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# Preliminary Report: Vitamin D Deficiency in Advanced Cancer Patients with Symptoms of Fatigue or Anorexia

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## ABSTRACT

***Background.*** **Vitamin D deficiency in noncancer patients is associated with symptoms of fatigue, muscle weakness, and depression. These symptoms are common among advanced cancer patients. We investigated the prevalence of low serum vitamin D levels in cancer patients with fatigue or poor appetite and their association with symptom burden and other correctable endocrine abnormalities.**

***Methods.*** **This was a retrospective review of 100 consecutive cancer patients with appetite or fatigue scores of ≥4 of 10 referred to a supportive care clinic. We investigated serum levels of 25(OH) vitamin D, cortisol, thyroid-stimulating hormone, and bioavailable testosterone. Symptoms were measured by the Edmonton Symptom Assessment Scale. Serum 25(OH) vitamin D <20 ng/mL was considered deficient; ≥20 ng/mL and <30 ng/mL were considered insufficient.**

***Results.*** **Patients were predominantly male (68%) and white (66%), with a median age of 60 years (range, 27–91 years). Gastrointestinal (30%) and lung (22%) cancers were predominant. Forty-seven patients (47%) were vitamin D deficient and 70 (70%) were insufficient. Thirteen of 70 patients (19%) with vitamin D insufficiency were on supplementation. Vitamin D deficiency was more common among nonwhites (82% versus 36%) and females. No significant association was found between vitamin D and symptoms. Hypogonadic males had a significantly lower mean 25(OH) vitamin D level than eugonadic males.**

***Conclusions.*** **Low vitamin D levels were highly prevalent among advanced cancer patients with cachexia or fatigue. Vitamin D deficiency was more frequent among nonwhite and female patients. Vitamin D levels were also significantly lower in male patients with hypogonadism.** ***The Oncologist*** 2011;16:1637–1641

## INTRODUCTION

Among noncancer patients, vitamin D deficiency is associated with joint pain, muscle weakness [1, 2], cognitive changes, and depression [3]. Although these symptoms are frequently found among advanced cancer patients, there are limited data on the association between vitamin D deficiency and other endocrine abnormalities among these patients.

Fatigue and anorexia/cachexia often occur together in patients with cancer [4]. Because these symptoms may share

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common underlying mechanisms, an effective therapy might alleviate more than one symptom simultaneously. Additionally, patients with fatigue and poor appetite may be at greater risk for vitamin D deficiency/insufficiency because of lower exposure to sunlight and/or low oral intake and a reduced ability to absorb dietary vitamin D. Consequently, we investigated the association of vitamin D deficiency and symptoms as well as other potentially correctable endocrine and laboratory abnormalities among ambulatory advanced cancer patients with moderate to severe symptoms of poor appetite and fatigue.

## Methods

We performed a retrospective chart review, which was approved by the MD Anderson Institutional Review Board. In total, 100 consecutive cancer patients referred by their primary oncologists with moderate to severe symptoms including fatigue or poor appetite were evaluated in the Supportive Care Clinic at the University of Texas MD Anderson Cancer Center during January 2009 to December 2010. As a part of a standardized evaluation of all patients referred to our clinic, symptom intensity was measured by the Edmonton Symptom Assessment Scale (ESAS). The ESAS is a validated assessment tool quantifying a patient's response to 10 common symptoms in the past 24 hours, including pain, fatigue, nausea, depression, anxiety, sedation, shortness of breath, appetite, sleep, and sense of well-being [5]. Symptoms are scored for intensity at 0 (best) to 10 (worst). All patients had an ESAS score ≥4 for appetite or fatigue prior to their laboratory tests.

The standardized evaluation of these patients with fatigue or appetite scores ≥4 also included the following laboratory tests—serum 25(OH) vitamin D, bioavailable testosterone (males only), thyroid-stimulating hormone (TSH), and a.m. cortisol. Serum 25(OH) D was measured by chemiluminescent immunoassay (DiaSorin Liaison 25 OH Vitamin D TOTAL Assay, DiaSorin Corporation, Stillwater, MN). Although there is controversy regarding the optimal serum level of vitamin D, we used common cutpoints for vitamin D deficiency and insufficiency: <20 ng/mL and <30 ng/mL, respectively [6]. A consensus regarding the cutpoint of serum testosterone that defines testosterone deficiency for adult males is not established [7]. However, age-associated testosterone deficiency is characterized by symptoms and a deficiency in serum testosterone levels below the young healthy adult male reference range [8]. Because the reference range for bioavailable testosterone (BT) using mass spectrometry and the ammonium precipitation method (Mayo Clinic, Rochester, MN) for men aged 30–39 years is 72–235 ng/dL, we used a cutoff of 70 ng/dL BT as our definition for testosterone deficiency.

