Comparative Absorption of Calcium Sources and Calcium Citrate Malate for the Prevention of Osteoporosis

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Abstract

Anthropologically speaking, humans were high consumers of calcium until the onset of the Agricultural Age, 10,000 years ago. Current calcium intake is one-quarter to one-third that of our evolutionary diet and, if we are genetically identical to the Late Paleolithic *Homo sapiens*, we may be consuming a calcium-deficient diet our bodies cannot adjust to by physiologic mechanisms. Meta-analyses of calcium and bone mass studies demonstrate supplementation of 500 to 1500 mg calcium daily improves bone mass in adolescents, young adults, older men, and postmenopausal women. Calcium citrate malate has high bioavailability and thus has been the subject of calcium studies in these populations. Positive effects have been seen in prepubertal girls, adolescents, and postmenopausal women. The addition of trace minerals and vitamin D in separate trials has improved the effect of calcium citrate malate on bone density and shown a reduction of fracture risk.

(*Altern Med Rev* 1999;4(2):74-85)

Introduction

Whether calcium actually effects bone density has been an ongoing debate for 20 years.[1,2] Retrospective and prospective epidemiological studies yield both positive and negative results.

On the one hand, opponents of the belief that high calcium diets have a positive effect on bone cite many studies to substantiate that calcium supplementation neither increases peak bone mass nor minimizes menopausal bone loss.[3,4] Opponents of the calcium/bone gain theory argue that while calcium deficiencies may cause osteoporosis, calcium supplementation only produces a transient pharmacological manipulation of bone by altering parathyroid hormone levels.[5]

On the other hand, positive conclusions can be drawn about calcium supplementation and bone mass. Unfortunately, calcium studies are difficult to interpret and few studies that looked at bone mass included the confounding variables known to affect bone loss. Heaney, an investigator in the field of calcium absorption and metabolism, has pointed out several important factors which must be considered when attempting to evaluate calcium studies.[6]

First, osteoporosis is a disease of multifactorial character. Exercise, hormonal status, heredity, medications, smoking, alcohol consumption, weight fluctuation, inactivity due to injury,

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and nutritional variables (protein, sodium, phosphorus, trace minerals) are all variables affecting bone mass and strength, and are seldom, if ever, adequately considered in calcium trials. Calcium is believed only to affect bone mass, not bone strength or fragility. Bone density can be increased without decreasing fracture rate, as in the case of sodium fluoride which increases bone mass but causes the formation of an abnormal crystalline structure that is more fragile. Fracture risk is due to bone fragility; what determines bone fragility in osteoporosis is largely unknown.[6]

Second, some studies look at populations with a small range of calcium intakes. The calcium intake in The Netherlands, for example, is high, and so is the incidence of osteoporosis. Studies there have found no correlations between the two; in other words, higher intakes within this high range do not correlate with protection from bone loss.[7] The possibility that other causes of bone loss determine osteoporosis incidence must be considered in these cases.

Third, most studies are unable to assess the other causes of dietary calcium deficiency: inefficient absorption and high renal losses. It appears 25 percent of the variance in calcium balance is a result of absorption, and 50 percent is a result of urinary loss.[8] Heaney found, in calcium balance studies, that calcium absorption in postmenopausal women varied as much as 61 percent, and that 40 percent of the women in such trials could not absorb enough calcium to stay in positive calcium balance even with an intake of 800 mg daily.[9] High levels of calcium excretion via renal losses are seen with both high salt and high protein diets, in each case at levels common in the United States.[10,11]

Fourth, studies assessing calcium effect in menopause often fail to recognize the unique biochemistry of menopausal women**.** In menopause the body readjusts the set point of bone, as in the case of women who stop producing ovarian hormones due to surgery or medication, women who have anorexia nervosa or athletic amenorrhea, or men who lose testosterone. The body appears to sense it has more bone than it needs and adjusts the bone mass downward, approximately 15 percent. This is a short-term adjustment, lasting three to six years, and only rarely more than five years.[12] If peak bone mass is high enough (one standard deviation above the young adult mean on a DEXA scan), the body can withstand this loss without consequent risk as long as calcium nutrition is adequate during these years. Due to the fact that falling estrogen levels have a negative influence on calcium absorption and renal conservation, calcium needs increase during menopause.[12]

