Prevalence of Vitamin D Deficiency in Patients with Bone Metastases and Multiple Myeloma

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Abstract. *Background/Aim: Breast and prostate cancer are amongst the most prevalent malignancies globally and up to 40% of patients will develop metastatic disease, particularly to the skeleton. Multiple myeloma is the most common cancer to affect bone with up to 90% of patients developing bone lesions. Although several studies demonstrated that endocrine changes such as vitamin D deficiency promote secondary cancer growth in bone, relatively few have reported its prevalence. For this reason, the purpose of the present study was to evaluate the prevalence of hypovitaminosis D in patients with bone metastases and multiple myeloma. Patients and Methods: Serum 25-OH-D levels of patients with metastatic bone disease were measured on admission. Statistical analyses was performed to evaluate for possible confounders of hypo-vitaminosis D. Results: We found a widespread and alarming rate of vitamin D deficiency in patients with metastatic bone disease and multiple myeloma. Of note, patients with bone metastases due to breast cancer, prostate cancer and multiple myeloma rarely reached sufficient serum 25-OH-D levels. Conclusion: It is of utmost clinical importance to assess vitamin D levels in cancer patients, especially in those with, or at high risk of developing metastatic bone disease.*

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Vitamin D deficiency is the most common nutritional deficiency worldwide (1, 2). It is estimated to affect more than 1 billion people of all races, age groups, and ethnic backgrounds (3). As vitamin D is produced endogenously in the skin *via* a UVB-dependent mechanism, the most important risk factors for developing hypo-vitaminosis D include low annual sunlight exposure, darker skin tone and heavy sunscreen use (4, 5).

Traditionally, the bioactive 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] acts *via* the vitamin D receptor (VDR) and has hormonal actions mainly in the kidney, bowel, parathyroid and bone affecting calcium and phosphate homeostasis. Low vitamin D levels have been associated with an increased risk of cardiovascular diseases, type 2 diabetes as well as mental illness (6-8). Moreover, several studies suggest that vitamin D also regulates innate and adaptive immune function, by activating macrophages, dendritic cells and lymphocytes (9, 10). In addition, vitamin D deficiency leads to an increase in bone turnover and secondary hyper-parathyroidism promoting cortical bone loss. In certain cases, severe vitamin D deficiency can also result in osteomalacia (11). Furthermore, vitamin D deficiency has been linked to the pathogenesis of osteoporosis and hip fractures (12, 13).

Apart from its effects on bone, several studies reported an association between low vitamin D levels and increased cancer risk (*e.g.* in breast, prostate and colon cancers) (14, 15). Epidemiological data suggest that vitamin D deficiency is associated with increased prostate cancer incidence and related deaths (16, 17). Patients with multiple myeloma showed a high prevalence of vitamin D deficiency in two recent studies (18, 19). Association of vitamin D deficiency with higher serum CRP, serum creatinine and International Staging System stage at the time of diagnosis suggested that vitamin D deficiency may portend poorer outcomes in patients with multiple myeloma (19). In breast cancer it was shown that vitamin D exerts anti-proliferative and pro-apoptotic effects on breast cancer cells (20, 21). Moreover,

Table I. *Patients' characteristics*

Characteristics	Breast cancer	Prostate cancer	Multiple myeloma
No. of patients	89	58	49
Men sex	0	58(100%)	29 (59%)
Female sex	89 (100%)	0	20 (41%)
Mean age in years	51 (+/-9.3)	59 (+/-8.2)	57.4 (+/-1.6)
Alcoholism	2 (3%)	3 (5%)	1 (2%)
Nicotine Abuse	46 (51%)	27 (46%)	20 (40%)
Obesity (BMI >30kg/m^2)	17 (19%)	13 (22%)	11 (22%)
Osteoporosis	9 (10%)	4 (8%)	6 (12%)
Hypertension	47 (53%)	25 (43%)	23 (47%)
Cardiovascular disease (chronic/congestive heart failure, myocardial infarction)	18 (20%)	14 (24%)	13 (27%)
Thyreotic Abnormality (Hypo-/Hyperthyroidism)	31 (35%)	23 (40%)	18 (37%)
Pulmonary disease (COPD, Asthma)	9 (10%)	7 (12%)	8 (16%)
Renal failure	11 (12%)	7 (12%)	8 (16%)
Infectious diseases (HIV, Hepatitis A, B, C, Tubercolosis)	2 (2%)	1 (2%)	0
Oral Vitamin D supplementation	16 (18%)	6 (10%)	9 (18%)
Diabetes	19 (21%)	13 (22%)	11 (22%)

vitamin D deficiency has been shown to increase the incidence of breast cancer and to accelerate disease progression (22, 23).

