ORIGINAL ARTICLE

DOI: 10.4274/nkmj.galenos.2023.34936
Nam Kem Med J 2023;11(2):158-162

Relationship Between Serum Periostin Level and Bone Marrow Fibrosis in Newly Diagnosed Multiple Myeloma Patients

Yeni Tanı Multipl Miyelom Hastalarında Serum Periostin Düzeyi ile Kemik İliği Fibrozisi İlişkisi

Ali Kürşat TUNA[1], Atakan TEKİNALP[2], İbrahim KILINÇ[3], Sinan DEMİRCİOĞLU[2], Bahattin Engin KAYA[1], Özcan ÇENELİ[2], Fahriye KILINÇ[4]

[1]Necmettin Erbakan University, Meram Faculty of Medicine, Department of Internal Medicine, Konya, Turkey
[2]Necmettin Erbakan University, Meram Faculty of Medicine, Department of Internal Medicine, Clinic of Hematology, Konya, Turkey
[3]Necmettin Erbakan University, Meram Faculty of Medicine, Department of Medical Biochemistry, Konya, Turkey
[4]Necmettin Erbakan University, Meram Faculty of Medicine, Department of Pathology, Konya, Turkey

ABSTRACT

Aim: In this study, it was aimed to compare serum periostin levels of patients with and without bone marrow fibrosis among newly diagnosed multiple miyeloma (MM) patients.

Materials and Methods: Thirty patients who were diagnosed with fibrosis in bone marrow biopsy from 36 MM patients over the age of 18 who were newly diagnosed in our center in line with the recommendations of national and international guidelines and were selected for serum periostin levels were included in the study. The patients were divided into two groups as those with and without fibrosis.

Results: While the serum periostin level of the patients with bone marrow fibrosis was 29.22 ng/mL, the serum periostin level of the patients without fibrosis was 17.97 ng/mL, which was statistically significantly higher ($p<0.03$). The median age of patients with fibrosis was found to be significantly lower than patients without fibrosis (59.4±11.01 years versus 68.07±10.27 years, $p<0.03$). There was no significant difference between the two groups in terms of disease stage, MM subtype and response rates.

Conclusion: In this study, the use of serum periostin level as a follow-up parameter in MM patients with bone marrow fibrosis and the design of new studies provided an important insight into the literature.

Keywords: Multiple myeloma, periostin, bone marrow fibrosis

ÖZ

Amaç: Bu çalışmada yeni tanı multipl miyelom (MM) hastaları içinde kemik iliği fibrozisi olan ve kemik iliği fibrozisi olmayan hastaların serum periostin düzeylerinin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya merkezimizde ulusal ve uluslararası kılavuz önerileri doğrultusunda yeni tanı konulan 18 yaş üstü, serumda periostin düzeyi bakılması için seçilen 36 MM hastasından kemik iliği biyopsisinde fibrozis değerlendirmesi yapılan 30 hasta dahil edildi. Hastalar fibrozisi olan ve olmayan şeklinde iki gruba ayrıldı.

Bulgular: Kemik iliği fibrozisi olan hastaların serum periostin düzeyi 29,22 ng/mL iken, fibrozisi olmayan hastaların serum periostin düzeyi 17,97 ng/mL olup, istatistiksel olarak anlamlı yüksek bulundu ($p<0,03$). Fibrozisi olan hastaların medyan yaşı fibrozisi olmayan hastalara göre anlamlı olarak düşük saptandı (59,4±11,01 yıla karşın 68,07±10,27 yıl, $p<0,03$). Hastalık evresi, MM alt tipi ve yanıt oranları bakımından iki grup arasında anlamlı farklılık saptanmadı.

Sonuç: Bu çalışmada, serum periostin düzeyinin kemik iliği fibrozu olan MM hastalarında bir takip parametresi olarak kullanılabilmesi ve yeni çalışmaların tasarlanması açısından literatüre önemli bir fikir sunmuştur.

Anahtar Kelimeler: Multipl miyelom, periostin, kemik iliği fibrozisi

Address for Correspondence: Ali Kürşat TUNA MD, Necmettin Erbakan University, Meram Faculty of Medicine, Department of Internal Medicine, Konya, Turkey
Phone: +90 554 244 63 68 **E-mail:** tunaalikursat@gmail.com **ORCID ID:** orcid.org/0000-0002-7453-326X
Received: 22.02.2023 **Accepted**: 21.04.2023

Presented in: It was presented as an oral presentation on the 5th Internal Medicine Congress of the University of Health Sciences Turkey on June 3, 2022.

