DOI: 10.4274/tod.galenos.2022.68094
Turk J Osteoporos 2022;28:1-5

Osteoporosis: An Underdiagnosed Problem in Patients with Ankylosing Spondylitis

Osteoporoz: Ankilozan Spondilitli Hastalarda Yeterince Tanı Konmamış Bir Problem

Yeşim Kirazlı, Ece Çınar

Ege University Faculty of Medicine, Department of Phsyical Medicine and Rehabilitation, İzmir, Turkey

Abstract

Patients with ankylosing spondylitis (AS) are at an increased risk of osteoporosis (OP) and subsequent osteoporotic fractures due to bone fragility. Although AS is a risk factor for developing new-onset OP, there are no existing guidelines to routinely assess patients with AS for OP, and young men are less likely to be screened. Given that the underestimation of OP in patients with AS can have serious health consequences, a greater emphasis should be placed on this association. Major risk factors for vertebral fractures in AS include low bone mineral density (BMD) at the femoral neck and total hip (but not lumbar spine), male sex, longer disease duration, higher disease symptom scores, inflammatory bowel disease, and structural severity of the disease. The major pathophysiological mechanisms for osteoporosis appear to be systemic inflammation and low BMD resulting from decreased daily physical activity caused by pain, stiffness, and ankyloses. The weight of evidence is strongly in favor of the interleukin (IL)-17–IL-23 axis, tumor necrosis factor-α and gut immunopathobiology as central components affecting bone in AS.

Keywords: Ankylosing spondylitis, osteoporosis, fracture, systemic inflammation

Öz

Ankilozan spondilitli (AS) hastalar, kemik frajilitesi nedeni ile osteoporoz (OP) ve kırık gelişimi açısından artmış risk altındadırlar. AS varlığı, OP gelişimi açısından risk oluşturmakla birlikte, AS hastalarında OP taramasına yönelik bir kılavuz bulunmamaktadır ve genç erkek hastalar daha da nadir taranmaktadır. AS hastalarında OP tanısının gözden kaçırılmasının ciddi sonuçları olabileceği gözönüne alındığında, bu ilişkinin önemi daha da belirginleşmektedir. AS hastalarında vertebral fraktür gelişimi açısından risk faktörleri femur total ve femur boynunda saptanan düşük kemik mineral yoğunluğu (KMY), erkek cinsiyet, uzun hastalık süresi, yüksek hastalık semptom skorları, enflamatuvar barsak hastalığı varlığı ve hastalığa bağlı deformitelerin fazla olmasıdır. Lomber KMY ile ilişki yoktur. OP gelişimi açısından ana patofizyolojik mekanizma, sistemik enflamasyonun yanı sıra, ağrı, ankiloz ve tutukluğa bağlı azalmış fiziksel aktivite ve buna bağlı düşük KMY'dir. AS hastalarında kemik ve KMY üzerine interleukin (IL)-17, IL-23 aksı, tümör nekrozis faktör–α ve barsak immünopatobiyolojisinin etkilerine dair de kanıtlar mevcuttur.

Anahtar kelimeler: Ankilozan spondilit, osteoporoz, kırık, sistemik enflamasyon

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease involving the sacroiliac joints and spine; in some cases, the peripheral joints, entheses, and/or extraarticular structures may also be involved (1). Osteoporosis is considered to be a musculoskeletal disease identified by a decreased bone mineral density (BMD); the disease has also been shown to correlate with subsequent fragility fractures (2). Studies have indicated that patients with AS are at increased risk of osteoporosis and subsequent osteoporotic fractures due to bone fragility (3). The likelihood of a vertebral fracture occurring in AS is up to four times the risk compared with control groups (3,4). However, evidence on the risk of hip fractures in patients with AS is inconsistent and fragility fracture incidence at other sites is not well known (3). It has been demonstrated that, in AS patients, a low BMD and bone loss are observed within the first 10 years of disease (5). Quantitative computed tomography

Address for Correspondence/Yazışma Adresi: Ece Çınar MD., Ege University Faculty of Medicine, Department of Phsyical Medicine and Rehabilitation, İzmir, Turkey
Phone: +90 537 225 70 18 **E-mail:** ececinar1@gmail.com **ORCID ID:** orcid.org/0000-0002-9710-1582
Received/Geliş Tarihi: 14.03.2022 **Accepted/Kabul Tarihi:** 21.03.2022

(QCT) measurements of AS patients showed that osteopenia/osteoporosis in the cortex of proximal femur is general in early stage of the disease (6). QCT can also estimate BMD in vertebral bodies avoiding bone-adjacent osteoproliferative changes. QCT can detect early vertebral bone loss in AS and shows deterioration of vertebral body bone loss with progressive spinal disease, where AP lumbar spine BMD, assessed by DXA, shows increased bone mass.

