Debating the Role of Vitamin D in COVID-19 – An interview with Dr. David Meltzer

The audio file is also available at: https://academic.oup.com/ofid/pages/Podcasts

In episode 34 of the OFID podcast, OFID Editor in Chief Paul Sax, MD, PhD, professor and chief of hospital medicine at the University of Chicago, about his research linking low vitamin D levels with COVID-19 susceptibility, the limitations of currently available data, and if vitamin D supplementation is wise.

Hello, this is Paul Sax [MD]. I’m editor in chief of Open Forum Infectious Diseases (OFID) and this is the OFID podcast. And a reminder, that’s O-F-I-D and not “Oh-fid.”

Well, one of the great unknowns in the COVID-19 [coronavirus disease 2019] pandemic is host susceptibility. Why do some people get infected and other people don’t, even with the same exposure? And in September, a fascinating paper was published in JAMA [Journal of the American Medical Association] Network Open, finding a strong association between low vitamin D levels and testing positive for COVID-19. This opened up a whole new world to me about vitamin D status and respiratory virus infections. Hence it gives me great pleasure to welcome today, the first author of that paper, Dr. David Meltzer [MD, PhD]. He is the Fannie Pritzker professor and chief of the section of hospital medicine at the University of Chicago. In addition to his medical training, he has a PhD in economics and holds secondary appointments in the Harris School of Public Policy and the Department of Economics. David, welcome today.

Great. Thanks for having me.

So start out by telling us a little bit about yourself. How did you decide to become a doctor and choose your particular, very interesting pathway?

I was actually, in college, a double major in economics and molecular biophysics and biochemistry. And I started on that path thinking I would choose one or the other and discovered that although I loved designing experiments in biology, I didn't particularly care how they turned out. And I was fascinated by economics, but it seemed very purely mathematical and wasn't as applied as I wanted it to be at the time. And I realized that the synthesis of medicine and economics was a wonderfully interesting area where one could bring together an interest in policy and economic theory, but also the real practical problems of, at that point, an aging society – now even more so – and rising healthcare costs and health disparities. So that gave me the idea of putting them together and started me on this path.

Well, that’s really fascinating. What I’d like to do now is focus on the main topic of today’s discussion, vitamin D. In general, you’re aware that observational studies consistently show a relationship between low vitamin D level and poor health outcomes, yet vitamin D supplementation studies are often very disappointing. So as a general internist, how do you view these studies? And feel free to mention whichever examples you’d like, because there are numerous failed studies out there.

Sure. There are lots of failed studies. First of all, the idea that the observational studies do not always translate into the results of experimental studies is no surprise, I would hope, to any well-educated physician and certainly no surprise to any economist. We don’t get to do experiments as economists where we randomize societies to different interest rates or people very often, although we’ve done them to different incomes. And so you have to think really hard about how to learn from those situations, what their limitations are. That is a really important concern in this particular area.

To get to the point in vitamin D, what got me interested in this was the results of randomized trials. I was not thinking at all about vitamin D, I was thinking about how do we deal with our hospitalist services back in March when I got a random email that had the header on it, “Vitamin D associated with decreased viral respiratory tract infections.” And I clicked inside and looked at it, and it was a report of this 2017 study done by Adrian Martineau [PhD], which was an individual level meta-analysis of randomized trials of the effects of vitamin D supplementation on viral respiratory tract infection. So I went over it with a couple of my epidemiologist friends and obviously there are individual studies in there that one may not be thrilled with and there’s a lot of heterogeneity in it. But there’s a big subset of studies where they give vitamin D intermittently, they don’t see such big effects in that bolus dosing, it doesn’t seem to produce this effect. But in the studies that give vitamin D on a daily or weekly basis, they see immense, approximately 70% reductions in viral respiratory tract infections.

So I thought, “Wow this is interesting.” And obviously at that point in time, we really didn’t have any therapeutic options that were getting us anywhere. And here I was in Chicago with all...
these patients coming into our hospital, who were getting tested or at least coming to get tested for COVID, and some of these were people who had been in our health care system for years. And I thought “Wow, we might have historical vitamin D levels for them. Here’s an opportunity to take a look at this association and see whether there’s anything there.” And so that’s what got me started.

**Just so the listeners who may not be as familiar with general medicine as you are, I think it’s only fair to say that there have been studies of vitamin D for cancer prevention, cardiovascular prevention and I think, most recently, falls and other things. They really haven’t shown much of anything, right?**

That’s absolutely right. There’s no question that vitamin D levels can be associated with various co-morbid conditions and that those comorbidities themselves, some of which could be medical, some could be social, might well be associated with differences in disease outcomes so that the result is due to confounding. And there’ve been many such studies where you’ve seen an observational association, but then you haven’t seen it in an RCT [randomized controlled trial]. That’s completely understandable and that’s why you do RCTs.

