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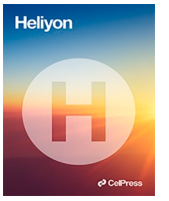

Increased serum visfatin level is associated with fat deposition of the lumbar spine in ankylosing spondylitis patients

Jie Shen [a,b,1], Sha-Sha Tao [c,d,1], Rui-Yuan Wang [a,b], Shi-Kui Shi [e], Chao Jiang [a,b], Yong-Jun Mei [a,b,*]

[a] Department of Rheumatology and Immunology, The First Affiliated Hospital of Bengbu Medical College, 287 Changhuai Road, Bengbu, Anhui, 233004, China
[b] Anhui Province Key Laboratory of Immunology in Chronic Diseases, 2600 Donghai Avenue, Bengbu, Anhui, 233030, China
[c] Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei, Anhui, China
[d] Experimental Teaching Center for Preventive Medicine, School of Public Health, Anhui Medical University, No 81 Meishan Road, Hefei, 230032, Anhui, China
[e] Department of Radiology, The First Affiliated Hospital of Bengbu Medical College, 287 Changhuai Road, Bengbu, Anhui, 233004, China

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ABSTRACT

Objectives: To assess the serum visfatin levels in patients with ankylosing spondylitis (AS), as well as its correlation with fat deposition of the lumbar spine.
Methods: Serum visfatin levels were detected by enzyme-linked immunosorbent assay (ELISA) in 50 AS patients and 75 sex-and age-matched healthy controls. The clinical and laboratory indexes of AS patients were recorded, and the lumbar spine magnetic resonance scan was performed to evaluate the lumbar spine fat deposition in AS patients. The level of serum visfatin and its correlation with lumbar fat deposition were analyzed, and the risk factors of AS lumbar MRI fat deposition were evaluated by Logistic regression.
Results: Serum visfatin levels in AS patients were elevated compared with that in healthy controls ($p < 0.001$), and were more significant in patients with fat deposition and syndesmophyte formation ($p = 0.017$ and $p = 0.014$, respectively). Serum visfatin levels were positively correlated with CRP, BASDAI, mSASSS and fat deposition (all $p < 0.05$). Age (OR = 1.085, 95% CI: 1.005–1.173, $p = 0.038$), disease duration (OR = 1.267, 95% CI: 1.017–1.578, $p = 0.035$), and visfatin (OR = 1.846, 95% CI: 1.004–3.393, $p = 0.048$) were risk factors for fat deposition in AS patients.
Conclusions: The level of serum visfatin in AS patients is significantly increased, which is associated with fat deposition on lumbar MRI. Elevated visfatin level is an independent risk factor for AS lumbar fat deposition.

1. Introduction

Ankylosing spondylitis (AS) is a chronic progressive inflammatory disease, which is more common in men and mainly affects the

* Corresponding author. Department of Rheumatology and Immunology, The First Affiliated Hospital of Bengbu Medical College, 287 Changhuai Road, Bengbu, Anhui, 233004, China.
E-mail addresses: jieshen0151@163.com (J. Shen), taoshasha1212@126.com (S.-S. Tao), meiyongjun@bbmc.edu.cn (Y.-J. Mei).
[1] Jie Shen and Sha-Sha Tao contributed equally to this work and should be considered co-first authors.

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axial joint. Sacroiliac joint involvement is usually considered a sign of the disease. AS is insidious and the most common and characteristic symptoms are low back pain and back stiffness [1]. It is characterized by new bone formation during disease progression and can cause spinal ankylosis and ligamentous calcification in advanced stages, manifesting as hunchback or bamboo-like changes. Many studies have investigated the radiological progression of AS by imaging methods, such as radiographs and magnetic resonance imaging (MRI), and therefore imaging has an important role in the diagnosis and prognosis assessment of the disease.

