The prevalence of vitamin D deficiency in patients with vertebral fragility fractures

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The prevalence of vitamin D deficiency in patients with vertebral fragility fractures

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Hypovitaminosis D has been identified as a common risk factor for fragility fractures and poor fracture healing. Epidemiological data on vitamin D deficiency have been gathered in various populations, but the association between vertebral fragility fractures and hypovitaminosis D, especially in males, remains unclear. The purpose of this study was to evaluate serum levels of 25-hydroxyvitamin D (25-OH D) in patients presenting with vertebral fragility fractures and to determine whether patients with a vertebral fracture were at greater risk of hypovitaminosis D than a control population. Furthermore, we studied the seasonal variations in the serum vitamin D levels of tested patients in order to clarify the relationship between other known risk factors for osteoporosis and vitamin D levels. We measured the serum 25-OH D levels of 246 patients admitted with vertebral fractures (105 men, 141 female, mean age 69 years, SD 8.5), and in 392 orthopaedic patients with back pain and no fractures (219 men, 173 female, mean age 63 years, SD 11) to evaluate the prevalence of vitamin D insufficiency. Statistical analysis found a significant difference in vitamin D levels between patients with vertebral fragility fracture and the control group ($p = 0.036$). In addition, there was a significant main effect of the tested variables: obesity ($p < 0.001$), nicotine abuse ($p = 0.002$) and diabetes mellitus ($p < 0.001$). No statistical difference was found between vitamin D levels and gender ($p = 0.34$). Vitamin D insufficiency was shown to be a risk factor for vertebral fragility fractures in both men and women.

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Vitamin D is a key player in bone metabolism.[1] Deficient vitamin D levels lead to malabsorption of intestinal calcium, and cause osteomalacia in adults as well as rickets in children.[1,2] Furthermore, chronic vitamin D deficiency leads to secondary hyperparathyroidism, progressive bone loss and an increased risk of fragility fractures.[3,4] Epidemiological data show vitamin D deficiency to be a worldwide phenomenon.[5-7] Variations in the prevalence of vitamin D deficiency, however, are dependent on the study population, vitamin D fortification of foods, geographical location (mainly latitude) and season.[8,9]

The relationship between vitamin D status and osteoporosis is of growing interest.[10] Several studies have demonstrated that vitamin D status influences various outcomes of osteoporosis.[10,11] One serious outcome of osteoporosis is fracture,[10] with hip fractures being one of the most common fractures in the elderly.[12] It has also been suggested that measurement of vitamin D serum levels might serve as an indicator for hip fracture risk among the elderly.[13-15] Further studies have shown a high level of vitamin D deficiency in women with hip fractures.[16,17] Such fractures contribute significantly to morbidity and mortality in the elderly, with up to 50% having permanent functional disability after hip fracture and nearly 20% dying within the first subsequent year.[12,18] Supplementation with vitamin D has, however, been shown to reduce the risk of both falls[19] and hip fractures.[20]

Another common complication of osteoporosis is vertebral fragility fracture, and a distinct relationship between these fractures and vitamin D levels has been suggested.[21,22] Vertebral fractures have direct and indirect effects on quality of life, with increased morbidity and mortality.[23,24] Reports have revealed a high rate of hypovitaminosis D in post-menopausal women with osteoporotic vertebral fractures.[22,25] A recent study showed a possible role for vitamin D in the occurrence of post-kyphoplasty recurrent vertebral compression fractures,[26] but few reports have looked specifically at orthopaedic patients or at patients of both genders with vertebral fractures.

The purpose of this study was to evaluate serum levels of 25-hydroxyvitamin D (25-OH D) in patients presenting with vertebral fragility

