



Surprising New Research About the Foundations of Bone Health

In this special issue of *Advances*, we've heralded the coming of **Menatetrenone** and **Strontium**, two revolutionary new supplements which have only just been made available to North Americans wanting to take good care of their bones. But in our excitement over these vanguard bone-health nutrients, we should also remember that bone health is a total lifestyle commitment. While most people know the importance of "the basics" (like calcium, magnesium, and vitamin D), there are controversies that need to be addressed even surrounding the right dose and *form* of even these well-known nutrients. The facts about these and other lifestyle choices may surprise you.

• **Get Enough Calcium.** Current "official" recommendations suggest an intake of 1000 milligrams of calcium for younger adults, and 1200 milligrams for people over the age of 50. Some evidence suggests that a still higher intake (**1300-1600 milligrams**) of calcium is more effective for lowering fracture risk in the elderly.¹ But these numbers are your *total* calcium need. The more calcium you get in your diet, the less you need from supplements. There is little evidence that ever-higher intake of calcium does your bones any additional good, and indeed taking *too much* calcium can inhibit the absorption and utilization of other important bone nutrients, such as zinc and copper.²

The best food sources of calcium are skim milk and many other low-fat dairy products. Contrary to what you may have heard, the

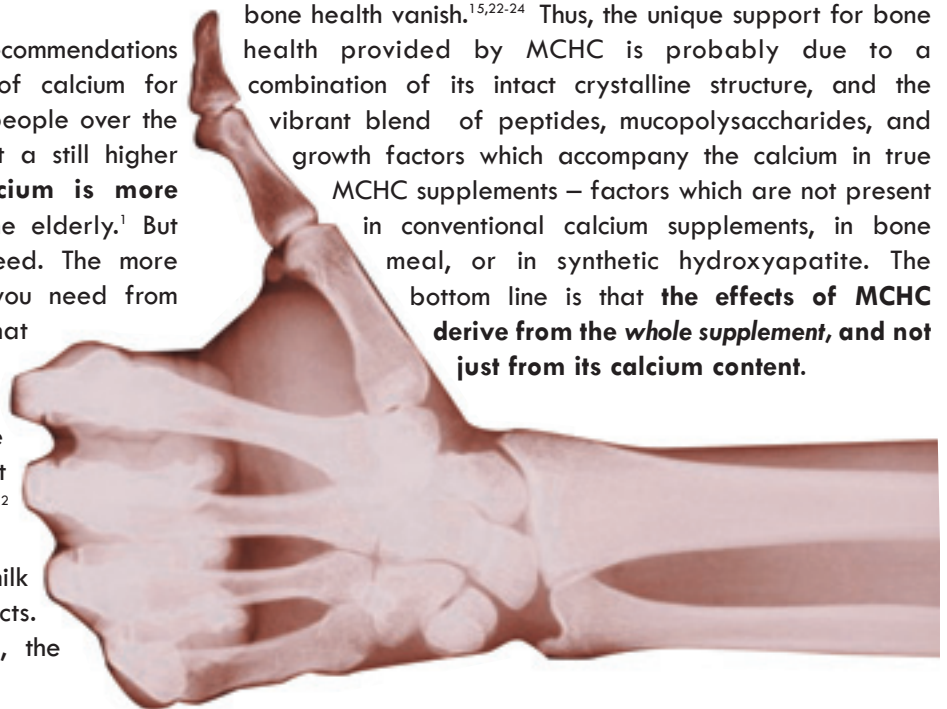
balance of the evidence overwhelmingly favors the conclusion that **milk is good for your bones.**³

• **Get the Right Kind of Calcium.** Too many health-conscious people believe that conventional calcium supplements (or conventional calcium plus vitamin D) can put an end to bone loss. They can't. As multiple studies have documented, **conventional calcium supplements – such as calcium gluconate, calcium citrate, calcium carbonate, and even calcium citrate-malate – slow, but do not halt or reverse, menopausal bone loss**, whether taken alone or with vitamin D.⁴⁻¹⁶ You can't force the bones to take in more calcium, and build more bone, by taking more calcium: calcium *itself* can only *support* your existing bone mass, or the building of bone induced by the *other* factors in your skeletal health program.^{1,17}

But there is one *seeming* exception. **Ossein microcrystalline hydroxyapatite complex (MCHC) consistently halts, or even reverses, bone loss in controlled, scientific studies.**^{11,14,15,16,18-20} When put head-to-head against other calcium supplemental forms, MCHC consistently trumps the conventional calcium supplement.^{11,14,15,16,20-24} But actually, this is the exception that proves the rule, because **MCHC's bone-building powers do not lie in the calcium itself.**

True MCHC is not just a form of calcium, but is a calcium-based crystalline *nutrient complex*, which is how the mineral is actually stored in your bones. When the calcium form that is present in MCHC is given *in isolation* from this nutrient matrix (as synthetic hydroxyapatite (calcium orthophosphate) or as bone meal (which retains MCHC's calcium content but breaks down the MCHC crystalline structure and destroys the non-mineral components of the complex)), the unique effects of MCHC on parameters of bone health vanish.^{15,22-24} Thus, the unique support for bone health provided by MCHC is probably due to a combination of its intact crystalline structure, and the vibrant blend of peptides, mucopolysaccharides, and growth factors which accompany the calcium in true MCHC supplements – factors which are not present in conventional calcium supplements, in bone meal, or in synthetic hydroxyapatite. The bottom line is that **the effects of MCHC derive from the whole supplement, and not just from its calcium content.**

1300-1600 milligrams of calcium is more effective for lowering fracture risk.



