Managing bone health: Focus on calcium citrate malate and vitamin D₃

OPTIMAL CALCIUM INTAKE
Calcium is the most abundant mineral in the body with 99% of it deposited in the bones and teeth. The remaining 1% of calcium is used for numerous functions including muscle contraction, blood clotting, vitamin D metabolism and nerve transmission.

Dietary constituents, hormones, drugs, age, and genetic factors influence the amount of calcium required for optimal skeletal health. On the basis of the most current information available, optimal calcium intake is estimated to be:

- 400 mg/day (birth-6 months) to 600 mg/day (6-12 months) in infants;
- 800 mg/day in young children (1-5 years) and 800-1,200 mg/day for older children (6-10 years);
- 1,200-1,500 mg/day for adolescents and young adults (11-24 years);
- 1,000 mg/day for women between 25 and 50 years;
- 1,200-1,500 mg/day for pregnant or lactating women;
- 1,000 mg/day for postmenopausal women on estrogen replacement therapy;
- 1,500 mg/day for postmenopausal women not on estrogen therapy.
- Recommended daily intake for men is 1,000 mg/day (25-65 years).
- For all women and men over 65, daily intake is recommended to be 1,500 mg/day.

These guidelines are based on calcium from the diet plus any calcium taken in supplemental form. Calcium intake, up to a total intake of 2,000 mg/day, appears to be safe in most individuals.

CALCIUM CITRATE MALATE
Calcium citrate malate (CCM) is a water-soluble calcium supplement. It is the calcium salt of citric acid and malic acid. Calcium citrate malate’s bioavailability stems from its water-solubility and its method of dissolution. When dissolved, it releases calcium ions and a calcium citrate complex. Calcium ions are absorbed directly into intestinal cells, and the citrate complex enters the body through paracellular absorption. There has been considerable investigation into the health benefits of CCM since it was first patented in the late 1980s.

CCM has been shown to facilitate calcium retention and bone accrual in children and adolescents. In adults, it effectively promotes the consolidation and maintenance of bone mass. In conjunction with vitamin D, CCM also decreases bone fracture risk in the elderly, slows the rate of bone loss in old age, and is of benefit to the health and well-being of postmenopausal women.

CCM is exceptional in that it confers many unique benefits that go beyond bone health. Unlike other calcium sources that necessitate supplementation be in conjunction with a meal to ensure an appreciable benefit is derived, CCM can be consumed with or without food and delivers a significant nutritional benefit to individuals of all ages.

The chemistry of CCM makes it a particularly beneficial calcium source for individuals with hypochlorhydia or achlorhydia, which generally includes the elderly and those on medications that decrease gastric acid secretion.

CCM is also recognized as a calcium source that does not increase the risk of kidney stones, and in fact it protects against stone-forming potential.
placebo group had greater increases of lumbar spine bone density, received placebo pills. The supplemented group compared with the supplementation, 500 mg/d calcium as CCM; whereas the controls 11.9 + 0.5 years at study entry were chosen and given calcium bone mass was conducted. In it 94 girls with a mean age of 18 months of calcium supplementation on bone density and A randomized, double-blind, placebo-controlled trial of the effect ccm and BMD in adolescent girls

The main outcome measure was the area under the curve (AUC) for the increase in serum calcium from 0 to 9 hours after ingesting the test calcium source. AUC 9 was 48% greater for calcium citrate malate than for tricalcium phosphate/calcium lactate; absorbed calcium calculated from AUC 9 values was 148 +/- 9.0 mg and 100 +/- 8.9 mg for calcium citrate malate and tricalcium phosphate/calcium lactate, respectively. CCM is not the same thing as calcium citrate, or as a simple admixture of calcium citrate and calcium malate. It is prepared in such a way that a significant number of its calcium atoms are bound to both citrate and malate molecules at once. This unique form makes calcium citrate-malate six to nine times more easily dissolved in the stomach than plain calcium citrate.

