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ORIGINAL ARTICLE

Clinical Recommendations for The Diagnosis and Correction of Increased Osteoclastogenesis in Patients with Myeloma

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ABSTRACT
The main objective of this study is to analyze the relationship between increased osteoclastic activity and bone complications in patients with multiple myeloma (MM), as well as to evaluate laboratory parameters indicating osteoblastic activity and inflammatory processes. The study aims to identify factors that contribute to osteolysis and their role in disease progression, which can help optimize the diagnosis and treatment of patients with MM. The main focus is on finding correlations between the levels of various laboratory parameters (including total protein, osteocalcin, alkaline phosphatase, and C-reactive protein) and the presence or absence of skeletal complications. This will improve diagnostics and develop more effective treatment approaches for this category of patients.
Keywords: *multiple myeloma, osteoclastogenesis, diagnostics, pathology, therapy, microbiota*

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INTRODUCTION

Multiple myeloma (MM) is a plasma cell disorder characterized by the infiltration of the bone marrow by clonal plasma cells, the formation of monoclonal immunoglobulin (paraprotein), and organ damage, including bone destruction, kidney failure, hypercalcemia, and anemia [1-3]. This condition is associated with the proliferation of abnormal plasma cells in the bone marrow, leading to multiple disorders in the body. One of the most significant problems arising from myeloma is its complications, especially those that directly affect osteoclastogenesis. These complications lead to osteoporosis and an increased risk of bone fractures, significantly worsening the quality of life for patients suffering from this disease [4, 5]. The process of osteoclastogenesis, responsible for the resorption of bone tissue, is regulated by a complex system of interactions involving RANK, RANKL, and OPG molecules. In the context of myeloma, there is an increase in the level of RANKL, which leads to active osteoclastogenesis [1,6-10]. This, in turn, causes high resorption of bone tissue, resulting in serious complications such as osteolysis and pathological fractures. These clinical manifestations of myeloma disease were detailed in the study by Coleman et al. (2017), highlighting the importance of understanding these processes [11].

Given the above, it is necessary to conduct a more in-depth and detailed study of the interaction between myeloma cells and osteoclasts. This understanding will help identify the mechanisms leading to the development of these serious complications and ultimately contribute to the development of new therapeutic approaches. Research aimed at studying these interactions is not only relevant but also critically important for improving treatment methods for myeloma disease. It can lead to significant improvements in the quality of life for patients, which is one of the priorities of modern medicine. Furthermore, research in this area may contribute to the identification of new biomarkers that allow for more accurate prediction of the risk of complications in patients with myeloma. This, in turn, can enhance

treatment strategies, making them more individualized and effective. As a result, such research not only deepens our understanding of the pathogenesis of myeloma but also opens new horizons for clinical practice, ultimately leading to a reduction in the burden of this disease on public health.

Organ damage is a key sign of both symptomatic and asymptomatic forms of MM. In the case of myeloma bone disease (MBD), lesions may present as solitary lytic foci (plasmacytomas), osteopenia, or multiple lytic lesions affecting various parts of the skeleton, primarily the spine, skull, and long bones. The greater the number of lesions, the less favorable the prognosis. The primary mechanism of MBD is increased osteoclast activity with insufficient osteoblast activity. Recent studies highlight the significance of the RANKL and osteoprotegerin (OPG) system in this process. Patients with MM and MBD require comprehensive treatment, including standard anti-myeloma drugs, bisphosphonates, as well as pain management and, in some cases, radiotherapy and surgical interventions [12, 13]. This methodological recommendation discusses the factors contributing to the development of MBD and approaches to its therapy.

Normal bone tissue remodeling includes both the mineralized and organic components, consisting of collagen as well as non-collagenous proteins. The process involves the resorption of old bone (osteoclastic activity) and the formation of new bone (osteoblastic activity), which helps maintain bone health. The main cells involved in bone remodeling are osteoclasts and osteoblasts, which operate with the assistance of various cytokines and hormones [14]. Osteoclasts, first described in 1873, are multinucleated cells derived from hematopoietic stem cells, capable of causing the resorption of bone tissue [15]. They contain specific proteins, such as tartrate-resistant acid phosphatase and cathepsins, which play an important role in the mechanism of bone destruction. Osteoblasts, in turn, originate from mesenchymal stem cells and are actively involved in collagen synthesis and bone mineralization, while osteocytes, formed from osteoblasts, also secrete biochemical agents that promote remodeling [16].