INTRODUCTION

Multiple myeloma (MM) is characterized by the presence of osteolytic bone disease. Interactions between myeloma cells and bone marrow stromal cells lead to overproduction of various chemokines and cytokines, causing the disruption of the balance between osteoclast and osteoblast activity. It is known that approximately 80% of myeloma patients at the beginning and up to 90% of patients at some stage of their disease have bone loss leading to devastating skeletal complications[1]. Bone marrow stroma cells, osteoblasts and osteoclasts, primarily interleukin-6 (myeloma growth factor), release tumor necrosis factor-alpha, insulin-like growth factor-1, and vascular endothelial growth factor and thus play an important role in the development of MM[2]. In order to remain in the bone marrow and continue to multiply, MM cells release high levels of CXCR4, which leads to the secretion of various growth factors and chemokines[3]. MM cells increase osteoclast functions by producing the receptor activator of NF-kappaB ligand[4]. As a result, there is a clinical picture characterized by an increase in osteoclast activity and a decrease in osteoblast activity in MM.

Periostin was first discovered as an adhesion protein in mouse osteoblastic cell line and was defined as an osteoblast-specific factor but was later renamed because it was primarily localized in the periosteum[5]. Although the release of periostin from healthy tissues is low, its production increases after inflammatory and fibrotic processes in the tissues[6]. It has been shown that periostin, when secreted from the fibroblast, can regulate collagen deposition by supporting the fibrosis process and changing the mechanical properties of the connective tissue, and play a role in the management of chronic inflammation[7]. In the light of this information, it is estimated that the serum periostin level will increase in MM, which causes structural and functional disorders in the bone marrow microenvironment, progresses with inflammation, and fibrotic changes in the bone marrow occur.

MATERIALS AND METHODS

The study was designed as cross-sectional. Approval for the study was obtained from the Ethics Committee of Necmettin Erbakan University, Meram Faculty of Medicine, with the number 2020/2467 (date: 08.05.2020). Among 36 MM patients over the age of 18 years, who were newly diagnosed in our center in line with the recommendations of national and international guidelines and selected for the assessment of serum periostin levels, 30 patients who were diagnosed with fibrosis in bone marrow biopsy were included in the study. Participation in the study was carried out on a voluntary basis. Volunteers were given detailed information about the study and, after signing informed consent forms, they were included in the study. Patients with diseases such as additional malignant disease, rheumatic disease, diabetes mellitus, advanced stage asthma-chronic obstructive disorders, which might increase serum periostin levels, and non-voluntary patients were excluded from the study. Serum periostin samples were obtained from patients at the time of diagnosis. The samples taken from the patients were centrifuged at 4000 g for 7-10 minutes within 4 hours and stored at -80 °C until the study day. The samples were studied with the enzyme-linked immunosorbent assay method in Necmettin Erbakan University, Meram Medical Faculty Biochemistry Laboratory with the kits purchased from Bioassay Technology Laboratory (Shanghai, China). For the supply of serum periostin kit, support was received from the Scientific Research Projects Board of Necmettin Erbakan University. All patients were given VCD (bortezomib-cyclophosphamide-dexamethasone) protocol according to current guidelines and the official regulations in our country. The patients were divided into two groups as those with and without fibrosis. Two samples were compared in terms of their demographic data, serum periostin levels, hemogram and biochemical laboratory values, MM subtype, disease stage and MM-related clinical features of the patient group. Interim response evaluation of patients after 3 cycles of therapy was performed by assessing the bone marrow plasma cell ratio in bone marrow biopsy, serum and urine immunoelectrophoresis according to the criteria of the standard international MM study group.

Statistical Analysis

In our study, the sample size was determined with a ratio of 1:1 by predicting 80% power, 5% type 1 error margin ($p<0.05$) and impact power 0.5 according to G-Power analysis. Statistical analysis of the study was performed with the IPSS IBM software version 25. The distribution of continuous numerical data was evaluated with the Shapiro-Wilks test. Mean±standard deviation was used for descriptive features in normally distributed data, and groups were compared with an independent sample t-test. Median (minimum and maximum values) was used for data not normally distributed, and the groups were compared with the Mann-Whitney U test. Categorical variables were expressed as a percentage (%). Statistically, $p<0.05$ was considered significant.

