

The Impact of Osteoporosis in Patients with Ankylosing Spondylitis and Its Relationship to Physical Activity

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Abstract

Background: Osteoporosis (OP) is a major fracture risk in ankylosing spondylitis (AS), and there are few qualitative reports on bone mass in AS. **Objective:** The aim of this study was to correlate the bone mineral density (BMD) with disease activity and physical activity (PA) in AS. **Materials and Methods:** Sixty-two participants who met the criteria for diagnosis of AS (28 males and 34 females) were recruited from Al-Yarmouk Teaching Hospital Baghdad, Iraq. The study was conducted at baseline and after 6 months of exercises. European health-related quality of life was used to reflect physical function. The erythrocyte sedimentation rate and C-reactive protein were used to evaluate AS disease as markers for disease activity. The study measured BMD at two events, before and after performing the relevant exercise. **Results:** Results found that 9.6% of patients reported fractures. Low bone mass in the AS patients were 17 (27%) in number. Osteopenic patients were 9 (14%) in number, while osteoporotic patients were 8 (13%) in number. An association ($P = 0.05$) between BMD and PA was noticed in AS participants. There was a weak ($P < 0.055$) significant association of higher European health-related quality of life scores with lower spinal and hip BMD. No association of AS disease activity with BMD was found, although bone loss in AS is common in persistent active disease; regular PA seems to be a positive factor for improving bone quantity and prevent fracture. Programmed exercise promotes healthy bone. The severity of AS in Iraq is less than the other countries. **Conclusion:** PA in AS patients has a positive effect on bone status. This implies that AS disease-related loss in BMD is preventable by the relevant exercise program. This information is important, as it can be utilized while designing preventive and treatment plans for AS patients.

Keywords: Ankylosing spondylitis, bone mineral density, European health-related quality of life, physical activity

INTRODUCTION

Ankylosing Spondylitis (AS) is the prototype and the most common type of spondyloarthropathy (SpA). The AS disease is a chronic inflammatory arthritis, mainly targeting the spine, peripheral joints, and 95% of patients express a positive HLA-B27. The SpA group is commonly affecting the axial region, causing an inflammatory arthropathy; however, the large peripheral joints can be involved in many occasions. The disease ultimately, if not properly treated, may lead to stiff and calcified spines. The group targets around 2% of the population. Nevertheless, the prevalence of SpA was 0.30% in 2009. Enthesopathy, an inflammation at the site of insertion of tendons and ligaments, is the main *in situ* pathological process, which is usually started by erosion and proceeds to osteitis, ossification, and periosteal bone formation. The large peripheral joints and enthesitis can be involved in 30%–50% of patients. SpA is associated with several systemic diseases

and they are underrecognized.^[1] Patients may present with chronic inflammatory low back pain and stiffness, most often of the spine and asymmetrical arthritis, predominantly of the lower limbs.

The SpA group was subdivided into AS, Reiter's/reactive arthritis, psoriatic arthritis, inflammatory bowel disease-associated arthritis, and undifferentiated spondyloarthritis.^[2] It often targets a young age group, usually before the age of 40 years. The incidence and prevalence rates of AS, and of SpA as a whole, are strongly associated with HLA-B27 in 95% of the population. The incidence rate of AS is between

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0.5 and 8.2/100,000 of population, while the prevalence of AS and nonradiographic axial SpA is 0.35%, respectively. The AS disease is usually targeting the male of young age group of 2-3 times than the female group. Family members of affected people are at higher risk.^[3]

The etiology of decreased bone density in the AS is yet to be fully understood.^[4] The recent use of tumor necrosis factor (TNF) inhibitors is exciting and may represent true disease-modifying drugs for these conditions; the biological response modifiers offer a suitable condition for increasing AS patients' quality of life (QoL) and social participation.^[5,6] Diagnosis of AS is crucial for ideal management, generally made by combining clinical criteria of inflammatory back pain and enthesitis or arthritis with radiologic findings.^[7]

There is an uneven ethnic distribution of AS. The highest frequency appears in the far north in cultures such as Alaskan and Siberian Eskimos and Scandinavian Lapps (also called Samis), who have a higher frequency of HLA-B27. It also occurs more often in certain Native American tribes in the western United States and Canada. African-Americans are affected less often than other races. The frequency of AS in the USA is 0.5%, while the frequency for axial spondyloarthritis is 1.4%.^[7] Early diagnosis of AS and other types of SpA is crucial for ideal management. Therefore, an attention has recently focused on earlier diagnosis of AS among young patients with chronic low back, in particular a small group of mild degree of clinical manifestation. This approach becomes more essential for effective therapies for those who present with early disease.

