



Nutrients and Bone Health

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ABSTRACT: Osteoporosis is a major epidemic in the United States, responsible for at least 1.2 million fractures per year. Current management of bone loss consists primarily of estrogen therapy and calcium supplements. This approach is helpful in many cases, but its success is limited.

This review presents a new concept: that bone health depends not just on estrogen and calcium, but on a wide range of other nutrients, including vitamins B6, C, D, K, folic acid, magnesium, manganese, boron, zinc, copper, strontium and silicon. The typical Western diet, with its high content of sugar and refined foods, appears to be deficient in many of these vitamins and minerals. Furthermore, the requirement for certain nutrients may be increased by genetic factors or by metabolic changes that occur at the time of menopause. Failure to meet one or more of these nutritional needs could result in accelerated osteoporosis. On the other hand, supplementation with a balanced combination of appropriate micronutrients may prove to be a useful adjunct to calcium and estrogen therapy.

Alan R. Gaby, M.D. and Jonathan V. Wright,

Introduction

Nearly one-third of all American women will, during their lifetime, develop osteoporosis severe enough to cause a fracture. At least 1.2 million fractures (primarily of the hips, vertebrae or wrists) occur each year as a direct result of osteoporosis. The medical and social costs of this epidemic are estimated to be \$6.1 billion annually.¹

In women, bone mass begins to decline at 35 years of age, and then accelerates rapidly for 8 to 10 years around the time of menopause. Thereafter, bone loss continues at a slower rate. The risk of developing fractures is closely related to bone mass. However, fracture risk is also influenced by other factors, such as 1) break-down of the protein matrix and other supporting structures in bone and 2) accumulation of microfractures from repeated mild trauma.² Preventing fractures therefore requires attention to at least three factors: 1) preserving adequate mineral mass, 2) preventing loss of protein matrix and other structural elements, and 3) assuring optimal repair mechanisms to remodel damaged areas of bone.

Current Therapy: Estrogen and Calcium

Current management of osteoporosis focuses primarily on estrogen therapy and calcium supplements. Numerous studies have shown that, although estrogen retards bone loss, it does not completely prevent it.³

Fractures do occur, although less frequently, in estrogen-treated women. The benefit of estrogen must be weighed against its risks, particularly an increased incidence of endometrial cancer.

Calcium supplements, usually in dosages of 800-1,500 mg/day, play an important role in prevention and treatment of bone loss. However, it is becoming increasingly clear that calcium

alone is not enough. There is no question that calcium deficiency can cause osteoporosis, and that some women consume less than the Recommended Dietary Allowance (RDA) for calcium. However, skeletal calcium depletion is present in only about 25% of osteoporotic women. Calcium supplements were found to increase bone mass in these women, but had no effect in the other 75% who were not calcium deficient.

A number of early studies showed that calcium supplements partially prevent bone loss.^{5,6,7,8} The validity of these studies is called into question, however, because of technical limitations, which restricted measurements to the forearm, metacarpal bones, and fingers. Bone mass at these sites is known to correlate poorly with that of clinically important areas, such as the hips and spine. The development of dual photon absorptiometry eventually made it possible to measure bone mass of the hip and spine.⁹ Using this technique, Riis et al.¹⁰ found that calcium supplementation to post-menopausal women (2,000 mg/day for 2 years) did not significantly reduce bone loss.

Thus, although estrogen and calcium therapy have a definite place in the overall management of osteoporosis, new approaches are needed.

Possible Role of Other Nutrients

The estrogen/calcium approach could probably be improved upon if proper attention were given to other nutrients. The evidence reviewed below suggests that supplementation with certain vitamins and minerals might be a useful adjunct to current therapy.

It is sometimes forgotten that bone is more than just a collection of calcium crystals. Bone is active, living tissue, continually remodeling itself through osteoblastic (bone forming) and osteoclastic (bone resorbing) activity, constantly participating in a wide range of biochemical reactions. Like any living tissue, bone has diverse nutritional needs. Failure to meet these needs could presumably compromise the strength and integrity of bone tissue.

The typical Western diet, with its high proportion of refined sugar, white flour, fat, and canned foods, contains far less of certain vitamins and minerals than diets consumed by our ancestors. Furthermore, the requirement for certain nutrients may be increased by genetic factors or by metabolic changes that occur at the time of menopause. Inadequate intake of any one of these nutrients could play a role in the development of osteoporosis.

Multiple deficiencies over a prolonged period of time may have even greater significance. This possibility is supported by the work of Albanese, who found that adding "all known micronutrients" to a calcium supplement reduced bone loss to a significantly greater degree than calcium alone.¹¹ Some of the nutrients that may play a role in bone health are discussed below.