In multiple myeloma (MM), the mechanism of interaction between osteoclasts (OC) and osteoblasts (OB) is disrupted, which differs from the normal process of bone tissue remodeling (Figure 1).

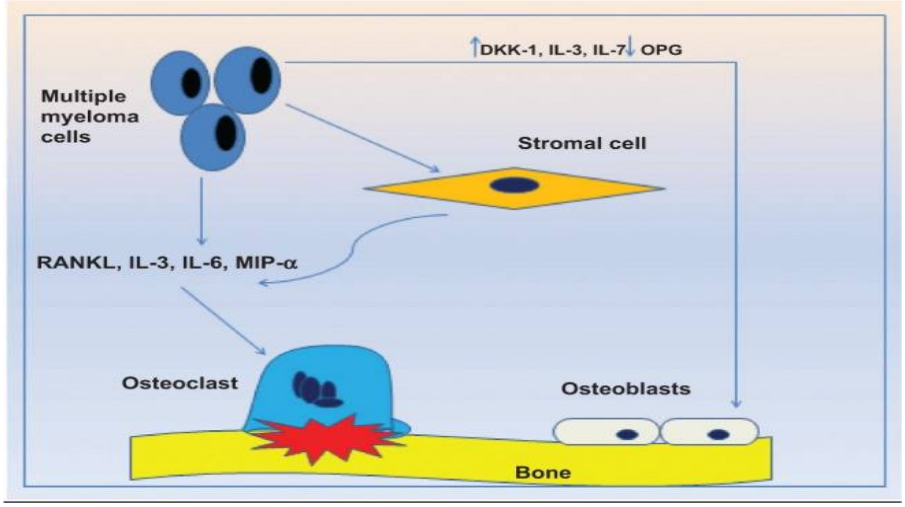

Figure 1. Disruption of the interaction between osteoclasts and osteoblasts in multiple myeloma

Activation of osteoclasts, leading to bone resorption, combined with suppressed function of osteoblasts, responsible for bone tissue formation, becomes key factors contributing to bone complications. Research indicates that tissue hypoxia plays an important role in the progression of the disease and metastasis of both solid tumors and malignant blood cells. The increase in the number of plasma cells and neovascularization leads to a decrease in the oxygen level in the bone marrow, which promotes the metastasis of myeloma cells [17, 18]. This process occurs through the activation of the epithelial-mesenchymal transition, which reduces cell adhesion in the bone marrow and increases the entry of myeloma cells into the peripheral bloodstream. The increase in osteoclast genesis is associated with high levels of bone resorption markers in patients with myeloma. Interactions between myeloma cells, T-lymphocytes, and stromal cells ensure the development of osteolysis, in which the RANKL and OPG system plays an important role [19].

Purpose of the research

The aim of this study is to analyze and assess the factors influencing the activity of osteoclasts and osteoblasts in patients with myeloma (MM), as well as to identify clinical and laboratory markers

associated with bone complications, with the goal of improving diagnostics and developing effective treatment methods to reduce the risk of osteolysis and enhance the quality of life of patients.

MATERIAL AND METHODS

Research Materials

The study involved 208 patients. Participants were divided into two groups using pre-established inclusion and exclusion criteria: the first group included 208 patients with multiple myeloma (MM) who sought diagnosis and treatment at the Republican Specialized Scientific and Practical Medical Center of Hematology of the Ministry of Health of the Republic of Uzbekistan (RSSPMCH MH RUz); the second group, serving as the control, consisted of 90 "conditionally healthy" individuals who had no clinical signs of the mentioned disease either currently or in their medical history. These participants were represented as both inpatients and volunteers, who were comparable in age and gender to the patients in the first group and had no hereditary hemoblastoses. Blood was collected in a thioglycolate nutrient medium with a volume of 5-10 ml, adhering to aseptic conditions. Samples were labeled with the date and time of collection.

Research Methods

To measure parameters in our study, we used the following methods:

X-ray - to assess bone tissue damage and identify destructive changes in the bones, such as "moth-eaten" areas.

Magnetic resonance imaging (MRI) for a more detailed examination of osteodestructive changes in the spine and metastatic lesions.

