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ORIGINAL RESEARCH

Anti-Osteoporosis Is Imperative in Prevention of Progress of Ankylosing Spondylitis

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Background: Ankylosing spondylitis (AS) is a chronic autoimmune disease that affects the spine and peripheral joints, often leading to kyphosis, joint stiffness, and even ankylosis. Sagittal parameters, such as total thoracic kyphosis (TTK), thoracic kyphosis (TK), major thoracic kyphosis (MTK), and thoracolumbar kyphosis (TLK), are crucial indices for evaluating spinal alignment in AS patients and can reflect disease progression. This study aims to explore the relationship between bone mineral density (BMD), sagittal parameters, and joint ankylosis in AS patients.

Methods: A retrospective study was conducted on 147 AS patients. Participants were divided into three groups based on cervical and hip joint mobility. BMD was measured using quantitative computed tomography (QCT). Sagittal parameters (TTK, TK, MTK, TLK) were assessed using X-rays. Ordinal multinomial logistic regression and Spearman correlation analyses were performed to identify factors influencing joint stiffness.

Results: Significant differences in age, BMD, and sagittal parameters (TTK, TK, MTK, TLK) were observed among the groups. Ordinal logistic revealed that BMD (Estimate = 0.012) was negatively correlated with joint stiffness, while TTK (Estimate = 0.020) and TLK (Estimate = 0.030) were positively correlated. Age, TK, and MTK do not have a significant impact on joint stiffness. Spearman analysis showed no correlation between BMD and sagittal parameters (TTK and TLK). Besides, TTK and TLK were correlated.

Conclusion: In AS patients, BMD is an independent protective factor against joint stiffness, whereas sagittal parameters (TTK and TLK) contribute to increased joint stiffness. These findings highlight the importance of monitoring both bone mineral density and key sagittal parameters in clinical practice. Early anti-osteoporosis treatment, alongside interventions targeting abnormal spinal alignment, may help preserve joint mobility and potentially prevent progression to joint ankylosis.

Plain Language Summary: BMD is independent protective factor for joint ankylosis in ankylosis spondylitis. It is imperative to start early anti-osteoporosis treatment to preserve cervical and hip mobility.

Keywords: ankylosis spondylitis, BMD, osteoporosis, kyphosis, sagittal parameters

Introduction

Ankylosing spondylitis (AS) is a chronic progressive autoimmune disease primarily affecting the sacroiliac joints, spine processes, paraspinal soft tissues, and peripheral joints. It can also present with extra-articular manifestations. Clinically, it mainly manifests as pain in the lower back, neck, buttocks, hips, and swelling of joints.[1–3] In severe cases, spine deformities, cervical ankylosis, and hip joint ankylosis can occur.[4–6] The primary sites of inflammation are the attachments of ligaments and joint capsules. In the early stages, there is local congestion, edema, and infiltration of inflammatory cells, leading to the formation of granulation tissue, which quickly undergoes fibrosis and ossification. Secondary ossification and the formation of new bone result in bone sclerosis and joint ankylosis.[7]

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Osteoporosis is the most common bone disease, characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to increased bone fragility and susceptibility to fractures.[8] Dual-energy X-ray absorptiometry (DXA) is the most recognized and accepted method for measuring bone mineral density (BMD).[9,10] Quantitative computed tomography (QCT) is another method for measuring BMD, based on clinical CT scan data analyzed using QCT software. Due to the technical advantages of QCT and the rapid development of CT technology, QCT is gaining increasing attention in the field of osteoporosis research and clinical application globally.[11–14]

Bone is a target in ankylosing spondylitis, characterized by extensive changes in bone remodeling due to the interaction between inflammation and bone. Combined analysis of DXA and QCT in patients with early and long-term disease has shown low BMD and bone loss in the spine and hips of AS patients.[15–17] Normal cervical spine and hip joints, rich in spongy trabecular bone, are lightweight and act more like springs than levers, promoting flexibility rather than stiffness. Based on this pathological process, cervical spine and hip joint mobility are affected during the course of AS, potentially leading to ankylosis, which is a significant complication.[18]

Previous research has primarily focused on kyphosis and BMD in ankylosing spondylitis. There is currently no comprehensive study on the characteristics and relationship between BMD and joint ankylosis in patients with ankylosing spondylitis. This paper conducts a retrospective analysis of patients with AS who also have hip or cervical ankylosis to further explore the relationship between BMD and joint ankylosis.

