Vitamin D Deficiency: A Common Occurrence in Both High-and Low-energy Fractures

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Abstract As a consequence of newly elevated standards for normal vitamin D levels, there is a renewed interest in vitamin D insufficiency and deficiency (<32 and <20 ng/ml, respectively) in the orthopedic patient population. This study tests the hypothesis that vitamin D insufficiency is comparably prevalent among both high- and low-energy fracture patients. A retrospective analysis of the medical records for 44 orthopedic trauma in-patients with non-vertebral fractures was conducted from June 1, 2006 to February 1, 2007. The obtained data included a 25-hydroxyvitamin D level, age, gender, and reason for admission; high-energy vs. low-energy fracture. Vitamin D insufficiency, 25(OH)D <32 ng/ml, was found in 59.1% of the patients. Significantly, more women (75%) than men (40%) were vitamin D insufficient among all fracture patients and specifically among high-energy fractures, 80% women insufficient vs. 25% men insufficient. In women, both high- and low-energy fractures present with vitamin D insufficiency (80% of high-energy fractures and 71.4% of low-energy fractures). In men, the mean vitamin D level was lower for low-energy fractures (16 ng/ml) compared to high-energy fractures (32 ng/ml). In addition, men with low-energy fractures were significantly older than men with high-energy fractures and women with low-energy fractures were also older. Statistically, more vitamin D insufficiency is seen in women and our results are

consistent with the gender difference seen in the general population. Even among younger men who sustain a high-energy fracture, 25% are vitamin D insufficient. Women with fractures regardless of age or fracture energy level have low vitamin D levels. Levels of 25(OH)D should be measured in all orthopedic trauma patients and the American Society for Bone and Mineral Research and National Osteoporosis Foundation currently recommend that vitamin D levels should be corrected.

Keywords vitamin D · 25(OH)D · fracture · vitamin D insufficiency · vitamin D deficiency

Introduction

Vitamin D insufficiency is an underrecognized problem in adults in the United States. National population statistics from the 3rd National Health and Nutrition Examination Survey (NHANES III) indicate that 41% of men and 53% of women in the United States have hypovitaminosis D [28]. Forty-one percent of adult outpatients have also been found to be vitamin D insufficient [16].

Vitamin D influences skeletal integrity through its effect on Ca homeostasis [9, 29]. Vitamin D aids in the prevention of fractures by maintaining bone mineral density as well as muscle strength [2, 6, 19, 25]. Supplementation with vitamin D and calcium is standard for the treatment and prevention of osteoporosis [3, 20]. Due to the high cost of osteoporotic fractures, there is a clear cost-effective benefit of calcium and vitamin D supplementation for those with a known risk, elderly individuals with calcium and/or vitamin D deficiency [15, 27]. We investigated whether patients with fractures sustained from high- or low-energy impacts have comparable risks for vitamin D insufficiency.

Level of evidence: level IV

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Multiple studies have shown a high prevalence of vitamin D deficiency among various subgroups of patients; postmenopausal women [7, 12, 14, 15, 17], general medical in-patients [24], and geriatric patients [5, 10, 11, 18, 21]. The prevalence of vitamin D insufficiency among male and female orthopedic patients with fractures has been limited to low-energy fractures [1, 22]. Given vitamin D's multitude of positive effects on bones and muscular function, its importance to patients who have undergone traumatic injury to the bones may be critical. What is the prevalence of vitamin D insufficiency, defined as a serum level of 25(OH)D below 32 ng/ml, among both high- and low-energy fracture patients? How does gender influence vitamin D insufficiency in fracture patients? What is the relationship between age and 25(OH)D level for high-energy fracture patients compared to low-energy fracture patients?

Patients and methods

This institutional review board approved retrospective review analyzed 44 orthopedic trauma in-patients admitted from June 1, 2006 to February 1, 2007 for fracture care. The 44 patients comprised a consecutive series of patients seen by one physician on the metabolic bone disease team. As standard protocol, all patients admitted to the trauma service at this hospital were seen by both the orthopedic trauma service and the metabolic bone disease team. This standard of care was established based on an increased awareness of vitamin D deficiency and osteoporosis seen in orthopedic arthroplasty patients [7]. Patients were included if they sustained a documented fracture, had a 25-hydroxyvitamin D level drawn after surgery in the hospital, and were greater than or equal to 18 years of age. Patients were excluded if they had any known risk factors for vitamin D deficiency, such as renal insufficiency (as indicated by a creatinine level of ≥ 2 mg/dl), malabsorption, gastrectomy, active liver disease, acute myocardial infarction, alcoholism, anorexia nervosa, or steroid dependency. In this study, the 25(OH)D metabolite was used as a measurement of vitamin D status. Although calcitriol (1,25-dihydroxyvitamin D) is the most potent vitamin D metabolite, the metabolite 25(OH)D provides a more accurate account of vitamin D status [9, 20, 26, 29]. Serum 25(OH)D levels were measured through the use of liquid chromatography/mass spectrometry.