Laboratory analyses:

Blood tests to determine the levels of total protein, osteocalcin, alkaline phosphatase, and C-reactive protein (CRP).

Biochemical tests to evaluate the levels of calcium and other trace elements in the blood.

Clinical observations for collecting data on symptoms, such as bone pain, and their intensity, which can be done through surveys and patient questionnaires.

Statistical analysis to compare the obtained data between groups of patients with and without skeletal complications, as well as to assess the significance of differences (for example, using the t-test).

These methods allow for a comprehensive picture of the condition of patients with multiple myeloma and assess the impact of various factors on their health.

RESULTS AND DISCUSSION

In the analyzed group of 208 patients, the distribution by sex showed that 111 individuals (53.3%) were men, while 97 (46.7%) were women. Table 1 demonstrates the distribution of participants in the main group by age categories and sex. According to the data in Table 2, the most affected age group among patients with multiple myeloma was individuals aged 50 to 70 years, accounting for 46-47% of the total number of patients. In the category of middle-aged and elderly patients with multiple myeloma, it was observed that 47% were in the age range of 50-60 years, while 46% were individuals aged 60-70 years. On the other hand, the lowest incidence rate was recorded in the 20-30 age group, which accounted for only 4%.

Table 1: Distribution of patients in the main study group

№	Gender	Number of patients, abs.	%
1.	Man	111	53,3
2.	Woman	97	46,7
Total:		208	100,0

Table 2: Classification of patients by age categories

Age	Number of patients, abs.	Number of patients, %
Up to 40 years	-	
40-50 years	4	1,5
50-60 years	16	7,8
60-70 years	114	55,1
Over 70 years old	74	35,4
Total	208	100

According to the analysis of clinical data, X-rays showed bone tissue lesions in 68% (141) of patients. Major destructive changes were observed in the skull (defects reminiscent of 'moth-eaten' areas) and in the pelvic bones. MRI revealed osteodestructive changes in the lumbar and sacral vertebrae in 61% (126)

of patients, as well as metastatic bone lesions. 80% of patients reported bone pain of varying intensity. Laboratory results showed that all patients had elevated levels of total protein: normal values were found in 63 (30.2%) patients, while 53% of patients exceeded normal levels. High protein levels indicate advanced disease and serve as a poor prognostic sign.

As part of the study, we also assessed laboratory markers of osteoblast activity. Osteoblasts are located on the surface of bones, where they are responsible for forming new bone tissue. In 71.2% (148) of patients, osteocalcin levels were found to be below normal, indicating suppressed osteoblast activity. The initiation of specific therapy and the addition of bisphosphonates led to a recovery of this activity. As a second marker of osteoblast activity, alkaline phosphatase (ALP) was studied. Out of 208 patients examined with multiple myeloma, 121 (58.1%) had ALP levels below normal, further confirming the decrease in bone-forming activity.

Mineralization of bone tissue occurs due to trace elements, which include calcium, magnesium, phosphorus, potassium, sodium, and others. Calcium is the primary source for strengthening organic compounds. Our research established that the level of calcium is relatively increased: in 43.8% of participants, it exceeded the normal range, while in 42.8% of patients, the level was below standard values. Although the literature states that calcium levels should be above normal, our results indicate a relative increase. This may be related to disturbances in mineral metabolism or loss of calcium from the body for other reasons.

Additionally, within our studies, inflammatory markers such as C-reactive protein (CRP) were analyzed. All participants in the main group exhibited elevated levels. For example, in 51% of patients, the level of CRP exceeded the norm by 20-40 times.

Table 3: Distribution of certain laboratory parameters in the main study group

Indicators	**Measuring range**	**n** (208)	**%**	**Indicators**	**Measuring range**	**n** (208)	**%**
Total protein g/l	< 65	35	16,8	SCHF 35-129 units/l	< 35	121	58,1
	65 - 86	63	30,2		35 - 129	75	36,0
	87 - 100	48	23,1		129 <	12	5,9
	101 - 120	50	24,0	CRP 0-5.0 mg/l	< 5	88	42,3
	121 - 140	12	5,9		6 - 20	14	6,7
	141<	-	-		21 - 40	106	51,0
Osteocalcin 14-70 ng/ml	< 14	148	71,2	Calcium 2.08-2.6 mmol/l	< 2,08	89	42,8
	14-70	25	12,0		2,08-2,6	28	13,4
	70 <	35	16,8		2,6 <	91	43,8