Adipokines are highly biologically active factors secreted by adipose tissue, mainly including visfatin, adiponectin, leptin, and resistin, which can affect different tissues and cells systemically and locally, contributing to immune regulation and bone reconstitution mechanisms [2]. It has been found that visfatin, a novel adipokine, leads to the release of pro-inflammatory factors, plays an important role in various acute and chronic inflammatory responses, and plays a role in bone homeostasis by stimulating osteoblast proliferation and inhibiting osteoclast production [3]. In this study, the level of visfatin in the serum of AS patients was detected, and the difference between AS patients and the control group was observed. Combined with imaging data, the correlation between visfatin and lumbar MRI fat deposition in AS patients was analyzed, and the effect of serum visfatin level on AS lumbar fat deposition was evaluated.

2. Materials and methods

2.1. Study subjects

A total of 50 AS patients (42 males, 8 females, aged 16–62 years, with an average age of 34.40 ± 12.64 years) who were admitted to the Department of Rheumatology and Immunology of the First Affiliated Hospital of Bengbu Medical College from October 2020 to December 2021 were selected as the AS group, all patients met the New York criteria for AS 1984 revision. Seventy-five healthy controls (62 males and 13 females, range from 20 to 60 years, mean age 35.67 ± 10.09 years) were collected during the same period. The enrolled patients were excluded from infections, tumors, and other rheumatic diseases. The age, disease duration, body mass index (BMI), HLA-B27, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelet count (PLT), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and Bath Ankylosing Spondylitis Function Index (BASFI) were recorded for all AS patients. Normal reference range of erythrocyte sedimentation rate: male ≤15 mm/h, female ≤20 mm/h; the normal reference range of CRP was ≤6 mg/L. The study was approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College. Written informed consent was obtained from all individuals before the initiation of the study.

2.2. Laboratory analysis

Blood samples of 5 ml were collected from all the individuals, and centrifuged at 1000 r/min for 20 min after natural clotting and the serum samples were stored at −80 °C until analysis. Visfatin levels were detected by enzyme-linked immunosorbent assay (ELISA). The reagents were purchased from Wuxi Donglin Sci & Tech Development Co., Ltd. The detection was performed according to the manufacturers' instructions.

2.3. Imaging

All AS patients underwent MRI scanning of the lumbar spine in sagittal position with T1, T2 (Fig. 1a) and short-tau inversion recovery (STIR) phases (Fig. 1b), mainly to observe fat deposition in the vertebral horn (Fig. 1), and to record the number of fat-

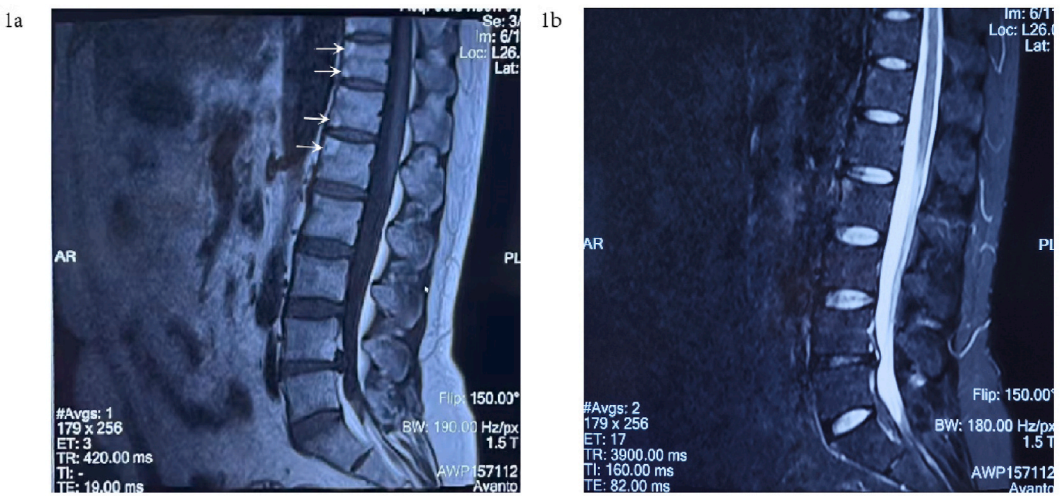

Fig. 1. (1a) Lumbar MRI T1 sequence, fat deposition as shown in the arrow; (1b) STIR sequence images of the same lumbar spine.