RESULTS

Thirty patients were included in the study. The number of patients with and without fibrosis was equal, as 15. While the median age was 59.4±11.01 years in patients with fibrosis, it was 68.07±10.27 years in patients without fibrosis, which was statistically significantly lower ($p<0.03$). Serum periostin level was found to be significantly higher in patients with fibrosis compared to patients without fibrosis (17.97 ng/mL vs. 29.22 ng/mL, $p<0.03$) (Figure 1).

There was no statistically significant difference between the two groups in terms of basic hematological and biochemical parameters (Table 1).

In addition, gender distribution, International Staging System (ISS) and Revised-ISS stages, and MM subtypes were found to be similar between the two groups (Table 2).

When the treatment responses were evaluated, the number of patients who achieved complete response in both groups was detected to be 6. Rapidly progressive disease was observed in 3 patients in the fibrosis group and they died before the time for response evaluation. One patient in the group without fibrosis showed progression. Since 4 patients in the group without fibrosis did not com efor follow-up, response evaluation could not be performed (Table 2).

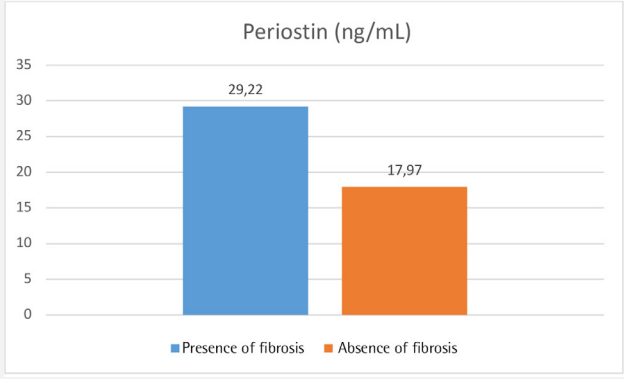

Figure 1. Comparison of serum periostin levels in patients with and without bone marrow fibrosis

Table 1. Comparison of age, serum periostin level and biochemical parameters

Parameter	Presence of fibrosis (n=15)	Absence of fibrosis (n=15)	p
Age	59.4±11.01	68.07±10.27	0.03[a]
Periostin (ng/mL)	29.22 (12.6-94.87)	17.97 (11.21-27.05)	0.03[b]
Hemoglobin (g/dL)	10.86±2.18	10.27±2.7	0.51[a]
Wbc (µLx10^3)	7.96 (4.1-14.23)	6.81 (2.06-10)	0.61[b]
Platelet (µLx10^3)	251.6 (22-572)	233 (79-567)	0.49[b]
Calcium (mg/dL)	10.22 (8.04-13.85)	9.82 (7.3-14.7)	0.43[b]
Urea (mg/dL)	43.66 (7.7-75)	60.28 (31.8-186.6)	0.17[b]
Creatinine (mg/dL)	1.72 (0.66-5.17)	1.72 (0.77-5.18)	0.69[b]
Uric acid (mg/dL)	7.36 (3.9-11.3)	6.7 (3.1-15.8)	0.23[b]
B-2 microglobulin (mg/L)	14.75 (3.08-109.56)	12.12 (2.91-47)	0.35[b]
T. protein (g/dL)	91.94±26.57	76.11±27.94	0.12[a]
Albumin (mg/dL)	36.08±7.71	36.5±9.44	0.89[a]
LDH (U/L)	219.24±101.36	291.93±122.3	0.08[a]

[a]Independent sample t test, [b]Mann-Whitney U test

DISCUSSION

In the study, serum periostin level was found to be significantly higher in patients with bone marrow fibrosis than in patients without bone marrow fibrosis. When we review the literature, there is no study examining the relationship between periostin level and bone marrow fibrosis in MM patients. Our study is the first study in this field. There are two types of fibers that contribute to bone marrow fibrosis. Although the increase in reticulin fibers has limited association with the severity of the underlying malignancy, collagen fibers are strongly associated with abnormal blood counts and poor outcomes. While reticulin fibrosis is often reversed after therapeutic intervention, collagen fibrosis is less likely to resolve with therapy. Fibrosis with an increase in reticulin or collagen fibers in the bone marrow is observed in MM as well as in many hematological malignancies[8]. Bone marrow fibrosis in chronic myeloid leukemia and MM is a predictor of decreased

