Original Article

# Comparison of Outcome in Multiple Myeloma with or without Adjuvant Vitamin D Therapy



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## ABSTRACT

**Objective:** To determine vitamin D levels in newly diagnosed cases of multiple myeloma and to determine effects of vitamin D supplementation using laboratory parameters on outcome of the disease.

**Study Design:** Comparative study.

**Place and Duration of Study:** This study was conducted at the Haematology Department of Shaikh Zayed Hospital, Lahore and INMOL Hospital, Lahore from January to June 2018.

**Materials and Methods:** Thirty two patients of multiple myeloma were included in the study and were divided into two equal groups A and B. Baseline laboratory parameters;vitamin D, β2 microglobulin and serum albumin levels were performed. Patients in group A were given vitamin D supplementations along with standard myeloma chemotherapy. Whereas patients in group B were without adjuvant vitamin D supplementation. Laboratory parameters in both groups were repeated and compared at 12 and 18 weeks follow-up.

**Results:** At baseline, mean vitamin D level in group A was 17.86 ± 14.23 ng/ml and in group B was 25.95 ± 15.89 ng/dl. At 18th week follow-up, mean vitamin D level in group A was 44.14 ± 20.99 ng/ml and in group B was23.92 ± 14.11 ng/dl, which was statistically significant (p-value 0.003).Comparison of mean β2 microglobulin and albumin levels between the two groups were found insignificant at 18th week follow-up.To determine the effect of vitamin D supplementation on outcome of multiple myeloma, hypothetical scoring was calculated and compared between the two groups which was found statistically insignificant.

**Conclusion:** Significant low vitamin D levels (78.12%) had been found in multiple myeloma. There was significant improvement of vitamin D levels with oral supplementations, but laboratory parameters alone has shown no significant results at short term follow-up.


**Key Words:** Multiple myeloma, vitamin D, β2 microglobulin

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## INTRODUCTION

Multiple myeloma is a rarehaematological malignancy of the plasma cells which evolves in the bone marrow.Malignant plasma cells produce abnormal antibodies which are called 'M proteins'.[1, 2]

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Musculoskeletal pains, hypercalcemia, renal insufficiency, anemia and pathological fractures are common complications of multiple myeloma.[3]Ninety eight percent myeloma cases report over the age of forty years with peak incidencein the 7th decade of life.[4]

Vitamin D is a secosteroid that helps in absorption of calcium and phosphate in the body.Recent studies reported its rolein cell differentiation, multiplication and apoptosis.[5, 6]Multiple myeloma causes increase production of matrix metalloproteinases (MMPs) that enable cancer cells to migrate into other tissues. Vitamin D reduces MMPs production and hence the ability of cancer to spread.[7]

Vitamin D deficiency has been associated with potential risk for pathological fractures and development of various malignancies.[8, 9]Serum vitamin D levelshave shownits prognostic role in patients with breast orcolorectal carcinomas,but its role in haematological malignancieslike multiple myeloma is still unclear.[10, 11, 12]

# MATERIALS AND METHODS

This cross-sectional study was conducted at. Haematology Department of Shaikh Zayed Hospital, Lahore and INMOL Hospital, Lahore

Thirty two newly diagnosed patients of multiple myeloma were taken as study population and were divided equally into two groups A and B. All the patients were staged using International staging System (ISS). Baseline laboratory parameters; vitamin D, β2 microglobulin and serum albumin levels were performed and documented on the designed proforma.

**Group A:** Patients from Sheikh Zayed Hospital, Lahore were given standard myeloma therapy and adjuvant vitamin D therapy.

**Group B:** Patients from INMOL Hospital, Lahore were given standard myeloma therapy alone (without adjuvant vitamin D therapy).

Laboratory parameters were repeated after 12 and 18 week intervals.

