Controversies in Nutrition

By Alan R. Gaby, M.D.

Does calcium cause heart disease?

Meta-analysis of 15 randomized controlled trials: participants who received supplemental calcium as monotherapy (i.e., without other nutrients) had a 30% increase in the incidence of myocardial infarction ($p = 0.035$ to 0.038).

BMJ 2010;341:c3691

Does calcium cause heart disease?

The data were derived from secondary (post hoc) analyses of studies (mainly osteoporosis studies) that were not designed to test the effect of calcium on heart disease risk.

BMJ 2010;341:c3691

Does calcium cause heart disease?

Findings of borderline statistical significance from post hoc analyses are more likely to be due to chance than are findings of borderline statistical significance from primary analyses.

Calcium-magnesium interrelationships

(Effects of a high-calcium diet in rats and pigs)

Decreased tissue magnesium levels
Fed Proc 1986;45:374

Increased magnesium requirements
J Nutr 1960;70:103-111

Increased severity of magnesium deficiency in animals fed a magnesium-deficient diet
Am J Physiol 1951;166:408-12

Calcium-magnesium interrelationships

(Effects of high-calcium intake in humans)

2 g/day of calcium (citrate) decreased Mg absorption and plasma Mg levels in healthy volunteers. Clin Sci 1967;32:11-18

Calcium supplementation had no effect on Mg balance in adolescent girls.
Am J Clin Nutr 1996;63:950-3

Magnesium: a cardioprotective nutrient

Inhibits platelet aggregation

Vasodilator

Anti-arrhythmic activity

Required for ATP synthesis

Promotes intracellular potassium uptake

Possibly lowers BP and increases HDL-C

Magnesium: a cardioprotective nutrient

Rats fed a Mg-deficient diet developed myocardial necroses. Am J Pathol 1964;45:757-68

In rats, epinephrine-induced myocardial necroses were prevented by Mg. Arzneimittelforschung 1983;33:205-10

Mg prevented myocardial infarction induced by coronary artery ligation in rats. Can Med Assoc J 1960;82:212-3

Mg prevented the development of atherosclerosis in animals fed an atherogenic diet. Proc Natl Acad Sci 1990;87:1840-4

Magnesium intake is frequently low

NHANES 1999-2000: 50% of Caucasians consumed < 75-80% of the RDA; Mg intake was about 25% lower in African-Americans than in Caucasians.
J Nutr 2003;133:2879-82

Mean Mg intake by high school and college women was 125 mg/day (60-65% below the RDA)
J Am Diet Assoc 1969;55:38-43

Calcium-magnesium interrelationships

In people with low or suboptimal Mg status, administration of calcium without concomitant Mg supplementation could further compromise Mg status, and thereby increase the risk of developing heart disease.

Calcium-silicon interrelationships

In rats, calcium supplementation decreased the silicon content of bone. Fed Proc 1970;29:565

As a cross-linking agent, silicon may help protect arteries from injury. Lancet 1977;1:454-7

Silicon prevented the development of atherosclerosis in rabbits fed an atherogenic diet. Atherosclerosis 1979;33:397-408

Calcium: to supplement or not?

Adequate calcium intake is essential for optimal bone health.

In most instances, calcium supplementation should be accompanied by Mg (usual ratio, approximately 2:1), and possibly by silicon (perhaps 2-5 mg/day, as part of a multi-mineral formula).

High-dose vitamin D:

Is it safe

and effective?

Vitamin D deficiency

- Rickets
- Osteomalacia, osteoporosis
- Myopathy

Potential benefits of supplementation

- Fewer falls & fractures, better bone density
- Prevention of influenza & asthma attacks
- Increased insulin sensitivity?
- Improvement of hypertension?
- Prevention of some cancers, autoimmune diseases, tooth decay? (circumstantial)

Vitamin D: effective dosages

800-1,200 IU/day generally effective

400 IU/day generally ineffective

New RDA (2010): 600 IU/day for ages 1-70; 800 IU/day for ages ≥ 71

2,000 IU/day was used for prostate cancer: slowed disease progression, decreased pain.

