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Review

The effects of dietary protein and amino acids on skeletal metabolism

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ABSTRACT

Dietary protein is required for optimal skeletal growth and maturation. Although Recommended Dietary Allowances (RDAs) exist for global dietary protein intake, the level and sources of dietary protein that are optimal for skeletal health over the life continuum have not been established. This is partly due to the difficulty in quantifying the effects of variable levels of a nutrient's intake over a lifetime as well as the complex nature of the relationships between dietary protein and calcium economy. Areas of current uncertainty include the precise source and amount of dietary protein required for optimal skeletal accretion and maintenance of skeletal mass, as well as the site-specific effects of dietary protein. The cellular and molecular mechanisms that underpin the actions of dietary protein on mineral metabolism and skeletal homeostasis remain unclear. This review attempts to summarize recent data bearing on these questions.

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1. Introduction

There is no question that dietary protein is required for skeletal health. Dietary protein is essential for collagen synthesis and the production of non-collagenous matrix proteins in bone (Barbul, 2008). A variety of bone specific extracellular matrix proteins such as osteopontin, bone sialoprotein and fibronectin are also important for the orderly mineralization of the skeleton.

Although recommendations have been made regarding levels of protein intake that are considered adequate for children, adolescents and adults (Food and Nutrition Board IoM, 2002/2005), the level of dietary protein that is optimal for skeletal health is a largely unexplored area. The potential relationship between dietary protein and bone health is particularly relevant to skeletal health in later adult life, at which time bone loss and fracture risks increase. In that context concern has been raised that diets rich in animal protein are deleterious to the adult skeleton (Bushinsky, 2001; Remer, 2000). This is commonly referred to as the acid–ash hypothesis. According to this formulation, the endogenous acid load imposed by the metabolism of sulfur-containing amino acids requires buffering in bone that causes increased bone resorption, which in turn results in the loss of calcium from bone. However, recent data have led to a reconsideration of dietary protein's actions vis-à-vis the skeleton because of studies suggesting a beneficial effect of protein on mineral metabolism, bone mass and fracture risk (Beasley et al., 2014; Hannan et al., 2000; Kerstetter et al., 2005). This review summarizes recent data bearing on this controversy.

2. The impact of dietary protein on bone accretion during growth

During skeletal growth, it appears that there may be regional differences in the response to a given source of dietary protein. In the

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setting of a modestly restricted protein intake, 10-week-old mice fed a casein-based diet for 60 days showed a greater increase in femoral bone mineral density (BMD) than mice fed an equivalent soy-based protein diet (Table 1, Rouy et al., 2014). In contrast, spinal BMD was not influenced by either the level or source of dietary protein. Assessment by micro computed tomography revealed significantly greater bone area at the femoral diaphysis, after correcting for changes in weight, in animals on the casein-based, protein restricted diet compared to the soy diet of equal protein level. Indices of bone formation, including osteoid surface and mineral apposition rate, as estimated by micro CT were reduced in the soy fed protein-restricted animals, but not in the animals fed the protein-restricted, casein based diet or a soy-based diet containing a normal amount of protein (20%). Ten-week-old growing rats were fed an energy restricted diet or diet in which both protein and energy were restricted. When casein was supplemented to either one of these diets such that the percent of energy from protein equaled or exceeded that in a normal diet the animals demonstrated a significant protective effect against bone loss (Table 1, Mardon et al., 2009). BMD was lowest in animals that were placed on the energy and protein restricted diets compared to animals whose diets were solely calorically restricted. Conversely, diaphyseal BMD of the femur was not impacted by level of dietary protein when caloric intake was limited, suggesting that during periods of caloric restriction dietary protein may influence trabecular BMD to a greater extent than cortical BMD. As anticipated, restrictions in energy and protein intake prevented increases in body weight in growing animals. However, a shift in the macronutrient composition of the diet to include a greater proportion of calories from casein allowed for some weight gain (albeit not normal) despite deprivation of total energy. Thus, higher casein intakes appear to offset some of the deleterious effects on growth of a calorically restricted diet. In the same study, energy restriction was accompanied by a fall in circulating levels of the anabolic hormone, insulin-like growth factor-1 (IGF-1), which could not be fully compensated by an increase in dietary protein intake even when protein exceeded 20% of total energy. In summary, this latter study suggests that in the setting of limited energy intake and impaired growth rates, dietary casein supplementation may provide site-specific protective effects on bone that are independent of IGF-1.