Multiple myeloma is the most common cancer to affect bone with up to 90% of patients developing bone lesions (24). It is characterised by increased bone resorption and the majority of patients have pathological fractures at diagnosis (25). Secondary spread of prostate cancer and breast cancer frequently involves metastases to bone, resulting in debilitating pain, immobility, fractures and spinal compression syndromes (4, 26). Recently, it was demonstrated in a murine model, that vitamin D deficiency promotes breast cancer growth in bone, partly through direct anti-proliferative effects of vitamin D on cancer cells, but also indirectly *via* modulation of the bone microenvironment (20, 27). These findings are consistent with clinical observations showing that accelerated bone turnover is associated with higher rates of skeletal-related events and poorer prognosis in patients with breast cancer (28). Additionally, there is *in vitro* evidence that vitamin D deficiency itself has an impact on the invasive potential of human breast cancer cells (29). In another study, it was shown that vitamin D deficiency accelerated prostate cancer growth in bone through modulating the bone environment (30).

Although numerous studies have demonstrated a correlation between vitamin D deficiency and cancer risk, prevalence and progression, relatively few have reported its prevalence. The purpose of the present study was to evaluate the prevalence of hypovitaminosis D in patients with bone metastases derived from different primary tumors and multiple myeloma. Moreover, the aim was to elucidate whether or not there are significant differences in 25-hydroxyvitamin D (25-OH-D) serum levels between the patient groups tested.

Patients and Methods

Between January 1st, 2011 and December 31st, 2012, serum 25-OH-D levels (referred to as vitamin D) of 196 patients consecutively admitted to the orthopaedic department of the university hospital in Mainz, Germany (50° N latitude), were measured on admission. Patients were admitted due to bone metastases of breast cancer (n=89), prostate cancer (n=58) or multiple myeloma (n=49). Generally, blood was taken on the day of admission. The mean age of the patients was 58 years (+/-8.1 years) (Table I).

Measurement of serum 25-OH-D was standardised; the hospital laboratory used the ARCHITECT® 25-OH Vitamin D assay (Abbott GmbH & Co KG, Wiesbaden-Delkenheim, Germany). Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

As yet there is no universally accepted classification of vitamin D levels, we defined sufficient vitamin D status as a serum 25-OH-D level of above 30 ng/ml. Vitamin D inadequacy was defined as serum 25-OH-D level under 30 ng/ml and further divided into vitamin D insufficiency (20 to 30 ng/ml) and vitamin D deficiency (under 20 ng/ml), as described previously (3). Hypovitaminosis D was defined as a serum 25-OH-D level below 20 ng/ml according to the definition of the World Health Organization.

Patients' demographic variables and background data were evaluated by retrospective chart review and were used as potential confounders. Included variables were age, sex, origin of the primary tumor, body-mass index (BMI), comorbidities, oral medication and any vitamin D supplements taken before admission. Patients' characteristics were summarised using either means and standard deviations or frequencies and percentages.

All patients with a valid 25-OH-D measurement were included in the statistical analysis.

Serum Vitamin D levels were compared between different sexes, as well as between different primary tumors using the Student's *t*-test for independent samples.

After the initial analyses, an analysis of covariance (ANCOVA) and analyses of variance (ANOVA) were performed to evaluate possible effects of known risk factors of vitamin D deficiency within the tested groups. ANCOVA was used to control for the effect of age and ANOVA's were used to analyse possible effects of age, renal failure, obesity (defined as a BMI over 30 kg/m^2), diabetes mellitus, nicotine abuse, osteoporosis, hypertension, cardiovascular diseases, alcoholism, hyperthyroidism/hypothyreosis, pulmonary diseases, infectious disease and to check for possible interactions between the group variable and the above-mentioned categorical variables.

Statistical analyses was performed using IBM SPSS Statistics software (Ver. 21; IBM Corporate, Armonk, NY, USA).

Results

A total of 196 patients participated in this study. 59.4 % of study participants were women, 40.5% men. Ages ranged from 41 to 97 years, with a mean age of 58 (±8.1) years. Serum 25-OH-D levels for all participants were normally distributed, with a mean of 15.2 ng/ml (±7.2 ng/ml). Lowest measured level was <8 ng/ml, highest measured level was 48.5 ng/ml.

Patients with bone metastases of breast cancer showed a mean serum 25-OH-D level of 15.3 ng/ml (±4.7 ng/ml). Patients with metastatic bone disease due to prostate cancer had an average serum vitamin D level of 14.7 ng/ml (±8.3 ng/ml). In the patients group of bone lesions due to multiple myeloma, the mean 25-OH-D level was 14.8 ng/ml (±6.3 ng/ml).

The Student's *t*-test showed no significant difference between serum 25-OH-D levels of the 3 patient groups. No statistical difference in vitamin D levels was found in respect to male patients with bone metastases (mean vitamin D level of 14.94 ng/ml) compared to female patients with bone metastases (15.04 ng/ml) (p=0.78).

Following the univariate analyses, analyses of covariance were performed to evaluate the effect of age on vitamin D levels in the tested groups. Analyses of variance were performed to check for main effects and interactions for nicotine abuse, gender, renal failure, obesity and diabetes mellitus on vitamin D levels in the subgroups. After adjustment for the covariate age, mean differences between our patient groups were similar (Grade of Freedom F=0.03; p=0.71). After adjustment for possible confounders, we found no significant main effect of the tested variables obesity (p=0.98), nicotine abuse (p=0.31) and diabetes mellitus (p=0.077) on serum vitamin D levels in the tested groups. Vitamin D levels were not dependent on gender (p=0.57), renal failure (p=0.69) and other tested possible confounders.

