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Low Plasma 25-Hydroxyvitamin D and Risk of Tobacco-Related Cancer

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Guest:
Dr. Børge Nordestgaard is Chief Physician in Clinical Biochemistry at Copenhagen University Hospital and a Clinical Professor at the University of Copenhagen in Denmark.

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

For decades, vitamin D deficiency was thought a thing of the distant past, but recent evidence has associated low vitamin D levels with a number of diseases and conditions. Tobacco smoke chemicals may influence vitamin D metabolism and function, and vitamin D itself may modify the carcinogenicity of tobacco smoke.

In the May 2013 issue of *Clinical Chemistry,* a study from the University of Copenhagen in Denmark examined this relationship. Dr. Børge Nordestgaard is the Chief Physician in Clinical Biochemistry at Copenhagen University Hospital and a Clinical Professor at the University of Copenhagen in Denmark. He is the author of that study and is our guest in this podcast.

Doctor, we hear a lot about vitamin D, but what exactly is it, and why do some people have low vitamin D concentrations in their blood?

Dr. Børge Nordestgaard: Vitamin D is a fat-soluble vitamin, it increases the calcium absorption in the intestine and lack of vitamin D for example that leads to compensatory secondary hyperthyroidism and then to increase bone reabsorption. So it's the real classical vitamin D deficiency is what's called rachitis and osteomalacia.

Why do some people have low vitamin D levels? Well, the most important source of vitamin D is sunshine, when the sun shines on your skin, then you by yourself produce vitamin D, so therefore, it's not really vitamin but we call it anyway, and then you also have vitamin D in the food and then some people take supplements.

Bob Barrett: Well, many people are concerned about low vitamin D concentrations, now. What are the novel findings of your study related to that topic?

Dr. Børge Nordestgaard: In our particular study in *Clinical Chemistry,* we found that for people with low vitamin D there was two-fold risk of tobacco related cancer, which is novel, and this was for either people with levels less than 5, versus more than or equal to 20 nanograms per million, or we also looked at it whether they had lower than the 5th percentile versus higher than the 66th percentile.

And then we were able to find that for different individual tobacco related cancers. These finding were significant for lung cancer by itself, for head and neck cancer, for bladder cancer and for kidney cancer.

And then very importantly we found no increased risk of other cancers; that means; those cancers not related to tobacco smoking.

I should also add that another novel part is that this study is very, very big. It's based on the 10,000 individuals, of which 2500 developed cancer, from when we had the blood samples in 1981 to '83, until 2008, as long as we follow them up to 28 years, and all these 10,000 individuals, they are from the Danish general population. And we had 100 complete follow-up, because we have registration Denmark.

Another important aspect is that there hasn't been much vitamin D supplement in Denmark and not even yet, but way back in time, and no foods are supplemented with vitamin D. And as we also live in the Northern European country, with not so much sunshine in the winter time, we really look at the natural history of low vitamin D in the study.

Bob Barrett: Well, there are number of diseases associated with low vitamin D levels, what are the most serious of these diseases?

Dr. Børge Nordestgaard: Certainly, I don't know the most serious, but the most well studied is osteoporosis, which is like we already knew from vitamin D, in the beginning something with calcium and bone reabsorption. So osteoporosis is very important and for that reason many people take vitamin D with calcium supplements, but then other diseases have been examined and we ourselves had done a very vast

study in what's called osteonecrosis thrombosis and vascular abnormalities, already the Journal published in 2012, where we found an 81% increased risk of fatal ischemic heart disease and 27% increased risk of any death when you have low vitamin D.

And we even did meta-analysis with all the previous studies and substantiated that this was a very robust finding. Then we have a different paper that came in and also *Neurology* also published in 2012, where there was 82% increased risk of ischemic stroke, and there we also did a meta-analysis of all the previous studies and they all combined, confirmed that low vitamin D does have an association with increased stroke risk.

And then in *Clinical Chemistry* in 2012 we had yet another paper, but there we looked at increased risk of diabetes and there was 35% increased risk of diabetes in those with the lowest levels of vitamin D, and there again, there was a meta-analysis substantiating all the previous studies that combined found that low vitamin D, more diabetes risk.

And then finally, and really the contrary finding, when you have low vitamin D, you're protected against common skin cancer, so we had this paper that came in *Journal of Investigative Dermatology* also in 2012, where for those with the highest vitamin D levels, so it's the other way around, they had five-fold risk of skin cancer.

Of course, if you have high vitamin D, that's because you went in the sun a lot, so therefore you have skin cancer risk. So I think these are the most important diseases by now, but there are a number of other diseases that have also been associated with low/high vitamin D levels.