This superior solubility may be at least part of the reason for the fact that CCM is considerably better-absorbed than calcium citrate. It has been used successfully in many controlled trials to support bone mass and/or to lower fracture risk. Some of these trials have involved a direct face-off between CCM and other forms of calcium. Such trials demonstrate that, as might be expected from its greater bioavailability, CCM gives better protection to the bones than other calcium sources (Table 1).

CCM VS CONVENTIONAL CALCIUM SALTS

As multiple studies have documented, conventional calcium supplements – such as calcium gluconate, calcium citrate, and calcium carbonate – slow, but do not halt or reverse, menopausal bone loss, whether taken alone or with vitamin D. CCM is not the same thing as calcium citrate, or as a simple admixture of calcium citrate and calcium malate. It is prepared in such a way that a significant number of its calcium atoms are bound to both citrate and malate molecules at once. This unique form makes calcium citrate-malate six to nine times more easily dissolved in the stomach than plain calcium citrate.

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CCM AND BMD IN ADOLESCENT GIRLS

A randomized, double-blind, placebo-controlled trial of the effect of 18 months of calcium supplementation on bone density and bone mass was conducted. In it 94 girls with a mean age of 11.9 + 0.5 years at study entry were chosen and given calcium supplementation, 500 mg/d calcium as CCM; whereas the controls received placebo pills. The supplemented group compared with the placebo group had greater increases of lumbar spine bone density, lumbar spine bone mineral content, total body bone mineral density, and 24-hour urinary calcium excretion, respectively.

Therefore increasing daily calcium intake from 80% of the recommended daily allowance to 110% via supplementation with CCM resulted in significant increases in total body and spinal bone density in adolescent girls, which may provide protection against future osteoporotic fracture.

**CCM FOR THE PREVENTION OF OSTEOPOROSIS**

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.

**STONE-FORMING POTENTIAL OF CCM**

Milk and orange juice (OJ) fortified with calcium-citrate-malate (CCM) were evaluated for their potential to alter urine chemistries and crystallization during the course of an eleven week, crossover study. The data indicated that either milk or CCM-fortified orange juice can be consumed, at least within the limits tested, as a dietary source of calcium without increasing the risk of stone formation in a calcium-sensitive subpopulation. That the urine chemistries and crystallization of such calcium-sensitive individuals does not significantly change with the consumption of either beverage implies that the urine of normal individuals would be exceedingly unlikely to change as well.

**CALCIUM AND VITAMIN D SKELETAL EFFECT IS COMPLEMENTARY**

Vitamin D is also essential for intestinal calcium absorption and plays a central role in maintaining calcium homeostasis and skeletal integrity. Much evidence indicates that both calcium and vitamin D are efficacious in protecting the skeleton, particularly when these 2 nutrients are used in combination. Each nutrient is necessary for the full expression of the effect of the other, and where their actions are independent, their effects on skeletal health are complementary.

Since vitamin D is found naturally only in a limited number of foods, the usual dietary vitamin D intake by many populations is not

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<th>Drug</th>
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<tr>
<td>CACITATE M</td>
<td>Calcium Citrate Malate 250 mg., Vitamin D3 100 I.U.</td>
<td>10 Tablets</td>
<td>1 TDS</td>
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sufficient to maintain adequate vitamin D status. While cutaneous biosynthesis upon exposure of skin to ultraviolet B light is the major source of vitamin D for most people, this does not occur during winter time.7,8

**EFFECTIVENESS AND SAFETY OF VITAMIN D IN BONE HEALTH**

Two independent reviewers completed a multi-level process of screening the literature to identify eligible studies (title and abstract, followed by full text review, and categorization of study design per key question). 167 studies met their eligibility criteria (112 RCTs, 19 prospective cohorts, 30 case-controls and six before-after studies).