Table 2. Distribution of patients according to gender, clinical features and response to treatment

n (%)	Presence of fibrosis (n=15)	Absence of fibrosis (n=15)
Gender		
Female	9 (60)	8 (53)
Male	6 (40)	7 (37)
ISS		
1	1 (7)	1 (7)
2	6 (40)	2 (13)
3	8 (53)	12 (80)
R-ISS		
1	1 (7)	1 (7)
2	8 (53)	4 (27)
3	6 (40)	10 (66)
MM subtype		
IgG	6 (40)	8 (53)
IgA	4 (27)	4 (27)
Free K	2 (13)	2 (13)
Free L	3 (20)	1 (7)
Response to the treatment		
Complete response	6 (40)	6 (40)
Partial response	6 (40)	4 (27)
Progressive disease	0	1 (6)
Patient not evaluated*	3 (20)	4 (27)

*Ex or non-followed patients.
MM: Multiple miyeloma

response to commonly used treatment regimens[9,10]. In a study examining the relationship between myelodysplastic syndrome (MDS) and bone marrow fibrosis, it was stated that bone marrow fibrosis was a poor prognostic factor even if it was seen during the course of the disease and should be included in MDS risk classification systems[11]. In a study evaluating the relationship between the presence of bone marrow fibrosis and response to treatment in MM patients, the mean age of patients with fibrosis was 60.8 years, and no significant difference was found with the group without fibrosis[12]. In our study, the mean age of the group with fibrosis was similar and there was no significant difference with the group without fibrosis. In a study in which the diagnostic biopsies of 330 patients diagnosed with primary myelofibrosis (PMF) were reevaluated and the prognostic effect of adding bone marrow fibrosis grade to the traditional prognostic scoring system was evaluated, they confirmed the independent prognostic impact of fibrosis grade and the important clinical significance of the revised 2016 World Health Organization classification for PMF. In the same study, the mean age of patients with stage 0-1 fibrosis was 51 years, and the mean age of patients with stage 2-3 fibrosis was 57 years, which was statistically significantly higher. In our study, the mean age of patients with fibrosis was 59.4±11.01 years, and it was statistically significantly lower than patients without fibrosis[13]. In a study examining the effect of bone marrow fibrosis on survival in patients with acute myeloid leukemia, high bone marrow fibrosis at the time of diagnosis was associated with early recurrence and shorter survival[14]. In the study of Babarović et al.[15], it was showed that a significant number of MM patients had bone marrow fibrosis and MM patients with bone marrow fibrosis had worse survival. In the same study, while 4 of 22 patients with bone marrow fibrosis at the time of diagnosis had complete response, 9 of 20 patients without fibrosis had complete response and no statistically significant difference was found between them (p=0.95). In our study, 6 of 15 patients with fibrosis at the time of diagnosis had complete response, while 6 of 15 patients without fibrosis had complete response and no statistically significant difference was found. In the study of Paul et al.[12], it was shown that MM patients with bone marrow fibrosis had worse overall survival and progression-free survival than patients without fibrosis, even when treated with immunomodulatory agents and proteasome inhibitors. Periostin is a remarkable regulator of the extracellular matrix. It plays a key role in maintaining the normal tissue matrix in the lung, and periostin abnormalities significantly contribute to the pathophysiology of various chronic respiratory diseases with fibrosis[16]. In an animal experiment on mice, periostin was shown to increase renal fibrosis via the p38 MAPK pathway following acute kidney injury induced by a hypoxic or ischemic pathway[17]. In a study examining the relationship of periostin in patients with diffuse large B cell lymphoma, the median serum periostin level of patients with bone marrow involvement was found to be higher than those without bone marrow involvement (12.7-21.7 ng/mL, p=0.018) and similar results were obtained also in our study (17.97 ng/mL vs. 29.22 ng/mL, p<0.03)[18].

Bone marrow fibrosis was detected in 34 (37%) of 91 MM patients in a study performed by Koshiishi et al.[19], and there was no statistically significant difference when evaluated in terms of response to the first treatment. Similar results were obtained also in our study.

Study Limitations

The main limitation of our study is the small number of patients, and also the lack of fibrosis grading and response evaluation. Despite this, it is the first example in the literature to examine the relationship between bone marrow fibrosis and serum periostin level in patients with MM.

CONCLUSION

In conclusion, in our study, serum periostin level was found to be high in MM patients with bone marrow fibrosis, whose prognosis was known to be poor. This suggests that serum periostin level can be used as a follow-up parameter especially in this patient group. Our study has provided an important idea to the literature in terms of designing new studies that examine the periostin level during the response evaluation period.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Ethics Committee of Necmettin Erbakan University, Meram Faculty of Medicine, with the number 2020/2467 (date: 08.05.2020).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices - Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: A.K.T., A.T., İ.K., S.D., B.E.K., Ö.Ç., F.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Christoulas D, Terpos E, Dimopoulos MA. Pathogenesis and management of myeloma bone disease. Expert Rev Hematol. 2009;2:385-98.