The majority of studies indicate calcium cannot stop bone loss during the first five years of menopause.[13] These studies may be simply reflecting normal physiological phenomena that calcium supplementation alone cannot interrupt. If bone loss during the first few years of menopause is more than 15 percent, there is a possibility the body is in negative calcium balance due to insufficient intake or excessive elimination of calcium.[12] It appears the positive effect calcium does have in menopause is more related to building peak bone mass before the onset of menopause and doesn't affect the quantity of bone lost during the initial years of menopause.[14]

Meta-analyses of calcium studies on bone mass provide a clearer picture of this difficulty in calcium research evaluation. Heaney's meta-analysis of 43 calcium studies,[12] using some of the parameters listed above, shows some interesting results. In 19 of 43 studies, calcium intake was controlled by the investigator instead of calculated from dietary recall. In 16 of those studies, calcium had a significant affect on bone mass. Twenty-three of 28 studies that excluded early postmenopausal women (within five years of

Table 1. NIH optimal requirements recommended by the National Institutes of Health Consensus Panel, 1994.

Age Group	Optimum daily intake of calcium, mg
Infant	
Birth-6 months	400
6 months-1 year	600
Children	
1-5 years	800
6-10 years	800-1200
Adolescents/ Young Adults	
11-24 years	1200-1500
Men	
25-65 years	1000
Over 65 years	1500
Women	
25-50 years	1000
Over 50 years	
On estrogens	1000
Not on estrogens	1500
Over 65 years	1500
Pregnant and nursing	1200-1500

onset of menopause) were positive. In 12 studies that controlled for calcium intake and excluded women who were 0-5 years postmenopausal, all 12 showed a significant effect of calcium.

Another meta-analysis of calcium and bone mass yielded similar results.[15] Using 49 separate studies and the criteria listed above, Cumming concluded the literature was consistent in showing calcium supplementation at 1000 mg/day had a favorable effect on bone mass and would prevent loss of approximately one percent of bone mass per year in postmenopausal women not on estrogen.

A third meta-analysis on bone mass in young adults found 33 well-designed studies from 1966 to 1994.[16] The authors agreed a 1000 mg daily calcium intake in premenopausal women and adult men could prevent the loss of one percent bone per year at all bone sites except the ulna.

If we accept the premise that calcium supplementation is merited, dosage and bioavailability need to be investigated. The question of dosage has been explained by taking an anthropological approach.

Calcium and The Paleolithic Diet

The anthropological approach to nutritional needs has received attention lately due to the popularity of the "Paleolithic Diet" concept.[17] This theory asserts that calcium played a major role in the evolution of mammals, of primates and, for the last 35,000 years, of *Homo sapiens*. This latter period was the last time the human gene pool was able to evolve as a result of human interaction with the environment. The anthropological approach says, with the exception of a few small changes related to genetic blood diseases, that humans are basically identical biologically and medically to the hunter-gatherers of the late Paleolithic Era.[17] During this period, calcium content of the diet was much higher than it is currently. Depending on the ratio of animal to plant foods, calcium intake could have exceeded 2000 mg per day.[17] Calcium was largely derived from wild plants, which had a very high calcium content; animal protein played a small role, and the use of dairy products did not come into play until the Agricultural Age 10,000 years ago. Compared to the current intake of approximately 500 mg per day for women age 20 and over in the United States,[18] hunter-gatherers had a significantly higher calcium intake and apparently much stronger bones. As late as 12,000 years

