"Dietary Protein in Bone Health: Friend and Foe"

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This is to acknowledge that Dr. Khashayar Sakhaee has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Khashayar Sakhaee will not be discussing off-label uses in his presentation.

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His interests include clinical evaluation and research in the areas of calcium, phosphorus and uric acid metabolism, with a special emphasis on the pathogenetic mechanisms of osteoporosis and kidney stone formation.

INTRODUCTION

Osteoporosis is a complex disorder characterized by an imbalance between bone resorption and bone formation, which results in deterioration of bone mass and of the microstructural integrity of bone. It is a major health issue with a significant impact on the economic burden in the nation. The number of physician visits for osteoporosis has increased significantly over the past decade (1). Moreover, the increased awareness of osteoporosis has been associated with a significant rise in the number of prescriptions for anti-osteoporosis medications. Pathophysiological mechanisms of osteoporosis are diverse and include a strong genetic predisposition (2-7), environmental risk factors, and the dysregulation of hormonal metabolism (8-15). Although new medications for osteoporosis are now available, the specific role of diet as a modifier should not be ignored.

The NIH consensus panel on optimal calcium intake (9) has acknowledged the importance of dietary protein intake in the development of an optimal calcium balance. However, guidelines for an optimum protein intake were not provided due to the assumption that such dietary modifications may cause a great deal of confusion in the public domain. The objective of this review is to explore the potential pathophysiological associations between dietary protein intake and the development of skeletal bone loss.

Dietary Proteins and Bone Health

The recommended dietary allowance (RDA) for protein is 0.8 g/kg/day (16). The typical American diet provides 1.2 g protein/kg/day (17, 18), exceeding the established RDA. Dietary protein intake greater than 1.6 g/kg/day is considered to be high (19, 20). The widespread use of low carbohydrate high fat-diets including the Atkins' Diet and the South Beach Diet emphasizes the importance of long-term consideration of the impact of high dietary protein intake on bone health and kidney stone disease (21).

Epidemiology

Epidemiologic studies have provided conflicting results on the role of dietary protein intake on bone health (22-27). The population-based Framingham osteoporosis study showed a protective role of high protein intake on bone mineral density in elderly men and women (25). In this observational study, subjects in the lowest quartile of protein consumption demonstrated the largest loss in bone mineral density at the vertebral spine and femoral neck over 4 years of follow-up (Figure 1). Moreover, few studies have also shown that hip fractures occur with an increased frequency in malnourished elderly (26-28). Furthermore, most epidemiological studies have demonstrated a positive relationship between protein intake and bone mineral density (25, 29-31).

The results of these population-based studies differ from a cross-cultural comparison, showing the incidence of non-traumatic hip fractures to be directly associated with the amount of protein consumption. The incidence of non-traumatic hip bone fractures was found to be related to per person consumption of protein of an individual country, with a higher incidence in

industrialized compared to less industrialized societies (23). However, it has been argued that the differences in hip fracture incidence in this study may have been related to the ethnic differences in the studied population (32, 33) as lower rates were detected in countries inhabited by Blacks and Asians. These ethnic groups, either due to a higher bone mass (Blacks) or because of the different architectural structure of hip (Asians), may inherently carry a lower risk of non-traumatic hip fractures. Nevertheless, the result of this study was subsequently supported by a larger cross-cultural comparison (34) in which the incidence of hip fracture in only Caucasian population was shown to be directly related to the consumption of animal proteins (Figure 2). Furthermore, the incidence of hip fractures was demonstrated to be significantly reduced in relation to an increased consumption of vegetable foods. This study suggests that vegetable foods, by provision of alkali, may possibly mitigate the deleterious effect of acid generating animal protein intake on bone.

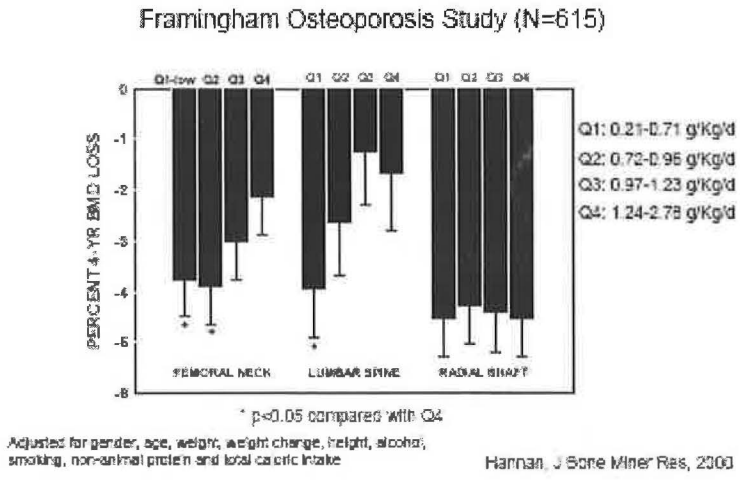


Figure 1. BMD according to quartile of protein intake

The results of these cross-cultural reports are consistent with another epidemiological study in a cohort of 85,900 women, age 35-59 years, who were participating in Nurse's Health Study (25). The risk of forearm bone fractures was found to be significantly higher in those women with a protein consumption exceeding 95 g/day compared with those who consumed less than 68 g/day. In this study no such relationship was detected between the consumption of vegetable protein and the risk of forearm bone fractures.

