Vitamin D deficiency in the oncology setting

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Background Vitamin D deficiency is common in the United States. Regardless of whether or not vitamin D deficiency increases the risk of cancer and decreases survival of cancer, the established adverse impact of its deficiency on bone health is of particular concern for cancer patients. The extent of vitamin D deficiency is not well defined in the oncology setting, and there are no standardized protocols for screening and supplementation for individuals found to be deficient in vitamin D.
Objective To determine the prevalence of vitamin D deficiency as measured by levels of serum 25-hydroxyvitamin D (25[OH]D) in cancer patients at an outpatient oncology practice.
Methods A total of 177 patients representing a range of oncologic diagnoses were tested for 25(OH)D between January 1, 2011 and December 31, 2011. Suboptimal vitamin D levels were defined either as less than 20 ng/mL or less than 30 ng/mL, according to standards proposed by the Institute of Medicine and the Endocrine Society, respectively.
Limitations The point of testing was subjective to the clinician. Some patients may have had their vitamin D levels tested and treated elsewhere, therefore that data was not captured.
Results At baseline, 18.1% of patients tested had vitamin D levels of less than 20 ng/ml, and 49.1% of patients had vitamin D levels of less than 30 ng/ml. Follow-up rates were low. In all, 54% of patients with 25(OH)D levels of less than 30 ng/ml obtained a second reading, and only 38% of those patients achieved sufficient levels at the second reading.
Conclusion Vitamin D deficiency is prevalent in patients with cancer and should be monitored in patients who are at high risk for vitamin D deficiency or poor bone health.

The overall objective of this project was to analyze the vitamin D status of patients representing a variety of oncology diagnoses in an urban outpatient practice to determine the prevalence of vitamin D deficiency and to assess efficiency of repletion through supplementation in this setting. Vitamin D was also analyzed in terms of season, gender, race, diagnosis, and the age of the patient when the blood was tested. The prevalence of vitamin D deficiency in this population was compared with generally recognized rates of vitamin D deficiency, which may aid in determining if a practice protocol is warranted.

About vitamin D

Mechanism of action

Vitamin D, a fat-soluble substance, is not a vitamin in the traditional sense because the human body has the ability to synthesize it when the skin absorbs ultraviolet B (UV-B) radiation. Most of the circulating vitamin D in our bodies – up to 90% – comes from exposure to sunlight, with a small amount obtained through diet and supplements.[1,2,3] When exposed skin is irradiated by UV-B, 7-dehydrocholesterol, a hormone precursor, is converted to vitamin D.[4,5] The liver then hydroxylates most of the vitamin D to produce 25-hydroxyvitamin D (25[OH]D), which is currently the best measure of vitamin D stores in the body.[4,6,7] 25(OH)D is activated by 25(OH)D-1α-hydroxylase, an enzyme found in most tissues, to produce 1,25-dihydroxyvitamin D ($1,25(OH)_2D$),[4,5] which is the active metabolite that aids in calcium absorption and bone metabolism.[5,7] After binding to the vitamin D binding protein, $1,25(OH)_2D$ enters the cell and binds the vitamin D receptor, which allows for transcription and translation of proteins.[5]

Effects of vitamin D deficiency

Vitamin D deficiency is associated with numerous diseases, including rickets, osteomalacia, bone fractures, hyperparathyroidism, bone resorption, multiple sclerosis, and diabetes Type I[1,5,8] and can present with fatigue and weakness, or people may be asymptomatic.[8] Vitamin D deficiency may also be associated with multiple cancers. This

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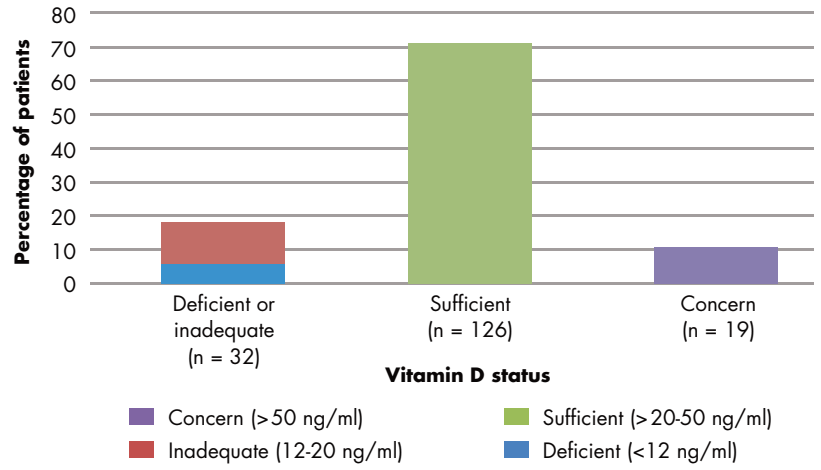