ago, Stone Age hunters had an average of 17-percent more bone density (as measured by humeral cortical thickness). Bone density also appeared to be stable over time with an apparent absence of osteoporosis.[17] With the advent of the Agricultural Age, low-calcium, high-phosphorus cereal grains replaced high-calcium wild plant foods and calcium intakes dropped (uncultivated plants have approximately four times the calcium of cereal grains). Bone densities decreased in the agricultural age and the incidence of osteoporosis increased in both the Near East and the Americas.[19] The only hunter-gatherers that seemed to fall prey to bone loss were the aboriginal Inuit (Eskimos). Although their physical activity level was high, their osteoporosis incidence exceeded even present-day levels in the United States. The Inuit diet was high in phosphorus and protein and low in calcium.[20]

It appears that the Paleolithic diet was a very calcium-rich diet. The physiology of those who consumed it adapted to that diet. Today, the intestinal tract does not have effective absorption mechanisms for calcium. It actually may be that in a high-calcium environment, the evolutionary necessity for an absorption barrier for calcium existed.[12] Contrasted with sodium, which is absorbed with 100-percent efficiency, typical calcium absorption averages 25-35 percent at median intakes, and only 50 percent at very low calcium intakes. Net calcium accumulation in present-day humans is only 4-8 percent because of renal, fecal, and perspiration losses.[21] About 150 mg/day of calcium is excreted via digestive secretions, no matter what our intake, whereas sodium excretion in sweat can be reduced drastically if dietary levels are low.[21] If estimated dietary levels of sodium in the Paleolithic diet were a fraction of current intake, sodium physiology might also reflect adaptation.[22] As a result of physiological inability to hold on to calcium and absorption difficulties that arise with age, negative calcium balances may be common.[23]

Calcium Absorption and Recommendations

The current recommended dietary intakes for calcium were formulated as a result of epidemiological, balance, and supplementation studies. However, most of these studies did not factor in absorption difficulties nor did they always look at calcium loss.[23] As many researchers point out, the evidence for high urinary loss not withstanding, insufficient net calcium retention may be evidence of an obligatory renal mechanism for calcium excretion that cannot be changed.[24] Evidence for this mechanism exists even in adolescent females on low-calcium diets. Balance studies that look at threshold intakes (the point at which calcium levels ensure maximal skeletal retention), find levels consistently higher than recommended dietary intakes for all age groups.[24]

In 1994, the National Institutes of Health developed optimal calcium intake recommendations based on the agreement that osteoporosis prevention begins with the development of optimal levels of peak bone mass as early as 6-10 years of age (Table 1).[8]

These results of the current NIH Consensus Panel are closer than previous recommendations to what may be genetically determined needs for calcium nutriture. The problem is these levels appear to be difficult, if not impossible, to achieve with current dietary patterns. The average U.S. adult consumes 350-400 mg calcium per 1,000 kcal.[25] Dairy products are the most common calcium-dense foods eaten in the United States today. But, according to current levels, the average postmenopausal woman would have to increase current dairy product intake by five times to reach a daily calcium intake of 1500 mg from dairy products.[25] Furthermore, calcium intake is dropping; current national calcium intake is eight percent lower than in the early 1970s.[26] Although supporting optimal dietary habits is always a prudent policy,

Table 2. Absorbability of calcium supplements.

Source	Approximate Solubility mM/liter	Number of Subjects Tested	Fractional Absorption With a Meal	Fractional Absorption Without a Meal
Calcium oxalate	0.04	39	0.102 ± 0.040	
Hydroxyapatite	0.08	21		0.166 ± 0.090
Calcium carbonate	0.14	10/43	0.296 ± 0.054	0.235 ± 0.123
Tricalcium phosphate	0.97	10	0.252 ± 0.130	
Calcium citrate	7.3	7		0.242 ± 0.049
Calcium citrate malate	80	20	0.363 ± 0.076	
Bisglycinocalcium	1500	13		0.440 ± 0.104

