

This Month in *Preventive Medicine*

Vitamin D as in different

Randomized studies have now essentially debunked the naïve vision of *all* vitamins as being good for health no matter what the dose. The first shock came from the demonstration that high doses of beta-carotene compared to placebo increased lung cancer risk among smokers in Finland (ATBC, 1994) and in the US (Hennekens et al., 1996; Omenn et al., 1996). Then came the evidence that vitamin E was ineffective for preventing cardiovascular diseases (Sesso et al., 2008) or cancer (Lin et al., 2009), and at high doses could even be life-threatening (Miller et al., 2005). Finally there are the continuing sobering negative results about the potential benefits of high doses of multivitamin, multimineral supplements, vitamin C, for all types of indications (e.g., Douglas et al., 2007; Lin et al., 2009; Mulholland and Bedford, 2007; Huang et al., 2006), even though there seem to be no major side effects in the case of vitamin C.

Vitamins A, C, and E are all anti-oxidants. They are believed to trap free radicals and thus protect cells from their damaging oxidative effects. We definitely need them, they are indispensable for our metabolism, but they should not and need not be used beyond the daily dietary recommended doses. Indeed, a too-neglected positive message came from the French large community trial SU.VI. MAX, in which a cocktail-pill of vitamins A, E, and C and of anti-oxidant minerals, not exceeding the dietary recommended doses, was found to have a protective effect against cancer in men, but not women (Herberg et al., 2004).

Vitamin D is different. First, it is not an anti-oxidant. The more we learn about vitamin D, the more healthful it seems to be. Most tissues and cells in the body have a vitamin D receptor involved in the regulation of cellular proliferation, differentiation, and death (Holick, 2007). Its effects on bone mass, osteoporosis, and fractures are well known and established, but vitamin D also has beneficial effects on many chronic illnesses, including autoimmune and infectious diseases (Holick, 2007). Dietary supplementation with vitamin D appears to reduce the risks of cancer (Lappe et al., 2007) and overall mortality (Autier and Gandini, 2007).

What about cardiovascular diseases, the most common cause of death in many regions of the world (WHO, 2008)? A deficit of vitamin D seems to be detrimental in this major health domain too. This issue of *Preventive Medicine* includes a study by Grandi et al. reporting the results of a systematic review and meta-analysis of cohort studies relating serum vitamin D (25-hydroxyvitamin D, abbreviated 25-OH-D) to cardiovascular disease incidence and mortality (Grandi et al., 2010). Compared to those in the highest category of vitamin D intake, defined either by quartiles or quintiles, those in the lowest categories of serum vitamin D had an increased meta-analytic risk of cardiovascular events of 1.5 for incidence and of 1.8 for death.

Vitamin D is different from vitamins A and E in another way which can be decisively important when designing community interventions. It has been used at very high doses for many months without toxic effects. This makes sense if you will permit us a small speculative digression. Vitamins are molecules that are so common in our environment that there was no evolutionary pressure for humans to self-synthesize them. There is a limited natural supply of vitamins A and E, so there was no selection advantage of consuming doses superior to those that we can reasonably find in our food. But we get vitamin D from exposure to sunlight, which our ancestors had in huge amounts. We are therefore likely to be configured to stand high daily doses of vitamin D over long periods.

Dependence on sunlight also makes vitamin D intake different from that of other vitamins, because protecting ourselves from UV exposure has resulted in widespread vitamin D deficiency in many regions of the world (Holick, 2007).

Doesn't vitamin D appear as the perfect candidate for community supplementation trials? Its deficit is prevalent. It seems associated with increased risk for common chronic diseases. To our knowledge, there is a good dose margin before it can become toxic, at least among people free of kidney diseases. Too good to be true? We would welcome in *Preventive Medicine* data or ideas that would take us further in this direction.

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