Several studies have demonstrated that the prevalence of osteoporosis among AS patients varies widely, from 9% to 40.7% (6,7). The difference in the follow-up period, as well as differences in geographical region [Netherlands (9%), China (9.7%), Morocco (25%), and Germany (40.7%)], different BMD measurements and sex disparity may contribute to this variability. In addition, studies describing the association between AS and osteoporosis are relatively small-scale [504 cases (7) and 17 cases (8)].

But, a nationwide retrospective cohort study to investigate this epidemiologic evidence was conducted in Taiwan and data were obtained from the Taiwan National Health Insurance Research Database (NHIRD) (9). Of 10,290 participants, 2,058 patients with AS and 8,232 patients without AS were enrolled from the NHIRD between 2000 to 2013. Cumulative incidences of osteoporosis were compared between 2 groups and the study explored the incidence of newly diagnosed osteoporosis in patients with and without AS. The incidence rate ratio of osteoporosis in AS patients was 2.17 times higher than that non-AS group (95% confidence interval, 1.83-2.57). This is much lower than has been previously shown in the small-scale studies. This may be due to the younger population in this study (38 years old), the male/female ratio, genetic heterogeneity, and the duration of disease. Old age (>65 years old), female sex, and dyslipidemia may be considered as potential risk factors for developing subsequent osteoporosis in this study (9). According to other studies, major risk factors for vertebral fractures in AS include low BMD at the femoral neck and total hip (but not lumbar spine), male sex, longer disease duration, higher disease symptoms scores, inflammatory bowel disease, and the duration and structural severity of the disease (3,10). Two notable issues arise from these data. Firstly, there is a need to understand the relative effects of vertebral body bone loss and of disease-specific-related changes in spinal structure in contributing risk to fracture; and secondly it is important to understand that dual-energy X-ray absorptiometry (DXA) derived lumbar spine BMD does not predict vertebral fractures (11).

Why Osteoporosis in AS is Underdiagnosed and Underestimated?

Many studies have highlighted the possibility of underdiagnosis of osteoporosis among the AS population (9,12). There are several potential reasons for this underestimation (9,13). First, AS-related syndesmophytes falsely increase the BMD measured by DXA. Second, patients with AS usually don't seek medical treatment unless severe symptoms occur; this, in turn, may result in low DXA or X-ray utilization and thus fewer opportunities for a diagnosis of osteoporosis. One study supports this speculation, reporting that only patients with the most severe vertebral fracture will seek medical advice. Third, clinicians may overlook osteoporosis due to the aim of the initial treatment frequently being directed at the control of symptoms. Fourth, osteoporosis is not usually suspected in a young-male dominant patient group and young men are less likely to be screened according to practice guidelines.

Consequences of Vertebral Body and Spinal Fractures in AS

The surgical literature is rich with case reports highlighting the consequences of sustaining spinal, not just vertebral body, fragility fractures in AS (11,14). Serious complication risk is high, and effects can be catastrophic (67% of patients with neurological complications; 3% mortality within 3 months). Such consequences probably relate to the mechanical effects of fracture through a rigid, or semi-rigid, spine where extra-skeletal new bone formation (e.g. syndesmophytes, posterior vertebral element ankylosis) results in reduced dissipation of loading forces at the time of fracture and displacement of large, rather than small, segments of bone tissue. A large number of the 345 patients with AS in the literature have had cervical spine fractures, not an area in the spine typically associated with vertebral osteoporosis in the general population. This suggests that cervical spine fractures, and by logical extension all spinal fractures in AS, may relate critically to skeletal fragility from compromised vertebral structure and strength as well as low vertebral body bone mass (14).