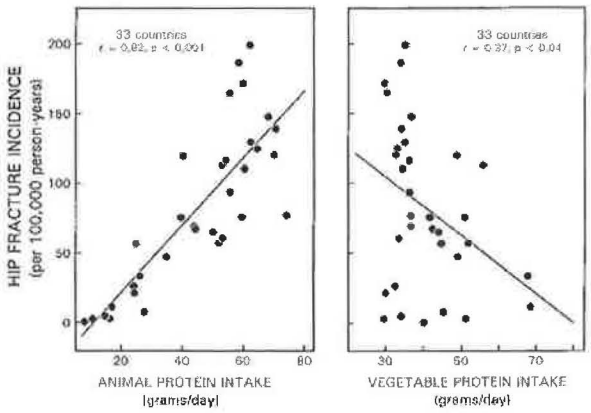


Figure 2. Cross-Cultural Relationship Between Hip Fracture and Protein Intake

The differences in the results of these epidemiologic studies underscore the difficulties involved in estimating the exact amount of protein intake using food frequency questionnaires, the baseline protein intake and the type of protein consumed (such as whole meal protein or purified protein). Furthermore, contributions of other nutrients to calcium balance including sodium, calcium, and phosphorus have not been examined closely. In addition, a potential for bias exists assuming food consumption for whole population is also reflective of

dietary consumption of the studied population. However, population and epidemiological studies have several strengths including large sample size and lack of selection bias.

Pathogenetic mechanisms of protein-induced bone loss

Extracellular calcium is in constant equilibrium between intestinal calcium absorption, renal reabsorption of calcium, and bone resorption. In a steady state, when an individual is in balance, net intestinal absorption of calcium is matched by urinary calcium excretion, and calcium exchanges across the bone are equal. Urinary calcium excretion plays a significant role in calcium homeostasis. The importance of urinary calcium excretion in overall calcium balance is evident from 560 balance studies performed in healthy middle-aged women (35). Calcium intake and absorption accounted for 25% and urinary calcium for 50% of the changes in calcium balance (Figure 3). The current scheme for the development of bone loss with a high protein intake has centered on the effects of high protein diet on increasing urinary calcium excretion.

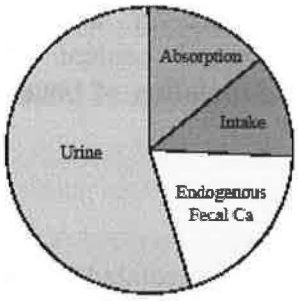


Figure 3. Determinants of Calcium Balance (35)

The metabolic processes that contribute to the endogenous acid load with consumption of animal protein play a key pathogenetic role in protein-induced bone loss. These processes involve oxidation of the sulfhydryl groups of the aminoacids cystine and methionine found in protein to form sulfuric acid. In this model, protons generated from increased animal protein intake elevate urinary calcium excretion by involving the three target organs regulating calcium homeostasis.

Role of bone in protein-induced acidosis

Metabolic acidosis primarily promotes bone resorption through three different mechanisms: (a) physicochemical mechanism involving dissolution of bone mineral, (b) cellular mechanisms mediated by osteoclastic bone resorption, and (c) hormonal mechanism through stimulation of PTH secretion secondary to inhibition of renal tubular calcium reabsorption.

Physicochemical Mechanism

Bone is major source of calcium in the body as 99% of body calcium is contained in the bone. Bone also contains 35% of total body sodium and 60% of total body magnesium (36). In addition, bone is a major reservoir of alkali and contains 80% of total carbon dioxide in the body (including carbonate, bicarbonate and CO_2) and 80% of body citrate (37) (Table 1). Thus, bone

Table 1. Ionic Composition of Bone Mineral

Cations	Anions
Calcium (6.66)	Phosphate (4.02)
Sodium (0.32)	Carbonate (0.79)
Magnesium (0.18)	Citrate (0.05)
Potassium (0.02)	Chloride (0.02)