Unfortunately, of course, vegetarians cannot consume MCHC because it is an animal product (although premium MCHC supplements use free-range, pasture-fed livestock from countries like New Zealand or Australia as sources for the raw materials). **For vegetarians, the best calcium source is calcium citrate-malate.**

Calcium citrate-malate is *not* the same thing as calcium citrate, or as a simple admixture of calcium citrate and calcium malate. Calcium

Ossein microcrystalline hydroxyapatite complex (MCHC) consistently halts, or even reverses, bone LOSS in controlled, scientific studies.

citrate-malate 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 six²⁵ to nine²⁶ 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 **calcium citrate-malate is considerably better-absorbed than calcium citrate.** In fact, despite what is often said, nearly all studies have reported that **plain calcium citrate is actually no better absorbed than calcium carbonate** when taken with food.^{26,27-32} Most studies find that about 22 to 26% of calcium from calcium carbonate or citrate is absorbed, whereas calcium citrate-malate absorption is consistently found to be around 36 to 37% in capsules and tablets,^{25,32-34} and can be as high as 42% when dissolved in orange juice.³⁵

Calcium citrate-malate has been used successfully in many controlled trials to support bone mass and/or to lower fracture risk.^{5,7,8,11,12,39-44} Some of these trials have involved a direct face-off between calcium citrate-malate and other forms of calcium. Such trials demonstrate that, as might be expected from its greater bioavailability, **calcium citrate-malate gives better protection to the bones than other vegetarian calcium sources** – although its effects are still not as impressive as those of MCHC.



How Rumors Get Started

The widespread myth of calcium citrate's superior absorption is in part the result of poorly-designed studies, which used calcium excretion as a measure of absorption. The reasoning for using this method is based on the fact that, once your body has used all of the calcium which it can at the time that a dose of calcium is taken in, any *extra* calcium initially absorbed will then be passed out in the urine. Thus, by giving a dose of calcium so high that the body can't use it all, and then measuring how much calcium passes out through the urine, the comparative bioavailability of two calcium forms can in theory be gauged by seeing how much calcium excretion they cause.

That's a sensible-sounding and inexpensive testing method, and in many cases it probably gives a good picture of calcium absorption. But it falls down in comparing calcium citrate with the carbonate salt. First, the alkalinizing effect of the carbonate reduces the amount of calcium excreted through the urine, making its absorption look *lower*; and then, some studies suggest, the citric acid in calcium citrate *increases* the body's excretion of calcium, making its absorption look *higher*!^{28,36,37}

Faith in calcium citrate's higher bioavailability was also shored up by a recent "meta-analysis" paper.³⁸ Meta-analysis is done by combining the results of several separate studies into one mondo-report, which gives a clearer picture of the *overall* results of the available scientific evidence. But the authors of *this* meta-analysis made one critical mistake: in combining studies, they assumed that calcium citrate was basically the same as calcium citrate-malate, and lumped the results for the two forms together. In fact, of course, the two forms are considerably different. By combining studies on calcium citrate with studies on the much more bioavailable citrate-malate form, the citrate salt acquired an undeserved glitter, reflected from citrate-malate's radiance.

On the other hand, the hype surrounding so-called "ionic coral calcium" is not the result of understandable errors in otherwise solid science, but of a lack of even the most elementary scientific credibility. Not one clinical trial has ever been performed using this calcium source to show that it is better absorbed or better utilized than other conventional calcium sources. Instead, astoundingly, **the claims of high bioavailability for "coral calcium" are not based on controlled studies in humans, but on the stuff's ability to dissolve in water**; and as has been shown, such a silly test bears little relationship to the ability of a *living body* to absorb calcium.³² Indeed, this kitchen-counter method of testing absorption leads to ridiculous exaggerations of calcium absorption, such as 50% absorption for calcium citrate, or 95% absorption for "coral calcium" itself. In the real world, *no* calcium source has such a high bioavailability.

In one such trial,¹² a subgroup of women in late menopause and a low dietary intake of calcium took 500 milligrams of calcium (either calcium citrate-malate or calcium carbonate) or a dummy pill for two years. By the end of the trial, all of the women in the study had lost some bone mineral density: again, conventional calcium supplements can *slow*, but cannot reverse, the loss of BMD over the body as a whole that accompanies menopause. The women receiving the placebo were in the worst shape, having lost 2.27% on the BMD in their spines. Women given calcium carbonate did get some benefits – they endured 15% less loss of BMD than the women receiving the fake pills – but **women taking calcium citrate-malate fared much better than women receiving the more common calcium supplement**, having escaped 60% of the loss of spinal bone mineral density suffered by the placebo group in the same period.¹²

Both calcium supplements were more protective at the hip. While women receiving only a dummy pill lost 2.11% of their hip BMD, women taking calcium carbonate held their hip BMD steady as a group (with most women ranging from a gain of 1.16% to a loss of 0.90%). But again, calcium citrate-malate demonstrated its superiority, with women



taking this form of calcium actually experiencing a *gain* in hip BMD (on average, 0.87%, although the typical change in these women ranged from a gain of 1.88% to a loss of 0.14%). Similar results were seen in the lower arm bone.¹²

Bottom line: take your calcium in the form of MCHC if you are comfortable with animal products; choose calcium citrate-malate if you're not.

- **Rock Around the Clock.** Several recent studies have suggested that *when* you take your calcium can make a big

difference in terms of both the amount of calcium you'll absorb, and the *effects* of that calcium on your bones.