**Inclusion Criteria:**

1. New cases of multiple myeloma
2. Adults of both genders

**Exclusion Criteria:**

1. Patients with malabsorptive disorders (e.g. celiacdisease, cystic fibrosis, short bowl syndrome)
2. Patients on antiepileptic medicines that increases vitamin D metabolism (e.g. phenytoin and phenobarbital)

**Data Analysis:** Data for gender and stage of the disease were presented by using frequency and percentage. All quantitative variables (including age, vitamin D, albumin and β2 microglobulin levels) were presented by using Mean ± S.D for two groups. Comparison of above parameters between the groups was made by using Independent Sample t-test.

# RESULTS

Mean age of the patients was 59.56 ± 13.02 years in Group A, while 55.50 ± 10.64 years in Group B. In Group A, there were 9 (56.25%) male and 7 (43.75%) female patients while in Group B, there were 10 (62.5%) male and 6 (37.5%) female patients.

In this study, Minimum vitamin D level found among both groups was 4.6 ng/ml and maximum was 58.91 ng/ml. In Group A, Mean vitamin D was 17.86 ± 14.23 ng/ml at baseline, 28.61 ± 11.96 ng/ml at 12 weeks and 44.14 ± 20.99 ng/ml at 18 weeks follow-up. In Group B, mean vitamin D was 25.95 ± 15.89 ng/dl at baseline, 23.74 ± 14.31 ng/dl at 12 weeks and 23.92 ± 14.11 ng/dl at 18 weeks follow-up respectively. It was found statistically significant between the both groups at 18th week(p-value 0.003). (Table-1) (Figure 1)

In Group A, mean β2 microglobulin was 14.76 ± 15.03 mg/L at baseline, 6.81 ± 6.14 mg/L at 12 weeks and 3.35 ± 0.70 mg/L at 18 weeks follow-up. In Group B, mean β2 microglobulin was 12.12 ± 12.78 mg/L at baseline, 6.36 ± 8.06 mg/L at 12 weeks and 3.13 ± 3.35mg/L at 18 weeks follow-up. At 18th week follow-up, comparison between the two groups was found statistically insignificant. (Table-1) (Figure -2)

In Group A, mean serum albumin was 3.22 ± 1.62 mg/L at baseline, 3.47 ± 0.60 mg/L at 12 weeks and 3.47 ± 0.57 mg/L at 18 weeks follow-up. In Group B, mean serum albumin was 3.33 ± 0.97 mg/L at baseline, 3.25 ± 0.71 mg/L at 12 weeks and 3.13 ± 0.67 mg/L at 18 weeks follow-up. Similarly, at 18th week follow-up comparison between the two groups was found statistically insignificant. (Table-1) (Figure-3)

In our study, we compared ISS stage of myeloma patients between group A and group B at baseline, 12 week and 18 week intervals. In group A; at baseline, 10 patients were in stage-III,3 were in stage-II and 3 were in stage-I. Whereas at 18 weeks, 3 patients left in stage-III, 7 in stage-II and 6 were in stage-I of disease.In group B, at baseline, 12 patients presented in stage-III, 3 in stage-II and 1 in stage-I. Whereas at 18 weeks, one patient was in stage-III, 11 in stage-II and 4 in stage-I of disease. (Figure-4)

**Table No.1: Comparison of vitamin D, β2 microglobulin and albumin levels at baseline, 12th week and 18th week in both study groups**

| | Laboratory Parameters | Group A | Group B | p-value |
|---|---|---|---|---|
| At Baseline | Vitamin D level (ng/dl) | 17.86 ± 14.23 | 25.95 ± 15.89 | 0.140 |
| | β2 microglobulin level (mg/L) | 14.76 ± 15.03 | 12.12 ± 12.78 | 0.597 |
| | Albumin level (mg/L) | 3.22 ± 1.62 | 3.33 ± 0.97 | 0.645 |
| At 12th Week | Vitamin D level (ng/dl) | 28.61 ± 11.96 | 23.74 ± 14.31 | 0.304 |
| | β2 microglobulin level (mg/L) | 6.81 ± 6.14 | 6.36 ± 8.06 | 0.860 |
| | Albumin level (mg/L) | 3.47 ± 0.60 | 3.25 ± 0.71 | 0.353 |
| At 18th Week | Vitamin D level (ng/dl) | 44.14 ± 20.99 | 23.92 ± 14.11 | 0.003* |
| | β2 microglobulin level (mg/L) | 3.35 ± 0.70 | 3.13 ± 3.35 | 0.140 |
| | Albumin level (mg/L) | 3.47 ± 0.57 | 3.13 ± 0.67 | 0.241 |