Values are indicated as mmol/g of dry fat-free bone

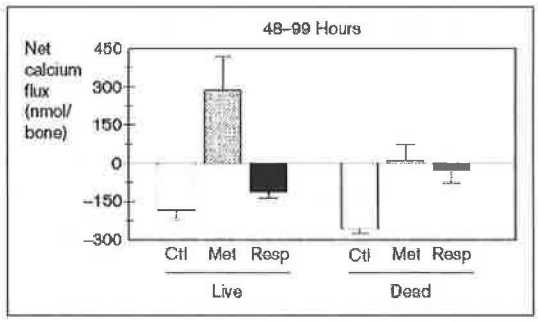
acts as a major extracellular buffer by releasing alkali to the surrounding extracellular environment to support acid-base homeostasis. In vitro studies in fetal mouse calvaria have shown that acute metabolic acidosis stimulates calcium release from both dead bone and live bone into the surrounding medium (38, 39). This suggests that with acute acid exposure, physiochemical mechanisms are operating to resorb bone and release calcium. The initial physiochemical reaction to acute metabolic acidosis involves an exchange of sodium for hydrogen and release of bone bicarbonate from the mineral surface (40). This process is accompanied by a small release of calcium from bone (Table 2). In chronic metabolic acidosis, release of calcium carbonate comprises the main buffering mechanism. Thus, in chronic metabolic acidosis, in contrast to acute metabolic acidosis, there is a significant reduction in total mineral content of bone accompanied by the dissolution of bone crystal (Table 2).

Table 2. Ionic Fluxes in Metabolic Acidosis

	Metabolic Acidosis	
	Acute	Chronic
H^+ influx	↑ ↑ ↑	↑ ↑ ↑
Ca^{++} Efflux	↑ ↑	↑ ↑ ↑
Efflux of Ions other than Ca^{++}	HCO_3^-, Na^+, K^+	CO_3^{-2},PO_4^{-3}

Cell-mediated mechanism

It has been demonstrated that with chronic metabolic acidosis, cell-mediated osteoclastic bone resorption predominates over the physicochemical mechanisms (41) (Figure 4). With chronic metabolic acidosis, calcium efflux was shown to occur only with live bone, indicative of the predominance of a cell-mediated pathway (Figure 4). Moreover, chronic metabolic acidosis-induced release of calcium was shown to be associated with an increased release of the osteoclastic enzyme β-glucuronidase into the culture medium (42), suggestive of an increase in osteoclastic cell activity. This was accompanied by inhibition of osteoblastic collagen synthesis and consequently reduction of alkaline phosphatase release from osteoblasts (42).



Bushinsky, Am J Physiol, 1989

Figure 4. Net Calcium Flux From Live and Dead Bone During Chronic Acidosis

The molecular mechanisms by which metabolic acidosis modulates cell-mediated bone remodeling has recently been elucidated (43, 44). Metabolic acidosis inhibits specific osteoblastic matrix protein synthesis and alkaline phosphatase activity and stimulates production of prostaglandin E_2 (PGE_2) by osteoblasts (45, 46). The increased osteoblastic production of PGE_2 increases the osteoblastic expression of receptor activator of nuclear factor Kappa B ligand (RANKL). RANKL is the major downstream cytokine that stimulates osteoclastogenesis by binding to its receptor (receptor activator of nuclear factor Kappa B; RANK) on osteoclastic precursor cells, transforming them into activated bone-resorbing osteoclasts, and thereby buffering the proton load to regulate acid-base homeostasis.

Despite extensive in vitro experiments, the role of chronic metabolic acidosis on bone

histomorphometry in vivo using animals and human subjects has not been fully investigated. Recently, a high casein diet (a model of high animal protein intake) compared to low casein diet (a model of low animal protein intake) provided for two months in pair-fed rats caused a higher urinary calcium excretion and increased the propensity for kidney stone formation in the high casein group (47). Moreover, histomorphometric analysis of femur after 59 days on the diet showed a marked increase in bone resorption in the high casein group.

Hormonal Mechanism

The effects of chronic metabolic acidosis on calcium metabolism are complex and depend on the response of calcitropic hormones to calcium and phosphate fluxes in the gut, the skeleton and the kidney. Parathyroid hormone (PTH) secretion could increase or decrease depending on the prevailing serum ionized calcium concentration which is altered by renal calcium wasting or calcium flux from the bone respectively. The changes in PTH secretion directly influences skeletal bone turnover independent of the prevailing acid-base status (38).

Role of kidney in protein-induced hypercalciuria

Another potential mechanism of hypercalciuria with increased animal protein intake includes the inhibition of the renal tubular reabsorption of calcium. This inhibition of renal tubular calcium reabsorption has been identified both in human and animal studies (48-50) using animal protein or ammonium chloride-induced metabolic acidosis. However, until recently the molecular mechanism for this inhibitory effect was not fully explored.