For starters, **take your calcium with food**, as doing so will increase absorption.^{32,33} It's also important to **spread your calcium supplements over the course of the day**. Taking

Calcium citrate-malate gives better protection to the bones than other vegetarian calcium sources.

a smaller dose of calcium at each meal has several advantages over taking it all at once. For one thing, it will increase your total absorption of calcium (by as much as 80-100%).⁴⁵ And by keeping calcium levels in your serum high throughout the day and

night, a multi-dose approach keeps **parathyroid hormone (PTH)** under control *throughout the day*, whereas a one-shot dose of your *entire* day's calcium supplementation causes only a temporary lowering of this hormone.^{46,47} (Keeping PTH under control is important: the hormone is released in response to low serum calcium, triggering your body to rob the bones of this mineral to meet needs elsewhere in the body). And to get the best possible results, **take the largest single dose of calcium later in the day**, at dinner or with a late-night snack. Studies show that this last daily calcium dose does a better job of reducing markers of bone teardown,^{48,49} perhaps by keeping PTH low while you're sleeping (and thus not taking any calcium).

So, for instance, if you were taking a total of six calcium capsules a day, you might take one with breakfast, one with lunch, and three with dinner – or you might take two with each meal, and then go to bed with a nice glass of warm milk to help you sleep (and yes, Mom was right: a late-night glass of milk leads to sounder sleep,⁵⁰ probably thanks to its content of the amino acid **tryptophan** which (along with its calcium and magnesium content) increases levels of the sleep hormone **melatonin**).

- **Take Enough Vitamin D.** Aside from improving calcium absorption, vitamin D is needed for proper muscle function, which may play a role in protecting against fractures by reducing falls.⁵¹ So getting enough vitamin D is important. And you simply *can't* rely on the sun to meet your requirements, especially in Northern climates. **Flat-out vitamin D deficiency is found in one third of otherwise-healthy Canadians at least once over the course of the year.**⁵² Indeed, the whole reason that our milk is now fortified with vitamin D is that rickets (bone disease caused by vitamin D deficiency) was epidemic in children in the Northern United States at the turn of the twentieth century – when kids spent a *lot* more time out-of-doors than do today's adults. There's a good reason for this: studies in human skin suggest that the amount of sun to which a person in Boston or Edmonton is exposed in the winter is not enough to make the body produce the vitamin.⁵³ But even in sunny Spain, researchers have found that 80% of children have inadequate vitamin D levels in March and October,⁵⁴

and the situation is much the same in France.⁵⁵

From what we now know, **the old RDA of 400 IU will not protect you from vitamin D insufficiency** except in the



sunnier of climates. A controlled trial in teen and preteen girls in Finland showed that a 400 IU vitamin D supplement was not enough to keep serum levels of the active vitamin above the cutoff for insufficiency,⁵⁶ and studies in the health of large populations confirm the finding in Canadian⁵⁷ and Danish⁵⁸ women lead to the same conclusion. More importantly, the use of standard 400 IU supplements have *not* been shown to reduce fracture rates,^{59,60} and even 600 IU has little effect on BMD.⁵

So how much vitamin D do you need? For optimal bone health – as opposed to simply avoiding a case of obvious rickets – scientists are now suggesting that the proper test is to see how much of the vitamin it takes to minimize the elevation of **parathyroid hormone**,⁶¹ which as we've noted leeches calcium from the bones when serum calcium levels are low. To reach this target, doses of as much as **4000 IU per day** are recommended by some legitimate authorities,⁵⁴ and such doses have been used successfully and with apparent short-term safety to achieve the goal.⁶²

But it's premature to start using this high a dose: for one thing, taking this much vitamin D may be toxic when taken in the vegetarian form of **ergocalciferol (vitamin D₂)** – although apparently not when you use **cholecalciferol (vitamin D₃)** – the animal-sourced form).⁵⁴ But clinical trials show that we don't need to self-experiment with these massive doses to get results. **Controlled studies show that vitamin D, together with calcium, helps to reduce the risk of fracture at a dose of 800 IU per day.**^{10,63,64}

Vitamin D, together with calcium, helps to reduce the risk of fracture at a dose of 800 IU per day.

- **Take a Magnesium You Can Absorb.** Magnesium is critical to various aspects of bone metabolism, and borderline magnesium deficiency is surprisingly common. Unfortunately, far too many bone health formulas rely on magnesium oxide as the source of this mineral, for the simple reason that it takes up less room in a capsule, and therefore requires fewer capsules to be taken to reach the daily dose. But compared to other sources of the mineral, **magnesium oxide has “extremely low” bioavailability (22.8%).**^{77a} Additionally, **magnesium oxide is an antacid**, which can impair digestion and nutrient absorption. This is an especial concern in many older people, whose low stomach acid may even trigger pernicious anemia (flat-out B₁₂ deficiency).

Magnesium citrate is certainly somewhat better, at 29.64% absorption,^{77a} but it's still far from the best magnesium you can choose; and, indeed, much of the supposed “magnesium citrate” on health-food store shelves is not true, *fully-reacted* magnesium citrate, but a mixture of magnesium oxide and magnesium citrate.

Much better absorption is available from other forms of magnesium. Among the available options, **fully-reacted magnesium monospartate stands out as the best**, with a remarkable 41.7% bioavailability.^{77a}

- **Remember the neglected nutrients.** Calcium, magnesium, and vitamin D are very well-known as nutrients with an important place in bone health. By contrast, you may never have heard of the powerful support that **Menatetrenone** and **Strontium** can lend your bones before reading this special issue of *Advances*.