deposited vertebrae. Frontal and lateral radiographs of the cervical, thoracic and lumbar spine were performed, and the modified Stoke ankylosing spondylitis spine score (mSASSS) was used to assess structural damage of the spine. The examination reports were obtained by two radiologists who reviewed the films individually.

2.4. Statistical analysis

Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) statistical software for Windows, version 21.0 (SPSS Inc., IL, USA). Normal distribution data were presented as mean ± SD, skewed data were presented as median (interquartile range, IQR). Independent samples *t*-test or rank sum test was used to compare differences between groups, and chi-square test was used for comparison of categorical variables. Spearman correlation coefficients were calculated to determine the association between visfatin levels and other variables, and risk factors for fat deposition in patients with AS were analyzed using Logistic regression analysis, p values less than 0.05 were considered statistically significant.

3. Results

3.1. Characteristics of patients

The patients' demographic and clinical characteristics are summarized in Table 1. We examined two groups of subjects: 50 AS patients and 75 healthy controls. Their mean age (±SD) was 34.40 ± 12.64 and 35.67 ± 10.09 years, respectively. Males accounted for 84% of the AS group and 82.7% of the healthy controls. According to the Goutellier criteria, which measures the fat content of muscle tissue by imaging techniques such as CT or MRI, and divides the fat deposits into 5 grades from 0 to 4, we classified fat deposits of AS patients on the basis of fat infiltration of paravertebral muscles. AS patients were classified into 0–4 grade with 22, 17, 5, 2, and 4 patients, accounting for 44%, 34%, 10%, 4%, and 8%, respectively. Which corresponded to 22, 17, 5, 2, and 4 patients with AS, with the proportions of 44%, 34%, 10%, 4%, and 8%, respectively.

3.2. Serum visfatin levels are elevated in patients with AS

Serum visfatin levels were significantly higher in patients with AS than in healthy individuals [(5.57 ± 2.20) *vs*. (1.41 ± 0.82) pg/ml; $p < 0.001$] (Fig. 2a). After dividing the patients into with fat deposition and without fat deposition, the results showed that the serum visfatin level was higher in AS patients with fat deposits [(6.21 ± 2.49) *vs.* (4.74 ± 1.43) pg/ml]; $p = 0.017$] (Fig. 2b). The visfatin levels in AS group were compared according to the presence or absence of syndesmophyte formation, and the serum visfatin levels were significantly higher in AS patients with syndesmophyte formation than those without syndesmophyte formation [(6.38 ± 2.55) *vs*. (4.87 ± 1.58) pg/ml; $p = 0.014$)] (Fig. 2c).

3.3. Association between visfatin levels and other clinical parameters

Serum visfatin levels in AS patients were positively correlated with CRP (Fig. 3a), BASDAI (Fig. 3b), mSASSS (Fig. 3c) and fat deposition (Fig. 3d) (all $p < 0.05$), but no significant association with age, disease duration, ESR, PLT and BASFI were observed (all $p > 0.05$) (Table 2).

Table 1
The general features of study subjects.

