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Vitamin D Can Reduce the Risk of T2D in Prediabetic Patients

Dr. Buse:
Vitamin D has numerous benefits. It's essential for bone health, it's anti-inflammatory, and it's even reported to have neuroprotective properties; but can it also decrease the risk of diabetes for patients with prediabetes? One clinician is joining us to answer that question.

Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse. And joining us to explore the role of vitamin D on the risk of type 2 diabetes in patients with prediabetes is Dr. Anastassios Pittas. Dr. Pittas is a Professor of Medicine and Chief of Endocrinology at Tufts Medical Center.

Tasso, thank you so much for joining us today.

Dr. Pittas:
Thank you, John. Great to be with you today.

Dr. Buse:
I notice you've published over 50 papers on vitamin D through the last 20 years. Can you tell us how you first identified the relationship between vitamin D and the risk of type 2 diabetes and where you went from there?

Dr. Pittas:
Yeah, absolutely. It's been quite a journey. The idea that vitamin D is linked to risk of type 2 diabetes was conceived in July 2002, and I remember that because I was enrolled in a master's degree program, and my final assignment for a course I was taking at the time was to design a study to apply what we were learning in the course. So around that time, I was intrigued by a couple of publications reporting a link between vitamin D and type 1 diabetes, so I thought that if there's a link between vitamin D and type 1 diabetes, perhaps there's a link between vitamin D and type 2 diabetes.

I was able to find a couple of cross-sectional studies from a few decades earlier but not much more, so I thought this would be a good area to pursue, or at least it would give me a good project for my course. So subsequently, I applied what I learned in my master's degree, and I collaborated with two amazing collaborators, Bess Dawson-Hughes and Frank Hu, and we ran an observational analysis in the Nurses' Health Study and an answer analysis in a completed trial with vitamin D and calcium in older people. The results were very promising. And others were also publishing results supporting this hypothesis. Now at the time, as you recall, vitamin D was becoming increasingly popular, so the timing for this was right. And then one thing led to another, and here we are 20 years later, and I'm here conversing with you.

Dr. Buse:
Can you give us some background on this meta-analysis that you published on vitamin D and type 2 diabetes risk in patients with prediabetes?

Dr. Pittas:
Absolutely. So our team and others published longitudinal observational studies and short-term mechanistic studies, and they all provided good evidence of a link between vitamin D and type 2 diabetes, and we were very fortunate to secure NIH funding to conduct a D2d study, which was a multicenter clinical trial to test the hypothesis that vitamin D lowers risk of diabetes in adults with high-risk prediabetes. So as I keep telling my fellows, that whenever you have an idea, others have the same idea, but only a few people will test that idea in studies. So in addition to the D2d study, there are two other trials that were specifically designed to test this hypothesis: one in Norway and one in Japan. In all three trials, the risk of diabetes was reduced with vitamin D compared to placebo and did so in markedly similar ways. However, in each trial, the observed differences missed statistical significance because the reported risk

reductions were smaller than each trial had the power to detect.

Now unfortunately, most people judge study results based on this arbitrary dichotomous statistical threshold of P value of 0.05, but it is now increasingly appreciated that studies are not positive or negative but they report a range of possible effects based on the observed data. So when we combine individual participant data, we improve the precision around it to effect size, in this case for vitamin D in diabetes risk reduction, and that was the goal of the meta-analysis.

Dr. Buse:
I agree completely with your point about not pinning all your hopes and dreams to a P level of 0.05. So let's jump into the results. You had a P less than 0.05.

Dr. Pittas:
So after combining data from the individual participants from these three trials—so we found vitamin D reduced the risk of progression from prediabetes to diabetes by 15 percent compared to placebo— we also found that vitamin D increased the likelihood of regression to normal glucose regulation by 30 percent, so it's not just that you're not progressing to prediabetes, but you're actually going back to having normal glucose regulation.

Interestingly, we also found that participants in the vitamin D group only who maintained intratrial blood 25-hydroxy D level about 15 ng/mL had a 76 percent risk reduction in new-onset diabetes compared to those who maintained blood vitamin D level between 20 and 29, which is generally considered adequate for general bone health by most guidelines, so we were excited about this test result because any time you have a dose response finding, this is important because it increases the credibility of the main result.

Dr. Buse:
Well, that's a very exciting and impressive result. Were there any adverse events that were noted in the meta-analysis?