Vitamin K

Vitamin K is known primarily for its effect on blood clotting. However, this vitamin is also required to synthesize osteocalcin, a protein found uniquely and in large amounts in bone.¹² Osteocalcin is the protein matrix upon which calcium crystallizes. The component of osteocalcin that attracts calcium ions is a modified amino acid, gamma-carboxyglutamic acid, formed by the vitamin K-dependent carboxylation of glutamic acid. Because of its role in osteocalcin production, vitamin K is essential for bone formation, remodeling, and repair.

It is generally assumed that vitamin K deficiency is rare. However, assessment of vitamin K status is based on relatively insensitive tests, such as prothrombin time. Recent advances have made it possible to measure vitamin K levels in blood. In a series of 16 patients with osteoporosis, mean serum vitamin K concentration was only 35% that of age-matched controls.¹³ If osteocalcin synthesis is sensitive to changes in serum vitamin K levels, then the low levels in osteoporotic patients may have clinical significance. That possibility was supported by a recent study in which vitamin K supplementation of a typical Western diet increased urinary excretion of gamma-carboxyglutamic acid by 23%.¹⁴

Vitamin K deficiency is probably more common



than previously believed. Deficiency may occur in individuals whose vegetable consumption is low. Another factor that could promote deficiency is frequent use of antibiotics, which can destroy naturally occurring vitamin K-producing bacteria in the intestines.

Rats fed a vitamin K deficient diet had significantly increased urinary calcium excretion.¹⁵ Furthermore, vitamin K supplementation accelerated the healing of experimental fractures in rabbits, even though they were already receiving "adequate" levels in their diet.¹⁶ In a preliminary study of osteoporotic patients, treatment with vitamin K reduced urinary calcium loss by 18-50%¹⁷ The evidence suggests that, when accelerated bone formation is desirable, as in osteoporosis or after a fracture, a greater amount of vitamin K is required.

Vitamin D

Vitamin D is required for intestinal calcium absorption. Reduced plasma vitamin D levels are common in elderly individuals, especially women.¹⁸ Factors that lower vitamin D levels in the elderly include reduced exposure to sunlight, decreased dietary intake, and malabsorption. Impaired conversion of vitamin D to its biologically active form, 1,25-dihydroxyvitamin D3, may in some cases exacerbate a marginal deficiency. Indeed, abnormal metabolism of vitamin D precursors may sometimes be a more significant problem than dietary deficiency.

Treatment of osteoporotic patients with 1,25-dihydroxyvitamin D3 increased calcium absorption, improved calcium balance,¹⁹ and reduced bone loss²⁶ in some studies. However, in other trials, this treatment was without benefit.²¹ Routine use of 1,25-dihydroxyvitamin D3 has been limited by its high cost and by the risk of hypercalcemia associated with long-term therapy.

Vitamin D should be supplemented in cases where dietary intake and sunlight exposure are inadequate. Measures should also be taken to enhance the conversion of vitamin D precursors to the biologically active 1,25-dihydroxyvitamin D3. This conversion may be facilitated by treatment with magnesium and boron.

Magnesium

Magnesium participates in a number of biochemical reactions that take place in bone. Alkaline phosphatase, an enzyme involved in forming new calcium crystals, is activated by magnesium.²² The conversion of vitamin D to its biologically active form, 1,25-dihydroxyvitamin D3, also appears to require magnesium.²³ Deficiency of magnesium can produce a syndrome of "vitamin D resistance."²⁴

Whole-body content and bone concentrations of magnesium were below normal in 16 of 19 osteoporotic women.²⁵ All sixteen women with low magnesium levels also had abnormal crystal formation in their bones, a factor which might increase the risk of fractures. The three women with normal magnesium status had normal crystal formation.

The typical American diet is often low in magnesium. Dietary surveys have shown that 80-85% of American women consume less than the RDA for this mineral.²⁶ Daily magnesium intake in two other studies was only about two-thirds of the RDA.^{27,28} These studies suggest that magnesium deficiency is common in the United States.

Manganese

Manganese is required for bone mineralization,³⁰ and for synthesis of connective tissue in cartilage

and bone.³⁰ Rats fed a manganese deficient diet had smaller, less dense bones .with less resistance to fractures than those fed adequate amounts of manganese.²⁹ The optimal intake of manganese is not known, but at least half of the manganese in a typical diet is lost when whole grains are replaced by refined flour.³¹ Genetic factors influence the susceptibility of animals to manganese deficiency.³² It is therefore likely that certain subsets of the human population are unusually sensitive to the effects of marginal manganese intake.