Age, gender, and type of fracture were recorded for each patient. This study included a total of 44 patients, 45.5% men ($n=20$) and 54.5% women ($n=24$). The mean age for all patients was 59 ± 20 years, range 19–95 years. The mean age for men was younger at 51 ± 21 years than for women, which was 66 ± 17 years ($p=0.02$). The fractures were classed as low-energy fracture vs. high-energy fracture. Low-energy fractures were defined as fractures sustained from a fall of standing height or less, while high-energy fractures resulted from a fall greater than standing height or a motor vehicle impact.

Univariate analysis was run on all variables; means, standard deviations, medians, frequencies, etc., as appropriate. All demographic and clinical variables were assessed

statistically for an association with the occurrence of vitamin D depletion. Differences between groups were assessed using the Student's *t* test for normally distributed data, and the Mann–Whitney test for non-parametric data. Categorical data were analyzed using a two-tailed Fisher's Exact test. Alpha was set to 0.05. The results reported here are not adjusted for multiple comparisons due to the small sample size, but was powered to test the concept of vitamin D deficiency. Data analysis was conducted using SPSS version 14 (SPSS Inc., Chicago, IL) and StatXact v7 (Cytel, Cambridge, MA).

Results

This study showed that there was a high prevalence of vitamin D insufficiency among fracture patients on the orthopedic trauma service, not limited to only low-energy fractures. We found vitamin D insufficiency, 25(OH)D < 32 ng/ml, in 59.1% (26/44) of the patients. The mean 25(OH)D was $30 \text{ ng/ml} \pm 13$ and the median was 29.5 ng/ml (Fig. 1).

The women in this series were more likely to be vitamin D insufficient than the men, ($p=0.03$). Seventy five percent (18/24) of women and 40% (8/20) of men were vitamin D insufficient. Specifically, this gender difference was seen within the high-energy fracture group in which significantly more women (80%, 8/10) than men (25%, 4/16) were vitamin D insufficient ($p=0.01$; Table 1a). There was a

Fig. 1. Vitamin D levels in this patient population sorted by patient gender

higher prevalence of vitamin D insufficiency in low-energy fractures (77.8%, 14/18) vs. high-energy fractures (46.2%, 12/26) when both sexes were combined ($p=0.06$). There was no significant difference between vitamin D insufficiency among men vs. women with low energy fractures, ($p=0.5$) as 100% (4/4) of men and 71.4% (10/14) of women were insufficient ($p=0.5$; Table 1b). In the women in this sample, both high- and low-energy fractures present with comparable vitamin D insufficiency: 80% (8/10) and 71.4% (10/14), respectively ($p=0.999$). In men, significantly more vitamin D insufficiency was seen in low energy fractures vs. high energy fractures: 100% (4/4) vs. 25% (4/16), respectively ($p=0.01$; Table 1c). In men, the median vitamin D level was significantly lower for low energy fractures (19.5 ng/ml) compared to high energy fractures (34 ng/ml; $p=0.007$).

Overall, the low energy fracture group (mean 71 years) was significantly older than the high-energy fracture group (mean 51 years; $p<0.001$). In addition, men with low energy fractures were significantly older (mean 73 years) than men with high-energy fractures (mean 46 years; $p=0.02$) (Table 2a). Women with low-energy fractures (mean 71 years) were older than those with high-energy fractures (mean 58 years; $p=0.053$). For women, there was no difference in the median vitamin D level for high-energy fractures (27 ng/ml) vs. low energy fractures (28 ng/ml; $p=0.7$) (Table 2b). The mean 25(OH)D level for women and men by fracture type is shown in Fig. 2. Women showed a significant correlation between age and 25(OH)D ($\rho=0.46$; $p=0.2$). Older women had higher values of 25(OH)D than younger women. For men, there was no significant correlation between age and 25(OH)D ($\rho=-0.2$; $p=0.2$) (Fig. 3).

