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Nutrition Update

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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 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

Bonferoni – hypothesis

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.

Does calcium cause heart disease?

Meta-analysis of 24 randomized controlled trials: In trials in which calcium was given with vitamin D, the death rate was significantly reduced by 9%, compared with placebo. In trials in which vitamin D was given alone, mortality was reduced nonsignificantly by 4%.

J Clin Endocrinol Metab 2012;97:2670-81

CA & Vit D

Does calcium cause heart disease?

Those findings suggest that if there is a deleterious effect of calcium supplementation on cardiovascular health, it might be negated by taking calcium with vitamin D.

J Clin Endocrinol Metab 2012;97:2670-81

Does calcium cause heart disease?

Calcium can cause gastrointestinal side effects (including acute abdominal pain), which can mimic symptoms of MI.

Hospitalized patients may be confused about the final diagnosis, particularly if they are admitted to the CCU.

Does calcium cause heart disease?

In both the Women's Health Initiative and the Nurses' Health Study, there was a 32% false-positive rate for self-reported myocardial infarction.

J Bone Miner Res 2012;27:719-722

Does calcium cause heart disease?

In a pooled analysis of 7 RCTs (n = 10,128) that examined the effect of calcium supplementation, there were 82% more hospitalizations for acute abdominal pain in the calcium group than in the placebo group (4.0% vs. 2.2%).

J Bone Miner Res 2012;27:719-722

Does calcium cause heart disease?

In a pooled analysis of 2 studies, the incidence of self-reported MI was 3.6% with calcium and 2.1% with placebo (RR = 1.69; p = 0.02), whereas the incidence of confirmed MI was 2.4% with calcium and 1.6% with placebo (RR = 1.45; p = 0.15).

J Bone Miner Res 2012;27:719-722

Does calcium cause heart disease?

The incidence of incorrectly classified self-reported MI was higher in the calcium group than in the placebo group (1.2% vs. 0.5; $p < 0.05$).

J Bone Miner Res 2012;27:719-722

Calcium-magnesium interactions

(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 interactions

(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 and the heart

Inhibits platelet aggregation

Vasodilator

Anti-arrhythmic activity

Required for ATP synthesis

Promotes intracellular potassium uptake

Possibly lowers BP and increases HDL-C

Magnesium and the heart

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

RDA 350-450 mg/QD

Therapeutic

Best @

~~At~~ mealtime ↓

Kidney Stones

with bind Oxylates

@ meal time

N.E.J.M.

How much?

Calcium-magnesium interactions

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.

Fish oil and heart disease

A meta-analysis of 20 randomized controlled trials (n = 68,680) concluded that omega-3 fatty acid supplementation had no significant effect on all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke.

JAMA 2012;308:1024-1033

Fish oil and heart disease

The data showed that omega-3 fatty acids reduced all-cause mortality by 4% and cardiac death by 9%. Neither of these differences was statistically significant.

JAMA 2012;308:1024-1033

Fish oil and heart disease

Failure to demonstrate that an effect was statistically significant is not the same as demonstrating the absence of an effect (particularly when the statistical significance threshold was set at 0.0063 to adjust for multiple comparisons).

JAMA 2012;308:1024-1033

Fish oil and heart disease

The increasing use of statins in recent years might negate some of the beneficial effect of fish oil, and could account for the failure to observe a beneficial effect in recent secondary prevention trials.

Fish oil and heart disease

Both statins and fish oil work in part through a similar mechanism (decreasing inflammation). In a large-scale trial, the effect of omega-3 fatty acids on cardiovascular events tended to be greater in statin nonusers than in statin users.

Eur Heart J 2012;33:1582-1588

Individual trials in the meta-analysis

In 11,324 patients who had survived a recent MI, compared with placebo, omega-3 fatty acids significantly reduced all-cause mortality by 20% and cardiovascular deaths by 30%. However, these beneficial effects were "diluted" in the meta-analysis by the inclusion of potentially flawed negative studies.