Vitamin D: new definition of deficiency

Traditional definition:
deficiency = serum 25(OH) < 10-15 ng/ml (< 25-37.5 nmol/L)

New definition:
deficiency = serum 25(OH)D < 20 ng/ml (< 50 nmol/L)

insufficiency = < 30 ng/ml (< 75 nmol/L)

Vitamin D: new definition of "optimal"

A review article concluded that a protective effect with respect to various outcomes (i.e., bone health, falls, fractures, dental health, and cancer) began at a serum 25(OH)D level of 30 ng/ml (75 nmol/L) and that the best outcomes were seen in people with levels of 36-40 ng/ml (90-100 nmol/L).

Am J Clin Nutr 2006;84:18-28

Dosage requirements for new "adequate" and "optimal"

Only 50% of people will achieve "adequacy" (≥ 30 ng/ml) with 1,000 IU/day.

1,600-3,400 IU/day (depending on the study) will achieve "adequacy" in nearly all healthy adults.

Even larger doses (4,000-10,000 IU/day?) may be needed to achieve "optimal" levels.

Tolerable Upper Intake Level = 4,000 IU/day (recently increased from 2,000 IU/day)

Examining the evidence

Is routine use of vitamin D in dosages greater than 2,000 IU per day beneficial?

Is it safe?

My conclusions

Serum 25(OH)D may not be a reliable indicator of vitamin D status.

The new definitions of vitamin D deficiency and insufficiency may not be valid.

Evidence supporting the benefit of pushing 25(OH)D to an "optimal" level is weak.

My conclusions

Evidence supporting the long-term safety of dosages > 2,000/day is weak.

The safety and efficacy of vitamin D supplementation cannot be inferred from data regarding the safety and efficacy of sunlight exposure.

Why 25-hydroxyvitamin D?

Serum vitamin D: unreliable; serum half-life is only 24 hours.

Serum 1,25-dihydroxyvitamin D: unreliable; may be normal or elevated in people with vitamin D deficiency. Am J Clin Nutr 2004;79:362-371

Serum 25-hydroxyvitamin D: serum half-life is 3 weeks; more reliable than vitamin D itself.

Serum 25-hydroxyvitamin D: how reliable?

Serum 25-hydroxyvitamin D

↓

Serum 25-hydroxyvitamin D

Serum 25(OH)D: quality control issues

Substantial variations from one lab to another and with different assay methods

With nearly identical serum samples, one lab found that 90% were below 32 ng/ml; another lab found that only 17% were below 32 ng/ml.

Am J Clin Nutr 2008;87:1087S-91S

Serum 25(OH)D: E pluribus unum

25(OH)D is only one of more than 50 vitamin D metabolites identified.

Vitamin D nutritional status may be a function of complex interactions between many different vitamin D metabolites.

Different people may have different serum 25(OH)D "set points" for adequate or "optimal" vitamin D nutritional status.

25(OH)D level altered by inflammation

Serum 25(OH)D levels decline in response to inflammation. Therefore, 25(OH)D may be an unreliable indicator of vitamin D status in people with inflammatory diseases.

Am J Clin Nutr 2011;93:1006-1011

Serum 25(OH)D at high vitamin D doses

Serum 25(OH)D may be even less reliable as an indicator of vitamin D status when vitamin D doses are greater than 2,000 IU/day, because 25-hydroxylases become saturated at those dosages. Storage of large amounts of unmetabolized vitamin D may not be reflected in serum 25(OH)D measurements.

Am J Clin Nutr 2008;87:1738-42

New definition of deficiency: is it valid?

Definition is based on biochemical markers:

As 25(OH)D levels go up, fractional calcium absorption tends to increase and parathyroid levels tend to go down.

New definition of deficiency: is it valid?

Vitamin D sufficiency is inferred when a further increase in serum 25(OH) does not further increase fractional calcium absorption or further depress parathyroid hormone levels. In population studies, the average 25(OH)D level at which vitamin D "sufficiency" occurred was around 30 ng/ml (75 nmol/L).

N Engl J Med 2007;357:266-81

New definition of deficiency: is it valid?

Recent studies have questioned whether 25(OH)D levels above those associated with rickets or osteomalacia influence calcium absorption. Earlier studies that showed such an association may have used inappropriate methods for measuring fractional calcium absorption.

Am J Clin Nutr 2010;92:835-840

New definition of deficiency: is it valid?

In the absence of severe vitamin D deficiency, the association between serum 25(OH) and parathyroid hormone is weak.

Variations in 25(OH)D levels explain, at most, 13% of the variation in parathyroid hormone levels.