FIGURE 1 Vitamin D status in an outpatient oncology setting – IOM standards

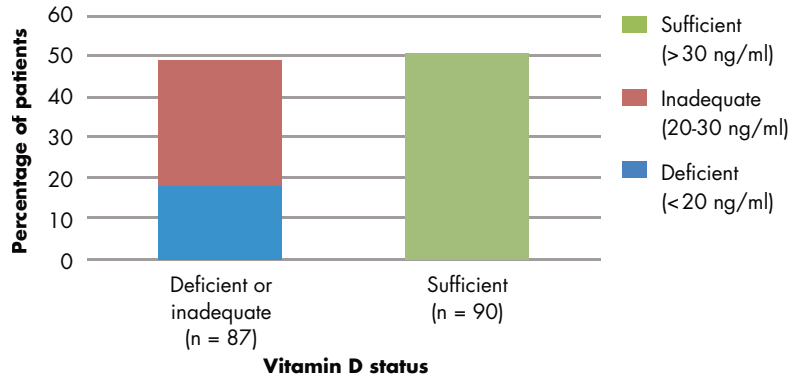

FIGURE 2 Vitamin D status in an outpatient oncology setting – Endocrine Society standards

is plausible because the active metabolite of vitamin D, 1, 25(OH)$_2$D, has been shown to have anticancer effects such as cell cycle arrest, induction of apoptosis, and inhibition of proliferation.[5,9,10,11]

Measuring vitamin D status

There is no direct way to measure the amount of vitamin D in the body because the physiologically active metabolite of vitamin D has a relatively short half-life. In contrast, its hydroxylated form, 25(OH)D has a half-life of 2-3 weeks and therefore has been widely accepted as the best measure of serum vitamin D levels.[12] Cut-off levels for vitamin D deficiency have been variably defined.

The Institute of Medicine (IOM) defines vitamin D deficiency relative to bone health at serum 25(OH)D levels below 12 ng/ml, inadequacy at 25(OH)D levels between 12 and 20 ng/ml, and sufficiency at levels of at least 20 ng/ml (Table 1). The IOM concludes that levels of about 30 ng/ml are not consistently associated with increased benefit, and levels above 50 ng/ml are a cause for concern. The Endocrine Society provides a different set of cut-off points (Table 2). In a 2012 report, the society defined vitamin D deficiency as a 25(OH)D level below 20 ng/ml, the minimum level to prevent rickets and osteomalacia. The society further specifies inadequacy at levels of 21 to 30 ng/ml, and sufficiency as levels of at least 30 ng/ml; the minimum level to maximize vitamin D's effect on calcium, bone, and muscle metabolism. The society also finds that levels above 20 ng/ml may have additional health benefits, such as reducing the risk of common cancers. It states there is no evidence that there is a downside to increasing vitamin D intake, except for those who have a chronic granuloma-forming disorder or lymphoma.

Prevalence of vitamin D deficiency

The reported prevalence of vitamin D deficiency will vary depending on the parameters used to assess vitamin D status. The IOM determined that the extent of vitamin D deficiency in North America may be overestimated due to use of inflated cut-off points by laboratories. However, data from the National Health and Nutrition Examination Surveys 2001-2006 shows that about 33% of the US population had 25(OH)D levels lower than 20 ng/ml, which is categorized as inadequate by the IOM or deficient by the Endocrine Society. It is estimated that 30%-50% of healthy adults in the United States are vitamin D deficient (25(OH)D levels, < 20 ng/ml).[9] The incidence of vitamin D deficiency for men is about 25%, and for women, 35%.[13] Another study found that over 75% of community-dwelling adults over the age of 65 are deficient.[1] Risk factors of vitamin D deficiency include dark skin, increased body-mass index, older age, and sun avoidance behaviors, including the use of sun screen.[1,3] A large population-based study in the United States found that 42% of African American women were vitamin D deficient.[8] It is clear that vitamin D deficiency is, at the very least, an endemic problem.