The kidney plays a key role in regulation of calcium homeostasis and approximately 98% of calcium filtered at the glomerulus is reabsorbed by the nephrons. In the kidney, paracellular reabsorption of calcium is responsible for 80-85% across the proximal tubules and the thick ascending limb of Henle (51, 52). The transcellular reabsorption of calcium occurs principally in the distal convoluted tubule (DCT) (Figure 5). This transcellular calcium reabsorption starts with

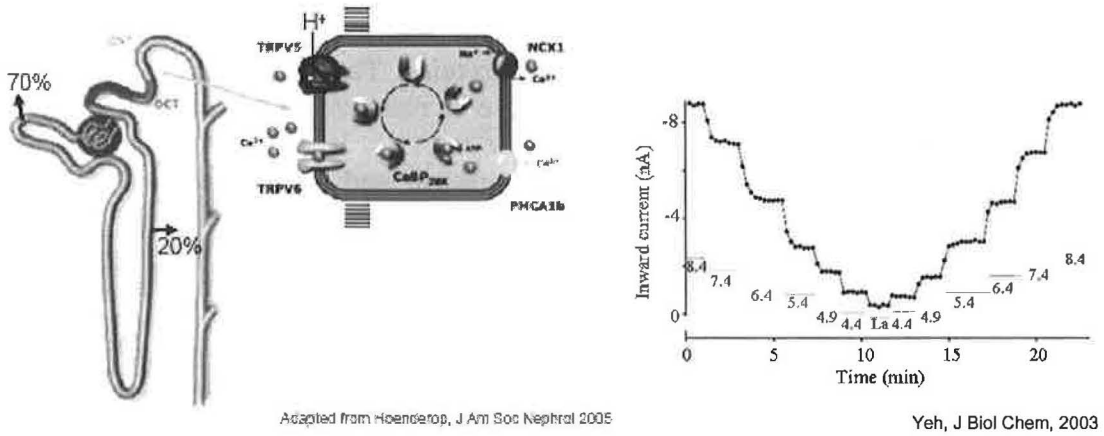


Figure 5. Renal Handling of Calcium and Effect of Extracellular pH on TRPV-5 (Calcium Channel)

passive entry of calcium through calcium channels in the apical membrane, is followed by diffusion through the cytosol facilitated by binding to calcium-binding protein calbindin–28K, and finally extrusion through the basolateral membrane. The calcium exit from the basolateral

membrane requires energy and is mediated by sodium/calcium exchanger and calcium-ATPase. The first step of passive entry through calcium channel in the apical membrane is the rate-limiting step in transepithelial calcium reabsorption in the distal nephron (53).

Recently, the transient receptor potential Type 5 (TRPV-5) channel present in kidney and intestine was shown to play a key role in transepithelial reabsorption of calcium in these target organs (54, 55). In a whole cell patch clamp study, extracellular protons inhibited TRPV-5 by titrating glutamate 522 in the extracellular loop between the putative fifth transmembrane domain and the pore region (Figure 5). Thus, direct proton sensing via titration of glutamate 522 appears to mediate acid-induced inhibition of TRPV-5 possibly by changing the protein conformation. Another mechanism may be through an increase in the abundance of TRPV-5 and TRPV-6 in chronic metabolic acidosis (56).

Role of intestine in protein-induced hypercalciuria

The potential role of intestine and its relationship to hypercalciuria in metabolic acidosis has not been fully elucidated. Decreased PTH secretion from a transient rise in serum ionized calcium concentration due to acidosis-induced excessive bone resorption may lower serum circulating 1,25-$(OH)_2$-D or directly impair conversion of 25 hydroxyvitamin D to 1,25-$(OH)_2$-D (57) and consequently lower intestinal calcium absorption (58). On the other hand, hypercalciuria from inhibition of renal tubular calcium reabsorption due to metabolic acidosis would transiently lower serum ionized calcium concentration which in turn raises serum circulating concentration of serum PTH and 1,25-$(OH)_2$-D (59, 60) and ultimately raises intestinal calcium absorption. Alternatively, a low serum phosphorous and an increase in renal mass caused by metabolic acidosis have been shown to increase 1,25-$(OH)_2$ D levels in human subjects (61, 62), which may increase intestinal calcium absorption. These opposing mechanisms may mitigate the effect of metabolic acidosis on intestinal calcium absorption. Indeed, most clinical balance studies have shown the lack of effects of metabolic acidosis on intestinal calcium absorption (63, 64).

Recently, two short-term metabolic studies (65, 66) have suggested that intestinal calcium absorption increases with consumption of high dietary proteins. The rise of intestinal calcium absorption during high protein diet was suggested in part to be responsible for the significant rise in urinary calcium excretion (66) with high protein consumption. It has been speculated that dietary protein and aromatic aminoacids may increase gastrin and gastric acid secretion, by interacting with calcium sensing receptors on antral G cells and parietal respectively (67, 68). In fact, the calcium sensor agonist Cinacalcet® which is currently used in the treatment of hyperparathyroidism has structural similarity to phenylalanine and tyrosine. It is plausible to suggest that increased gastric acid secretion perhaps by improving calcium solubility may increase intestinal calcium absorption.

