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A Clinical Protocol Demonstrating Rapid, Safe, and Effective Treatment of Vitamin D Deficiency: A Potential Role in Oncology Alongside Conventional Treatment

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Abstract

Vitamin D status has importance in the prevention and treatment of many malignancies. Patients with breast, colon, and lung malignancies with higher vitamin D status at the onset of treatment have an improved prognosis compared with those patients with a lower vitamin D status. Methods to improve vitamin D status are often unreliable and take time, often months, to be successful. A method that improves and normalizes the vitamin D status safely, quickly (within 1-2 weeks), and reliably is described herein. The use of this method will allow testing of the hypothesis that improving the vitamin D status of patients with various malignancies before treatment is initiated will improve their outcome.

Keywords

vitamin D, malignancies, treatment of vitamin D deficiency, vitamin D replacement therapy, vitamin D and oncology treatment

Vitamin D deficiency and insufficiency are extremely prevalent.[1-4] As measured by 25-hydroxy vitamin D (25-OH D), deficiency is defined as levels <15 ng/mL (if measured as mmol/L multiply by 2.5). Insufficiency is defined as levels <30 ng/mL. The known and hypothesized clinical consequences of this are significant because vitamin D has important effects on a wide range of physiological processes. It has long been known that inadequate vitamin D status has deleterious clinical effects on bone health. A large and growing body of studies have suggested that vitamin D has additional important effects on numerous other biologic processes, such as cell differentiation and immune system functioning.[2,3] Studies have shown that individuals with higher 25-OH D levels have a significantly lower incidence of many malignancies, autoimmune diseases, and cardiovascular diseases compared with those with less-adequate 25-OH D status.[5-9] From a related, but different perspective, intriguing studies have shown that when baseline vitamin D levels are measured in patients with numerous malignancies, including lung, colon and breast, before their oncological treatment begins, those patients with higher 25-OH D levels have improved outcomes compared with patients with the same malignancies but with lower levels of baseline 25-OH D.[10-14] This article describes a protocol that is able to safely normalize low vitamin D levels within 1 to 2 weeks with a high degree of predictability. The use of this protocol will allow the testing of the following hypothesis: if patients with various malignancies have their vitamin D deficiency corrected before formal oncological treatment begins, they will have an improved prognosis compared with patients who remain vitamin D deficient while receiving oncological treatment.

Most physicians and labs consider levels of 25-OH D ≥30 ng/mL (75 mmol/L) or higher to be normal, though some recent studies have questioned if normal is as low as 20 ng/mL. Most notable in this latter regard is the highly publicized report from the Institute of Medicine.[15] In the context of the present article, some clarifying comments about this report are in order. The authors of the report from the Institute of Medicine considered that effects of vitamin D, besides the well-known effects on bone health, were not sufficiently proven; therefore, their conclusion that normal levels should be considered to be as low as 20 ng/mL were only relevant for bone health. Suggestive extraskeletal effects of vitamin D were expressly excluded from their report and recommendations. In other words, potential effects of vitamin D status in malignancies, both regarding prevention and potential treatment, as will be discussed in this article, had no place in their report.

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Beyond the issue of what is normal, there is no consensus regarding what optimal levels are and what we should aim for in clinical practice.[16,17] Parathyroid hormone (PTH) levels (which increase with vitamin D deficiencies and lead to bone resorption and loss of calcium from the bones) are relatively elevated if 25-OH D is <30 ng/mL, often to the point of frank secondary hyperparathyroidism. Even if levels of 25-OH D are only in the mildly insufficient range, when 25-OH D status is improved to ≥30 ng/mL, PTH levels will decrease further.[18,19] After attainment of 25-OH D levels of 30 to 40 ng/mL, PTH levels plateau, and the rate of bone reabsorption is normalized. Further increases of 25-OH D status do not continue to lower PTH levels. 25-OH D levels of 30 to 40 ng/mL are, therefore, from this perspective, considered adequate for bone health.[1-3] However, determining optimal levels is not as clear regarding other extraskeletal effects of vitamin D, for instance, in its association with a decreased prevalence of various malignancies.[1] Studies with breast and colon cancer suggest that higher levels of 25-OH D (beyond 30-40 ng/mL) might confer additional protection.[17,20] Though controversy exists, some physicians consider that optimal levels in particular clinical situations, such as treating patients with malignancies and autoimmune diseases, might be between 40 and 60 ng/mL.[21] Attempts to attain these levels are very safe because there appears to be a wide range of safety between these levels and those considered to be toxic (at least 100 ng/mL for extended periods of time).[4]

