Evaluation of Bone Density in Ankylosing Spondylitis Patient on Biologic Agents in Erbil City Case Control Study

Mohammed Ibrahim Rasul (MBChB,MSc)[1] **and Shwan Kader Media**(MBChB,PhD)[2]

[1] Menistrey of Health , Erbil ,Iraq
[2] College of Medicine, Hawler Medical University, Erbil ,Iraq

Correspondence Address:
Mohammed Ibrahim Rasul
Menistrey of Health , Erbil ,Iraq
email: shahenallany@yahoo.com

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Abstract

Background: Ankylosing spondylitis is a chronic autoimmune inflammatory disease, mostly affect young men. Reduced bone density is the most common complication in ankylosing spondylitis, since reduced bone density occurs in most of the patients. Assessment of bone density in the early stages of the disease by using X- ray absorptiometry is essential.
Objective: To determine and evaluate the bone mineral density of ankylosing spondylitis patients compared healthy to control group.
Patients and Methods: This is a cross-sectional case control study of 50 patients with ankylosing spondylitis according to the Modified New York criteria and 50 healthy control group. The data were collected including socio demographic information of all patients (age, gender, medical history); systemic diseases type of biology treatment, using supplements, duration of ankylosing spondylitis, regular exercise, and smoking. The body mass index was calculated. Bone mineral density of the lumbar spine (L1-L4), and the left femoral neck were measured by using a dual energy x-ray absorptiometry. Statistical analysis was done by using a statistical package for social sciences (SPSS) version 22; Fisher's exact, and Student's t tests were used to compare two means. A p value of ≤ 0.05 was considered statistically significant.
Results: The prevalence of osteoporosis and osteopenia among patients group according to T-spine score were 12% and 42% respectively, compared with 0% and 26% respectively among the control group (p= 0.002) which was statistically significant. According to the T-left femur none patients group and the control group had osteoporosis, but 46% of the cases had osteopenia, compared with 8% of the controls which was statistically significant. There was a

significant but non-consistent association between the disease duration and the osteoporosis, and osteopenia in spine and femur. The prevalence of osteopenia and osteoporosis in the spine and femur were highest among those with low body mass index.

Conclusion: Osteoporosis and osteopenia are common among patients with ankylosing spondylitis. In the early stage of disease osteoporosis can occur. The osteoporosis of the spine is more common than in the femur. Osteoporosis related to the duration of the diseases and body mass of the patient.

Keywords: Dual energy x-ray absorbiometry (DEXA); Ankylosing spondylitis; Osteoporosis; osteopenia; Bone mineral density

Introduction

Ankylosing spondylitis (AS) is a chronic auto immune inflammatory rheumatic disease, that involves sacroiliac joint and spine, vertebra and intervertebral disc causing syndesmophyte formation and reduced back mobility, mostly affect young male[1,2].

The early presentation of ankylosing spondylitis starts with low back pain and stiffness in most of the cases [3-7]. It is uncommon for ankylosing spondylitis to start before the age of 45 years of age [8]. As a consequence of this, there will be a reduced range of movement in the lower back, changes in the spine curvature can be seen on physical examination of the patient with AS. Other findings of ankylosing spondylitis patient are increased kyphosis in the thoracic area and loss of lordosis in lumbar and cervical area with abnormal hip flexion and pain and stiffness of the joints other than the low back [7].

There are two enhanced but opposite bone remodeling process that occurs within the spine of patients with AS; which are pathologic new bone formation in the cortical zone of the vertebrae the zygoapophyseal joints, and the ligamentous apparatus with excessive loss of trabecular bone in the center of the vertebral body leading to osteoporosis (OP).A previous study found that osteoporosis and osteopenia incidence is higher in AS patients compared with age and gender healthy controlled. Also AS patients have significantly lower bone mineral density (BMD) [1,2].