Lancet 1999;369:1090-1098

Individual trials in the meta-analysis

In 18,645 hypercholesterolemic Japanese patients, omega-3 fatty acids nonsignificantly increased all-cause mortality by 9%. This study had a strong influence on the pooled results, since it included 27.2% of all patients in the meta-analysis.

Lancet 2007;369:1090-1098

Individual trials in the meta-analysis

Fish consumption is high in Japan. The cardioprotective effects of fish oil are obtained at low doses, and little or no additional benefit can be achieved by increasing the dose.

Individual trials in the meta-analysis

Another study (n = 3,851) found no beneficial effect of omega-3 fatty acids, as compared with an olive oil "placebo," in patients with a recent MI. The "placebo" is a known cardioprotective agent.

Circulation 2010;122:2152-2159

Individual trials in the meta-analysis

Another study (n = 4,837) found no beneficial effect of EPA/DHA-fortified margarine, as compared with regular margarine, in patients with a history of myocardial infarction.

N Engl J Med 2010;363:2015-2026

Individual trials in the meta-analysis

EPA and DHA are unstable molecules that can oxidize spontaneously in room air to form potentially cardiotoxic lipid peroxides.

Individual trials in the meta-analysis

The margarine used in this study was distributed only once every 12 weeks. It was not stated whether the tubs were airtight, or whether patients were advised refrigerate after opening and to put the top back on immediately after use.

N Engl J Med 2010;363:2015-2026

What is a meta-analysis?

Meta-analyses are supposed to pool the results of homogeneous studies, in order to increase statistical power. However, few studies are truly homogeneous with respect to methodology, patient population, choice of placebo, and other factors.

What is a meta-analysis?

Questions such as what is the optimal way to administer fish oil and what types of people are most likely to benefit cannot be answered by the recent meta-analysis. To answer those questions, one should examine the trials that produced the best results, and determine how they differed from the negative studies.

High-dose vitamin D:

Is it safe

and effective?

Potential benefits of supplementation

Strong evidence: Fewer falls and fractures, better bone mineral density

Weaker evidence: Prevention of influenza

Weak evidence: Increased insulin sensitivity, improvement of hypertension, prevention of some cancers, autoimmune diseases, and tooth decay

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

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 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.

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 appears to be an unreliable 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(OH)D: serum half-life is 3 weeks; more reliable than vitamin D itself.

Serum 25-hydroxyvitamin D:
gold standard or bronze?

Serum 25-hydroxyvitamin D

↓

Serum 25-hydroxyvitamin D

Serum 25(OH)D: quality control

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. For example, 20(OH)D, present in serum at about 5% of the concentration of 25(OH)D, induced keratinocyte differentiation and inhibited the growth of melanoma cells *in vitro*.

FASEB J 2012;26:3901-15; Anticancer Res 2012; 32:3733-42; J Invest Dermatol 2008;128:2271-80

Skin CA
20(OH)D

Serum 25(OH)D: E pluribus unum

Vitamin D nutritional status may be a function of complex interactions between many different vitamin D metabolites. Consequently, the serum 25(OH)D "set point" for adequate or "optimal" vitamin D status may differ from person to person, depending on the concentrations of other metabolites.

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

Gets shifted into fat storage may become toxic

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

CU ↑ c inflammation
ZN ↓
FE ↓
SE ↓
25 OH D ↓

25(OHD) level influenced by gonadal function

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

25(OHD) correlates with testosterone

Among 1,362 men participating in the Health Professionals Follow-up Study, serum 25(OH)D was positively correlated with serum free and total testosterone (p for trend = 0.003 to 0.03).

Clin Endocrinol 2012;77:106-112

25 OHD r/t Testosterone

25(OHD) level influenced by gonadal function

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.

Vitamin D requirement: racial differences?

Nested case-control study within the Women's Health Initiative Observational Study: Among white women, compared with 25(OH)D levels < 20 ng/ml, levels of 20 to < 30 ng/ml were associated with an 18% reduction in fracture risk, and levels ≥ 30 ng/ml were associated with a 44% reduction in risk (p for trend = 0.02).