Typical methods used to clinically correct vitamin D deficiencies take months and are not consistently effective.[4,22,23] It is generally considered that 25-OH D levels will increase by 1 ng/mL for every 100 IU of vitamin D given orally over extended periods of time.[24] This is, however, a statistical average, and in practice, many patients do not respond as the statistics might predict. If routine approaches are not successful, a commonly used treatment method is to prescribe 50 000 IU of oral vitamin D2 weekly over 8 to 16 weeks. This method, while safe, is also not successful for many patients.[22] Other published methods, such as giving a loading dose of 100 000 to 200 000 IU for 1 day, followed by daily doses of 800 IU, or giving 50 000 IU daily for 10 days are only partially successful.[23,25,26] It is also difficult to raise 25-OH D levels into the range of 40 to 60 ng/mL with these methods of supplementation. A method developed by Reid is of particular relevance to the present article.[25] In this study, 3 protocols were explored. One group received a single loading dose of 500 000 IU of vitamin D. The second group received the loading dose and then an additional 50 000 IU monthly. The third group received 50 000 IU monthly but no loading dose. The groups receiving the loading dose of 500 000 IU had normalization of 25-OH D levels within 1 month, which was maintained at a higher level by the group receiving an additional 50 000 IU monthly. The group that did not get the loading dose only reached normalization at 3 to 5 months. The similarity of these results to the present study will be addressed in the discussion section.

Patients newly diagnosed with malignancies need oncological treatment initiated in a timely manner, often within weeks. The results of all the above methods of correcting vitamin D deficiency, except the method developed by Reid, have significant limitations when rapid normalization is needed. These methods are also frequently not successful in attaining levels of at least 30 to 40 ng/mL. Some studies show that if patients with malignancies begin active oncological treatment when they have higher 25-OH D levels, they have a better outcome than those who begin oncological treatment with less optimal vitamin D status.[10-14] The exact mechanisms behind these results are not known. Benefit might occur because of an immediate interaction between vitamin D and the active treatment (surgery, radiation, and chemotherapy) at the time these treatments are administered. Another possibility is that the presumed long-term increased 25-OH D status correlates with improved general health, and this improved general health status is what leads to the better outcome. Despite the uncertainty as to the exact mechanism, it is reasonable to hypothesize that if vitamin D-deficient/insufficient patients with colon, lung, or breast cancer could have this deficiency/insufficiency rapidly corrected before treatment begins, their prognosis might be improved. It was with this group of patients in mind that the following study was performed.

Methods

A retrospective chart review revealed that from January 2008 until January 2009, 50 unselected patients in the author's private practice, located near Philadelphia, Pennsylvania, had 25-OH D levels checked as part of routine evaluations. All the assays were performed by Quest Laboratories. If baseline 25-OH levels were <30 ng/mL, they received oral doses of vitamin D3 (given as a liquid preparation where 1 drop = 2000 IU) according to the following schema, where "deficient" patients had values <15 ng/mL and "insufficient" patients had levels ≥15 ng/mL but <30 ng/mL.

1. Deficient: day 1, 300 000 IU in 3 divided doses; day 2 and after, 4000 IU/daily
2. Insufficient: day 1, 150 000 IU in 3 divided dose; day 2 and after, 4000 IU/daily

After establishment of the baseline 25-OH D levels, at 1 and 2 weeks after the beginning of treatment, the following labs were drawn: 25-OH D and calcium.

Patients were questioned regarding any adverse symptoms concurrent with or for a few months after the vitamin D replacement treatment. The study was reviewed and

approved by the institutional review board of the Lankenau Institute for Medical Research.

Results

Group 1 (Deficient)

There were 18 patients in this group; baseline values ranged from 4 to 14 ng/mL, with 8/18 <10 ng/mL. Most patients in this group had initial measurements taken between January and April, when less sun exposure would be expected to lead to decreased levels. After treatment, 11/18 patients had labs drawn 1 and 2 weeks after the loading doses; 7/18 patients only had labs drawn 1 week after the loading dose. The 3 highest posttreatment values of 25-OH D were 81, 76, and 70 ng/mL; the 3 lowest values were 20, 28, and 28 ng/mL. Also, 16/18 (89%) patients attained levels >28 ng/mL (ie, essentially in the normal range); 10/18 patients attained levels >40 ng/mL.