Predicting Osteoporosis and Fracture Risk in AS

Osteoporosis and fracture risk will be a function of both nonspecific and AS disease-specific factors. There are some data showing that general fracture risk assessment tools (e.g. FRAX® or Q-Fracture) can be legitimately applied for AS patients. FRAX® predicts a higher 10-year risk of fracture in axSpA compared with controls (15) but FRAX® fracture prediction has not been widely examined across different SpA populations. Hip BMD measurement assessed by DXA predicts vertebral fracture in AS but anteroposterior lumbar spine BMD measurement does not; a likely result of syndesmophytes and calcification of ligaments. Another study (which has a 5-years of long follow-up, many measuring sites) suggested that the best site to assess bone loss in AS patients is the femoral neck and that inflammation has an adverse effect, and the use of bisphosphonates and tumour necrosis factor (TNF) inhibitors has a positive effect, on BMD in AS patients (16).

Trabecular bone score (TBS) is a bone texture measurement derived from the spine DXA image that indicates bone quality and fracture risk independent of BMD. Using the Manitoba Bone Density Program database, it was shown that TBS was lower in AS patients with incident major osteoporotic fractures compared to AS patients without fractures (1.278±0.126, compared to 1.178±0.136, $p<0.001$) (17). It is the first analysis of TBS for

fracture prediction as an incident event in AS. TBS independently predicted major osteoporotic and clinical spine fracture in AS independent of FRAX (17).

In addition to that, trabecular bone loss assessed using TBS is longitudinally associated with spinal progression of axSpA. The more severe the trabecular bone loss, the stronger the effect on the progression of the spine (18).

TBS is not influenced by syndesmophyte formation, negatively correlates with systemic inflammatory markers, and is a promising technique for monitoring vertebral body osteoporosis, specifically in axSpA (17).

Pathophysiological Mechanisms

The major pathophysiological mechanisms for osteoporosis appear to be systemic inflammation and low BMD resulting from decreased daily physical activities caused by pain, stiffness, and/or ankyloses (9).

Over the past several years, a pathophysiological role for the interleukin (IL)-23-IL-17 pathway in human disease has been defined. AS, is now acknowledged to be triggered by dysregulated IL-23-IL-17 pathway activation. The unique bone phenotype that occurs in AS is a surprising coexistence of both systemic bone loss and periosteal and entheseal bone formation and is likely to be the result of the actions of IL-23 and/or IL-17 on bone. However, the effects of these cytokines on bone cells are complex, and controversy remains regarding their exact roles in the specific bone microenvironments relevant to AS (19).

According to a study that investigated the effect of miR-214, the production of which is stimulated by IL-17A, on bone loss in AS showed that the levels of IL-17A and miR-214 were much higher in the serum of patients with AS than in that of healthy controls (20). The level of miR-214 in the serum of AS patients has potential diagnostic value. The production of miR-214 in osteoblasts is stimulated by IL-17A. It is an important inhibitor of bone formation in AS, and the serum level of miR-214 might be of potential diagnostic value for AS (20).

There is extensive experimental and clinical evidence linking tumor necrosis factor-α to osteoclast development however a direct role on osteoblast formation has remained somewhat controversial; on balance most studies report that TNF-α inhibits osteoblast differentiation (11). The TNF superfamily includes the osteoclast differentiation factor, receptor activator of NF-κB ligand (RANKL), and its decoy receptor, osteoprotegerin (OPG). General inflammatory cell infiltration makes a significant contribution to osteoclast formation and bone turnover. The RANKL: OPG ratio determines the extent of osteoclastogenesis (11).

Alterations in the human microbiome are associated with various disease states; but it is not known whether there are direct roles on bone loss and/or formation. Osteomicrobiology refers to the role of microbiota in bone health and how the microbiota regulate postnatal skeletal development, bone ageing, and pathologic bone loss (21). In patients with SpA, itis unclear whether enteral dysbiosis and gut immunopathobiology are direct contributors to bone changes but a growing body of literature shows that there are links between the gut and bone that may go beyond inflammation alone (22,23). Addressing dysbiosis may be fruitful: the probiotic Lactobacillus reuteri reduces intestinal dysbiosis, prevents intestinal barrier dysfunction and suppresses osteoclast differentiation; and the results of how the SpA inflammasome and AS pathogenesis might be influenced by faecal microbiota transplantation, are awaited with interest.