Thus, it should be concluded that primary patients have an imbalance between the activity of osteoclasts and osteoblasts. The suppression of osteoblast function is determined by markers such as osteocalcin, alkaline phosphatase and calcium levels. In the course of our research, we also compared these indicators with the results of patients who do not have skeletal complications. Studies have shown that among 208 patients with multiple myeloma, 68% (141 cases) of X-ray examinations revealed bone damage, while 32% (67 patients) had no skeletal complications.

Table 4: Transformation of biochemical parameters in osteoskeletal and non-osteoskeletal complications of myeloma.

Indicators	**Measuring range**	**n** (141)	**%**	**n** (67)	**%**	**p**
With skeletal complications				**Without skeletal complications**		
Total protein g/l	< 65	**12**	8,8	**3**	4,8	**t-2,84 p<0,05**
	65 - 86	**35**	24,5	**28**	41,2	**t-2,62 p<0,05**
	87 - 100	**44**	31,4	**18**	26,8	**t-5,17 p<0,05**
	101 - 120	**44**	31,2	**17**	24,9	**t-5,31 p<0,05**
	121 - 140	**6**	4,1	**2**	2,3	t-1,80 p>0,05
	141<	**-**	-	**0**	0	
Osteocalcin 14-70 ng/ml	< 14	**111**	78,5	**11**	16,9	**t-19,43 p<0,05**
	14-70	**15**	10,8	**45**	67,4	**t-2,85 p>0,05**
	70 <	**15**	10,7	**11**	15,7	t-1,77

						p<0,05
SCHF 35-129 units/l	< 35	**95**	67,3	**15**	21,9	**t-13,87 p<0,05**
	35 - 129	**36**	25,7	**41**	61,3	t-1,27 p>0,05
	129 <	**10**	7	**11**	16,8	t-0,68 p>0,05
CRP 0-5.0 mg/l	< 5	**58**	41,3	**26**	38,1	t-6,05 p<0,05
	6 - 20	**12**	8,6	**28**	41,3	t-1,48 p>0,05
	21 - 40	**71**	50,1	**14**	20,6	**t-9,58 p<0,05**
Calcium 2.08-2.6 mmol/l	< 2,08	**30**	21,3	**15**	21,8	**t-3,62 p<0,05**
	2,08-2,6	**24**	16,7	**23**	34,8	t-1,55 p>0,05
	2,6 <	**87**	62	**29**	43,4	**t-10,06 p<0,05**

The studied data indicate that patients with bone complications had an increased level of total protein, which was statistically significantly different from the indicators of the group without such complications (t-5.17, p<0.05). According to the literature, osteocalcin is an indicator of osteoblast activity, and its level increases with an increase in bone formation. In patients with bone complications, osteocalcin levels were significantly lower (t-19.43, p<0.05) compared with the group without such problems. This suggests that in the initial stages of myeloma, there is a decrease in osteoblastic activity. Another marker we studied, alkaline phosphatase, also indicates osteoblastic activity. In 67.3% of patients with bone complications, the level of alkaline phosphatase was significantly reduced (t-13.87, p<0.05) relative to the group without fractures.

C-reactive protein, a marker of inflammatory processes, was analyzed among patients with and without bone complications. It had elevated values in both groups, but the level from 21 to 40 mg/l was observed in 71 patients (50.1%) with bone complications, while in the group without complications, this level was observed only in 14 (20.6%). This indicates a significant increase in the level of inflammation in patients with bone complications (t-9.58, p<0.05).

CONCLUSION

Analysis of data on patients with multiple myeloma indicates that this disease mainly affects men. The most vulnerable age group is people between 50 and 70 years old. Bone complications were found in most patients, with the most frequent lesions of the skull and pelvic bones. Laboratory tests showed abnormalities in protein levels and markers of osteoblastic activity. Violations in bone mineralization and the presence of high levels of inflammatory markers were also noted. The study also revealed an imbalance of activity between osteoblasts and osteoclasts in patients with multiple myeloma. These findings highlight the importance of early diagnosis and continuous monitoring of patients with this disease.

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