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Excessive Vitamin A Consumption and Fractures: How Much is Too Much?

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Introduction

The term vitamin A is a generic reference to a family of essential, fat-soluble dietary compounds that have the biologic activity of retinol (1). They are required for vision, growth, reproduction, cell proliferation, cell differentiation, and the integrity of the immune system (2). Dietary sources of vitamin A include animal products (fish, liver, and dairy products), fortified foods (milk, butter, and cereal), and supplements (3). Carotenoids can serve as a source of precursors of vitamin A and are found in fruits and vegetables such as carrots, tomatoes, cantaloupe and spinach (4). Vitamin A activity is expressed as retinol equivalents (RE). One RE is equal to 1 µg retinol or 3.33 international units (IU) of vitamin A activity as retinol.

For more than half a century it has been known that ingestion of toxic amounts of vitamin A leads to adverse skeletal effects (5). In animals, retinoic acid antagonizes the ability of vitamin D to maintain normal calcium levels in serum (6). It also stimulates osteoclast formation and suppresses osteoblast activity (7). Each of these mechanisms may contribute to the accelerated bone resorption and fractures seen with hypervitaminosis A (8). It has also been shown in humans that large amounts of vitamin A can lead to hypercalcemia and gross bone abnormalities, including irregular bone turnover in patients treated with retinoids for skin diseases (9).

Although there is little question that consuming large amounts of vitamin A can have detrimental effects on bone, until recently it received little attention because the levels consumed in the studies and clinical cases (25,500 – 37,500 RE/day) were much higher than an average person could consume even with the modest use of vitamin supplements (8). However, growing evidence suggests that long-term ingestion of slightly elevated amounts of vitamin A—amounts approaching the currently recommended levels—can contribute to decreased bone mineral density (BMD), osteoporosis, and fractures. These findings raise the question: how much vitamin A is too much?

Evaluation of Vitamin A Recommendations

In 2001, the Food and Nutrition Board (FNB) of the Institute of Medicine reviewed the possible risks associated with high intake of retinol (10). At their disposal were several epidemiologic studies comparing vitamin A consumption with decreased BMD and fractures in humans. Four of the studies found no association between BMD and vitamin A intake (11, 12, 13, 14). One study found that vitamin A intake was negatively correlated with bone mass at a level that approached statistical significance (15). Another large, well-designed study, done in 1998 by Melhus et al., had been the focus of much attention and found a large association between hip fracture risk and vitamin A intake in Swedish women. Melhus et al. concluded that for vitamin A intake greater than 1,500 RE/day compared with intake less than 500 RE/day, BMD was reduced by up to 14% and the risk for hip fracture was doubled (16).

After reviewing the evidence, the FNB decided to ignore it in their recommendations. They found the relevant studies “provocative but conflicting” and concluded that “they are not useful for setting an upper limit for vitamin A (10).” Instead they based their recommendations on other effects, such as the risk of birth defects, more widely recognized as related to excessive vitamin A consumption. The FNB suggested females and males consume 700 RE/day and 900 RE/day of vitamin A, respectively, with an upper limit of 3,000 RE/day (10). These recommendations are troublesome in that Melhus et al. demonstrated adverse skeletal effects at

intake levels of 1,500 RE/day, half of the recommended upper limit. In addition, consumption of greater than 1,500 RE/day is easily obtainable using supplements. Perhaps more convincing evidence is needed.

Since the FNB review was completed in 2001, eight other studies have probed the relationship between vitamin A, BMD, and fractures. Although not all of the studies found a relationship between these variables, the majority of them found a significant negative association. Review of these studies warrants attention in determining safe amount of vitamin A intake.

Studies Finding No Vitamin A/Bone Relationship

Of the eight current studies, three of them determined no relationship between vitamin A and BMD or fractures. One of these studies is strong; the other two are questionable. The strongest study was based on data collected in the Third National Health and Nutrition Examination Survey, 1988-1994 (NHANES III). NHANES III was a complex, stratified probability sample intended to be representative of the noninstitutionalized population of the United States. The NHANES III survey collected data on BMD and fasting serum retinyl esters (a marker of potential excess vitamin A). BMD was measured in four sites using dual-energy x-ray absorptiometry. After excluding participants with conditions or characteristics that might affect vitamin A metabolism or BMD, the study included 5,790 males and females. Although the prevalence of high fasting serum retinyl esters concentration and low BMD were both substantial in the sample, there was no significant association between the variables (17). These findings may be difficult to interpret, however, because there was a single measurement of blood retinyl esters without evidence that this reflects long-term retinol intake.

A second prospective, randomized, single-blind study of vitamin A supplementation was conducted in 80 healthy men. The sample size was small and the results are not directly applicable because it only assessed short-term supplementation (six weeks). Men were given a vitamin A supplement bought at a local health food store or a placebo to take on a daily basis. Throughout the six weeks, markers of bone turnover were measured in serum samples. The study found that vitamin A supplementation does not affect bone turnover (18). However, as noted, the results may not be directly applicable as even the authors noted, "Whether long-term vitamin A supplementation might have adverse skeletal effects remains to be determined."

