

Bob Barrett:

This is the podcast from *Clinical Chemistry*. I am Bob Barrett.

Until recently, there has been little concern within medical and pediatric communities regarding the vitamin D status of their patients. It was just assumed that everyone was vitamin D sufficient and that only people with fat malabsorption syndromes were at risk.

However, over the past few years, several retrospective studies that evaluated the long-term impact of ingesting vitamin D either during the first year of life or through adult life, revealed associations between a higher intake of vitamin D and decreased risks for a wide range of health problems, such as autoimmune diseases, hypertension, cancer, heart-diseases, and stroke as well as upper respiratory tract infections, wheezing disorders, asthma, and falling. The May issue of *Clinical Chemistry* reported that the 25-hydroxyvitamin D assay is now one of the most ordered assays in the United States.

Michael F. Holick, the author of the article, suggested that it could be more cost effective to implement a vitamin D supplementation program for all children and adults until there is higher fortification of vitamin D and more foods in addition to promoting sensible sun exposure.

Michael F. Holick is Professor of Medicine, Physiology, and Biophysics, and Director of the Bone Healthcare Clinic at Boston University Medical Center, and he is our guest in this podcast.

Dr. Holick, what are the health consequences of vitamin D deficiency in children and adults?

Michael F. Holick:

I will give you some perspective. We showed at our hospital, in pregnant women taking 600 units of vitamin D a day from supplement and from dairy sources, 86% of instance, at the time they gave birth, were vitamin D deficient, and 76% of the moms were vitamin D deficient. We went on to show that during pregnancy, vitamin D deficiency increases the risk of preeclampsia, working with Dr. Bodnar at the University of Pittsburgh.

We also showed that you have 400% higher risk of requiring a C-section when you are giving birth if you are vitamin D deficient. With children, there is a study done in Finland where they showed that children getting 2,000 units of vitamin D a day

during their first year of life reduce their risk of getting type 1 diabetes by 88%.

We know that if you are vitamin D deficient during the first ten years of life, you will have 100% increase risk of developing multiple sclerosis for the rest of your life. For adults, we know that vitamin D deficiency will not only participate and exacerbate osteoporosis, but causes a painful bone disease, osteomalacia, which is associated often with aches and pains in bones and muscles that is misdiagnosed as fibromyalgia.

But we also know in adults that vitamin D deficiency increases risk of deadly cancers of colon, prostate, breast by as much as 50%, increases risk of having a heart attack by more than 50%, increases risk of type 2 diabetes by 33%, and increases risk of infectious diseases as well.

Bob Barrett:

Many physicians are confused about which vitamin assay to order on their patients to determine their vitamin D status. Why should you only measure 25-hydroxyvitamin D and not its active form, 125-dihydroxyvitamin D? In addition, what blood level of 25-hydroxyvitamin D should physicians aim for to maximize vitamin D's health benefits for the patients?

Michael F. Holick:

Bob, these are excellent questions, and I know that it is very confusing for some physicians and healthcare professionals. It turns out that 25-hydroxyvitamin D is the major circulating form of vitamin D and it circulates at 1,000 times higher concentration than its active form, which is made in the kidneys called 125-dihydroxyvitamin D.

We also know that as you are becoming vitamin D deficient and your target tissue levels of the active form of vitamin D are declining. As a result parathyroid hormone increases and it tells the kidneys to make more 125-dihydroxyvitamin D. Therefore, in patients who are vitamin D deficient and insufficient, where 25-hydroxyvitamin D is low, 125-dihydroxyvitamin D is either normal, or even elevated.

So, if the doctor was to get 125-dihydroxyvitamin D level and find it to be normal, they would be misled in thinking that the patient was vitamin D sufficient when the patient is likely to be deficient or insufficient. The blood level of 25-hydroxyvitamin D that we are now all shooting for is 30 ng/ml and up

to 100 ng/ml is perfectly safe. I like all of my patients to be between 40 and 60 ng/ml only because it just gives me a little bit of latitude. You just keep people at around 30. Sometimes that could come in at 25 or 28; in other times, it come in at 32.

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So above 30 is where you want to shoot for, but 40-60 is the preferred range of 25-hydroxyvitamin D. For maximizing, these health benefits, adults that are taking 2,000 to 3,000 units of vitamin D a day and children if they take 400 up to 1000 units of vitamin D a day, usually can achieve these levels.

Bob Barrett:

So, is there a clinical use for the 125-dihydroxyvitamin D assay?

