



Assessment of Neutrophil Gelatinase-Associated Lipocalin, Osteocalcin, and Selected Biomarkers in Patients with Multiple Myeloma

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Abstract

Background: Multiple myeloma causes progressive bone destruction and renal impairment, highlighting the need for reliable biomarkers including NGAL, osteocalcin, and others. **Aims of the study:** This study aimed to evaluate neutrophil gelatinase-associated lipocalin (NGAL), osteocalcin, and selected biochemical biomarkers in patients with multiple myeloma and assess their diagnostic performance and clinical associations. **Methodology:** This case-control study was conducted at Baghdad Teaching Hospital, Iraq, between February and May 2024, including 48 patients with confirmed multiple myeloma and 52 healthy controls aged 25–90 years. Patients were classified according to renal function status. Fasting blood samples were collected for biochemical and immunological analyses. Blood urea, creatinine, and calcium were measured using an automated chemistry analyzer, while serum NGAL, osteocalcin, fetuin-A, and β 2-microglobulin were quantified by sandwich ELISA under standardized quality-controlled laboratory conditions. **Result:** Patients with multiple myeloma and healthy controls were comparable in age and sex ($P > 0.05$). Serum creatinine, NGAL, β 2-microglobulin, and osteocalcin levels were significantly higher in patients, whereas calcium and Fetuin-A concentrations were significantly lower (all $P < 0.001$). No significant sex-related differences were observed among patients. Correlation analysis revealed predominantly weak-to-moderate biomarker associations. ROC analysis identified β 2-microglobulin (AUC = 0.949) and NGAL (AUC = 0.924) as the most accurate diagnostic biomarkers, followed by Fetuin-A and osteocalcin. **Conclusions:** The sensitivity and specificity of NGAL and β 2-microglobulin were excellent for multiple myeloma, and the levels of osteocalcin and Fetuin-A revealed disease-related bone remodeling. Biomarker assessment could be used to enhance the diagnosis, evaluation of renal and skeletal involvement, and clinical monitoring of disease course.

Keyword: Multiple myeloma; Neutrophil gelatinase-associated lipocalin (NGAL); β 2-microglobulin; Osteocalcin; Fetuin-A.

Introduction:

Multiple myeloma (MM) is a malignant hematological neoplasm with an excessive production of monoclonal immunoglobulins or free light chains due to clonal proliferation of plasma cells in the bone marrow. It accounts for about 10% of all hematological malignancies and nearly 1-2% of all cancers worldwide, is a disease of older ages with a median age of diagnosis of about 65-70 years (Cowan et al ,2022; Padala et al,2021). Multiple myeloma is still an incurable disease with relapses and progressive organ dysfunction, despite the spectacular progress in diagnostic techniques and therapeutic strategies. The clinical symptoms of MM are believed to be caused mainly by the infiltration of plasma cells and the toxic effect of the monoclonal proteins, and the characteristic CRAB (hypercalcemia, renal failure, anemia, and osteolytic bone lesions) features are well known. Therefore, early detection of biochemical changes that are linked to the disease process is crucial for appropriate diagnosis, risk categorization, treatment choices and treatment response monitoring (Fend et al,2023).

Renal involvement is one of the most common and clinically relevant complications of MM, occurring in 20-40% of patients at diagnosis and in even more patients throughout disease progression. Kidney injury caused by myeloma is mainly caused by the filtration of large amounts of free light chain from myeloma in the glomeruli, followed by reabsorption by the epithelial cells of the proximal tubule (Wang et al,2024). This process results in oxidative stress, inflammatory signaling, tubular apoptosis and cast nephropathy, eventually leading to progressive renal dysfunction. In general, conventional renal function test (CFT) (blood urea nitrogen and serum creatinine) are not useful in detecting early tubular damage because they are abnormal after a significant loss of nephrons. Thus, there has been a growing desire to find new markers that could be used to identify subclinical renal damage, before the onset of irreversible renal dysfunction (Yadav et al ,2016; Dimopoulos et al ,2016).

