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CALCIUM LEVELS IN MULTIPLE MYELOMA PATIENTS BEFORE AND AFTER CHEMOTHERAPY

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ABSTRACT

Objective: This study was done to assess calcium levels in multiple myeloma patients before and after chemotherapy.

Material and Methods: The present study was conducted in the Department of Biochemistry in collaboration with Department of Medicine, Pt B D Sharma PGIMS, Rohtak. Twenty newly diagnosed patients of Multiple Myeloma (MM) were enrolled for the study. Five mL of venous blood was collected aseptically from antecubital vein in a plain red capped vacutainer after taking written consent. Samples were processed by centrifugation and analysed on the same day. We had been done calcium levels were analyzed on auto-analyzer (Randox Suzuka, United Kingdom, model no. 6L7WD5J) by using kits provided by Randox laboratories.

Results: It was observed that mean S.calcium levels were (10.40±1.19) before and (9.23±0.80) after chemotherapy in MM patients.

Conclusion: Hypercalcemia is the most common metabolic complication of multiple myeloma. Bone destruction in patients with myeloma occurs due to increased osteoclastic bone resorption.

Key Words: Multiple myeloma (MM), calcium levels, chemotherapy

INTRODUCTION

Multiple myeloma is a neoplastic plasma-cell disorder that is characterized by a single clonal proliferation of malignant plasma cells in the bone marrow, monoclonal protein in the blood or urine and which cause organ dysfunction.[1] Its incidence increases with age and is higher in males. It is more common at 60-70 yrs of age.[2]

The common signs and symptoms of MM are anemia, renal failure, hypercalcemia, skeletal events like bone pain or bone fractures, infection, fatigue, loss of appetite and weight loss.[3]

Osteolytic bone lesions are most common in patients with MM. It cause bone pain or bone fracture either spontaneously or due to trivial injury. Bone destruction in patients with myeloma occurs due to increased osteoclastic bone resorption. New bone formation is also inhibited in them. Lymphotoxin, interleukin-1β, parathyroid hormone related protein (PTHrP), and IL-6 produced by the myeloma cells act as osteoclast-activating factors (OAF)

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in multiple myeloma. Lymphocytes produces interleukin-1 (IL-1), IL-6, colony-stimulating factors and lymphotoxins and the macrophages produces TNF-α, IL-1, granulocyte-macrophage-colony stimulating factor (GM-CSF), IL-6 and macrophage-colony stimulating factor (M-CSF). All these cytokines increase osteoclast formation and/or osteoclastic bone resorption.[4] Bone lesions also occurred due to imbalance between osteoblasts and osteoclasts.

Diagnosis of MM is done by identification of abnormal monoclonal plasma cells in the bone marrow, M protein in the serum or urine. A complete blood count, peripheral blood smear, bio-chemistry includes calcium, creatinine, β2-M, lactate dehydrogenase and routine urinalysis. Serum protein electrophoresis, immunofixation, nephelometric quantitation of immunoglobulins and measurement of free light chains.[5]

Treatment options for MM are chemotherapy and stem cell transplantation. In bone pain use systemic analgesic (paracetamol), bisphosphonates and local measures. Intravenous pamidronate or zoledronic acid is beneficial in pain caused by osteolytic disease and as an adjunctive treatment for patients receiving radiation therapy, analgesics or surgical intervention to stabilize fractures or impending fractures. The patients who develops deterioration of renal function after starting bisphosphonates in these patients should stop the drug.[6] Zoledronic acid reduced the overall risk of developing skeletal complications by an additional 16% as compared to pamidronate.[7] Bisphosphonates are very useful for the management of malignancy-related hypercalcemia, but they can cause renal failure and hypocalcemia in MM patients.[8] Calcitonin also reduce calcium levels without causing hypocalcemia and risk of renal toxicity.

AIM & OBJECTIVES

This study was done to assess serum calcium levels in multiple myeloma patients before and after chemotherapy.

MATERIAL AND METHODS

The present study was conducted in the Department of Biochemistry in collaboration with the Department of Medicine (Clinical Hematology Unit), Pt. B.D. Sharma PGIMS, Rohtak. Twenty newly diagnosed patients of MM were enrolled for the study. The diagnosis was made by history, clinical examination, bone marrow examination and electrophoretic studies and other tests. Patients were included and excluded as per following criteria.

Inclusion criteria: Multiple myeloma patients after confirmed diagnosis.

Exclusion criteria: Patients on steroids, suffering from any renal, liver pathology or any other malignancy.

Cases were categorized into two groups:

Group I: At the time of presentation (pre-treatment) i.e. before the start of chemotherapy.

Group II: After 6 months of chemotherapy.