The emerging treatment of biological response modifiers offers a suitable condition for increasing AS patients' QoL and social participation.^[6] Briot and Roux reported that a decrease in bone density is a common feature in patients with AS and related to increased C-reactive protein (CRP). The WHO criteria for osteoporosis (OP) is defined that bone mineral density (BMD) lies 2.5 standard deviation (SD) or more below the average value for young healthy women (a T-score of <-2.5 SD);^[1,6] this criterion is accepted internationally.^[8]

The dual-energy X-ray absorptiometry (DXA) is a common measuring technique for BMD by which a diagnostic criterion of osteopenia and OP was used and validated, based on the T-score for BMD. Decreased BMD was defined as a T-score <-1.0 , including both osteopenia and OP.^[9-11]

OP is frequently occurs in the group of inflammatory arthritis, whereas there is a probability of negative correlation with degenerative changes of osteoarthritis (OA).^[12] It may be present as localized erosions or be a generalized condition which results in OP. The etiology of decreased bone density in the SpA is yet to be fully understood.^[4] Although there are improvements in the treatment of patients with AS, still there are limitations to certain related disorders.^[13] Nevertheless, the introduction of anti-TNF- α and the improvement in the rehabilitation play an important role in the relieving symptoms and step up the QoL for the disease.^[14]

There are reports on the effect of physical exercise on decreasing inflammation, expressed by the decrease in CRP. Short-term exercise may increase inflammatory response, while it has a long-term anti-inflammatory action. This anti-inflammatory response may contribute to the beneficial effects of a regular and continuous physical activity (PA).^[15] CRP appears 1–2 days of acute MI, peaks at 3 days, and diminishes from the blood within 7 days. If it remains high, may indicate the presence of tissue damage or inflammation. Studies of exercise suggest significant bone changes. It has a promising effect for strengthening bones, particularly during childhood and adolescence. However, the positive effect of a programmed exercise on bone loss in older adults and in women after menopause requires research on a mechanism of exercise programs on AS; by which the bone mineral development may be promoted.^[16] The main aim for prevention of OP is upgrading bone density early in individual adult life and decrease of bone loss later in life.^[17,18]

One of the generally accepted strategies to make the skeleton more resistant to fracture is to minimize the decline in PA, and other factors.^[19] The Fourth International Symposium on Osteoporosis and the Consensus Development Conference advised exercise for attending and maintaining maximal bone mass.^[20,21] Bone mass reflects bone strength. However, other factors such as bone quality and muscle action also help in promoting bone strength. Heritable trait is the single factor, most important for determining bone mass and its structural solidity.^[22]

PA, a lifestyle factor, has been considered as an essential external factor for maintaining bone mass and architecture. However, the knowledge of the effect of exercise on bone mass needs elaboration and may carry controversial issues.^[23,24]

The European health-related QoL (EQ5D5 L) is a standardized, nondisease-specific instrument for describing and valuing health status by the EuroQol Group. The EuroQol instrument is intended to complement quality-of-life measures.^[25]

The aim of the study was to determine changes in the BMD, using dual-energy DXA, and to explore the association of BMD with PA and disease activity (erythrocyte sedimentation rate [ESR] and CRP) in patients with AS before and after 6 months of physical exercise.

