REDUCTION OF DIETARY ACID LOAD AS A POTENTIAL COUNTERMEASURE FOR BONE LOSS ASSOCIATED WITH SPACEFLIGHT

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Abstract
In several studies we tested the concepts that diet can alter acid-base balance and that reducing the dietary acid load has a positive effect on maintenance of bone. In study 1, (n = 11, 60-90 d bed rest), the renal acid load of the diet was estimated from its chemical composition, and was positively correlated with urinary markers of bone resorption ($P < 0.05$); that is, the greater the acid load, the greater the excretion of bone resorption markers. In study 2, in males (n = 8, 30 d bed rest), an estimate of the ratio of non-volatile acid precursors to base precursors in the diet was positively correlated ($P < 0.05$) with markers of bone resorption. In study 3, for 28 d subjects received either a placebo (n = 6) or an essential amino acid supplement (n = 7) that included methionine, a known acid precursor. During bed rest (28 d), urinary calcium was greater than baseline levels in the supplemented group but not the control group ($P < 0.05$), and in the supplemented group, urinary pH decreased ($P < 0.05$). In study 4, less bone resorption occurred in space crew members who received potassium citrate (n = 6) during spaceflight of 4-6 months than in crew members who received placebo or were not in the study (n = 8) ($P < 0.05$). Reducing acid load has the potential to mitigate increased bone resorption during spaceflight, and may serve as a bone loss countermeasure.

Keywords: Nutrition; Diet; Acid-base balance; Bone

1. Introduction

Changes in diet alone probably would not mitigate bone loss associated with space flight. A suboptimal diet can, however, exacerbate bone loss associated with disuse or space flight. In this review, we focus on acid-base homeostasis in the diet and its effects on bone health.

2. Acid-base homeostasis and bone

One of the theories describing a mechanism for a detrimental effect of acidosis on bone is based on the chemical makeup of bone. Because bone is a substantial reservoir of ions that can buffer excess acid loads, chronic small perturbations of acid-base balance in the body can induce prominent changes in the chemical makeup of bone [1, 2]. *In vitro* studies show that acidic environments stimulate osteoclast activity and increase bone resorption [1, 3, 4]. A small change, close to the physiological range, in pH of culture medium also stimulates bone resorption [4, 5]. *In vivo*, conditions that induce metabolic acidosis are also commonly associated with altered bone metabolism [6-9].

Dietary intake can influence endogenous acid production, not because of the pH of the food itself, but because non-volatile acid and base precursors (compounds that yield acid, or base, after they are absorbed and metabolized) exist in foods [10]. If the diet contains more acid precursors than base precursors, chronic low-grade metabolic acidosis can result [11]. Endogenous acids include sulfuric acid produced from the catabolism of sulfur-containing amino acids [12]. Diets high in protein (and/or sulfur-containing amino acids), particularly ketogenic diets, are commonly associated with increased urinary calcium excretion and lower urinary pH [13-20].

3. Effect of dietary protein on bone

The effect of dietary patterns, specifically protein intake, on bone has been examined in many studies. Frassetto and colleagues developed a model for estimating net endogenous acid production from the amount of acid and base precursors in the diet [21]. According to their model, renal net acid excretion can be predicted from only two dietary components: total protein and potassium. Diet can influence endogenous acid production because food contains acid and base precursors (compounds that yield acid or base according to their metabolism post-absorption) [10, 22]. If the diet contains more acid precursors than base precursors, chronic low-grade metabolic acidosis can result [11].

Dietary protein is essential for bone health because of its structural and functional roles in bone metabolism. Low-protein diets (containing less than the recommended United States dietary allowance of 0.8 g protein/kg body weight per day) have a negative impact on bone metabolism [23-27]. Low-protein diets acutely decrease calcium absorption in healthy young women, and this decrease is accompanied by an increase in serum parathyroid hormone that persists for 2-4 weeks [25]. Kerstetter and colleagues found that a low-protein (0.7 g/kg) diet resulted, within 4 days, in secondary hyperparathyroidism that persisted for 4 weeks in the young women [25]. Similar results from men and postmenopausal women were reported [27]. Giannini and colleagues [26] drew similar conclusions when 18 patients with idiopathic hypercalciuria consumed 0.8 g protein/kg for 15 days.

A very consistent calciuric response to high intakes of pure protein or amino acids has led to the tentative conclusion that high protein intakes might be injurious to bone, but

studies addressing this research question have produced inconclusive results. Many studies show positive associations between increased animal or total protein intake and bone loss, meaning that a higher protein intake is associated with more bone loss [28-33], and many others show negative associations [23, 34-38]. The answer to the controversial question of whether high protein intake is detrimental or beneficial to bone likely lies in its interactions with other nutrients in the diet such as potassium, calcium, sodium, or other minerals, or with non-nutrients such as phytate and oxalate.

