Acid diet (high-meat protein) effects on calcium metabolism and bone health
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Introduction
Protein is the major structural constituent of bone (50% by volume) and dietary protein is essential for bone formation because a substantial amount of bone collagen amino acids produced during bone turnover cannot be reutilized. Protein, especially from animal sources, is also a source of metabolic acid [1] because it contains sulfur amino acids that generate sulfuric acid. Consequently, for several decades the production of metabolic acid by modern high-protein Western diets was thought to promote calcium mobilization from the skeleton and be detrimental to bone health [2,3]. This thought was strengthened by the finding that high-protein diets increased urinary calcium excretion. Therefore, diets with high amounts of protein, especially from animal sources rich in the sulfur amino acids (cysteine and methionine), often have been considered a risk factor for osteoporosis and bone fractures [4].

Emerging evidence suggesting that the current Recommended Dietary Allowance for protein, which is 0.8 g protein/kg body weight/day for adults, is significantly underestimated for optimal health, particularly in the elderly [1,5], combined with the rising use of high-protein (defined as an intake above the current Recommended Dietary Allowance) diets for weight reduction [6] and for maintaining optimum physical performance for endurance and strength-training athletes [7], has resulted in enormous public and scientific attention toward the impact of increased dietary protein intake on calcium metabolism and bone health.

This review will summarize pertinent findings regarding high protein (meat) intakes on acid–base balance, calcium retention and overall bone health.

Acid–base balance and calcium excretion
The acid–base balance in the body, which is modifiable by food or diets, influences calcium metabolism [8]. Dietary acid loads can be estimated by calculating the potential renal acid load, which provides a reliable estimate of renal net acid excretion [9]. The dietary potential...
renal acid load is calculated by determining the counterbalance of the acidic potential of dietary protein and phosphorus by dietary alkaline potassium, calcium, and magnesium [9].

Low-grade, or mild metabolic acidosis induced by diet may have a negative effect on bone by enhancing bone resorption. It has been proposed that in response to an acid challenge, the skeleton supplies buffer by releasing calcium carbonate through active bone resorption, in addition to the kidneys reabsorbing less calcium; consequently, urinary calcium excretion is increased [10]. Low-grade or mild metabolic acidosis can reduce the pH and bicarbonate concentration in bone resorbing osteoclasts, which promotes their adhesion to bone resorptive sites and the secretion of H^+. Additionally, the metabolic acidosis suppresses the activity of the bone-forming osteoblasts [10].

Diet-induced metabolic acidosis and net acid excretion are closely related to the quantity of calcium excreted in urine. In a meta-analysis, Fenton et al. [11] examined 25 studies in which acid–base balance was manipulated through foods or supplemental salts and reported the changes of net acid and calcium excretion by healthy adults. Their analysis resulted in the estimation that a change in 47 mEq (mmol) of net acid excretion is associated with 66 mg (1.65 mmol)/day of calcium in acidic urine [11].

Counteracting acidosis with base-forming minerals, such as potassium bicarbonate, has been shown to decrease the urinary calcium excretion attributed to high-protein intake [12–14]. In a double-blind, controlled trial, potassium bicarbonate supplementation lowered urinary calcium excretion and bone resorption in older men and women [15*]. In another study, the oral administration of potassium bicarbonate to postmenopausal women neutralized endogenous acid, improved calcium balance, and increased serum osteocalcin (a bone formation biomarker) concentrations and decreased urinary hydroxyproline (a bone resorption biomarker) excretion [12].

Long-term diet-induced metabolic acidosis has been found associated with increased bone resorption and decreased bone mineral density. In an epidemiological study involving 5119 women aged 45–54 years, Macdonald et al. [16] found that low-dietary potassium (alkaline salt) intakes and high dietary estimates of net endogenous acid production were associated with low-bone mineral density in premenopausal women and increased bone resorption markers in postmenopausal women. In another prospective study of 401 women aged 75 years and older, low-dietary acid load was correlated with higher broadband ultrasound attenuation [17].