MATERIALS AND METHODS

A cohort of 62 participants, 28 males and 34 females, mean age of 58.2 ± 12.2 years, and disease median duration of 17.4, range 10–22.6, were recruited from Al-Yarmouk Teaching Hospital Baghdad, Iraq, and private clinics. The study used the European Spondyloarthropathy Study Group criteria for diagnosis of AS. It is sensitive (80%) and specific criteria combining clinical findings of the disease such as arthritis associated with radiologic findings.^[27,28] This is available for diagnosis of SpA in general and it omits the

genetic assessment of the presence of HLA-B27, which is not available in most of the medical laboratories. It also used the WHO criteria for measuring BMD of the lumbar spine and femoral neck using DXA scan. The Eq5D5 L was used as a functional scale to reflect exercise value. The two most common biological acute-phase reactant markers for disease activity (ESR and CRP) were used to evaluate AS disease activity. The outcomes determined BMD, before and after a programed exercise for 6 months. The EuroQol Group is a new facility for the measurement of health-related QoL. The EQ-5D™ is a trademark of the EuroQol Group. It is a standardized, nondisease-specific instrument for describing and valuing health, mainly used and completed by participants and is suitable to use in individual surveys and interviews. It is easy to use and takes little time.^[29]

Ethical approval for the study was obtained from the Middle Technical University Scientific Committee, Iraq. All participants were filled written consent in According to the research guide of Helsinki declaration. Patients were identified from patients' files available at Al-Yarmouk Hospital, Baghdad, Iraq. Healthy controls were recruited from patients' relatives or career. Patients were excluded if they were irregularly receiving anti-TNF treatment. The study reviewed participants' demographic data, medical history, medications, laboratories, and data related to bone mass.

The study was conducted at two events, at baseline and after 6 months of exercise program. For the determination of bone quantity, the study measured BMD for the lumbar spines and the femoral neck using dual-energy DXA study at the Al-Yarmouk Teaching Hospital. Eq5D5 L self-reporting questionnaire was utilized to assess the PA that is reflected by the degree of QoL. The participants had reported their level of PA, on average, during per month for 6 months. The disease activity was determined by the two most common acute-phase reactants: ESR and CRP. The outcomes assessed BMD before and after a programed exercise for 6 months. The study used the WHO criteria for osteopenia and OP.^[13] OP is defined by the WHO as a BMD that is 2.5 SDs or more below the mean peak bone mass (average of young, healthy adults) as measured by DXA.

For exercise therapy, brisk walking, weight-bearing, and strengthening exercise were suggested to prevent OP.^[30] Therefore, all the included participants received instructions to implement weight-bearing and specific resistance exercises related to the disease at outpatient rehabilitation centers and been asked to perform exercise, at home, at a regular basis for 1.5 h four times a week.

For statistical analysis, an independent two-tailed Student's *t*-test was used for comparison between the two study groups. $P \leq 0.05$ was used for determining the statistically significant difference. The analysis was used with Statistical Package SPSS Version 18.0 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

The characteristics of 62 participants (28 male and 34 females) included in the study are presented in Table 1. All the study participants ($n = 62$) have evidence of sacroiliac joint lesion, the most characteristic feature of AS. Those participants ($n = 7$) with short disease duration showed bone marrow edema by magnetic resonance imaging. There was no significant difference in the body mass index (BMI) before and after PA.

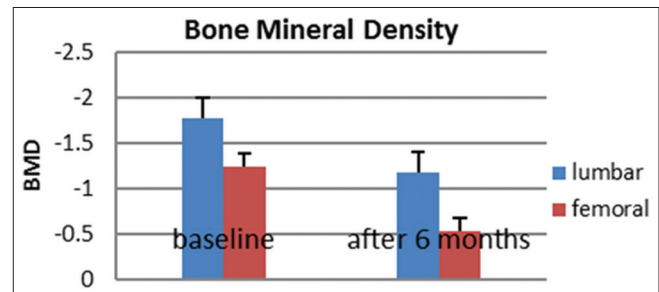


Figure 1: Comparison of mean $\pm$ standard deviation for bone mineral density between lumbar spine and femoral neck at baseline and after 6 months of physical activity

Table 1: Characteristic and disease activity at baseline and after 6 months for patients with ankylosing spondylitis