The effects of high dietary protein: short-term clinical studies

The exact causal relationship between high protein consumption and bone disease could not be derived from observational studies. Furthermore, to date, there is no large scale controlled study that has investigated the pathogenic role of high animal protein intake on bone. Our

knowledge of a causal relationship between high protein consumption and bone disease is limited to short-term physiological studies.

In one 2-week study in 39 healthy premenopausal women, dietary protein was reduced from a habitual intake of 1.1 g protein /kg body weight/day to the U.S. recommended dietary allowance (RDA) of protein of 0.8 g protein/ kg body weight/day (69). This change significantly decreased urinary nitrogen (a marker of protein intake) and significantly reduced net acid excretion. On the diet with RDA protein content, urinary calcium decreased significantly by 1 mmol/day (42 mg/day) and urinary N-telopeptide (a marker of bone resorption) decreased significantly (Figure 6). These changes were achieved despite similar caloric intake and constant dietary compositions of sodium, potassium, and phosphorus between the two diets.

In another study, consumption by 10 healthy subjects of a low-carbohydrate high-protein diet (70) for six weeks delivered a significant acid load of 50 meq/day and increased urinary calcium by 2.5 mmol/day (100 mg/day). The increase in urinary calcium was not compensated by an increase in fractional intestinal calcium absorption. As a result, the estimated

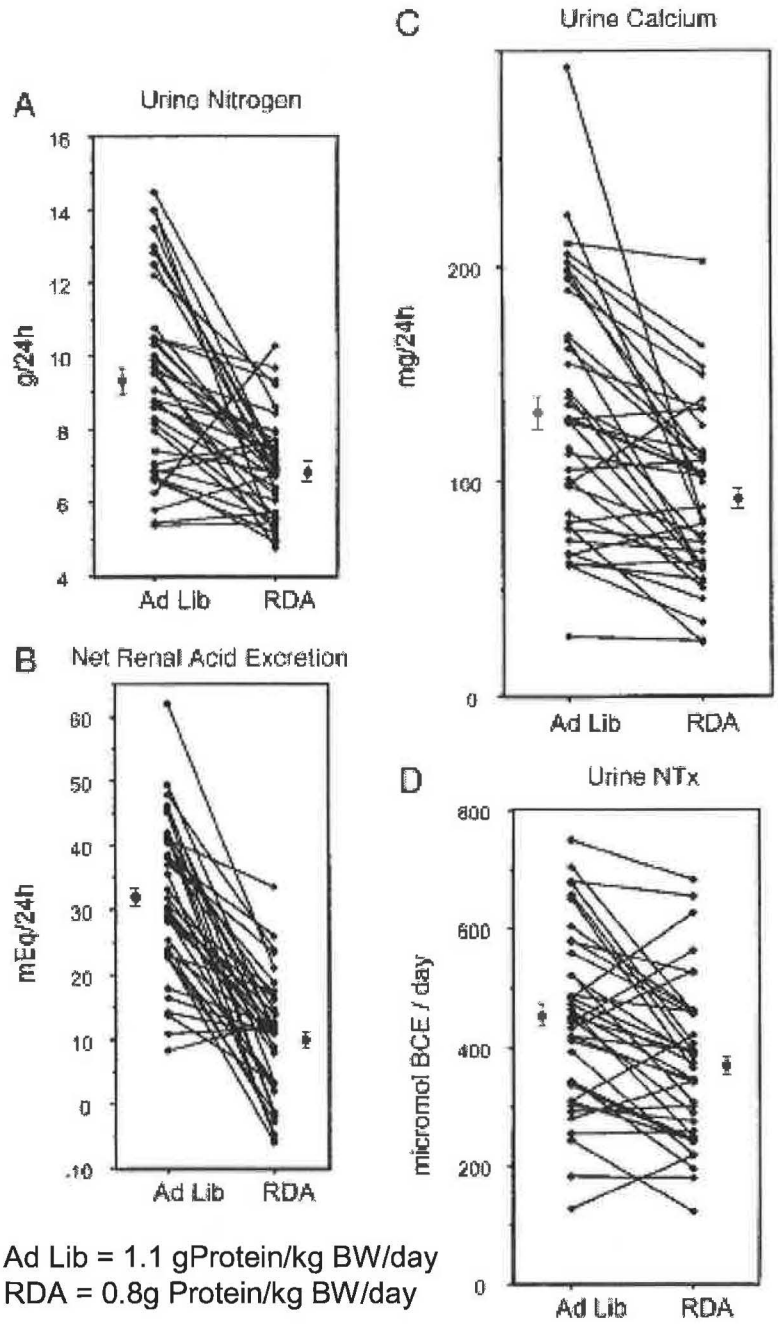


Figure 6. Changes in Urinary Parameters with Reduction in Protein Intake to the Recommended Daily Allowance (0.8g of Protein/kg Body Weight/day).

calcium balance decreased significantly by 90 to 130 mg/day (2.25 to 3.24 mmol/day). The serum total carbon dioxide concentration did not change significantly, despite the delivery of a markedly high acid load. Thus, it is plausible to suggest a potential role of bone as an extracellular buffer to maintain normal acid-base homeostasis (71), despite marked endogenous acid production.