Neutrophil gelatinase associated lipocalin (NGAL) or lipocalin-2 has proven to be one of the most promising biomarkers of acute and chronic kidney injury. NGAL is a glycoprotein of approximately 25 kDa, which is synthesised during inflammation, ischemia, oxidative stress and tissue trauma by activated neutrophils, renal tubular epithelial cells, hepatocytes and several epithelial tissues (Romejko et al ,2023; Ning et al ,2018).After renal tubular injury, NGAL is quickly excreted in serum and urine within just a few hours, and is thus significantly more sensitive than the conventional renal biomarkers. In addition to playing a role in kidney injury, NGAL is involved in the transport of iron, an innate immunity modulator, inflammatory response, cell proliferation, and tumor progression (Andreucci et al ,2016). Although NGAL has been associated with renal damage, it has also been observed at higher levels in different hematologic malignancies, and this protein could also be related to tumor associated inflammation and disease activity. Thus, the measurement of NGAL in multiple myeloma patients could be useful to assess not only renal involvement but also to measure disease severity (Woziwodzka et al,2021).

Another important feature of MM is bone disease which causes a major morbidity such as bone pain, pathological fractures, spinal cord compression, and hypercalcemia. The development of myeloma bone disease is a result of a significant alteration of normal bone turnover, with an overactive bone-resorbing osteoclast population and a suppression of osteoblast differentiation and activity (Bernstein et al , 2022). Regulated by complex interactions between malignant plasma cells, bone marrow stromal cells, inflammatory cytokines, receptor activator of nuclear factor-kappa B ligand (RANKL), osteoprotegerin, Dickkopf-1 (DKK-1), sclerostin, and other signaling pathways that act together to stimulate osteolysis and suppress new bone formation. Due to the significant impact of skeletal complications on quality of life and survival, biomarkers reflecting bone turnover have been gaining greater clinical interest (O'Donnell et al ,2017; Zhang et al,2022).

The non-collagenous protein, produced mainly by mature osteoblasts, has been recognized as a biochemical marker of bone formation and skeletal remodeling, and is called osteocalcin. Circulating levels of osteocalcin under physiological conditions play a role in the mineralisation, and in calcium

homeostasis; a decrease or increase in circulating levels reflect disturbances of osteoblast activity and bone metabolism (Martiniakova et al , 2024). In patients with MM, osteocalcin levels can be affected by disease stage, the degree of osteolytic lesions, renal function, inflammatory status and current antiresorptive treatment. Evaluation of osteocalcin levels may offer valuable clues to the extent of bone remodeling and help guide imaging in the diagnosis of bone disease associated with myeloma, but conflicting results have been reported regarding levels in previous studies (Han et al ,2018).

There are several other biomarkers that have also shown potential to be used to assess disease burden and organ involvement in MM: β 2-Microglobulin is a well-established biomarker that is included in the International Staging system due to the fact that it reflects both tumour mass and renal clearance (Argyropoulos et al , 2017). The levels of both creatinine and blood urea have been traditionally used to measure renal dysfunction, but they are not sensitive for early renal injury. Disturbed bone metabolism and osteoclastic activity are indicated by calcium abnormalities, while Fetuin-A, a hepatically synthesized glycoprotein known for its anti-inflammatory and anti-calcification properties, has recently been drawn to its role in mineral metabolism, vascular calcification, and inflammation. Concurrently measuring these markers may thus enable a broad idea of the renal damage, skeletal involvement, inflammatory activity and disease progression in patients with MM (Frantzi et al, 2026).

While several studies have individually studied renal biomarkers or bone turnover markers in multiple myeloma, studies looking at all three together (NGAL, osteocalcin, β 2-microglobulin, Fetuin-A and conventional biochemical parameters) have not been conducted in an identical patient population. In addition, the evidence of the diagnostic performance and interrelationships of these biomarkers is still limited, especially in Middle Eastern populations. Hence, the present study was designed to determine the levels of serum neutrophil gelatinase-associated lipocalin, osteocalcin and some biochemical markers in patients with multiple myeloma, and to compare them with healthy controls, investigate their correlation with renal and bone metabolism markers and explore their diagnostic value in the diagnosis of multiple myeloma.