Characteristic	Baseline
Female	34
Male	28
Age	58.2 (12.2)
BMI (kg/m ²), median (range)	27.3 (19.2-35.9)
Disease duration (years) (range)	17.4 (10-22.6)

BMI: Body mass index

Table 2: Mean $\pm$ standard deviation of bone mineral density at baseline and after 6 months of physical activity

BMD	Baseline	After 6 months	Difference	Significant
Lumbar spine (g/cm ²)	-1.761 $\pm$ 0.23	-1.171 $\pm$ 0.04	-0.59	NS
Femoral neck (g/cm ²)	-1.235 $\pm$ 0.54	-0.527 $\pm$ 0.15	-0.70	S

BMD: Bone mineral density, S: Significance, NS: Not significant

Table 3: Disease activity at baseline and after 6 months for patients with ankylosing spondylitis

Clinical features	Baseline	6 months later
Pain at rest (VAS)	6.40 $\pm$ 1.50	3.11 $\pm$ 1.13
Spine stiffness (>30 min) (%)	74	65
EQ5D5L (mobility, level 1) (%)	65.10	85.80
ESR (mm/h)	34.09 $\pm$ 8.2	31.37 $\pm$ 7.3
CRP (mg/l)	13.30 $\pm$ 2.5	11.14 $\pm$ 1.8

AS: Ankylosing Spondylitis, VAS: Visual analog scale, EQ5D5L: European Health-Related quality of life; ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

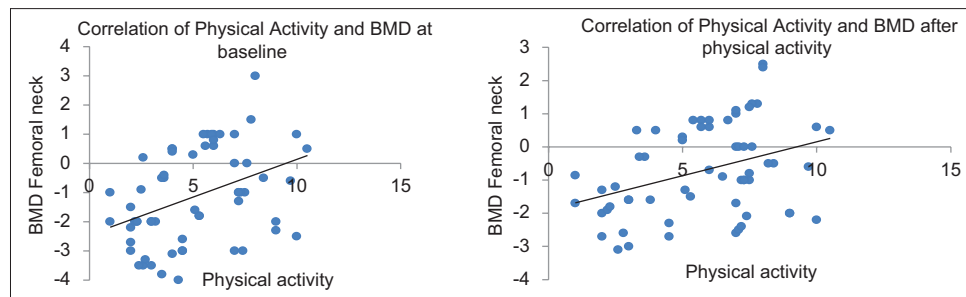


Figure 2: Correlation of bone mineral density at baseline and after 6 months of physical activity for femoral neck

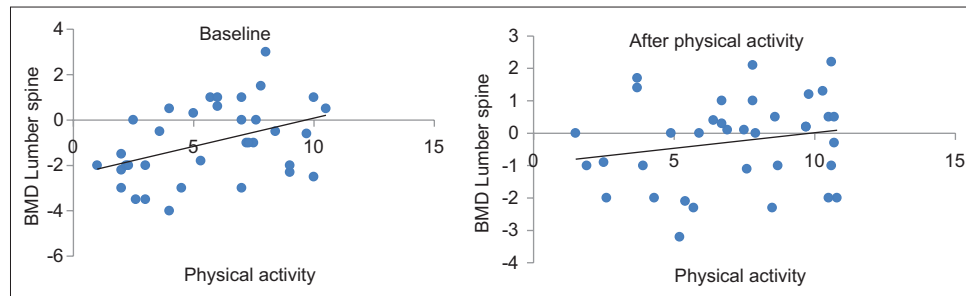


Figure 3: Correlation of bone mineral density at baseline and after 6 months of physical activity for lumbar neck

