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Vitamin D: The More We Know, the Less We Know

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Guests:
Dr. Ravi Thadhani is Professor of Medicine at the Harvard Medical School and Chief, Division of Nephrology at the Massachusetts General Hospital. Dr. Mitchell Scott is Professor in the Department of Pathology and Immunology at Washington University School of Medicine in St. Louis.

Bob Barrett: This is a podcast from *Clinical Chemistry,* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

Over the past 20 years or so there have been several studies published showing an association between decreased concentrations of vitamin D in blood and the risks of cardiovascular disease, stroke, cancer, fractures, even overall mortality.

However, particularly recently other studies have failed to show that low vitamin D concentrations are associated with risk for any non-skeletal chronic conditions. In addition, there are suggestions that perhaps we should be measuring bioavailable vitamin D rather than total vitamin D.

The March 2015 issue of *Clinical Chemistry* published a question and answer article entitled "Vitamin D: The More We Know, the Less We Know." That article presented the opinions of four experts representing their views on the subject of Vitamin D and its measurement.

Today, we have with us the lead moderator of the session, Dr. Mitchell Scott, who is Professor in the Department of Pathology and Immunology at Washington University School of Medicine in St. Louis.

We also have one of the panelists, Dr. Ravi Thadhani, Professor of Medicine at the Harvard Medical School and Chief of the Division of Nephrology at the Massachusetts General Hospital. Dr. Thadhani was lead author of the 2013 study on the discovery of genetic polymorphisms in vitamin D binding proteins that may explain differences in vitamin D concentrations between blacks and whites.

Now Dr. Scott, let's start with you. Simply, why is vitamin D important?

Dr. Mitchell Scott: Well, vitamin D in the simplest term is a hormone that allows bones to stay healthy. Without vitamin D your bones

become extremely unhealthy and severe deficiency leads to rickets in children and osteomalacia in adults, and these are the typical bowed and bent postures that you see with rickets, the bones are deformed, they are softened, you can get bending of the spine, bowing of the legs, and much, much increased risk of fractures.

The hormone vitamin D increases calcium absorption in the gut, so that you need calcium to build bones and vitamin D as a hormone also increases bone resorption to maintain calcium for good bone formation.

So again, in the simplest terms, vitamin D is necessary for good bone health.

Bob Barrett: And why has vitamin D gained such interest recently?

Dr. Mitchell Scott: Well, it really goes back more 10, 20 years, there have been numerous studies over the last 20 years showing an association and I have to emphasize the word 'association,' not causation, of low vitamin D with a host of adverse outcomes. These include infectious diseases, critical care unit admissions, all-cause mortality, cardiovascular disease, hypertension, increases in BMI, insulin resistance, you name it. There is hardly any adverse outcome that hasn't been associated with low vitamin D.

And at the same time the National Health and Nutrition Survey (NHANES) between 1994 and 2004 showed a decrease in blood levels of vitamin D in the general population. For instance, in 1994, 50% of the population had vitamin D levels in their blood greater than 30 nanograms per mil, while in 2004 only 30% of the population did.

The reason for that is not exactly clear; some postulate that the increased use of sunscreens has decreased sun exposure, and I forgot to mention in the first question that most of our vitamin D actually comes from the skin, where the precursor molecule to vitamin D3 is converted to 25-hydroxy D3 by sunlight.

So, decreased sun exposure will lead to a decrease in blood levels of vitamin D. And at the same time from 1994 to 2004, there has been an increase in obesity in the population, and vitamin D can get mobilized in fat tissue where it's not really available for circulation or for its use in good bone health.

So if you think about it, if you are poorly nourished or you are not getting sufficient vitamin D due to change in diet, or if you are overweight, you are more likely to be in poor

health. So that was one reason that people said vitamin D is just associated with all these adverse outcomes.

But regardless, about 10 years ago many organizations, professional societies, institutions, changed the definition of vitamin D deficiency to 30 nanograms per mil from 20 nanograms per mil, and this all occurred around 2003-2004.

