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# The Effects of Vitamin D Level on Bone Lesions and Prognostic Factors in Multiple Myeloma

## *Multipl Miyelomda D Vitamini Düzeyinin Kemik Lezyonları ve Prognostik Faktörler Üzerine Etkileri*

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**Keywords**
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### Abstract

**Objective:** Several studies have found that low vitamin D levels are associated with an increased risk of hematologic malignancies and a poor prognosis. In this study, we investigated the relationship between 25-hydroxyvitamin D levels and bone lesions as well as prognostic factors in patients with multiple myeloma. **Materials and Methods:** We evaluated 184 people who had just been diagnosed with multiple myeloma. Complete blood count, biochemical parameters, serum 25-hydroxyvitamin D [25(OH)D] level, presence of lytic bone lesion and fracture, and disease stage were all recorded. The patients were divided into three groups based on their 25(OH)D levels: deficient (<20 ng/mL), insufficient (20-29 ng/mL), and normal (≥30 ng/mL). SPSS-21 was used to perform statistical analyses. **Results:** The 25(OH)D was deficient in 121 patients (65.8%), insufficient in 28 patients (15.2%), and normal in 35 patients (19%). Age, presence of lytic bone lesion and bone fracture, plasma cell rate in bone marrow, and stage of disease (p=0.02; p=0.01; p=0.007; p=0.02, respectively) all differed significantly between these groups. Patients with normal 25(OH)D levels had lower risk of lytic bone lesion and fracture. Furthermore, deficiency and insufficiency of 25(OH)D had a negative impact on disease stage, and advanced disease stage is a poor prognostic parameter for multiple myeloma. **Conclusion:** Patients with normal 25(OH)D levels have a lower risk of lytic bone lesion and vertebral fracture. The stage of the disease is influenced by 25(OH)D deficiency and insufficiency. Therefore, early detection and treatment of 25(OH)D deficiency and insufficiency in patients with multiple myeloma may reduce mortality and morbidity rates.

### Öz

**Amaç:** Birkaç çalışma, düşük D vitamini düzeyinin, hematolojik malignitelerin artmış insidansı ve kötü prognozu ile ilişkili olduğunu bildirmiştir. Biz bu çalışmada multipl miyelomlu hastalarda, 25-hidroksivitamin D [25(OH)D] düzeyi ile kemik lezyonları ve prognostik faktörler arasındaki ilişkiyi araştırdık. **Gereç ve Yöntemler:** Yeni tanı almış 184 multipl miyelom hastası değerlendirildi. Tam kan sayımı, biyokimyasal parametreler, serum 25(OH)D düzeyi, litik kemik lezyonu ve kırık varlığı, hastalık evresi kaydedildi. Hastalar 25(OH)D düzeyine göre 3 gruba ayrıldı; eksik (<20 ng/mL), yetersiz (20-29 ng/mL) ve normal (≥30 ng/mL). İstatistiksel değerlendirmeler SPSS-21 programı ile yapıldı.

**Bulgular:** 25(OH)D düzeyi 121 hastada (%65,8) eksik, 28 hastada yetersiz (%15,2) ve 35 hastada (%19) normaldi. Bu gruplar arasında yaş, litik kemik lezyonu ve kırık varlığı, kemik iliğinde plazma hücre oranı ve hastalık evresi açısından anlamlı fark vardı (sırasıyla p=0,02, p=0,01, p=0,007, p=0,02 ). 25(OH)D düzeyi normal olan hastalarda litik kemik lezyonu ve kırık daha azdı. Ek olarak; 25(OH)D eksikliği ve yetersizliği hastalığın evresini olumsuz etkiledi ve hastalığın ileri evresi multipl miyelom için kötü prognostik parametredir. **Sonuç:** 25(OH)D düzeyi normal olan hastalarda litik kemik lezyonu ve kemik kırığı daha az görülür. 25(OH)D eksikliği ve yetersizliği hastalığın evresini olumsuz etkiler. Bu nedenle; 25(OH)D eksikliği ve yetersizliğinin erken tespiti ve tedavisi multipl miyelomlu hastalarda mortaliteyi ve morbidite oranını azaltabilir.