In children and adolescents up to 18 years of age the current Recommended Dietary Allowance (RDA) for protein ranges from 0.85 to 1.1 g/kg (Food and Nutrition Board IoM, 2002/2005). Recently, it has been suggested that intakes above the current recommendation and in particular certain sources of dietary protein may accelerate bone accretion during growth and thereby increase peak adult bone mass. In healthy, white prepubertal boys, total protein intake from mixed animal sources remained significantly associated with bone mineral content (BMC) after controlling for physical activity (Table 1, Chevalley et al., 2008). In addition, a protein intake of approximately 2.0 g/kg, which is above the current RDA for this age group, augmented the positive impact of physical activity on BMC. Moreover, long-term total protein intake (g/d), assessed by weighed and semiquantitative food records, was found to be a significant positive predictor of bone modeling (as estimated by the rate of cortical apposition) in 229 male and female children (Table 1, Alexy et al., 2005). Dietary sulfur containing amino acids did not appear to attenuate this effect, although the estimated potential renal acid load (PRAL) did.

3. The effect of dietary protein on adult skeletal health

The effect of dietary protein on the mature skeleton after epiphyseal closure and particularly on the aging skeleton remains an area of considerable controversy. For nearly 90 years, we have known that dietary protein affects calcium metabolism (Sherman, 1920). It has long been known that increasing dietary protein increases urinary calcium excretion (Kerstetter et al., 2003). Balanced studies conducted in the 1970s and 1980s suggested that dietary protein did not change intestinal calcium absorption despite the hypercalcuria (Allen et al., 1979; Anand and Linkswiler, 1974; Hegsted and Linkswiler, 1981; Kim and Linkswiler, 1979), leading to the conclusion that increasing dietary protein resulted in a net negative calcium balance. Consistent with this, earlier epidemiologic studies suggested that increasing dietary protein was associated with an increased risk for fracture in middle-aged and elderly women and men (Table 2, Abelow et al., 1992; Feskanich et al., 1996; Frassetto et al., 2000; Meyer et al., 1997). However, more recent short-term studies using dual-stable calcium isotopes have demonstrated that increasing dietary protein improves intestinal calcium absorption and that the increment in urinary calcium can be quantitatively explained by the increase in intestinal calcium absorption (Kerstetter et al., 1998, 2005). Furthermore, data from the Framingham Osteoporosis Study showed that higher protein intakes in both men and women was associated with slower rates, not higher rates, of bone loss at the femoral neck and spine (Table 2, Hannan et al., 2000). Two recent epidemiological studies also reported a positive relationship between dietary protein and skeletal health, with higher protein intakes being associated with greater total and hip BMD and total BMC, and lower rates of forearm fracture (Table 2) (Beasley et al., 2014; Kim et al., 2013). Potential mechanisms by which dietary protein affects calcium metabolism and skeletal homeostasis will be reviewed later.

3.1. Dietary protein-induced changes in calcium absorption efficiency

For every 40 g increment in dietary protein, urinary calcium increases by approximately 50 mg (Kerstetter et al., 2003). It was generally assumed that the dietary protein-induced increases in urinary calcium results from the release of skeletal buffer and calcium in response to the metabolic load imposed by sulfur-containing amino acids (Barzel and Massey, 1998; Bushinsky, 2001; Bushinsky and Frick, 2000; Remer, 2000). However, as just noted, studies using dual stable calcium isotopes have found that in the short term, dietary protein profoundly affects intestinal calcium absorption (Fig. 1). In particular, Kerstetter et al. demonstrated that as compared to a high protein diet (2.1 g protein/kg/d), restricting dietary protein to 0.7 g protein/kg/d results in hypocalciuria caused by a reduction in fractional intestinal calcium absorption (Kerstetter et al., 1998). Additionally, increasing dietary protein from 1.0 to 2.1 g protein/kg/d resulted in an increase in urinary calcium that is not accompanied by evidence for increased bone resorption. The incremental change in urinary calcium could be nearly quantitatively explained by the improvement in intestinal calcium absorption that accompanied the increase in dietary protein (Kerstetter et al., 2005). In this experiment, natural foodstuffs were used and the dietary contents of calcium, sodium and phosphorus were controlled so that they were the same or very similar on both the 1.0 g/kg and 2.1 g/kg protein diets. Dietary protein was increased using both animal and vegetable protein sources (Fig. 1).

There is some evidence to suggest that the effect of dietary protein on intestinal calcium absorption differs by protein source (Fig. 1; Heaney et al., 2000; Kerstetter et al., 2006). In one study in a small cohort of adult women calcium absorption tended to be lower when soy protein was substituted for meat protein (Kerstetter et al., 2006). A second study in 16 young and middle-aged males compared the bioavailability of calcium from a fortified soy protein beverage to that from cow's milk (Heaney et al., 2000). The investigators observed a 25% reduction in calcium absorption from the soy beverage as compared to milk. These differences may be due to the phytic acid contained in soy, which is known to bind calcium. The aforementioned studies solely evaluated acute changes in intestinal