*Statically significant

In order to study stage regression in our cohort and to relate it to vitamin D supplementation, a hypothetical number was assigned to each patient according to stage of the disease. Cumulate score of patients was calculated in a particular stage at baseline, 12 weeks and 18 weeks. This hypothetical scoring helped in understanding the effect of vitamin D supplementation on outcome of treatment in multiple myeloma patients. In this, stage-I patient was assigned a score of 1, stage-

II patient was assigned a score of 2 and stage-III patient was assigned a score of 3. In Group A, the cumulate score at baseline was 39, at 12 weeks was 34 and at 18 weeks was 29. In Group B, the cumulate score at baseline was 43, 30 at 12 weeks and 29 at 18 weeks. (Table-2)

When we calculate that in group A, the reduction in scoring, it was 5 point reduction at 12weeks and 10 points at 18 weeks from the baseline score of 39. In group B, reduction in scoring was 13 points at 12 weeks and 14 points at 18 weeks from baseline score of 43.Reduction in scoring from baseline, at 12 weeks and 18 weeks was compared between the both groups and was indicative of stage regression. P-value was 0.07 which was statistically insignificant. (Table-3)

**Table-No.2. Three stages of Multiple Myeloma in group A and B with hypothetical scoring according to ISS stage and number of patients**

| Groups | Stage | At Baseline Level | | At 12th week | | At 18th week | |
|---|---|---|---|---|---|---|---|
| | | Number of Patients | Score | Number of Patients | Score | Number of Patients | Score |
| Group A (With Vitamin D therapy) | I | 3 | 3 | 4 | 4 | 6 | 6 |
| | II | 3 | 6 | 6 | 12 | 7 | 14 |
| | III | 10 | 30 | 6 | 18 | 3 | 9 |
| | Total | 16 | 39 | 16 | 34 | 16 | 29 |
| Group B (Without Vitamin D therapy) | I | 1 | 1 | 5 | 5 | 4 | 4 |
| | II | 3 | 6 | 8 | 16 | 11 | 22 |
| | III | 12 | 36 | 3 | 9 | 1 | 3 |
| | Total | 16 | 43 | 16 | 30 | 16 | 29 |

(Score= ISS stage and number of patient in a particular stage at one point of time)

**Table-3. Comparison of Reduction in Hypothetical Score at Baseline, 12th week and 18th week in both groups**

| Groups | No. of Patients | Score at Baseline | Reduction at 12th week | Reduction at 18th week | va |
|---|---|---|---|---|---|
| **Groups A** (With Vitamin D) | 16 | 39 | 5 | 10 | |
| **Group B** (Without Vitamin D) | 16 | 43 | 13 | 14 | **0** |