Well, when we went from 20 being deficient, to 30 being deficient, over 50% of our population is deficient by this new criteria, not so new anymore. But the combination of all these association studies, and the new reference target, led to in a dramatic increase in the number of vitamin D assays performed in clinical labs all across the country. For instance, our volume for vitamin D assays went from about 300 a month in 2004 to 3,000 a month in 2010, ten-fold increase in the number of vitamin D assays, really resulting from these association studies, and the changes in the definition of deficiency.

More recently there have been meta-analyses that failed to show an association of low vitamin D with anything other than bone conditions, and in 2010 the Institute of Medicine issued a report that vitamin D supplementation was unlikely to be beneficial for anything other than bone health, which is what vitamin D has been known to be important for all along.

And the Institute of Medicine recommended in 2010 the definition of deficiency return to 20 nanograms per mil and that supplementation amounts be decreased.

The Endocrine Society at the same time took a slightly different slant; they agreed with 20 being the definition of deficient sort of had a gray zone of 20 to 30 nanograms per mil being “insufficient” but stuck with 30 nanograms per mil as being sufficient. And that's pretty much where we stand today, but this year one of our experts in the question-and-answer piece, Dr. Ian Reid from New Zealand, published in the January 11, 2014 issue of *Lancet* a meta-analysis showing that vitamin D supplementation in the general population without any risk factors for vitamin D deficiency didn’t even improve bone density.

In other words, if you're above 20 nanograms per mil and you don't have other risk factors for bone disease, you are going to be fine according to Dr. Reid. Now you add to all this the methodological issues, in that vitamin D assays are not all the same, they differ in the recognition of vitamin D2 and D3, and D2 is a plant version of vitamin D that’s used for supplementation. CAP proficiency testing data with accuracy based standards as shown up to 20% of vitamin D methods fail to accurately determine vitamin D, and in some

samples up to 40% fail to identify or quantify the correct amount of vitamin D.

So this just adds to the complications of how you define vitamin D deficiency, it can be method-dependent, it's controversial in terms of whether or not vitamin D is causative other than bone disease problems, and even more recently, Dr. Thadhani, who is part of our Q&A piece, determined that there are genetic differences in vitamin D protein and that what we really should be measuring is bioavailable vitamin D. And I believe that you'll be speaking with Dr. Thadhani next, and I will let him expand as the expert on that issue.

Bob Barrett: Thanks so much Dr. Scott! We do turn now to Dr. Ravi Thadhani.

Dr. Thadhani, let me start by asking you about your 2013 *New England Journal of Medicine* article that led to so much of the excitement in this area.

Dr. Ravi Thadhani: Sure, and thank you of course for the interest. The article was focused on asking the question, why is it that African-Americans continue to be diagnosed with vitamin D deficiency in the United States? Yet we know vitamin D is strongly linked to bone health and vitamin D historically in many studies has been linked to risk of fractures, and because of that you would expect African-Americans then because they are very frequently, if not almost universally, diagnosed with low vitamin D levels they have the best bone health, compared to white, they have better bone health compared to whites.

So we have this paradox where whites in the United States have higher vitamin D levels and blacks have lower vitamin D levels, yet blacks have higher bone mineral density than whites, they have the lowest rates of fractures compared to whites, they have the lowest rates of osteoporosis compared to whites, but yet we continue to define them as vitamin D deficient and it's that paradox that this paper was trying to address.

Bob Barrett: Given these data, do you think we should be measuring bioavailable 25 hydroxy vitamin D as opposed to total?

Dr. Ravi Thadhani: Right now we don't have good validated assays for bioavailable vitamin D, but we do have our reasonable assays for total vitamin D. And as a result of this paper and perhaps accumulating evidence from other sources, what it should do is force us to think about how do we diagnose vitamin D deficiency. If we see somebody with low-levels, perhaps in African-American population, do we consistently define them as being deficient or do we look at the risk

factors for deficiency, the risk for bone fractures, and other manifestations of vitamin D deficiency and then consider treatment.