2. Ghobrial IM. Myeloma as a model for the process of metastasis: implications for therapy. Blood. 2012;120:20-30.

3. Alsayed Y, Ngo H, Runnels J, Leleu X, Singha UK, Pitsillides CM, et al. Mechanisms of regulation of CXCR4/SDF-1 (CXCL12)-dependent migration and homing in multiple myeloma. Blood. 2007;109:2708-17.

4. Giuliani N, Bataille R, Mancini C, Lazzaretti M, Barillé S. Myeloma cells induce imbalance in the osteoprotegerin/osteoprotegerin ligand system in the human bone marrow environment. Blood. 2001;98:3527-33.

5. Merle B, Garnero P. The multiple facets of periostin in bone metabolism. Osteoporos Int. 2012;23:1199-212.

6. Malanchi I, Santamaria-Martínez A, Susanto E, Peng H, Lehr HA, Delaloye JF, et al. Interactions between cancer stem cells and their niche govern metastatic colonization. Nature. 2012;481:85-9.

7. Huang Y, Liu W, Xiao H, Maitikabili A, Lin Q, Wu T, et al. Matricellular protein periostin contributes to hepatic inflammation and ibrosis. Am J Pathol. 2015;185:786-97.

8. Kuter DJ, Bain B, Mufti G, Bagg A, Hasserjian RP. Bone marrow fibrosis: pathophysiology and clinical significance of increased bone marrow stromal fibres. Br J Haematol. 2007;139:351-62.

9. Kvasnicka HM, Thiele J, Schmitt-Graeff A, Diehl V, Zankovich R, Niederle N, et al. Bone marrow features improve prognostic efficiency in multivariate risk classification of chronic-phase Ph(1+) chronic myelogenous leukemia: a multicenter trial. J Clin Oncol. 2001;19:2994-3009.

10. Subramanian R, Basu D, Dutta TK. Significance of bone marrow fibrosis in multiple myeloma. Pathology. 2007;39:512-5.

11. Jain AG, Zhang L, Bennett JM, Komrokji R. Myelodysplastic Syndromes with Bone Marrow Fibrosis: An Update. Ann Lab Med. 2022;42:299-305.

12. Paul B, Zhao Y, Loitsch G, Feinberg D, Mathews P, Barak I, et al. The impact of bone marrow fibrosis and JAK2 expression on clinical outcomes in patients with newly diagnosed multiple myeloma treated with immunomodulatory agents and/or proteasome inhibitors. Cancer Med. 2020;9:5869-80.

13. Li B, Zhang P, Feng G, Xu Z, Qin T, Zhang Y, et al. Bone marrow fibrosis grade is an independent risk factor for overall survival in patients with primary myelofibrosis. Blood Cancer J. 2016;6:e505.

14. Wu Z, Chen R, Wu L, Zou L, Ding F, Wang M, et al. Bone marrow fibrosis at diagnosis predicts survival for primary acute myeloid leukemia. Clin Transl Oncol. 2017;19:1462-8.

15. Babarović E, Valković T, Štifter S, Budisavljević I, Seili-Bekafigo I, Duletić-Načinović A, et al. Assessment of Bone Marrow Fibrosis and Angiogenesis in Monitoring Patients With Multiple Myeloma. J Clin Pathol. 2012;137:870-8.

16. O'Dwyer DN, Moore BB. The role of periostin in lung fibrosis and airway remodeling. Cell Mol Life Sci. 2017;74:4305-14.

17. An JN, Yang SH, Kim YC, Hwang JH, Park JY, Kim DK, et al. Periostin induces kidney fibrosis after acute kidney injury via the p38 MAPK pathway. Am J Physiol Renal Physiol. 2019;316:426-37.

18. Tekinalp A, Kars TU, Tuna AK, Kılınç İ, Demircioğlu S, Çeneli Ö. Might periostin serve as a marker of bone marrow involvement in patients with diffuse large B-cell lymphoma?" Turkish Journal of Biochemistry 2022;47:770-4.

19. Koshiishi M, Kawashima I, Hyuga H, Nakadate A, Matsuura M, Hosokawa E, et al. Presence of bone marrow fibrosis in multiple myeloma may predict extramedullary disease. Int J Hematol 2022;116:544-52.