Methodology:

This case-control study was carried out at Baghdad Teaching Hospital, Baghdad, Iraq from February to May 2024. The study involved 100 people, with 48 of them having been diagnosed with multiple myeloma and 52 who were apparently healthy, and who served as the control group. The age range of the participants was from 25 to 90 years. The diagnosis of MM was confirmed by a specialist hematologist, using clinical, laboratory, radiological and medical history. Based on renal function status, patients were then divided into 2 groups – normal serum urea and creatinine and abnormal serum urea/creatinine level (renal impairment). The healthy controls consisted of hospital employees, patients' relatives who had completed medical history forms that showed no history of hematological malignancy, renal disease, or other chronic systemic disease. Demographic and clinical data were gathered by a standardised structured questionnaire that included drug history, clinical history of the medication and other relevant medical history, age and sex. About 8 mL of serum obtained from each person after a period of fasting was placed in a serum-separator gel tube, then centrifuged at $3,500 \times g$ for 10 minutes. The separated serum was aliquoted and one portion was frozen for routine biochemical analysis while the other portions were kept at -20°C for immunological analysis. Blood urea, blood creatinine and calcium level were measured by automated clinical chemistry analyzer (BS-240) following the manufacturer's instructions. The concentrations of the serum markers, namely neutrophil gelatinase associated lipocalin (NGAL), osteocalcin, fetuin-A and β 2-microglobulin (β 2M), were measured using commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kits from MyBioSource and Bioss Inc. The assays were carried out by a double-antibody sandwich ELISA based principle, where the target antigen

was specifically captured by the pre-coated monoclonal antibodies on the microplate wells, after which it was detected by a biotinylated polyclonal antibody and enzyme-conjugated reagents. The optical density was quantified by microplate reader and the concentration of each biomarker was determined by standard calibration curve for each assay. Analyses in the laboratory were carried out under standard conditions and with a quality control system to ensure the analytical accuracy and repeatability.

Statistical analysis:

Data were analyzed statistically using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). The quantitative data was presented as mean $\pm$ standard deviation (SD), and the qualitative data was presented as frequencies and percentages. Independent-samples t-test was used for differences between two groups and one-way analysis of variance (ANOVA) was used for comparisons among more than two groups, with suitable post hoc tests employed for groups that showed significant differences. Pearson's correlation coefficient was used to evaluate associations between continuous variables. The diagnostic ability of NGAL, osteocalcin, Fetuin-A, β 2-microglobulin, urea, creatinine and calcium was evaluated using receiver operating characteristic (ROC) curve analysis, and the area under the curve (AUC), optimal cutoff value, sensitivity and specificity were determined, along with the 95% confidence interval. A two-tailed P value of less than 0.05 was regarded as being statistically significant.

Ethical approval:

Ethics and Research Committee of Baghdad Teaching Hospital, Baghdad, Iraq reviewed and approved the study protocol. The procedures were all performed in the ethical standards of the Declaration of Helsinki. All subjects gave informed consent prior to enrollment and collection of blood samples, and that no personal information was shared or used for anything other than research purposes.

Results

Comparison of age and sex distribution between patients with multiple myeloma and healthy controls to evaluate baseline demographic comparability.

The demographic parameters for patients with multiple myeloma and healthy controls are shown in Table 1. In terms of age, both the groups were equally matched, and there was no statistically significant difference between the mean age of patients (63.14 ± 18.17 years) and controls (62.41 ± 16.95 years; $P = 0.602$). Likewise, there was no significant difference in sex distribution between the groups ($P = 0.981$). There were more males than females in the patient group (73.5% of patients and 35.3% of controls) and more females than males in the control group. The results found that there were no age or sex related confounding factors that could significantly affect the subsequent biomarker analysis, as the study groups were demographically comparable.

Table 1. Baseline Demographic Characteristics of Patients with Multiple Myeloma and Healthy Controls

Variable		Patient	Control	p-value
Age, mean $\pm$ SD		63.14 ± 18.17	62.41 ± 16.95	0.602
Sex	Male, n (%)	36 (73.5%)	33 (64.7%)	0.981
	Female, n (%)	13 (26.5%)	18 (35.3%)	

Comparison of biochemical parameters and novel biomarkers between patients with multiple myeloma and healthy controls to identify disease-associated alterations.

