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Vitamin D and Your Patients: Don't Accept Wimpy

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This editorial is for you. You as a doctor telling your specialty to be bolder, and you as a patient, helping you decide what should you do personally. Caregivers at the end of winter are not different than their patients and often have low concentrations of vitamin D. So physicians and anesthesia health care providers, take care of yourself.¹ But first the disclaimer. The elder of the authors works at, and loves, the Cleveland Clinic; although this article came from that coauthor's previous institute within the Cleveland Clinic, the editors judged us independent enough to let the data rule. We hope we do not lose friends with this editorial as the data rule.

Don't be Wimpy

Is lack of 25-hydroxyvitamin D (25-OHD; we explain the Ds below) a cause of poor outcomes after surgery? And if so, does preoperative repletion 2 to 3 weeks before surgery improve outcomes? These are questions stimulated by the elegant report using sophisticated statistical analyses from Outcome Researchers in the Anesthesiology Institute at Cleveland Clinic.² They conclude:

While causality cannot be determined from our retrospective analysis, the association suggests that a large prospective observational study of preoperative vitamin D concentrations and postoperative outcomes is warranted.

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Conflicts of Interest: Michael F. Roizen chairs the Scientific Advisory Board of the Martek division of DSM. Another division of DSM produces multivitamins, including vitamin D2/3. Dr. M. Roizen does not have an equity interest in DSM and has not advised them on any scientific studies relating to multi-vitamins or vitamin D2 or D3. Dr. M. Roizen also has a small but definite financial interest in the parent company, Sharecare. com, that now owns the RealAge.com website. Dr. M. Roizen does not know of any relationship of Sharecare or RealAge with a vitamin D provider or manufacturer.

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What a wimpy conclusion. The data they developed and reviewed are strong enough to deserve better than such a wishy-washy conclusion. Similarly, there are other perioperative association data to indicate that vitamin D deficiency is a potential cause of poor outcomes.^{3,4} It is time for a worthwhile double-blind, randomized, controlled trial (DBRCT) rather than just continuing to generate more associative data that point to the need for a proper study.

Why Anesthesia is A Specialty

We're not a trade or a craft that just provides more of the same and safe care, technicians could do that. We're a specialty that innovates. We are the specialty that first granted pain relief to allow surgery of >2 minutes. We are also the specialty that started intensive care units and neonatal and step down intensive care units to improve 2-month survival. Anesthesiologists started preoperative clinics to insure the patient's optimal condition to withstand the stress of surgery and improve outcomes. We are the specialty that reduced costs by reducing unnecessary perioperative testing, and that eliminated unneeded transfusions. And anesthesiology is the specialty that improves perioperative outcomes with optimal inflammation, temperature, and oxygen management. Anesthesiologists started checklists, simulation, and brought transesophageal echocardiogram and brain electricity extracts (the Bispectral Index) to the operating room to make intraoperative anesthesiology safer. In addition, our specialty is redefining how to make the intraoperative period safer with version 3.0+ IT.

These are all major steps buttressed by science. But baby steps make our science second rate. Hamilton didn't tell Gregory to study positive end-expiratory pressure in a laboratory for a decade before seeing if his tight bag could help preemies. Cahalan et al. (the older author of this editorial was one of those colleagues) didn't diddle around before determining if increasing small left ventricular volumes improves outcome, and Ebert didn't pause for 3 more years when he saw a less than perfect mitral valve repair. Let's continue to take bold steps to improve outcome. Vitamin D has enough association studies...let's determine whether vitamin D is just a fireman (showing up at every fire, but seldom causing them), or has some real fire power in improving perioperative outcomes.

We want to share some of those other association studies to indicate why we believe a DBRCT is merited.

First A Primer On the Ds

Vitamin D has classically been thought of as critical for regulating the absorption of calcium and phosphorous in our bones; recent association studies lead to thinking of D as having greater responsibility for immune signaling. All forms of vitamin D are fat soluble, but, in contrast to many other fat soluble vitamins, they do not appear just to be stored in fat depots but perhaps mainly in muscle.^{5,6}

Historically, your main source of vitamin D comes from the generation of cholecalciferol in your skin after exposure to sunlight (UVB). Since moving from the equator, diet became the critical source of vitamin D, particularly in the winter. If your skin makes it, or it is from

most animal sources in your diet, that form of vitamin D is D3 (chole-calciferol). If it is from some nonanimal sources (fungi, yeast, or some plankton), it is D2 (ergocalciferol). D2 and D3 have nearly the same effect in your body, but D3 may be a little better in the long run than D2. Both D2 and D3 are 25-hydroxylated in your liver. This 25-hydroxylated form of vitamin D (calcidiol or 25-OHD) is typically measured in your blood. Most state-of-the-art centers use mass spectrometry for its measurement, but some still use radioactive immunoassay or enzyme immunoassay. There is controversy about the interconvertability of these measures that is beyond the scope of this editorial, but the reliability of each of these is thought to be good.

Once it is 25-hydroxylated, vitamin D travels in your blood bound to its binding protein. At the kidney, it is freely filtered and then resorbed (attached to the vitamin D-binding protein). Recent cutting-edge work⁷ reports racial differences in the vitamin D-binding protein may alter concentrations of “free” vitamin D. This work, however, is controversial; it is not clear that free vitamin D is the important form. The resorbed form (25-OHD) is 1- α hydroxylated at the kidney under control of parathyroid hormone to generate 1, 25-OHD that is the active form of vitamin D. The short half-life of 1, 25-OHD precludes it from being used as a measure of vitamin D stores.