Demographic information was collected on age, gender, race, primary cancer diagnosis, Zubrod performance scale, and medications (opioids, megestrol acetate, corticosteroids, and chemotherapy within 3 months of laboratory assessments).

Data were summarized using descriptive statistics and 95% confidence intervals. Spearman's correlation was used to determine associations between laboratory abnormalities and symptom burden. Two-sample *t*-tests were used when the data were approximately normally distributed, the Wilcoxon two-sample test was used if the data were skewed, and $\chi^2$ tests were used for dichotomous variables. A two-sided *p*-value <.05 was considered statistically significant.

**Table 1.** Patient demographics and clinical characteristics of advanced cancer patients with fatigue or cancer cachexia

| Clinical characteristic | *n* of patients (%)[a] (*n* = 100) |
|---|---|
| Median age (range) | 60 (27–91) |
| Race | |
| White | 66 (66) |
| Nonwhite | 34 (34) |
| African American | 18 (18) |
| Hispanic/South American | 9 (9) |
| Asian-Pacific Islander | 4 (4) |
| East Indian | 3 (3) |
| Male gender | 68 (68) |
| Primary tumor | |
| Gastrointestinal | 31 (31) |
| Lung | 22 (22) |
| Head and neck | 13 (13) |
| Genitourinary | 8 (8) |
| Breast | 5 (5) |
| Hematologic | 4 (4) |
| Gynecological | 3 (3) |
| Other | 14 (14) |
| ESAS, mean (±SD) | |
| Pain | 3.8 (±2.7) |
| Fatigue | 5.4 (±2.7) |
| Nausea | 1.6 (±2.2) |
| Depression | 2.7 (±2.5) |
| Anxiety | 2.7 (±2.7) |
| Drowsiness | 3.4 (±2.8) |
| Appetite | 5.1 (±2.8) |
| Well-being | 4.9 (±2.4) |
| Dyspnea | 2.7 (±2.9) |
| Sleep | 4.4 (±2.7) |
| Zubrod performance status score | |
| 0 | 5 (5) |
| 1 | 38 (38) |
| 2 | 37 (37) |
| 3 | 20 (20) |
| Chemotherapy within 3 months | 69 (69) |

[a]Unless otherwise specified.
Abbreviations: ESAS, Edmonton Symptom Assessment Scale; SD, standard deviation.

**Table 2.** Clinical characteristics of cancer patients with vitamin D deficiency (<20 ng/mL) and vitamin D insufficiency (<30 ng/mL)

| Patient characteristic ($n = 100$) | Vitamin D <20 ng/mL | Vitamin D ≥20 ng/mL | *p*-value | Vitamin D <30 ng/mL | Vitamin D ≥30 ng/mL | *p*-value |
|---|---|---|---|---|---|---|
| Percentage of patients (95% CI) | 47% (37%–57%) | 53% (42%–63%) | | 70% (60%–79%) | 30% (21%–40%) | |
| Median age (range), yrs | 60 (27–82) | 61 (29–91) | 0.99 | 58.5 (27–82) | 63 (29–91) | .32 |
| Race, *n* (%) | | | | | | |
| White, $n = 66$ | 24 (51) | 42 (79) | <0.01 | 42 (60) | 24 (80) | .05 |
| Nonwhite, $n = 34$ | 23 (49) | 11 (21) | | 28 (40) | 6 (20) | |
| Gender, *n* (%) | | | | | | |
| Male, $n = 68$ | 27 (57) | 41 (77) | 0.03 | 46 (66) | 22 (73) | .45 |
| Female, $n = 32$ | 20 (43) | 12 (23) | | 24 (34) | 8 (27) | |
| Patients on vitamin D supplementation, *n* (%) | 7 (15) | 21 (40) | 0.01 | 13 (19) | 15 (50) | <.01 |
| Mean (SD) vitamin D dose, IU | 571 (454) | 1,095 (1,214) | 0.28 | 646 (530) | 1,240 (1,372) | .15 |

Abbreviations: CI, confidence interval; SD, standard deviation.

## Results

Baseline characteristics of the patients are summarized in Table 1. The median age was 60 years (range, 27–91 years). The majority of patients were male ($n = 68$, 68%) and white ($n = 66$, 66%). The most common cancer types were gastrointestinal ($n = 31$, 31%) and lung ($n = 22$, 22%).

