

Jeffrey Bland Video Blog Transcript
6/2/2008

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You know, there has been a lot of discussion, hasn't there, about vitamin D recently? And always when we have this discussion about something that looks positive, then we are going to have the pendulum swing back and we'll have something to say negative. We recently had a paper published out of a very responsible investigator in Australia who has suggested that excessive vitamin D might have an adverse effect through its hormonal influence on 1,25-dihydroxyvitamin D3 (or 1,25-dihydroxycholecalciferol) on aspects of cellular signaling.

I want to put that in context, if I can, because I know there is some concern about excessive vitamin D supplementation. We should be somewhat concerned because vitamin D can produce hypercalcemia, it can lead to hypercalcemia that induces cardiovascular injury, and you can probably recall when we had this very sad experience a number of years ago when milk was inadvertently fortified at a much higher level than it should have been by mistake with vitamin D2. Children who consumed that milk ended up with hypercalcemia of infancy and there were a couple of deaths of these infants due to calcification of the aorta. So this is certainly a very serious problem when in excess, but I want to emphasize that the level that was in the milk was some hundred times higher than that which would normally have been in there, so we are really talking about a mistake. But everything, again, has a dose and a response curve. Everything is toxic at some level, including air and water. What about vitamin D?

I went back to the literature and I took a quick look at what's known. As you probably know, Dr. Michael Holick and Dr. Vieth (from Canada) are two of the world's renowned investigators in this area. Dr. Vieth authored an article in 1990 in the *Journal of Bone Mineral Metabolism* on vitamin D toxicity in which he (at that point—in 1990) said that its toxicity was not to be of concern below 20,000 IUs a day. More recently, in 2007, he authored another paper that appeared in the *Journal of Bone Mineral Metabolism* reviewing the more contemporary data on vitamin D toxicity, again saying (a little more conservative view) that 10,000 units a day would not pose a risk to adults.

However, again, I think, as always the safe case, we ought to be measuring serum calcium levels and 25-hydroxy D3 levels in our patients when we supplement at high dose vitamin D.

Now, why are we so concerned about vitamin D? Because, as you know, it is a pro-hormone. It is not just a substance a lot like a vitamin that is excreted rapidly. It is converted into this hormonal form (1,25-dihydroxy D3) that is a member of the nuclear orphan receptor family of ligands that induces gene expression. So it affects all cells, really, through this influence it has on cellular signaling and induction through G protein signaling. If you start talking about individuals who are undergoing inflammatory processes where they have activation of certain kinases involved with inflammation, like mitogen-activated kinases that can actually lower the activity of vitamin D. It can interrupt the conversion to the hormonal form of vitamin D. So inflammation can have an antagonistic effect on vitamin D. You may not get the same results with vitamin D supplementation in a person that has inflammation as you would in a person without inflammation. So there is kind of the interrelationship between kinases and the inflammation signaling pathway (MAP kinase) and the kinases that are regulated in the nuclear orphan receptor family that is related to vitamin D's hormonal form. But as it relates to vitamin D excess and toxicity, I think that the one report that I saw recently from the *Annals of Internal Medicine*, which was published in 1998, was a case report of 12 individuals who had clinical evidence of vitamin D intoxication, and in this case their 25-hydroxyvitamin D levels were all in excess of 100+ nanomols per d/L. So if you get into ranges of hundreds of nanomols of 25-hydroxyvitamin D, that is obviously getting into the range of toxicity.

You might say, what is a safe range to shoot for? Dr. Vieth has looked at lifeguards who are exposed to a lot of sun exposure and they are probably maximally producing vitamin D in their skin; they have serum levels that are about 80 nanograms per m/L. So when you start asking about what would be maybe the upper tolerable limits in a normal individual (if you assume the body is not going to produce a toxic amount on its own), you say about 80—generally somewhere between 50 and 80 is a good range to shoot for. Again, serum calcium should be a normal range, and I think that those safeguards would protect against vitamin D intoxication. Recall, if you would, that there

is evidence even from the Australian/New Zealand Medical Association in a recent paper that they published. It is a position paper on vitamin D that one cannot assume that even with a sunny climate that people are adequately nourished with vitamin D. They go on to say that supplementation somewhere up to 2000 units may be required on a daily basis for normalization of the serum 25-hydroxy levels. So there is very good press in the medical literature. This particular report appeared in 2008, so we are starting to see more and more evidence that the problem is more insufficiency than excess. But again, like all things, I think we should be concerned about taking things to extremes. Everything is toxic at some level. Make sure you measure serum calcium and 25-hydroxy D, and if it is in the safe range, then the patient is being fortified correctly.

I hope that is helpful and gives you some sense of the literature.