Parameters	AS (n = 50)	HCs (n = 75)	*p* value
Age (years)	34.40 ± 12.64	35.67 ± 10.09	0.536
Gender (male/female)	42/8	62/13	0.845
Visfatin (pg/ml)	5.57 ± 2.20	1.41 ± 0.82	<0.001
BMI (kg/m^2)	23.87 ± 3.04	23.43 ± 2.22	0.348
Duration (years)	3.00 (0.88, 10.00)	–	–
ESR (mm/h)	31.00 (15.50, 55.25)	10.00 (8.00, 13.00)	<0.001
CRP (mg/L)	44.85 (11.70, 117.95)	4.20 (3.30, 5.20)	<0.001
PLT ($\times 10^9$/L)	311.14 ± 84.35	199.31 ± 59.20	<0.001
BASDAI	4.92 ± 1.00	–	–
BASFI	5.42 ± 1.56	–	–
mSASSS	12.54 ± 7.39	–	–
HLAB27 (±)	47/3	–	–
Syndesmophyte formation (yes/no)	15/35	–	–
Number of fat deposits in the lumbar spine		–	–
0	22 (44%)	–	–
1	17 (34%)	–	–
2	5 (10%)	–	–
3	2 (4%)	–	–
4	4 (8%)	–	–

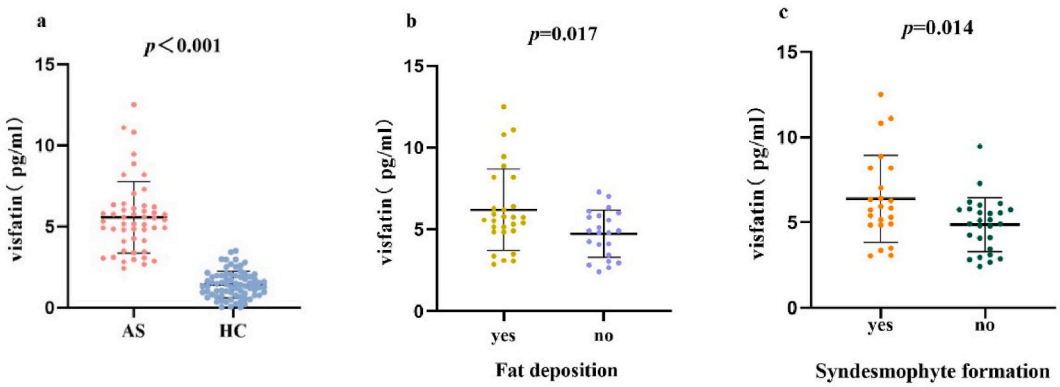

Fig. 2. Serum visfatin levels in AS patients were elevated compared with that in healthy controls (**a**), and were more significant in patients with fat deposition and syndesmophyte formation (**b c**).

3.4. The difference of fat deposition rate in AS patients between different general index groups

The difference of lumbar fat deposition rate between different age and course groups was statistically significant ($x^2 = 8.179$, $p = 0.004$; $x^2 = 9.149$, $p = 0.002$). There was no significant difference in lumbar fat deposition rate between different gender, BMI and HLA-B27 groups ($x^2 = 0.628$, $p = 0.428$; $x^2 = 2.710$, $p = 0.100$; $x^2 = 0.968$, $p = 0.325$) (Table 3).

3.5. Analysis of risk factors associated with fat deposition

Age, sex, disease duration, BMI, visfatin, and mSASSS were used as independent variables, and the presence or absence of fat deposition in lumbar MRI (0 = no fat deposition, 1 = fat deposition) was used as a response variable. The risk factors affecting fat