Forty-seven patients (47%) had 25(OH) vitamin D levels <20 ng/mL and 70 patients (70%) had levels <30 ng/mL (Table 2). Compared with whites, among whom 36% (24 of 66) were vitamin D insufficient (<30 ng/mL), vitamin D insufficiency was significantly more common among nonwhites (28 of 34, 82%)—African Americans, 16 of 18 (84%); Hispanics, nine of nine (100%); East Indian or Middle Eastern patients, two of three (67%); and Pacific Islanders, one of three (33%) ($p = .02$). Only 13 of 70 patients (19%) with vitamin D insufficiency were currently on vitamin D supplementation (Table 2). Vitamin D deficiency was statistically less common in males than in females ($p = .03$); however, vitamin D insufficiency had no correlation with gender (Table 2).

Vitamin D levels were correlated with total serum calcium (Spearman's $\rho = 0.31$; $p < .01$) and serum albumin (Spearman's $\rho = 0.23$; $p = .02$) (Table 3). The correlation between serum vitamin D and serum calcium was no longer significant when calcium was corrected for low albumin (Spearman's $\rho = 0.08$; $p = .49$) (Table 3). No significant correlation was noted between vitamin D and symptoms as measured by the ESAS, the Zubrod performance scale, or chemotherapy. Thirteen of 99 patients (13%) had biochemical hypothyroidism (TSH >5.5 mU/mL), and of the patients not receiving megestrol acetate or corticosteroids, none were noted to have a suppressed a.m. cortisol level (<4 μg/dL) diagnostic for hypoadrenalism.

Among 39 male patients taking strong opioids (morphine equivalent daily dose, >0), vitamin D levels were positively associated with bioavailable serum testosterone levels (Spearman's $\rho = 0.31$; $p = .07$) (Table 3). Fifty-two of 61 male patients (85%) were hypogonadic (bioavailable testosterone <70 ng/dL). Hypogonadic males had a median 25(OH) vitamin D level of 21.5 ng/mL (interquartile range [IQR], 16 ng/mL) versus 29.2 ng/mL (IQR, 25 ng/mL) for males with testosterone levels ≥70 ng/dL ($p = .05$) (Table 4).

**Table 3.** Spearman correlation between vitamin D and endocrine abnormalities in advanced cancer patients

| Laboratory Abnormality | Spearman's ρ | *p*-value |
|---|---|---|
| Testosterone,[a] $n = 61$ | 0.24 | .08 |
| Patients not on strong opioids, $n = 22$ | 0.14 | .57 |
| Patients on strong opioids, $n = 39$ | 0.31 | .07 |
| Calcium | 0.31 | >.01 |
| Albumin | 0.21 | .02 |
| Corrected calcium | 0.08 | .49 |

[a]Excluding patients on megestrol acetate or corticosteroids.

**Table 4.** Relationship of cancer patients with hypogonadism and vitamin D deficiency (<20 ng/mL)

| Male patients with bioavailable testosterone, $n = 61$ | Bioavailable testosterone <70 ng/dL ($n = 52$) | Bioavailable testosterone ≥70 ng/dL ($n = 9$) | *p*-value |
|---|---|---|---|
| Vitamin D <20 ng/mL, *n* (%) | 24 (46) | 3 (33) | .48 |
| Mean (IQR) level of serum 25(OH) vitamin D, ng/dL | 21.5 (16) | 29.2 (25) | .05 |

Abbreviation: IQR, interquartile range.

## Discussion

Advanced cancer patients referred to our supportive care clinic for symptoms of fatigue or poor appetite have a high prevalence of vitamin D deficiency (47%) and insufficiency (70%). Vitamin D deficiency was significantly more common in nonwhites patients, females, and hypogonadal men.

Other authors have reported vitamin D deficiency among cancer patients, although the prevalence in ambulatory patients with advanced cancer is not well documented [9, 10]. A small study of 41 inpatient palliative care patients [11] reported that 88% had low vitamin D levels. In a large, heterogeneous population of new or previously treated cancer patients, vitamin D insufficiency was found in 75% of patients [12]. We found similar rates of vitamin D insufficiency (70% of patients with levels <30 ng/mL), and although 28% of patients were on some form of supplementation, inadequate levels of vitamin D were found among 46%. Not surprisingly, those patients on higher replacement doses of vitamin D had higher serum vitamin D levels. Whether patients were not prescribed vitamin D or were not compliant with recommendations for replacement or the dose of vitamin D supplementation prescribed was inadequate is unclear [12]. The type of cancer may play a role, because, in a recent study, prostate and lung cancer patients were more likely to respond to oral vitamin D supplementation after 8 weeks (levels >32 ng/mL) than were patients with colorectal and pancreatic cancers. Those authors suggested that the gastrointestinal toxicity (stomatitis and diarrhea) associated with chemotherapy for colorectal cancer may result in poor absorption of vitamin D [9].