Nutr Res 2009;29:671-5; J Bone Miner Res 2001;16:2066-73

New definition of deficiency: is it valid?

Of 93 young adults living in Hawaii who had sun exposure a mean of 29 hours a week, 25-51% had a 25(OH)D level < 30 ng/ml and 3-8% had a level < 20 ng/ml. There was no correlation between 25(OH)D and parathyroid hormone levels.

J Clin Endocrinol Metab 207;92:2130-5

New definition of deficiency: is it valid?

Those findings suggest either that the cut-off level for 25(OH)D used to define vitamin D sufficiency is either inappropriately high for some groups or that 25(OH)D is not always a reliable indicator of vitamin D nutritional status.

J Clin Endocrinol Metab 207;92:2130-5

New definition of deficiency: is it valid?

In the late 1990s, the standard RIA for 25(OH)D was changed. The new method decreased measured values by 4 ng/ml (10 nmol/L). Am J Clin Nutr 2008;88:1519-27

The new cut-off points for deficiency and insufficiency were based in part on studies done prior to the late 1990s.

New definition of "optimal": is it valid?

To answer the question: Randomize people to receive high-dose (e.g., 5,000-10,000 IU/day) or moderate-dose (e.g., 800-2,000 IU/day) vitamin D, or individualized dosages designed to achieve a pre-specified 25(OH)D level, and compare outcomes.

No such studies have been done.

New definition of "optimal": is it valid?

Evidence is derived mainly from observational studies in which serum 25(OH)D was correlated with health outcomes. Findings conflicting.

Evidence is also derived from controlled trials in which vitamin D-supplemented patients who achieved higher 25(OH) levels had better outcomes than did supplemented patients whose 25(OH)D levels were lower.

Limitations of observational studies

Failure to control for confounders such as age, BMI, co-morbidities, chronic inflammation

High 25(OH)D levels result mainly from sunlight exposure. People who spend time in the sun differ from those who do not.

If sun exposure is beneficial, the effect may not be due entirely (or even primarily) to vitamin D.

Limitations of controlled trials

Studies that assessed health outcomes as a function of the serum 25(OH)D response to vitamin D supplementation might simply be identifying differences in body chemistry, rather than an effect of vitamin D supplementation per se.

Limitations of controlled trials

A higher serum 25(OH)D response to supplementation might reflect:

More efficient nutrient absorption in general

More efficient 25-hydroxylation of vitamin D

Hepatic hydroxylase enzymes

Four different cytochrome P_{450} enzymes are thought to be capable of 25-hydroxylating vitamin D.

Trends Biochem Sci 2004;29:664-73

Cytochrome P_{450} enzymes also help detoxify xenobiotic chemicals.

Extra-hepatic 25-hydroxylase enzymes

Human testis (androgen-producing Leydig cells) and possibly ovary are also capable of 25-hydroxylating vitamin D.

25(OH)D levels were 60% lower in young men with h/o orchiectomy for bilateral testicular cancer than in matched controls.

Lancet 2010;376:1301

Extra-hepatic hydroxylase enzymes

Observational studies on 25(OH)D levels and health outcomes may be confounded by differences in gonadal function, and therefore, differences in levels of testosterone and DHEA. Both of these hormones may have positive influences on health.

Is high-dose vitamin D safe?

Tolerable Upper Intake Level for adults is 4,000 IU per day (recently increased from 2,000 IU/day).

Some investigators have argued that up to 10,000 IU per day is safe for most adults.

Basis of the argument that long-term use of 10,000 IU/day of vitamin D safe

Hypercalcemia uncommon with 10,000 IU/day

Whole-body sun exposure results in the production of at least 10,000 IU/day without causing vitamin D toxicity.

Weaknesses of the safety argument

1. High-dose supplementation studies were of short duration.

2. Absence of hypercalcemia is not proof of safety.

3. Unclear whether human skin really can produce 10,000 IU/day of vitamin D

4. Physiological effects of sunlight exposure differ from those of vitamin D supplementation.

High-dose supplementation studies were of short duration

10,000 IU/day was given for a maximum of 20 weeks. As a fat-soluble nutrient, vitamin D can accumulate with continued administration.

Absence of hypercalcemia is not proof of safety

An increase in urinary calcium excretion (even within the normal range) might increase the risk of developing kidney stones.