## Introduction

Vitamin D promotes calcium absorption from the intestine and provides sufficient serum calcium and phosphate concentrations for mineralization of the bones. Vitamin D deficiency mainly causes loss of bone density and it can contribute to osteoporosis and bone fractures. In addition; low vitamin D level is associated with cardiovascular diseases, solid organ and hematological cancers, metabolic syndrome, infectious and autoimmune diseases (1,2). Vitamin D receptors are present in hematopoietic cells and variety of tissues in the body (3). Vitamin D regulates various genes that responsible for cell proliferation by binding to the active vitamin D receptor and inhibits the growth of cancer cells (4-6). Vitamin D deficiency may contribute to carcinogenesis by impairing these normal regulatory processes. In some studies reported that vitamin D deficiency was associated with inferior event free survival and overall survival in patients with diffuse large B cell and T cell non-Hodgkin lymphoma and a worse outcome in patients with acute myeloid leukemia (7,8).

Multiple myeloma (MM) is a non-curative hemalogical malignant disease and it originates from plasma cells. The patients with MM have some prognostic marker e.g; plasma cell labeling index, the presence of some cytogenetic abnormalities, gene expression profile, the stage of disease (9). Bone lesions occur in 80-90% of all cases with MM at the time of diagnosis and are among the most important causes of morbidity (10). Osteoclast-mediated bone destruction increases and osteoblastic activity reduces significantly because of cytokines and chemokines that released from tumor cells and stroma cells in bone marrow (11). In addition, vitamin D deficiency causes hyperparathyroidism that increases osteoclastic activity and decreases osteoblastic activity. Therefore vitamin D deficiency can contribute to the formation of bone lesions, risk of fall in MM. Bone lesions are often seen in the vertebral column, skull, ribs, pelvis and long bones and it may cause impairment in quality of life, neurological deficit, pathological fracture and hypercalcemia. Conventional radiography, computerized tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) can be used to detect bone lesion. The aim of the present study was to verify the potential association between the level of 25 hydroxyvitamin D [25(OH)D] and lytic bone lesion, vertebral fracture, prognostic factors in MM.

## Materials and Methods

In this study, we studied 184 newly diagnosed and treated MM patients at the Department of Hematology of the Atatürk University. Approval of the Atatürk University Ethics Committee was obtained for the study and informed consent was received from all participants (decision no: 31, date: 27.02.2020). The patients who measured the level of serum 25(OH)D at the time of admission were received in this study. The patients with chronic kidney failure and receving regular vitamin D supplements were excluded of this study.

We retrospectively examined the medical files of all cases and recorded sex, age, the levels of hemoglobin, serum creatine, blood urea nitrogen, total protein, albumin, calcium, globulin, serum immunoglobulin (G,A,M), 25(OH)D, the presence of lytic bone lesion and fracture, plasma cell rate in bone marrow, stage of disease. The presence of lytic bone lesion and fracture were evaluated by using conventional radiography and CT/MRI/PET-CT findings. We used International Staging System (ISS) as the prognostic score. In this scoring system, if the albumin level ≥3.5 mg/dL and β2 microglobulin level <3.5 mg/dL is stage 1, β2 microglobulin level ≥5.5 mg/dL is stage 3 and patients who don't fulfill the stage 1 or 3 criteria are evaluated as stage 2.

Vitamin D level is often measured by automated immunoassays techniques (12). The serum level of 25(OH)D was measured using the CLIA method in the Siemens ADVIA Centaur XP device in our study. Vitamin D sufficiency, insufficiency and deficiency were defined as 25(OH)D level of 30-100 ng/mL, 20-29 ng/mL, and less than 20 ng/mL, respectively in Clinical Practice Guideline that it was published by the endocrine society's (13). In this study, the patients were divided into 3 groups according to this guideline; deficient [25(OH)D<20 ng/mL], insufficient [25(OH)D= 20-29 ng/mL], and normal [25(OH)D≥30 ng/mL].