Therapeutic Measures to Address Osteoporosis in SpA

Therapeutically addressing bone pathophysiology in SpA is a challenge. Therapies will need scrutiny for their success at reducing and not worsening the fracture risk.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the initial treatment in SpA, and clearly work well in reducing symptoms; however, whether NSAIDs reduce fracture risk, is unknown. Accordingly, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) have not been studied for their effect on vertebral fracture risk or osteoproliferation otherwise (24).

Directly inhibiting osteoclast function with intravenous bisphosphonate increases lumbar spine bone mass in the short term in AS patients (25). However, the effect of bisphosphonates on spinal fracture risk, is unknown. Bisphosphonates might promote osteoproliferation. It is not known if the structural integrity of ossified spinal entheses and syndesmophytes have incorporated bisphosphonate into their structure. Would bisphosphonate incorporation lead to even less strength than might be present otherwise in the spinal structure overall? It is not known at all (11).

In another study, the efficacy, safety, and persistence on the treatment of the combination of biologic DMARDs (bDMARDs)/ denosumab versus bDMARD in patients with rheumatic musculoskeletal diseases were tested (26). The combination of bDMARD and denosumab did not not alter the efficacy and the safety profile of the bDMARD in patients. Future studies verifying the radiological disease inhibition could support denosumab use in rheumatic musculoskeletal diseases other than rheumatoid arthritis, when complicated by OP.

TNF inhibitors: Inhibiting TNF-α is associated with increases in spinal bone mass of the AS patients in the short term. One-year anti-TNF therapy halted generalized bone loss in association with clinical improvement in AS (27). It will be important to know where exactly and how bone is gained with anti-TNF therapy at a tissue level and how that affects fracture risk. The first longitudinal HRpQCT study in patients with AS strengthen the importance of controlling disease activity to maintain bone density in the peripheral skeleton. Treatment with TNF inhibitor $\geq$4 years during follow-up of AS patients was associated with increases in cortical vBMD and cortical area at tibia, whereas exposure to bisphosphonates was associated with increases in cortical measurements at radius. No disease-related variables or

treatments were associated with changes in trabecular vBMD. This study strengthen the importance of controlling disease activity to maintain bone density in the peripheral skeleton (28). Also, an increase of BMD in the lumbar spine after 2 years of secukinumab treatment in patients with AS was found that was probably unrelated to radiographic progression. No relevant effects of secukinumab on bone turnover biomarkers were documented (29).

Calcium: Calcium is involved in many physiopathological processes, including inflammation, bone loss and bone formation, all of which occur in AS. Many AS patients suffer from concomitant osteopenia or osteoporosis, which represent indications for calcium supplementation. Conversely, there are still concerns about the use of calcium salts for the prevention of bone fragility generally. In these cases, biologic agents may indirectly normalize calcium dysmetabolism by rebalancing the cytokine milieu, in turn associated with bone remodeling. Calcium supplements may be disadvantageous for entheseal calcifications, but so far there are no clear data confirming that such an association exists (30).

Vitamin D: According to a study, the mean serum 25-hidroxyvitamin D [25-(OH)D] levels in AS patients were significantly lower compared to healthy controls (27.73±14.27 vs. 38.46±8.11 ng/mL, p<0.001) (25). Among the AS patients, 60% exhibited hypovitaminosis D. AS patients scores. Additionally, BMD and Z scores at lumbar and femoral sites were significantly reduced in patients with hypovitaminosis D (p<0.05). Serum 25-(OH)D was positively correlated with lumbar and femoral BMD and lumbar and femoral Z scores, whereas, negatively correlated with AS disease activity score with C-reactive protein (ASDAS-CRP), bath ankylosing spondylitis functional index, and modified stoke ankylosing spondylitis spine score. ASDAS-CRP was the only significant predictor of hypovitaminosis D in AS patients (31).

Hypovitaminosis D is prevalent among AS patients and is associated with increased risk of active disease, impaired function, radiographic severity and bone mineral loss. Future studies with a larger sample size are recommended to assess the impact of vitamin D deficiency on radiological progression in AS and to address whether or not vitamin D supplementation will help control the active disease (31).

Treatment of vitamin D deficiency was proposed as an effective way to improve bone strength in AS patients with hip involvement. In this study, it was shown that AS patients have lower bone strength once the disease progresses to include radiologic hip involvement. The stiffness index (SI) calculated by quantitative ultrasound (QUS) was used to compare the bone strength between patients with AS with radiographic hip involvement and those without radiographic hip involvement (32).