3 of 45 elderly individuals who received 5,000 IU/day of vitamin D for 12 months showed evidence of hypercalciuria. Am J Clin Nutr 2009;89:1132-7

Absence of hypercalcemia is not proof of safety

Swine fed human equivalent of 11,500 IU/day of vitamin D_3 developed pathological changes in the aorta that were indistinguishable from human atherosclerosis. Am J Clin Nutr 1979;32:58-83

Increasing vitamin D_3 intake only modestly (equivalent to a total of 917 IU/day for humans) exacerbated atherosclerosis in swine induced by a diet high in butterfat. Nutr Rep Int 1983;28:1111-8

Can human skin can produce 10,000 IU/day?

This claim is based in part on a study in which UV irradiation of 5% of body surface area was equivalent to oral administration of 400 IU/day.

J Bone Miner Res 1998;13:1238-42

No evidence that it is appropriate to extrapolate this finding to full-body irradiation

Can human skin can produce 10,000 IU/day?

One-time exposure to 1 minimal erythemal dose of UV irradiation was equivalent to oral administration of 10,000-25,000 IU of vitamin D_2.

This finding is of doubtful relevance to long-term vitamin D homeostasis.

Can human skin can produce 10,000 IU/day?

Repeated sun exposure results in photodegradation of vitamin D that has not yet entered the circulation. Am J Clin Nutr 1995;61(Suppl):638S-45S

Therefore, net vitamin D production may be substantially lower on subsequent days than on the first day.

UV light and oral vitamin D are not the same

One photodegradation product of vitamin D (5,6-*trans*-vitamin D) has effects similar to 1,25-dihdroxyvitamin D, but is 20-40 times less potent.
Biochemistry 1972;11:2715-9

5,6-*trans*-Vitamin D might compete with $1,25(OH)_2D$ and thereby function as a regulator of vitamin D activity.

UV light and oral vitamin D are not the same

Sunlight (but not vitamin D):

Produces photodegradation products

Produces corticotropin-releasing hormone

May directly influence hypothalamic and pituitary function through the retina

Vitamin D and cancer: controlled trial

Women's Health Initiative, double-blind trial: 36,282 postmenopausal women received vitamin D (400 IU/day) and calcium (1 g/day) or placebo for 7 years.

Overall, vitamin D/calcium had no effect on incidence of colorectal or breast cancer.

Am J Clin Nutr 2011; doi: 10.3945/ajcn.111.015032.

Vitamin D and cancer: controlled trial

Among women not taking personal calcium or vitamin D supplements at randomization, vitamin D/calcium treatment significantly decreased the incidence of breast cancer and total cancer, and nonsignificantly decreased colorectal cancer incidence.

Am J Clin Nutr 2011; doi: 10.3945/ajcn.111.015032.

Vitamin D and cancer: controlled trial

Among women taking personal calcium or vitamin D supplements at randomization (maximum permitted personal vitamin D dose, 600-1,000 IU/day), vitamin D/calcium treatment nonsignificantly increased total cancer, breast cancer, and colorectal cancer incidence by 6-26%.

Am J Clin Nutr 2011; doi: 10.3945/ajcn.111.015032.

Vitamin D and cancer: controlled trial

These data are consistent with the possibility that modest doses of vitamin D reduce the risk of cancer, but that slightly higher than modest doses provide no additional benefit and could even negate the benefit of lower doses or increase the risk of cancer.

Am J Clin Nutr 2011; doi: 10.3945/ajcn.111.015032.

What to make of it all

RDAs of 400-600 IU/day are not sufficient to promote optimal health. 800-1,200 IU/day is more effective than 400 IU/day.

It is not known whether 2,000 IU/day is more effective than 800-1,200 IU/day for the average person.

What to make of it all

Doses > 800-1,200 IU/day may be considered for patients with risk factors for deficiency, such as obesity, advanced age, malabsorption, dark skin, lack of sun exposure, or distance from the equator.

The safety and efficacy of using high doses (such as > 2,000 IU/day) for the sole purpose of achieving a target 25(OH)D level have not been established.

What to make of it all

Sunlight exposure of 5-15 minutes 2-3 times a week between 10 a.m. and 3 p.m. in spring, summer, and autumn is frequently sufficient for skin types II and III.

