Protein and calcium: antagonists or synergists?1,2

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One might have thought that nutritional science would have figured out decades ago most of what needed to be known about protein to ensure optimal health. Instead, we see the Food and Nutrition Board currently deliberating whether the recommended dietary allowance for protein for adults should be raised, especially for the elderly. At the other extreme, protein, particularly of animal origin, is caught up in political correctness (1). Some argue, in fact, that we consume too much protein and that, for example, we would not have such a high calcium requirement if only we would eat less meat.

In a sense, current research in the field of protein nutrition is a microcosm of much of what is happening in nutritional science generally. With protein, as with many other nutrients, the field is moving away from the use of the absence of an index disease as the criterion of nutritional adequacy and at the same time is becoming distinctly more quantitative. The interactions of protein with calcium illustrate both developments.

It has been known for nearly 80 y that increasing protein intake increases urinary calcium loss (2). Because urinary calcium excretion is the most important physiologic determinant of calcium retention, excess protein intake should be bad for bone, other things being equal. Indeed, a few observational studies reported an adverse association of high protein intakes with bone health (3). However, others found exactly the opposite (4). More persuasive is the outcome of randomized controlled trials showing that augmented protein intakes, rather than being harmful, substantially improve recovery after hip fracture and reduce age-related bone loss in the contralateral hip (5, 6).

Considered in isolation, a positive effect of protein on bone is not surprising, inasmuch as bone tissue is nearly 50% protein by volume. A substantial fraction of the amino acids in bone collagen cannot be reutilized in new protein synthesis. Hence, bone turnover requires continuous ingestion of new protein. In the face of inadequate intake, bone rebuilding is low on the body’s priority list. But the other 50% of bone is mineral, and here calcium plays the crucial role (7). Without a diet containing both nutrients in adequate quantities, new bone formation will be limited. It has, in fact, been speculated that the seemingly paradoxical effect of protein on bone can be explained by variations in calcium intake.

In this issue of the Journal, Dawson-Hughes and Harris (8) present data confirming this speculation. In a secondary analysis of the data accumulated in a calcium intervention trial, Dawson-Hughes and Harris found that protein intake in the calcium-supplemented group was positively associated with bone gain, whereas there was a nonsignificant trend in the opposite direction in the placebo group. The calcium-supplemented subjects as a group gained bone mass over the 3-y course of the trial, whereas the unsupplemented group lost bone. Within the calcium-supplemented group, bone status at the total body and hip was proportionate to protein intake. Those with the highest protein intakes gained bone, whereas those with the lowest intakes actually lost bone. Clearly, calcium was not enough to protect the skeleton when protein intakes were low. Equally clearly, high protein intakes did not adversely affect bone status.

Bone gain means positive calcium balance, which in turn means improved absorption or reduced excretory loss of calcium (or both). Dawson-Hughes and Harris found that urinary calcium rose slightly, although not significantly, with protein intake. Despite this probably increased excretory loss of calcium, the gain in total-body bone mineral measured across the 3-y treatment period was clear evidence that the body was in positive calcium balance. Calcium absorption, as measured, was greater in the calcium-supplemented group, but there was no detected effect of protein on calcium absorption at either calcium intake level, despite the clear difference in measured bone mass. Unfortunately, the investigators used a calcium absorption method that has been shown to correlate poorly with net absorption (9); hence, it is not possible within this study to reconcile the measured change in bone mineral density with the estimated inputs and outputs of the calcium economy.

The quantitative aspect of the calcium-protein interaction story can be approached best as follows. As urinary calcium rises, a potential hypocalcemic stress is created, to which the parathyroid glands respond with elevated parathyroid hormone (PTH) secretion. PTH in turn acts on 3 end organs: bone, gut, and kidney. The gut effect is mediated by increased renal synthesis of 1,25-dihydroxyvitamin D, which in turn leads to improved calcium absorption. At the same time, PTH enhances bone resorption, so that some of the calcifiuc loss is offset from the bony reserves, rather than exclusively from the diet. It is in this way that high protein intakes, leading to incompletely offset urinary calcium loss, might produce bone loss.

These qualitative aspects of the effects are well established. The quantitative features of the system, while still being elucidated, relate to the amounts each effect produces. To begin with, the amount of PTH secreted depends directly on how much cal-

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cium the 3 effectors yield. Moreover, the relative contributions of diet and bone depend both on the relative responsiveness of the respective end organs (9) and on the quantity of calcium in the diet. It has been tentatively estimated that a 30-mg additional urinary calcium loss evokes hormonal responses that lead to an improvement in calcium absorption efficiency of from 1 to 2 absorption percentage points (10). Much more work needs to be done to define this relation more precisely, but it is easy to calculate, for example, that if the improvement is 2%, such an increase can extract no more than 10 mg additional Ca from a diet containing 500 mg Ca/d. The same absorption improvement extracts 30 mg Ca from a diet containing 1500 mg Ca/d. The contrast is undoubtedly greater than this approximation suggests because with the lower calcium intake, calcium absorption is already up-regulated and may be close to maximal. With the higher intake, absorption is down-regulated and hence a considerable capacity to increase absorptive efficiency remains. The homeostatic feedback system controlling the calcium economy does not regulate calcium intake and has no mechanism for assessing it. The system simply uses the combined calcium input from the 3 effector organs to prevent or offset a decrease in serum ionized calcium resulting from an augmented calcium leak from the body. In this way, any calciuric agent would be predicted to affect bone negatively, mainly at low calcium intakes. In brief, it appears increasingly well established that protein and calcium act synergistically on bone if both are present in adequate quantities in the diet, but that protein may seem effectively antagonistic toward bone (because of its calciuric effect) when calcium intake is low.

REFERENCES