J Bone Miner Res 2011;26:2378-2388

Vitamin D requirement: racial differences?

In black women, 25(OH)D levels ≥ 20 ng/ml, as compared with levels < 20 ng/ml, were associated with a 45% higher risk of fracture (p for trend < 0.05).

J Bone Miner Res 2011;26:2378-2388

Vitamin D requirement: racial differences?

In Asian women, 25(OH)D levels ≥ 30 ng/ml, as compared with levels < 20 ng/ml, were associated with a 178% higher fracture risk, after adjusting for vitamin D-binding protein (p for trend = 0.04).

J Bone Miner Res 2011;26:2378-2388

Vitamin D requirement: racial differences?

In NHANES III (1988-94), among Caucasians, after adjustment for potential confounding variables, 25(OH)D levels < 15 ng/ml were associated with an increased risk of fatal stroke (hazard ratio = 2.13; 95% CI, 1.01-4.50).

Nutrition 2012;28:367-371

Vitamin D requirement: racial differences?

Among blacks, however, 25(OH) levels < 15 ng/ml (as compared with higher levels) were associated with a nonsignificant decrease in risk of fatal stroke (hazard ratio = 0.93; 95% CI, 0.49-1.80).

Nutrition 2012;28:367-371

Vitamin D requirement: racial differences?

The relationship between serum levels of 25(OH)D and parathyroid hormone was examined in participants in the Multicenter Osteoarthritis Study.

Osteoporos Int 2012;23:2283-2291

Vitamin D requirement: racial differences?

The 25(OH)D threshold at which no further change in parathyroid hormone levels was observed was approximately 30 ng/ml in Caucasians and 20 ng/ml in African Americans.

Osteoporos Int 2012;23:2283-2291

Vitamin D requirement: racial differences?

These findings suggest that the reference ranges for serum 25(OH)D should be different for Caucasians and African Americans (and possibly Asians).

Osteoporos Int 2012;23:2283-2291

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 calcium absorption.

Am J Clin Nutr 2010;92:835-840; Bone 2008;42:1021-1024

New definition of deficiency: is it valid?

In the absence of severe vitamin D deficiency, the association between serum 25(OH)D 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 2007;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 inappropriately high for this group, or that 25(OH)D is not always a reliable indicator of vitamin D nutritional status.

J Clin Endocrinol Metab 2007;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?

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 hepatic 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.

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 is safe

Hypercalcemia is 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 ~ 11,500 IU of vitamin D_3 per 70 kg of BW/day 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 (from ~ 140 IU/70 kg of BW/day to ~ 920 IU/70 kg/day) exacerbated atherosclerosis in swine induced by a diet high in butterfat. Nutr Rep Int 1983;28:1111-8

Can human skin 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 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.

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

Can human skin produce 10,000 IU/day?

Repeated sun exposure results in photo-degradation 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-dihydroxyvitamin 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

UV light and oral vitamin D are not the same

When people with various skin diseases were exposed to UV light for 4 weeks, certain changes in parameters of immune function were observed. Some of these changes correlated with increases in 25(OH)D levels, and some did not, which suggests that some effects of UV on the immune system occur independently of vitamin D.

J Allergy Clin Immunol 2012;129:1554-1561

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;94:1144-1149

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;94:1144-1149

Vitamin D and cancer: controlled trial

Among women taking personal vitamin D or calcium or 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;94:1144-1149

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;94:1144-1149

Vitamin D and bone: controlled trial

Double-blind trial: 297 postmenopausal women (aged 50-80 years) received 800 IU per day or 6,500 IU per day of vitamin D_3 for 1 year. All women received 1,000 mg per day of supplemental calcium. Mean baseline 25(OH)D level was 28.4 ng/ml.

Osteoporos Int 2012;23:201-211

Vitamin D and bone: controlled trial

Mean BMD of the total hip, femoral neck, lumbar spine, and total body increased in both groups. Mean increases were nonsignificantly greater with 800 IU/day than with 6,500 IU/day at each of the four measured sites.