Interest in the relationship between manganese and osteoporosis was stimulated by observations on a famous professional basketball player, who had repeatedly suffered poorly healing fractures and who was found to have unexplained osteoporosis. Examination of his blood revealed no detectable manganese, as well as deficiencies of other minerals. Within six weeks of supplementing his diet with these minerals, he was back to playing basketball. These observations led to a study of osteoporotic women, in whom blood manganese levels were found to be only 25% that of controls.³³

Folic acid

The importance of folic acid for bone health seems to be related to its role in homocysteine metabolism. Methionine, one of the eight essential amino acids present in food, is converted in part to homocysteine, a potentially toxic compound. The danger of homocysteine has been discovered by studying individuals with a genetic disorder in which abnormally large amounts of homocysteine accumulate. These individuals develop severe osteoporosis at an early age, possibly due to an adverse effect of homocysteine on bone.³⁴

Prior to menopause, women are especially efficient at converting homocysteine to less toxic compounds. This unique metabolic efficiency may account in part for the resistance of premenopausal women to bone loss.³⁵

The following study suggests that, at the time of menopause, a breakdown of homocysteine metabolism occurs, which can be partly corrected by folic acid supplementation. Serum homocysteine levels were measured in female volunteers after administration of methionine. These levels were substantially greater in post-menopausal than in premenopausal women, with no overlap between the two groups. Treatment with folic acid partially prevented the methionine-induced rise in serum homocysteine, even though none of the women were deficient in folic acid by standard laboratory criteria.³⁶ Thus, it appears that menopause is associated with an increased requirement for folic acid which, if unmet, may result in an elevation of serum homocysteine.

Folic acid deficiency is relatively common, occurring in as many as 22% of individuals 65 years of age.³⁷ Typical American diets often contain only half of the RDA for folic acid.³⁸ Tobacco smoking, drinking alcohol, and using oral contraceptives also tend to promote folic acid deficiency.

Boron

Previously thought to be essential only for plants, boron now appears to play a role in human nutrition, particularly in relation to bone health. Post-

menopausal women were fed a standard diet for 119 days, supplying about 0.25 mg of boron/day. Supplementation of this diet with boron (3 mg/day) reduced urinary calcium excretion by 44% and markedly increased serum concentrations of the estrogenic hormone, 1713-estradiol.^{39,40} In fact, the levels of 1713-estradiol in boron-supplemented women were the same as in women receiving estrogen therapy. This increase in hormone concentration maybe important, since 1713-estradiol is the most biologically active form of naturally occurring human estrogen.

The way in which boron acts in the body is not known. However, it seems to be required for the formation of activated (hydroxylated) forms of certain steroid hormones. Boron is known to complex with organic com-pounds containing hydroxyl groups. It may therefore participate in hydroxylation steps necessary for the synthesis of 1713-estradiol and 1,25-dihydroxy vitamin D3. Boron deficiency exacerbated signs of vitamin D deficiency in chicks, including abnor-mal bone formation and elevation of alkaline phosphatase.⁴¹

Based on animal studies, Nielsen has estimated the human boron requirement to be approximately 1-2 mg/day. Fruits, vegetables and nuts are the main dietary sources of boron. Diets containing inadequate amounts of these foods may be deficient

in boron.

Toxicity studies in animals have shown a comfortable margin of safety for "nutritional" doses of boron (1-3 mg/day). No adverse effects were seen in dogs and rats fed chronically with 350 ppm of boron,⁴² which corresponds to approximately 117 mg/day in humans. In certain parts of the world where the diet contains as much as 41 mg of boron/day,⁴³ no problems have been reported.

The fact that boron raised endogenous estrogen levels does not suggest that this mineral poses the same risks as estrogen therapy. The cancer-causing effect of estrogen is dose-related. Because orally administered 1713-estradiol (conjugated estrogens) is mostly converted to estrone by the gastrointestinal tract, large amounts of estrogen must be given by mouth to achieve a clinically useful serum level of 1713-estradiol. In contrast, the amount of endogenously produced 1713-estradiol required to maintain beneficial serum levels may be as little as 5% of the oral dose.⁴⁴ Thus, boron appears capable of producing an estrogenic effect without exposing the body to dangerous amounts of estrogen.

Another factor that argues against a cancer risk is the apparent participation of boron in hydroxylation reactions. Synthesis of estriol, a weak estrogen with documented anti-cancer activity, involves a hydroxylation step, which would presumably be catalyzed by boron. Increasing estriol levels (as a proportion of total estrogens) may reduce the incidence of certain types of cancer.⁴⁵ If boron does



indeed increase estradiol production, then it might actually help prevent cancer.

