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ORIGINAL ARTICLE

Prevalence, Supplementation, and Impact of Vitamin D Deficiency in Multiple Myeloma Patients

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Here, we studied 83 unselected multiple myeloma patients from December 2007 through December 2014. Lower 25(OH) D levels (<10 ng/mL) were associated with higher number of plasma cells in the bone marrow. Supplementation of vitamin D was accompanied with a significant increase in hemoglobin (11.8 to 12.3 $p = .039$), leukocyte (4.9 to 5.8 $p = .011$), and erythrocyte (3.8 to 4.0 $p = .004$) levels, while thrombocytes (200.5 to 175.2 $p = .036$) decreased. In conclusion, the present study found a high incidence of vitamin D deficiency and insufficiency in MM patients. In myeloma patients, vitamin D levels and supplementation should be more widely taken into account.

Keywords: Multiple myeloma, Treatment, Supportive care & symptom control, Vitamin D deficiency

INTRODUCTION

In patients with multiple myeloma (MM), vitamin deficiency and insufficiency is widely prevalent. (1) Skeletal and renal complications are a major cause of morbidity in MM and vitamin D is a fundamental mediator of skeletal metabolism. (2, 3) In addition, patients with chronic kidney disease are disproportionately deficient in the necessary substrate, 25-(OH) vitamin D, beginning in the very early stages of their disease (9). Given these dynamics, the purpose of this study is to assess the efficacy of a vitamin D (vit. D) repletion strategy in MM patients.

MATERIAL AND METHODS

We used a cohort of 83 diagnosed MM patients at the University of Bonn from December 2007 through December 2014. This study is a retrospective cohort study of participants who had MM. Our subjects were unselected, and thus, represented a broad spectrum of time points of MM diagnosis and treatment. In total, 17 subjects had a new diagnosis of MM.

The effect of vitamin D replacement using laboratory parameters, were also examined. Non-fasting blood was collected for measuring serum calcium, sodium, potassium, creatinine, CRP, albumin, vitamin D levels, serum parathyroid hormone, bone-specific alkaline phosphatase, TRAP, immunoglobulins, free light-chains K and Λ and a complete blood count. At the time of the laboratory measurement, 30 patients had a renal insufficiency.

Table 1 details the sex, age, stage of disease, osteolytic lesions and plasma cells in the bone marrow of patients in the deficient, insufficient and sufficient groups.

In addition, of the 83 patients with MM, the mean age was 66.3 years (range, 43 to 86 years) and 61.5% were male.

As seen in Table 1, subjects were supplemented ($n = 32$) with cholecalciferol or calcitriol. However, to note, 19 subjects had already been supplemented, in which 13 of these cases it was because of a renal insufficiency.

Determination of serum 25(OH) vitamin D levels

Serum 25(OH) D levels were measured by competitive chemiluminescence immunoassay (CLIA) in all subjects.

Outcome measures

We defined vitamin D deficiency as a serum 25 (OH) D level < 10 ng/mL, vitamin D insufficiency as a serum 25 (OH) D level between 10 and 30 ng/mL and sufficiency as a serum 25 (OH) D level > 30 ng/mL.

MM subjects were staged using the Durie and Salmon Staging System and ISS.

Statistical analysis

The statistical significance of differences in categorical variables associated with vitamin D deficiency was assessed using Pearson's Chi-Square/Fisher's Exact test, while continuous variables were assessed using *t*-test.

Kaplan–Meier curves and Cox–Mantel test were used to assess the association of vitamin D levels and outcomes. All statistical tests, which were two-sided of less than 0.05, were considered to be significant. All the data was obtained and extracted from patient medical records.