Table I. Patient characteristics in the vertebral fracture and control groups

	Vertebral fragility fracture (n, %)	Control group with back pain (n, %)
Number of patients	246	392
Men	105 *(43)*	219 *(56)*
Women	141 *(57)*	173 *(44)*
Mean age (yrs)	69 (44 to 81; SD 8.5)	63 (36 to 74; SD 11)
Alcoholism	19 *(8)*	23 *(6)*
Smoking	100 *(41)*	180 *(46)*
Obesity (BMI> 30 kg/m^2)	47 *(19)*	102 *(26)*
Osteoporosis	157 *(64)*	117 *(30)*
Hypertension	113 *(46)*	196 *(50)*
Cardiovascular disease (chronic/congestive heart failure, myocardial infarction)	81 *(33)*	94 *(24)*
Hypo-/hyperthyroidism	59 *(24)*	133 *(34)*
Pulmonary disease (Chronic obstructive pulmonary disease, asthma)	44 *(18)*	35 *(9)*
Renal failure	22 *(9)*	27 *(7)*
Infectious diseases (HIV, hepatitis A, B, C, tuberculosis)	7 *(3)*	7 *(2)*
Oral vitamin D supplements	39 *(16)*	43 *(11)*
Diabetes mellitus	84 *(34)*	110 *(28)*

Table II. Distribution of fracture levels in 246 patients

Location of fractured vertebra	Number of patients
T6	6
T7	7
T8	10
T9	9
T10	15
T11	34
T12	39
L1	36
L2	29
L3	16
L4	27
L5	18

fractures and to see if patients with a vertebral fracture were at greater risk of having hypovitaminosis D than a control population of orthopaedic patients without vertebral fractures. We also analysed seasonal variations in the serum vitamin D levels of these patients in order to clarify the relationship between other known risk factors for osteoporosis and vitamin D levels in patients with vertebral fractures.

Patients and Methods

Between 1 January 2011 and 31 December 2013 the serum 25-OH D levels of every patient admitted with a vertebral fracture to the orthopaedic department of the Johannes-Gutenberg-University Hospital in Mainz, Germany, were measured, usually on the day of admission. There were 246 patients in total. Inclusion criteria were radiologically-confirmed vertebral fractures. All patients had plain radiographs of the spine, 203 underwent MRI, and 43 had a CT scan for reasons such as claustrophobia or the presence of a cardiac pacemaker. Patients with fractures due to tumour were excluded from the study. For comparison, we measured vitamin D levels in 392 orthopaedic patients presenting with back pain but without a fracture. In this control group the presence of a fracture was excluded by radiographs. In addition, in 103 of the controls, minor vertebral fractures were excluded by MRI. In 303 patients back pain was caused by muscular imbalance or chronic musculoskeletal pain, 67 patients had lumbar disc herniations and 22 were diagnosed with spinal stenosis. The measurement of serum 25-0H D was standardised, using the ARCHITECT 25-OH vitamin D assay (Fa Abbott Laboratories, Wiesbaden, Germany). Laboratory results were collected by means of retrospective review of the medical records. The patients' characteristics and the distribution of fractures are shown in Tables I and II. According to Holick,[2] we defined sufficient vitamin D status as a serum 25-OH D level > 30 ng/ml (70 nmol/l). Furthermore, we compared serum vitamin D levels in the summer months (April to September) and the winter months (October to March) for both genders.

Ethical permission was granted for this investigation and all patients provided informed consent.

Statistical analysis. All patients with valid 25-OH D measurement were included in the statistical analysis. Serum vitamin D levels were compared between the genders using Student's *t*-test for independent samples. All hypotheses were evaluated using two-tailed *t*-tests, with statistical significance set at a p-value < 0.05. After the initial analyses, an analysis of covariance (ANCOVA) and analyses of variance (ANOVA) were performed to evaluate possible effects of known risk factors for vitamin D deficiency within the tested groups. ANCOVA was used to control for the effect of age, and ANOVAs were used to analyse possible effects of age, renal failure, obesity (defined as a body mass index (BMI) > 30 kg/m^2), diabetes mellitus, smoking carcinoma,

Table III. Analysis of variance of potential confounders for vitamin D deficiency

	Grade of freedom	p-value
Alcoholism	6.25	0.82
Nicotine abuse	2.53	0.002
Obesity (BMI > 30 kg/m^2)	7.68	0.001
Osteoporosis	5.67	0.079
Hypertension	3.64	0.1
Cardiovascular disease	2.86	0.73
Thyroid abnormality	4.43	0.32
Pulmonary disease	3.23	0.29
Renal failure	4.12	0.69
Infectious diseases	5.33	0.47
Vitamin D supplements	3.04	0.089
Diabetes mellitus	7.45	0.001
BMI		

osteoporosis, hypertension, cardiovascular disease, alcoholism, hyper-/hypothyroidism, pulmonary disease and infectious disease, and to check for possible interactions between the group variables and the above categorical variables. Statistical analysis was performed with IBM SPSS Statistics software (version 21, Armonk, New York).