The incidence of osteoporosis between 18.7% and 62%, and it is the most common complications of AS. The prevalence of osteoporosis is higher in male, and increases with increasing patient's age and disease duration [7]. Osteoporosis may also be seen in mild AS and in the early disease process [2,9].Vertebral fractures are another complication of AS, which is complicated by neurological injuries [10, 11].

The radiography is relatively insensitive in evaluating skeletal bone changes because 50% of the spine bone density has to be lost before demineralization become apparent on standard radiography. Patients who had long-standing ankylosing spondylitis the reduced bone density occur frequently. The sacroiliac joint is the first site in which radiological change occurred in ankylosing spondylitis. These changes need time to develop and sometimes take years before radiological findings become apparent. The x-ray may be

used to diagnose ankylosing spondylitis; MRI and CT-scan are no so valuable much and not routinely used. Dual Energy X-ray Absorption (DEXA) is the most reliable and dependable method for measurement of BMD [12].

The purpose of the current study was to evaluate the bone mass density of ankylosing spondylitis patient compared with the healthy control group.

Patients and Methods

This cross sectional case control study was conducted in the Hawler Teaching Hospital Department of Rheumatology. The study included 50 cases with AS and 50 healthy, socioeconomic matched controls subjects. The study protocol was approved by the ethical committee at the Kurdistan board for medical specialist. Informed consent was signed from the patients after a complete explanation of the aim of the study, and the patients data were kept confidential. Inclusion criteria including ankylosing spondylitis patients according to the modified New York criteria [13].

Exclusion criteria include, inflammatory bowel disease, psoriasis thyroid disease, pregnancy, other secondary cases that predispose to osteoporosis especially drugs, for example steroids, and disease modifying drugs were excluded from the study.

The consent was obtained according to the declaration of Helsinki physical examination and questioners. The data were collected from October 2019 –January 2020 including socio demographic variables of all patients; age, gender, and past medical history. Systemic disease type of biology treatment, using supplements duration of AS, regular exercise, smoking, were included in this study.

The weight and height were addressed in light clothes and without wearing shoes. Body mass index (BMI) was calculated from the weight and height recorded while performing DEXA scan and based on the formula weight (kg)/[height (m)]^2. The standard categorization of BMI by CDC [14], 18.5 was regarded as Underweight, normal as 18.5–24.9, over weight as 25.0– 29.9, and 30.0 and above as obese morbidity.

Bone mineral density BMD of the lumbar spine region anteroposterior view (AP) in (vertebrae L1 to L4), and the neck of left hip femur were measured using a DXA scanner. Following World Health Organization (WHO) definitions of osteopenia and osteoporosis were used: osteopenia, T-score < -1 to > -2.5 SD (compared to the young normal mean), and osteoporosis, T-score ≤ -2.5 SD. The lowest value of bone mineral density BMD measured in the lumber spine, femoral neck or total hip was used [15]. For that patient with the age of fewer than 50 a Z-score ≤ -2.0 SD (compared to the matched age) was considered to be below the expected range for age [16]. For the purpose of calculation of T-score and Z –score the BMD value of patient were compared with reference values provided by the DEXA scanner.

Statistical analysis

Data were analyzed using the statistical package for social science (SPSS, version 25). Chi square test of association was used to compare proportions. Fisher's exact test was used when the expected count of more than 20% of the cells of the table was less than 5. For comparison of two mean

Student's t-test was used. Variables significantly were found to be associated with low bone mineral density were entered into a binary logistic regression model. A p value of ≤ 0.05 was considered statistically significant.

Results

Fifty cases with ankylosing spondylitis were compassed in the study, in addition to 50 persons with no such disease. It is evident in table 1 that the mean age ± SD of the cases was 37.56 ± 9.92 years which was significantly (p < 0.001) higher than that of the control (31.18 ±6.62 years). The table shows also that 42% of the cases were aged 40 years or more compared with 10% of the controls (p = 0.003). The majority (78%) of the sample were males, but there was no significant difference between the two groups regarding the gender distribution (p = 0.629). It is evident in the table that 18% of the cases had systemic diseases compared with 2% of the controls (p = 0.008). No significant differences were detected between the two groups regarding practicing exercise (p = 0.229) and smoking (p = 0.656). The proportion of the controls who used to take supplements was 72% which was statistically significantly (p = 0.039) higher than the proportion between the cases (52%).