There are important biochemical and biomarker differences between multiple myeloma patients and healthy controls, as shown in Table 2. The mean age ($P = 0.602$) and mean blood urea concentration ($P = 0.550$) of the two groups were not significantly different. Patients, however, had significantly higher serum creatinine levels than controls (0.82 ± 0.20 vs. 0.67 ± 0.15 mg/dL, $P < 0.001$), reflecting impaired renal

function. Serum neutrophil gelatinase-associated lipocalin (NGAL) and β 2-microglobulin concentrations were markedly elevated in patients (420.71 ± 200.89 vs. 168.98 ± 96.93 ng/mL and 42.41 ± 18.41 vs. 14.64 ± 8.02 mg/L, respectively; both $P < 0.001$). Conversely, calcium and Fetuin-A levels were significantly reduced in the patient group compared with healthy controls (8.82 ± 0.89 vs. 9.70 ± 0.50 mg/dL and 2.93 ± 0.83 vs. 4.91 ± 1.59 , respectively; both $P < 0.001$). Additionally, the osteocalcin level was significantly elevated in multiple myeloma patients compared to controls (28.04 ± 8.69 ng/mL vs 18.39 ± 4.45 ng/mL, $P < 0.001$). The overall results suggest that there are significant changes in renal injury markers, bone metabolism biomarkers, and mineral homeostasis in patients with multiple myeloma, which may have clinical applications in the evaluation and monitoring of this disease.

Table 2. Comparison of Renal Function, Bone Metabolism, and Selected Biomarkers Between Patients with Multiple Myeloma and Healthy Controls

Variable	Patient mean $\pm$ SD	Patient median (IQR)	Control mean $\pm$ SD	Control median (IQR)	p-value
Age (years)	63.14 ± 18.17	70.00 (51.00–77.00)	62.41 ± 16.95	66.00 (56.00–73.00)	0.602
Blood urea	30.42 ± 11.49	30.00 (19.00–42.00)	31.73 ± 8.63	30.00 (24.00–39.00)	0.550
Serum creatinine	0.82 ± 0.20	0.80 (0.69–1.01)	0.67 ± 0.15	0.60 (0.58–0.80)	<0.001
NGAL	420.71 ± 200.89	399.00 (231.00–599.00)	168.98 ± 96.93	151.00 (125.00–176.00)	<0.001
β 2-microglobulin	42.41 ± 18.41	37.40 (28.60–56.60)	14.64 ± 8.02	11.70 (9.35–16.50)	<0.001
Calcium	8.82 ± 0.89	8.80 (8.10–9.50)	9.70 ± 0.50	9.90 (9.33–10.10)	<0.001
Fetuin A	2.93 ± 0.83	2.93 (2.48–3.10)	4.91 ± 1.59	5.22 (3.95–6.03)	<0.001
Osteocalcin	28.04 ± 8.69	27.98 (25.10–32.83)	18.39 ± 4.45	18.68 (14.94–21.52)	<0.001

Comparison of demographic, renal, and bone metabolism biomarkers between male and female patients with multiple myeloma to evaluate sex-related differences.

Demographic, renal and biochemical data are compared between male and female patients with multiple myeloma in Table 3. There was no significant sex related difference in any of the variables evaluated (all $P > 0.05$). There were no significant differences in age, blood urea and serum creatinine levels in males and females, suggesting similar demographic characteristics and renal function. Similarly, there were no significant differences between the concentration of each of the following serum markers according to sex: Neutrophil gelatinase-associated lipocalin (NGAL), β 2-microglobulin, calcium, Fetuin-A, and osteocalcin. Patients of female sex showed a slightly higher median and mean of NGAL, β 2-microglobulin, calcium, fetuin-A and osteocalcin compared to patients of male sex; however, these differences did not prove to be statistically significant. In conclusion, as a whole, these results indicated that the renal injury markers, bone metabolism markers, and biochemical markers observed in patients with MM were not measurable as a result of sex, suggesting that these biomarker changes were more likely to be pathophysiological changes associated with MM disease than sex differences.