But there are a host of nutrients important to bone health which are too often neglected in putting together a total lifestyle program. These would most prominently include manganese, zinc and copper,^{2,4,65-67} and would extend to other, even more commonly-neglected nutrients such as silicon,⁶⁸ boron,⁶⁹ and vitamin C.⁵⁸ Methylating nutrients such as vitamin B₁₂ and folic acid may also be important to bone health,^{70,71} perhaps because of the toxic effects of **homocysteine** on the protein fibers in bone.^{72,73}

- **Eat an “alkaline-ash” diet.** When the body metabolizes minerals bound to certain organic ligands, alkaline ions are produced. These alkaline ions help to keep the body's acid-base load in balance. When the body becomes too acidic, calcium phosphate is leached from the bones in order to bring the balance back, contributing to the destruction of your bones.⁷⁴

Foods rich in such minerals are called “alkaline-ash.” The most important “alkaline” foods are vegetables and fruits

(see **Table 1**). But the widespread belief that whole grains and fish are “alkaline-ash” foods is a myth: in fact, these foods are “acid-ash” – that is, they contain moieties which, when metabolized, tend to lower the body’s pH. Many grains are as acidic as meat, whose acidifying tendencies are more widely known. The more “acid-ash” foods you consume, the more important it is to get plenty of “alkaline-ash” fruits and vegetables to balance them. The “alkalinity” of these foods is probably a big part of the reason why people eating diets rich in fruits and veggies have better bone health and metabolism.^{65,75-77}

Protein makes a positive contribution to bone health.

•**The Phosphorus Paradox.** It’s widely believed that Western diets are too rich in this mineral, and that excess phosphorus is bad for bone health. But phosphorus is an essential mineral, which makes up more than half of the mineral content of bone and which is needed for osteoblast function. And nearly a third of older Americans don’t get the DRI of this essential mineral. The concerns with phosphorus stem from theoretical speculations related to its



effects on parathyroid hormone, and the belief that phosphorus causes you to lose calcium in your urine. But studies show that it’s the *form* of phosphorus that counts: *phosphoric acid* (the acidic phosphorus compound in some sodas) may cause increased calcium excretion because of its acidifying effect, but neutral phosphorus forms do not,^{77b} and indeed, one study^{77c} found that even when sodas contain phosphoric acid, they don’t increase calcium excretion unless they also contain caffeine.

Indeed, a recent study^{77d} has raised concerns that, with so many people taking calcium as supplements instead of drinking milk (in which calcium and phosphorus come together as a bone-building team), folks who don’t get plenty of phosphorus in their diets (such as persons on low-protein diets and many of the elderly) may actually become phosphorus *deficient*, because calcium supplements can reduce phosphorus absorption. Several recent reviews in the scientific literature have emphasized the importance of getting enough of this “black sheep” in the bone-health nutritional family.^{65,67,77e}

• **Get enough protein.** Like phosphorus, protein has a bad rep’ in many health-conscious circles because of its “acid-ash” properties. Surprisingly, however, the latest and best research consistently reports that protein – including animal **protein – makes a positive contribution to bone health**, especially when protein intake is somewhat *higher* than the RDA.^{38,78-81} The authors of studies which have commonly been presented as “proof” that animal protein is bad for bone health^{82,83} have come forward to state that their results have been misrepresented.^{84,85}

In fact, higher protein intake increases the bone-health benefits of taking calcium supplements.³⁸ Furthermore, research clearly shows that *low* protein intake results in impaired bone metabolism, reduced calcium absorption, and bone-draining elevations in **parathyroid hormone**.^{86,87} And, importantly, **the RDA does not provide enough protein to prevent impaired calcium metabolism**.^{88,89}

So despite its “acidifying” influence – which can be countered with a rich intake of fruits and vegetables – the

Table 1. “Alkaline-Ash” and “Acid-Ash” Foods. Average values for a class of food are given after the class name, which is given in full capitals; exceptional specific foods are also listed beneath the category name. Foods assigned more “negative” values are more alkaline; those with higher “positive” values are more acidic. Values are per 100 g of food. Data taken from (94).

FATS AND OILS: 0	MEATS: +9.5
FISH: +7.91	Corned beef: +13.2
Brown trout: +10.8	Lean pork: 7.9
FRUITS: -3.1	MILK AND DAIRY: +8.7
Raisins: -21	Buttermilk: +0.5
Currants: -6.5	Cheddar Cheese: +26.4
NUTS: +4.1	Cottage Cheese: +8.7
Peanuts: +8.3	Soft Cheese: +4.3
Hazelnuts: -2.8	Whole Milk: +0.7
Walnuts: +6.8	Parmesan: +34.2
GRAINS: +5.7	Yogurt: +1.5
Bread: +3.5	Ice Cream: 0.6
Rye bread: +4	Skim Milk: +1.2
Whole wheat: 1.8	VEGETABLES: -2.8
Flour: +7.0	Spinach: -14
Spaghetti: +6.7	Zucchini: -4.6
White rice: +1.7	Cauliflower: -4.0
Brown Rice: +12.5	Carrots: -4.9
Oats: +10.7	Asparagus: -0.4
LEGUMES: +0.53	Cucumbers: -0.8
French Beans: -3.1	
Lentils: +3.5	

overall effect of protein on bone health is favorable. The optimal intake of protein to support a healthy skeletal system appears to be in the range of 1.0 to 1.5 grams per kilogram of body mass, or 2.2 to 3.3 grams of protein for each pound that you weigh.⁵⁸ This is an intake significantly higher than the RDA for protein, which is set at 0.8 milligrams of protein per kilogram of body mass.

- **Keep active.** Exercise clearly helps build bone mass in young people. And it also improves balance, muscle mass, and strength, which reduces your chances of taking a fall by about 25%. Despite these facts, it isn't *totally* clear whether exercise actually increases bone mass, or protects against fracture risk, when people don't get started until their middle years or beyond.^{82,90} Despite this uncertainty, getting active is clearly a good idea, if only for the many *other* ways that it will improve your life, from energy levels to heart health to looking good. The kinds of exercise *most likely* to specifically support bone health are weight-bearing and/or high-impact activities, such as weightlifting and jogging.⁸¹

- **Maintain a healthy weight.** While there are all kinds of good reasons to avoid the overweight that's creeping its way across every sector of our society, it's also important not to *lose* too much weight – or to lose weight too quickly. Low body weight, and quick weight loss, are associated with thinner bones, and higher fracture risk.⁸²

- **Quit smoking.** Smokers are between half-again and twice as likely to suffer a fracture as nonsmokers,⁵⁸ apparently because the toxins in cigarette smoke interfere with normal estrogen metabolism and calcium absorption, and brings on early menopause.⁹¹ For help quitting – especially if you've tried to quit before and have not yet escaped the addiction – see the resources at:
<http://www.hc-sc.gc.ca/hecs-sesc/tobacco/quitting/index.html>
... or talk to your doctor.