Table (1): Basic characteristics of the studied sample

	Case		Control		Total		
	No.	**(%)**	**No.**	**(%)**	**No.**	**(%)**	**P**
Age							
< 30	12	(24.0)	20	(40.0)	32	(32.0)	
30-39	17	(34.0)	25	(50.0)	42	(42.0)	
40-49	16	(32.0)	4	(8.0)	20	(20.0)	
≥ 50	5	(10.0)	1	(2.0)	6	(6.0)	0.003*
Mean(±SD)	37.56	(±9.92)	31.18	(±6.62)			<0.001†
Gender							
Male	38	(76.0)	40	(80.0)	78	(78.0)	
Female	12	(24.0)	10	(20.0)	22	(22.0)	0.629**
Systemic disease							
Yes	9	(18.0)	1	(2.0)	10	(10.0)	
No	41	(82.0)	49	(98.0)	90	(90.0)	0.008**
Regular exercise							
Yes	30	(60.0)	24	(48.0)	54	(54.0)	
No	20	(40.0)	26	(52.0)	46	(46.0)	0.229**
Smoking							
Yes	13	(26.0)	15	(30.0)	28	(28.0)	
No	37	(74.0)	35	(70.0)	72	(72.0)	0.656**
Supplement							
Yes	26	(52.0)	36	(72.0)	62	(62.0)	
No	24	(48.0)	14	(28.0)	38	38.0)	0.039**
Total	50	(100.0)	50	(100.0)	100	(100.0)	

* Fisher's exact test. **Chi square test. † t -test

According to the t-spine scores, the prevalence of osteopenia and osteoporosis among cases were 42% and 12% respectively, compared with 0% and 26% respectively among the controls (p = 0.002). According to the t-left femur scores, none of

the patients had osteoporosis, but 46% of the cases had osteopenia, compared with 8% of the controls ($p < 0.001$) as presented in Table (2).

Table (2): Prevalence of reduced bone mineral density among cases and controls

	Case		Control		Total		
	No.	**(%)**	**No.**	**(%)**	**No.**	**(%)**	**P**
t-spine							
Osteoporosis	6	(12.0)	0	(0.0)	6	(6.0)	
Osteopenia	21	(42.0)	13	(26.0)	34	(34.0)	
Normal	23	(46.0)	37	(74.0)	60	(60.0)	0.002*
t-left femur							
Osteopenia	23	(46.0)	4	(8.0)	27	(27.0)	
Normal	27	(54.0)	46	(92.0)	73	(73.0)	< 0.001
Total	50	(100.0)	50	(100.0)	100	(100.0)	

Table (3) shows that, among the cases, the more the age, the more the prevalence of osteoporosis except for the age group 40-49 years where the prevalence was 0% ($p = 0.003$). There was significant but non-consistent association between the disease duration and the prevalence, where it evident that the prevalence was 25% when the duration was less than 5 years, and it was 18.2% when the duration was 15 years or more, while it was 0% in the other duration categories ($p = 0.038$). The prevalence of osteoporosis was 30% among those with normal BMI, and it was 0% among those with a BMI of ≥ 35 Kg/m^2 ($p = 0.003$). No significant association was detected between the t-spine scores with gender ($p = 0.898$), regular exercise ($p = 0.556$), smoking ($p > 0.999$), and taking supplements ($p = 0.790$).