Study Design

This study is a retrospective study investigating 147 AS patients from January 2016 to December 2019 in Peking University People's Hospital. Participants were divided into three groups based on cervical and hip joint mobility: Group A, with AS and both neck and hip joint ankylosis; Group B, with AS and either neck or hip joint mobility; and Group C, with AS but normal neck and hip joint mobility. This study has been approved by the Ethics Committee of Peking University People's Hospital (Ethics Approval Number: 2018PHC076), and all participants provided written informed consent.

Inclusion criteria were as follows: (1) diagnosed with ankylosing spondylitis; (2) preoperative X-rays and magnetic resonance imaging (MRI) of the spine and sacroiliac joints; (3) complete data for rheumatologist evaluation. Exclusion criteria included: (1) individuals with a history of spinal surgery; (2) individuals with spinal tumors, infections, or fractures; (3) individuals with incomplete patient information.

Data Collection

Data were obtained by reviewing hospital records and assessing disease status by rheumatologists and spine surgeons. Primary measurement indicators included patient symptoms, neck and hip joint mobility, MRI of the sacroiliac joints, BMD measured by QCT, and full-length anteroposterior and lateral X-rays of the spine.

Parameter Measurement

X-ray evaluations included comprehensive anteroposterior (AP) and lateral X-rays of the entire spine as the basis for morphological analysis., (1) Total Thoracic kyphosis (TTK): Sagittal angle between T1 and T12 (2) Thoracic kyphosis-(TK):Sagittal angle between T5 and T12 (3) Major Thoracic kyphosis(MTK): The angle between the proximal endplate of the vertebra above and the distal endplate of the vertebra below in the segment affected by kyphosis. (4) Thoracolumbar kyphosis(TLK) was determined by the angle between the superior endplate of the tenth thoracic vertebra (T10) and the inferior endplate of the second lumbar vertebra (L2).

Statistical Analysis

SPSS 29.0 software was used for analysis. The study was divided into three groups based on the presence of hip and neck ankylosis, with joint ankylosis as the dependent variable in an ordinal multinomial logistic regression analysis to explore the related influencing factors of joint stiffness in patients. Descriptive analysis was first used to describe the basic characteristics of all potential factors affecting joint stiffness in AS patients. Continuous and categorical variables between the three groups were analyzed using ANOVA. Subsequently, parameters with

statistical differences were subjected to ordinal multinomial logistic regression analysis to identify potential influencing factors. Finally, correlation analysis was performed to explore the relationships between influencing factors. All statistical tests were two-tailed, and statistical significance was defined as $P < 0.05$.

Results

Basic Characteristics of Study Patients

A total of 147 patients were included in this study, with 19 patients diagnosed AS with both cervical and hip joint ankylosis, 84 patients with AS and either cervical or hip joint ankylosis, and 44 patients with AS without cervical or hip joint ankylosis. Table 1 records the basic conditions of the three groups. ANOVA results indicate no differences in gender, but significant differences in age, BMD, TTK, TK, MTK, and TLK among the groups (P<0.05). The AS+ cervical or hip ankylosis group has the highest mean age (43.26±9.66), while the AS-only group is the youngest (36±13). The AS-only group has the highest QCT value (89.39±34.14). AS+cervical and hip ankylosis group has the highest values for TTK, TK, MTK, and TLK.