p value < 0.05 is significant

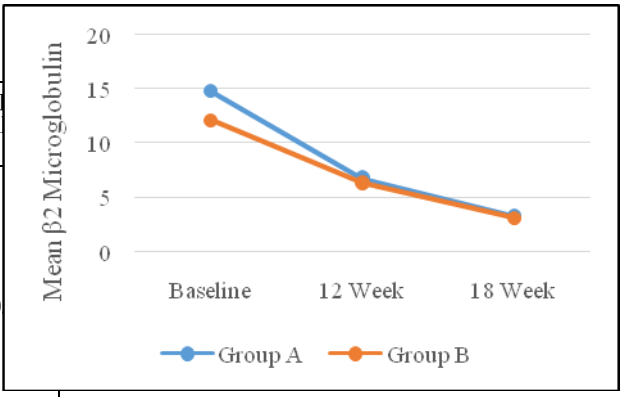


**Figure No.2: Comparison of β2 microglobulin levels at baseline, 12th week and 18th week in both groups**

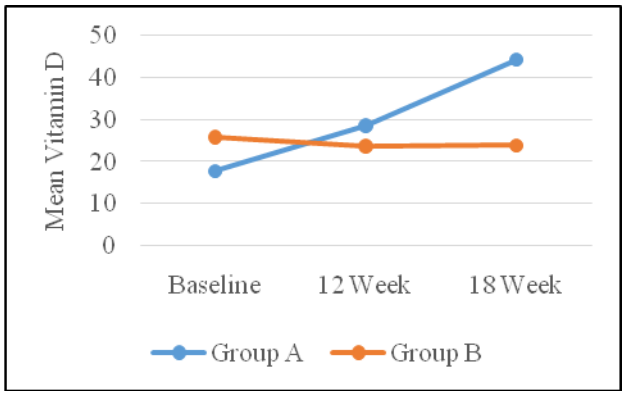


**Figure No.1: Comparison of vitamin D levels at baseline, 12th weeks and 18th weeks in both groups**

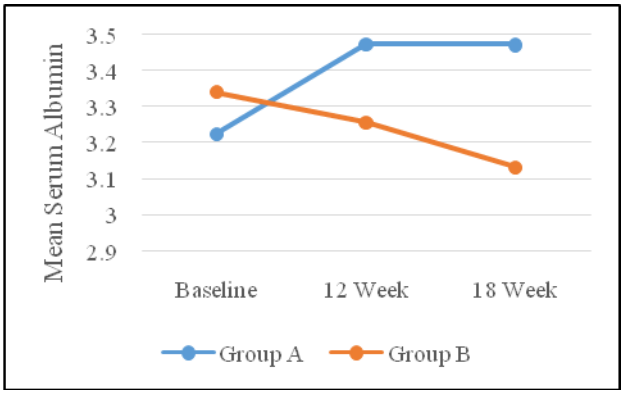


**Figure No.3. Comparison of serum Albumin levels at baseline, 12th week and 18th week in both groups**

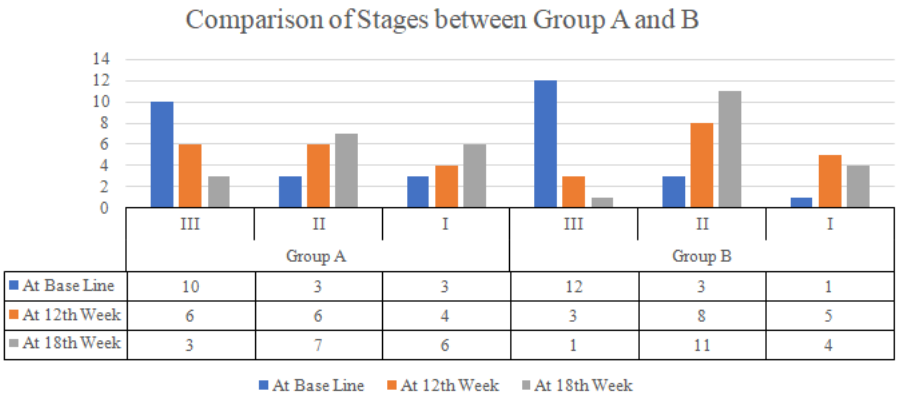


**Figure No.4. Comparison of stages between group A and group B at baseline, 12th week and 18th week**

## DISCUSSION

Multiple myeloma is a debilitating malignancy of plasma cells that constitutes 1% of all malignancies and 10% of all haematological neoplasms.[13] Five year relative survival rate is 52.2%.[14, 15, 16]

In our study, out of total 32 patients of multiple myeloma, 22 (68.75%) had clinical stage-III, while 6 (18.75%) were in stage-II and only 4 (12.5%) were in stage-I of disease. All the patients in both the groups received chemotherapy. In an American study by Ng AC et al in 2009, only 3 (2.8%) patients had clinical stage-III, while 71 (67%) patients were in stage-II and 32 (30.2%) patients were in stage-I of disease respectively.[17] In a Turkish study by Yokus O et al in 2017, 15 (48.4%) patients had clinical stage-III, while 11 (35.5%) patients were in stage-II and only 5 (16.1%) patients were in stage-I of disease respectively.[18]

A higher number of patients in our study were in stage-III in contrast to the American study. This may be due to the fact that many patients in our population present late to specialized centers due to many socio-economic factors.