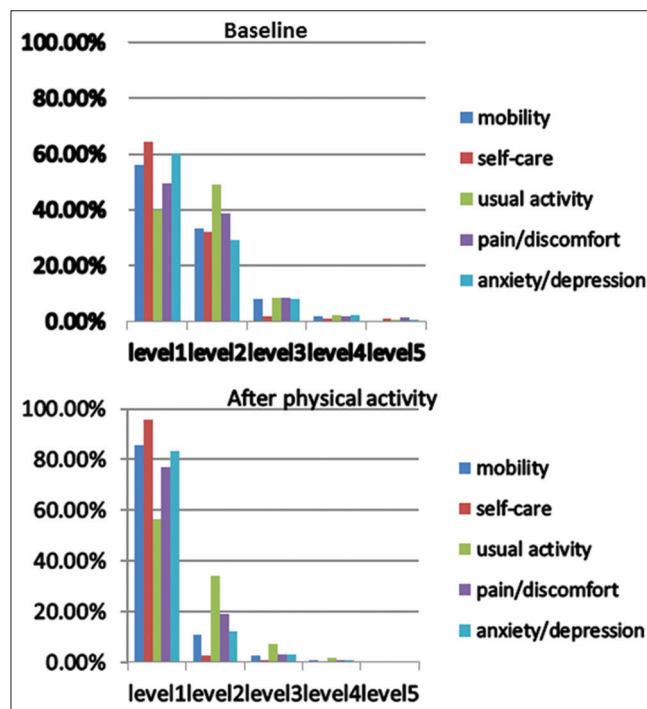


Figure 4: Comparison of mean for physical activity on European Health-Related quality of life at baseline and after 6 months. Levels of problem: 1: no; 2: slight; 3: moderate; 4: severe; 5: extreme

Table 2 describes lumbar spine and femoral neck BMD at baseline and after 6 months of PA. BMD increased significantly in femoral neck after 6 months compared to the baseline bone density.

In this study, a low BMD than normal (≤ -1.0) was found in 17 (27%) of AS patients. The osteopenic patients were

9 (14%) while the osteoporotic patients were 8 (13%). All the osteoporotic patients gave a history of longer disease duration than the osteopenic patients. They expressed longer disease durations and lower EQ5D5L in comparison to those with normal BMD or osteopenic patients. Six (10.6%) patients reported history of femoral, spine, and humeral fractures. For the PA, a non significant (0.055) association of higher Eq5D5 L scores with lower spinal and hip BMD. While no significant association of AS disease activity with BMD.

Table 2 and Figure 1 show the lumbar spine and femoral neck BMD for AS participants: at baseline and after 6 months of PA. A significant difference in the change in BMD was observed at the femoral neck ($P < 0.05$); however, it was not statistically significant ($P = 0.61$) at the lumbar spine.

For the disease activity [Table 3], all the participants at baseline had positive laboratory markers of active disease (CRP cutoff score ≥ 10 mg/l and ESR cutoff score ≤ 30 mm/h). There was a nonsignificant decrease in acute-phase reactant (ESR and CRP) in the participants.

An association between BMD and PA expressed by EQ5D5L was noticed in AS patients, in particular in those with short and moderate disease duration. Figures 2 and 3 describe the correlation of PA with BMD of femoral neck and lumbar spine, respectively. A significant positive correlation was observed between total PA and BMD of the femoral neck after 6 months of PA ($P < 0.05$); nevertheless, it was insignificant in the lumbar spine, although BMD was increased in both areas and genders by increasing PA.

Figure 4 shows the results of PA on mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. As shown in

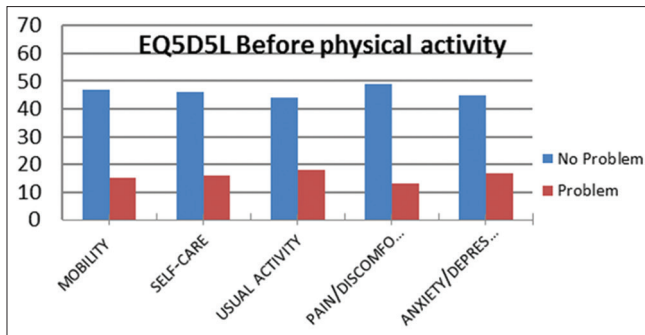


Figure 5: The presence of problems and no problems for the five dimensions of the European Health-Related quality of life at baseline and after 6 months of physical activity