- **If you drink, do so in moderation.** Heavy drinking (more than two drinks a day) definitely puts you at risk for bone loss.⁵⁸ But more *moderate* drinking – say, between one and two drinks a day – doesn't seem to harm the bones, and some studies even suggest that it might be *protective* in women,^{58,82} though there's no real reason to believe that's true of men. If there is a bone-shielding effect, it might be related to the fact that a drink or two daily increase the body's formation of some estrogens from their precursors.⁹²

But the very changes in estrogen metabolism which might help shield a woman's bones can also promote breast cancer – and even one drink a day is linked to greater risk of this killer, *especially* (though not exclusively!) if you're taking estrogen replacement therapy.⁹³ Throw in the well-known heart-health benefits of moderate drinking, and trying to fit together the *total* puzzle of alcohol's risks

and benefits can be a frustrating, dizzying challenge. Best advice: don't *start* or *increase* your drinking just to support your bones – but if you already make a glass of wine a part of your dinner every day, talk with your doctor, weigh your priorities and family history, and choose carefully.

To some, this “to do” list for bone health will seem too long, and they may become discouraged. But there really aren't *that* many steps along the way. A single, well-designed multinutrient bone-health supplement can help ensure that you're getting the right *kind* and *amounts* of the basic vitamins and minerals you need for bone health. The shift to a diet rich in fruits and vegetables, with adequate protein, can be reached in simple – and delicious! – steps. And remember that **each of these choices also has positive impacts on other aspects of your lifestyle.** Each easy adjustment that you make brings you closer to the balance point of total health and vitality.

References

- 1 Heaney RP. Calcium needs of the elderly to reduce fracture risk. *J Am Coll Nutr.* 2001 Apr;20(2 Suppl):192S-197S.
- 2 Lowe NM, Fraser WD, Jackson MJ. Is there a potential therapeutic value of copper and zinc for osteoporosis? *Proc Nutr Soc.* 2002 May;61(2):181-5.
- 3 Heaney RP. Calcium, dairy products and osteoporosis. *J Am Coll Nutr.* 2000 Apr;19(2 Suppl):83S-99S.
- 4 Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: a randomized controlled trial. *Am J Med.* 1995 Apr;98(4):331-5.
- 5 Peacock M, Liu G, Carey M, McClintock R, Ambrosius W, Hui S, Johnston CC. Effect of calcium or 25OH vitamin D3 dietary supplementation on bone loss at the hip in men and women over the age of 60. *J Clin Endocrinol Metab.* 2000 Sep;85(9):3011-9.
- 6 Riggs BL, O'Fallon WM, Muhs J, O'Connor MK, Kumar R, Melton LJ 3rd. Long-term effects of calcium supplementation on serum parathyroid hormone level, bone turnover, and bone loss in elderly women. *J Bone Miner Res.* 1998 Feb;13(2):168-74.
- 7 Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med.* 1997 Sep 4;337(10):670-6.
- 8 Dawson-Hughes B, Harris SS, Krall EA, et al. Rates of bone loss in postmenopausal women randomly assigned to one of two dosages of vitamin D. *Am J Clin Nutr.* 1995 May;61(5):1140-5.
- 9 Chevalley T, Rizzoli R, Nydegger V, Slosman D, Rapin CH, Michel JP, Vasey H, Bonjour JP. Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. *Osteoporos Int.* 1994 Sep;4(5):245-52.
- 10 Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. *N Engl J Med.* 1992 Dec 3;327(23):1637-42.
- 11 Dawson-Hughes B, Dallal GE, Krall EA, Harris S, Sokoll LJ, Falconer G. Effect of vitamin D supplementation on wintertime and overall bone loss in healthy postmenopausal women. *Ann Intern Med.* 1991 Oct 1;115(7):505-12.
- 12 Dawson-Hughes B, Dallal GE, Krall EA, Sadowski L, Sahyoun N, Tannenbaum S. A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. *N Engl J Med.* 1990 Sep 27;323(13):878-83.
- 13 Castelo-Branco C, Pons F, Vicente JJ, Sanjuan A, Vanrell JA. Preventing postmenopausal bone loss with ossein-hydroxyapatite compounds. Results of a two-year, prospective trial. *J Reprod Med.* 1999 Jul; 44(7): 601-5.
- 14 Ruegsegger P, Keller A, Dambacher MA. Comparison of the treatment effects of ossein-hydroxyapatite compound and calcium carbonate in osteoporotic females. *Osteoporos Int.* 1995 Jan; 5(1): 30-4.
- 15 Anfeld M, Caviezel R, Schacht E, Schicketanz KH. The influence of ossein-hydroxyapatite compound ("Ossopan") on healing of a bone defect *Curr Med Res Opin* 1986;10(4):241-50.
- 16 Epstein O, Kato Y, Dick R, Sherlock S. Vitamin D, hydroxyapatite, and calcium gluconate in treatment of cortical bone thinning in postmenopausal women with primary biliary cirrhosis. *Am J Clin Nutr.* 1982 Sep; 36(3): 426-30.
- 17 Netelenbos C. Osteoporosis: intervention options. *Maturitas.* 1998 Nov 16;30(3):235-9.
- 18 Ringe JD, Keller A. Risk of osteoporosis in long-term heparin therapy of thromboembolic diseases in pregnancy: attempted prevention with ossein-hydroxyapatite. *Geburtshilfe Frauenheilkd.* 1992 Jul;52(7):426-9.
- 19 Ruegsegger P, Dambacher MA. Therapy of osteoporosis with an ossein-hydroxyapatite compound evaluated with quantitative computed tomography. *J Bone Miner Res.* 1987 Jun; 2(Suppl1):A325.
- 20 Stellon A, Davies A, Webb A, Williams R. Microcrystalline hydroxyapatite compound in prevention of bone loss in corticosteroid-treated patients with chronic active hepatitis. *Postgrad Med J.* 1985 Sep;61(719):791-6.
- 21 Dent CE, Davies JJ. Calcium metabolism in bone disease: effects of treatment with micro-