Results of Ordinal Multinomial Logistic Regression Analysis

Age, BMD, TTK, TK, MTK, and TLK were subjected to ordinal multinomial logistic regression, with the regression results shown in Table 2. The results indicate that BMD, TTK and TLK are related to joint stiffness in AS patients. BMD

Table 1 Characteristic of Three Groups

	Kyphosis+Cervical and Hip Ankylosis	Kyphosis+Cervical or Hip Ankylosis	Kyphosis	P
Age	40.1±8.19	43.26±9.66	36±13	P=0.001
Gender				P=0.772
Male	18	76	34	
Female	1	8	10	
QCT	70.53±21.84	76.06±33.28	89.39±34.14	P=0.041
TTK	91.28±41.13	63.94±25.52	46.46±24.63	P<0.001
TK	63.33±23.67	60.3±20.03	47.80±23.88	P=0.004
MTK	62.17±24.87	49.26±18.98	37.45±16.97	P<0.001
TLK	49.74±20.87	36.62±15.06	23.22±20.35	P<0.001

Table 2 Results of Ordinal Logistic Regression

	Estimate	Std. Error	Wald	df	P	95% CI	
Age	0.029	0.017	2.88	1	0.09	−0.004	0.062
BMD	−0.012	0.006	4.34	1	0.04	−0.023	−0.001
TTK	0.02	0.008	6.56	1	0.01	0.005	0.035
TK	−0.009	0.013	0.47	1	0.495	−0.035	0.007
MTK	0.028	0.015	3.39	1	0.066	−0.002	0.057
LTK	0.03	0.011	7.51	1	0.006	0.009	0.051

Table 3 Spearman Correlation Analysis Between Relevant Factors

	QCT	TTK	TLK
QCT	–	–	–
TTK	−0.052	–	–
TLK	−0.029	0.497*	–

Note: *P<0.05, there is a correlation between the two parameters.

is negatively correlated with joint stiffness (Estimate=−0.012), while TTK (Estimate=0.02) and TLK (Estimate=0.03) are positively correlated with joint stiffness.

Spearman Analysis Results

To further clarify the intrinsic influencing factors between BMD, TTK and TLK, Spearman analysis was conducted, with the results shown in Table 3. It was found that BMD is not related to TTK and TLK, while TTK and TLK are mutually correlated.

Discussion

Inflammation in ankylosing spondylitis involves small joints, leading to bone erosion, joint space narrowing, and ankylosis. The initial stage of small joint ankylosis is the fusion of cartilage surfaces, progressing to bony ankylosis. Small joint ankylosis impairs normal joint function and affects joint mobility, resulting in joint stiffness.[4,5] Figure 1 demonstrates a typical case of AS with hip joint and cervical ankylosis.

Previous research has primarily focused on the relationship between BMD and fractures in ankylosing spondylitis,[19–21] with no studies on the relationship between joint stiffness and BMD. This study uses QCT to evaluate BMD. Unlike DXA, QCT provides volumetric measurements of BMD and can differentiate between cortical and trabecular bone. Since syndesmophytes or bridging ankylosis may be present in AS, changes in cortical and trabecular bone may differ.[22,23]

Descriptive studies have found that QCT-measured BMD is lower in AS patients compared to normal individuals. Moreover, patients with joint stiffness have lower QCT-measured BMD than those with only AS, meeting the current diagnostic criteria for osteoporosis. Inflammatory cytokines, glucocorticoid therapy, immobilization, and reduced physical activity due to joint pain and muscle weakness are considered major risk factors for low BMD in these diseases.[24,25]

As the disease progresses, patients frequently develop significant sagittal spinal imbalance, including increased TK, decreased LL. Measuring and analyzing sagittal parameters (spinopelvic parameters) can provide a better assessment of the degree of deformity caused by ankylosing spondylitis, guide clinical decision-making, and predict prognosis.