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An informed written consent was obtained from the patients who participated in the study. Two mL of venous blood sample was collected under aseptic conditions from the patients before and after the treatment in a plain red capped vacutainer. Samples were processed within one hour of collection. Serum was separated by centrifugation (2000rpm for 10 minutes) after clotting and analysed on the same day. We had done serum calcium levels were analyzed on auto-analyzer (Randox Suzuka, United Kingdom, model no. 6L7WD5J) by using kits provided by Randox laboratories. All the analyses were performed by using the statistical package (IBM SPSS 20). Data were considered to be significant if p value < 0.05. Results were expressed as Mean± SD.

RESULTS AND OBSERVATIONS

Table 1: Mean serum total calcium (mg/dL) levels in group I and group II expressed in Mean±SD (Range).

Parameters with normal range	Group I	Group II	p-value
S. total calcium (8.1 to 10.4 mg/dL)	10.40±1.19 (8.0 to 12.5)	9.23±0.80 (7.2 to 10.5)	**0.000**

Mean±SD of S. total calcium levels in MM patients was 10.40±1.19 mg/dL in group I and 9.23±0.80 mg/dL in group II patients. This difference in mean serum total calcium levels was statistically **significant** with p-value 0.000.

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Figure 1: Mean serum total calcium levels in group I and group II

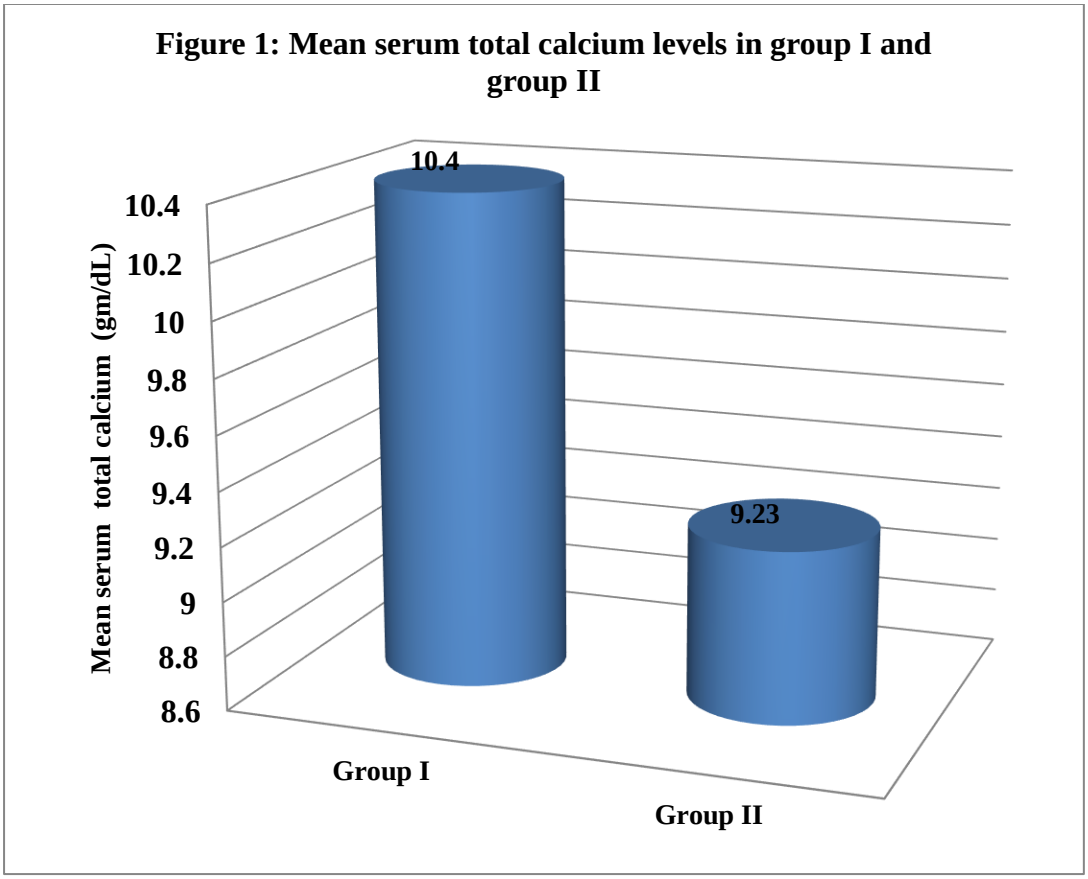

Table 2: Showing patient distribution based on serum total calcium levels in group I and group II

S.total calcium (mg/dL)	Group I		Group II	
	No. of cases	Percentage (%)	No. of cases	Percentage (%)
<8.1	1	5%	1	5%
8.1 to 10.4	7	35%	18	90%
>10.4	12	60%	1	5%