The third study that found no association between vitamin A intake and BMD was conducted in Iceland (19). This study was very small, criticized for not controlling for several confounding variables, and has received little merit.

Mounting Evidence

Since the FNB review of vitamin A in 2001, five of the eight studies found a significant relationship between vitamin A intake and its actions on bone. The first two studies provide indirect evidence for this relationship while the other three are large, well-designed studies that provide direct evidence of an association between vitamin A intake and fractures.

Indirect Evidence Supporting Vitamin A/Bone Relationship

One piece of indirect evidence for this relationship came from a December 2002 study in rats (20). As previously mentioned, it has long been known that extremely high levels of vitamin A

consumption can lead to bone deformations and fractures. This study, however, showed that an intake level one-third that of any previous dose reported to cause skeletal lesions was also able to reduce BMD and bone strength. The authors concluded, “that long-term ingestion of modest excesses of vitamin A may contribute to fracture risk.” The study, of course, is not without some weaknesses. Even the one-third dosage is still a relatively high amount of vitamin A for rats. Still, the study showed that vitamin A levels significantly lower than previously considered are detrimental to bone and may increase the risk of fractures. The same may be true for humans.

More indirect evidence for the case came from a study showing that, at least in this case, what was true for rats was also true for humans—vitamin A antagonizes the ability of vitamin D to maintain normal serum calcium levels. As already noted, the ability of vitamin A to antagonize vitamin D in rats was known (6). This study, however, was the first to show that the same thing happened in humans (21). The active metabolite of vitamin D plays an important role in intestinal calcium absorption. Calcium, in turn, is important for bone formation and maintaining BMD. Besides directly causing bone resorption, this study suggests that vitamin A can also indirectly lead to decreased BMD by interfering with the action of vitamin D.

Direct Evidence Supporting Vitamin A/Bone Relationship

In January 2002, an impressive study was published of an 18-year prospective analysis of vitamin A intake and hip fractures among postmenopausal women in the Nurses’ Health Study (22). The Nurses’ Health Study (NHS) began in 1976 when female registered nurses living in 1 of 11 US states responded to medical questionnaires. At least 90% of the cohort has responded in each two-year follow-up cycle. After including only postmenopausal women and excluding women with previous hip fractures or conditions that might alter dietary habits, the study was left with a total of 72,337 participants ranging in age from 34 to 77 years. After accounting for confounding factors and adjusting for covariates, the risk of hip fracture was almost doubled among women with retinol intakes of about 2,000 RE/day or more compared with those with intakes of less than about 500 RE/day. These results confirm the similar results reported by Melhus et al. in 1998. This study of mostly middle-class nurses, of which 98% are white, doesn’t represent the population as a whole. The results are no less impressive and concerning, though, given the large sample size and 90% follow-up rate over 18 years.

Another large study of an ambulatory community-dwelling cohort of men and women became available in August 2002 (23). This study, termed the Rancho Bernardo Study, consisted of nearly 1000 elderly men and women initially 55 – 92 years old. Retinol intake, assessed using food-frequency questionnaires, and BMD were measured at the beginning of the study and then again four years later. The study found that BMD was optimal when vitamin A intake was 600 – 900 RE/day, indicating that both low and high intakes of vitamin A may compromise bone health. Interesting, the current recommended intake of vitamin A is similar to the optimal intake levels found in the Rancho Bernardo Study. However, the study also found that annual bone loss was associated with consumption levels less than the current tolerable upper intake level of 3,000RE/day.

A final study in January 2003 found an association between serum retinol levels and fracture risk (24). The data came from 2,322 men enrolled in a population-based, longitudinal cohort study. Over the 30 years of follow-up, 266 fractures were documented within the group. Serum retinol

levels were measured only once at the onset of the study. The study concluded that the risk of fracture was highest among men with the highest levels of serum retinol. The men in the highest quintile for serum retinol as compared with those in the middle quintile were 1.64 times more likely to sustain any type of fracture and 2.47 times more likely to sustain a hip fracture. Furthermore, men with retinol levels in the 99th percentile had an overall risk of fracture greater than seven times that of men among the lower levels.

Reevaluation Needed

Although only two years have past since the FNB evaluated vitamin A recommendations, mounting evidence suggests that a reevaluation is warranted. More and more studies are demonstrating a significant risk of fractures and decrease BMD associated with levels of vitamin A consumption less than the currently defined tolerable upper intake level of 3,000 RE/day. This research not only calls into question the tolerable upper intake level of vitamin A, but also casts doubt on the wisdom in vitamin A food fortification and supplement consumption in the United States. This is especially relevant since there are no known benefits of consuming extra vitamin A and although vitamin A deficiency is a serious problem in other parts of the world, in Western countries the occasional case is usually associated with an extremely insufficient diet (25). By reevaluating vitamin A recommendations and lowering the tolerable upper intake level to a value more consistent with fracture risk studies, the stage would be set for future changes to fortified foods and vitamin supplements. These changes have the potential to lead to a healthier consumption level of vitamin A for the entire population.

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