**Statistical Analysis**

Statistical evaluations were made by SPSS-21 windows software (Armonk, NY: IBM Corp). Demographic variables were evaluated with simple descriptive analysis. We used independent t-test for determine difference between two goups if normal distribution was present, Mann-Whitney U test was used if the group distribution was abnormal. One-way ANOVA was applied to test the mean differences between multiple groups. For all analyses, p-value <0.05 was considered to indicate statistical significance.

## Results

The mean age of our cases was 68.74±10.47 years and 55 (29.9%) patients were female and 129 (70.1%) patients were male. The median 25(OH)D level at the time of diagnosis, was 19.6±18.2 ng/mL (range =3-71 ng/mL) in 184 patients. There were 121 cases (65.8%) with the 25(OH)D deficiency, 28 (15.2%) cases with 25(OH)D insufficiency, and 35 (19%) cases with 25(OH)D normal. Vitamin D deficiency increased with increasing age (Table 1).

Fifty seven (31%) patients had stage 1, 53 (28.8%) patients had stage 2, 74 patients (40.2%) had stage 3. The level of 25(OH)D was 22.95±21.22 ng/mL in patients with stage 1, 20.72±16.21 ng/mL in cases with stage 2, and 13.72±14.18 ng/mL in cases with stage 3. As the disease stage increased, the 25(OH)D level decreased statistically significantly (p=0.01).

Eighteen (9.8%) of all patients had bone fracture and 105 of all patients (57.1%) had lytic bone lesion. Bone fracture and the presence of lytic bone lesion were associated with 25(OH)D sufficiency and insufficiency (Table 2).

Laboratory findings of the patients were presented in Table 3. We didn't find a relationship between

**Table 1. The association with 25-hydroxyvitamin D level and age**

| Vitamin D level | Age | | | |
|---|---|---|---|---|
| | Mean ± SD | Minumum | Maximum | p-value |
| 25(OH)D deficiency (n=121) | 73.14±8.9 | 50 years | 88 years | 0.02 |
| 25(OH)D insufficiency (n=28) | 68.39±9.04 | 47 years | 78 years | |
| Normal 25(OH)D level (n=35) | 67.55±10.92 | 24 years | 92 years | |

25(OH)D: 25-hydroxyvitamin D, SD: Standard deviation

**Table 2. The association with 25-hydroxyvitamin D level and bone fracture, lytic bone lesion**

| Bone fracture | | |
|---|---|---|
| **Vitamin D level** | **Present (number patient) (%)** | **p-value** |
| 25(OH)D deficiency (n=121) | 15 (12.39%) | 0.007 |
| 25(OH)D insufficiency (n=28) | 2 (7.14%) | |
| Normal 25(OH)D level (n=35) | 1 (2.85%) | |
| **Lytic bone lesion** | | |
| **Vitamin D level** | **Present (number patient) (%)** | **p-value** |
| 25(OH)D deficiency (n=121) | 90 (74.38%) | 0.01 |
| 25(OH)D insufficiency (n=28) | 8 (28.57%) | |
| Normal 25(OH)D level (n=35) | 7 (20%) | |

25(OH)D: 25-hydroxyvitamin D

the levels of 25(OH)D and hemoglobin, calcium, sedimentation rate, albumin, globulin, creatine, β2 microglobuline (Table 4). The statistically significant relationship was between the level of 25(OH)D and plasma cell count in bone marrow (Table 5).

## Discussion

Vitamin D mainly provides the protection of calcium, phosphorus homeostasis and bone mineralization and its deficiency is a common public health problem around the world (14). Vitamin D deficiency causes rickets in children and osteomalacia in adults. But the consequences of its deficiency are not limited to rickets and osteomalacia. Several studies reported vitamin D deficiency was associated with diabetes mellitus, hypertension, obesity, metabolic syndrome, cardiovascular disease, infectious and autoimmune diseases (15,16). In addition, it is known that one of the causes of colon, breast and ovarian cancers is vitamin D deficiency (17,18). In the northern states of the United States, prostate, breast