Nonwhites in the U.S. are at greater risk for vitamin D deficiency for a variety of reasons, including skin pigmentation and dietary differences [13]. UVB light at wavelengths of 290–315 nm converts 7-dehydrocholesterol to previtamin $D_3$ in the skin and then immediately to vitamin $D_3$ in a heat-dependent process. Because few foods (except for oily fish) contain significant amounts of vitamin D, and supplemented foods (e.g., milk, margarine, orange juice) have very modest levels, patients may be unable to maintain adequate levels of vitamin D through diet alone [6]. Consistent with many other studies, we found a higher prevalence of vitamin D deficiency among females. Although this gender difference is often interpreted to reflect the greater outdoor exposure of males, this explanation seems unlikely in the setting of patients with advanced disease. We speculate that this gender difference may be related to the positive correlation observed between serum 25(OH) vitamin D and serum testosterone. Conversely, this may be a chance finding because the number of female patients ($n = 32$) was small.

Interventions such as increasing exposure to natural light or oral vitamin D supplementation could maintain adequate vitamin D levels; however, prospective studies are needed to determine their efficacy in cancer patients. A recent study with geriatric nursing home residents reported that weekly exposure to UVB lamps after showering resulted in a significant increase in serum levels of 25(OH) vitamin D [14]. Although sunlight exposure is an inexpensive and effective therapy [15, 16], a cluster randomized controlled trial in the elderly reported poor adherence to the intervention [17]. Many [18–20], but not all [21], observational studies show associations between higher serum 25(OH) vitamin D levels and better survival outcomes in cancer patients, but a survival benefit from vitamin D replacement has yet to be observed in intervention studies.

We found that low vitamin D levels were moderately associated with lower bioavailable testosterone levels in patients on potent opioids (Table 3). Low testosterone levels could be a potential mechanism underlying the association of vitamin D deficiency with fatigue and poor muscle strength. A recent study of men referred for coronary angiography noted that vitamin D levels had a positive association with testosterone levels [22]. Notably, in a placebo-controlled trial among overweight, otherwise healthy men, vitamin D replacement over a period of 1 year significantly increased testosterone levels [23]. In patients with cancer, chronic use of opioid analgesics can result in low testosterone [24], and in combination with low vitamin D levels this could predispose patients to loss of muscle mass and increase the insulin resistance associated with cancer cachexia [25] or obesity. Both vitamin D [26] and testosterone [27] supplementation have been reported to increase insulin sensitivity in selected noncancer populations.

Our study noted an association between vitamin D and albumin, which could be related to poor nutritional status or the metabolic derangements associated with advanced cancer. A lower albumin level has frequently been reported in association with a poor prognosis in cancer patients [28], and whether or not vitamin D has additional prognostic value needs to be examined.

There were no significant correlations between vitamin D levels and symptoms as measured by the ESAS, the Zubrod performance scale, or chemotherapy, which may be attributed to the highly selected nature of our patient cohort. All our clinic patients who underwent laboratory testing for vitamin D deficiency had appetite or fatigue scores of moderate to severe intensity (≥4 on the ESAS). Because of the strong bias in this select group of highly symptomatic patients, future studies should compare groups by including advanced cancer patients with a lower symptom burden. If, however, hypovitaminosis D is truly not associated with a symptom burden, this may explain why health care providers fail to identify patients with vitamin D deficiency.

Limitations of our study include the retrospective nature of the data collection and the lack of measurements of function or muscle strength. A small pilot study of 21 inpatient hospice patients showed an association between vitamin D deficiency and greater functional impairment [29], and a randomized trial of vitamin D supplementation in elderly women showed improved lower limb muscle strength and mobility [30]. Many studies in the elderly [31–33], but not all [34], demonstrate a beneficial effect of vitamin D supplementation in reducing the incidence of falls. One study reported that higher physiological testosterone levels in older men and women may protect against falls, and that the benefit may be additive in those taking vitamin D supplementation [35]. In critically ill patients, a single oral ultrahigh dose of 540,000 IU cholecalciferol corrected vitamin D deficiency within 2 days without causing hypercalcemia [36]. Because vitamin D and testosterone

replacement are relatively inexpensive and could improve symptoms, function, and quality of life, prospective intervention studies in patients with cancer are warranted.

## Conclusions

Vitamin D deficiency was highly prevalent and largely untreated in advanced cancer patients with cachexia or fatigue. Low levels of vitamin D were more frequent among nonwhites and male patients with hypogonadism. No association was noted between a low vitamin D level and symptom burden. Further studies examining the potential benefits of vitamin D supplementation on functional status, including testosterone levels, among patients with advanced cancer are warranted.

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Rony Dev and Egidio Del Fabbro share first authorship.

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## Author Contributions

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