

# Reply to W.B. Grant 'Re: Vitamin D deficiency among northern Native Peoples'

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Dear Editor:

Dr. Grant seems to assume that all humans share the same vitamin D metabolism, an assumption that is doubtful even on theoretical grounds (1). We know that natural selection can alter the way the human body synthesises, transports and uses this vitamin. We also know that the relevant selection pressures (from solar UV and skin color) vary from one human population to the next. So it is not necessarily unhealthy for a population to have low blood levels of vitamin D. The underlying metabolism may simply be different.

Vitamin D levels are normally low not only in northern Natives but also in other darker-skinned humans, even those who still live in the tropics and are routinely exposed to strong solar UV (2). Indeed, if we look at the human species as a whole, the outlier actually appears to be lighter-skinned humans and their relatively high levels. This outlier, however, also tends to decide what is medically normal and what is not. Therein lies part of the problem.

Why do these differences in metabolism exist? At present, we can only speculate. Lighter-skinned humans can more easily synthesise vitamin D on their own and may thus use it less efficiently. Conversely, darker-skinned humans may have had to ration its use and develop alternate metabolic pathways.

This has been especially true at high northern latitudes, where solar UV is too weak for synthesis in the skin. An alternative is to consume fatty ocean fish, but this food source was formerly available only in coastal regions. The interior of Alaska and northern Canada had few natural sources of vitamin D.

Over time, northern Natives should have adapted to this situation through natural selection. And they had time: some 15,000 years in Arctic North America and longer still if we include their remote ancestors in Beringia and northern Eurasia. Natural selection also had many possible ways to make their bodies less dependent on vitamin D: receptors that bind this molecule more

strongly; greater storage in the body and better transport in the bloodstream to target tissues; increased uptake of calcium and phosphorus through alternate metabolic pathways, etc. Indeed, the Inuit show high uptake of calcium despite low levels of vitamin D (3).

Such adaptation is also indicated by data from earlier periods. Precontact skeletons show little evidence of vitamin D deficiency, i.e., rickets (4). In 1942, a medical survey found no cases of rickets among northern Manitoba Indians, even though they lived above 55°N and consumed no foods of marine origin (5).

Yet, today, rickets is becoming common among northern Natives. Like Grant, I blame the change in diet. I disagree, however, with his view that the key dietary change was abandonment of ocean fish, since non-coastal Natives did not consume seafood. One key change seems to have been the shift away from a high meat diet, which reduces the risk of rickets independently of vitamin D intake. Another was increased consumption of certain reactive substances: phytic acids in commercially processed cereals; sodium bicarbonate in baking soda; and aluminum hydroxide in antacids. These substances react in the body with calcium or phosphorus to form insoluble salts, thereby creating an artificial deficiency of both elements (2).

This deficiency can be treated with vitamin D supplements. Northern Natives may even show a stronger response to such treatment because they less easily produce this vitamin on their own. But supplementation would also expose them to levels of this molecule that their body tissues have not experienced in 15,000 years or more. We can imagine the eventual outcome by plotting the incidence of various age-related diseases as a function of the body's vitamin D level. The result is generally a U-shaped curve (2). If northern Natives are healthiest within a "trough" that normally lies farther to the left, what will happen if they are pushed out of this trough and into a range of values that is normal for Europeans but not for them?

Grant denies the validity of this U-shaped curve for any human population, saying that it is probably an artifact of long follow-up time, i.e., the interval between measurement of vitamin D levels in human subjects and the much later assessment of their disease outcomes. Since these levels can change over time, the measured level may differ from the one that actually prevails when a disease first appears. It would be better to take measurements several times before the follow-up, perhaps every 2 years and in different seasons (6).

Grant has pointed to a real methodological problem, but it is one that actually strengthens my argument. The harder it is to measure a causal factor, the more the resulting data will be muddled by “noise” and the harder it will be to link this factor to its presumed effects, whether harmful or beneficial. The dose-response curve should thus become flatter, not U-shaped.

Indeed, it is surprising just how strong these effects are despite the noise in the data. The most recent follow-up study shows a clear U-shaped relationship between vitamin D levels and mortality in elderly Swedish men. The total mortality rate was 50% higher among those in the lowest 10% (<46 nmol/L) and highest 5% (>98 nmol/L) than among those in-between (7). These findings are especially noteworthy in light of a recent recommendation to set the minimum levels for human health at 100–150 nmol/L (8).

Harmful effects likewise appear in animal studies. Persistently high levels of vitamin D cause mice to age prematurely, as evidenced by osteoporosis, atherosclerosis, calcification, skin and organ atrophy and shorter lifespan (9–12). This experiment has also been performed on humans, albeit unwittingly: “After the Second World War in Europe, especially in Germany, children received extremely high oral doses of vitamin D<sub>3</sub> and suffered hypercalcemia, nephrocalcinosis, early aging, cardiovascular complications and early death, supporting the possibility that hypervitaminosis D<sub>3</sub> can accelerate aging” (11).

Such effects are consistent with the view that vitamin D is not so much a vitamin as a hormone that regulates growth via different signalling pathways. Its effects are beneficial as long as its levels remain within a relatively narrow range. Outside this range, normal growth processes will be disrupted or even accelerated (11).

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