Enough Association Studies

The association vitamin D study of Turan et al.² continues a long series of association studies. Similar to other association studies, this study is bedeviled by the following problems: (a) there may be selection bias (i.e., it is not clear why vitamin Ds were obtained in these patients); (b) the population examined is a heterogeneous one, in that vitamin Ds were obtained at different times (though this drawback is also a strength in that, it shows the association is true regardless of the time of sampling, and so may not simply be an effect due to postoperative inflammation); and (c) the group with low vitamin D also had worse preoperative ASA physical status classification. Other studies have shown that higher concentrations of vitamin D (calcidiol, 25-OHD) are associated with a cornucopia of improved health outcomes. Included in this list are improved bone health, fewer falls, fewer bone fractures, reduced risk of heart attack and stroke, reduced risk of, and death from, colon, breast, and prostate cancer. In addition, increased vitamin D is associated with decreased asthma and allergies, reduced infections, inflammation, disordered sleep, lesions of multiple sclerosis, and with reduced prematurity and preeclampsia. In addition to each of these disease states, higher concentrations of vitamin D (calcidiol, 25-OHD) are associated with a 7% to 26% reduction in all-cause mortality.^a A few DBRCTs have been done for some of these conditions.

The few DBRCTs that administered vitamin D to achieve levels >20 ng/mL for bone fractures,⁸ cancer,⁹ fu prevention in kids,¹⁰ and all-cause mortality¹¹ show benefits. But the medical establishment is not yet sure of what D level your patients and you maintain, let alone enter an operating room with (either as a patient or a physician). We need to further patient care, not just advance a question.

^aAvailable at: www.consumerlab.com/results/print.asp?reviewid=vitamin_D

How Much D to Give and to Take

We do not know with certainty what level has most benefit with least harm. People with levels >20 ng/mL have fewer falls, broken bones, cancers, and deaths than people with lower levels. Some data show fewer cardiovascular events and mental dysfunction at levels >35 ng/mL, and even at 50 to 80 ng/mL. In the RealAge database (unpublished data—the elder author also has a conflict here as he founded the RealAge.com company, and still has a financial interest in the company), 99+% of North Americans got less than the Daily Value of vitamin D, and 93% of participants in the National Health and Nutrition Examination Survey¹² got less than the Estimated Annual Requirement, about 80% of Daily Value from diet. Data show that 57% of adult hospitalized patients have levels <20 ng/mL.¹³

Kidney stones and too high calcium levels do not appear to be a problem in typical patients at doses $<10,000$ IU a day or at levels <110 ng/mL. Thus, it appears to be a very minor risk to bring a preoperative patient's level to even 80 ng/mL.

We should note here that the Institute of Medicine recommends supplementing with much less than we recommend with the goal of raising the 25-OHD to >20 ng/mL.¹⁴ Their recommendations are controversial, and the Endocrine Society recommends considering doses up to, and above, 1000 IU/d with the goal of attaining a 25-OHD of >30 ng/mL.¹⁵

If we were to devise a DBRCT with limited funds, we would enroll patients with D levels under a certain number (probably 13.7 based on Turan et al.²), undergoing operations with measurable complication risks. We would enroll enough people to power the study so that a 10 ng/mL increase in 25-OHD levels would reveal a decrease in complication rates of 10% (based on Turan et al.²). We would enroll patients who were undergoing operations 18 to 24 days from their preoperative visit. We would give approximately 1000 additional IU of vitamin D (cholecalciferol) a day via injection to those randomized to treatment groups of (a) 20,000 IU on leaving the preoperative clinic for people with a body mass index (BMI) <27 , (b) 30,000 IU for people with a BMI between 27 and 31, (c) 40,000 IU for people with a BMI >31 , and (d) placebo injection for control group participants. We would remeasure vitamin D (cholecalciferol) levels in preoperative holding areas on all subjects. (We would expect some of the control group to start vitamin D after informed consent.)

If we had enough funding, we would study 3 more groups in addition to the control, (a) one with a dose of D aiming for a blood level of 20 ng/mL, (b) one for a blood level of 35 ng/mL, and (c) one for 50 ng/mL. This we believe is the proper study that would bring honor to our specialty.

What To Do Till A Study is Done

In the meantime, what we do and recommend you do is: (1) ask your doctor what your 25-OHD level is, and ask if you need more (we personally aim for 50 to 80 ng/mL, but your doctor may feel differently), (2) get more vitamin D_{2/3} in supplements if your level is <50 . Although it is hard to get from food now, salmon is a rich source: wild salmon have about 800 IU per 3 ounce serving and farm-raised salmon 250 IU per 3 ounces. In addition, most skim milks (almond and soy included) are now fortified with 120 IU per 8 ounces. So a

supplement daily and measurement of levels yearly seem reasonable (it takes 6 weeks to reach a steady-state level for even thin patients with an oral supplement).

And no matter what you decide for yourself, let us be bold (and beneficial to the rest of medicine and our patients) as a specialty

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