Michael F. Holick:

That's an excellent question, Bob. It turns out that there is. So patients that have hypercalcemia due to a granulomatous disorder like sarcoidosis or histoplasmosis or tuberculosis, their hypercalcemia is due to the overproduction of 125-dihydroxyvitamin D by macrophages that are part of the sarcoid granuloma. So it's very helpful in the differential diagnosis of hypercalcemia to rule in the cause being a chronic granulomatous disorder rather than being a cause for a malignancy such as a lung cancer, squamous cell carcinoma of the lung, for example. But there is one cancer that actually does make 125-dihydroxyvitamin D, and this is some lymphomas associated with hypercalcemia is in fact associated with high levels of 125-dihydroxyvitamin D.

There are also acquired and inherited disorders that the 125-dihydroxyvitamin D assay can be used for, and good examples would be in patients with chronic kidney disease, as the kidneys are the major source for the active form of vitamin D, but also in oncogenic osteomalacia. It's caused by a tumor that makes fibroblast growth factor 23, and what's pathognomonic for this disease is not only very low blood phosphorus level, but an inappropriately low or normal blood level of 125-dihydroxyvitamin D.

Bob Barrett:

Well, because vitamin D deficiency is so common in children and adults, should everyone be screened for their vitamin D status or the 25-hydroxyvitamin D assay?

Michael F. Holick:

Bob, it's an excellent question, and indeed, at this time, the most ordered assay by physicians is the 25-hydroxyvitamin D assay. In fact, patients now

know their blood level of 25-hydroxyvitamin D as well as they know their blood cholesterol level. So does that mean that everybody should be screened? In my opinion, I don't think that that's necessary. Certainly, it's traumatic for young child to get their blood drawn to be able to measure the 25-hydroxyvitamin D level, and we know from a lot of studies that if children are taking at least 400 units of vitamin D a day, and 1000 units, in my opinion, is preferred, along with some sensible sun exposure and getting some vitamin D from dietary sources like milk, for example, some orange juice that's fortified with vitamin D, that in total should satisfy their body's vitamin D requirement.

For adults, I recommend that they should be taking at least 1,500 to 2,000 units supplement a day, along with getting vitamin D from dietary sources and some sensible sun exposure. If they do that, they should be fine.

However, if you are obese, we know that obesity is associated with vitamin D deficiency and the reason is that the body fat sequesters the vitamin D. So it's difficult often to know whether you are correcting vitamin D deficiency on an obese patient. So getting a blood level as you are evaluating them and then two to three months later, after treating them, is very appropriate.

Patients on glucocorticoids, anti-seizure medications, even AIDS medications, these drugs destroy 25-hydroxyvitamin D and these patients should be screened for vitamin D deficiency, should be treated for the vitamin D deficiency, and they should have a follow-up blood level of 25-hydroxyvitamin D to make certain that their vitamin D status has been corrected, and it is now in the normal range.

It's also important to be sure, that people of color are at extremely high risk for vitamin D deficiency. So, if they are not able to take a vitamin D supplement easily or not taking dietary sources of vitamin D, it's worthwhile to get a blood level and to make it clear to the patient that they are deficient and that they need to be treated for the vitamin D deficiency and insufficiency and then to follow-up by measuring it as well.

We know that by increasing your vitamin D intake and maintaining a 25-hydroxyvitamin D level of 30 ng/ml improves muscle strength, reduces risk of falling, improves bone mineral density, reduces risk

of developing osteoporosis and fracture, as well as reduce risk of many serious chronic diseases.

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Such as malignant, deadly cancers of colon, prostate, breast, reducing risk of hypertension, heart disease, type 2, diabetes and studies have now demonstrated that if you increase your vitamin D intake, reduce risk of upper respiratory tract infections, and even influenza A infection.

Bob Barrett:

There are several different assays for 25-hydroxyvitamin D, some laboratories report total 25-hydroxyvitamin D, other reference laboratories report not only the total 25-hydroxyvitamin D, but also 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3.

Now, in your opinion, is one assay better than the other and is there any value to having blood levels of 25-hydroxyvitamin D2 and 3?

Michael F. Holick:

Yeah, I know that it can be confusing and in fact, I get a lot of emails from physicians who when they are getting reports back that the 25-hydroxyvitamin D2 is normal, but the 25-hydroxyvitamin D3 is low, does that mean that the D2 is not being converted to D3 or vice versa. It turns out that vitamin D2 which is typically found in yeast and is found in some supplements and in fortified foods is coming from yeast and also mushrooms contain vitamin D2 and that's the major source of vitamin D2 for people that gets converted to 25-hydroxyvitamin D2.

When you are exposed to sunlight, you are making vitamin D3 and most supplements, and a lot of fortified foods contain vitamin D3. The bottom line, however, is, all you care about is your total blood level of 25-hydroxyvitamin D. So for those laboratories that send out to Quest Diagnostics or to the Mayo Clinic or to LabCorp who are doing liquid chromatography-tandem mass spectrometry assay, it specifically gives you blood levels of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3.