Table 3. Sex-Based Comparison of Clinical and Biochemical Characteristics Among Patients with Multiple Myeloma

Variable	Male mean ± SD	Male median (IQR)	Female mean ± SD	Female median (IQR)	p-value
Age (years)	64.00 ± 18.66	70.00 (52.50– 77.75)	60.77 ± 17.24	62.00 (45.00– 75.00)	0.511
Blood urea	31.44 ± 11.13	32.50 (21.00– 42.00)	27.62 ± 12.47	21.00 (16.00– 39.00)	0.275
Serum creatinine	0.84 ± 0.19	0.81 (0.69– 1.02)	0.78 ± 0.23	0.77 (0.69– 0.97)	0.427
NGAL	410.67 ± 206.73	313.50 (227.00– 592.25)	448.54 ± 188.80	441.00 (253.00– 604.00)	0.563
β2-microglobulin	41.67 ± 16.49	35.35 (29.20– 54.73)	44.46 ± 23.59	39.00 (27.90– 56.80)	0.794
Calcium	8.80 ± 0.87	8.80 (8.15– 9.43)	8.90 ± 1.00	8.80 (8.10– 9.90)	0.776
Fetuin A	2.86 ± 0.83	2.84 (2.41– 3.04)	3.12 ± 0.84	3.04 (2.83– 3.18)	0.147
Osteocalcin	28.02 ± 7.94	27.46 (25.18– 32.57)	28.10 ± 10.87	28.05 (18.04– 33.94)	0.981

Correlation analysis among demographic characteristics, renal function parameters, and bone metabolism biomarkers in patients with multiple myeloma.

The correlation analysis of the various biochemical markers with the demographic factors in Multiple Myeloma patients is summarized in Table 4. There were weak correlations between age and all parameters measured, with no significant association with renal and bone metabolism biomarkers. Blood urea showed weak positive correlations with serum creatinine ($r = 0.379$), NGAL ($r = 0.286$), β2-microglobulin ($r = 0.093$), calcium ($r = 0.116$), Fetuin-A ($r = 0.036$), and osteocalcin ($r = 0.233$). Serum creatinine showed moderate positive association with blood urea ($r = 0.379$) and Fetuin-A ($r = 0.288$), while there were inverse correlation between serum creatinine and NGAL ($r = -0.211$) and between serum creatinine and β2-microglobulin ($r = -0.370$). The strongest positive correlation with NGAL was with β2-microglobulin ($r = 0.371$), indicating that both these renal injury markers increased in parallel, whereas there were weak correlations with calcium, Fetuin-A and osteocalcin. A weak inverse correlation was found between fetuin-A and β2-microglobulin ($r = -0.127$) and between fetuin-A and osteocalcin ($r = -0.233$), while calcium had only low correlations with the other variables. Overall, the correlation coefficients were rather small and moderate, suggesting that there is only limited interdependence among the evaluated biomarkers, and that each of them may yield complementary clinical information with respect to different pathophysiological aspects of multiple myeloma.

Table 4. Correlation Matrix of Demographic Variables and Biochemical Biomarkers in Patients with Multiple Myeloma

Marker	Age (years)	Blood urea	Serum creatinine	NGAL	β 2-microglobulin	Calcium	Fetuin A	Osteocalcin
Age (years)	1	0.141	-0.074	0.026	0.111	-0.039	-0.121	-0.008
Blood urea	0.141	1	0.379	0.286	0.093	0.116	0.036	0.233
Serum creatinine	-0.074	0.379	1	-0.211	-0.370	-0.001	0.288	0.023
NGAL	0.026	0.286	-0.211	1	0.371	-0.012	-0.036	0.173
β 2-microglobulin	0.111	0.093	-0.370	0.371	1	0.040	-0.127	-0.023
Calcium	-0.039	0.116	-0.001	-0.012	0.040	1	0.086	-0.098
Fetuin A	-0.121	0.036	0.288	-0.036	-0.127	0.086	1	-0.233
Osteocalcin	-0.008	0.233	0.023	0.173	-0.023	-0.098	-0.233	1

Receiver operating characteristic analysis evaluating the diagnostic accuracy of biochemical and novel biomarkers for identifying patients with multiple myeloma.