Vitamin D and cancer

While there is strong evidence supported by both the Institute of Medicine and the Endocrine Society that vitamin D is essential for skeletal health, there has been much debate about the potential influence of vitamin D on non-skeletal outcomes and overall mortality. Numerous observational studies have indicated that optimal vitamin D status is linked to positive effects on health, including reduced cancer risk and recurrence, and improved prognosis. The link between vitamin D and cancer first emerged when researchers found an inverse relationship between sun exposure and colorectal cancer risk.[14] Since then, in vitro studies have elu-

cidated a mechanism by which vitamin D may act to reduce cancer risk. Many normal and neoplastic cells possess the enzyme required to convert the serum-circulating form of vitamin D into its active form, which then binds to vitamin D receptors that regulate the transcription of genes involved in proliferation, such as p21 and p27, differentiation, apoptosis, angiogenesis, and adhesion.[15] Treatment of cancer cells in culture with vitamin D resulted in slowed proliferation and enhanced differentiation and sensitivity to apoptosis of cancer cells, providing evidence for a cancer protective role of vitamin D, with the strongest evidence involving colorectal cancer cells,[16,17] followed by breast cancer[18,19?] then prostate cancer.[20,21]

Vitamin D deficiency in the oncology setting

Regardless of whether vitamin D prevents cancer or decreases mortality, the relatively high frequency of vitamin D inadequacy in the United States and the adverse impact of many cancer treatments on bone health makes assessment of vitamin D deficiency in an oncology setting of particular importance.[22] All oncology therapies that induce hypogonadism may cause osteoporosis. This may occur in the context of hormone-dependent tumors such as breast and prostate cancer, in which hypogonadism is often part of the treatment plan. Hypogonadism may also occur as an undesired effect of tumor therapy in nonhormone-dependent malignancies. Sex hormones play a fundamental role in maintaining bone mass.[23,24] Thus, postmenopausal women are at increased risk of bone loss because of estrogen deficiency, which can be further accelerated by the use of estrogen-depleting therapies such as aromatase-inhibitors that are often used in breast cancer treatment.[25] This increased risk for bone loss is not limited to older women. Ovarian insufficiency generally develops within 1 year of chemotherapy in 63%-96% of premenopausal women with breast cancer.[26] These patients experience decreases in estradiol and increases in follicle-stimulating hormone similar to those observed in postmenopausal women. Among 35 women defined as having chemotherapy-induced ovarian failure, researchers observed highly significant bone loss in the lumbar spine by 6 months and the loss had increased further at 12 months.[27] Calcium and vitamin D supplementation have been shown to significantly reduce vertebral fractures and may be used to treat therapy-induced osteoporosis.[26,28] In addition, a recent study shows that improved vitamin D status using supplementation is associated with the attenuation of aromatase-inhibitor associated bone loss. They also suggest a threshold 25(OH)D level of 40 ng/ml after 3 months of supplementation is a reasonable target to achieve the protective effects of vitamin D on bone loss.[29] Another study of breast cancer patients receiving treatment found that supplementation with 2,000 IU (the tolerable upper intake level as defined by the IOM) a day of vitamin D failed to normalize 25-OH levels in 50% of participants.[30] Thus, Khan and Fabian[31] suggest that all individuals who initiate therapy that can impact bone mineralization, including premenopausal women undergoing chemotherapy or medical or surgical ablation and postmenopausal women beginning aromatase-inhibitor therapy, be screened for baseline vitamin D levels.

As with estrogen-suppressing therapy in breast cancer, androgen-suppressive therapy is often used in patients with prostate cancer. Androgen withdrawal in men can have deleterious effects on bone mass.[32] Maillefert and colleagues[33] observed a 7.1% decrease in bone mineral density in the lumbar spine and a 6.6% decrease in the femoral neck within 18 months of therapy.

In the absence of chemotherapy-induced hypogonadism, patients may still experience vitamin D deficiency. Khan and Fabian[31] suggest screening individuals who are at high risk for deficiency. These individuals include the elderly, the darkly pigmented, and those who have osteoporosis or osteopenia, avoid any sun exposure without sunscreen, are typically veiled, live in a highly polluted environment, or have Crohn's disease.

