Vitamin D and Mortality Risk: Should Clinical Practice Change?

An Expert Interview With Cedric F. Garland, DrPH

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Vitamin D and Mortality -- Are They Linked?

Vitamin D, "the sunshine vitamin," is rarely out of the news nowadays, with reports of new studies contributing regularly to the ongoing debate about optimal levels of the hormone, indications for testing, and need for supplementation. Traditionally associated with skeletal disease including osteoporosis and fractures, low levels of serum 25-hydroxyvitamin D (25[OH]D), the metabolite usually measured as a mark of vitamin D status, more recently have been linked to a wide range of nonskeletal diseases, including some cancers and autoimmune, cardiometabolic, and neurologic diseases.

A number of studies also have reported an inverse association between 25(OH)D concentration and all-cause mortality. However, most of the evidence for (and against) this association has come from observational studies and has yet to be confirmed in clinical trials. Meta-analyses have almost all concluded that lower 25(OH)D levels are associated with a significantly increased mortality risk.[1-7]

To explore this association more, Medscape reached out to Dr. Cedric Garland, a well-known expert on vitamin D. Dr. Garland is a professor in the Division of Epidemiology, Department of Family and Preventive Medicine, and a Fellow of the American College of Epidemiology. He has a Doctor of Public Health degree from University of California San Diego and studied epidemiology at Johns Hopkins. His research has focused on vitamin D status in health and the association between vitamin D deficiency and increased risk for disease, including some common cancers (breast cancer, colon cancer, leukemia, and melanoma) and diabetes. He is active in seeking to reduce the risk for cancer and diabetes by improving vitamin D status among the US population.

To examine the relation between serum 25(OH)D and mortality, Dr. Garland and colleagues at the University of California San Diego and others in the United States pooled data from 32 studies published between 1966 and 2013.[6] They found an overall relative risk of 1.8 (95% confidence interval [CI]: 1.7-1.8; *P* <.001) comparing the lowest (0-9 ng/mL) with the highest (>30 ng/mL) category of 25(OH)D for all-cause mortality. Serum 25(OH)D concentrations ≤30 ng/mL were associated with higher all-cause mortality than concentrations >30 ng/mL (*P* <.01).

The investigators noted that these findings confirmed observations from the Institute of Medicine (IOM) that 25(OH)D levels of <20 ng/mL are too low for safety,[8] but they suggested a cut-off point of >30 ng/mL rather than >20 ng/mL for all-cause mortality reduction. This level "could be achieved in most individuals by intake of 1000 IU per day of vitamin D3," the investigators said, noting that this is described as a safe dose in almost all adults by both the IOM[8] and Endocrine Society[9] clinical guidelines on dietary intake of vitamin D.

Dr. Garland spoke with Linda Brookes, for Medscape, about research, both his own and others, examining the relationship between vitamin D status and mortality and the implications for clinical practice.

Vitamin D Level Discordance

Medscape: What inspired you to do a meta-analysis looking at the association between 25(OH)D levels and all-cause mortality?

Dr. Garland: What motivated us initially was our observation that when we gave talks to family doctors and other primary care physicians about treating vitamin D deficiency, almost invariably someone would say, "I would do it for my patients, but I am worried about increasing their risk for kidney stones or heart disease," or they would be worried

about something else that might occur to the disadvantage of their patients. We found that they understood the benefits of vitamin D, and many of them were taking it themselves, but they were reticent about using it in practice because they thought that there might be adverse effects.

The whole purpose of our study was to produce something that could help physicians to use their own judgment about the appropriate targets for their patients. That was the reason we did it.

Medscape: There is a lack of consensus about the levels of 25(OH)D that define "deficiency." According to the IOM, deficiency is defined as <12 ng/mL and "inadequacy" as 12-20 ng/mL.[8] However, the Endocrine Society defines deficiency as <20 ng/mL and "insufficiency" as 21-29 ng/mL.[9] What levels of vitamin D concerned the physicians in your audiences?

Dr. Garland: Usually we heard they did not have any concerns if 25(OH)D was 20 ng/mL or above because their feeling was that it was clinically indicated to bring it up to 20 ng/mL, if only for reduction of fracture risk. But they were not certain about people who were in the range of 20-29 ng/mL. More often they were concerned that, without a documented vitamin D deficiency, there wasn't an indication to prescribe a supplement, which they worried could possibly increase complications.