The receiver operating characteristic (ROC) analysis for the evaluated biomarkers to identify multiple myeloma (MM) patients from healthy controls is shown in Table 5. β 2-microglobulin had the best diagnostic performance (AUC = 0.949; 95% CI: 0.903–0.984), with an optimal threshold at ≥ 28.50 , having an 83.7% sensitivity and a 96.1% specificity. In addition, neutrophil gelatinase-associated lipocalin (NGAL) had the best AUC value of 0.924 (95% CI: 0.868–0.968), and the highest sensitivity of 98.0% at the cutoff value of ≥ 185.00 , with a specificity of 78.4%. Fetuin-A exhibited very good discriminatory ability (AUC = 0.857), 89.8% sensitivity and 88.2% specificity at a cutoff value of ≤ 3.18 , whereas osteocalcin had high discriminatory ability (AUC = 0.841) with 75.5% sensitivity and 96.1% specificity at a value of ≥ 25.10 . Calcium showed good diagnostic accuracy (AUC = 0.795) and the serum creatinine showed fair discrimination (AUC = 0.734). Blood urea however showed a poor diagnostic value (AUC = 0.535) with limited ability to distinguish patients with multiple myeloma from healthy individuals. In general, NGAL and β 2-microglobulin proved to be the most strong biomarkers for the diagnosis of multiple myeloma, while the other biomarkers (Fetuin-A and Osteocalcin) were found to be of complementary diagnostic value.

Table 5. Diagnostic Performance of Renal and Bone Metabolism Biomarkers for Discriminating Patients with Multiple Myeloma from Healthy Controls

Marker	AUC	AUC 95% CI	Best cutoff	Sensitivity	Specificity
Blood urea	0.535	0.416–0.652	≤ 21.00	34.7%	88.2%
Serum creatinine	0.734	0.637–0.827	≥ 0.64	85.7%	54.9%
NGAL	0.924	0.868–0.968	≥ 185.00	98.0%	78.4%
β 2-microglobulin	0.949	0.903–0.984	≥ 28.50	83.7%	96.1%
Calcium	0.795	0.699–0.878	≤ 8.90	61.2%	86.3%
Fetuin A	0.857	0.760–0.934	≤ 3.18	89.8%	88.2%
Osteocalcin	0.841	0.747–0.925	≥ 25.10	75.5%	96.1%

Discussion:

In the present study, patients with MM showed marked differences in renal injury markers, bone metabolism markers and mineral homeostasis markers from healthy controls, with similar age and sex distribution between the study groups. This age- and sex-similarity enhances the internal validity of the results as it decreases the chance that variance in biomarker concentrations was due to age- or sex-related confounding effects, instead of the disease process. There are several reported case-control studies of novel biomarkers in multiple myeloma in which investigators deliberately matched patients and controls for age and sex in order to attribute the biochemical changes to the disease biology rather than to physiological variation (Späth et al ,2019).

This is one of the most significant findings of the present study, where there was a marked increase in serum NGAL levels in multiple myeloma patients. NGAL has been identified as a highly sensitive marker of early tubular injury, as it is rapidly released from damaged renal tubular epithelial cells in response to inflammation, ischemia, oxidative stress and nephrotoxic injury (Rajeev ,2016; Papassotiriou et al, 2016).In MM, the abnormally high levels of free light chains present in the blood lead to tubular obstruction, oxidative stress, and inflammatory activation, leading to increased NGAL production. Therefore, elevated levels of NGAL could indicate renal injury prior to renal function changes (Hammed et al, 2025). The findings are similar to those of Abed et al., in their study on an Iraqi population, who found that NGAL levels were significantly elevated in patients with myeloma even if serum creatinine was within normal limits, meaning that NGAL is able to detect subclinical renal impairment earlier than conventional renal biomarkers (Hammed et al, 2025).

The significant elevation of β 2-microglobulin in the present study is in line with its known biological function as one of the most important prognostic markers in multiple myeloma, as it is continuously secreted from the malignant plasma cells, and is normally removed by glomerular filtration (Muñoz et al ,2025). Rising plasma cell proliferation and decreasing renal clearance thus simultaneously increase plasma levels. Numerous investigations have shown that elevated β 2-microglobulin is linked to more advanced International Staging System (ISS) stage, decreased treatment response and poor outcome in terms of overall survival, therefore, it is recommended for the regular measurement during diagnostic evaluation and risk stratification as per the international guidelines (Torres et al,2021).