Osteoporos Int 2012;23:201-211

Vitamin D and influenza: controlled trial

Double-blind trial among Japanese children (mean age, 10 years): 1,200 IU/day of vitamin D for 4 months in the winter. Compared with placebo, 42% reduction in incidence of influenza A with vitamin D.

Am J Clin Nutr 2010;91:1255-1260

Vitamin D and influenza: controlled trial

Among children not taking other vitamin D supplements, vitamin D treatment reduced flu incidence by 64% compared with placebo.

Among children taking other vitamin D supplements (average, 1,000-1,200 IU/week), vitamin D treatment nonsignificantly increased flu incidence by 11% compared with placebo.

Am J Clin Nutr 2010;91:1255-1260

Vitamin D and COPD: controlled trial

Double-blind trial: COPD patients given 100,000 IU of vitamin D_3 every 4 weeks for 1 year.

Among patients with severe vitamin D deficiency (< 10 ng/ml; 16% of all patients) vitamin D supplementation decreased the exacerbation rate by 43% compared with placebo ($p < 0.05$).

Ann Intern Med 2012;156:105-114

Vitamin D and COPD: controlled trial

Among patients with baseline 25(OH) levels ≥ 10 ng/ml (84% of all patients) vitamin D supplementation increased the exacerbation rate by 8% compared with placebo (p value not stated).

Ann Intern Med 2012;156:105-114

Vitamin D and COPD: controlled trial

Among patients who were not taking vitamin D supplements at baseline, the exacerbation rate was nonsignificantly lower by 10% in those assigned to receive vitamin D than in those assigned to receive placebo ($p = 0.3$).

Ann Intern Med 2012;156:105-114

Vitamin D and COPD: controlled trial

Among patients who were taking 400-880 IU/day of vitamin D at baseline for osteoporosis, the exacerbation rate was 41% higher in those assigned to receive vitamin D than in those assigned to receive placebo (p value not stated).

Ann Intern Med 2012;156:105-114

Vitamin D and MS: controlled trial

Double-blind trial: 23 patients with relapsing-remitting multiple sclerosis received high-dose (~ 13,000 IU/day) or low-dose (~ 1,000 IU/day) vitamin D_2 for 6 months. The dose in the high-dose group was adjusted to maintain a serum 25(OH)D level of 130-175 nmol/L.

Neurology 2011;77:1611-1618

Vitamin D and MS: controlled trial

The primary endpoints (the number of new gadolinium-enhancing lesions and the change in the total volume of T2 lesions) did not differ significantly between groups.

Neurology 2011;77:1611-1618

Vitamin D and MS: controlled trial

The median Expanded Disability Status Scale (a secondary endpoint) was significantly worse in the high-dose group than in the low-dose group (3 vs. 2 on a 10-point scale; $p = 0.04$).

Neurology 2011;77:1611-1618

Vitamin D and MS: controlled trial

The relapse rate (a secondary endpoint) was significantly higher in the high-dose group than in the low-dose group (36% vs. 0%; $p = 0.04$).

Neurology 2011;77:1611-1618

Vitamin D: what to make of it all

800-1,200 IU/day is more effective than 400 IU/day.

Preliminary evidence suggests that, for the average person, dosages substantially above 800-1,200 IU/day may be less effective than 800-1,200 IU/day.

Vitamin D: what to make of it all

Doses greater than 800-1,200 IU/day may be considered for patients with risk factors for deficiency, such as advanced age, malabsorption, lack of sun exposure, or distance from the equator. The risk/benefit ratio associated with aggressively treating blacks, Asians, and obese people is unclear.

Vitamin D: what to make of it all

The safety and efficacy of long-term use of high-dose vitamin D (such as more than 2,000 IU/day) for the sole purpose of achieving a target 25(OH)D level have not been established. Short-term use of high doses for the purpose of rapidly correcting a deficiency seems reasonable.

Vitamin D: what to make of it all

Sunlight exposure of 5-15 minutes 2 to 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

High-dose iodine during pregnancy

Three infants in Portland, OR, were found on newborn screening to have congenital hypothyroidism. The mothers of the each of the 3 infants had taken 12.5 mg/day of iodine (Iodoral) during pregnancy.