Conclusion

Patients with AS have a higher risk of developing osteoporosis. Although AS is a risk factor for the development of new-onset osteoporosis, there are no existing guidelines to routinely assess patients with AS for osteoporosis, and young men are less likely to be screened. Given that the underestimation of osteoporosis in AS patients can have serious health consequences, a greater emphasis should be placed on this association.

The major pathophysiological mechanisms for osteoporosis appear to be systemic inflammation and low BMD resulting from decreased daily physical activities caused by pain, stiffness, and ankyloses. The weight of evidence is strongly in favour of the IL-17–IL-23 axis, TNF-α and gut immunopathobiology as central components affecting bone in AS.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: Y.K., E.Ç., Design: Y.K., E.Ç., Data Collection or Processing: Y.K., Analysis or Interpretation: Y.K., Literature Search: Y.K., Writing: Y.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. Rudwaleit M, van der Heijde D, Landewé R, Akkoc N, Brandt J, Chou CT, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis 2011;70:25-31.
2. Kirazlı Y, Atamaz Çalış F, El Ö, Gökçe Kutsal Y, Peker Ö, Sindel D, et al. Updated approach for the management of osteoporosis in Turkey: a consensus report. Arch Osteoporos 2020;15:137.
3. Pray C, Feroz NI, Nigil Haroon N. Bone mineral density and fracture risk in ankylosing spondylitis: a meta-analysis. Calcif Tissue Int 2017;101:182-92.
4. Zhang M, Li XM, Wang GS, Tao JH, Chen Z, Ma Y, et al. The association between ankylosing spondylitis and the risk of any, hip, or vertebral fracture: a meta-analysis. Medicine (Baltimore) 2017;96:e8458
5. van der Weijden MA, Claushuis TA, Nazari T, Lems WF, Dijkmans BA, van der Horst-Bruinsma IE. High prevalence of low bone mineral density in patients within 10 years of onset of ankylosing spondylitis: a systematic review. Clin Rheumatol 2012;31:1529-35.
6. Cai PL, Yan YY, Wei W, Chen XS, Zhao J, Zhang ZK, et al. The bone mineral density of hip joint was reduced in the initial stage of ankylosing spondylitis? Medicine (Baltimore) 2020;99:e19132.
7. Wang DM, Zeng QY, Chen SB, Gong Y, Hou ZD, Xiao ZY. Prevalence and risk factors of osteoporosis in patients with ankylosing spondylitis: a 5-year follow-up study of 504 cases. Clin Exp Rheumatol 2015;33:465-70.
8. Emohare O, Cagan A, Polly DW Jr, Gertner E. Opportunistic computed tomography screening shows a high incidence of osteoporosis in ankylosing spondylitis patients with acute vertebral fractures. J Clin Densitom 2015;18:17-21.
9. Hu LY, Lu T, Chen PM, Shen CC, Hung YM, Hsu CL. Should clinicians pay more attention to the potential underdiagnosis of osteoporosis in patients with ankylosing spondylitis? A national population-based study in Taiwan. PLoS One 2019;14:e0211835.
10. Ghozlani I, Ghazi M, Nouijai A, Mounach A, Rezqi A, Achemlal L, et al. Prevalence and risk factors of osteoporosis and

vertebral fractures in patients with ankylosing spondylitis. Bone 2009;44:772-6.

