ISSN: 0975-3583, 0976-2833 VOL16, ISSUE1, 2025

PROGNOSTIC SIGNIFICANCE OF SERUM ALBUMIN IN MULTIPLE MYELOMA PATIENTS BEFORE AND AFTER CHEMOTHERAPY

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ABSTRACT

Objective: To study the estimation of serum albumin 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. Two 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. Serum albumin estimation was done by BCG (bromo cresol green) albumin assay method on Randox autoanalyzer.

Results: It was observed that mean serum albumin levels in MM patients at the time of presentation was 2.43±0.21 gm/dL. After completing six months of chemotherapy, serum albumin levels showed an increase with a mean value 4.09±0.47 gm/dL. This difference in mean albumin levels was statistically significant with p value = 0.001.

Conclusion: In conclusion, decreased level of serum albumin in MM is due to plasmocytic infiltration of hepatic tissues. After treatment liver function improves which leads to improvement in serum albumin levels.

Key Words: Multiple myeloma (MM), Albumin, Chemotherapy.

INTRODUCTION

The plasma cell disorders are monoclonal neoplasms that develops from common progenitors in the B-lymphocyte lineage. Mature B lymphocytes are destined to produce IgG bear surface immunoglobulin molecules of both M and G heavy chain isotypes. Under normal circumstances, maturation to antibody secreting plasma cells and their proliferation is stimulated by exposure to the antigen for which the surface immunoglobulin is specific but in the plasma cell disorders, the control over this process is lost. The clinical features of all the plasma cell disorders are due to expansion of the neoplastic cells, secretion of cell products and due to host response to the tumor [1].

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Multiple Myeloma (MM) is a neoplastic disorder characterized by a single clone abundance of plasma cells in the bone marrow and generating a monoclonal immunoglobulin which cause end organ damage and related complications such as anemia, renal insufficiency, hypercalcemia, skeletal events like bone pain or bone fracture, infection and nausea & vomiting [2].

MM arises from an asymptomatic premalignant proliferation of monoclonal plasma cells that are derived from post germinal center B cells. Multistep genetic and micro environmental changes lead to the transformation of these cells into a malignant neoplasm [3]. Its incidence increases with age and is more common in males than females and blacks have twice the incidence rate in comparison to whites. It accounts 1.3% of all malignancies in whites, 2% in blacks and 13% of all hematologic cancer in whites & 33% in blacks. It is more common at 60-70 years of age [1]. In India, the incidence varies from 0.3-1.9/100,000 for males and 0.4-1.3 / 100,000 for females [4].

Diagnostic criteria for multiple myelom [5]

1. Clonal bone marrow plasma cells more than or equal to 10% or biopsy proven plasmacytoma.
2. Presence of serum or urinary monoclonal protein (except in patients with true non secretory multiple myeloma).
3. Evidence of myeloma related organ dysfunction commmonly summerized under the CRAB acronym.

a. C: Hypercalcemia: serum calcium more than or equal to 11.5mg/dl.
b. R: Renal insufficiency: Serum creatinine > 2mg/dL or estimated creatinine clearance< 40ml/ min.
c. A: Anemia: normochromic, normocytic with a hemoglobin value of 2g/dL below the lower limit of normal or a hemoglobin < 10g/dL.
d. B: Bone lesions: Radiologically detected lytic lesion, severe oesteopenia or pathologic fracture.

Staging system for MM :

International Staging System [1]

Stage I - β_2M< 3.5, ALB ≥ 3.5

Stage II - β_2M< 3.5, ALB<3.5or β_2- 3.5 to 5.5

Stage III - β_2M>5.5

MM is common in those individuals who works in agriculture field or with allergies. Hypersensitivity and defective immune response play a role in the occurence of this tumor [6]. Myeloma cells bind to bone marrow stromal cells (BMSCs) and extracellular matrix (ECM) via cell surface adhesion molecules which cause myeloma cell growth, survival and migration in the bone marrow. These effects are due to direct myeloma cell-BMSC binding

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and due to induction of various cytokines including interleukin-6 (IL-6), insulin-like growth factor type I (IGF-I), vascular endothelial growth factor (VEGF) and stromal cell derived growth factor (SDF-1α). Growth and migration are mediated via Ras/Raf/mitogen-activated protein kinase, PI3K/Akt and protein kinase C signaling cascades [1].