1. Mean 25-OH D at baseline, 9 ng/mL (range = 4-14 ng/mL)
2. Mean 25-OH D at week 1, 41 ng/mL (range 19 - 76)
3. Mean 25-OH D at week 2, 41 ng/mL (range 20 - 81)

After week 1, patients had received a total of 328 000 IU of vitamin D3, with an average increase of 1.17 ng/mL 25-OH D for each 10 000 IU vitamin D3 given. This is shown in Figure 1.

Group 2 (Insufficient)

There were 32 patients in this group; 16 of them had labs drawn 1 and 2 weeks after treatment, whereas 16/32 only had labs drawn 1 week after treatment The 3 highest levels of 25-OH D attained were 75, 74, and 66 ng/mL. The 3 lowest values were 23, 23, and 28 ng/mL. Of 32 patients, 29 (89%) patients attained levels >29 ng/mL by 2 weeks, with 20/32 (63%) attaining levels >40 ng/mL.

1. Mean 25-OH D at baseline, 22 ng/mL (range)
2. Mean 25-OH D at week 1, 44.5 ng/mL (range 38 - 75)
3. Mean 25-OH D at week 2, 43 ng/mL (range 23 - 74)

After week 1, patients had received a total of 178 000 IU of vitamin D3, with an average increase in 25-OH D level of 1.36 ng/mL for each 10 000 IU vitamin D3 given.

None of the 50 patients developed hypercalcemia. No clinical adverse effects were reported. Because this was a retrospective chart review study, levels of PTH were not measured because this is not standard clinical practice. It would be expected that at least some of the patients in the frank deficiency states of <15 ng/mL had probably developed secondary hyperparathyroidism. This would likely have been normalized with the vitamin D replacement regimen.

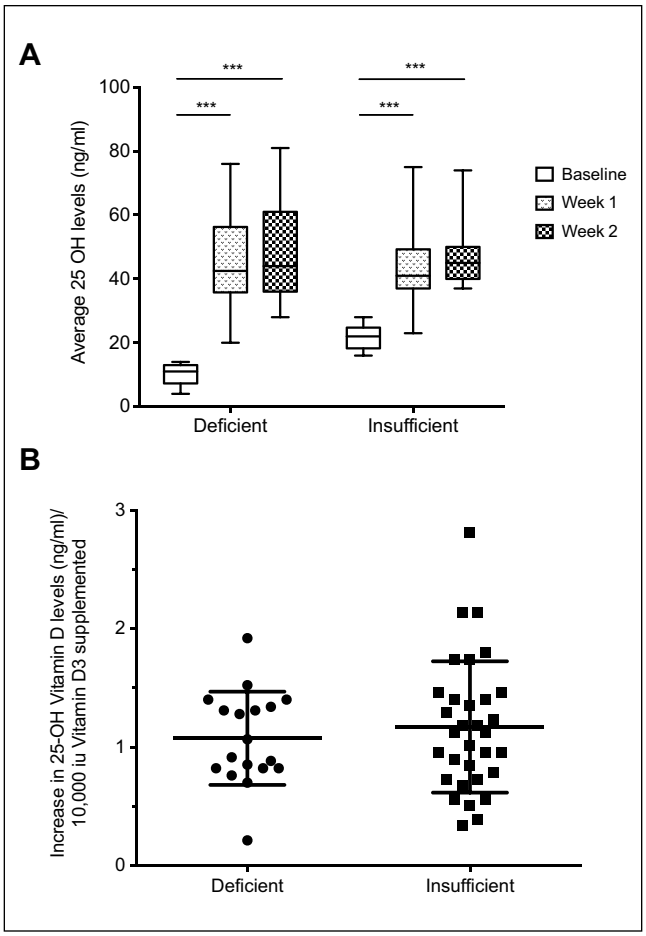

Figure 1. A: Represents patients with low vitamin D (left, deficient; right, insufficient) at baseline, after 1 week, and after 2 weeks of replacement. The range of values as well as the mean value is represented. ***$P < .001$ as determined by Student's 2-tailed *t* test. B. Represents the increase in 25-hydroxy vitamin D (25-OH vitamin D) levels per each 10 000 units of vitamin D3 replacement over a 2-week period. The range of values as well as the mean value is represented.