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Table 1. Patient Characteristics

	Vitamin D deficient $N = 27$	Vitamin D insufficient $N = 45$	Vitamin D sufficient $N = 11$
Female/Male	13/14	16/29	3/8
Age (years)	63.9	67.9	62.8
% (total) renal insufficiency	51.9 (14)	28.9 (13)	27.3 (3)
% Stage Durie & Salmon (1/2/3)	4/32/64	16.3/30.3/53.5	11.1/22.2/66.6
% (total) Supplementation yes/no/already	44.4(12)/25.9(7)/29.6(8)	42.2(19)/40.0(18)/17.8(8)	9.1(1)/63.6(7)/27.3(3)
Supplementation UI per week	11261.9	11332.14	9625
% Osteolytic lesions	68	88.4	90
% Plasma cells	44.8	20.6	13.3

Vitamin D status: Deficiency is defined as 25(OH) D < 10 ng/ml, Insufficiency is defined as 25(OH) D 10–30 ng/ml and sufficiency as 25(OH) D > 30 ng/ml.

RESULTS

The present study found a high incidence of vitamin D deficiency and insufficiency in MM patients.

Among 83 patients, 32.5% had vitamin deficiency, 54.1% had vitamin D insufficiency and only 13.3% had sufficient levels.

Patients with 25(OH) levels >10 ng/mL were on average given 11261.9 IU weekly, patients with 25(OH) D levels 10–30 ng/mL were on average given doses of 11332.14 IU weekly and patients with normal 25(OH) D levels were on average given 9625 IU weekly.

As seen in Figure 2(E), results were favorable in most patients, with general increase of vitamin 25(OH) D levels after supplementation (14.8 ng/mL to 24.0 ng/ml; $p = .001$).

When 25(OH) D levels were reassessed, participants without renal insufficiency (Figure 1(A/B)) had a significant increase in serum 25(OH) D levels (18.1 to 27.3; $p = .007$ and