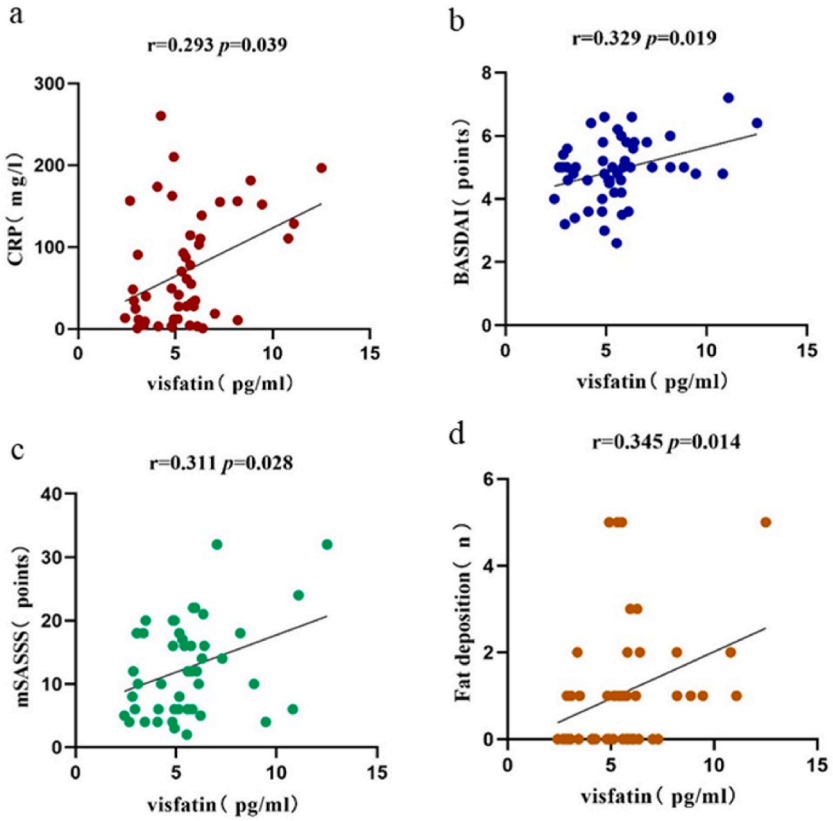

Fig. 3. Serum visfatin levels in AS patients were positively correlated with CRP (**a**), BASDAI (**b**), mSASSS (**c**) and fat deposition (**d**) ($p < 0.05$).

Table 2
Correlation between visfatin level and clinical indexes of AS.

Parameters	visfatin	
	r	p
Age	0.029	0.844
Disease duration	0.090	0.536
ESR	0.018	0.900
CRP	0.293	0.039*
PLT	−0.149	0.301
BASDAI	0.329	0.019*
BASFI	0.069	0.636
mSASSS	0.311	0.028*
Fat deposition	0.345	0.014*

Note: *$p < 0.05$.

deposition in the lumbar spine of patients with AS were analyzed by logistic regression. The results showed that age, disease duration, and visfatin were risk factors for fat deposition in patients with AS (Fig. 4).

4. Discussion

Visfatin is an adipocytokine that causes inflammation by activating human white blood cells to release Proinflammatory cytokines such as IL-1β, IL-6, and tumor necrosis factor-α [4]. Studies have found that visfatin is associated with numerous diseases such as acute lung injury, sepsis, atherosclerosis, and rheumatoid arthritis, its serum level is elevated in a variety of acute and chronic inflammatory diseases and plays an important role in the pathogenesis of these diseases. Comparing the serum of AS patients with that of healthy controls, we found that serum visfatin levels were significantly higher in AS patients than in the normal population, this proves that the expression level of serum visfatin in Chinese Han AS population is consistent with that in German and Czech [5,6], suggesting that visfatin plays a role in the course of AS.

Inflammation (bone marrow edema), fat deposition, and syndesmophyte formation as a trilogy of bone structure progression in AS can lead to spinal stiffness and ankylosis in patients with AS in the later stages of the disease. Rademacher et al. [7] demonstrated that visfatin levels were significantly associated with imaging progression in patients with AS. MRI can show the fat deposition of joint bone marrow in the early stage by its sensitivity [8], reflecting metabolic changes in the marrow tissue noninvasively at the molecular level. Studies have shown that the fatty lesions in the anterior horn of the spinal vertebral on MRI predict the formation of new bone [9]. T1 weighted sequences can show spinal structural damage (such as fatty lesions, erosion, and stiffness). After the inflammation in the erosion subsides, it fills the cavities in the eroded bone through fat metaplasia and evolves into bridging ankylosis [10]. MRI links the inflammatory lesions of the spine with new bone formation and becomes a bridge to observe the progression of AS. To further investigate the role of visfatin in the progression of AS patients, we observed lumbar spine MRI fat deposition in AS patients, combined with the level of visfatin detected, we found that AS patients with elevated serum visfatin levels had a higher frequency of fat deposition in the lumbar spine and were more likely to have syndesmophyte formation. In the histological analysis of the joints of AS patients, it was found that the joint remodeling process of AS has many similarities with osteoarthritis (OA) patients [11,12]. Studies have found high levels of visfatin production in the joint tissues of patients with osteoarthritis, especially in synovial and adipose tissues [13]. Therefore, we believe that visfatin may be involved in the new bone formation of AS.