Discussion

This study demonstrates that within a short span of 1 to 2 weeks, and with a very high degree of efficacy and safety, vitamin D levels (measured as 25-OH D) can be normalized in patients with varying ranges of vitamin D insufficiency/deficiency. The average posttreatment levels were in the range of 40 to 45 ng/mL, a range with no known toxicities,

and considered normal. The highest level was 81 ng/mL, well below levels of toxicity, and no patient reported adverse symptoms. Of the 50 patients with levels below 29 ng/mL, 90% achieved normal vitamin D status in 1 week, with an average level of about 43 ng/mL. In addition, all patients remained in the normocalcemic range. The potential for developing hypercalcemia was of concern. A similar study by Reid where a cohort of patients was treated with a high loading dose (500 000 IU of D3) followed by monthly maintenance doses also noted that no patient developed hypercalcemia.[25] The corroboration of our experience in this regard is reassuring.

This supplementation method differed from most known clinical approaches and from all previously published studies known to the author, in that it individualized the replacement dose depending on the baseline vitamin D levels.[4,22,23] As an average, across all baseline levels, after 2 weeks, there was an increase of 1.29 ng/mL for each 10 000 IU vitamin D3 supplemented. Although not studied formally, the great majority of patients who remained on 4000 IU/d and had levels checked months later remained in a range similar to their 1- and 2-week measurements). Although the groups were divided into <15 ng/mL and ≥15 ng/mL but <30 ng/mL, further individualization of dosing could be applied. For instance, if the baseline were 20 ng/mL and the goal was approximately 50 ng/mL, 300 000 IU (which would include a loading dose and then a daily maintenance dose over a 2-week period) might accomplish this, whereas if the baseline were 25 ng/mL, 250 000 IU could be chosen.

A few words should be mentioned about the similarity to a previous study by Reid. In that study,[25] there was one cohort with a similar treatment method. They gave this cohort, irrespective of their baseline 25-OH D levels, a loading dose of 500 000 IU, followed by a monthly maintenance dose of 50 000 IU. The patients in our study who had initial 25-OH D levels <15 ng/mL received a loading dose of 300 000 IU with an additional 120 000 IU for the first month, given as a daily dosage of 4000 IU. The Reid study only reports results at 1 month, and the levels attained as a whole are very similar to ours (120 mmol/L, equivalent to 48.5 ng/mL, which might reflect their higher dose for the first month)

There are numerous clinical and research applications of this study. As mentioned above, various studies have suggested that patients with lung, colon, and breast malignancies have improved clinical outcomes if their baseline 25-OH D levels are higher at the time of the initial treatment. In these studies, it is of interest to note that even among those who had improved clinical outcomes, most did not even attain 30 ng/mL, which most physicians consider the beginning of the normal range, and therefore remained vitamin D insufficient.[10-14] It is reasonable to hypothesize that if vitamin D deficient patients could raise their levels to at least the normal range (≥30 ng/mL) before active treatment began, they might fare better than a similar group who remained in a deficient state. Many of these patients require urgent, nonelective treatment, so that waiting months until vitamin D status improved would clearly not be appropriate. The method of supplementation described in this article allows rapid increase of levels, so that they will have normal, and possibly more optimal, vitamin D levels at the time of treatment. This will allow us to test this hypothesis.

There are other clinical situations where rapid normalization of vitamin D status could be beneficial. One group consists of elderly, frail patients at a high risk of fractures.[26] Vitamin D has also been shown to lessen bronchospasm and improve reactive airway treatment outcomes.[27] A clinical approach of rapidly improving 25-OH D levels along with conventional anti-inflammatory and antispasmodic treatment might lead to improved clinical outcomes in this group of patients. Vitamin D has been shown to have beneficial effects in autoimmune diseases.[7,8] Acute flares of illnesses such as rheumatoid arthritis, inflammatory bowel disease, or multiple sclerosis might be affected by the use of vitamin D, along with the usual anti-inflammatory and immunomodulatory treatments. Supplementation with vitamin D has been shown to decrease the incidence of influenza A.[28, 35] There might be a protective effect against other pathogens. Patients who are at increased risk of infection, such as those undergoing chemotherapy or with altered immune function (such as transplant patients), might benefit from rapid normalization of vitamin D status.[29,30] These clinical benefits are hypothetical at present but can be tested using this supplementation method.

