would produce such a state of metabolic acidosis as to overwhelm the above systems so that bone would be mobilized (6). The mechanism by which acidosis-induced bone loss occurs might be from the activation of osteoclasts or from the physico-chemical dissolution of bone (6). The pH of extracellular fluid bathing cells is probably <7.36 , and the initial activation of osteoclastic resorption requires an extracellular pH <7.2 (3). It would seem unlikely that such a low pH would occur after a high-protein meal (6). Furthermore, the manipulation of systemic pH by adding pharmacologic doses of acid or base while measuring calcium and bone outcomes (as reported in some human and animal studies) is quite physiologically different from changing one's protein intake. Humans generally consume a variety of foods that generate varying amounts of acids and bases, and we typically consume dietary protein throughout the day, so that the acid generation (and subsequent neutralization) also occurs gradually. Finally, 3 well-controlled, short-term isotopic studies failed to show any reduction in calcium retention and absorption during high-protein conditions at 1 wk (9) and 2 mo (10, 11); if anything, there were slight improvements. These isotopic studies are entirely consistent with Darling et al's (1) qualitative and quantitative review.

Several important questions remain unanswered. Older adults are at the highest risk of osteoporosis, and they naturally consume the least amount of protein per kilogram of body weight (12). We need to know if adding a modest amount of protein to the diets of older individuals is a safe and effective way to improve skeletal health and forestall fractures. Large, long-term intervention trials are needed to answer this question. The lack of an association (either positive or negative) between dietary protein and fractures in the Darling et al (1) study warrants further investigation. Perhaps this observation speaks to the complex multifactorial etiology of a bone fracture and the difficulty in holding only one component of the diet culpable.

Clearly, bone fracture is the ultimate outcome, and intervention trials are needed to clarify dietary protein's effect on this critical result. In the meantime, let us make it a goal to add a small protein source to the "tea and toast" meals of many of our frail older adults. On the basis of the work of Darling et al (1), this appears to be safe advice that will not harm their bone health.

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