Elevated CRP and ESR can be used the reference index of AS disease activity, and BASDAI is a common indicator to evaluate the activity of ankylosing spondylitis. Tsiklauri et al. [14]found that visfatin participated in the bone remodeling of adipose tissue/bone interface by inducing pro-inflammatory factors and imbalanced MMP/TIMP during the differentiation of mesenchymal stem cells, and changed the balance between bone resorption and bone formation. In a study of 64 patients with axSpA and 61 age-and sex-matched

Table 3
Comparison of lumbar fat deposition rate between different general index groups of AS patients.

Parameters	Group	N	Fat deposition	
			n	%
Age	<40	35	15	42.9*
	≥40	15	13	86.7
Gender	male	42	22	52.4
	female	8	6	75.0
BMI	<24	23	10	43.5
	≥24	27	18	66.7
Disease duration	<5	29	11	37.9*
	≥5	21	17	81.0
HLA-B27	+	3	3	100.0
	-	47	25	53.2

*$p < 0.05$.

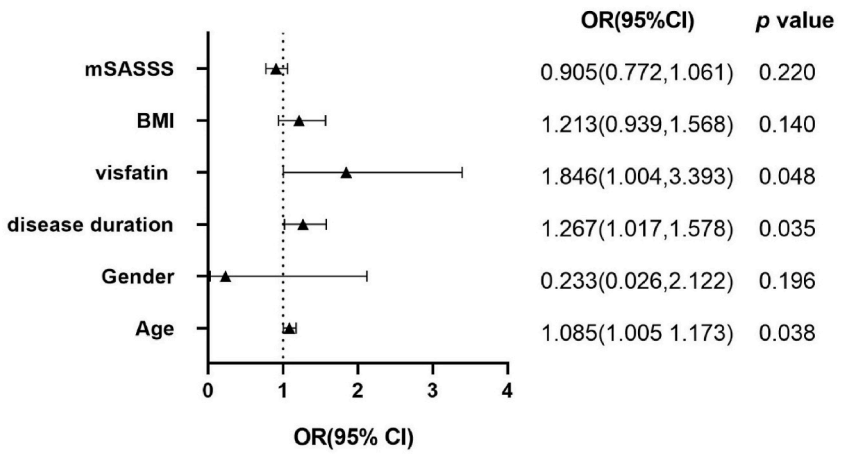

Fig. 4. Baseline characteristics were used for analysis
Age, course of disease, visfatin were risk factors for fat deposition in AS patients. The non-effective line was OR = 1.

healthy controls, Hulejová et al. [6] not only found elevated serum visfatin levels in patients with axSpA, moreover, visfatin level was positively correlated with mSASSS score. Therefore, we used Sperman to analyze the correlation between serum visfatin and clinical indicators in AS patients. The results showed that there was a correlation between serum visfatin level and CRP, BASDAI, mSASSS and fat deposition in AS patients, and there was a positive correlation between them, which indicated that visfatin could reflect the activity of AS to a certain extent. However, this correlation was not found in ESR, which could explain the majority of AS patients in this study being repeat patients, and the difference in study results could be related to the control of inflammatory markers between individual AS patients after treatment and the bias of the small sample size. In addition, we did not observe a correlation between visfatin levels and age, disease duration, PLT or BASFI.