No definitive conclusion could be derived from the results of the short-term physiological investigations to the effect of chronic protein load on skeletal bone health. Further prospective investigation of the potential increase in risk of bone loss with a high protein intake is warranted.

Pathogenetic mechanisms of high dietary protein and aging-induced bone loss

In healthy adult subjects in a steady state, the endogenous acid production (EAP) matches net acid excretion (NAE) (72). The homeostatic mechanism regulating acid-base balance is finely tuned. It has been shown that changes within a wide range of EAP induced by diet ranging from 0 to 150 meq/day (73) resulted in minimal changes in serum extracellular bicarbonate concentration. However, the stimulation of this homeostatic mechanism has a "trade off" similar to the adaptation mechanism previously described in the regulation of calcium, phosphorus and PTH homeostasis during the progression of chronic renal failure. The adaptation mechanism with chronic metabolic acidosis in response to the increase in EAP involves the release of alkali salts from the bone in addition to the increase in the urinary ammonium (NH_4^+) and titratable acidity excretion by the kidney to neutralize an excess acid load and to maintain a near normal serum bicarbonate concentration (Figure 7).

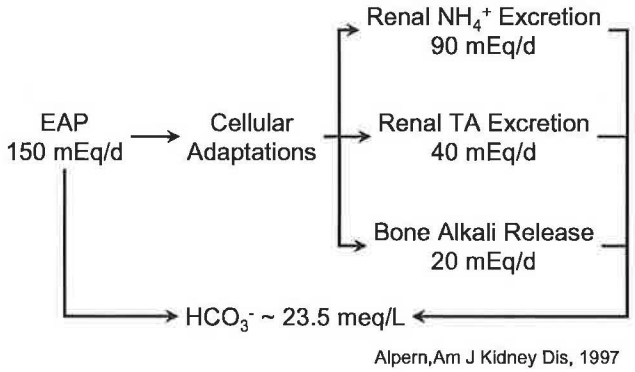


Figure 7. Acid-Base Homeostasis in Elderly Subjects and Individuals on "High Protein" Diets

Two commonly unrecognized clinical conditions associated with chronic metabolic acidosis are aging and excessive meat intake. Several investigators have provided evidence of a progressive decline in plasma bicarbonate concentration and blood pH with aging (74). These changes were shown to occur despite a habitual dietary intake. Aging is associated with a progressive loss of nephron mass, which results in progressive decrease in glomerular filtration rate (75). It has been demonstrated that the renal capacity to excrete an acid load is diminished in older individuals (74). Therefore, it is conceivable that a low grade chronic metabolic acidosis is created in the elderly consuming a habitual Westernized acid ash diet. The impact of this condition will be grave in this population due to its high risk of osteoporosis and bone fractures.

Pathogenesis of the protective role of protein in bone health

Over 6 decades ago, Fuller Albright suggested that osteoporosis may not be due to "lack of calcium and phosphorus in the diet, but may be really due to protein starvation" (76). Additional data has emerged in the recent years to support Albright's hypothesis of a protective role of protein in bone health.

Pathogenetic mechanisms of protein-reduced bone loss

Dietary proteins play a key regulatory role in the production and the metabolism of insulin-like growth factor 1 (IGF-1) (Figure 8) (77). IGF-1 has been shown to stimulate both proliferation and differentiation of osteoblasts, and thereby increases bone collagen synthesis (78-80). The serum circulating concentrations of IGF-1 and IGF-1 binding protein 3 have been shown to be lower in osteoporotic patients with vertebral fractures than in osteoporotic individuals without fractures (Figure 9) (81). A defect in osteoid mineralization has also been recently demonstrated in the selective knockout of IGF-1 receptor gene in mouse osteoblasts (82). Moreover, protein intake may directly affect bone collagen structure as abnormalities in lysine residues in the α1 Type 1 collagen of bone have been shown in protein-restricted rats (83). Lysine plays a significant role in Type 1 collagen cross linking which is predominantly found in bone. It has not been clearly elucidated whether lysine directly affects calcium homeostasis. Furthermore, protein malnutrition due to an impaired anabolic effect (27) has been shown to reduce muscle strength and perhaps increase frailty and fall in older subjects, which in turn increases the risk of bone fractures.