Table (3): Prevalence of reduced bone mineral density (assessed by t-spine scores) by the studied factors among cases

	t-spine scores categories						
	Osteoporosis		**Osteopenia**		**Normal**		
	No.	**(%)**	**No.**	**(%)**	**No.**	**(%)**	**P**
Age							
< 30	1	(8.3)	9	75.0)	2	(16.7)	
30-39	3	(17.6)	8	(47.1)	6	(35.3)	
40-49	0	(0.0)	3	(18.8)	13	(81.3)	
≥ 50	2	(40.0)	1	(20.0)	2	(40.0)	0.003*
Gender							
Male	5	(13.2)	15	(39.5)	18	(47.4)	
Female	1	(8.3)	6	(50.0)	5	(41.7)	0.898*
Duration							
< 5	4	(25.0)	7	(43.8)	5	(31.3)	
5-9	0	(0.0)	7	(50.0)	7	(50.0)	
10-14	0	(0.0)	6	(66.7)	3	(33.3)	
≥ 15	2	(18.2)	1	(9.1)	8	(72.7)	0.038*
BMI							
< 25	3	(30.0)	4	(40.0)	3	(30.0)	

25-29	1	(6.7)	8	(53.3)	6	(40.0)	
30-34	2	(13.3)	9	(60.0)	4	(26.7)	
≥ 35	0	(0.0)	0	(0.0)	10	(100.0)	0.003*
Regular exercise							
Yes	5	(16.7)	12	(40.0)	13	(43.3)	
No	1	(5.0)	9	(45.0)	10	(50.0)	0.556*
Smoking							
Yes	1	(7.7)	6	(46.2)	6	(46.2)	
No	5	(13.5)	15	(40.5)	17	(45.9)	>0.999*
Supplement							
Yes	4	(15.4)	10	(38.5)	12	(46.2)	
No	2	(8.3)	11	(45.8)	11	(45.8)	0.790*
Total	6	(12.0)	21	(42.0)	23	(46.0)	

* Fisher's - exact test

In Table (4), the results of the cases were analyzed, where the prevalence of osteopenia (assessed by left femur t scores) was compared between the different categories of the studied factors. Among cases, the prevalence of osteopenia among females (75%) was statistically significantly (p = 0.021) higher than the prevalence between males (36.8%). The prevalence was highest (60%) among those with a BMI of 25-29 and 30-34 Kg/m^2 (p = 0.046) but this association was not consistent as the prevalence was 40% among those with normal BMI, then increased to 60%, then decreased to 10%. All the other associations were not significant.

Table(4): Prevalence of osteopenia (assessed by left femur t scores) among cases

	Prevalence of osteopenia†		
	Cases		
	N	**No.**	**(%)**
Age			
< 30	12	7	(58.3)
30-39	17	10	(58.8)
40-49	16	3	(18.8)
≥ 50	5	3	(60.0)
P value			**0.059***
Gender			
Male	38	14	(36.8)
Female	12	9	(75.0)
P value			**0.021**
Duration of the disease			
< 5	16	7	(43.8)
5-9	14	7	(50.0)
10-14	9	4	(44.4)
≥15	11	5	(45.5)
P value			**>0.999***
BMI			
< 25	10	4	(40.0)
25-29	15	9	(60.0)

30-34	15	9	(60.0)
≥ 35	10	1	(10.0)
P value			**0.046***
Regular exercise			
Yes	30	12	(40.0)
No	20	11	(55.0)
P value			**0.297**
Smoking			
Yes	13	5	(38.5)
No	37	18	(48.6)
P value			**0.526**
Supplement			
Yes	26	12	(46.2)
No	24	11	(45.8)
P value			**0.982**
Total	50	23	(46.0)

* Fisher's exact test (the others are by the Chi square test). †None of the patients was diagnosed as osteoporosis according to T-left femur scores

No statistically significant relation was determined between the prevalence of reduced bone mineral density with the type of treatment taken by the patients whether this prevalence was assessed by the t-spine scores (p = 0.537), or the t-left femur scores (p = 0.791).