Serum albumins are found in blood plasma, in tissues and body secretions. In extravascular proteins, 60% is albumin. Human serum albumin is a protein synthesized in the liver having molecular weight 65K and 585 amino acids. Its amino acid sequence contains 17 disulphide bridges, one free thiol and a single tryptophan [7]. It is a stable protein, resists denaturation to higher temperatures than other plasma proteins. Albumin has a high abundance of charged amino acids that contribute to its high solubility and it has a net negative charge of about 12 at neutral pH. So albumin contributes about 6 to 10 mmol/L to the anion gap at normal albumin concentrations of 0.5 to 0.8 mmol/L.

The concentration of serum albumin is mainly maintained by hepatic albumin synthesis and endogenous catabolism. Transient shift in the intravascular/interstitial albumin distribution, with or without changes in the plasma and interstitial fluid volumes may temporarily alter the serum albumin levels. Albumin maintained the colloid osmotic pressure or transport many substances including fatty acids, bilirubin, drugs, calcium and metals. Increased albumin concentration occur with dehydration and low concentration seen in some pathologic conditions like excessive protein loss through urinary or gastrointestinal tract. In patients with MM, hypoalbuminemia occurs due to renal failure & proteinuria which leads to excess protein loss, coexisting liver disease and poor nutritional state impairing albumin synthesis. Patients who have a positive urine protein test have a slightly lower albumin level than those with a negative test. Many inflammatory disorders lower the albumin levels by increasing capillary permeability, decreased synthesis due to inflammatory cytokines or increased catabolism by cells. Albumin levels also decreased in burn patients [8].

Hypoalbuminemia is most common in patients with MM. Albumin helps to differentiate MM from benign monoclonal gammopathy and also serves as an important prognostic factor in patients with MM. Hypoalbuminemia in patients with MM is related to the extent of tumor cell growth. The serum albumin level act as a simple index of disease activity. Pre treatment serum albumin had the better predictive value in the early course of the disease [9].

Serum albumin level is closely related to the severity of MM. Low hemoglobin level, high concentrations of serum β2M and M protein are positively related to low albumin levels and are associated with disease severity in MM. Low serum albumin levels are associated with poor prognosis in MM. Serum albumin levels are inversely related with the serum IL-6 levels. IL-6 is a potent myeloma cell growth factor. IL-6 is a proinflammatory cytokine that stimulates B cell maturation and proliferation and its overproduction occur in a variety of B cell malignancies including MM, Non-Hodgkin's lymphoma and chronic lymphocytic leukemia. IL-6 levels are high in patients with MM and myeloma cells have high levels of IL-6 receptors. Serum albumin levels decrease in MM due to inflammation mediated by cytokines such as TNF and IL-6 [10].

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AIM & OBJECTIVES

The aim of this study is to estimate serum albumin 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.

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 for estimation of serum albumin. 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. Serum albumin estimation was done by BCG (bromo cresol green) albumin assay method on Randox autoanalyzer [11]. 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

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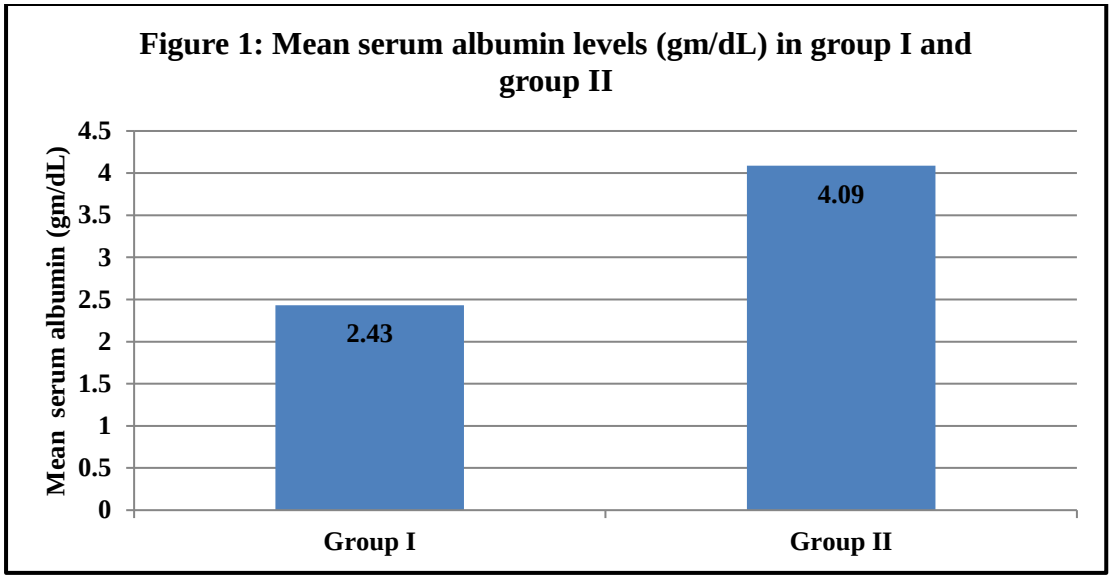