J Pediatr 2012;161:760-762

High-dose iodine during pregnancy

Levels of whole-blood iodine in the newborn screening samples were 10 times above mean control values. The iodine content of breast milk of one of the mothers was 18 times the upper limit of normal.

J Pediatr 2012;161:760-762

Magnesium for epilepsy

22 patients with epilepsy that had failed to respond to anticonvulsant medications were treated with magnesium oxide at a dosage of 420 mg (252 mg of elemental magnesium) 1 to 4 times per day.

J Neurol Sci 2012;39:323-327

Magnesium for epilepsy

Mean seizure frequency decreased by 33% at the first follow-up (3-6 months) ($p = 0.02$) and by 49% at the second follow-up (6-12 months) ($p = 0.004$). 36% of the patients had a reduction in seizure frequency of at least 75%, and 2 patients were seizure-free.

J Neurol Sci 2012;39:323-327

Magnesium for epilepsy

Most patients were well maintained with 252 mg of magnesium twice a day. No serious adverse effects were reported, although 4 patients experienced diarrhea.

J Neurol Sci 2012;39:323-327

Niacinamide for actinic keratoses

Double-blind trial: 76 healthy individuals (aged 48-90 years) with sun-damaged skin and multiple actinic keratoses received niacinamide (500 mg once or twice a day) or placebo for 4 months. All patients were advised to use sunscreen.

J Invest Dermatol 2012;132:1497-1500

Niacinamide for actinic keratoses

After 4 months, compared with placebo, niacinamide significantly decreased the number of actinic keratoses by one-third. The improvement at 2 months was also significant, but less pronounced.

J Invest Dermatol 2012;132:1497-1500

Niacinamide for actinic keratoses

Compared with placebo, niacinamide decreased the number of new skin cancers (basal or squamous cell carcinoma) by 76% ($p = 0.01$) and decreased the number of patients who developed at least one skin cancer by 86%.

J Invest Dermatol 2012;132:1497-1500

Niacinamide for actinic keratoses

The higher dose appeared to be slightly more effective than the lower dose, but because of the small sample size, firm conclusions could not be drawn. Niacinamide may work by preventing photoimmunosuppression.

J Invest Dermatol 2012;132:1497-1500

NAC for marijuana addiction

Double-blind trial: 116 patients (aged 15-21 years) seeking treatment for cannabis dependence received 1,200 mg of N-acetylcysteine (NAC) twice a day or placebo for 8 weeks. All patients received psychosocial interventions designed to facilitate abstinence.

Am J Psychiatry 2012;169:805-812

NAC for marijuana addiction

During the trial, the proportion of urine tests that were negative for cannabinoids was significantly higher in the NAC group than in the placebo group (40.9% vs. 27.2%; $p < 0.03$). NAC was well tolerated, with minimal adverse events.

Am J Psychiatry 2012;169:805-812

NAC for *H. pylori* eradication

Bacteria that are capable of producing a biofilm, such as *Helicobacter pylori*, may be more resistant than other bacteria to antibiotics, presumably because the protective matrix of the biofilm blocks the penetration of antibiotics.

Clin Gastroenterol Hepatol 2010;8:817-820.e3

NAC for *H. pylori* eradication

In vitro, N-acetylcysteine (NAC) has been found to prevent biofilm formation and to promote the degradation of existing biofilm.

Clin Gastroenterol Hepatol 2010;8:817-820.e3

NAC for *H. pylori* eradication

40 patients with at least 4 unsuccessful attempts at *H. pylori* eradication were randomly assigned to receive NAC (600 mg once a day) or no NAC (controls) for 1 week, followed by 1 week of conventional eradication therapy.

Clin Gastroenterol Hepatol 2010;8:817-820.e3

NAC for *H. pylori* eradication

The eradication rate was higher in the NAC group than in the control group (65% vs. 20%; $p < 0.01$).