It showed that out of 20 patients, in group I, twelve (60%) patients had increased serum calcium levels >10.4 mg/dL and seven (35%) patients had serum calcium levels between 8.1-

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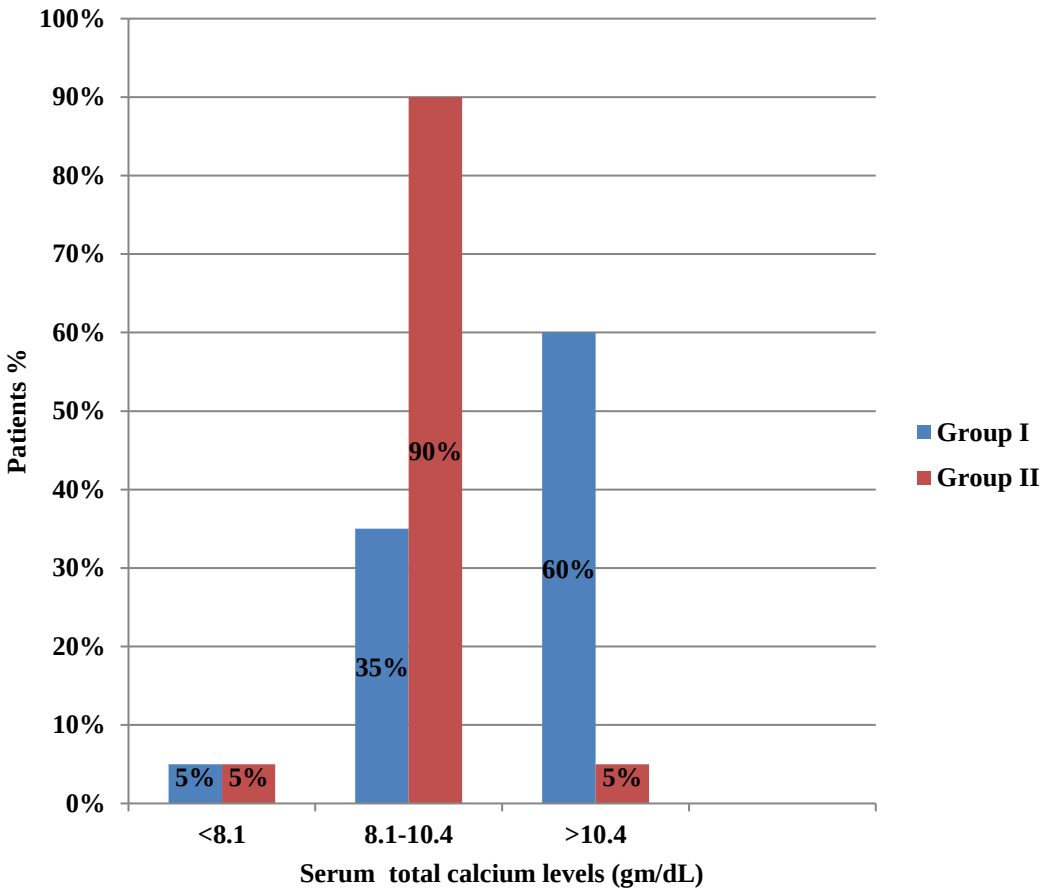
10.4 mg/dL. But in group II, eighteen (90%) patients had serum calcium levels between 8.1-10.4 mg/dL, one (5%) patient had serum calcium levels <8.1 mg/dL and one (5%) patient had serum calcium levels >10.4 mg/dL. It showed that after treatment in majority of the patients serum calcium levels becomes normal between 8.1 to 10.4 mg/dL.

Figure 2: Patients distribution based on serum total calcium levels (gm/dL) in group I and group II



DISCUSSION

Multiple myeloma (MM) is a plasma cell disorder in which proliferation of a single clone of plasma cells occur that are derived from the B cells in the bone marrow. It accounts for almost 10% of all the hematologic malignancies.[9]

Multipe Myeloma is asymptomatic or symptomatic, depending on the absence or presence of myeloma-related organ dysfunction, which are hypercalcemia, renal insufficiency, anemia, and bone disease. Bony lesions can occur in the 80% of patients. The other clinical features of MM are infection, fatigue, loss of appetite and weight loss.[3]

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The present study included 20 newly diagnosed patients of multiple myeloma. Serum calcium levels were analyzed before starting chemotherapy (group I) and after completing 6 months of treatment (group II).