But as I said, what got me started in this was seeing this individual-level meta-analysis of patients randomly assigned to different doses of vitamin D, where you saw this. Now you can criticize individual-level meta-analysis and meta-analysis in general, but individual-level meta-analysis of multiple RCTs, certainly is a somewhat higher form of evidence. Obviously, you can do subgroup analyses within that. So we were well aware of the limitations and by no means did I start this work thinking that observational studies would prove that vitamin D made a difference. But if it didn’t have an effect, certainly that would suggest it’s probably not worth spending as much time worrying about it. I thought it was at least worth a look.

We’ve seen some of the same things more recently in studies, not so much of prevention of COVID, but in potential therapeutic interventions. And there, if anything, the confounding is probably even worse, right? Because people who have more severe illness you might well expect would have lower vitamin D levels because of the illness and therefore worse outcomes.

But that much said, it’s really interesting. In some of our own internal analysis, it’s not clear to us that we’re seeing big drops from baseline and people who have vitamin D levels before they get COVID and then at the time they come in. So it’s not clear to me that there’s super strong evidence that type of confounding is what’s driving things. And then in addition, there is this study out of Spain by [Martin Entrenas-] Castillo, which is a small pilot randomized trial, where they gave activated vitamin D to patients who were being hospitalized and then looked to see whether they went into the ICU [Intensive Care Unit]. And there are some imperfections in that study, no question, but there are also some analyses that have been published that suggest that the magnitude of those biases is pretty hard to explain why they got the striking results they did …

**And what were the results?**

... which was dramatically lower rates of ICU transfer among people who got this activated vitamin D.

**So was it a randomized trial?**

They described it as a pilot randomized trial, actually randomized. I think there were 50 people in the control group and 100 in the intervention. I think it was two to one. The key thing that was fascinating is that basically half the people in the control group ended up going to the ICU, almost no one in the intervention group.

**That brings me to my next query. I highlighted a negative vitamin D randomized clinical trial for COVID treatment on Twitter and I have to say, it fell into my own preconceived biases about vitamin D studies, since it was negative. I confess that up front. But my post was immediately met with some extremely vociferous protests and some of them not so polite. So I want to ask you, how do you account for the extremely strong viewpoints held by people on this particular topic?**

I don’t know. You might need to talk to a psychologist or a sociologist to get a really good answer.

**Yeah, it was really quite striking.**

I think this is an area where there have been some very promising observational studies. There’ve been some, as you say, disappointing interventional studies. I personally think there’s a lot we still don’t understand about vitamin D. That probably drives a lot of these strong feelings, when you don’t have good, really great data. Also studying nutritional elements is incredibly difficult.

**Mm-hmm.**

There’s not just what people take in the intervention, but it’s the amount of sunlight they get and what they take in their diet and your ability to control it. The other thing is there’s a lot of dimensions here to giving vitamin D or not giving vitamin D – you can give it daily, you can give it weekly, you can give it monthly, you can give it at low doses, you can give it at high doses. Also a lot of heterogeneity. And there’s been a lot of confusion about that heterogeneity. I think that there are really profound differences between, for example, African Americans, Hispanics, as opposed to Northern Europeans in the biology of vitamin D. It’s not just production, it’s not just skin color, it’s vitamin D binding proteins.

The other thing, and I think this may be a part of an answer to your earlier question, is there’s a lot of focus on vitamin D levels and dihydroxy vitamin D that actually is the active part of it. And yet the vast majority of vitamin D is not that and is bound to proteins that may be differentially available, particularly for particular physiological functions when you need it. I think there’s a profound confusion in the field because the measure that we use clinically so much of the time is actually pretty imperfect. There’s a lot written about free vitamin D and the role of free vitamin D in the...
immune system, and yet we constantly see people going to conclusions based on levels. And I just think there’s a real disconnect between what we know, really know, and what we do and think.

And this is actually the other thing I’ll comment on. Particularly in the United States, you would go back to the National Academy of Medicine recommendations about vitamin D. I think people, clinicians and others, do not appreciate how heavily those were dominated in the end by bone metabolism issues and not by evidence on infection, because we don’t have good evidence about infection. So people say, “Vitamin D is not of value.” And what they should say is, “We can’t discern whether there is value in this regard. We have discerned that there is value in bone and therefore make certain conclusions about bone, but those conclusions may not carry over to the immune system.”

The more you get into this literature and you read it, I want to be clear. I have equipoise here.

**You do? Good.**

But when you do that, you understand there are different evolutionary pressures with respect to vitamin D, with respect to the immune system than there are with respect to bone. Some of them are probably much more recent and related to geography and other things. This is a complicated problem.

You use the word equipoise, which of course leads me to my next question. Where are we with the highest level of evidence, which would be a randomized clinical trial? What sort of research are you doing and what sort of research is ongoing elsewhere that you’re aware of on this topic?

As soon as we did these analyses, it became clear to us that one should be thinking about doing randomized trials, because we weren’t going to get an answer from observational studies alone. I’m aware of several groups, JoAnn Manson [MD, DrPH] at Harvard is doing a study of COVID prevention. Hers is in contacts, I believe, of people who have been infected. There’s a group from Medical University of South Carolina that is doing a randomized trial. I don’t exactly know the details of that one.

