



# Vitamin B12 Level Have Prognostic Significance in Multiple Myeloma Patients?

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## Abstract

**Aim:** The aim is to investigate retrospectively the association between vitamin B12 levels at the time of diagnosis and the complications including hypercalcemia and fractures in multiple myeloma patients.

**Material and Method:** The association between vitamin B12 level at the time of diagnosis and myeloma complications such as hypercalcemia and bone lesions were analyzed with chi-square in 140 multiple myeloma patients.

**Findings:** Vitamin B12 deficiency was found in 29 patients (20.7%). While the rate of hypercalcemia is 37.9% in patients with vitamin B12 deficiency, it is 18.9% in patients without deficiency. The fracture rate was 44.8% in vitamin B12 deficient group and 23.4% in the other group.

**Results:** Vitamin B12 deficiency at the time of diagnosis is associated with hypercalcemia and bone fracture rate (p=0.04, p=0.03).

**Discussion:** Vitamin B12 level might have prognostic significance since hypercalcemia and fracture rate is increased in the vitamin B12 deficient group. Further studies with a larger patient group are needed on this subject.

**Keywords:** Myeloma; Vitamin B12 deficiency; Myeloma bone disease

## Introduction

Multiple myeloma is a neoplasm with bone marrow-derived clonal plasma cell growth. Uncontrolled proliferation of plasma cells results in an end-organ damage, including an abnormal increase in the production of monoclonal immunoglobulins (paraproteinemia), lytic lesions in the bones, anemia, infections, hypercalcemia and renal involvement [1]. Multiple myeloma bone disease (MBD) can cause lytic lesions classic prevalent disease, osteopenia and especially in a specific portion of the spine, head, bones or long bones may be in the form of multiple lytic lesions [2]. The main mechanism of MBD is the increase in osteoclastic activity associated with the suppression of osteoblastic activity in bones. From the moment of diagnosis, bone pain is a major problem [3].

The primary causes of hypercalcemia in patients with myeloma are tumors associated with bone destruction. This leads to increased osteoclastic bone resorption caused by potent cytokines secreted from myeloma cells [4]. Another cause of hypercalcemia is the disruption in the functioning of the kidneys, impairment of the renal calcium load and increased calcium absorption [5].

There are studies in the literature showing that vitamin B12 deficiency and increased risk of osteoporosis, hip and spine fractures are linked. In these studies, the relationship between vitamin b12 deficiency and increased risk of osteoporosis and fracture in the healthy population has been associated with an increase in osteoclast activity, although not fully clarified [6-12]. In large-scale LASA studies, it has been shown that deoxyypyridinoline linkages (deoxyypyridinoline cross-links (DPD), the bone resorption marker, are increased in women with low vitamin B12 levels [13]. Also, in a study on a placebo-controlled healthy population, a reduction in fracture risk was associated with vitamin b12 supplementation [14].

There are reports that vitamin B12 deficiency increases the risk of fracture in healthy subjects, but a relationship between vitamin B12 deficiency and fracture risk in multiple myeloma cases has not been shown. The presence of increased osteoclastic activity in the etiology of MBD and

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**Table 1:** Demographic data of patients with Multiple Myeloma.

Demographic data of the study group	N (%)
Age<65	81 (%57,9)
Gender (m/f)	80/60 (%57,1/%42,9)
The presence of b symptoms	13 (%9,3)
Stage I	33 (%23,6)
Stage II	39 (%27,9)
Stage III	68 (%48,6)
Vitamin B12 level <220 pg/ml	29 (%20,7)
Albumin (gr/dL) <3,5	55 (%39,3)
Hypercalcemia (>10 gr/dL )	32 (%22,9)
Pathological fracture	39 (%27,9)
Anemia	55 (%39,3)
Renal dysfunction	57 (%40,7)
Lytic Lesion	75 (%53,6)

hypercalcemia seen in multiple myeloma is also known. We aimed to investigate retrospectively the association between vitamin B12 levels at the time of diagnosis and the complications including hypercalcemia and fractures in multiple myeloma patients.

## Materials and Methods

### Study population

140 multiple myeloma patients presented to hematology outpatient clinic at Ankara Atatürk Training and Research Hospital were included. The patient's charts and medical records were retrospectively analyzed. The routine anemia work up results including vitamin B12 levels and calcium levels were noted.

Patients with a vitamin B12 level below 220 pg/mL were considered to be low during the anemia period. Blood samples for vitamin B12 were taken from peripheral and sterile conditions, measured by chemiluminescence method in Roche cobas 6000 hormone autoanalyzer. A serum calcium level > 10 mg/dL at the time of diagnosis was considered as hypercalcemia. Bone fractures were demonstrated by magnetic resonance imaging and/or direct X-ray.