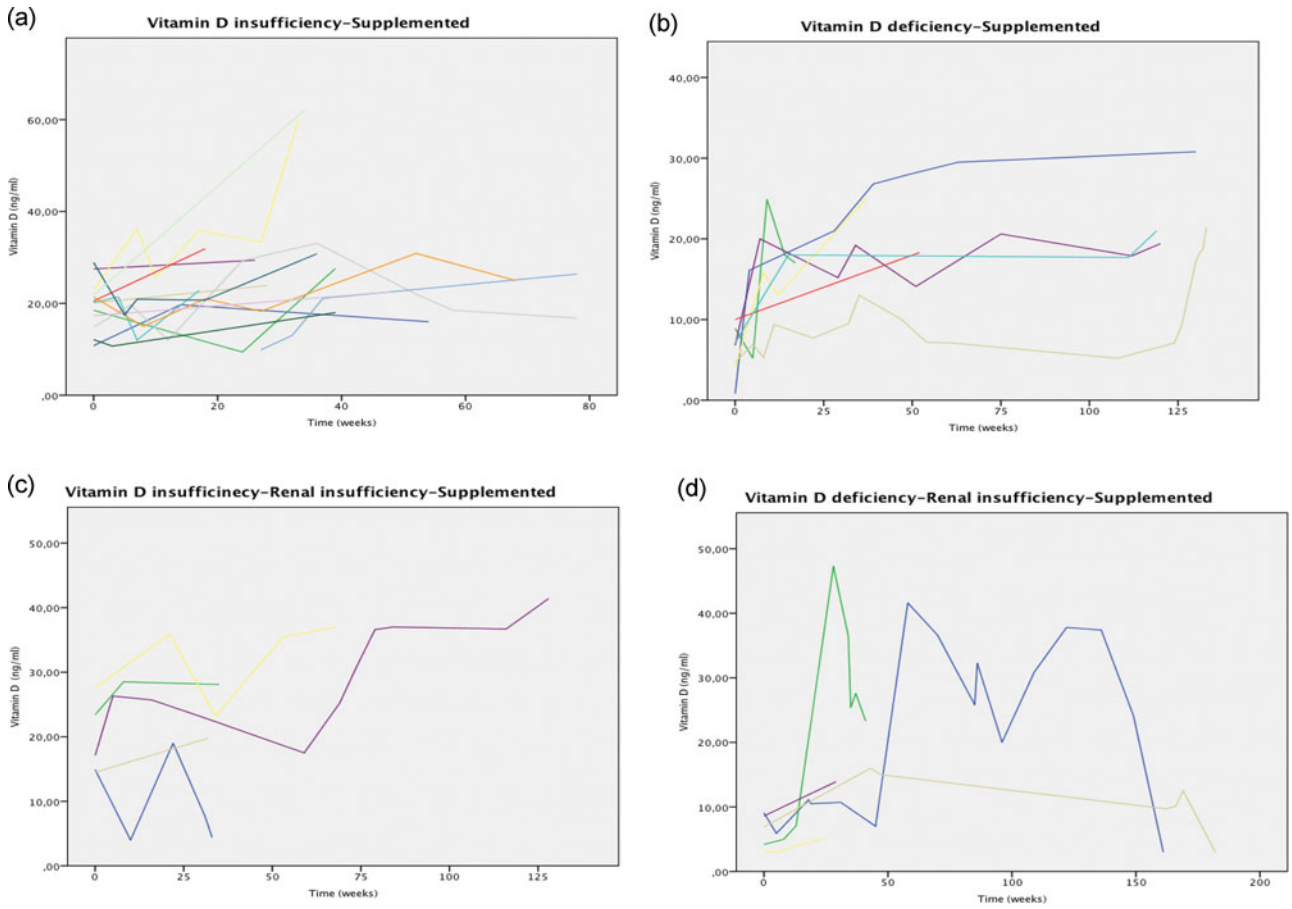

Figure 1A. (A) Serum level of vitamin D in patients with multiple myeloma and vitamin D insufficiency. *X*-axis: time in weeks; *Y*-axis: 25-OH-D serum level (ng/mL). In different colors subject's serum level of 25(OH) D. $p = 0.007$; mean: 18.1 ng/mL to 27.3 ng/mL. (B) Serum level of vitamin D in patients with multiple myeloma and vitamin D deficiency. *X*-axis: time in weeks; *Y*-axis: 25-OH-D serum level (ng/ml). In different colors subject's Serum level of 25(OH) D. $p = .001$; mean: 7.4 ng/mL to 18.5 ng/mL. (C) Serum level of vitamin D in patients with multiple myeloma, renal insufficiency and vitamin D insufficiency. *X*-axis: time in weeks; *Y*-axis: 25-OH-D serum level (ng/mL). In different colors subject's Serum level of 25(OH) D. $p = .193$; mean: 21.0 ng/mL to 26.2 ng/mL. (D) Serum level of vitamin D in patients with multiple myeloma, renal insufficiency and vitamin D deficiency. *X*-axis: time in weeks; *Y*-axis: 25-OH-D serum level (ng/mL). In different colors subject's Serum level of 25(OH) D. $p = .094$; mean: 6.6 ng/mL to 16.7 ng/mL.