Most of these patients remained on 4000 IU of vitamin D3 daily. In the ensuing months, subsequent measurements of 25-OH D showed that all patients remained in normal ranges. If the levels approached 70 to 80 ng/mL, dosages would be lowered to 2000 IU/daily. No patient developed laboratory or clinical toxicity. All patients used a liquid preparation, where 1 drop = 2000 IU, allowing them to take the initial high loading dose easily. Of interest, patients occasionally misunderstood instructions, and instead of taking a drop, took a dropper (about 20 drops or 40 000 IU). Their levels, after a few months, were between 90 and 110 and returned to normal on withholding the supplement; they then started taking vitamin D on normalization of levels. No patient developed any clinical toxicity.

Certain concerns should be raised. An article by Sanders et al[31] treated elderly patients at risk of fracture with a single high loading dose of vitamin D and unexpectedly found a higher rate of falls and fractures. The mechanism behind this is not known but was commented on in the editorial accompanying the article.[32] The commenting authors speculate that the patients treated with the high loading dose might have experienced an improvement in their clinical

status and were, therefore, more active. It was also noted that no maintenance dose of vitamin D was supplied after the initial loading dose, which might have had effects leading to the increased fracture incidence. The specific reasons remain unknown, and future studies need to consider this potential adverse outcome.

Another concern was raised in the article by Helzlsouer and Gallicchio.[33] They raise the issue that most substances have a normal range, with toxicity if levels go both above and below this range. Their comments speculate about an increase in certain malignancies if levels exceed the normal range. Though this might turn out to be true regarding vitamin D levels, and the author of this article agrees with the general thrust of their argument, for the purposes of the present article, the levels attained in the present study fall well within what is considered normal.

Most studies looking at the association between vitamin D levels and prognosis of malignancies have looked at the level of 25-OH D levels at the time of diagnosis. An example is a recent meta-analysis of patients with early-stage breast cancer showing a strong association of 25-OH levels at the time of diagnosis with both recurrence and survival (hazard radio of 2.13 and 1.76, respectively).[34] Vitamin D is associated with sun exposure; therefore, many patients with improved vitamin D status will have been more active, likely exercise outdoors more, and are likely in a better state of overall health compared with patients with suboptimal vitamin D status. It has therefore been considered by some that the reason these patients have an improved prognosis is because of their better overall health. On the other hand, vitamin D has well-known and wide-ranging effects on factors such as cell differentiation and immune status. The present study will allow us to look at improving 25-OH D status postdiagnosis by a specific intervention. This will allow us to look more closely at the specific effect of vitamin D status, separating it from its presumed association with general health status.

This retrospective chart review, performed in a busy internal medicine practice by one practitioner, limited itself to only a few measurements. Retrospective chart reviews have limitations and strengths. Limitations include incomplete data. This is illustrated in the above study by the fact that only about 50% of patients had follow-up 25-OH D levels drawn in both week 1 and 2. In addition, other related markers, such as PTH, 1-25OH D, vitamin D receptors, and so on, were not investigated. Retrospective chart reviews can be very helpful in generating hypotheses that can be more formally tested in further studies, including randomized, double-blind studies. There was no control group in the above study, and no statistical analysis was performed, but the improved levels of 25-OH D are so clear and marked that they are unlikely to have occurred by chance. Further studies can show if these results can be replicated and attain statistical significance.

One important issue is the optimal level of 25-OH D to be aimed for. Articles show that levels of 25-OH D in patients with malignancies who had an improved prognosis tended to be in the high 20 to 30 ng/mL range. It is speculated, but certainly not known, whether higher levels, such as 30 to 60 ng/mL will lead to improved prognosis. Because of the consistency and predictability of results, a lower loading dose could be administered if the aim is to attain levels lower than 40 to 45 ng/mL, the average posttreatment levels of the patients in this study.

Vitamin D has been largely looked at from an epidemiological perspective. Supplementation studies, when done, have required many months to affect levels and, even then, have often been with inadequate doses. The success rate of these other methods is less than optimal. The method discussed here, if confirmed by other studies, will allow us to rapidly, safely, and with a high level of success correct vitamin D deficiencies/insufficiencies. It will also allow us, in many clinical situations, to study patients after achieving an improved and normal vitamin D status, and because their treatment will often need to be given urgently, they will be able to attain this status within 1 to 2 weeks.

Declaration of Conflicting Interests

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