### Statistical analysis

The cases were divided into 2 groups with low and normal vitamin B12 levels and statistical evaluation was done. Statistical analyzes were performed using chi-square test using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). A value of less than 0.05 was considered significant.

### Findings

Vitamin B12 levels, calcium values and bone fracture status were evaluated retrospectively multiple myeloma in our study. Of the cases 80 (57.1%) was male, 60 (42.9%) was female. The mean age was 63.5 ( $\pm$  11.5). The demographic data of the study group are summarized in (Table 1).

## Results

132 (94.3%) patients have been diagnosed with anemia. Out of 132 cases 29 of them (20.7%) was identified with Vitamin B12 deficiency. While 41.4 percent of patients with vitamin B12 deficiency were female, 58.6 percent was male. Out of the 32 Hypercalcemia cases 11 (34.4%) of them has vitamin B12 deficiency. Hypercalcemia was found 37.9% in vitamin B12 deficiency group while 18.9% in vitamin

B12 normal group. ( $p=0.04$ ) The bone fracture rate at diagnosis was 44.8% in the group with vitamin B12 deficiency and 23.4% in the group without vitamin B12 deficiency and this difference was statistically significant. ( $p=0.03$ ).

## Discussion

In our study, we found that vitamin B12 deficiency was found in 20.7% of patients with multiple myelomas at the time of diagnosis and hypercalcemia and bone fracture frequency has been found increased in these cases. In a previous study in 32 patients with multiple myeloma, vitamin B12 deficiency was reported as 28% and there was no correlation between vitamin B12 deficiency and demographic features and complications [15]. In our study, the rate of hypercalcemia was higher in the group with vitamin B12 deficiency. Hypercalcemia in multiple myeloma is a metabolic disorder resulting in end-organ damage in the disease. Osteoclastic bone resorption and renal insufficiency, which are formed through the secretion of plasma cells, are effective in the formation of hypercalcemia. In our MM cases, the relationship between vitamin B12 deficiency and hypercalcemia is difficult to establish because of pathophysiological causes, as there is insufficient data in the literature. In an experimental study investigating the effect of vitamin B12 on calcium metabolism, it has been reported that vitamin B12 is effective at the intracellular entry of calcium into rat thymocytes [16]. The decrease in serum vitamin B12 level can be explained by this relationship mechanism. There are different publications on vitamin B12 levels in myeloproliferative diseases in which one or more hematopoietic series cells have excessive proliferation and vitamin B12 depletion due to the consumption of this rapid proliferation can be observed [17]. Various studies have shown changes in serum vitamin B12, transcobalamin 2 and haptocorrin levels in lymphoproliferative diseases involving plasmacell dyscrasias including multiple myelomas [18-21]. In an in vitro study, myeloma cells were shown to be able to consume vitamin B12 itself [22]. In a study comparing the vitamin B12 levels of myeloma bone marrow cells with the healthy control group, the concentration of vitamin B12 in the plasmacells of the bone marrow was found to be higher. In addition, compared with the healthy control group, myeloma patients had increased levels of transcobalamin 2 mediated vitamin B12 uptake in their bone marrow cells [23-24]. This reduction of vitamin B12 might show the contribution of plasmacells, but more extensive studies are needed to show this relation. In our study, we found that bone fracture frequency was increased in patients with vitamin B12 deficiency. In the literature, the relationship between vitamin B12 and bone fracture in multiple myeloma cases has not been shown. Therefore, we believe that our work is meaningful for this patient population. Pathologic and osteoporotic bone fractures are frequently observed in multiple myeloma [25]. In a meta-analysis, the incidence of bone fracture is very high even before diagnosis and after myeloma diagnosis, the incidence of fractures, mainly vertebrae and rib, are increased 9 times [26]. In the general population, there are many studies that have studied vitamin B12 deficiency and osteoporosis and bone fracture risk. In a meta-analysis of 27 cross-sectional and longitudinal studies conducted to observe the relationship between vitamin B12 and fracture risk, it was observed that every 50 pmol/L reductions in vitamin B12 increased the fracture risk by 4% [27]. Previous studies have shown that vitamin B12 is associated with decreased body mass index deficits and fracture risk [28-29]. There is a relationship between vitamin B12 deficiency and fracture risk can be partially explained by epidemiological studies [29]. However, it has

been suggested that osteoclast stimulation is primarily responsible for the relationship between vitamin B12 deficiency and bone structure deterioration [30].

As a result; it is known that the cases are at an advanced age, with a multifactorial fracture risk of disease-induced immobilization, chemotherapy and steroid use. In our study, vitamin B12 deficiency seems to be associated with an increased risk of fracture. We think that vitamin B12 is a clinical prognostic factor in the diagnosis of multiple myeloma in the presence of known effects of vitamin B12 as well as increased risk of fracture. There is a need for more extensive work on this particular subject.

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