Heany RP, et al, 1990, reprinted with permission.[27]

researchers have advocated calcium supplementation as a more realistic way to achieve optimal calcium intakes.[24]

Absorption of calcium varies with age, and the presence or absence of intestinal disease.[27] Calcium supplements vary in their absorption rates. It has been commonly believed that the solubility of a calcium source increases its absorbability. However, absorption studies indicate that although more soluble sources are generally more absorbable, there is no predictable or discernible linear relationship. Results from these studies are outlined in Table 2.[27] These data are from women between 20 and 40 years of age with no known calcium metabolism disorders or conditions that would influence calcium absorption. The subjects were given 200-300 mg calcium after abstaining from alcohol for 24 hours.

Other studies have confirmed these results;[28] calcium oxalate is consistently the least absorbable of the forms listed above. Fractional absorption studies vary, with some studies revealing calcium citrate malate absorption as high as 42 percent[29] and calcium carbonate as low as 22 percent.[30]

Absorption is only one part of the effectiveness of a calcium supplement. Efficacy involves evidence of positive effects on bone mass and fracture rates. Due to the bioavailability of calcium citrate malate (CCM), it has been the subject of studies looking at both acquisition of bone mass in adolescence and the prevention of bone loss in menopause, postmenopause, and senescence.

Calcium Citrate Malate and Adolescents

According to the NIH Consensus Development Panel on Optimal Calcium Intake, two important factors that influence osteoporosis risk are peak bone mass and the rate at which bone is lost in later life.[8] Peak bone mass development is thought to begin during the second decade of life and end somewhere between the second and third decades of life. Peak bone mass is genetically programmed so that beyond a certain threshold or amount, extra calcium does not produce greater bone mass. The calcium threshold for adolescents appears to be approximately 1500 mg/day.[24]

This is at the high end of the range listed in the NIH guidelines for adolescents (1200-1500 mg/day).

Lloyd studied 11- and 12- year-old females who were given 500 mg calcium as citrate malate or placebo for 18 months, in addition to dietary levels of 960 mg calcium daily.[31] At the end of the 18-month study, the calcium group had significantly greater gains in lumbar spine bone mineral density and total body bone mineral density, and had gained an average of 24 grams of bone per year – the equivalent of an additional 1.3 percent of the skeleton each year. If this bone mass gain were sustained until these adolescents reached age 50, they would hypothetically have significant protection from menopausal bone loss, the equivalent of one standard deviation above young adult normal for bone density.[31] As mentioned earlier, if women have bone densities equivalent to one standard deviation above the young adult normal, they can survive the 15-percent bone mass loss experienced during menopause without negative consequences to bone density.

Johnston et al[32] reported results of a randomized trial in 45 pairs of identical twins; one twin received 700 mg calcium as citrate malate and the other twin, placebo. After three years, significant gains in bone density were seen in the supplemented prepubertal children at all six sites measured. This group was receiving a total of 1370 +/- 303 mg calcium per day compared to the placebo group of 888 +/- 173 mg daily. There was a lack of significant results in the pubertal twins – a phenomenon that has been linked to the possible effects of puberty in this group or the small numbers in the study.

Further studies in adolescent girls revealed a similar phenomenon. Andon studied two groups of adolescent girls (n=248) who were either taking 500 mg/day calcium from CCM, 1000 mg/day, or placebo.[33] After six months, the group on the 500 mg CCM regimen had a bone mass gain of 13 +/- 7 gm, which was not significantly different from the placebo. Those on the 1000 mg regimen, however, had a substantial increase in skeletal mass: 29 +/- 7 gm. This was significantly different from both the placebo and the 500 mg regimen ($p < 0.05$). Compared to the results in the Johnston study (a total of approximately 1370 +/- 303 mg calcium per day and a gain in bone mass of 24 gm in 12 months) Andon's results were obtained on a total daily calcium intake of 1618 +/- 288 mg/day. The possibility of the transient effect of calcium on bone remodeling (which can last for about 12 months) should be ruled out by longer trials. The similarity of results in these two studies, however, is more evidence for the importance of calcium studies in adolescents and the need to perhaps re-evaluate the current recommendations for calcium supplementation in this population.