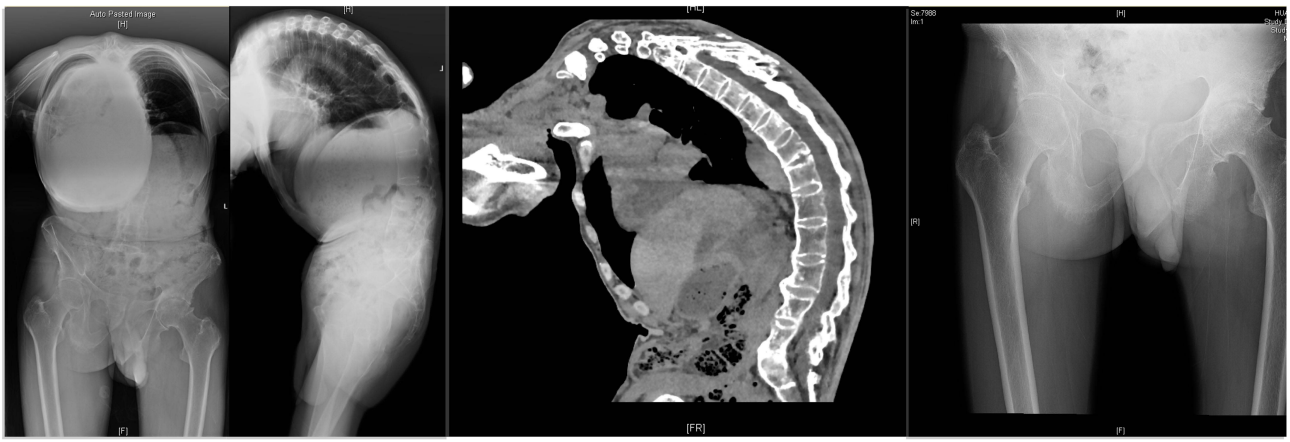

Figure 1 AS patients with neck and hip ankylosis.

The results of the ordinal multinomial logistic regression analysis indicate that BMD, TTK and TLK are factors affecting joint stiffness in AS patients. BMD is negatively correlated with joint stiffness, while TTK and TLK are positively correlated. These results suggest that higher BMD have a protective effect, while TTK and TLK are risk factors for increased joint stiffness. These findings provide important clinical treatment references, suggesting that changes in these indicators should be closely monitored in managing AS patients. Further Spearman correlation analysis shows no significant correlation between BMD and sagittal parameters (TTK and TLK), while TTK and TLK are significantly correlated with each other. This result suggests that BMD independently influences joint stiffness. And TTK and TLK also significantly influence joint stiffness, interacting with each other and further affecting joint ankylosis.

Changes in bone mineral density and sagittal parameters in AS patients are not necessarily directly related. While both impact the degree of joint stiffness, their underlying mechanisms are distinct. I. Changes in bone mineral density mainly reflect a "systemic" or "broad regional" pathophysiological process. Decreased BMD often indicates overall bone loss or a risk of osteoporosis, which can be influenced by immune inflammation, endocrine hormones, and various other factors, as well as the patient's level of physical activity and nutritional status. Although patients with AS frequently exhibit reduced bone mass, the rate and pattern of bone loss may not be consistent across different spinal segments or joints.[26] II.Changes in sagittal parameters mainly reflect "localized or structural" alterations: TTK, TLK and other parameters measure the thoracic or thoracolumbar kyphosis angles, indicating changes in vertebral alignment as new bone (syndesmophytes, bridging) forms around the sacroiliac and facet joints. In AS, bone overgrowth (osteophytes, syndesmophytes) and bone loss (osteopenia or osteoporosis) can coexist in the same patient, yet they may not overlap in distribution. Some segments may exhibit marked osteophyte formation and structural fusion, while others have considerable bone loss.[27–29] Hence, "loss of bone mineral density" and "increased thoracic or thoracolumbar kyphosis" do not necessarily share a straightforward one-to-one relationship. Although both affect the ultimate degree of joint stiffness, their underlying mechanisms may not be linearly interlinked.