Results

A total of 219 patients (89%) admitted with vertebral fragility fractures were found to have abnormally low levels of vitamin D, with a mean of 15.45 ng/ml (standard deviation (SD) 7.29) and minimum and maximum values of 3.8 ng/ml and 56.7 ng/ml, respectively; 235 patients (60%) presenting in the control group with back pain in the absence of a fracture showed insufficient vitamin D levels (mean 19.68 ng/ml; SD 8.34). Statistical analysis found a significant difference in vitamin D levels between patients with fractures and patients with back pain but no fracture (Student´s *t*-test, p = 0.036). No statistical difference in the mean vitamin D levels was found between male (14.97 ng/ml, SD 9.36) and female patients (15.87 ng/ml, SD 10.01) with vertebral fractures (Student´s *t*-test, p = 0.34). After adjustment for the covariate age, no statistical differences between our two patient groups were found (ANCOVA, Grade of Freedom F = 0.03; p = 0.71). After adjusting for possible confounders we found significant main effects of the tested variables for obesity (ANOVA, p < 0.001), nicotine abuse (ANOVA, p = 0.002) and diabetes mellitus (ANOVA, p < 0.001) on serum vitamin D levels in the tested groups. Vitamin D levels were not dependent on gender (ANOVA, p = 0.57), renal failure (ANOVA, p = 0.69) or other tested possible confounders (Table III), and stayed significantly lower in patients with vertebral fragility fractures after adjustment.

There is no universally accepted classification of vitamin D levels. The National Osteoporosis Society sets the following thresholds: < 30 nmol/l (12 ng/ml) = deficient, 30 to 50 nmol/l (12 ng/ml to 20 ng/ml) = inadequate and > 50 nmol/l (> 20 ng/ml) = adequate.[27] After adjusting our results to these thresholds, we found 191 patients (78%) with deficient 25-OH D in the vertebral fracture group (mean 38.6 nmol/l, SD 23.7) compared with 203 patients (52%) of the control group with back pain deficient in vitamin D (mean 49.2 nmol/l, SD 26.2).The statistical difference between the tested groups remained significant after adjustment (Student's *t*-test, p = 0.032). We also observed significant variations in vitamin D levels between the summer and winter in all patients, whether they had vertebral fracture or not. During the summer months the mean 25-OH D level was 19.75 ng/ml (SD 9.2), and during the darker six months of the year the mean level was 15.9 ng/ml (SD 8.9) (Student´s *t*-test, p = 0.042).

Discussion

In this study we identified an 89% prevalence of hypovitaminosis D in patients with vertebral fractures. By comparison, a well-matched group of patients with back pain and no fracture from the same geographical area, namely Mainz, Germany, which lies on the latitude 50° N and at around the same time of year, had a prevalence of hypovitaminosis D of 60%. It has been reported that there is high prevalence of hypovitaminosis D in orthopaedic patients, regardless of the reason for clinical presentation,[6,28] which confirms our results. In 2011 we showed that out of the 1119 patients treated in our orthopaedic department at the University Hospital of Mainz, Germany, 84% had insufficient levels of vitamin D and 60% were deficient in vitamin D.[5] Bogunovic et al[28] reported a 43% rate of vitamin D insufficiency in 723 patients, 40% of whom were vitamin D deficient. A possible explanation for this low rate of vitamin D deficiency compared with our results may be the exclusion of patients with comorbid medical conditions which precluded surgery.

However, our data show that patients who present with a vertebral fragility fracture are significantly more likely to be vitamin D insufficient – or even deficient – than patients without a vertebral fracture. These results are in line with the findings of former studies, suggesting that high serum levels of vitamin D contribute to healthy bone metabolism and prevent osteoporosis as well as osteoporotic