Menopause and Calcium Citrate Malate

The other major area of calcium research involves bone mass in postmenopausal women. As mentioned above, the first three to six years after menopause is the time when bone loss is the most accelerated.[12] The meta-analysis of calcium and bone mass mentioned previously[15] revealed a common consensus. In 49 separate studies on bone mass and calcium, the data was in agreement that calcium supplementation was able to reduce bone loss at every site measured in postmenopausal women except the spine. Spinal bone is mostly trabecular in nature and is more affected by estrogen loss than femoral or radial bone (mainly cortical bone).[12] This meta-analysis also concluded that calcium had a more beneficial effect in pre- and postmenopausal women than in menopausal women. The research using CCM alone and in combination with other nutrients may shed new light on this older picture of calcium's role in menopause.

Table 3. Adjusted mean change in bone mineral density in late postmenopausal women after two years on calcium citrate malate, calcium carbonate, or placebo.

Spine	% Change from baseline
Calcium citrate malate	-0.92 ± 0.50
Calcium carbonate	-1.91 ± 0.51*
Placebo	-2.27 ± 0.46*

* $p \leq 0.01$ for comparison with baseline values.

Adapted from Dawson-Hughes, 1990.[34]

Dawson-Hughes first looked at the use of CCM in menopausal and postmenopausal women.[34] The trial included 301 women, divided into early menopause (onset to 6 years), and late menopause (> 6 years since onset). None of the women in the study had a past history of or present use of hormone replacement therapy. Both groups were given either 500 mg calcium as carbonate or as CCM, or placebo for two years. The groups were also divided into those who had low-calcium diets (less than 400 mg/day) and those who had high calcium diets (400-650 mg/day). In the subgroup of women who were early menopausal (six years or less), neither form of calcium was able to stop bone loss at any of the sites measured. When compared to placebo, the effect of CCM in late menopausal women was significantly better than calcium carbonate. The CCM group had a 60-percent reduction in spinal bone loss while the calcium carbonate group had a 15-percent reduction (Table 3). At radial sites, the CCM group had a significant gain in bone mass while the calcium carbonate group had no gain. In addition, although both forms of calcium were found to suppress parathyroid hormone (and thus slow bone demineralization), calcium citrate malate was better absorbed, evidenced by a significant change in urinary calcium in the women with the lower calcium intake. The women who were late menopausal and had a dietary calcium intake above 400 mg all lost spinal bone mass during the study, regardless of the regimen.

In this study, although the use of 500 mg calcium as citrate malate attenuated bone loss by 60 percent, a total of 900 mg calcium by itself was not always enough to stop spinal bone loss in late menopausal women. Women who had low calcium intakes appeared to benefit the most from calcium supplementation. Of course in 1990, 800 mg of calcium met the RDA requirement. The awareness of increasing requirements, currently about twice this level for postmenopausal women, is reflected in further research.

Later studies using higher levels of calcium alone have still been unable to demonstrate a halting of spinal bone loss, even at a total daily intake of 2500 mg per day.[35] The slowing of bone loss at this level of supplementation, however, was significant: the investigators estimated a 50-percent reduction in fracture risk (including vertebral fractures) if the women continued on this dosage the next 30 years.

Calcium Citrate Malate and Trace Minerals

Bone matrix is a combination of phosphorus and calcium-mineralized tissue in a framework made up of collagen and noncollagenous proteins and glycoproteins.[36] Trace minerals are necessary for the production of this matrix. Deficiencies of certain trace minerals, specifically copper and manganese, have been correlated with lower bone mineral density and bone strength.[37]

Copper is a cofactor for lysyl oxidase and is required for the incorporation of collagen and elastin into the organic component of bone.[38] Manganese is an essential factor in the production of organic matrix proteins in animals.[39] Serum levels of manganese in osteoporotic women were found to be 25 percent of normal.[40] Rats fed copper- and

manganese-deficient diets showed an imbalance in osteoblastic vs. osteoclastic activity, resulting in altered bone remodeling.[41] Both the protein component and the mineral component of bone were broken down and the organic (protein) component had to be resynthesized before it could be mineralized. On the copper and manganese deficient diets, bone loss identical to osteoporotic bone loss in humans was identified.