Oncology patients may also be more susceptible to vitamin D deficiency due to insufficient dietary intake, malnutrition, and being homebound because of fatigue and a poor performance status. Despite the established adverse effects of vitamin D deficiency on bone health for cancer patients, the extent of vitamin D deficiency in an oncology setting is not well documented, and there are currently no standardized protocols outlining when to screen individuals for vitamin D deficiency in an oncology setting and the action to be taken thereafter.

Methods

Data collection and analysis

We used available electronic medical record information to compile data on 25(OH)D levels in outpatient oncology patients for the year 2011. Results were transferred to a Microsoft Excel spreadsheet substituting patient name identification with a numeric identifier. Other participant data including date of visit(s), age, gender, race, diagnosis, and presence or absence of metastasis was also documented. Physicians' notes were examined to check recommendations and supplementations. Data was categorized according to Institute of Medicine and Endocrine Society standards for deficiency, inadequacy, or sufficiency and compared. The percentage of vitamin D-deficient patients was calculated and stratified by age, gender, disease, and time of year and compared to established deficiency rates.

Participant inclusion criteria

A retrospective electronic medical record review of outpatients at a community medical oncology practice was conducted. In all, 177 outpatients who had a blood test for vitamin D between January 1, 2011 and December 21, 2011 were included. Patients who were tested at least once

TABLE 1 Vitamin D status – IOM standards

	No. of patients	Deficient, < 12 ng/ml; %	Inadequate, 12-20 ng/ml; %	Sufficient, 20-50 ng/ml; %	Concern, >50 ng/ml; %
Season					
Fall	28	0.00	10.71	71.43	17.86
Winter	76	6.58	21.05	67.11	5.26
Spring	30	16.67	6.67	70.00	6.67
Summer	43	0.00	2.33	79.07	18.60
Sex					
Male	48	8.33	18.75	68.75	4.17
Female	129	4.65	10.08	72.09	13.18
Race					
African American	32	6.25	18.75	68.75	6.25
Asian	4	0.00	25.00	75.00	0.00
Latino	6	0.00	16.67	83.33	0.00
White	135	5.93	10.37	71.11	12.59
Age range, y					
20-59	83	7.23	15.66	63.86	13.25
60+	94	4.26	9.57	77.66	8.51
Diagnosis					
Breast	99	6.06	8.08	75.76	10.10
MLL	20	0.00	20.00	65.00	15.00
Sarcoma	11	18.18	9.09	72.73	0.00
Gynecologic	7	0.00	57.14	14.29	28.57
Head & neck	20	0.00	15.00	70.00	15.00
Other	7	14.29	0.00	85.71	0.00
Esophageal/gastric	4	0.00	50.00	25.00	25.00
Lung	6	0.00	0.00	100.00	0.00
Pancreatic	3	33.33	0.00	66.67	0.00
Mets/nonmets					
Mets	38	10.53	13.16	68.42	7.89
Nonmets	139	4.32	12.23	71.94	11.51

for serum-circulating levels of 25(OH)D were stratified by vitamin D status using cut-off levels recently defined by the IOM and the Endocrine Society (ES): deficient (< 12 ng/ml and < 20 ng/ml, respectively), inadequate (12-20 ng/ml and 20-30 ng/ml), sufficient (> 20 ng/ml and > 30 ng/ml), and above limit (> 50 ng/ml, IOM only). For subsequent visits, the change in vitamin D levels will be noted and compared with documented recommendations for treatment intervention.

Results

Vitamin D at baseline

Most of the 177 outpatients who were tested for vitamin D levels were aged 60 years or older (n = 94, 53.1%; median age, 61 years). Forty-eight patients (27%) were men, and 129 (73%) were women. Most – 135 (76%) – were white and had been diagnosed with breast cancer (n = 99, 55.9%). The median serum-circulating 25(OH)D level was 30.3 ng/ml, and the mean was 31.5 ng/ml. According to IOM standards, upon initial visit, 32 (18.1 %) patients were deficient (10 patients, 5.6%) or inadequate (22 patients, 12.4%), 126 (71.2%) patients were sufficient, and 19 (10.7%) patients were above the revised upper limits for serum 25(OH)D levels (Figure 1). According to ES standards, upon initial visit, 87 (49.2%) patients were deficient (32 patients, 18.1%) or inadequate (55 patients, 31.1%), and 90 (50.9%) patients were sufficient (Figure 2). Vitamin D status by season, age, gender, diagnosis, and presence or absence of metastasis according to both IOM and ES standards is presented in Tables 1 and 2, respectively. Seasons

were classified as fall (September-November), winter (December-February), spring (March-May), and summer (June-August).