Discussion

In the present study, a high percentage (59%) of adult fracture patients were vitamin D insufficient, defined as a serum 25(OH)D level less than 32 ng/ml. Our results are consistent with data from previous studies indicating that low-energy fracture patients are often associated with vitamin D insufficiency [1, 22]. The present study also

Table 2 Age and 25(OH)D level vs. fracture etiology

	Low-energy fractures	High-energy fractures	<i>p</i> value
a. Men			
Age ^a	72.5±16	45.9±19	0.02 ^c
25(OH)D ^b	19.5	34	0.007 ^d
b. Women			
Age ^a	71.1±14	57.8±18	0.053 ^c
25(OH)D ^b	28	27	0.7 ^d

^a Mean age in years ± standard deviation

^b Median 25(OH)D ng/ml

^c *p* values were calculated using the *t* test

^d *p* values were calculated using the Mann–Whitney test

demonstrated a large subset of high-energy fracture patients who were also vitamin D insufficient. Though one may not have previously suspected vitamin D insufficiency in a patient that sustained a high-energy fracture, this study indicates that any fracture patient has a considerable risk for vitamin D insufficiency, not just low-energy fractures in the common osteoporotic sites. The influence of vitamin D insufficiency on muscle strength and bone health may be increasing the fracture risk among both high- and low-energy impacts.

This study had several limitations. Our study was limited to a small sample size, and the 25(OH)D levels were drawn after surgery since this test was ordered as postoperative fracture care. The differences between vitamin D insufficiency (25(OH)D <32 ng/ml) and vitamin D deficiency (25(OH)D <20 ng/ml) could not be assessed due to the small sample size. Also, the quality vs. quantity of bone could not be assessed in this retrospective review. In addition, we included patients into this study irrespective of their previous treatment history of calcium and/or vitamin D. The benefit of including all these patients was to report the prevalence of vitamin D insufficiency among fracture patients, regardless of whether they were replete due to prior supplementation. The disadvantage is that some patients may have been on supplementation prior to their fracture and the length of time on treatment and how it correlated to their 25(OH)D level and bone health was not assessed.

A standard vitamin D treatment protocol was used to treat all patients identified with vitamin D insufficiency. The protocol consisted of 50,000 IU of vitamin D2 given at varying frequencies depending on the severity of insufficiency. Patients with 25(OH)D levels in the range of 25–35 ng/ml were treated with 50,000 IU of vitamin D2 monthly for 2 months; 25(OH)D levels in the range of 15–25 ng/ml were treated with 50,000 IU every other week for a total of 8 weeks. Patients with 25(OH)D levels less than 15 ng/ml were treated with 50,000 IU weekly for 8 weeks, in addition to vitamin D3 1,200 IU maintenance daily. All vitamin D insufficient patients were either treated with this protocol and followed by the metabolic bone disease team or the treatment protocol was recommended to their primary

Table 1 Vitamin D status vs. gender

	Men	Women	Men vs. Women <i>p</i> value ^a
a. High-energy fractures			
Replete ^b	12	2	0.01
Deficient ^c	4	8	
b. Low-energy fractures			
Replete ^b	0	4	0.5
Deficient ^c	4	10	
c. High-energy fractures vs. low-energy fractures <i>p</i> value ^a	0.01	0.999	

^a *p* values were calculated using the Fisher's Exact test

^b ≥32 ng/ml

^c < 32 ng/ml

Fig. 2. Vitamin D level vs. fracture type. With regard to high-energy fractures, women had a mean 25(OH)D of 27.9 ng/ml $\pm$ 4.4 and men had a mean 25(OH)D of 32.4 ng/ml $\pm$ 1.9. Within the low-energy

fracture group, women had a mean 25(OH)D of 32.1 ng/ml $\pm$ 4.4 and men had a mean 25(OH)D of 16.5 ng/ml $\pm$ 4.3

medical physician for continued follow-up. There was no standardized treatment protocol for replenishing vitamin D at the time of this study but the treatment protocol used was agreed upon by expert consensus from the metabolic bone disease team at this hospital.