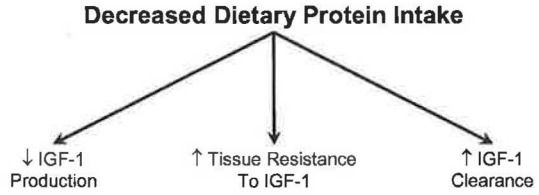


Figure 8. Impaired IGF-1 Action associated with Decreased Protein Intake

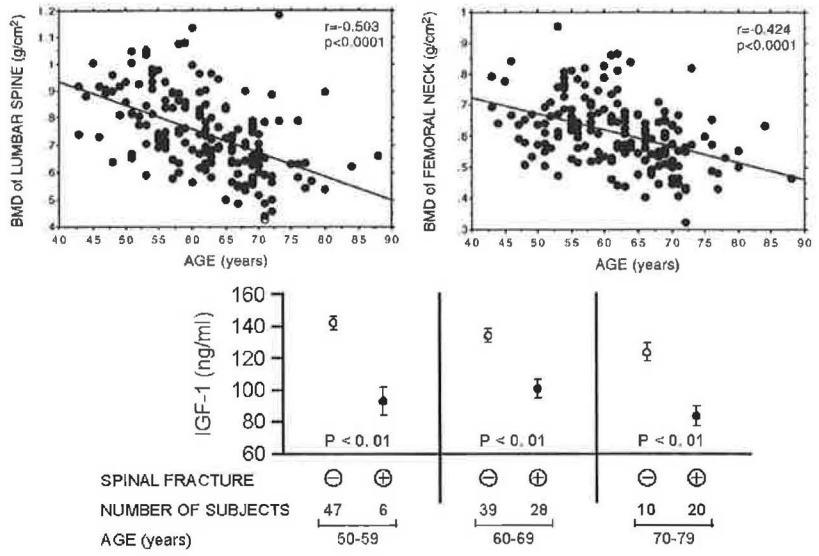


Figure 9. Correlation Between Serum IGF-1 Levels, BMD, and Fractures

Protein deficiency may also enhance skeletal bone resorption. Bone resorption is mediated by the upregulation of cytokine release, as well as by the dysregulation of gonadal hormonal metabolism (84, 85). The impact of protein deficiency has been recently examined in an experimental animal model, by inserting titanium rod implants into tibial bone (85). Low protein

(2.5%) isocaloric diet compared to a normal protein isocaloric diet (15%) was shown to induce defective bone microarchitecture, and to significantly diminish resistance to implant pull-out (85).

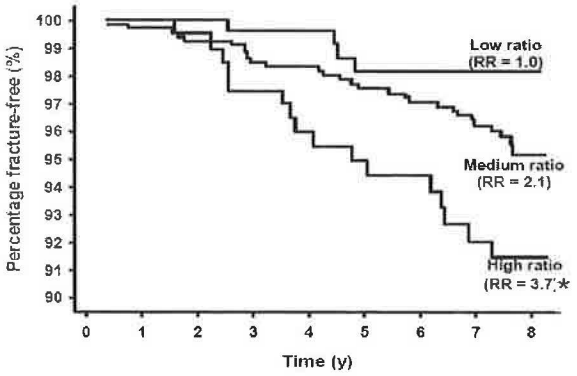
Protein supplementation and reduced bone loss-clinical studies

There is substantial observational evidence to suggest that protein supplementation influences the outcome of hip fractures. Moreover, a randomized double-blind study conducted in 82 elderly patients with recent hip fractures demonstrated that protein supplementation compared to isocaloric placebo (86) resulted in a significantly higher serum circulating concentration of IGF-1, significantly lower proximal femoral bone mineral density loss, and shortened recovery period. This study did not conclusively exclude the possibility that IGF-1 induced increased muscle strength that in turn lowered the loss of bone mineral density at the proximal femur.

However, there has been disagreement on the effects of protein consumption and its impact on bone fractures (11). High protein consumption has been shown to be associated with an increased incidence of bone fractures in observational cross-cultural studies (22, 23, 34), as well as within population studies. The low bone mineral density and hip fractures in subjects with underlying protein malnutrition does not totally preclude the association of high protein consumption with an increased risk of bone fractures, in an otherwise healthy protein-replete population.

Countermeasures to dietary protein induced-bone loss

Alkali therapy is believed to prevent bone loss by several mechanisms. It may inhibit osteoclastic bone resorption by the direct action of alkali (87). Furthermore, alkali treatment may indirectly prevent bone resorption by reducing urinary calcium (88, 89). Finally, there is also some evidence that alkali treatment may stimulate bone formation (87).