So the specific answer to your question is, we do not have good validated assays for bioavailable vitamin D, and until we do we certainly can't consider measuring it.

Bob Barrett: Well should the findings about vitamin D binding protein polymorphisms affect how we interpret the association of 25 hydroxy vitamin D concentrations with cancer, diabetes, and cardiovascular disease mortality. I guess in other words, should those studies be repeated?

Dr. Ravi Thadhani: So what we do know is that the genetics of vitamin D binding protein is strongly linked to vitamin D levels, certain genetics associated with higher levels, certain genetics with lower levels.

What we're also learning, because of that relationship, is that there is something different about vitamin D binding protein, for example in patients who are Caucasian versus patients who are African-American, is it the characteristics of that protein, the way that protein binds, 25-hydroxy vitamin D, how long that protein lasts in the bloodstream, all those questions have yet to be determined.

But we do know from genetic studies there was a strong link with those levels. Should those studies be repeated? Specifically to your question we have to wait for validated assays that incorporate vitamin D binding protein levels or bypass those levels and directly measure bioavailable vitamin D to then determine its relationship to various outcomes, cancer, heart disease, and so forth.

The fact that there have been many studies that demonstrate when we replaced vitamin D we don't necessarily change blood pressure, we don't necessarily change the risk of heart disease and other outcomes, should force us to pause as to whether or not we're measuring the right type of vitamin D.

Now that said, there have been other studies of course that suggest there may be a benefit and certainly larger studies are being done to answer those questions.

Bob Barrett: How do you think vitamin D deficiencies should be defined?

Dr. Ravi Thadhani: Vitamin D deficiency should be defined in the context of not just a simple level and a simple cut point, but in the context of risk for bone disease; in the context of low calcium levels which is what vitamin D does, it raises calcium levels; in the

context of normal levels or abnormal levels of parathyroid hormone, in which it plays an intimate biology.

The context of defining the deficiency should again not just be based on a simple cut point, and in fact the cut points may need to be different based on race. Again, we are learning more about that.

So the diagnosis in my mind should pause and we should realize that sort of high-low levels based on a certain race, certain population, is maybe one step of several steps in terms of defining a deficiency, it should be taken into the context of the whole clinical scenario.

Bob Barrett: What about the limitations to measuring bioavailable vitamin D?

Dr. Ravi Thadhani: We don't have a good assay for measuring bioavailable vitamin D. If we take the example of a similar concept for other hormones, testosterone, thyroid hormone, the development of those assays to become more precise to those bioavailable fractions took us 10, 15, 20 years to understand, develop, and validate. So we think we're in that direction, we think it will take some time, we think ultimately that should be what we measure, but we are certainly years away from developing the right assay.

Bob Barrett: A couple of years ago, vitamin D became the new wonder drug. It was the rock-star supplement. Has that died down a bit now?

Dr. Ravi Thadhani: You can't open up a newspaper, magazine, throw-away journal every few months without seeing something related to vitamin D. The fact that we have not had a remarkable success story to celebrate in vitamin D has to some extent tempered the enthusiasm going back to your analogy of rock-star status. There have been, and are, ongoing large randomized trials, and by 2017 or so we'll have some answers to some of the major questions, vitamin D and heart disease, vitamin D and cancer, and so forth.

I think then we'll have certainly a reconciliation of how people view this. In the meantime, I think it's reasonable to think about vitamin D deficiency and its potential benefits of replacing, but again in the context of the whole clinical scenario.

Bob Barrett: That was Dr. Ravi Thadhani, Professor of Medicine at the Harvard Medical School and Chief, Division of Nephrology at the Massachusetts General Hospital. He was joined by Dr. Mitchell Scott who is Professor in the Department of Pathology and Immunology at Washington University School of Medicine in St. Louis. They have been our guests in this

podcast from *Clinical Chemistry* on vitamin D and vitamin D testing.

I am Bob Barrett. Thanks for listening!