Table(5): Prevalence of reduced bone mineral density by type of treatment

	Treatment						
	Etanarcept		**Infliximab**		**Adalimumab**		
	No.	**(%)**	**No.**	**(%)**	**No.**	**(%)**	**P**
T-spine							
Osteoporosis	2	(6.9)	3	(23.1)	1	(12.0)	
Osteopenia	12	(41.4)	6	(46.2)	3	(37.5)	
Normal	15	(51.7)	4	(30.8)	4	(50.0)	0.537*
T-left femur							
Osteopenia	13	(44.8)	7	(53.8)	3	(37.5)	
Normal	16	(55.2)	6	(46.2)	5	(62.5)	0.791*
Total	29	(100.0)	13	(100.0)	8	(100.0)	

*By Fisher's exact test

The factors found to be significantly associated with the development of reduced bone mineral density (osteoporosis or osteopenia) were the disease ankylosing spondylitis (OR = 4.731, p = 0.002), BMI of < 25 Kg/m^2 (OR = 16.97, p = 0.022), and BMI 30-34 Kg/m^2 (OR = 18.49, p = 0.013) as presented in Table (6).

Table(6): SPSS output for binary logistic regression analysis where the dependent variable is reduced bone mineral density

				95% C.I.for OR	
	B	**P**	**OR**	**Lower**	**Upper**
Group					
Ankylosing spondylitis	1.554	**0.002**	4.731	1.801	12.426
Controls (reference)					
Age (years)		0.573			
< 30 (reference)					
30-39	0.185	0.728	1.203	0.424	3.411
40-49	-0.695	0.393	0.499	0.101	2.458
≥ 50	0.755	0.492	2.129	0.246	18.388
BMI (Kg/m^2)		0.051			
< 25	2.832	**0.022**	16.977	1.507	191.286
25-29	2.122	0.080	8.350	0.775	90.014
30-34	2.918	**0.013**	18.499	1.832	186.799
≥ 35 (reference)					
Constant	-3.508	0.005	0.030		

Discussion

This study revealed that patients with AS are more susceptible to osteoporosis, but is often undiagnosed and untreated, this study also suggested that AS patients are at risk of osteoporosis and have lower B level in comparison to the control. The decreased bone density at the spine region and femur area is well demonstrated in AS. However, there has been wide variation in the prevalence of osteoporosis ranging from 18.7% and 62% [7]. We reported A significant reduction of the bone mineral density of AS patients at lumbar spine, and femur, as compared to the control group. In this study we observed that 12% of patients with ankylosing spondylitis had osteoporosis, 42% had osteopenia in the spine; where-as in the control group none had osteoporosis, 26 % had osteopenia in the spine. In the current study, a significant difference in the change in BMD was present at the femoral neck ($P < 0.05$); at the femoral neck we found none of the patients and control had osteoporosis but 46% of cases had osteopenia, compared with 8% of the control group which was similar to the result, found by the Diab, 2018 [17]. This study recorded a significant reduction in BMD in both spine and femur in AS. There are several studies that examined bone mass in ankylosing spondylitis patients, the result was similar, showing that BMD is reduced in AS patients in comparison with controls, with some difference according to the duration of the disease.

The AS typically occurs in the third and fourth decade of life, many patients are younger than the traditional cohort of older patient with low, even patients who had AS for less than 10 years are at high risk for low bone mineral density [18], in the current study the more age the more prevalence of osteopenia the older age has been found to be at significant for low BMD in patients with AS compared with the control group.

In the present study osteopenia and osteoporosis in the lumbar spine were more common in men than in women and thus more men were diagnosed as osteoporotic but the difference was not significant.AS is

usually diagnosed in the third and fourth decade of life, with male predominating in most population surveys, at a ratio of 5:1[19]. It is likely that the sex ratio is closer to the unity in reality ,with males being prone to more severe disease [21] and to the development of osteopenia [22].This might be due to the natural protective effect of estrogen hormone against the occurrence of osteopenia more common in male AS than in females.