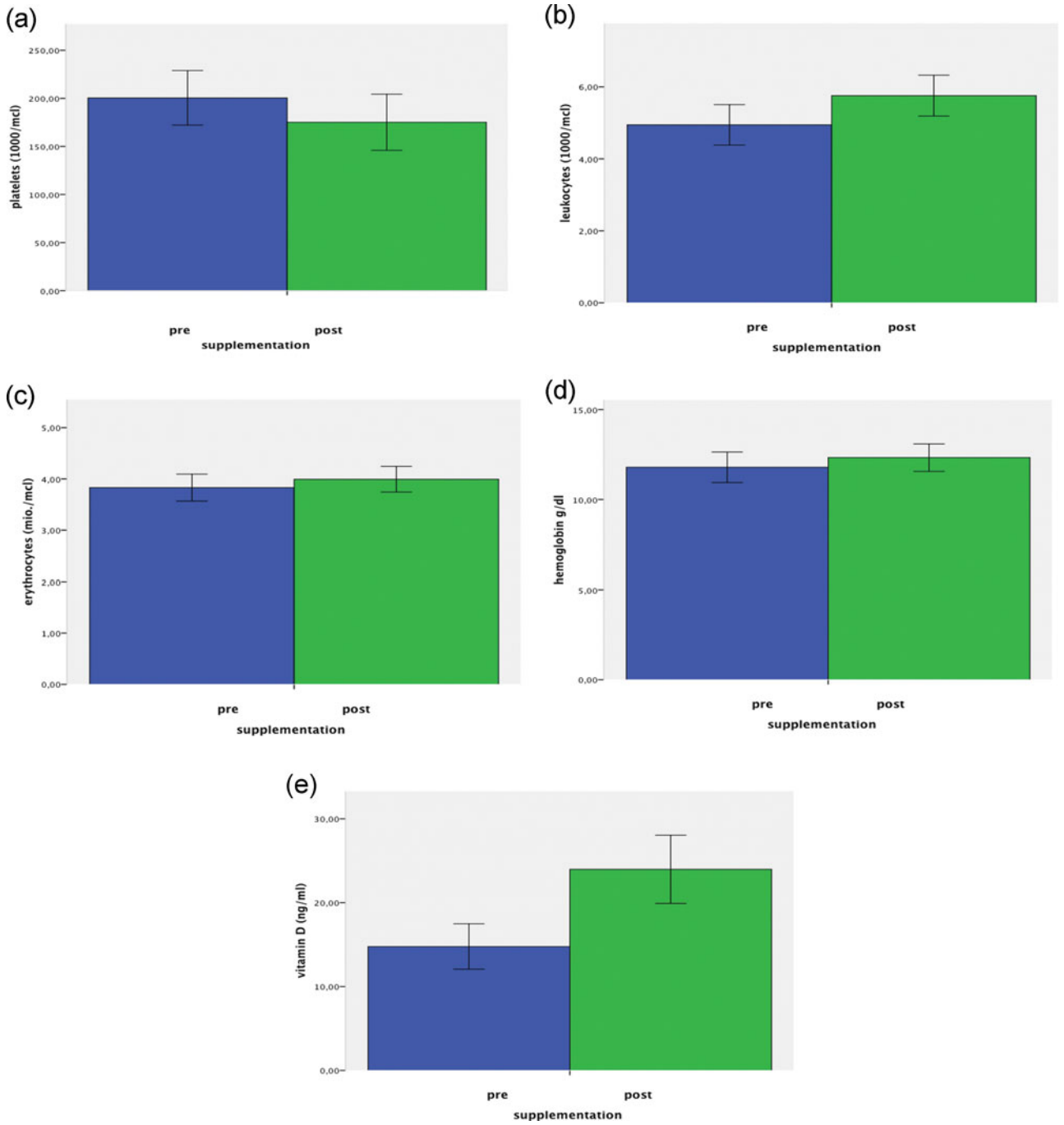

Figure 2. (A) Platelets pre and post supplementation; $n = 29$. (B) Leukocytes pre and post supplementation; $n = 30$. (C) Erythrocytes pre and post supplementation; $n = 30$. (D) Hemoglobin pre and post supplementation; $n = 29$. (E) Vitamin D pre and post supplementation $n = 32$.

7.4 to 18.5; $p = .001$) while those with renal insufficiency (Figure 1(C/D)) had no significant change (21.1 ng/mL to 26.2 ng/mL; $p = .193$ & $p = 0.094$ & 6.6 ng/mL to 16.7 ng/mL; $p = .094$).

The majority did not achieve sufficient serum 25 (OH) levels, suggesting that MM patients need higher on-going oral maintenance doses to maintain normal levels.