The alleged detrimental effect of diet-induced metabolic acidosis on bone may not be as severe as commonly thought. In a cross-sectional study involving 14563 men and women aged 42–82 years living in Norfolk, UK, Welch et al. [18] found only a small association between dietary potential renal acid load and bone ultrasound measures in women, and no association in men. The study also found that, although dietary potential renal acid load was inversely related to calcaneal broadband ultrasound attenuation, the detrimental effect associated with the potential renal acid load was small relative to other known risk factors affecting bone metabolism, such as age, smoking, and physical activity [18].

Diets or foods that increase the potential renal acid load do not necessarily increase urinary calcium excretion or bone resorption. For example, increased intake of phosphate, which contributes to the dietary acid load [8], should increase urinary calcium excretion according to the acid-ash hypothesis. However, based on a meta-analysis of 12 intervention studies, Fenton et al. [19*] found that higher phosphate intakes were actually associated with decreased urinary calcium excretion and increased calcium retention, and concluded that there is no evidence that higher phosphate intakes are detrimental to bone health.

Although increasing dietary acid load promotes calcium loss in urine, many studies have shown that it does not affect whole body calcium balance nor contribute to osteoporosis development. A meta-analysis by Fenton et al. [20*] showed that neither calcium balance nor the bone resorption marker, N-telopeptides, was affected by diet-induced changes in renal net acid excretion despite a significant linear relationship between an increase in renal net acid excretion and urinary calcium.

Dietary protein, calcium utilization and bone health

The assumed detrimental effects of protein on bone health have been mainly based on observations that high-protein intakes increased renal acid and urinary calcium excretion [21,22], especially when increased amounts of purified proteins were ingested [23]. It was estimated that each gram increase in dietary protein would result in a 1 mg (25 μmol) increase in urinary calcium excretion [24]. This finding led to the thought that the urinary calcium increase meant a loss of calcium from bone or bone demineralization. If bone were the source of increased urinary calcium, one would expect that long-term high-protein intakes would have a profound negative effect on the skeleton and would lead to decreased bone mineral density and mass. In contrast to this expectation, a majority of epidemiological studies involving this concern have clearly shown that long-term
high-protein intake is actually associated with increased bone mineral density [25–27]; only a few studies found negative associations [28]. In the Framingham Osteoporosis Study of 391 women and 224 men, higher dietary protein intake was positively associated with less bone loss at femoral and spine sites [27]. Additionally, a prospective study involving 229 healthy children and adolescents aged 6–18 years, where adjustment was made for age, sex, and energy intake, and which controlled for forearm muscularity, BMI, growth velocity, and pubertal development, long-term (4-years) dietary protein intake was positively associated with periosteal circumference, cortical area, bone mineral content, and polar strength strain index [26]. Data from a recent longitudinal study of 560 young women aged 14–40 years suggested that a higher protein intake (in the upper range of typical protein consumption in the USA) does not have an adverse effect on bone mineral density [29**]. In a systematic review and meta-analysis, Darling et al. [30**] found that protein intake was positively associated with lumbar spine bone mineral density in randomized placebo-controlled trials and in cross-sectional surveys.

With obesity growing in prevalence around the world, weight reduction is recommended to reduce obesity-associated chronic disorders. However, studies show that bone loss often occurs with weight loss [31]. A high-protein diet, an often recommended dietary means for weight loss and weight maintenance, has been shown to reduce bone mineral content loss associated with weight loss [32].

Because protein from animal sources is richer in the sulfur amino acids cysteine and methionine than vegetable protein, and thus generates more acid, diets high in animal protein (meat) intake may induce a greater increase in urinary calcium excretion (and supposedly be more detrimental to bone health) than diets high in vegetable protein. However, the increased urinary calcium excretion apparently is counterbalanced by changes in calcium metabolism other than through loss of calcium from bone. For example, short-term high meat diets did not affect whole body calcium retention [33] and high intakes of animal protein have been found significantly associated with increased bone mineral density or reduced hip fracture [25,27,34]. Furthermore, a negative association between vegetable protein and bone mineral density was observed in both sexes [25], and elderly women on a vegetarian diet were found to be at higher risk of osteoporosis development than nonvegetarian women [35].