In rheumatoid arthritis (RA), visfatin is expressed in joint sites of arthrocyte destruction and in periarticular adipose tissue [15]. In the present study, it was found that the increase in visfatin level had an important effect on the fat deposition in the vertebral angle of patients with AS. In addition, advanced age and long disease duration are also factors that affect fat deposition in AS patients. However other factors may also contribute to the fat deposition at older age group, and what is the correlation between age and disease duration, we have not investigated deeply, which needs further study and discussion. Several studies have found that fat deposition is associated with new bone formation in AS, and Machado et al. [16] concluded that there is a sequential link between vertebral corner inflammation (VCI), vertebral corner fat deposition (VCFD) on MRI, and radiologic of the same vertebral body, and the results revealed that both VCI and VCFD promoted new bone formation in AS, especially when VCI occurred before VCFD, confirming the relationship between fat deposition and new bone formation. Hartl et al. [17] showed a positive correlation between visfatin and radiological spine progression. Similar results were also verified in the study of Syrbe et al., who proposed that elevated serum visfatin level was an independent predictor of radiological progress and intervertebral process formation/progress in AS patients. Therefore, visfatin plays an integral role in the disease progression of AS and is an important indicator of fat deposition and new bone formation in AS. In patients with AS who have developed fat deposition, single anti-inflammatory therapy is limited in inhibiting new bone formation and delaying imaging progression. At present, various targeted drugs have emerged in clinical practice, and the prognosis of AS patients has been continuously improved. In the future treatment of patients with AS, the goal of our therapy is to pursue anti-inflammation while delaying disease progression and preventing structural damage. Visfatin not only plays a role in the inflammation of AS but also is a key mediator affecting bone remodeling, providing us with new possible therapeutic research directions for the treatment of AS in the future. In this study, we found that serum visfatin levels in patients with active AS was increased, and the serum visfatin level was associated with fat deposition on lumbar MRI in AS patients. These results indicate that AS patients are more likely to experience spinal imaging progression. In our daily clinical practice, elevated visfatin may be used as a biomarker of increased disease activity and new bone formation in AS patients. Patients with elevated visfatin levels should be given timely attention and treatment. Visfatin, as one of the possible therapeutic targets for AS, the development of its inhibitor needs further study.

Based on the fact that our study is a cross-sectional study, some limitations are unavoidable, on the one hand, the inability to dynamically observe changes in serum visfatin levels before and after fat deposition in patients with AS, on the other hand, the observation of fat deposition could not be assessed using fat quantification techniques due to the limitations of the conditions, and there is a slight limitation to the accurate calculation of fat deposition objectively. In the future, it may be necessary to increase the longitudinal research direction and adopt more accurate methods to evaluate the level of fat deposition.

5. Conclusion

In conclusion, increased serum visfatin level is associated with fat deposition of the lumbar spine in ankylosing spondylitis patients, suggesting that it may play an important role in the pathophysiological process of new bone formation in AS. In addition, the increased

serum visfatin level is an independent risk factor for lumbar spine fat deposition in AS patients. This finding reveals the relationship between visfatin and fat deposition, which helps us to further explore the pathogenesis of new bone formation in AS and provides new ideas for preventing spinal stiffness and delaying disease progression.

Ethics statement

The studies involving human participants were reviewed and approved by the ethics committee of the First Affiliated Hospital of Bengbu Medical College ([2020 No. 134]). The participants provided their written informed consent to participate in this study. Among them, the written informed consent was obtained from the patient of which images were included in this study for the publication of his images.

Data availability statement

The datasets generated for this study are available on request to the corresponding author.

CRediT authorship contribution statement

Jie Shen: Writing - original draft, Formal analysis. **Sha-Sha Tao:** Writing - review & editing, Writing - original draft. **Rui-Yuan Wang:** Investigation. **Shi-Kui Shi:** Investigation. **Jiang Chao:** Visualization. **Yong-Jun Mei:** Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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