And then we’re doing three studies here in Chicago – the first one is a quasi-randomized trial where we have a group of medically complex patients in this disease management program that I described earlier, where we’re trying to help them optimize vitamin D levels. And then they’re being compared to a group which is not in the program and where presumably usual care is being followed, which probably means they’re not giving too much attention to vitamin D levels. We’ll be following those patients. Honestly, the biggest learnings that are going to come from that is how to manage vitamin D, practically, in these very complex patients.

The other two are randomized trials, they are blinded. One is a trial which we’ve started in healthcare workers and is funded by NIH [National Institutes of Health], but we’re hoping to broaden to the general population as healthcare workers increasingly get vaccinated. And that is comparing low-dose vitamin D, which is 400 IUs [international units] per day, to high-dose vitamin D, which would either be 4,000 or 10,000 units per day.

The subject can decide whether they’re comfortable with 4,000 or 10,000, and then they’ll be randomized to either 400 versus 4,000, or 400 versus 10,000. And for that we’re checking calcium levels and parathyroid hormone vitamin D levels and so on, so that we can monitor for safety.

The other trial is community-based and there we’re looking at 400 versus 4,000. And in both of these trials, we’re going to be looking for people reporting symptomatic COVID and then eventually looking at antibodies at the end.

**That last study, does that have a placebo arm?**

It’s 400 versus 4,000 or 10,000. And there’s a part of me in a way, that would love to do a placebo study, just because it would be easier to understand if there’s an effect there, but I personally have genuine equipoise as to whether 400 is really just as good as 4,000. And if 400 is just as good as 4,000 and everyone’s already taking 400 or should be at least perhaps, then fine, go ahead and just take 400. In the end 400 versus 4,000 or whatever other comparison is the right one. I also didn’t feel comfortable telling people to take none when the recommendation is that you should take 400.

**Is that the recommendation for everyone or just people who are deficient?**

To be clear, the RDA [recommended dietary allowance] is right between 600 and 800 and the vast majority of Americans don’t get that much.

**But they also, to be fair, are not taking 400 right now.**

Well, sure they’re not. And it may be that 400 is totally fine, so at least we’re getting people to take 400.

**But if I’m going to challenge you, I’m going to say, I don’t even know that 400 a day versus nothing is of benefit.**

Well, that’s true. Although I guess you could argue that it’s of benefit potentially for bone, right? One of the fascinating things in this field also is what the role of testing should be.

**Yes.**

And it’s a very unusual thing when you’re thinking about testing for something, where at least if you use levels as an appropriate standard, almost half of Americans are deficient. And substantially more like 70 / 80 percent of people of color. So there’s a very reasonable case to be made for a public health approach and I’m not aware of anyone who believes that taking 400 IUs of vitamin D a day is a public health risk.

**That’s an important question because if you’re a primary care doctor and you’re advising people in your practice who are afraid of COVID, should you advise them practically, today, to take vitamin D or should they wait for a placebo-controlled study or for one of your studies?**

I guess the question is, is it going to help you or hurt you? And I don’t know whether it’s going to help you or not. Is it likely to hurt you? I think very, very unlikely. It could help you for other reasons, it might just make your bones stronger.
Okay, and I’ve got another group for you – not the ones who were afraid of having COVID, but the ones with mild disease who are home.

Again, I don’t think it’s going to hurt. Would it help? I really don’t know. Would I do it? Yes, honestly, I would. I just have to say, you’re in excellent company. I work with a very fine, experienced primary care clinician, he’s also a superb teacher, and he took me to task on my vitamin D views with COVID-19 as well saying that there’s so little harm and there’s potential benefit and why not?

What do you think practically, the availability, gradually, of the vaccine over the next three-to-six months will do to these studies? Do you think that they’re still going to read out?

I think it’s going to decrease the likelihood that they’ll read out. Presumably, the bigger the exposure is to risk, which is a combination of both the probability and the time over which it played out, the less likely they will be informative. On the other hand, unfortunately, we’ve done such an abysmal job of controlling risk in this country that when I look back at the power calculations we did when we started thinking about these things, our rates are way above that.

The other thing is, when we’re doing these studies, we’re really trying to very proactively reach out to communities of color…

Great.

… where we know that risk is much higher and levels of vitamin D deficiency are also much higher. So that may help us as well – we’ll see. It’s plausible we’ll learn things. I think we’ll be able to have estimates of event rates when this is all done, among the people we recruited, because they’re randomized trials and we can tell what, retrospectively, our power would have been. But if I have to have a less successful study in order to get rid of COVID, I’ll take it.

I think we’re all in the same camp there.

David, this has really been a fascinating discussion. I want to thank you for taking the time to talk to me. And once again, I’ve been talking to Dr. David Meltzer, the Fannie L. Pritzker professor and chief of the section of hospital medicine at the University of Chicago. Thanks a lot, David.

Thanks for having me.