Vitamin D deficiency or inadequacy was more common among patients who were tested during the winter or spring (59.2%, 56.7% by ES standards, respectively) compared with other seasons. Higher prevalence of vitamin D deficiency or inadequacy was also found among men compared with women, and among Asians or African Americans compared with other races. Of the African American individuals, 25% were vitamin D deficient or inadequate according to IOM standards, and 56.3% were vitamin D deficient or inadequate according to ES standards. Higher prevalence of suboptimal levels was also found for patients with ovarian, cervical, or uterine cancer, esophageal and gastric cancer, and sarcoma, and for patients with metastasis compared to patients without metastasis. Esophageal and gastric cancer patients had the highest prevalence of suboptimal vitamin D (≤ 30 ng/ml) at 75%, though the small sample size may not have provided adequate statistical power. Patients with sarcoma were found to have the lowest average 25(OH)D levels (24.5 ng/ml). Patients with lung cancer were found to have the highest average 25(OH)D levels (35.1 ng/ml). In breast cancer patients, 14.1% were characterized as having suboptimal vitamin D levels according to IOM standards (< 20 ng/ml), while that number increased to 44.4% when using ES standards (< 30 ng/ml). In colon cancer patients, 14.3% were characterized as vitamin D insufficient according to IOM standards, but again, that number increased to 57.1% when the cut-off level for insufficiency was defined as 30 ng/ml rather than 20 ng/ml.

TABLE 2 Vitamin D status – Endocrine Society standards

	No. of patients	Deficient, < 20 ng/ml; %	Inadequate, 21-30 ng/ml; %	Sufficient, > 30 ng/ml; %
Season				
Fall	28	10.71	25.00	64.29
Winter	76	27.63	31.58	40.79
Spring	30	23.33	33.33	43.33
Summer	43	2.33	32.56	65.12
Sex				
Male	48	27.08	31.25	41.67
Female	129	14.73	31.01	54.26
Race				
African American	32	25.00	31.25	43.75
Asian	4	25.00	50.00	25.00
Latino	6	16.67	33.33	50.00
White	135	16.30	30.37	53.33
Age range, y				
20-59	83	22.89	28.92	48.19
60+	94	13.83	32.98	53.19
Diagnosis				
Breast	99	14.14	30.30	55.56
MLL	20	20.00	40.00	40.00
Sarcoma	11	27.27	45.45	27.27
Gynecologic	7	57.14	14.29	28.57
Head/neck	20	15.00	20.00	65.00
Other	7	14.29	42.86	42.86
Esophageal/gastric	4	50.00	25.00	25.00
Lung	6	0.00	33.33	66.67
Pancreatic	3	33.33	33.33	33.33
Mets/nonmets				
Mets	38	23.68	34.21	42.11
Nonmets	139	16.55	30.22	53.24

Vitamin D at first follow-up

Twenty-three patients were instructed to supplement with vitamin D. Sixty-eight (38.4%) patients were retested at least once within the year period. Of the 32 patients categorized as deficient or inadequate according to IOM standards at baseline reading, 20 (62.5%) patients were retested, and 11 (55%) patients had improved 25-OH-D concentration to sufficient levels at the time of the second reading. Of the 87 patients categorized as deficient or inadequate according to ES standards at baseline reading, 47 (54%) were retested, and 18 (38.3%) patients were sufficient at the time of the second reading.