Favorable increases in mean vitamin D level from 17.86 ± 14.23 ng/ml at baseline to 44.14 ± 20.9 ng/ml at 18 week was seen in group A patients where as in group B patients, it was 25.95 ± 15.89 ng/dl at baseline to 23.92 ± 14.11 ng/dl at 18 weeks follow-up respectively. Comparison of mean vitamin D levels at 18 week follow-up among both groups was statistically significant with p value 0.003.

In German study by Lauter B et al in 2015, mean vitamin D levels among multiple myeloma patients was 14.8 ng/mL which increased to 24.0 ng/ml after vitamin D supplementation for 1 year. Results were significant with p value 0.001.[19] Comparatively good response in shorter period of time was observed in our study due to difference of dose of vitamin D supplementation. In our study, vitamin D supplementation in group A patients was given in the form of oral capsules at a dose of 5000 IU per day (35000 IU weekly).

In our study, comparison of β2 microglobulin between the two groups at 18th week follow-up was found statistically insignificant. In Australian study by Diamond T et al in 2009, β2 microglobulin level in Quartile-1 (severely deficient) was 5.5 ± 6.5 mg/L, in Quartile-2 (deficient) was 4.5 ± 4.1 mg/L, in Quartile-3 (insufficient) was 5.5 ± 4.8 mg/L and in Quartile-4 (sufficient) was 4.0 ± 3.8 mg/L respectively.[20]

β2 microglobulin is an important prognostic indicator of multiple myeloma. A patient with a level less than 4 mg/L is expected to have a median survival of 43 months, while one with a level over 4 mg/L has a median survival of only 1 year.[21] In our study, however a little rapid fall in β2 microglobulin level was observed in patients of group A but on comparison with group B at 18th weeks was found statistically insignificant. Our follow-up was maximally up to 18 weeks only which was one of the limitations of the study.

In our study, comparison of mean serum albumin between the two groups at 18th week follow-up was found statistically insignificant. In study at Mayo clinic by Ng AC et al, among 35 myeloma patients of vitamin D deficient group, serum albumin was 3.12 g/dl and among 113 patients of non-vitamin D deficient group, serum albumin was 3.39 g/dl.[17]In Australian study by Diamond T et al, mean serum albumin level in Quartile-1 (severely deficient) was 30 ± 8 mg/L, in Quartile-2 (deficient) was 36.1 ± 6 mg/L, in Quartile-3 (insufficient) was 35.9 ± 4 mg/L and in Quartile-4 (sufficient) was 35.5 ± 5 mg/L respectively.[20] Results of these studies were similar to results of our study and were found insignificant.

On relationship of vitamin D with multiple myeloma, largest published series is from the Mayo Clinic comprising of 148 newly diagnosed multiple myeloma patients for which no survival association was found, but there were associations between low vitamin D levels (< 20 ng/mL) and higher serum CRP, serum creatinine and ISS stage.[17]

Interestingly, according to our original hypothesis vitamin D therapy along with chemotherapy in multiple

myeloma showed improvement in overall outcome in patients in all three stages of disease. Deficient group showed more skeletal morbidity, pathological fractures and vertebral compressions than sufficient groups.

# CONCLUSION

Although our study provided cross sectional perspective of significant improvement of vitamin D levels in multiple myeloma patients with supplementation, suggesting its potential role on natural history and clinical progression but using laboratory parameters like β2 microglobulin and serum albumin alone has shown no statistically significant results at short term follow-up. This suggests a need for larger population based studies both to confirm our findings at long term follow-up and to prospectively assess the role of vitamin D deficiency in disease progression and overall survival of multiple myeloma patients.

**Author's Contribution:**

| | |
|---|---|
| Concept & Design of Study: | Faiza Shafqat |
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| Revisiting Critically: | Faiza Shafqat |
| Final Approval of version: | Faiza Shafqat |

**Conflict of Interest:** The study has no conflict of interest to declare by any author.

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