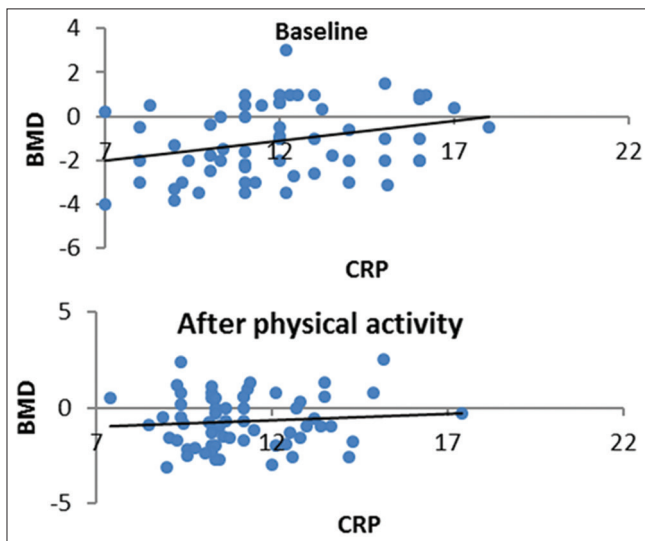


Figure 7: Correlation graph of bone mineral density versus C-reactive protein at baseline and after 6 months performing physical activity

Figure 4, mobility and self-care had a significant relationship with BMD ($P < 0.05$) after 6 months of PA, but was not significant at baseline.

A number of differences were observed across Eq5D5 L categories in comparison between at baseline and after 6 months of PA. Statistically significant differences with the presence of problems between the three categories (mobility, self-care, and anxiety/depression) were observed at baseline and after 6 months of AS relevant exercise [Figure 5].

Pearson's correlation was applied to establish the relationship between disease activity (ESR and CRP) and BMD at baseline and after 6 months of AS relevant PA [Figures 6 and 7], respectively. The results revealed that the correlation is weak significant ($P = 0.55$) between BMD and ESR and CRP at baseline and after 6 months of PA. The same result was obtained regarding the correlation between BMD measurements. Therefore, the result was insignificant correlation which may indicate no relationship between changes in bone mass and the acute phase reactants.

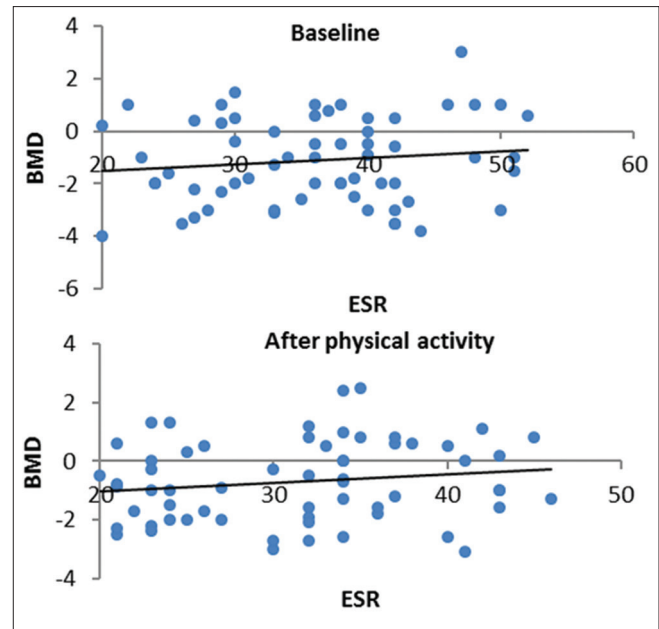


Figure 6: Correlation graph of bone mineral density versus erythrocyte sedimentation rate at baseline and after 6 months performing physical activity

DISCUSSION

Bone is a living structure that has a continuous dynamic action of bone turnover and remodeling.^[31] This may take 6 months to complete. BMD is the amount of mineral (g/cm^2) per square centimeter of bones; it is an indirect indicator of OP and fracture risk in clinical medicine (BMD and sport). The maintenance of the BMD is very important to prevent the OP.