Strontium

Strontium occurs in relatively large concentrations in bones and teeth, where it is thought to replace a small fraction of the calcium in hydroxyapatite crystals.⁴⁶ Awareness of the nutritional significance of strontium has been overshadowed by the fear of radioactive strontium, a component of nuclear fallout. Because strontium tends to accumulate in bone tissue, radioactive strontium maybe particularly hazardous to vertebrates. On the other hand, non-radioactive strontium occurs naturally in food. This mineral is apparently quite safe, even with long-term administration at doses hundreds of times greater than the usual dietary intake.⁴⁷

Several studies suggest a beneficial effect of strontium on calcified tissues. The incidence of dental caries was reduced in geographical regions with high levels of strontium in drinking water. Furthermore, addition of 0.27% strontium to the drinking water of mice reduced bone-resorbing activity by 11.3%.⁴⁸ The effect of strontium in human osteoporosis has also been investigated. Thirty-two patients were given pharmacologic doses of strontium (1.7 g/day) for periods ranging from 3 months to 3 years (10 also received estrogen and testosterone). Twenty-seven (84%) experienced marked reduction in bone pain. Radiologic examination showed possible improvement in 78% of the strontium-treated patients.⁴⁷

The effect of physiologic doses of strontium (several milligrams/day) has not been studied. However, chronic consumption of strontium-depleted, refined foods⁴⁹ may adversely affect bone strength.

Silicon

High concentrations of silicon are found at calcification sites in growing bone.⁵⁰ This mineral appears to strengthen the connective tissue matrix by crosslinking collagen strands.⁵¹ Chicks fed a silicon deficient diet developed gross abnormalities of the skull and had unusually thin leg bones. The number of trabeculae was reduced and there was evidence of impaired calcification.^{51,52}

It is not known whether the typical American diet provides adequate amounts of silicon. As with other nutrients, subclinical deficiencies could result from over consumption of refined foods. In patients with osteoporosis, where accelerated bone regeneration is desirable, silicon requirements may be increased.

Pyridoxine (Vitamin B6)

Vitamin B6 deficient diets produced osteoporosis in rats.⁵³ The effect of B6 on bone health may involve several different mechanisms. This vitamin is a cofactor in the enzymatic crosslinking of collagen strands,⁵⁴ which increases the strength of connective tissue. Vitamin B6 also helps break down homocysteine,⁵⁵ a methionine metabolite which is believed to promote osteoporosis (see section on folic acid).

Dietary surveys indicate that B6 intake by American women is frequently less than the RDA.^{56,57} Biochemical evidence of B6 deficiency was found in more than half of a group of presumably healthy volunteers.⁵⁸

Zinc

Zinc is essential for normal bone formation.⁵⁹ This mineral also enhances the biochemical actions of

vitamin D.⁶⁰ Zinc levels were low in serum and bone of elderly patients with osteoporosis.⁶¹ Low serum zinc levels were also found in individuals with accelerated bone loss of the alveolar ridge of the mandible.⁶²

The typical American diet is low in zinc. In one dietary survey, 68% of adults consumed less than two-thirds of the RDA for zinc.⁶³ Widespread dietary zinc deficiency has been reported in other studies,^{64,65}

At present, the picolinic acid salt of zinc (zinc picolinate) appears to have a greater degree of bioavailability than other zinc supplements.⁶⁶ Picolinate is a naturally occurring metabolite of tryptophan which is believed to enhance zinc absorption and transport in humans.

Copper

Rats fed a copper deficient diet had reduced bone mineral content and reduced bone strength.^{67,68} Copper supplementation also inhibited bone resorption in vitro.⁶⁹ THE mechanism of action of copper is not known. However, this mineral is a cofactor for the enzyme lysyl oxidase,⁷⁰ which strengthens connective tissue by crosslinking collagen strands.

Since a typical American diet contains only about 50% of the RDA (2 mg/day) for copper,⁷¹ deficiency of this trace mineral may be quite common.

Ascorbic acid (Vitamin C)

Osteoporosis can result from vitamin C deficiency.⁷² Although frank scurvy is rare in the United States, subclinical ascorbic acid deficiency may be common. Biochemical evidence of vitamin C deficiency was found in 20% of elderly women, even though they were consuming more than the RDA of 60 mg/day.⁷³

A Note on Calcium Absorption

Individuals with osteoporosis often absorb calcium poorly,⁷⁴ Impaired calcium absorption may be caused by vitamin D deficiency. Hypochlorhydria (inadequate production of gastric acid), which is relatively common in women over the age of 50,^{75,76} may also reduce absorption of most forms of calcium.^{77,78,79,80} Recent studies suggest that calcium citrate is more efficiently absorbed by both achlorhydric and normal individuals than calcium carbonate.^{77,81}

Conclusion

This review has presented evidence that a wide range of nutrients affect bone health. Chronic deficiencies of one or more of these nutrients may play an important role in the etiology of osteoporosis.

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