11. Clunie G, Horwood N. Loss and gain of bone in spondyloarthritis: what drives these opposing clinical features? Ther Adv Musculoskel Dis 2020;12: 1759720X20969260
12. Klingberg E, Lorentzon M, Mellström D, Geijer M, Göthlin J, Hilme E, et al. Osteoporosis in ankylosing spondylitis - prevalence, risk factors and methods of assessment. Arthritis Res Ther 2012;14:108.
13. Davey-Ranasinghe N, Deodhar A. Osteoporosis and vertebral fractures in ankylosing spondylitis. Curr Opin Rheumatol 2013;25:509-16.
14. Ramírez J, Nieto-González JC, Curbelo Rodríguez R, Castañeda S, Carmona L. Prevalence and risk factors for osteoporosis and fractures in axial spondyloarthritis: a systematic review and meta-analysis. Semin Arthritis Rheum 2018;48:44-52.
15. Kang KY, Kwok SK, Ju JH, Hong YS, Park SH. Assessment of fracture risk in patients with axial spondyloarthritis: a case-control study using the fifth Korean National Health and Nutrition Examination Survey (KNHANES V). Scand J Rheumatol 2016;45:23-31.
16. Deminger A, Klingberg E, Lorentzon M, Geijer M, Göthlin J, Hedberg M, et al. Which measuring site in ankylosing spondylitis is best to detect bone loss and what predicts the decline: results from a 5-year prospective study. Arthritis Res Ther 2017;19:273.
17. Richards C, Hans D, Leslie WD. Trabecular Bone Score (TBS) Predicts Fracture in Ankylosing Spondylitis: The Manitoba BMD Registry. J Clin Densitom 2020;23:543-8.
18. Jung JY, Kim MY, Hong YS, Park SH, Kang KY. Trabecular bone loss contributes to radiographic spinal progression in patients with axial spondyloarthritis. Semin Arthritis Rheum 2020;50:827-33.
19. Gravallese E, Schett G. Effects of the IL-23-IL-17 pathway on bone in spondyloarthritis. Nat Rev Rheumatol 2018;14:631-40.
20. Liu Z, Huang F, Luo G, Wang Y, Du R, Sun W, et al. miR-214 stimulated by IL-17A regulates bone loss in patients with ankylosing spondylitis. Rheumatology (Oxford) 2020;59:1159-69.
21. Van de Wiele T, Van Praet JT, Marzorati M, Drennan MB, Elewaut D. How the microbiota shapes rheumatic diseases. Nat Rev Rheumatol 2016;12:398-411.
22. Jones RM, Mulle JG, Pacifici R. Osteomicrobiology: the influence of gut microbiota on bone in health and disease. Bone 2018;115:59-67.
23. Ohlsson C, Sjögren K. Effects of the gut microbiota on bone mass. Trends Endocrinol Metab 2015;26:69-74.
24. Noureldin B, Barkham N. The current standard of care and the unmet needs for axial spondyloarthritis. Rheumatology (Oxford) 2018;57(Suppl 6):vi10-vi17.
25. Clunie GP, Ginawi A, O'Conner P, Bearcroft PW, Garber SJ, Bhagat S, et al. An open-label study of zoledronic acid (Aclasta 5 mg iv) in the treatment of ankylosing spondylitis. Ann Rheum Dis 2014;73:1273-4.
26. Bruni C, Cigolini C, Tesei G, Cometi L, Bartoli F, Fiori G, et al. Combination of denosumab and biologic DMARDs in inflammatory muscle-skeletal diseases and connective tissue diseases. Eur J Rheumatol 2021;8:190-5.
27. Gulyás K, Horváth Á, Végh E, Pusztai A, Szentpétery Á, Pethö Z. Effects of 1-year anti-TNF-α therapies on bone mineral density and bone biomarkers in rheumatoid arthritis and ankylosing spondylitis. Clin Rheumatol 2020;39:167-75.
28. Deminger A, Klingberg E, Lorentzon M, Hedberg M, Carlsten H, Jacobsson LTH, et al. Factors associated with changes in volumetric bone mineral density and cortical area in men with ankylosing spondylitis: a 5-year prospective study using HRpQCT. Osteoporos Int 2022;33:205-16.
29. Braun J, Buehring B, Baraliakos X, Gensler LS, Porter B, Quebe-Fehling E, et al. Effects of secukinumab on bone mineral density and bone turnover biomarkers in patients with ankylosing spondylitis: 2-year data from a phase 3 study, MEASURE 1. BMC Musculoskelet Disord 2021;22:1037.
30. Talotta R, Rucci F, Scaglione F. Calcium physiology, metabolism and supplementation: a glance at patients with ankylosing spondylitis. Reumatologia 2020;58:297-311.
31. Elolemy G, Hassan W, Nasr M, Baraka E. Hypovitaminosis D in Patients with Ankylosing Spondylitis: Frequency and Consequences. Curr Rheumatol Rev 2021;17:365-72.
32. Liu W, Song H, Man S, Li H, Zhang L. Analysis of Bone Strength and Bone Turnover Markers in Ankylosing Spondylitis with Radiological Hip Involvement. Med Sci Monit 2021;27:e932992.