What you care about is the total 25-hydroxyvitamin D, and you want it to be above 30 ng/ml. Other laboratories do the assay by a radioimmunoassay where they can't distinguish 25-hydroxyvitamin D2 from 25-hydroxyvitamin D3 and therefore, they report out in their laboratory report as the total 25-hydroxyvitamin D.

So what you want to do is to look at the lab report and what you care about most is that the total 25-hydroxyvitamin D is at least 30 ng/ml and up to 100 ng/ml is perfectly safe.

Bob Barrett:

That's staggering to learn that more than half of the children and adults in the US are vitamin D deficient or insufficient. What are the major reasons for this epidemic of vitamin D deficiency?

Michael F. Holick:

There are three major causes for the increase in the prevalence of vitamin D deficiency and insufficiency in the United States. The first is, over the past 30 years, we have been taught you should never be exposed to direct sunlight without sun protection. If you put a sunscreen on with a sun protection factor of 30 properly, it reduces your ability to make vitamin D in your skin by 95 to 99%. As a result, by not getting adequate sun exposure, it has really put both children and adults at very high risk of vitamin D deficiency because it has always been the major source of vitamin D for humans throughout evolution.

Foods such as dairy products, some orange juices, breads and some cereals are fortified with vitamin D, but often children are no longer drinking milk or drinking juices that are fortified with calcium and vitamin D, and as a result, is increasing the risk for vitamin D deficiency as is avoidance of any direct sun exposure. And then the final cause is obesity because as I had mentioned before, obese people are very prone to vitamin D deficiency and even if you give them vitamin D, they need 2 to 3 times more vitamin D to satisfy their body's requirement because the fat basically holds onto the vitamin D and doesn't release it back out to the body.

So a study was done from the NHANES III dataset showing that from 1994 to 2004, the population in United States, children and adult, are becoming more vitamin D deficient on average about 20% higher prevalence now of vitamin D deficiency and insufficiency, and the three causes are decrease in milk consumption, increase in sun protection, and obesity.

Bob Barrett:

Now, it's my understanding that there will be new recommendation from the Institute of Medicine this summer. Do you have any insight as to what they may be and do you have any recommendations based on your own clinical experience?

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Michael F. Holick:

My hope is that they will come out with recommendations that are substantially higher than what is now recommended. Physicians may not be aware that when I was on that committee back in 1997 and we came out with those recommendations, the recommendations for all children and adults up to the age of 50, the adequate intake recommendation was 200 units; for adults 50-70, 400 units, and for adults 70 and above, 600 units. This was based on the published literature before 1997. At that time we essentially had very little literature to go on, and that's why they were so low.

But now with all of the new information that's out there, we now recognize that everybody needs a lot more vitamin D that we are probably off by a factor of at least five- if not tenfold for the total amount of vitamin D that both children and adults need to satisfy the requirement.

The hope is that they will substantially increase that recommendation and I suspect that they probably at least come in at 800 to 1,000 units for children and adults alike and hopefully, even more. But what we should care about the most is to raise what is considered to be the upper limit. That is the safe upper amount that you could take without worrying about any toxicity. At the moment, the recommendation for children up to 1 year of age is 1,000 units and for children and adults after the age of 1 is 2,000 units.

We know from our studies and other studies that 2,000 units of vitamin D for adults is what they need to satisfy their body's requirement. So if we can raise the upper limit to about 10,000 units of vitamin D a day for adults, 5,000 units for children until their teen years, and at least 2,000 units for infants and children up to 1 year of age, that would have a substantial impact on giving food manufacturers and vitamin D supplement manufacturers the latitude to increase the amount of vitamin D in their products and to increase the number of foods and the amount of vitamin D preserving. That will have the most benefit in improving the vitamin D status for children and adults in the United States.

What my recommendation is, at a minimum, children should be taking 400 units of vitamin D a day from the time they are born at least until they're teenagers, that's what's recommended by the

American Academy of Pediatrics but I think that children should be taking 1,000 units of vitamin D a day and the safe upper level for children is 5,000 units a day. For teenagers and adults, they should be taking at least 2,000 units of vitamin D a day from diet and supplements and that up to 10,000 units a day is perfectly safe.

Bob Barrett:

Michael F. Holick is Professor of Medicine, Physiology, and Biophysics and the Director of the Bone Health Care Clinic at Boston University Medical Center. He has been our guest in this podcast from *Clinical Chemistry*. I am Bob Barrett. Thanks for listening.

Total Duration: 18 Minutes.