Bob Barrett: So, low vitamin D levels are associated with increased risk of these different diseases, and in your study, also with tobacco related cancer, but is these a causal relationship? In other words does low vitamin D actually causes tobacco related cancer?

Dr. Børge Nordestgaard: Yeah, the chicken or the egg, I mean that's always the question, but what we show here is epidemiology, so it's an association between two things; tobacco related cancer and low vitamin D. So there are really three options for interpretation. One option is that the low vitamin D directly cause cancer, the second option is that the various tobacco related cancer lead to low vitamin D or that third

factor that is most likely here would be smoking, that smoking would lead to low vitamin D and to smoking related cancers.

So that's the likeliest one. I should say though, in our study we did something that's called mediator analysis and we found that it looks from our data that low vitamin D is involved in the pathway of tobacco smoking carcinogenesis; that's what we could indirectly show.

Bob Barrett: So we still don't really know who is the chicken and who is the egg here. So how will we ever know the answer to this question? What type of research is needed to solve this puzzle?

Dr. Børge Nordestgaard: There's two types of studies that can look at what's the chicken and what's the egg, and these are studies that are un-confounded, that where there is no problem with reverse causation and the classical one is the Randomized Intervention Trial. And there are some studies on the way now where you take people with low vitamin D and half of them, by flip of a coin, you give them vitamin D supplements, or you could have them more sun exposure to produce it themselves, and the other half you make them to control or placebo group.

And then if the vitamin D supplements will directly lead to less cancer risk and you think this is because of vitamin D.

The other option is to do what's called Mendelian Randomization Study. It's nature's own randomized trial, where what you do is you study genetic variance in the population where some people lifelong have lower vitamin D levels than others, and then you see if this genetically lifelong lower vitamin D levels means that these people have less cancer, and that's another way of addressing. And we also would do studies like that in the future and there are randomized intervention trials in the world, so hopefully in some years we will have the answer.

Bob Barrett: If a person does have low vitamin D level, would advise them to increase the vitamin D level in their blood? And if so, how would you do it, by what means should those levels be increased?

Dr. Børge Nordestgaard: Yeah, I think it's probably good, if you for some way or the other can increase it, that's probably a good advice. And I'm cautious, so I think the most natural way to have vitamin D in your blood is simply to

have your skin be exposed to sunshine. So I think that's the best way, but of course, you have to be very cautious, so that you get it in small doses, so that you do not get sunburn, because then you will have what I showed you before -- told you before that then you have an increased risk of skin cancer.

I mean common skin cancer causes not very dangerous, because you don't die from that. What is dangerous is the malignant melanoma. So you don't want to get a sunburn, but except for that, sunshine on your skin, that's probably a very good thing. I think there has been too much emphasis that you should not be in the sun because of the risk of skin cancer, but at the same time you have, the opposite problem here is that you have so many other diseases you have.

Then of course, there is also food, various food items there is fatty fish, there is meat, there is egg, there is milk products, with vitamin D. And in some countries, for example, in the United States, lot of food stuff have vitamin D added, so that's one way.

And then you can buy vitamin D supplements, but I'm a bit more cautious about that. I would prefer sunshine first and then food with vitamin D, and then last one, supplements. Of course, if have osteoporosis, then it is well shown the vitamin D supplements will help you and therefore it's advised for people with osteoporosis.

Bob Barrett: People would like to just pop a vitamin D pill, is it safe to do that? Would you advise people to take supplements?

Dr. Børge Nordestgaard: Yeah, I mean that's a problem. I mean that is for prevention from osteoporosis, then there are some good studies that I've shown, but the problem is, that if you give a supplement to huge part of the populations, you don't really know where there will be some hidden side effects that haven't noticed before. So I'm more concerned for some problems in the future, so I would really want to wait for the very last trials and there is a very big American trial called that Vital Study coming out of Boston where 20,000 men and women are randomized to vitamin D or placebo and that's supposed to finish in June 2016, and then we will really know. Is it beneficial, does it reduce diabetes, cardiovascular disease, cancer, when you have vitamin D and if this is safe, and if it is safe there, then I think it is wise to take vitamin D, but until then I will be a bit cautious.

Bob Barrett: Well, finally doctor, let's get personal. Do you take vitamin D supplements yourself?

Dr. Børge Nordestgaard: No, I don't actually, but I like to be in the sun, so that's what I do.

Bob Barrett: I agree with that wholeheartedly! Dr. Børge Nordestgaard is Chief Physician in Clinical Biochemistry at Copenhagen University Hospital and a Clinical Professor at the University of Copenhagen in Denmark. He has been our guest in this podcast from *Clinical Chemistry*.

I am Bob Barrett. Thanks for listening!