Biofilm disappeared in all patients in whom eradication was successful, but persisted in patients in whom eradication was unsuccessful.

Clin Gastroenterol Hepatol 2010;8:817-820.e3

Iron for fatigue without anemia

Double-blind trial: 198 women (aged 18-53 years) with fatigue, serum ferritin < 50 µg/L, and hemoglobin > 12 g/dl received 80 mg/day of iron or placebo for 12 weeks.

CMAJ 2012;184:1247-1254

Iron for fatigue without anemia

The mean score on the Current and Past Psychological Scale for fatigue improved significantly more in the iron group than in the placebo group (47.7% vs. 28.8%; $p = 0.02$). Compared with placebo, iron increased the mean hemoglobin level by 0.32 g/dl ($p = 0.002$).

CMAJ 2012;184:1247-1254

Cherry juice for gout

100 patients with a history of gout received 1 tbsp. of Brownswood Acres tart cherry juice concentrate twice a day for an unspecified period of time. 92% of the patients had at least a 50% reduction in the number of gout attacks. Uric acid levels did not change.

Fam Pract News 2010(September 1):38

Folate/B_{12} prevents cognitive decline

Double-blind trial: 900 men (mean age, 66 years) with increased psychological distress received daily folic acid (400 µg) and B_{12} (100 µg) for 2 years. Significantly greater improvement was seen in the vitamin group than in the placebo group for total cognitive functioning and for immediate and delayed memory function.

Am J Clin Nutr 2012;95:194-203

Zinc for hair loss

5 Japanese women with diffuse hair loss (with or without patchy hair loss) and a low serum zinc concentration received 33 mg/day of zinc, as polaprezinc (a zinc complex of L-carnosine). Hair loss was cured in 4 patients and improved in one.

Dermatol Ther 2012;25:210-213

Vitamin C for sudden deafness

Idiopathic sudden sensorineural hearing loss is defined as sensorineural hearing loss of 30 dB or more in 3 contiguous frequencies over a period of 72 hours or less. The cause is unknown, but free radicals appear to be involved.

Vitamin C for sudden deafness

About one-third of patients recover normal hearing, another one-third are left with hearing loss of 40-60 dB, and the remainder progress to total deafness. Conventional treatment includes systemic glucocorticoids.

Vitamin C for sudden deafness

72 patients with idiopathic sudden sensorineural hearing loss received systemic steroids for 15 days and were randomly assigned to receive or not to receive (control group) vitamin C (200 mg/kg/day I.V. for 10 days, then 2,000 mg/day orally for 30 days).

Eur Arch Otorhinolaryngol 2102 Dec 4 [Epub ahead of print]

Vitamin C for sudden deafness

The proportion of patients who recovered completely (47% vs. 24%; $p = 0.03$) and the proportion who had complete or partial recovery (66% vs. 42%; $p < 0.04$) was significantly greater in the vitamin C group than in the control group.

Eur Arch Otorhinolaryngol 2102 Dec 4 [Epub ahead of print]

EGCG for lymphoma

42 previously untreated patients with early stage chronic lymphocytic leukemia were treated with a green tea extract (Polyphenon E) for up to 6 months. The dosage provided 1,000 mg/day of EGCG twice a day for 7 days, then 2,000 mg/day.

Cancer 2013;119:363-370

EGCG for lymphoma

69% of the patients had a biological response, defined as a sustained decline of at least 20% in the absolute lymphocyte count and/or a reduction of at least 30% in the sum of the products of all lymph node areas at some point during the treatment period.

Cancer 2013;119:363-370

EGCG for lymphoma

The most common grade 3 side effects were elevated transaminase levels (1 patient), abdominal pain (1 patient), and fatigue (1 patient).

Cancer 2013;119:363-370

Green tea prevents influenza

Double-blind trial: Japanese healthcare workers received 378 mg/day of green tea catechins and 210 mg/day of theanine for 5 months (November to April). The incidence of clinically defined influenza was 69% lower with active treatment than with placebo (4.1% vs. 13%; $p = 0.02$).

BMC Complement Altern Med 2011;11:15