If the hypothesis is true that an imbalance in acid and base precursors in the diet can contribute to chronic low-grade metabolic acidosis and therefore to bone resorption, then it is erroneous to look only at protein intake in these studies. Many studies show that the highest quartile of protein intake is associated with the lowest incidence of bone resorption [35, 36, 39], but no attention was given to the base-forming components of the diet in these studies. Subjects in the highest quartile of protein intake could have been consuming the highest levels of base precursors as well. Unlike the controversy with protein, nearly all studies of the associations of potassium and/or excess dietary base with bone show positive results (lower incidence of bone resorption) with increased potassium intake or neutralization of the diet with bicarbonate [32, 40-48].

Since calcium is the most abundant mineral in bone, it is logical that calcium intake may also influence the effect of dietary protein on bone. The favorable effect of a high-protein diet on bone mass, as repeatedly observed in males and females, requires an adequate supply of vitamin D and calcium [34, 49, 50]. Results of several studies suggest that high protein intake is beneficial to bone when calcium intake is high, but detrimental when calcium intake is low [28, 34, 38, 45, 51]. In one observational study, no evidence was found for a relationship between hip fracture and calcium intake or protein intake from non-dairy animal sources, but subjects in the lowest quartile of calcium intake and highest non-dairy animal protein intake had twice the risk for this type of fracture [28]. Other food components, including phytate or oxalate, may exacerbate a negative effect of protein on bone because these compounds reduce intestinal absorption of calcium and other minerals [52, 53].

4. Implications for space flight

Bed rest, an analog of space flight, induces a state of negative calcium balance and bone loss [54, 55]. Thus, it provides an experimental design in which healthy subjects are studied, and dietary intake is both adequate and well controlled. We hypothesized that the effect of bed rest on bone would parallel the effect of low calcium intake on bone in ambulatory subjects; therefore, a higher acid load during bed rest would produce more of an effect on bone than when subjects are ambulatory with adequate calcium intake.

A series of 4 studies are presented here that demonstrate that an acid load in the diet does indeed have an impact on bone during real or simulated weightlessness. In the first study, 11 subjects participated in a 60-90 d bed rest study where we found that the

potential renal acid load (estimated from the diet [56]) was positively correlated with markers of bone resorption during bed rest. Urinary sulfur excretion and urine pH were also correlated with markers of bone resorption.

In another study (study 2) of male identical twins ($n = 8$), we found that dietary patterns had a noticeable effect on the degree of bone loss during bed rest [57]. The ratio of dietary animal protein to potassium was used to estimate the ratio of non-volatile acid precursors to base precursors in the diet. A higher ratio of acid to base precursors in the diet had a more substantial effect on bone and calcium metabolism during bed rest than during ambulatory conditions. The ratio of acid to base precursors in the diet was positively correlated ($P < 0.05$) with the rate of excretion of markers of bone resorption and calcium during the latter part of a 30 d bed rest [58, 59]. An increase of 30% in the ratio of animal protein to potassium intake was associated with an approximately 4-fold increase in urinary n-telopeptide excretion.

These findings were consistent with those of a similar 28-d bed rest study (study 3) in which use of an amino acid and carbohydrate supplement (45 g essential amino acids per day) was associated with increased bone resorption in subjects who did not perform any exercise [58, 59]. The supplemented group received about 215% of the recommended daily intake of methionine, a known acid precursor. Although the amino acid supplement protected against loss of lean body mass, the supplemented group ($n = 7$) tended to have more bone resorption than the placebo group ($n = 6$). During bed rest, the rate of urinary calcium excretion was greater than baseline levels in the supplemented group ($P < 0.05$) but not the control group, and urinary pH decreased ($P < 0.05$) in the supplemented group but not the control group, suggesting that the supplement may have altered acid/base balance. Because the supplement was the only difference between the groups, it is likely that the methionine (1.5 g/d) in the supplement was provided in excess of the amount needed for protein synthesis, and this contributed to a mild acidotic effect large enough to alter urinary pH and bone metabolism.

It is important to note that the latter two studies do not necessarily support the use of low-protein diets for bone health. Rather, they support the idea that a balanced diet with base precursors (vegetables and fruits), acid precursors (protein sources), and adequate calcium and phosphorus intake is optimal for bone health. These findings provide an example of space research that could have an impact on the health of the general public. Use of a space flight analog system has led to a better understanding of the role of diet in bone health, which has helped to clarify some of the discrepancies in the general scientific literature.

5. Space flight: effects of an alkali load

In addition to data from the ground-based analogs of space flight, limited space flight data are available. Preliminary data (study 4) provided evidence that less bone resorption occurred ($P < 0.05$) in crew members who received 20 mEq/d potassium citrate ($n = 6$)

during long-duration spaceflight (4–6 months) than in those who received placebo or those not in the study (n = 8). These data, which showed that the alkali supplement mitigated some of the bone loss associated with space flight, were consistent with data from ground-based studies in which potassium citrate supplementation decreased markers of bone resorption [60-62]. In ground-based studies, alkali salts inhibit osteoclast resorption and even stimulate osteoblast formation.

6. Summary

The bed rest studies, along with the preliminary space flight data, suggest that reducing acid load, either by ingesting an alkaline salt such as potassium citrate or by altering diet by decreasing the ratio of protein to potassium, has the potential to mitigate increased bone resorption during space flight. Reducing alkali load alone will likely not completely eliminate bone loss associated with space flight, but these data do suggest that an acid load can exacerbate bone loss.

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