**Table 3. Laboratory findings of all the patients**

| Variable | Minimum | Maximum | Mean |
|---|---|---|---|
| Plasma cell in bone marrow (%) | 10 | 65 | 30.8±11.76 |
| Hemoglobin (g/dL) | 4.6 | 13.2 | 10.91±2.37 |
| Sedimentation rate | 2 | 140 | 65.37±37.73 |
| Total protein (g/dL) | 6.1 | 15.5 | 8.45±2.14 |
| Albumin (g/dL) | 1.1 | 5.1 | 3.41±0.72 |
| Globulin (g/dL) | 1.8 | 10.7 | 5±2.42 |
| Calcium (mg/dL) | 8.5 | 15.2 | 9.27±1.51 |
| Creatine (mg/dL) | 0.3 | 8.1 | 1.45±1.32 |
| β2 microglobuline | 1.6 | 13.2 | 5.98±4.48 |
| Serum immunoglobulin G | 1.31 | 65.92 | 26.53±13.97 |
| Serum immunoglobulin A | 0.1 | 37 | 3.16±3.97 |
| Serum immunoglobulin M | 0.01 | 5.9 | 0.81±0.74 |

**Table 4. The relationship with 25(OH)D level and laboratory findings**

| Variable | 25(OH)D deficiency | 25(OH)D insufficiency | Normal 25(OH)D level | p-value |
|---|---|---|---|---|
| Hemoglobin (g/dL) | 10.83±2.37 | 11.28±2.01 | 10.91±2.37 | 0.66 |
| Sedimentation rate | 65.09±36.44 | 67.75±42.64 | 64.40±39.10 | 0.93 |
| Albumin (g/dL) | 3.38±0.71 | 3.52±0.83 | 3.38±0.68 | 0.64 |
| Globulin (g/dL) | 4.98±2.46 | 4.89±2.30 | 5.19±2.42 | 0.86 |
| Calcium (mg/dL) | 9.34±1.48 | 9.28±2.01 | 9.03±1.08 | 0.57 |
| Creatine (mg/dL) | 1.32±1.21 | 1.75±1.53 | 1.67±1.46 | 0.16 |
| β2 microglobuline | 5.90±4.38 | 5.66±5.40 | 6.52±4.12 | 0.71 |

25(OH)D: 25-hydroxyvitamin D

**Table 5. The relationship with 25(level and the rate marrow OH)D of plasma cell in bone (%)**

| | Plasma cell rate in bone marrow (%) | | | |
|---|---|---|---|---|
| **25(OH)D level** | **Mean ± SD** | **Minimum** | **Maximum** | **p-value** |
| 25(OH)D deficiency (n=121) | 68.39±9.04 | 47 | 88 | 0.02 |
| 25(OH)D insufficiency (n=28) | 67.55±10.92 | 24 | 92 | |
| Normal 25(OH)D level (n=35) | 35.75±13.53 | 18 | 65 | |

25(OH)D: 25-hydroxyvitamin D, SD: Standard deviation

and colon cancer were more frequently than the sunnier states. Therefore, the relationship between vitamin D deficiency and incidence of cancer has been investigated in some studies (19-21). The altitude of Erzurum province, where the study is conducted, is 1,900 meters and the number of sunny days is low. Therefore, only 19% of our patients had normal vitamin D level.

Vitamin D level is determined by measuring 25(OH)D. The half-life of 1.25(OH)$D_2$ is only 4 hours while the half-life of 25(OH)D is 2-3 weeks and 25(OH)D circulates at a 1,000-fold higher concentration than 1,25(OH)$D_2$. Therefore, we determined the patient's vitamin D status by using the 25(OH)D level. The vitamin D receptors are found in almost all cells in the human body. 25(OH)D affects angiogenesis by reducing the expression of vascular endothelial growth factor and interleukin 8. Vitamin D makes the antitumor effect by regulating proliferation, differentiation and apoptosis. We did not measure vitamin D receptor level in this study.