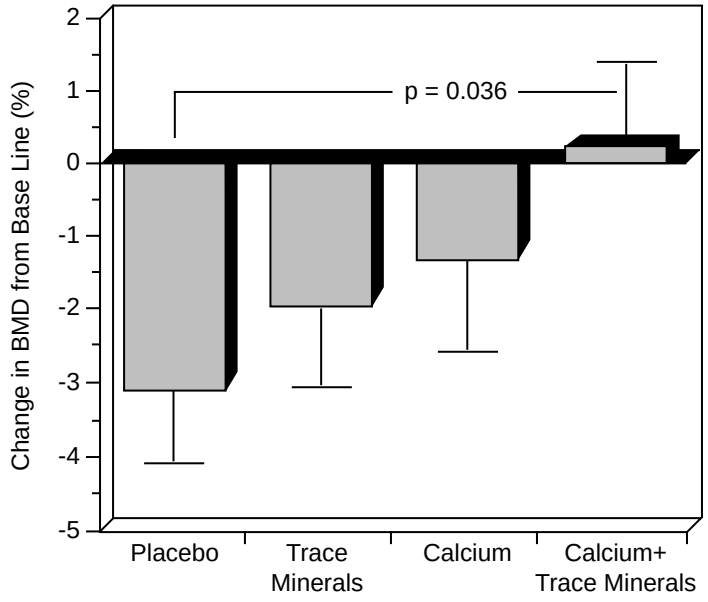
Zinc deficiency has a direct effect on osteoblastic activity, the production of collagen and chondroitin sulfate, and the activity of alkaline phosphatase.[42] Insulin-like growth factor 1 (IGF-1) is a critical regulator of bone formation, remodeling, and calcium homeostasis.[43] Recently it has been shown that dietary zinc is the main regulating factor in blood levels of insulin-like growth factor.[44] IGF-1 levels appear to decrease with age and low zinc levels have been correlated with low IGF-1 levels in postmenopausal women.[44] The authors speculated that low levels of IGF-1 could be associated with age-related bone loss.

Working with the hypothesis that trace mineral nutrition may be a factor in halting bone loss in postmenopausal women, researchers looked at the effect of trace mineral supplementation in addition to calcium citrate malate.[41,45] In a cohort of 225 postmenopausal women (median years since menopause: 17.5) a combination of 1000 mg calcium as citrate malate, 5.0 mg copper, 2.5 mg manganese, and 15 mg zinc was compared with placebo, CCM alone, and trace minerals (TMIN) alone. Lumbar bone mineral content was measured at baseline and two years later. For the 137 women who completed the study, the groups were divided into estrogen and non-estrogen using. The estrogen-using women showed no differences among any of the groups and had no significant bone loss or gain. Figure 1 includes the subjects not on estrogen therapy (n=76). The study results may be related to the small numbers of subjects – a greater effect of calcium and trace minerals might be seen in a larger cohort.

Vitamin D and Calcium Citrate Malate

Vitamin D deficient states lead to a secondary hyperparathyroidism and increased bone turnover. Inevitably, the progressive state of turnover leads to decreased bone mineralization and osteomalacia as well as playing a role in the demineralization of osteoporosis.[46] Supplementation with vitamin D increases bone mass and reduces the risk of fracture.[47] Although vitamin D deficiency states have been reported to be more common in those

Figure 1. Effect of calcium and trace mineral supplementation on spinal bone mineral density in postmenopausal women.