Am J Clin Nutr 2004;80(Suppl):1678S-88S

Iodine facts (µg/day)

Adult RDA	150
Median urinary [I] in US adults	168
Tolerable Upper Intake Level	1,100

Iodine: adverse effects

Very high doses 700-4,500 mg/day)

Thyroid dysfunction (mainly hypo-thyroidism), burning mouth, increased salivation, parotid and submandibular swelling, severe headache, acneiform eruptions, pulmonary edema, angioedema, heart failure, and death.

Iodine: adverse effects

Moderately high doses (3-6 mg/day)

10.9% of 1,365 women treated for fibrocystic breast changes experienced side effects including acne, nausea, diarrhea, thinning hair, skin rash, headache, hypothyroidism (0.3%), and hyperthyroidism (0.1%). Can J Surg 1993;36:453-60

Iodine: adverse effects

Modestly high doses (> 500 µg/day?)

Autoimmune thyroiditis
Hypothyroidism
Goiter or increased thyroid volume

N Engl J Med 2006;354:2783-93; Thyroid 2003;13:561-7; Clin Endocrinol 1991;34:413-6; Lancet 1987;2:257-9; Am J Clin Nutr 2005;81:840-4

"Orthoiodosupplementation"
(Guy Abraham, M.D.)

According to Abraham, the optimal dietary iodine intake is 13.8 mg/day, which is 92 times the RDA and more than 12 times the Tolerable Upper Intake Level.

http://www.optimox.com/pics/Iodine/IOD-02/IOD_02.htm

Basis of the claim

Japanese people consume an average of 13.8 mg/day of iodine, and are among the healthiest people in the world.

High-doses are needed to fully saturate the tissues, as demonstrated by an iodine-load test.

Do Japanese people consume 13.8 mg/day?

Claim based on a misinterpretation of a 1967 paper. Average seaweed consumption in Japan = 4.6 g/day. Seaweed contains average of 0.3% iodine.

4,600 mg x 0.003 = 13.8 mg

However, 4.6 g/day of seaweed was wet weight, whereas 0.3% iodine was based on dry weight.

J Clin Endocrinol Metab 1967;27:638-47

Amount of iodine consumed in Japan

In studies in the 1990s that specifically looked at iodine intake in Japan, mean dietary iodine (estimated from urinary iodine excretion) was 330-500 µg/day, which is 25-fold lower than 13.8 mg/day.

Nippon Naibunpi Gakkai Zasshi 1994;70:1093-1100; Nippon Naibunpi Gakkai Zasshi 1992;68:550-6

Amount of iodine consumed in Japan

According to a 2008 study, average iodine intake in Japan from seaweed was 1.2 mg/day in 2006 and 1.7 mg/day in 1986, which is 88-93% less than 13.8 mg/day.

Thyroid 2008;18:667

Abraham's iodine load test

Patient ingests 50 mg of iodine/iodide. Patient considered iodine-deficient if < 90% is excreted in the urine over the next 24 hours.

92-98% of patients taking the test have been found to be deficient.

Abraham's iodine load test

The validity of the test depends on the assumption that the average person can absorb at least 90% of a 50-mg dose.

No research in humans; proponents have not measured fecal iodine levels. In cows fed supraphysiological doses of iodine, 50% appeared in the feces. J Dairy Sci 1996;79:254-9

Adverse effects of "orthoiodosupplementation"

Toxic multinodular goiter
Graves' disease
Autoimmune thyroiditis
Hypothyroidism
Severe headaches
Deep acne
Hair loss, agitation, sweating
Esophagitis

Megadose iodine: conclusion

3-6 mg/day may be considered for fibrocystic breast changes that do not improve with methylxanthine avoidance, vitamin E, etc.

As an antimicrobial agent, iodine may produce clinical benefit in selected patients by killing intestinal pathogens.

Beneficial for some other conditions, such as erythema nodosum and possibly some types of cysts.

Megadose iodine: conclusion

Iodine is not indicated as a treatment for hypothyroidism except in cases of dietary iodine deficiency. High iodine intake can make hypothyroidism worse.

Megadose iodine: conclusion

There is no credible evidence that routinely giving high-dose iodine based on an iodine load test or on a misunderstanding of human iodine requirements is either safe or beneficial.

Side effects of high-dose iodine are common, and in a small proportion of cases side effects are severe and/or persistent.

Does folic acid cause cancer?