Some of this uncertainty arose after several members of the panel responsible for the 2011 IOM recommendations wrote commentaries suggesting that 20 ng/mL is sufficient for general internal medicine or family medicine practice.[10,11] However, the recommendations in the IOM report were based solely on bone outcomes,[8] and quite a lot of water has gone under the bridge since then. In 2011 the IOM committee decided that it would only address outcomes concerning bone because there were more clinical trials with these outcomes, although there were some clinical trials that covered nonskeletal aspects of vitamin D deficiency.[12-14]

In particular, a randomized clinical trial by Lappe et al[12] had demonstrated a reduced risk for all cancers with vitamin D supplementation in postmenopausal women. The IOM reported that a relationship between cancer incidence and vitamin D nutriture had not been "adequately and causally" demonstrated and that for some cancers, there might even be a small increase in incidence associated with higher serum 25(OH)D concentrations or higher vitamin D intake.[8]

The number recommended by the IOM, 20 ng/mL, caught on and became another barrier that we faced. Only one third of the US population is below 20 ng/mL,[15] but two thirds of the population is below 30 ng/mL.[16]

We decided to look at what would happen if we put together all the existing studies that have looked at the survival of "ordinary" people; that is, mostly people in general practices who did not, for the most part, have illnesses. Studies that only included people who were already ill were not eligible for inclusion in our analysis.

We found 88 relevant studies, of which 32 presented their data by quartiles of intake, allowing us to see a dose response. The research was a surprisingly tedious process because everyone expresses the data in different ways, with different units used to express vitamin D levels (ng/mL or nmol/L) and different ways of presenting their data.

The benefits of a meta-analysis are that it makes you go through the discipline of converting everything to the same units and tends to diminish the effects of variations in measurement; if one particular study has a measurement that is less valid, it will not strongly influence the dose-response curve. We tried several ways to compute the dose-response curve, with different assumptions, and they all looked the same.

At the time we were doing this, though, the literature was exploding. We re-did the whole analysis several times as new studies were published, but there was no way to have it continuously open-ended; you reach the point where you have to stop and show your results. I imagine that we will update our analysis at some point; and at the rate new studies are being published, we will probably have data from double the number of studies when we do.

A "Curve Ball" in Vitamin D Research?

Medscape: Your results suggested that the risk for all-cause mortality follows an inverse J-curve, with the effect stopping around 60-70 ng/mL, rather than a U-curve postulated in the IOM report, with potential risks at levels above 50 ng/mL (eg, mortality, cardiovascular disease, selected cancers, falls).[8]

Dr. Garland: It is definitely not a U-shaped curve. It also is not an inverse J-shaped curve. It is rather linearly downward. We did not see a U or inverse J shape between circulating 25(OH)D and all-cause mortality. With a few studies of other outcomes, there is sometimes what looks like what might be a very tiny uptick at around >70 ng/mL. This is usually related to random variation in the small numbers at the high end of the curve. Due to random fluctuation in a few studies, my colleagues and I don't place too much stock in "U" or inverse J shapes. They are usually the results of randomness in areas of the curve with few events or biases. One such bias is the self-administration of high-dose vitamin D by people who have the particular disease, in an effort to arrest symptoms that may appear before diagnosis or even an action that could occur in response to something like a high prostate-specific antigen test result

A colleague and I wrote a commentary on a study where the authors had presented a U-shaped curve, showing an apparent 2-fold higher risk for pancreatic cancer with 25(OH)D levels >100 nmol/L (>40 ng/mL) producing the upward "U."[17] We showed by reanalysis of the data that this was likely to be a statistical artifact associated with the cutoff groupings and that there was probably no U-shaped curve.[18]

Whether it is scurvy, pellagra, or beriberi, an increase in niacin for pellagra, vitamin C for scurvy, or thiamine for beriberi does not result in an increase in incidence of the disease. You may see something else, like thrush with too much niacin or occasionally kidney stones with the maximum amount of vitamin C, but generally you do not see a return to the higher incidence that is true of people who are highly deficient. I would challenge anybody to show me any example of that; it would be amazing if it were true for vitamin D and very unlikely.

Medscape: Most of the data used in your analysis came from healthy people, so would this rule out the possibility of reverse causation, where people who are ill can be said to have low levels of vitamin D because they spend less time outdoors and have a restricted diet?

Dr. Garland: Most of the people in the studies included in our analysis were in cohorts of healthy individuals, and I believe that that rules out reverse causation. But if there were any residuum of doubt about it, there are many studies in people with various diseases, cancer in particular, but also multiple sclerosis and heart disease, that have analyzed the incidence rates of vitamin D-related disease according to the intensity of ambient solar ultraviolet-B (UVB) irradiance in place of residence. We did such a study of colorectal cancer that was published in the 1980s.[19]

The incidence of colon cancer is very high in countries like Iceland and Sweden, and other countries nearer the North Pole, and in countries like New Zealand, which is closer to the South Pole, and intermediate in countries at intermediate latitudes such as the United States, which is, on average, 38º north of the Equator. By the time you get down within the tropics, which is 23º from the Equator, it begins to decrease, and within 5º of the Equator there are vanishingly low incidence rates of colon cancer.