In the present study, mean serum total calcium levels in group I was 10.40±1.19 mg/dL (range 8.0 to 12.5 mg/dL) and in group II was 9.23±0.80 mg/dL (range 7.2 to 10.5 mg/dL). It was decreased in group II and this decrease was statistically significant (p-value 0.000). Kyle et al, reported hypercalcemia (calcium level ≥11 mg/dL) in 13% of the patients.[10] Balwani et al, reported hypercalcemia in 28% cases.[11] Poudel et al, reported hypercalcemia in 15 (39.5%) cases.[12] Kaur et al, also reported hypercalcemia in 46% of the patients.[13]

In present study, out of 20 patients in group I, twelve (60%) patients had serum calcium levels above normal range and in group II, eighteen (90%) patients had serum calcium levels between normal range. Normal reference range for serum calcium was 8.1 to 10.4 mg/dL.[14] Hypercalcemia in MM patients is due to osteoclastic bone resorption which causes mobilization of calcium from the bone.

Kendler et al, studied that there is interaction between adhesive molecules which are expressed on the myeloma cells and the marrow micro environment. These adhesive molecules causes the production of cytokines that increase the growth of myeloma cells and induce the osteoclast formation and cause osteoclastic bone resorption. Myeloma cells binds to marrow stromal cells by the adhesive molecules such as Very late antigen-4 (VLA-4) and 5, Monocyte chemotactic protein-1 (MCP-1), Intercellular adhesion molecule-1 (ICAM-1), Cluster of differentiation (CD21), CD44, Leukocyte function- associated antigen-1 (LFA-1) and 3, which causes the production of IL-6 that enhance the growth of both myeloma cells and human osteoclastic bone resorption.[15]

Terpos et al, studied the role of cytokines in the pathogenesis of osteolytic bone lesions. IL-6 and IL-1β are the potential mediators of osteoclastic bone resorption in MM patients. IL-6 upregulates the stromal cell expression of receptor activator of nuclear factor-κB (RANK) ligand through a STAT-3 pathway and cause osteoclast formation. IL-1 causes osteolytic lesions by induction of prostaglandin-E2 which is produced by stromal cells and also acts directly on the osteoclast to increase its activity. Macrophage inflammatory protein (MIP)-1α and MIP-1β also plays a important role in bone resorption by MM cells. These chemokines stimulate the formation of osteoclast like cells (OCLs). Antibodies against MIP-1 completely suppress the osteoclast inducton. So MIP-1α and MIP-1β are the important factors for the development of lytic bone lesions.[16]

García-Ortiz et al, studied the role of dickkopf1 (DKK1) in the development of osteolytic bone lesions in multiple myeloma. DKK1 is the inhibitor of osteoblast

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differentiation and is associated with the presence of lytic bone lesions in MM patients. For the growth and differentiation of osteoblasts Wnt signaling pathway is important and acts in several developmental processes. But DKK1 is the antagonist of Wnt signaling pathway. DKK1 protein is present in myeloma patients with bone lesions but absent in the myeloma patients without bone lesions. The higher levels of DKK1 in the bone marrow of MM patients causes the loss of viability of osteoblastic stem cells.[17]

Hameed et al, studied that MM patients produce more levels of Stromal-Derived-Factor-1α (SDF) protein and elevated plasma levels of SDF-1α is related with the presence of multiple radiological bone lesions in individuals with MM. SDF-1α plays an important role in osteoclast precursor recruitment and activation. The activation of osteoclasts in response of SDF-1α is associated with an increase expression of osteoclast activation-related genes, which are Receptor activator of nuclear factor-kB (RANK), RANKL, Tartrate-resistant acid phosphatise (TRAP), Matrix metalloproteinase (MMP-9), Carbonic anhydrase-II (CA-II), and Cathepsin K.[18]

After treatment with bisphosphonates serum calcium levels becomes normal due to reduction in osteoclastic bone resorption and mobilization of calcium into bones. Ashcroft et al, studied that bisphosphonates concentrate at the interface of the active osteoclast & bone resorption surface and inhibits osteoclast activity. Bisphosphonates also act by normalising the deregulated cytokines to restore the bone-marrow microenvironment, interrupt the several feedback loops that causes the growth of malignant clone, osteoclast development and activity.[19] Serum calcium levels also decreased as a result of glucocorticoids and adequate hydration during treatment of MM. So after treatment serum calcium becomes normal.

CONCLUSION: Osteolytic bone lesions are most common in patients with MM. It cause bone pain or bone fracture. Bone destruction in patients with myeloma occur due to increased osteoclastic bone resorption. New bone formation is also inhibited in them. Bone lesions also occurred due to imbalance between osteoblasts and osteoclasts. After treatment serum calcium levels becomes normal.

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CONFLICT OF INTEREST: Nil

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