Double-blind study: 1 mg/day for 3-8 years was associated with a higher incidence of prostate cancer (9.7% vs. 3.3% for placebo) in patients with recent colorectal adenoma. J Natl Cancer Inst 2009;101:432-435

Double-blind *JAMA* study: 0.8 mg/day was associated with a significant 21% increase in cancer incidence, 38% increase in cancer deaths.

JAMA 2009;302:2119-2126

Does folic acid cause cancer?
Study weaknesses

1) Post-hoc analyses of earlier research that was designed to ask a different question.

2) Studies used folic acid alone or folic acid plus a few other nutrients. Effect might be different when part of a comprehensive nutritional program.

3) No increase in cancer incidence in the US since folic acid fortification of food began in 1998.

JAMA 2009;302:2152-2153

Does folic acid *prevent* cancer?

Double-blind studies: folic acid supplementation for 3.0-7.3 years associated with a nonsignificant decrease in cancer risk in health professionals.

JAMA 2008;300:2012-2021; Am J Clin Nutr 2009;90:1623-1631

Observational studies: Folic acid supplementation or higher dietary folate intake was associated with decreased incidence of cancer.

Folic acid prevented cancer in some animal studies.

Benefits of folic acid

Prevention of neural tube defects

Prevention of strokes (Lancet 2007;369:1876-1882)

Along with B_{12}, prevention of hip fractures in stroke patients (JAMA 2005;293:1082-1088)

Migraine prophylaxis in patients with elevated homocysteine levels (Headache 2007;47:1342-1344)

Folic acid and cancer: conclusion

Effect of folic acid on cancer risk and cancer mortality remains uncertain.

There does not appear to be any compelling reason to recommend that the general public avoid folic acid supplementation.

Folate supplements: synthetic vs. "natural"

Most supplements contain synthetic folic acid (pteroylglutamic acid; PGA).

PGA is metabolized *in vivo* to methylfolate, the form in which the vitamin is normally transported in the body.

Folate supplements: synthetic vs. "natural"

Administration of large doses of PGA (> 400 µg/day?) might lead to the presence of large amounts of unmetabolized PGA, which could theoretically have an anti-folate effect through competitive inhibition of folate-dependent enzymes.

Folate supplements: synthetic vs. "natural"

However, aside from that theoretical concern, there is no obvious reason to believe that synthetic folic acid is harmful. In addition, there is no evidence that other commercially available forms of supplemental folate (such as methylfolate, folinic acid, or 5-methyltetrahydrofolate) are safer than PGA.

Folate supplements: synthetic vs. "natural"

Virtually all of the research demonstrating a beneficial effect of folate has been done using synthetic folic acid. Other forms of folate have not been shown to prevent neural tube defects, strokes, migraines, or osteoporotic fractures. Synthetic folic acid would therefore seem to be preferable to other folate preparations in most circumstances.

Does vitamin A cause osteoporosis?

Observational studies: higher intake of vitamin A or higher serum vitamin A levels were associated with lower bone mineral density (BMD) or increased fracture risk.

Adverse effect seen even at low intake levels (≥ 6,667 IU/day; RDA = 2,333 IU/day).

Does vitamin A cause osteoporosis?

Other observational studies: no association between vitamin A intake or serum vitamin A levels and BMD or fracture risk.

One study: higher serum vitamin A levels were associated with a nonsignificant decrease in fracture risk.

J Bone Miner Res 2005;20:913-920

Does vitamin A cause osteoporosis?

Vitamin A at a human-equivalent dosage of 2.4 million IU/day caused bone abnormalities in rats, but the equivalent of 470,000 IU/day had no adverse effect. Bone 2003;31:685-689

Healthy men: 25,000 IU/day for 6 weeks had no effect on serum markers of bone turnover.

J Nutr 2002;132:1169-1172

Observational studies: confounding factors

Main dietary sources of vitamin A, aside from liver, are fortified breakfast cereals (usually with added sugar), fortified milk, and fortified margarine. Higher vitamin A intake may simply be a marker of increased consumption of these foods.

Diet and osteoporosis

Refined sugar: Adverse effect according to animal studies and observational studies.

Milk: effect unclear. Associated with increased fracture incidence on one study.

Am J Public Health 1997;87:992-997

Margarine: Butter contains vitamin K_2. Margarine contains hydrogenated vitamin K_2 (dihydrophylloquinine), which is inactive.