Intriguingly, our data showed that fetuin-A was significantly reduced in patients compared to healthy controls. Fetuin-A is a hepatic glycoprotein that has strong anti-inflammatory and anti-calcification properties and acts as an inhibitor of ectopic mineral deposition and bone remodeling. A low Fetuin-A level could thus be a marker of chronic systemic inflammation associated with myeloma bone disease. Reduced levels of circulating Fetuin-A have been reported in a wide range of inflammatory diseases with hyperproduction of cytokines and tissue destruction (Rudloff et al , 2022). The results were, however, different from a previous study conducted in Iraq which showed significantly higher Fetuin-A levels among multiple myeloma patients. This discrepancy could be due to the different stages of the disease, nutritional and treatment status, hepatic synthetic function, ELISA kits, and sample sizes (Vieceli et al, 2022). The previous study included fewer patients and included Fetuin-A in addition to resistin, while the present study assessed a wider array of biomarkers that could better reflect the intricate relationship among renal dysfunction, inflammation and bone metabolism. Furthermore, the concentration of Fetuin-A is a negative acute-phase protein and decreased levels are seen during periods of higher inflammatory activity, while relatively intact hepatic production during less severe disease can result in higher levels in the circulation (Nawaz et al ,2019).

In the patient group, their levels of osteocalcin increased significantly. Although traditionally recognized as a marker of osteoblast activity, the interpretation of osteocalcin is complicated in multiple myeloma due to a very disturbed bone remodeling. The excessive activation of the osteoclasts and abnormal suppression of osteoblasts causes increased bone turnover, which cause increased levels of several bone matrix proteins to circulate in the blood. The findings of previous studies exploring bone metabolism in MM have been inconsistent. Others have found that osteocalcin was reduced, due to low levels of osteoblast differentiation in the myeloma microenvironment because of the many inhibitory cytokines produced, such as DKK-1 and sFRP-2, while others have shown that this hormone is elevated during reparative bone reactions and in patients with active bone remodeling (Xu, Jie et al ,2023; Boyce et al , 2018). These increased osteocalcin levels in our cohort might therefore suggest accelerated bone turnover, rather than maintenance of osteoblastic function. The variability between published studies is likely explained by the variability in disease activity, presence of osteolytic lesions, bisphosphonate therapy, vitamin D levels, renal function and analytical methods (Goldvaser et al,2019).

Conclusion:

According to the present findings, the MM is related to significant changes in biomarkers indicating renal injury and bone metabolism. NGAL and β 2-microglobulin had been found to be very useful for diagnostics, and osteocalcin and Fetuin-A gave more insights in the skeletal remodeling and disease-related metabolic disturbances. The introduction of these biomarkers along with standard laboratory tests could lead to a greater diagnostic accuracy, allow earlier detection of organ involvement and improve clinical evaluation and monitoring of patients with multiple myeloma.

References

- Andreucci, Michele, et al. "The potential use of biomarkers in predicting contrast-induced acute kidney injury." *International journal of nephrology and renovascular disease* (2016): 205-221.
- Argyropoulos, Christos P., et al. "Rediscovering beta-2 microglobulin as a biomarker across the spectrum of kidney diseases." *Frontiers in medicine* 4 (2017): 73.
- Bernstein, Zachary S., E. Bridget Kim, and Noopur Raje. "Bone disease in multiple myeloma: biologic and clinical implications." *Cells* 11.15 (2022): 2308.
- Boyce, Brendan F., et al. "Bone remodeling and the role of TRAF3 in osteoclastic bone resorption." *Frontiers in immunology* 9 (2018): 2263.
- Cowan, Andrew J., et al. "Diagnosis and management of multiple myeloma: a review." *Jama* 327.5 (2022): 464-477.
- Dimopoulos, Meletios A., et al. "International Myeloma Working Group recommendations for the diagnosis and management of myeloma-related renal impairment." *Journal of Clinical Oncology* 34.13 (2016): 1544-1557.
- Fend, Falko, Ahmet Dogan, and James R. Cook. "Plasma cell neoplasms and related entities—evolution in diagnosis and classification." *Virchows Archiv* 482.1 (2023): 163-177.
- Frantzi, Maria, et al. "Peptidomic profiling reveals extracellular matrix remodeling signatures discriminative of multiple myeloma." *Proteomics* (2026): e70143.
- Goldvaser, Hadar, and Eitan Amir. "Role of bisphosphonates in breast cancer therapy." *Current treatment options in oncology* 20.4 (2019): 26.
- Hammed, Muhamad R. Abdel, et al. "Serum neutrophil gelatinase-associated lipocalin as a predictor of renal injury in patients with multiple myeloma." *The Egyptian Journal of Haematology* 50.4 (2025): 933-938.
- Han, Yujiao, et al. "Paracrine and endocrine actions of bone—the functions of secretory proteins from osteoblasts, osteocytes, and osteoclasts." *Bone research* 6.1 (2018): 16.