Figure 1: Mean±SD of serum albumin levels in MM patients before treatment was 2.43±0.21 gm/dL. After completing six months of chemotherapy, serum albumin levels showed an increase with a mean±SD of 4.09±0.47 gm/dL. This difference in mean albumin levels was statistically significant with p value 0.001.

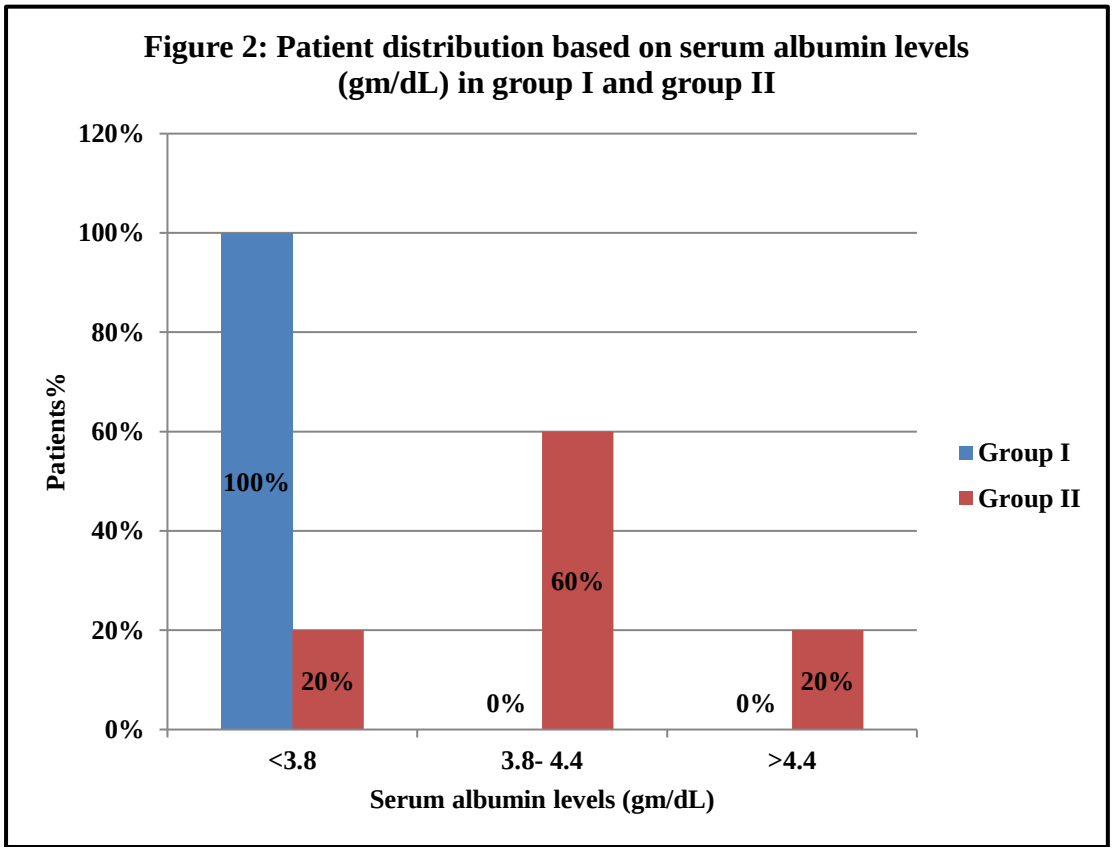

Figure 2: It showed that all the twenty (100%) patients had decreased serum albumin levels <3.8 gm/dL in group I. But in group II, Out of 20 patients, twelve (60%) patients had serum

ISSN: 0975-3583, 0976-2833 VOL16, ISSUE1, 2025

albumin levels between 3.8 to 4.4 gm/dL and four (20%) patients had serum albumin levels <3.8 gm/dL and other four (20%) patients had >4.4 gm/dL. It showed that after treatment in majority of the patients serum albumin levels becomes normal between 3.8 to 4.4 gm/dL.