The largest body of evidence on vitamin D status and bone health was in older adults with a lack of studies in premenopausal women and infants, children and adolescents. The quality of RCTs was highest in the vitamin D efficacy trials for prevention of falls and/or fractures in older adults. There was fair evidence of an association between low circulating 25(OH)D concentrations and established rickets. However, the specific 25(OH)D concentrations associated with rickets is uncertain, given the lack of studies in populations with dietary calcium intakes similar to North American diets and the different methods used to determine 25(OH)D concentrations. There was inconsistent evidence of an association of circulating 25(OH)D with bone mineral content in infants, and fair evidence that serum 25(OH)D is inversely associated with serum PTH.

In older adults, there was fair evidence for an association between 25(OH)D levels and changes in BMD. There were very few studies in pregnant and lactating women, and insufficient evidence for an association between serum 25(OH)D and changes in BMD during lactation, and fair evidence of an inverse correlation with PTH.

In older adults, there was fair evidence that serum 25(OH)D is inversely associated with falls, fair evidence for a positive association with BMD, and inconsistent evidence for an association with fractures. The imprecision of 25(OH)D assays may have contributed to the variable thresholds of 25(OH)D below which the risk of fractures, falls or bone loss was increased. There was good evidence that intakes from vitamin D-fortified foods (11 RCTs) consistently increased serum 25(OH)D in both young and older adults.

Eight randomized trials of ultraviolet (UV)-B radiation (artificial and solar exposure) were small and heterogeneous with respect to determination of the exact UV-B dose and 25(OH)D assay but there was a positive effect on serum 25(OH)D concentrations. It was not possible to determine how 25(OH)D levels varied by ethnicity, sunscreen use or latitude.

Seventy-four trials examined the effect of vitamin D3 or D(2) on 25(OH)D concentrations. Most trials used vitamin D3, and the majority enrolled older adults. In three trials, there was a greater response of serum 25(OH)D concentrations to vitamin D3 compared to vitamin D(2), which may have been due to more rapid clearance of vitamin D(2) in addition to other mechanisms.

An exploratory analysis of the heterogeneity demonstrated a significant positive association comparable to an increase of 1-2 nmol/L in serum 25(OH)D for every 100 additional units of vitamin D although heterogeneity remained after adjusting for dose. Vitamin D3 in combination with calcium results in small increases in BMD compared to placebo in older adults although quantitative synthesis was limited due to variable treatment durations and BMD sites.

The evidence for fracture reduction with vitamin D supplementation was inconsistent across 15 trials. The combined results of trials using vitamin D3 (700 - 800 IU daily) with calcium (500 - 1,200 mg) was consistent with a benefit on fractures although in a subgroup analysis by setting, benefit was primarily in elderly institutionalized women (fair evidence from two trials).

**REFERENCES**

New Calcium Delivery System

Cacitate-M
Calcium Citrate Malate eq. to elemental Calcium 250 mg. and Vitamin D₃ 100 I.U. Tablet

Calcium Citrate Malate is the calcium salt of citric acid and malic acid
- Most Bioavailable Calcium
- 100% Vegetarian
- Water Soluble

Indicated for
- Pregnancy and Adolescents
- Post Menopausal Women
- Elderly
- Adjuvant to Osteoporosis, Osteomalacia & Fractures
- Other Calcium deficiency states

Absorption: Cacitate-M Vs Calcium Carbonate
Absorption of calcium from calcium citrate-malate salt (CCM), was tested against calcium carbonate. In two separate experiments in humans, calcium from CCM was absorbed significantly better than from calcium carbonate or milk. It conclude that CCM exhibits excellent bioavailability.
Calcif Tissue Int 1997 Dec;41(6):351-2

Bone Density
Supplementation with calcium citrate-malate resulted in significant increases in total body and spinal bone density in adolescent girls which may provide protection against osteoporotic fracture.
JAMA 1993 Aug 18;270(7):841-4

Menopausal Women
Supplementation with calcium citrate-malate was more effective than supplementation with calcium carbonate.
NEngl J Med 1990 Sep 27;323(13):878-81

Dosage: 2 tablets daily

FINECURE PHARMACEUTICALS LIMITED
Fax: 079-30615693  email: sales@finecurepharma.com
website: www.finecurepharma.com