OP is an abnormal metabolic process, normally associated with aging, chronic diseases, and during menopause, that is, the leading risk factor for fractures.^[32-34]

The WHO worked during the last few years to reach a consensus on the criteria for the diagnosis of OP. The use of the T-score in DXA scan alone is not a proper method, due to age factor as a greater risk factor for decreased BMD. The WHO recommended guide to use number of interventions in particular on a modifiable type.

Bone loss due to life style modification such as increasing habit of less physical activity, an important independent risk factor for OP. Some of these depletion factors have deteriorating effects on BMD. A consent opinion on common fracture risks could be predicted according to the probability of fracture. A 10-year probability of fracture is preferred to lifelong risk. In developed countries, a supportive program for promoting appropriate osteoporotic relevant PA is currently applied for people at risk of fracture, according to the BMD and the clinical risk factors, which is becoming a routine test for detecting OP.^[35]

It was hypothesized that exercise can modify inadvertent bone loss. This was supported by Jone Aloia (1981) who suggested that loss of bone minerals may be prevented by increased PA.

Prevention and evaluation of OP through BMD assessment should be considered in all patients with AS owing to the disease activity and decreased PA. However, the management of OP in Iraq seems to be improved though the instability situation in the last 3 decades.

This study suggested that AS patients are at risk of OP and have lower BMD levels in comparison to the controls. Nevertheless, severe OP is uncommon in AS patients. In the current study, a significant difference in the change in BMD was present at the femoral neck ($P < 0.05$); however, it was statistically insignificant ($P = 0.61$) at the lumbar spine. This difference in the results of BMD changes needs more research. Nevertheless, it may be explained by physical activity targeted femoral region. The other explanation may be related to the presence of sedentary lifestyle which may have less stimuli for improving spinal BMD. However, Lawrence *et al*^[36] suggests variable explanations for the pathogenesis and treatment of postmenopausal and senile osteoporosis suggests the existence of postmenopausal and senile OP that are characterized by variable character of cortical and trabecular bone loss.

Disease activity and severity were not significant factors for lowering BMD, but organ system damage might be linked to the occurrence of BMD depletion. Our data suggest that, in addition to patients receiving nonsteroidal anti-inflammatory drugs irregularly, physically active patients might benefit from regular monitoring of BMD as secondary prevention of bone depletion.

Although the drug therapy for AS is crucial for managing the disease activity, rehabilitation should have a role in the management of AS, in particular, the relevant therapeutic exercise. Physiatrists should recommend the physical therapy as part of a full strategy for management of AS disease.

Several studies indicate that the PA has a positive relationship to the BMD, and this result can be applied to AS.^[37] A study done by the WHO group revealed that OP and fractures are the main complications in rheumatoid arthritis patients and considerably affect QoL.^[38] The current study explored positive correlations between PA and QoL, and the PA protocol showed a positive impact on AS patients QoL. The PA had the strongest correlation with mobility, self-care, and anxiety/depression categories. The presence of problem between the three categories (mobility, self-care, and anxiety/depression) was less after 6 months of PA among the participants. Previously, a similar significant relationship between PA and QoL was reported.^[39]

For AS patients' treatment, PA is widely recommended. Nonetheless, there is no consensus in the literature about the most efficient type of PA. This study investigated the association of PA with disease activity (ESR and CRP) in AS patients. No significant differences were observed between the disease activity results after 6 months performing PA, although the disease activity results were decreased after 6 months.

The short duration of exercise program is a confounder. Therefore, a long-term rehabilitation program should be

performed to confirm the prolonged effect of exercise on bone density. The probable cofounders such as BMI and age might affect the results; however, the use of bone formation enhancements such as bisphosphonate therapy was excluded in the analysis and suggested that BMI and increased age had a negative effect on bone density while BMI had a positive effect.

CONCLUSION

The present study analyses revealed that PA in AS patients has a positive effect on bone status. This implies that AS disease-related loss in BMD is preventable by the relevant exercise program that includes increased mechanical loading with PA of higher impact. Clinically, this information is important, as it can be utilized while designing preventive and treatment plans for AS patients.

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Conflicts of interest

There are no conflicts of interest.

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