Table 2 lists the significant changes in laboratory parameters pre and post supplementation. Vitamin D supplementation has been shown to increase the number of erythrocytes (3.8 to 4.0 $p = .004$), hemoglobin (11.8 to 12.3 $p = .039$) and leucocytes (4.9 to 5.8 $p = .011$), whereas the number of thrombocytes (200.5 to 175.2 $p = .036$) decreased. One limitation is that our cohort represented a broad spectrum of time points of MM diagnosis and treatment, so these improvements could be a side effect of other therapies as well.

We found an association between vitamin D levels and percentage of plasma cells in the bone marrow, wherein the deficient group had a higher number of plasma cells (44.8%) in the bone marrow than the insufficient (20.6%) or the sufficient (13.3%) group (Figure 4).

Table 2. Laboratory Parameters

	Pre	Post	*p*-Value
platelets	200.5	175.2	.036
leukocytes	4.9	5.8	.011
erythrocytes	3.8	4.0	.004
hemoglobin	11.8	12.3	.039
vitamin D	14.8	24.0	.001

Platelets in 1000/mcl; leukocytes in 1000/mcl; erythrocytes mio./mcl; hemoglobin in g/dL; vitamin D in ng/mL
Pre: before supplementation of vitamin D
Post: after supplementation of vitamin D

There were no significant correlations between vitamin D status and MM activity, presence or absence of lytic bone disease.

Concerning outcome

Seven subjects died of progressive MM, five of whom were part of the insufficiency group and one per group from the deficiency and the sufficiency group. There is no significant difference in survival between the three different groups (Figure 3. $p = .932$). These estimates were not statistically significant, most likely due to either the small number of patients with these types of MM included in the cohort and/or the few deaths during the relatively short follow-up time.

DISCUSSION

Recent studies found a high incidence of vitamin D deficiency in MM patients (1,2,5).

Among 83 patients, 32.5% had vitamin deficiency, defined by serum 25-hydroxyvitamin D levels < 10 ng/mL, 54.1% had vitamin D insufficiency, defined by levels of 10–30 ng/mL and only 13.3% had sufficient levels, defined as >30 ng/mL.

The most widely accepted optimal level of serum 25(OH) D is 35–55 ng/mL. One study showed that for all health-related end point, the most advantageous serum levels for

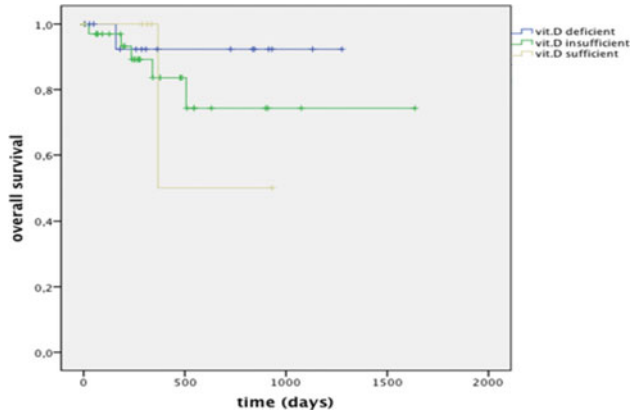

Figure 3. Kaplan-Meier survival curves among patients with multiple myeloma according to vitamin D level. Overall survival in patients with vitamin D deficiency (< 10 ng/mL) $n = 27$, insufficiency (10–30 ng/mL) $n = 45$ or sufficiency (> 30 ng/mL) $n = 11$ $p = .932$.

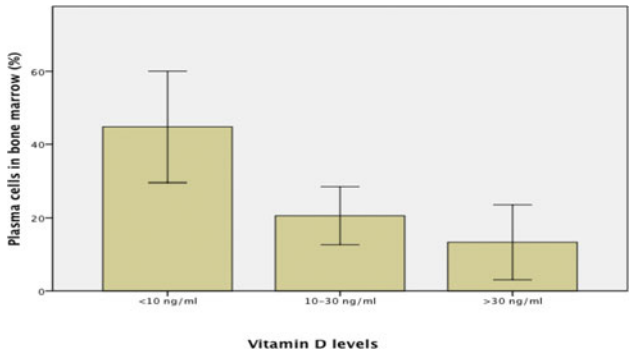

Figure 4. Percentage of plasma cells in bone marrow in vitamin D deficient ($n = 20$), insufficient ($n = 38$) and sufficient groups ($n = 9$). $p = .009$ deficient vs. insufficient; $p = .004$ deficient vs. sufficient.