In the past, some scientists theorized that the low incidence rates near the equator were due to intake of a high-fiber diet, but now my group believes -- and many others are leaning more in this direction -- that it is the high UVB irradiance and high circulating 25(OH)D year-around nearer the equator rather than a high-fiber diet that best explains the inverse association with solar UVB irradiance. In other populations, you can detect a slightly lower incidence rate of colon cancer in association with high intake of fiber, but it is generally just a slight reduction. As you get closer to the Equator, there is a vastly greater magnitude of lower risk associated with latitude of residence than could be associated with difference in intake of fiber consumed in the diet.

So with regard to the reverse causation, we regard it as a virtual impossibility in our analysis because most of the

people in these studies were healthy when they were enrolled, and ecological studies would not show such a pattern if the low vitamin D were a consequence of the disease rather than vice versa.

Other Research

Medscape: Soon after your study was published, another meta-analysis of vitamin D and mortality appeared in the *BMJ*.[7] The data came from a consortium of 8 prospective cohort studies: 7 population-based cohorts of the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES) and 1 from the third US National Health and Nutrition Examination Survey (NHANES III).

The investigators reported a "remarkably consistent" association between 25(OH)D level and all-cause and cause-specific mortality. The lowest 25(OH)D quintile was associated with increased all-cause and cardiovascular mortality and with cancer mortality in subjects with a history of cancer, although not in subjects without a history of cancer.

Dr. Garland: Their results looked almost the same as ours. They reported a consistent inverse association between 25(OH)D level and all-cause and cause-specific mortality despite strong variations in levels of 25(OH)D by country, sex, and season. Their pooled effect estimate for all-cause mortality showed a 1.6-fold higher mortality in the bottom quintile compared with the top quintile (risk ratio, 1.57), whereas we found 1.8 overall greater relative risk [RR] for people for lowest compared with highest category of serum 25(OH)D.

It was the same for cardiovascular mortality in people without a history of cardiovascular disease (RR, 1.41) and a little stronger in subjects with a history of cardiovascular disease (RR, 1.65). In terms of cancer mortality, their results were slightly more mixed as they found no association in people without a history of cancer, but vitamin D was very beneficial for people with a history of cancer, with a RR of 1.70, another clearly significant result.

Medscape: Were you surprised by the cancer mortality findings in this study?

Dr. Garland: Not at all. Raising the serum 25(OH)D from 30 to 40 ng/mL reduces the incidence of breast, bowel, and lung cancer by 80%, as reported by Lappe and colleagues in their clinical trial.[12] On the other hand, if you lump all cancers together, in both sexes, and include countries where there is a whole lot of cigarette smoking, then you may obscure the effect of the vitamin D. Vitamin D is not able to overcome the effect of heavy smoking, and the CHANCES analysis[7] included data from people in countries like the Czech Republic, Poland, and Lithuania, where there is a huge amount of smoking. Although the effects are still there, they are weakened.

Should Clinical Practice Change?

Medscape: Do you believe that your findings can really affect clinical practice?

Dr. Garland: Definitely. Around the United States, my colleagues and I have observed that physicians from areas like Maine, where 25(OH)D levels are routinely low, are not very impressed by vitamin D deficiency. They say to us, "We don't need to get up to a level like 30 ng/mL; most of my patients are at 12-15 ng/mL, and they are perfectly fine."

You see similar attitudes among other physicians whose practices are in high latitudes. Many physicians see that 20 ng/mL is quite common in quite healthy, vigorous people and conclude that it is OK. But what they don't have is a concern for the delayed harm that results from vitamin D deficiency. Cohort studies allow science to confirm how these patients are going to turn out if they continue to run such a low level as 20 ng/mL of 25(OH)D. Studies such as our meta-analysis have provided us an opportunity to not just be locked into the present but to predict mortality on the basis of vitamin D levels in the present. I had expected our results to be convincing, but we were shocked at the persistence of the belief that very low levels of vitamin D, such as approximately 20 ng/mL, are safe. They are not safe with regard to breast and colon cancer, several other cancers, diabetes in youth and adulthood, fractures, and

other complications of 25(OH)D <30 ng/mL. Even higher levels, such as 40-60 ng/mL, would be even safer, according to a letter of consensus of expert vitamin D scientists and physicians.

What About Ongoing Research?