Sellmeyer, Am J Clin Nutr, 2001

Figure 10. Animal - Vegetable Protein Ratio and Probability of Hip Fracture

Dietary measures

Animal proteins are a dietary source of acid ash, while vegetable proteins are metabolized without significant production of endogenous acid. In a recent longitudinal prospective study, the contribution of a high ratio of dietary animal to vegetable protein on bone mineral density and the risk of hip bone fractures in 1035 Caucasian elderly women was examined (90). The women

with a high ratio of animal to vegetable protein consumption had a higher rate of femoral neck bone mineral density loss than those with a low ratio. A proportional hazard model adjusting for age, weight, calcium intake, smoking habit, alcohol consumption, total protein consumption, physical activity and estrogen intake was used. Survival free of hip fracture was significantly lower in those with the high ratio of animal to vegetable protein intake (RR = 3.7, p=0.04) than those with low ratio (RR = 1.0) and subjects with medium ratio (RR = 2.1) (Figure 10). These results suggest that the effect of protein intake on bone is related to endogenous acid production.

Pharmacological countermeasures

In a recent study, calcium and phosphorus balances were examined in postmenopausal women with a high protein intake (89). Potassium bicarbonate treatment at the dosage equivalent to neutralize endogenous acid production caused a significant fall in urinary calcium excretion and a net positive calcium balance. This resulted in a significant fall in bone resorption and a rise in bone formation as assessed by the fall in urinary hydroxyproline excretion and the rise in serum osteocalcin concentration, respectively.

The above findings are in part consistent with our study in 18 healthy postmenopausal women with dietary protein intake equivalent to the recommended dietary allowance (RDA) of 0.8 g protein/kg/d for two weeks (91). Potassium citrate at a much smaller dose of 40 meq/day caused a significant reduction in urinary calcium excretion and a significant rise in estimated calcium balance (Figure 11).

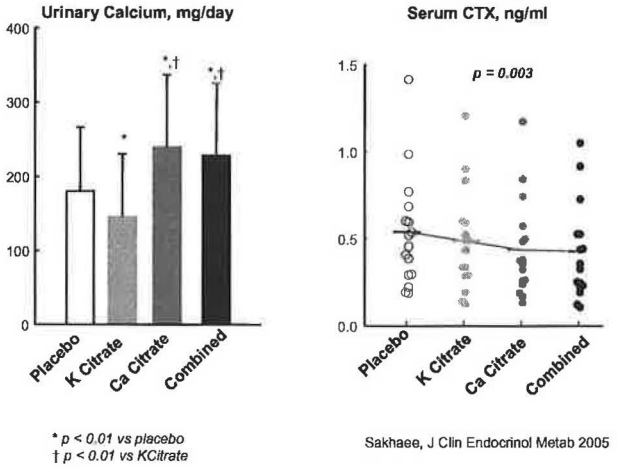


Figure 11. Change in Urinary Calcium and serum CTX (a marker of bone resorption) in healthy postmenopausal women treated with K Citrate, Ca Citrate or their Combination

The results of the above studies were also confirmed in healthy young subjects who were in a mild metabolic acidosis while maintained on habitual Westernized diet. An equimolar amount of sodium bicarbonate and potassium bicarbonate was substituted for sodium chloride and potassium chloride (92). Lowered urinary calcium excretion and urinary markers of bone resorption occurred independent of potassium intake. The result was suggestive of a protective effect of alkali treatment neutralizing the relatively high acid ash diet.

The hypocalciuric effect of alkali therapy has been shown to be sustained during chronic alkali treatment (93). This effect has been demonstrated to be dose-dependent and is greatest in those subjects with the highest baseline urinary calcium excretion. It has been inferred that with chronic alkali treatment and sustained hypocalciuria, a substantial amount of bone calcium content may be spared (93). However, it has also been argued (94, 95) that a reduction in intestinal calcium absorption from alkali-induced hypocalciuria may negate the bone sparing effect of alkali treatment. Therefore, it is necessary to design long-term clinical trials to examine whether chronic alkali treatment improves bone mineral density and reduces the incidence of bone fractures.

CONCLUSIONS

Protein malnutrition is associated with low bone mineral density and increased fall and fracture risk. On the other hand, there is increasing evidence that chronic subtle metabolic acidosis caused by aging and increased dietary protein consumption potentially contributes to bone loss and osteoporosis. However, due to the subtle nature of this effect, these conditions are generally unnoticed by most clinicians. Regardless of the deficiencies in our current knowledge, physicians must be reminded to provide appropriate care to patients to overcome the consequence of chronic subtle metabolic acidosis on bone. Alkali treatment is a logical choice to maintain the anabolic effect of protein on bone, while mitigating its deleterious influence. One major question is whether the hypocalciuric effect of long-term alkali treatment translates into a positive calcium balance or is due to an adaptive decline in intestinal calcium absorption. Further research must focus on innovative approaches that will help improve our current knowledge into the long-term effect of protein on bone.

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