Dr. Pittas:
So the overall frequency of the adverse events of interest we typically care about with vitamin D—for example, kidney stones, hypercalcemia, hypercalciuria—was very low, and there was no difference between the two groups. Last year we published specifically on the safety and tolerability of the daily 4,000 unit dose of vitamin D we used in the D2d study, and in that analysis, we were able to look at not just these specific AEs of interest, but all adverse events reported throughout the trial, and we found that they were overall less frequent in the vitamin D group. So overall, I would say that the evidence is that vitamin D appears to be safe in this specific population.

Dr. Buse:
For those just tuning in, you're listening to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse, and today I'm speaking with Dr. Anastassios Pittas about vitamin D and the risk for type 2 diabetes in people with prediabetes.

So, Tasso, if we apply these findings to clinical practice, how do you translate it into a message for patients about the benefits of vitamin D in reducing the risk of type 2 diabetes?

Dr. Pittas:
Yeah so overall, we can say that vitamin D has a beneficial effect in people with prediabetes without any safety signals, and there are three points I'd like to make in relation to how we apply the results. The first point is that all participants received and were encouraged to follow the recommended lifestyle base applied for diabetes prevention. So it is important for the listeners to understand that it's not that vitamin D is competing with lifestyle for diabetes prevention, but it's ideally in addition to that. But overall as an additional preventive option, vitamin D has several advantages over traditional diabetes prevention strategies because it's readily available, it's safe, and of course, no cost.

The second point I'd like to make is that the benefit-to-risk ratio for vitamin D depends on the target population and medical condition, and it is important to understand the difference between supplementation and treatment, and that's a good point I was making in the editorial. So the typical guidelines for vitamin D supplementation apply to the general population to avoid conditions typically associated with vitamin D through deficiency, like rickets and osteomalacia, and to promote bone health. These guidelines do not necessarily apply to other populations: prediabetes or conditions in metabolic health.

Now based on the results of our meta-analysis, the benefit-to-risk ratio of vitamin D as a treatment approach to lower risk of diabetes is favorable. However, these results should not be extrapolated to the general population of low or average risk for diabetes because the benefit-to-risk ratio in this population may be different, so really targeting your population is very, very important.

The last point is in terms of what dose to use, and that's not entirely clear, but what's clear is that the recommended doses by most guidelines with general health in terms of vitamin D are inadequate for diabetes prevention. And based on our results, I think we can

aim for blood 25-hydroxy D level close to or about 50 ng/mL to maximize benefit, again in this particular population.

Dr. Buse:
So for people with prediabetes at high risk for progression to diabetes consider treatment not supplementation on the background of comprehensive lifestyle intervention to achieve a vitamin D level of 50 ng/mL, perhaps 4,000 international units a day. Is that right?

Dr. Pittas:
That's exactly right, yeah.

Dr. Buse:
Before we close, do you have any final thoughts you'd like to leave the audience with?

Dr. Pittas:
So I just want to comment a bit about the strong opinions about vitamin D listed among healthcare professionals. So I often get the question "So what's the story with vitamin D?" It sounds like a reasonable question, but this is like asking me, "So what's the story with insulin?" or "What's the story with cancer?" So it's too general of a question to be answered.

There are several large studies—for example, the vitamin study—that have not shown significant benefits with vitamin D for cardiovascular disease, cancer or fractures, and these results are hardly surprising. The populations studied are low risk for fractures where vitamin D status is sufficient for bone health. Vitamin D will not lower risk in a measurable way, especially if the dose given is inadequate. Now regrettably, people draw general conclusions about vitamin D that are really not supported by these studies, such as the VITAL study. So I think it is important to understand that you can only answer specific questions by following a methodical approach.

So when people ask me, "What's the story with vitamin D?" I respond by asking them what populations and indications they're interested in. So if they're interested in diabetes prevention, I tell them that, yes, there are studies in people at high risk for type 2 diabetes where vitamin D lowered risk of developing diabetes without any safety concerns.

Dr. Buse:
With those considerations in mind, I'd like to thank my guest, Dr. Anastassios Pittas, for joining us to evaluate the role of vitamin D in reducing the risk of type 2 diabetes in patients with prediabetes. Tasso, thank you so much for being here.

Dr. Pittas:
It was a great pleasure, John. Thank you for the invitation.

Dr. Buse:
For ReachMD, I'm Dr. John Buse. To access this episode and others from our series, visit ReachMD.com/DiabetesDiscourse where you can Be Part of the Knowledge. Thanks for listening.