Studies of exercising individuals also indicate that animal protein may have advantages over vegetable protein for bone health, which can be considered a musculoskeletal issue [1]. Changes in bone mass, muscle mass and strength track together; thus, maintenance or an increase in muscle mass and function maintains or enhances bone strength and mineral density [1]. Leucine has been implicated as the primary amino acid signaling that quality protein is available for muscle protein synthesis [36]. Animal proteins typically contain a higher concentration of leucine.

Epidemiological observations that a high-protein intake is associated with greater bone mineral density [25–27,34] have discounted the thought that bone is the major source of increased urinary calcium with increased protein intake. Accumulating data suggest that the increased urinary calcium excretion may be the result of increased calcium absorption rather than increased bone resorption. Well controlled human trials with calcium isotopes have shown that a high-protein intake increases intestinal calcium absorption [33,37,38*], and such an increase in intestinal calcium absorption apparently offsets protein-induced hypercalciuria. Using dual stable calcium isotopes, Kerstetter et al. [37] found that a high-protein diet (2.1 g/kg body weight) increased intestinal calcium absorption by 8% when compared with a moderate protein diet (1.0 g/kg body weight) fed to women. Using radioisotope and whole-body counting, Hunt et al. [38*] found that high-dietary protein (mainly meat) increased calcium retention in postmenopausal women with a normal calcium intake (675 mg/day).

The observed beneficial effects of high-protein intakes, including that provided by meat, on bone may be partially the result of increased circulating concentration of IGF-I [38*,39–41], a potent anabolic agent that stimulates bone formation and increases bone mass, in addition to providing amino acid substrates for building the bone matrix [42]. High protein, or meat, intake also may positively affect bone metabolism through lowering serum parathyroid hormone (PTH) [43]. Chronic low protein intake has been linked to secondary hyperparathyroidism and low-bone mineral density [25,27,44]. Serum intact PTH hormone increases blood calcium by stimulating intestinal calcium absorption, renal calcium reabsorption, and bone resorption [45].

The relationship between meat intake and bone health is apparently dependent on other dietary and physiological (e.g., muscle maintenance or accretion) factors. A dietary factor that may influence the effect of protein on calcium metabolism and bone health is calcium intake. In a randomized controlled crossover feeding study, postmenopausal women consumed either low or high-meat protein (10 or 20% of energy as protein) with either 675 mg or 1510 mg calcium/day for 7 weeks. The increase in dietary protein provided by meat improved calcium absorption from the low-calcium diet but not
the high-calcium diet [38]. In another randomized, placebo-controlled trial involving 342 healthy men and women aged 65 or older, higher protein intake was significantly associated with greater femoral neck and body bone mineral density in individuals supplemented with calcium and vitamin D [46]. When calcium intakes were low (less than 675 mg/day), high-protein intake, especially from animal sources, had a negative effect on bone mass accrual in Chinese pubertal girls [47]. Reduction of dietary acid load by high intakes of foods rich in potassium and bicarbonate (acid buffering) such as fruits and vegetables also may assure that a high protein or meat intake is beneficial rather than detrimental to bone health [48].

Conclusion

Although a high meat or protein intake increases renal acid load and urinary calcium excretion, recent findings do not support the claim that bone is the source of the extra calcium lost in urine. In addition, evidence is lacking that shows high-protein intakes, including that from animal sources, affect whole body calcium balance or contribute to osteoporosis development and fracture risk.

Apparently increased calcium absorption, elevated circulating IGF-I, and decreased serum PTH compensate for any negative effect of acid load associated with a high-protein intake may have on bone health (Fig. 1). Thus, the calciuretic effect of protein should not be accepted as a concern that would necessitate the recommendation to decrease protein or meat intake. Such a recommendation would be contrary to findings that increased protein with adequate calcium intake and a balanced diet providing sufficient alkalinizing fruits and vegetables can be beneficial to bone health.

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