25(OH) D appear to be at least 30 ng/mL, and for cancer prevention desirable levels are between 36–48 ng/mL (4).

There were several limitations to this study. First, our study is retrospective.

Second, the majority of participants in this study were Caucasians, which may affect generalizability and applicability of the results to other races and/or ethnic populations (8). Furthermore our cohort represented a broad spectrum of time points of MM diagnosis and treatment, they were unselected, so the improvements in laboratory parameters could be a side effect of other therapies as well. Another limitation is the seasonal variation in vitamin D levels. It is well known that there is a higher prevalence of vitamin D deficiency during the winter compared to the summer (7). In our cohort, our follow-up period included the whole year.

In our study, after treatment, the insufficiency and deficiency groups without renal insufficiency had a significant increase in vitamin D level (Figure 1(A/B)), but did not achieve sufficient levels.

According to Badros, the recommended daily 400 IU of vitamin D is inadequate for healthy adults and that after correction of the deficit, a higher daily supplementation should be standard maintenance (1).

However, even a higher supplementation (>1000 IU) does not seem to be enough for MM patients. Additionally, the current study shows the difficulties to correct existing deficits, and the majority of our patients did not achieve sufficient long-term 25 (OH) levels during our follow up.

Furthermore, specific guidelines for repletion of 25(OH) D levels with vitamin D in patients with MM still do not exist and are really needed.

Studies regarding vitamin D supplementation, using cholecalciferol or ergocalciferol in patients has shown significant and favorable effects using laboratory parameters of bone and mineral metabolism and erythropoiesis stimulating agents (6). In addition, paricalcitol has potent anticancer activity against myeloma cells in vitro (10,11). In this study, favorable improvements in relevant laboratory parameters, such as hemoglobin (11.8 to 12.3 $p = .039$), erythrocytes (3.8 to 4.0 $p = .004$), and leukocytes (4.9 to 5.8 $p = .011$), were observed with cholecalciferol/calcitriol replacement. However, in one case, there were negative changes in parameters, such

as thrombocytes (200.5 to 175.1 $p = .036$). Our results should be interpreted in light of other potential explanations, including MM treatment. Patients in the vitamin D deficient group had a higher number of plasma cells in the bone marrow than the insufficient or the sufficient groups ($p = .009$ vs. insufficient $p = .004$ vs. sufficient). Regardless of whether we found out that lower 25(OH) D levels (<10 ng/mL) were associated with a higher number of plasma cells in the bone marrow, we did not find a significant difference in survival between the three different groups. In conclusion, whether normalizing vitamin D levels in these patients improves clinical outcomes will require testing in future trials. 25(OH) D deficiency and insufficiency, as well as renal insufficiency are common problems in MM patients. Myeloma remains an incurable disease, although major progress has been achieved. Therefore, new therapeutic strategies are still essential (12-15). Oral vitamin D replacement appears to be safe, but dosing strategies need to be adjusted for MM patients. Protocols developed for patients who have MM, with or without renal insufficiency, appear to be inadequate in the population used in this study. Future studies are also needed to delineate the optimal cholecalciferol/calcitriol repletion and maintenance dosing schedule in the MM population.

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AUTHORSHIP

BL collected data, interpreted data, performed research and wrote the manuscript; ISW designed, performed research and edited the manuscript.

DECLARATION OF INTEREST

None of the authors have any conflicts of interest to disclose. The authors alone are responsible for the content and writing of the article.

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