DISCUSSION

In the present study, mean serum albumin levels in group I was 2.43±0.21 gm/dL. In group II, mean serum albumin levels was 4.09±0.47 gm/dL (figure 1). Normal reference range for serum albumin was 3.8 to 4.4 gm/dL [11]. It was observed that serum albumin levels increased in MM patients after completing 6 months of chemotherapy (group II) and this increase in serum albumin levels was statistically significant (p value 0.001).

In group I, all the twenty (100%) patients had serum albumin levels below normal range and in group II, four (20%) patients had serum albumin levels below normal range, twelve (60%) patients had serum albumin level within normal range and four (20%) patients had serum albumin levels above normal range (figure 2). High serum albumin levels in these four patients may be due to increase in urine output which leads to dehydration, but the exact cause could not found.

Yuan et al, also reported marked hypoalbuminemia with serum albumin values of 2.0 gm/100 ml or less was present at the time of diagnosis [12].

Kim et al, also reported serum albumin levels <3.5 gm/dL in 32.4% of the patients and ≥ 3.5 gm/dL in 67.6% of the patients. In present study all the patients had low serum albumin levels because most of the patients are of older age. Kim et al, also reported lower serum albumin levels in older age patients [10]. Abnormalities of liver function and decreased level of serum albumin in MM are due to hepatic infiltration by plasma cells which is common in MM [13]. After treatment liver functions improves which leads to increase serum albumin levels.

Renal injury causes losses of proteins in urine. Both charge and size normally prevent plasma albumin, globulins, and other high-molecular-weight proteins from crossing the glomerular wall, but when this barrier is disrupted, plasma proteins may leak into the urine. Smaller proteins (<20 kDa) are freely filtered but are readily reabsorbed by the proximal tubule. Healthy individuals excrete <150 mg/d of total protein and <30 mg/d of albumin. The other proteins in the urine are secreted by the tubules (Tamm-Horsfall, IgA, and Urokinase) or small amounts of filtered β2-microglobulin, apoproteins, enzymes and peptide hormones. Another mechanism of proteinuria due to excessive production of an abnormal proteins that exceeds the capacity of the tubule for reabsorption. This is most commonly occurs with plasma cell dyscrasias, such as multiple myeloma, amyloidosis and lymphomas that are associated with monoclonal production of immunoglobulin light chains [14]. After treatment renal functions improves which decreases proteinuria leads to improvement in the serum protein levels.

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Kim et al also studied that serum albumin level is closely related to the severity of MM. Low hemoglobin level, high concentrations of serum β2M and M protein, all of these are positively related to low albumin levels and are associated with disease severity in MM. Low serum albumin levels are associated with poor prognosis in MM. Serum albumin level are inversely related with the serum IL-6 level. IL-6 is a potent myeloma cell growth factor. IL-6 is a proinflammatory cytokine that stimulates B cell maturation and proliferation and its over production occur in a variety of B-cell malignancies including MM, Non-Hodgkin's lymphoma and chronic lymphocytic leukemia. IL-6 levels are high in patients with MM and myeloma cells have high levels of IL-6 receptors. Serum albumin levels decrease in MM patients due to inflammation mediated by cytokines such as TNF and IL-6. Low serum albumin level, high levels of serum creatinine and advanced age are independent pretreatment prognostic factors for survival in MM patients [10].

In MM patients, serum CRP levels were significantly higher and its production is totally dependent on the IL-6. So serum albumin levels correlates inversely with the serum IL-6 levels and IL-6 act by inhibiting albumin synthesis in the hepatocytes [15].

CONCLUSION

In conclusion, serum albumin estimation helps to differentiate myeloma from benign monoclonal gammopathy and also serves as an important prognostic factor in patients with multiple myeloma. Albumin levels are low in multiple myeloma patients due to liver and kidney involvement and after treatment liver and kidney functions improves which leads to increase serum albumin levels.

ACKNOWLEDGMENTS: Nil

CONFLICT OF INTEREST: Nil

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