Furthermore, our AS patients with osteopenia was older, and had a longer disease duration than those without osteopenia.There was a significant but non-consistent association between the disease duration and the prevalence of osteoporosis ($p = 0.038$), which was agreed with the-study done, by Donelly *et al.*, who found that a significant reduction in the BMD at the neck of femur in patients with AS, and the reduction in proportion to the diseases duration and severity . They also found that the lumbar spine bone density was reduced in early disease, but in patients with advanced AS it was increased considerably [1].

In the present study, the osteopenia and osteoporosis in the lumber spine and osteopenia in the femoral neck are more common in thinner patients with AS, as has been found by another study. The correlation between BMD at the neck of femur and BMI was highly positive in cross sectional study conducted among post-menopausal women by Steinschneider *et al* [23].

Patient with low body mass index are more susceptible to developin osteopenia. In this study, the one of the factors found to be significantly associated with the development of a reduced BMD (osteoporosis or osteopenia), is low BMI, similar studies by Nguyen *et al* [24] and Baheiraei *et al* [25], also reported the consistent findings that lower BMI was associated with lower BMD.

In this study we found that osteoporosis in AS patients was more common in smokers than in non- smokers, but the difference was not statistically significant, and this finding was in agreement with that of Lorentzon *et al* [26], who reported that smokers had a significantly lower BMD on DEXA than nonsmokers. Cigarette smoking is a risk factor for osteoporosis and is related to a decreased of bone mass and increased risk of fractures [27].

In the current study it is found that regular exercise had no effect on BMD among patient with AS in spine and femur. It is accepted that weight bearing exercise improves bone mineral density. There is no current study to demonstrate the effect of exercise on BMD on patients with AS. However, improvement in physical function and disease activity has been noted in patients with AS who participated in the exercise program [28,29]. Recent guidelines also recommended consistent physical activity and stretching exercise in patient with ankylosing spondylitis [30].Many studies regarding physical activity as part of the management of osteoporosis in post-menopausal women and thus may not fully generalized to the population of patients with AS. However, given the benefits in patients with AS coupled with the benefits of physical activity in osteoporosis treatment prevention can be achieved in other demographics.

Regarding the activity of the disease, biological drugs may prevent bone loss via a

direct effect on bone metabolism and remodeling. It is well demonstrated that TNFα induces differentiation of osteoclast precursors through a synergistic action with receptors activator of nuclear factor-kappa B ligand (RANKL) [31]. The balance between TNF superfamily molecule RANKL- , osteoprotogerin, osteoclastogenesis inhibitory factors, and TNF-related apoptosis inducing ligand to regulate bone metabolism and remodeling [32-34], there is no significant difference in BMD change in biologics responders and non-responders [35,36]. In this study we found that biologics therapy was not significantly affected BMD, sequential evaluation of BMD during biological therapy should help to illuminate their influence on bone density.

There was no significant relation detected between the prevalence of reduced bone mineral density with the type of treatment taken by the patients whether this prevalence was assessed. There is no enough evidence to support the use of TNF inhibitors for the sole purpose of prevention of osteoporosis and low bone mass density in patent with ankylosing spondylitis. However we have a low threshold to start TNF blocker in patient noted to have low BMD and active AS with close monitoring of low bone density and osteoporosis by DEXA scanning at two years intervals.

Conclusions

The prevalence of osteopenia and osteoporosis are high in patient with ankylosing spondylitis. Osteoporosis was often undiagnosed and untreated, especially in male patients with AS. Older age , long disease duration,and a low BMI an indicate increased risk of osteoporosis.

Recommendations

We recommend another study measuring BMD after1 year to see the effect of biology in BMD and comparing it with this data.

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Ethical clearance: This study was approved by research ethical committee college of Medicine Hawler Medical University.

Conflict of interest: This research done by one researcher so no Conflict of Interest.

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