The exact definition of vitamin D deficiency is a topic of much debate; however, recent studies suggest that serum 25(OH)D levels need to be 32 ng/ml to achieve sufficiency and optimal bone health [8]. Expert consensus from the

2006 American Society for Bone and Mineral Research Meeting on Contemporary Diagnosis and Treatment of Vitamin D Related Disorders revealed that the optimum level for 25(OH)D is greater than or equal to 32 ng/ml. While deficiency is considered below 20 ng/ml, 25(OH)D levels below 32 ng/ml are classified as insufficient. Low values of 25(OH)D cause secondary hyperparathyroidism. As 25(OH)D levels rise to 25 ng/ml, the parathyroid hormone (PTH) value correlates to a "high normal" level;

Fig. 3. Vitamin D level vs. age. Women illustrated a significant correlation of increasing 25(OH)D levels with increasing age, $\rho=0.46$; $p=0.02$. Men did not demonstrate a significant correlation of 25(OH)D level with age, $\rho=-0.2$; $p=0.2$

however, further increasing the value of 25(OH)D to 32 ng/ml can continue to lower the PTH level. It is at 32 ng/ml that the PTH level plateaus as 25(OH)D increases and further increases in 25(OH)D no longer decrease the level of PTH [4, 23].

Previous studies have shown a decrease in fracture incidence following vitamin D supplementation. A randomized double-blind controlled trial of 100,000 IU oral vitamin D₃ (cholecalciferol) supplementation vs. placebo given every 4 months for 5 years revealed a 22% reduction for any first fracture and a 33% reduction for a first fracture in the common osteoporotic sites: hip, wrist or forearm, or vertebral fracture [25]. This demonstrates the profound benefits of vitamin D on fracture prevention and conversely indicates that its insufficiency may increase the fracture risk.

Prior investigations into the prevalence of vitamin D deficiency have revealed subgroups of patients at risk for vitamin D deficiency. Among inpatients in a general medical hospital the prevalence of vitamin D deficiency was found to be 57% [24]. Osteoarthritis was once thought to be protective for osteoporosis and correlated with elevated bone mineral density. A study of postmenopausal women undergoing total hip arthroplasty for osteoarthritis, however, revealed that osteoporosis was seen in 25% of these patients, and vitamin D deficiency was seen in 22% [7]. The majority of the group with vitamin D deficiency did not have low bone mineral density.

A study examining the vitamin D and PTH level of postmenopausal women with hip fractures, compared to postmenopausal women admitted for elective joint replacement, found that 50% of postmenopausal women with hip fractures had occult vitamin D deficiency and 37% had elevated PTH levels [12]. These results revealed lower vitamin D levels and higher PTH levels among the hip fracture group compared to non-osteoporotic and osteoporotic elective joint replacement group. Thus, the subset of fracture patients limited to postmenopausal women with hip fractures demonstrated lower levels of vitamin D compared to non-fracture patients with osteoporosis.

Our results indicate that among fracture patients, women (75% insufficient) have a higher prevalence of vitamin D insufficiency than men (40% insufficient). A woman with a fracture, regardless of age or fracture etiology, has a high likelihood of vitamin D insufficiency. Older women in this study actually demonstrated higher values of 25(OH)D than younger women. It is widely accepted, based on public health observations, that older women have a greater risk for vitamin D deficiency. Vitamin D typically decreases with age due to decreased synthesis in the skin and decreased renal production of 1,25(OH)D, as well as social changes that reduce the time generally spent in the sun and the variety of diet [13, 18]. The results of our study indicate that among women with fractures, young women and older women are both at risk for vitamin D insufficiency. One explanation for the observation in this study that vitamin D levels increase with age in women may be due to the fact that older women are more often tested and treated for vitamin D deficiency and osteoporosis than both younger women and men.

Though men had less vitamin D insufficiency than women, their vitamin D status should not be ignored. All of the low-energy male fracture patients were vitamin D insufficient and 25% of the high-energy fracture patients were vitamin D insufficient. The men with high-energy fractures were generally young (mean age 46 years) and had no prior reason to be suspected for vitamin D insufficiency; however, 25% of these patients were in fact vitamin D insufficient. The men from this group that were insufficient (mean age 49 years) were not significantly older than those who were replete (mean age 45 years). Therefore, even young men with high-energy fractures should be tested for vitamin D insufficiency to assess bone health.

In summary, adult fracture patients are at risk for vitamin D insufficiency regardless of fracture energy type. Women with fractures have a higher rate of vitamin D insufficiency than men. Both men and women with low-energy fractures were older than the men and women with high-energy fractures, but only men showed lower 25(OH)D levels for low-energy fractures compared to high-energy fractures. Women with high-energy fractures had a comparable risk of vitamin D deficiency compared to women with low-energy fractures. Due to the positive effects of vitamin D on bone health, 25(OH)D levels should be measured in all fracture patients. The American Society for Bone and Mineral Research and National Osteoporosis Foundation currently recommends that vitamin D levels should be corrected.

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