Vitamin D deficiency is common in patients with MM (22,23). Hudzik et al. (24) evaluated 675 MM patients. They reported that 25(OH)D level was <10 ng/mL in 52 (7.7%) patients and it was 10-30 ng/mL in 394 (51%) patients. Vitamin D deficiency was reported 16-37% of all patients with MM by Alvin C et al. (25). Graklanov et al. (26) evaluated 37 patients with newly diagnosed MM. They reported that 1 patient (2.7%) had vitamin D insufficiency (serum levels between 20-30 ng/mL) and 36 patients (97.3%) had vitamin D deficiency (levels below 20 ng/mL). Severe vitamin D deficiency (<10 ng/mL) was observed in 81% of all patients. Vitamin D deficiency was detected in 80.9% of all patients in our study. This may be explained by the lower exposure to sunlight due to high altitude and climate in the Erzurum. In addition, the fact that the people of Erzurum prefer the style of clothing that prevents the use of the sun can also contribute to this situation.

Vitamin D level was found significantly low in the patients with acute myeloid and lymphoblastic leukemias. It has been reported that vitamin D deficiency to be associated with poor prognosis and worse response to treatment in patients with hematological malignancies (27,28). Lauter et al. (29) determined that 25(OH)D insufficiency (<10 ng/mL) was associated with elevated plasma cells count in the bone marrow. Gedik et al. (30) and Graklonav et al. (26) did not find a relationship between 25(OH)D level and ISS staging of MM. In addition Nath et al. (31) 41 patients with MM and they reported that there was no association between vitamin D status and stage of myeloma. But, it was reported that the prevalence of vitamin D deficiency increased in parallel with ISS in another study (25). We detected that the patients with vitamin D deficiency and insufficiency had elevated plasma cell count in bone marrow and advanced stage disease. This two paramethers are negative prognostic factors in MM. Increased β2 microglobuline level is also a poor prognostic marker. We didn't define a relationship between β2 microglobuline level and vitamin D status. In addition, we could not evaluate the survival of patients due to lack of data.

Vitamin D deficiency was related to high C-reactive protein (CRP) and creatine levels and advanced stage disease in MM (32,33). But we didn't find any significant correlation between vitamin D status and serum creatine level. Alvin C et al. (25) examineted 148 patients with MM. They detected that the patients with vitamin D deficiency [25(OH)D<20 ng/mL] had higher serum CRP, creatine levels and lower serum albumin level than patients without vitamin D deficiency (25). But we didn't find any correlation between vitamin D status and serum albumin, creatine levels.

Vitamin D deficiency can cause musculoskeletal pain, proximal muscle weakness, increased risk of falls. Low levels of vitamin 25(OH)D can cause secondary hyperparathyroidism and bone resorption via osteoclasts, which may accelerate osteopenia and osteoporosis in adults. Skeletal complications, such as lytic bone lesion, hypercalcemia, compression fracture are the main causes of morbidity in MM. Therefore, early diagnosis and treatment of vitamin D deficiency may reduce skeletal complications. Alvin didn't find any correlation between low vitamin D level and skeletal morbidity. Badros et al. (33) evaluated 100 MM patients and they reported that there was no significant correlation between vitamin D status and presence of lytic bone disease and fracture. Nath et al. (31) reported that MM cases with vitamin D deficiency have higher skeletal morbidity, but this is not statistically significant (73% vs 50%, p=0.19). But we defined that the lytic bone lesion and bone fracture were more common in patients with vitamin D deficiency and insufficiency.

## Conclusion

Low vitamin D level is important public health problem. Because it is associated with increased malignancy incidence and worse prognosis in patients with hematological and solid organ malignancies. Therefore treatment of vitamin D deficiency may be reduce cancer devolopment and worse prognosis in patients with cancer. This hypothesis should be supported by studies involving more cases.

**Ethics**

**Ethics Committee Approval:** Approval of the Atatürk University Ethics Committee was obtained for the study (decision no: 31, date: 27.02.2020).

**Informed Consent:** Informed consent was received from all participants

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions**

Concept: G.S., F.E., Design: G.S., F.E., Supervision: G.S., F.E., Fundings: G.S., Materials: G.S., Data Collection or Processing: G.S., F.E., Analysis or Interpretation: F.E., Literature Search: F.E., Writing: G.S., F.E., Critical Review: F.E.

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