- crystalline calcium hydroxyapatite compound and dihydroxycholesterol. *J R Soc Med.* 1980 Nov;73(11):780-5.
- 22 Durance RA, Parsons V, Atkins CJ, Hamilton EB, Davies C. A trial of calcium supplements (Ossopan) and ashed bone. *Clin Trials J.* 1973 Nov;10(3):67-73.
- 23 Schmidt KH, Worner UM, Buck HJ. Examination of new bone growth on aluminium oxide implant contact surfaces after oral administration of ossein-hydroxyapatite compound to rats. *Curr Med Res Opin.* 1988;11(2):107-15.
- 24 Stepan JJ, Mohan S, Jennings JC, Wergedal JE, Taylor AK, Baylink DJ. Quantitation of growth factors in ossein-mineral-compound. *Life Sci.* 1991; 49(13): PL79-84.
- 25 Smith KT, Heaney RP, Flora L, Hinders SM. Calcium absorption from a new calcium delivery system (CCM). *Calcif Tissue Int.* 1987 Dec;41(6):351-2.
- 26 Heaney RP. Meta-analysis of calcium bioavailability. *Am J Therapeut.* 2001 Jan/Feb;8(1):73.
- 27 Heaney RP, Dowell SD, Bierman J, Hale CA, Bendich A. Absorbability and cost effectiveness in calcium supplementation. *J Am Coll Nutr.* 2001 Jun;20(3):239-46.
- 28 Heaney RP, Dowell MS, Barger-Lux MJ. Absorption of calcium as the carbonate and citrate salts, with some observations on method. *Osteoporos Int.* 1999;9(1):19-23.
- 29 Kohls K, Kies C. Calcium bioavailability: A comparison of several different commercially available calcium supplements. *J Appl Nutr.* 1992;44:50-62.
- 30 Sheikh MS, Santa Ana CA, Nicar MJ, Schiller LR, Fordtran JS. Gastrointestinal absorption of calcium from milk and calcium salts. *N Engl J Med.* 1987 Aug 27;317(9):532-6.
- 31 Recker RR. Calcium absorption and achlorhydria. *N Engl J Med.* 1985 Jul 11;313(2):70-3.
- 32 Heaney RP, Recker RR, Weaver CM. Absorbability of calcium sources: the limited role of solubility. *Calcif Tissue Int.* 1990 May;46(5):300-4.
- 33 Heaney RP, Smith KT, Recker RR, Hinders SM. Meal effects on calcium absorption. *Am J Clin Nutr.* 1989 Feb;49(2):372-6.
- 34 Miller JZ, Smith DL, Flora L, et al. Calcium absorption from calcium carbonate and a new form of calcium in healthy male and female adolescents. *Am J Clin Nutr.* 1988 Nov;48:1291-4.
- 35 Andon MB, Peacock M, Kanerva RL, De Castro JA. Calcium absorption from apple and orange juice fortified with calcium citrate malate. *J Am Coll Nutr.* 1996 Jun;15(3):313-6.
- 36 Gomari G, Gulyas E. Effect of parenterally administered citrate on the renal excretion of calcium.
- 37 Steggerda FR, Mitchell HH. The effect of the citrate ion on the utilization of calcium from salts by college women. *J Nutr.* 1955;55:519-26.
- 38 Sakhaee K, Bhuket T, Adams-Huet B, Rao DS. Meta-analysis of calcium bioavailability: a comparison of calcium citrate with calcium carbonate. *Am J Ther.* 1999;6:313-21.
- 39 Dawson-Hughes B, Harris SS. Calcium intake influences the association of protein intake with rates of bone loss in elderly men and women. *Am J Clin Nutr.* 2002 Apr;75(4):773-9.
- 40 Krall EA, Wehler C, Garcia RI, Harris SS, Dawson-Hughes B. Calcium and vitamin D supplements reduce tooth loss in the elderly. *Am J Med.* 2001 Oct 15;111(6):452-6.
- 41 Andon MB, Lloyd T, Matkovic V. Supplementation trials with calcium citrate malate. *J Nutr.* 1994 Aug;124(8 Suppl):1412S-1417S.
- 42 Strause L, Saltman P, Smith KT, Bracker M, Andon MB. Spinal bone loss in postmenopausal women supplemented with calcium and trace minerals. *J Nutr.* 1994 Jul;124(7):1060-4.
- 43 Lloyd T, Andon MB, Rollings N, et al. Calcium supplementation and bone mineral density in adolescent girls. *JAMA.* 1993 Aug 18;270(7):841-4.
- 44 Johnston CC Jr, Miller JZ, Slemenda CW, et al. Calcium supplementation and increases in bone mineral density in children. *N Engl J Med.* 1992 Jul 9;327(2):82-7.
- 45 Heaney RP, Berner B, Louie-Helm J. Dosing regimen for calcium supplementation. *J Bone Miner Res.* 2000 Nov;15(11):2291.
- 46 Reginster JY, Zegels B, Lejeune E, et al. Influence of daily regimen calcium and vitamin D supplementation on parathyroid hormone secretion. *Calcif Tissue Int.* 2002 Feb;70(2):78-82.
- 47 Karkkainen MU, Lamberg-Allardt CJ, Ahonen S, Valimaki M. Does it make a difference how and when you take your calcium? The acute effects of calcium on calcium and bone metabolism. *Am J Clin Nutr.* 2001 Sep;74(3):335-42.
- 48 Blumsohn A, Herrington K, Hannon RA, et al. The effect of calcium supplementation on the circadian rhythm of bone resorption. *J Clin Endocrinol Metab.* 1994 Sep;79(3):730-5.