Diet and osteoporosis

Liver: Accumulates lead and cadmium (both of which can cause osteoporosis). Also may accumulate various xenobiotic chemicals that could promote bone loss by inhibiting androgen activity.

J Endocrinol 1998;158:327-338

Strontium and bone: to dose or to megadose?

Typical diet provides 1-3 mg/day of strontium

Significant amounts lost in refining of flour

Strontium has high affinity for bone; promotes mineralization of bones and teeth

Stimulates bone formation, inhibits bone resorption

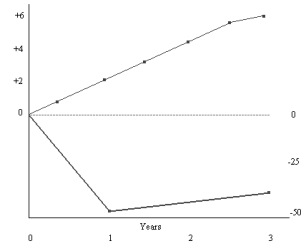
Distribution of strontium in bone

At high doses, most strontium is incorporated by exchange onto the crystal surface. This strontium, which may promote bone formation and inhibit bone resorption, is rapidly lost from bone and excreted in the urine when supplementation is stopped.

A few strontium atoms are incorporated into the crystal lattice; this strontium may enhance bone quality, and appears to persist in bone after supplementation is stopped. This effect may occur with “nutritional” doses.

Bone 2001;28:446-453

Three-year strontium clinical trial



1,649 postmenopausal women, 680 mg/day of strontium for 3 years. Top half: % increase in BMD. Bottom half: % reduction in fracture risk.

Adapted from N Engl J Med 2004;350:459-68.

Potential adverse effects of high-dose strontium on bone

- Syndrome resembling rickets in animals fed 1.5-3.0% strontium
- Bone mineralization defects in young rats at diet concentrations of 0.19% or greater in (equivalent to approximately 800 mg/day for humans). Rat diet contained 0.5% calcium. Bone 1990;11:313-9.
- High soil strontium concentrations associated with increased prevalence of rickets in Turkish children

Arch Dis Child 1996;75:524-6.

Other potential adverse effects of high-dose strontium

- Increased thyroid weight in rats fed 395 ppm of strontium
- Decreased pituitary weight in rats fed 98.7 ppm or 1,580 ppm, but not 395 ppm.
- Estimated no-observed-adverse-effect level = 98.7 ppm, equivalent to 41.1 mg/day for humans (calculation based on 2,000 kcal/day, 30% fat = 417 g/day of food, dry weight)

Toxicology 1977;7:11-21.

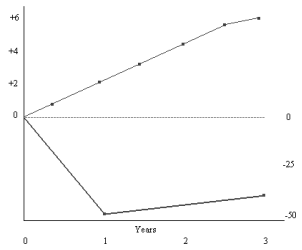
Adverse effects of strontium in 3-year clinical trial

Elevated CPK in 3.4% of patients receiving strontium, 1.8% of those receiving placebo. Elevations usually transient.

No mineralization defects found, but only mature (lamellar) bone was biopsied, whereas adverse effects would presumably be most pronounced in new bone.

N Engl J Med 2004;350:459-468.

Three-year strontium clinical trial



1,649 postmenopausal women, 680 mg/day of strontium for 3 years. Top half: % increase in BMD. Bottom half: % reduction in fracture risk.

Adapted from N Engl J Med 2004;350:459-68.

Two-year strontium clinical trial

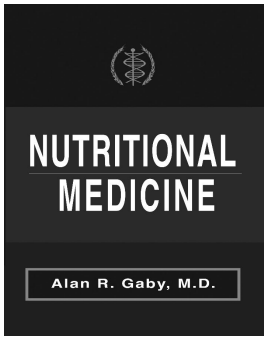
Strontium dose	% change in lumbar BMD	Incidence of new vertebral fractures
Placebo	+0.50	54.7%
170 mg/day	+1.35%	38.8%
340 mg/day	+1.65%	56.7%
680 mg/day	+2.97%	42.0%

Study of 353 postmenopausal women with osteoporosis and a history of at least one vertebral fracture. J Clin Endocrinol Metab 2002;87:2060-2066.

Strontium and bone: my opinion

For established osteoporosis, high-dose strontium (170-680 mg/day) appears to be appropriate for 1-3 years. Thereafter, consider "nutritional" doses (such as 2-6 mg/day) for longer-term use. Long-term clinical trials (> 3-5 years) needed to determine safety and efficacy of high-dose strontium.

For osteoporosis prevention, "nutritional" doses may be most appropriate.



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