Saltman PD, et al, 1993, reprinted with permission.[41]

over age 60,[48] a recent investigation of adults in an in-patient setting indicated otherwise. In a population of 164 patients with an average age of 44 (+/- 14 yrs.), in a general medical ward, 57 percent had low levels of 25-hydroxyvitamin D.[49] Of these, 22 percent were considered to have severe deficiencies (below 8 ng/ml). Only 68 percent of these patients had any known risk factors for vitamin D deficiency and 46 percent reported taking multivitamins. Thirty-seven percent reported daily vitamin D intake in excess of the recommended intake for their age. Although there is clear evidence that certain medications such as phenytoin, carbamazepine, and rifampin inhibit vitamin D activation, and that chronic liver and kidney diseases do the same, 32 percent of the vitamin D deficient patients in this population had none of these risk factors.

Studies looking at the effect of CCM and vitamin D supplementation have yielded interesting results. Dawson-Hughes looked at 249 postmenopausal women who were living at latitude 42 degrees.[50] At this latitude, it is not possible to manufacture vitamin D in the skin during the winter months and studies show that serum levels of vitamin D drop as parathyroid hormone levels rise seasonally in northern latitudes.[51] In this randomized trial of 400 I.U. vitamin D, both groups received approximately 400 mg calcium as CCM and bone density measurements were done at six month intervals for one year. The measurements were timed when plasma 25-hydroxyvitamin D levels were expected to be highest and lowest. The wintertime increase in parathyroid hormone was prevented in the vitamin D group. The net gain in spinal bone density in the vitamin D group was significant. Although both groups had lost bone mass during the winter, the vitamin D group had an overall gain in spinal bone mass of 0.85 percent (CI, 0.40% to 1.30%. $p < 0.001$). The significance of this figure is evident when compared to the 1-2 % spinal bone losses experienced by postmenopausal women each year.[52]

A second study by the same author using vitamin D and CCM involved 389 men and women over 65 years of age.[53] As in the former study, none of the women or men were on hormone replacement therapy or any other medication for bone loss. They were given 500 mg calcium as CCM and 700 I.U. vitamin D, or placebo for three years. At the end of the three-year period, there was a moderate improvement in total body bone mass in both sexes but more importantly, a significant decrease in the number of fractures. The relative risk of fracture in the CCM/vitamin D group was 0.5 – a 50-percent reduction in non-vertebral fracture incidence. Although the study was small, similar results have been seen in other studies. A large trial in 3270 women over age 65 involved 1200 mg calcium (as tricalcium phosphate) and 800 I.U. vitamin D (400 I.U. twice daily).[54] After 18 months, the number of hip fractures was reduced by 43 percent and the number of total non-vertebral fractures was reduced by 32 percent. Although this study used a higher dose of calcium, the triphosphate form is only 25 percent absorbable compared to CCM which has a mean absorption of 36 percent.[55] This study also used vitamin D3, which has been shown to raise blood levels of 1,25 dihydroxyvitamin D more effectively than standard vitamin D therapy.

The implications of any protocol in reducing fracture risk by 50 percent are very significant. Fracture risk reduction is the standard of efficacy of anti-resorptive agents; estrogen decreases risk for fracture by 50 percent.[56] Further trials with calcium and vitamin D are certainly warranted. Until then, the suggested doses for vitamin D supplementation are 800-1000 I.U. in sick and older adults. Complications with vitamin D do not arise until the daily dose exceeds 2400 I.U.[57]

Conclusions

The use of calcium as a supplement is warranted to help prevent osteoporosis by building greater peak bone mass and slowing the rate of bone loss after menopause. Calcium citrate malate, the most bioavailable form of calcium, has been shown to be effective in both of these areas, and more effective than calcium carbonate at slowing bone loss in postmenopause. The addition of vitamin D and trace minerals to calcium supplementation is an effective way to prevent bone loss and reduce fracture risk in postmenopausal women.

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