Medscape: The lack of data from controlled clinical trials looking at vitamin D and nonskeletal outcomes is often mentioned, but there are some large trials ongoing, some of which are due to report in 2-3 years' time.[20-25] For example, the Vitamin D and Omega-3 Trial (VITAL) will look at the effects of vitamin D3 supplementation on cancer and cardiovascular mortality.[22]

Some of the trial designs, including that of VITAL, have already been criticized (for using the wrong vitamin D doses, for the probability of confounding, for having no vitamin D goals, and for being of too short a trial duration).[20,26] Do you think these trials will be able to resolve the debate on the association between vitamin D and mortality and other outcomes?

Dr. Garland: I would like to respond with a resounding "Yes" to your question, but I don't think that is possible, for the reasons that you mentioned. Vitamin D is available on the market, and what happened in the Women's Health Initiative study[14] is likely to happen again, namely that women who are taking placebo are also going to be taking supplements, either on medical advice or on their own initiative, and that will diminish the gap between the patient groups.

In addition, 2 ongoing trials, the CAPS study[23] (aiming to replicate the findings of Lappe et al[12]) and the VITAL study,[22] are both using a vitamin D3 dose of 2000 international units (IU)/day. I think that if I were to design a trial, knowing what we know today, I would use 4000-5000 IU/day. It seems as though each time we do a clinical trial, by the time the trial is completed, we know that the doses were too small to elicit an effect.

I am also concerned that there may be not enough calcium to see an effect. In CAPS, the women are being given 1500 mg of calcium, which was done in the original randomized controlled trial in which 80% of the cancers in postmenopausal women were prevented. I would have stayed with this design and dose for the VITAL trial. We know that it helps because in their original trial, Lappe and colleagues[12] examined the effects of vitamin D alone vs vitamin D plus calcium, and the effects were stronger when the calcium was included.

The greatest strength of these trials will be to rule out the complications, although I think our meta-analysis goes quite far in that direction to the point where we don't have to wait with bated breath for the results of these studies. Most public health actions throughout history do not require clinical trials. For example, back when the industry wanted everybody to do clinical trials examining the effects of smoking, it wasn't feasible to compel some people to smoke. We realized, after half a century of bickering about it, that you can establish causality with a set of criteria that came from the scientists who worked directly on studies of the adverse effects of smoking.

It was Doll and Hill who published a set of 9 criteria for making causal conclusions from observational data, and vitamin D meets all of those criteria, including the temporal sequence, the strength of the association, the dose-response relationship, and biological possibility support by animal studies.[27,28] We have an excellent clinical trial and scores of supporting studies. We have many completed studies of vitamin D toxicity and understand it thoroughly. We're at the point in time now where we ought to start to prevent as much illness and rescue as many patients with vitamin D-related illness as we can during the interim and not wait for further clinical trials to end. If we need a course correction at that point, such as a change in the target 25(OH)D level or dose, we can make it then.

Should Everyone Get Presidential Treatment?

Medscape: Given the inconsistent findings of studies and meta-analyses, the variation among 25(OH)D assays,[29] and the costs that would be involved, do you think that screening for everyone could be justified, or should only certain higher-risk groups be tested?

No national, primary care professional organization currently recommends population-wide screening for vitamin D deficiency. A few organizations, including the Endocrine Society, have specifically come out against it.[30,31] The US Preventive Services Task Force has suggested that "current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency,"[32] and elsewhere there has been criticism of overtesting.[33,34]

Dr. Garland: I can't imagine a public health or clinical rationale for not screening for low circulating 25(OH)D. Testing should be universal. And ideally it should be done in March when the vitamin D is at its lowest levels. This will prevent hundreds of thousands of cases of serious diseases worldwide annually, beginning with postmenopausal breast cancer and including colon cancer and types 1 and 2 diabetes. Skipping this test would be equivalent to not measuring blood pressure, serum lipids, or weight at an annual exam.

Medscape: Should everyone aim for a vitamin D level over 30 ng/mL?

Dr. Garland: Yes. No one should run a serum 25(OH)D less than 30 ng/mL. This means that two thirds of the US population needs supplementation. You may have noticed that President Obama was recently tested for his vitamin D, and it was 22.9 ng/mL.[35] His physicians wisely decided to treat him, and he is now taking vitamin D. I salute the President's physicians for their clinical acumen in performing this good and noble deed to ensure the health of President Obama. It makes me burst with pride and admiration when physicians act in this way with their patients.

Medscape: Would you say that everyone should be tested like the President?

Dr. Garland: Yes, in my judgment. And without delay. We should introduce the population to a new Golden Era of Medicine, based on contemporary scientific discoveries of vitamin D's profound health benefits today rather than waiting for yet another minor increment of confirmation.

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