- 49 Aerssens J, Declercq K, Maeyaert B, Boonen S, Dequeker J. The effect of modifying dietary calcium intake pattern on the circadian rhythm of bone resorption. *Calcif Tissue Int.* 1999 Jul;65(1):34-40.
- 50 Southwell PR, Evans CR, Hunt JN. Effect of a hot milk drink on movements during sleep. *BMJ.* 1972 May 20;2(811):429-31.
- 51 Pfeifer M, Begerow B, Minne HW. Vitamin D and muscle function. *Osteoporos Int.* 2002 Mar;13(3):187-94.
- 52 Rucker D, Allan JA, Fick GH, Hanley DA. Vitamin D insufficiency in a population of healthy western Canadians. *CMAJ.* 2002 Jun 11;166(12):1517-24.
- 53 Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. *J Clin Endocrinol Metab.* 1988 Aug;67(2):373-8.
- 54 Docio S, Riancho JA, Perez A, et al. Seasonal deficiency of vitamin D in children: a potential target for osteoporosis-preventing strategies? *J Bone Miner Res.* 1998 Apr;13(4):544-8.
- 55 Guillemand J, Taupin P, Le Taupin HT, et al. Vitamin D status during puberty in French healthy male adolescents. *Osteoporos Int.* 1999;10(3):222-5.
- 56 Lehtonen-Veromaa M, Mattonen T, Irljala K, et al. Vitamin D intake is low and hypovitaminosis D common in healthy 9- to 15-year-old Finnish girls. *Eur J Clin Nutr.* 1999 Sep;53(9):746-51.
- 57 Vieth R, Cole DE, Hawker GA, Trang HM, Rubin LA. Wintertime vitamin D insufficiency is common in young Canadian women, and their vitamin D intake does not prevent it. *Eur J Clin Nutr.* 2001 Dec;55(12):1091-7.
- 58 Glerup H, Mikkelsen K, Poulsen L, et al. Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited. *J Intern Med.* 2000 Feb;247(2):260-8.
- 59 Cumming RG, Cummings SR, Nevitt MC, et al. Calcium intake and fracture risk: results from the study of osteoporotic fractures. *Am J Epidemiol.* 1997 May 15;145(10):926-34.
- 60 Lips P, Graafmans WC, Ooms ME, et al. Vitamin D supplementation and fracture incidence in elderly persons. *Ann Intern Med.* 1996 Feb 15;124(4):400-6.
- 61 Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr.* 1999 May;69(5):842-56.
- 62 Vieth R, Chan PC, MacFarlane GD. Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr.* 2001 Feb;73(2):288-94.
- 63 Chapuy MC, Arlot ME, Delmas PD, Meunier PJ. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *BMJ.* 1994 Apr 23;308(6936):1081-2.
- 64 Chapuy MC, Pamphile R, Paris E, et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalys II study. *Osteoporos Int.* 2002 Mar;13(3):257-64.
- 65 Ilich JZ, Kerstetter JE. Nutrition in bone health revisited: a story beyond calcium. *J Am Coll Nutr.* 2000 Nov-Dec;19(6):715-37.
- 66 Saltman PD, Strause LG. The role of trace minerals in osteoporosis. *J Am Coll Nutr.* 1993 Aug;12(4):384-9.
- 67 Heaney RP. Trace element and mineral nutrition in skeletal health and disease. In Bogden JD, Klevay LM (eds.). *Clinical nutrition of the essential trace elements and minerals.* 2000; Totowa, NJ: Humana Press, 239-49.
- 68 Eisinger J, Clairet D. Effects of silicon, fluoride, etidronate and magnesium on bone mineral density: a retrospective study. *Magnes Res.* 1993 Sep;6(3):247-9.
- 69 Volpe SL, Taper LJ, Meacham S. The relationship between boron and magnesium status and bone mineral density in the human: a review. *Magnes Res.* 1993 Sep;6(3):291-6.
- 70 Porteous L, Catterick J, Bishop JA. Nutritional influences on indices of bone health: preliminary results from the 'extent of osteoporosis in young British women' study. *Proc Nutr Soc.* 2001. In press.
- 71 Freudenheim JL, Johnson NE, Smith EL. Relationships between usual nutrient intake and bone-mineral content of women 35-65 years of age. *Am J Clin Nutr.* 1986 Dec;44(6):863-76.
- 72 Krumdieck CL, Prince CW. Mechanisms of homocysteine toxicity on connective tissues: implications for the morbidity of aging. *J Nutr.* 2000 Feb;130(2S Suppl):365S-368S.
- 73 Miyao M, Morita H, Hosoi T, Kurihara H, Inoue S, Hoshino S, Shiraki M, Yazaki Y, Ouchi Y. Association of methylenetetrahydrofolate reductase (MTHFR) polymorphism with bone mineral density in postmenopausal Japanese women. *Calcif Tissue Int.* 2000 Mar;66(3):190-4.
- 74 New SA. The role of the skeleton in acid-base homeostasis. *Proc Nutr Soc.* 2002 May;61(2):151-64.
- 75 Tucker KL, Hannan MT, Kiel DP. The acid-base hypothesis: diet and bone in the Framingham Osteoporosis Study. *Eur J Nutr.* 2001 Oct;40(5):231-7.