- Martiniakova, Monika, et al. "Current knowledge of bone-derived factor osteocalcin: its role in the management and treatment of diabetes mellitus, osteoporosis, osteopetrosis and inflammatory joint diseases." *Journal of Molecular Medicine* 102.4 (2024): 435-452.
- Muñoz, Lizeth Geraldine, Sixta Palencia Luna, and Andrés Felipe Chamorro. "Plasma Cell Myeloma: Biochemical Insights into Diagnosis, Treatment, and Smart Nanocarrier-Based Therapeutic Development." *Pharmaceutics* 17.12 (2025): 1570.
- Nawaz, Shaik Sarfaraz, et al. "Potential role of serum fetuin-A in relation with pro-inflammatory, chemokine and adhesion molecules in diabetic kidney disease: A case-control study." *Molecular biology reports* 46.1 (2019): 1239-1246.
- Ning, Mingzhe, et al. "Usefulness and limitations of neutrophil gelatinase-associated lipocalin in the assessment of kidney diseases." *Journal of Laboratory and Precision Medicine* 3.1 (2018).
- O'Donnell, Elizabeth K., and Noopur S. Raje. "Myeloma bone disease: pathogenesis and treatment." *Clin Adv Hematol Oncol* 15.4 (2017): 285-295.
- Padala, Sandeep Anand, et al. "Epidemiology, staging, and management of multiple myeloma." *Medical Sciences* 9.1 (2021): 3.
- Papassotiriou, Gerasimos-Petros, et al. "Neutrophil gelatinase-associated lipocalin and cystatin c are sensitive markers of renal injury in patients with multiple myeloma." *Clinical Lymphoma Myeloma and Leukemia* 16.1 (2016): 29-35.
- Rajeev Krishnan, Sabna. Microparticles isolated from multiple myeloma patients are indicative of tumor burden, disease progression and treatment unresponsiveness. Diss. 2016.
- Romejko, Katarzyna, Magdalena Markowska, and Stanisław Niemczyk. "The review of current knowledge on neutrophil gelatinase-associated lipocalin (NGAL)." *International journal of molecular sciences* 24.13 (2023): 10470.
- Rudloff, Stefan, Willi Jahnen-Dechent, and Uyen Huynh-Do. "Tissue chaperoning—the expanded functions of fetuin-A beyond inhibition of systemic calcification." *Pflügers Archiv-European Journal of Physiology* 474.8 (2022): 949-962.
- Späth, Florentin, et al. "Immune marker changes and risk of multiple myeloma: a nested case-control study using repeated pre-diagnostic blood samples." *haematologica* 104.12 (2019): 2456.
- Torres, H., R. Martínez, and J. González. "Correlation between β 2-microglobulin, grobulin levels & the number of plasmatic cells in patients with multiple myeloma." *Int J Biomed Res Prac* 1.2 (2021): 1-4.
- Viecei Dalla Sega, Francesco, et al. "Cardiac calcifications: phenotypes, mechanisms, clinical and prognostic implications." *Biology* 11.3 (2022): 414.
- Wang, Linhui, et al. "Update on kidney injury caused by multiple myeloma." *Annals of Hematology* 103.12 (2024): 5007-5018.
- Woziwodzka, Karolina, et al. "Renal impairment detectors: IGFBP-7 and NGAL as tubular injury markers in multiple myeloma patients." *Medicina* 57.12 (2021): 1348.
- Xu, Jie, et al. "The effect of cytokines on osteoblasts and osteoclasts in bone remodeling in osteoporosis: a review." *Frontiers in immunology* 14 (2023): 1222129.
- Yadav, Punit, Mark Cook, and Paul Cockwell. "Current trends of renal impairment in multiple myeloma." *Kidney Diseases* 1.4 (2016): 241-257.
- Zhang, Fujing, and Junling Zhuang. "Pathophysiology and therapeutic advances in myeloma bone disease." *Chronic Diseases and Translational Medicine* 8.04 (2022): 264-270.