Discussion

Breast and prostate cancer as well as multiple myeloma have a high propensity to metastasise to the skeleton and once tumors have spread to bone, they are usually incurable. Moreover, bone metastases have devastating consequences resulting in pathological fractures, severe pain, life-threatening hypercalcemia and nerve compression syndromes (31). Besides a significant decline in quality of life, metastatic bone disease may eventually lead to death due entirely to skeletal complications (32). For this reason, it is of utmost importance to identify factors that initiate and promote the growth of bone metastases.

In recent years, it has become evident that the bone microenvironment plays a pivotal role in the engraftment and growth of metastatic cancer cells. Upon arrival in bone, cancer cells parasitise the bone marrow and control the local environment to favour their own prosperity (33, 34). However, it is still largely unknown whether tumor cells specifically target a 'metastatic niche' in bone and what facilitates tumor cells to settle within the bone microenvironment.

It has been previously shown in mouse models that increased bone turnover accelerates the intra-skeletal growth of breast cancer cells. Furthermore, it was demonstrated that vitamin D deficiency promotes breast cancer growth in bone partly through changes in the bone microenvironment, but also through direct effects of vitamin D on cancer cells (20, 27). These experimental findings provide a conclusive rationale for the clinical observation that accelerated bone turnover is associated with higher rates of skeletal related events and poorer prognosis of patients with breast cancer (28). Often, vitamin D deficiency results in an increased level of parathyroid hormone (PTH) stimulating calcium mobilisation from skeletal stores (3, 35). PTH increases the expression of RANKL (receptor activator of NF-κB Ligand) stimulating and recruiting osteoclasts elevating bone resorption. Cancer cells are able to secrete PTH-related protein (PTHrP) that closely mimics PTH actions promoting osteolysis in bone (31, 33). These modulations in the bone microenvironment stimulate the release of other growth factors from the bone matrix, such as insulin-like growth factors, TGF-ß and other cytokines resulting in the previously described 'vicious cycle' of tumour growth in bone (26, 33, 36). Endocrine changes such as vitamin D deficiency contribute to a release of these growth factors providing a 'fertile' soil for tumour cells to thrive (37). Notably, it is known that release of bone-derived growth factors and cytokines from resorbing bone can both attract cancer cells and facilitate their growth and proliferation (32).

Moreover, the bone microenvironment houses haematopoietic stem cells (HSC) that persist in, as commonly referred to, the stem cell niche. It has recently been suggested, that metastatic tumor cells target this HSC niche and compete with HSCs for the occupancy of that niche within the bone microenvironment (38). Manipulating the size of the niche has been shown to alter the frequency of bone metastases. Most notably, in a study using metastatic prostate cancer, it has been demonstrated that an expansion of this HSC niche with PTH treatments resulted in significantly a greater number of bone metastases (34). Thus, changes of the bone microenvironment due to low vitamin D levels might also result in a conditioning of the pre-metastatic niche for cancer cells increasing skeletal susceptibility to cancer metastasis (33, 37, 39).

Collectively, it has been demonstrated that vitamin D deficiency promotes the growth of bone metastases. In addition, there is evidence that vitamin D deficiency increases skeletal susceptibility to cancer metastases. Further, metastatic destruction of bone reduces its load-bearing

capacity and the probability of developing a pathological fracture increases with the duration of metastatic involvement (32). The development of a pathological fracture is devastating to cancer patients. Thus, adequate clinical management of patients with, or in high risk of secondary cancer spread to bone is pivotal. This suggests that the maintenance of adequate vitamin D levels is of utmost clinical importance. Hence, correcting vitamin D deficiency using vitamin D supplements could have an effect on the development and the progression of metastatic bone disease as it inhibits bone resorption. Vitamin D supplementation is safe and simple, however, further randomized controlled trials on the impact of vitamin D supplementation are required to confirm this hypothesis.

Clearly, certain limitations of the study have to be taken into consideration. The majority of the patients in the present study had white skin tones. Due to the predisposition of darker skin-toned individuals toward lower 25-OH-D levels, hypovitaminosis D among darker skin-toned patients may be underrepresented in this study. Furthermore, the geographical localisation of Mainz (50˚ northern latitude) limits our results to regions around this latitude (*e.g.* Paris 48˚51' N, Vancouver (49˚15' N), Calgary (51˚3' N) or Kiev (50˚27')) or above 50˚ latitude.

In summary, the present study highlights a widespread and alarming rate of vitamin D deficiency in patients with metastatic bone disease and multiple myeloma. Of note, patients with bone metastases due to breast cancer, prostate cancer and multiple myeloma rarely reached sufficient serum 25-OH-D levels and yet vitamin D deficiency often goes unrecognised and therefore remains untreated. Hence, it is of utmost clinical importance to assess vitamin D levels in cancer patients, especially those with, or at high risk of developing metastatic bone disease.

Conflicts of Interest

All Authors certify that no funding or commercial associations exist that might pose a conflict of interest with regard to the present work.

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