Discussion

Our data show that nearly 20% of patients had serum-circulating vitamin D levels less than 20 ng/ml, a level considered inadequate for ensuring bone health by the Institute of Medicine. An additional 31% of patients had levels between 20 and 30 ng/ml, a level that the Endocrine Society considers insufficient for bone health. These lev-

TABLE 3 Endocrine Society's recommended protocol for vitamin D supplementation[a]

Patient characteristics	Recommendation
Routine supplementation	
19-65 years old	600 IU/day
65 years and older	800 IU/day
Obese or on medications	1,500-2,000 IU/day
Repletion with deficiency	
Younger than 18 years*	50,000 IU once a week for 6 weeks or 6,000 IU daily Retest to achieve 30 ng/ml, then 600-1,000 IU/day maintenance
Adults	50,000 IU once per week for 8 weeks or 6,000 IU daily Retest to achieve 30 ng/ml then 1,500-2,000 IU/day maintenance
Obese, malabsorption syndromes, or on medications	6,000-10,000 IU Retest to achieve 30ng/ml then 3,000-6,000 IU/day maintenance

[a]For the patients identified at risk or previously deficient, annual testing is recommended.

els indicate a higher vitamin D level than the estimated national frequency of vitamin D deficiency.

Recommended practices

There are several clinical implications of this work. First, the disparity between the recommendations of the Institute of Medicine and the Endocrine Society presents a dilemma when deciding how to address vitamin D monitoring. The oncology population may have a marginal food intake that leaves them at nutritional risk, be homebound due to the ill effects of treatment, and/or be at risk of falls and experience muscle weakness (a prominent symptom of vitamin D deficiency), so our practice has chosen the more stringent of the 2 guidelines. Screening of all patients with cancer is not recommended. This study highlights the need to test serum 25(OH) D levels in patients with cancer who are at risk for deficiency. According to the Endocrine Society's clinical guidelines, this would include patients of African American or Hispanic descent, those with osteomalacia or osteoporosis (or at risk for developing because of the therapies), malabsorption syndromes (such as pancreatic insufficiency or radiation enteritis), various medications (glucocorticoids, antiseizure or HIV medication,) as well as older patients (65 years and older) with a history of fall or nontraumatic fractures and patients with a BMI of more than 30 kg/m^2.

These data also highlight the need for a follow-up protocol after identification of vitamin D insufficiency, given the poor retesting follow-up rate (54%) that we observed. The efficacy of vitamin D supplementation in patients with suboptimal serum vitamin D levels should also be monitored. Our data also suggest that vitamin D insufficiency is prevalent in patients with gynecologic, esophageal, and gastric cancers and sarcoma, however this may be due to the low sample size and we recommend testing based on the above at risk guidelines. Our results suggest that testing 25(OH) D levels in late winter or early spring will provide an estimation of the lowest levels of vitamin D over the course of a year.

According to the Endocrine Society's recommendation, the following protocol will be used for vitamin D supplementation (Table 3). Further study is needed to determine the appropriate guidelines in the oncology population. As work in the area of cancer and vitamin D deficiency progresses, this most likely will be a changing landscape. In the meantime, best practice guidelines is unfortunately, left ambiguous. If not addressed, patients may take it upon themselves to self medicate. In this oncology practice, the above guidelines will be implemented and evaluated to efficacy and revised as needed.

This study highlights the need to test serum 25(OH)D levels in patients with cancer. It also highlights the need for a follow-up protocol upon identification of vitamin D insufficiency, as a poor follow-up rate was observed. The efficacy of vitamin D supplementation in patients with suboptimal serum vitamin D levels should also be monitored. Vitamin D insufficiency is prevalent in this population and should be routinely assessed, especially in breast and prostate cancer patients at high risk for bone loss caused by treatment-induced hypergonadism. Our data also suggests that vitamin D insufficiency should be assessed in patients with ovarian, cervical, or uterine cancers, esophageal and gastric cancers, and sarcoma, as high prevalence of vitamin D insufficiency for these groups was observed in this study. Our results suggest that testing 25(OH)D levels in late winter or early spring will provide an estimation of the lowest levels of vitamin D over the course of a year.

Conclusion

About 49.1% of patients seen at an outpatient oncology practice had suboptimal or deficient (< 30 ng/ml) serum-circulating concentrations of 25-hydroxyvitamin D. Optimal levels of serum vitamin D are critical for maintenance of good bone health, and thus the relatively high prevalence of vitamin D deficiency in the oncology setting highlights the need for standardized screening and supplementation protocols. Some studies have associated suboptimal vitamin D levels with poor prognosis. The relatively high prevalence of suboptimal vitamin D levels in this population makes further research in this area of paramount importance.

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