fractures.[11,29] Several studies have examined the association between fractures in post-menopausal women and low vitamin D levels. Nakamura et al[10] reported that in their six-year cohort study of 773 community-dwelling elderly Japanese women, patients with a sufficient level of vitamin D (> 71 nmol/l) had a 58% lower risk of an osteoporotic fracture than those with lower vitamin D levels. They suggested that high serum levels of vitamin D could reduce the risk of fracture. Gerdhem et al[8] evaluated 986 women and were able to show that patients with serum vitamin D levels < 20 ng/ml had a two-fold increased risk of osteoporotic fractures compared with women with vitamin D levels above this threshold. In 415 elderly Brazilian women assessed with a vertebral fragility fracture, vitamin D insufficiency was found to be one of the most important factors for sustaining a vertebral fracture.[13] El-Maghraoui et al[22] enrolled 178 menopausal Moroccan women in their cohort study to determine serum vitamin D status and to assess the association between bone mineral density and vertebral fracture. A widespread rate of vitamin D insufficiency (85% of tested patients) and deficiency (52%) was found. Furthermore, hypovitaminosis D was identified as an independent risk factor for vertebral fractures in post-menopausal women. On the other hand, epidemiological data on vitamin D levels in men with vertebral fractures are scarce. A total of 105 of our patients with vertebral fractures were men, 87 (83%) of whom were found to be vitamin D insufficient and 65 (62%) were vitamin D deficient. However, no significant gender-related difference in the prevalence of hypovitaminosis D was found between men and women with vertebral fragility fractures (Student's *t*-test, p = 0.34). There is a certain discrepancy in the literature regarding the association of gender with vitamin D levels and osteoporosis. Some studies indicate that women have a higher risk of being deficient in vitamin D than men,[30] whereas others have identified male gender as a risk factor.[3] These conflicting results indicate that gender may not necessarily be that important in vitamin D deficiency, which is supported by our data. Therefore, both men and women need to be monitored for hypovitaminosis D, as both are at high risk of fragility fractures.

We have also shown the extent of seasonal variations in 25-OH D levels. In the summer months serum vitamin D levels were higher than in winter months. However, even during the summer months the mean 25-OH D level was not sufficient, with a mean of 19.75 ng/ml SD 9.2 ng/ml. This suggests that increasing vitamin D production from sunlight is not a realistic option for most orthopaedic patients living in latitudes comparable to that of Mainz. Brustad et al[31] reported seasonal variations in vitamin D in northern regions (69° N) which are comparable to our results, but owing to a generally high dietary intake of vitamin D in the tested subjects the mean vitamin D levels were sufficient (> 30 ng/ml) in both tested seasons. Among the patients with vertebral fragility fractures we identified smoking, obesity and diabetes mellitus to be strongly associated with lower levels of vitamin D. Nevertheless, nicotine abuse and obesity were more prevalent in the back pain group than in the vertebral fracture group. Krall and Dawson-Hughes[32] demonstrated that smoking attenuated calcium absorption and promoted bone loss, and may therefore lead to low vitamin D levels. Obesity is a known risk factor for hypovitaminosis D owing to the sequestration of the lipid-soluble hormone in adipose tissue.[2,33] Our data suggest that particular concern for vitamin D insufficiency and deficiency is needed in patients with vertebral fragility fractures who smoke, are obese or have diabetes mellitus.

The strength of this study is that it compares serum vitamin D levels in patients with vertebral fragility fractures to those of a control group matched for age, seasonal variations and comorbidities. However, the study does have limitations. The majority of the patients were caucasian, and owing to the predisposition of people with darker pigmented skin to lower 25-OH D levels, hypovitaminosis D among such patients may be under-represented in this study. Furthermore, the geographical location of Mainz limits our results to regions around this latitude.[5] Also, due to the readily available vitamin D supplements, the effects of vitamin D supplementation may also be under-represented.

In this study we have demonstrated a high frequency of vitamin D deficiency among orthopaedic patients presenting with vertebral fragility fractures. More than 80% of the patients were vitamin D insufficient, with values below the target range of 30 ng/ml to 60 ng/ml. The screening and treatment of hypovitaminosis D is complex, but given that two separate meta-analyses have shown a > 20% risk reduction in non-vertebral fractures,[34,35] both are important in this patient population.

G. S. Maier, created the study, supervised the study, did the statistical analyses, wrote the manuscript.

J. B. Seeger, took blood samples, examined the patients, enrolled them into the study.

K. Horas, took blood samples, examined the patients, enrolled them into the study.

K. E. Roth, took blood samples, examined the patients, enrolled them into the study.

A. A. Kurth, helped with statistical analyses, supervised the study, corrected manuscript drafts.

U. Maus, helped with statistical analyses, supervised the study, corrected manuscript drafts.

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