- 76 New SA, Robins SP, Campbell MK, et al. Dietary influences on bone mass and bone metabolism. *Am J Clin Nutr.* 2000 Jan;71(1):142-51.
- 77 Tucker KL, Hannan MT, Chen H, Cupples LA, Wilson PW, Kiel DP. Potassium, magnesium, and fruit and vegetable intakes are associated with greater bone mineral density in elderly men and women. *Am J Clin Nutr.* 1999 Apr;69(4):727-36.
- 77a Ranade VV, Somber JC. Bioavailability and pharmacokinetics of magnesium after administration of magnesium salts to humans. *Am J Therapeut.* 2001 Sep-Oct;8(5):345-57.
- 77b Lau K, Wolf C, Nussbaum P, et al. Differing effects of acid versus neutral phosphate therapy of hypercalcaemia. *Kidney Int.* 1979 Dec;16(6):736-42.
- 77c Heaney RP, Rafferty K. Carbonated beverages and urinary calcium excretion. *Am J Clin Nutr.* 2001 Sep;74(3):343-7.
- 77d Heaney RP, Nordin BE. Calcium effects on phosphorus absorption: implications for the prevention and co-therapy of osteoporosis. *J Am Coll Nutr.* 2002 Jun;21(3):239-44.
- 77e Heaney RP. Constructive interactions among nutrients and bone-active pharmacologic agents with principal emphasis on calcium, phosphorus, vitamin D and protein. *J Am Coll Nutr.* 2001 Oct;20(5 Suppl):403S-409S.
- 78 Promislow JH, Goodman-Gruen D, Slymen DJ, Barrett-Connor E. Protein consumption and bone mineral density in the elderly. *Am J Epidemiol.* 2002 Apr 1;155(7):636-44.
- 79 Tytlavsky FA, Anderson JJ. Dietary factors in bone health of elderly lactoovoiveterian and omnivorous women. *Am J Clin Nutr.* 1988 Sep;48(3 Suppl):842-9.
- 80 Hannan MT, Tucker KL, Dawson-Hughes B, Cupples LA, Felson DT, Kiel DP. Effect of dietary protein on bone loss in elderly men and women: the Framingham Osteoporosis Study. *J Bone Miner Res.* 2000 Dec;15(12):2504-12.
- 81 Munger RG, Cerhan JR, Chiu BC. Prospective study of dietary protein intake and risk of hip fracture in postmenopausal women. *Am J Clin Nutr.* 1999 Jan;69(1):147-52.
- 82 Sellmeyer DE, Stone KL, Sebastian A, Cummings SR. A high ratio of dietary animal to vegetable protein increases the rate of bone loss and the risk of fracture in postmenopausal women. Study of Osteoporotic Fractures Research Group. *Am J Clin Nutr.* 2001 Jan;73(1):118-22.
- 83 Heaney RP, Recker RR. Effects of nitrogen, phosphorus, and caffeine on calcium balance in women. *J Lab Clin Med.* 1982 Jan;99(1):46-55.
- 84 Heaney RP. Protein intake and bone health: the influence of belief systems on the conduct nutritional science. *Am J Clin Nutr.* 2001 Jan;73(1):5-6.
- 85 Sebastian A, Sellmeyer DE, Stone KL, Cummings SR. Dietary ratio of animal to vegetable protein and rate of bone loss and risk of fracture in postmenopausal women. *Am J Clin Nutr.* 2001 Sep;74(3):411-2.
- 86 Kerstetter JE, O'Brien KO, Insogna KL. Dietary protein affects intestinal calcium absorption. *Am J Clin Nutr.* 1998 Oct;68(4):859-65.
- 87 Kerstetter JE, Caseria DM, Mitnick ME, Ellison AF, Gay LF, Liskov TA, Carpenter TO, Insogna KL. Increased circulating concentrations of parathyroid hormone in healthy, young women consuming a protein-restricted diet. *Am J Clin Nutr.* 1997 Nov;66(5):1188-96.
- 88 Kerstetter JE, Svasitalee CM, Caseria DM, Mitnick ME, Insogna KL. A threshold for low-protein-diet-induced elevations in parathyroid hormone. *Am J Clin Nutr.* 2000 Jul;72(1):168-73.
- 89 Giannini S, Nobile M, Sartori L, Dalle Carbonare L, Ciuffreda M, Corro P, D'Angelo A, Calo L, Crepaldi G. Acute effects of moderate dietary protein restriction in patients with idiopathic hypercalcaemia and calcium nephrolithiasis. *Am J Clin Nutr.* 1999 Feb;69(2):267-71.
- 90 Delmas PD. Treatment of postmenopausal osteoporosis. *Lancet.* 2002 Jun 8;359(9322):2018-26.
- 91 Guthrie JR, Dennerstein L, Wark JD. Risk factors for osteoporosis: a review. *Medscape Womens Health.* 2000 Jul-Aug;5(4):E1.
- 92 Dorgan JF, Boer DJ, Albert PS, et al. Serum hormones and the alcohol-breast cancer association in postmenopausal women. *J Natl Cancer Inst.* 2001 May 2;93(9):710-5.
- 93 Singletary KW, Gapstur SM. Alcohol and breast cancer: review of epidemiologic and experimental evidence and potential mechanisms. *JAMA.* 2001 Nov 7;286(17):2143-51.
- 94 Remer T, Manz F. Potential renal acid load of foods and its influence on urine pH. *J Am Diet Assoc.* 1995 Jul;95(7):791-7.