Osteoporosis is a common complication in ankylosing spondylitis. This study suggests that BMD has a protective effect against joint stiffness. The relationship between AS and osteoporosis may involve the following mechanisms: 1. Ankylosing spondylitis is a chronic inflammatory disease that primarily affects the spine and sacroiliac joints. Persistent inflammation keeps the immune system continuously activated. Pro-inflammatory cytokines stimulate the production of RANKL, a key factor in osteoclast differentiation and activation. Osteoclasts are responsible for bone resorption. Enhanced osteoclast activity leads to accelerated bone resorption, where bone tissue is broken down faster than it is replaced.[30,31] This imbalance in bone remodeling leads to localized osteoporosis, especially near the inflamed joints. Bone density decreases and becomes more porous. Osteoporosis itself further exacerbates bone resorption. As bones become more fragile, microfractures occur more easily, triggering local inflammation and further osteoclast activation.[32] While ankylosing spondylitis causes bone loss through osteoporosis, it also leads to new bone formation (ankylosis) in certain areas. Fragile bones are more prone to this abnormal bone growth, leading to joint ankylosis. The combination of osteoporosis and ankylosis significantly increases the risk of ankylosis in patients with AS, especially in the later stages of the disease. Therefore, treatment targeting the inflammation of ankylosing spondylitis (such as TNF inhibitors) may help reduce osteoclast activity.[33,34] Additionally, specific treatments for osteoporosis may be needed to prevent further bone loss, thereby slowing the progression of joint ankylosis. 2. AS patients often have limited mobility due to pain and inflammation, leading to osteoporosis due to prolonged lack of exercise. Lack of weight-bearing exercises and physical activities is a known risk factor for osteoporosis, a condition characterized by low bone mass and the deterioration of bone tissue.[35,36] This makes the bones fragile and more susceptible to fractures. As osteoporosis progresses, it can cause additional pain, especially in the spine and hips. This new source of pain further hinders physical activity, creating a vicious cycle: inactivity leads to more bone loss, which in turn leads to more pain and further reduces activity. Pain caused by osteoporosis further limits patient activity, exacerbating cervical and other joint stiffness. Lack of exercise not only affects bone density but also exacerbates joint stiffness, particularly in the cervical spine and other joints affected by AS. This increased stiffness can further restrict the patient's range of motion and overall quality of life. Appropriate exercise can improve BMD, maintain bone structure, and reduce the risk of falls and joint mobility.[37]

This study has several limitations. As a cross-sectional study, we did not assess whether BMD progression predicts the worsening of functional impairment. Longer prospective longitudinal studies are needed to examine the relationship

between joint stiffness and BMD in AS. Additionally, we did not quantify joint mobility limitations, making it difficult to grade joint abnormalities. Finally, although multiple indicators were included in this study, other potential factors, such as disease duration, medication use, or lifestyle factors, affecting joint stiffness were not included in the analysis. Future research should consider more comprehensive factors.

Conclusion

In AS patients, BMD is an independent protective factor against joint stiffness, whereas sagittal parameters (TLK and TTK) contribute to increased joint stiffness. These findings highlight the importance of monitoring both bone mineral density and key sagittal parameters in clinical practice. Early anti-osteoporosis treatment, alongside interventions targeting abnormal spinal alignment, may help preserve joint mobility and potentially prevent progression to joint ankylosis.

Ethics Approval

All procedures performed in studies involving human participants were in accordance with the 1964 helsinki declaration and its later amendments or comparable ethical standards, and this study has been approved by the Ethics Committee of Peking University People's Hospital (Ethics Approval Number: 2018PHC076).

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Disclosure

Bin Zheng, Panfeng Yu, Haiying Liu and Yan Liang declare no conflicts of interest.

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