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ORIGINAL ARTICLE

Prevalence and risk factors associated with vertebral osteoporotic fractures in patients with rheumatoid arthritis

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Abstract

Objectives To explore the prevalence and risk factors of osteoporosis (OP) and vertebral osteoporotic fracture (VOPF) in patients with rheumatoid arthritis (RA).

Methods Anteroposterior and lateral X-ray examination of the vertebral column (T4-L4) was used for the semi-quantitative assessment of VOPF. Bone mineral density was measured by dual-energy X-ray absorptiometry.

Results Of 865 RA patients, the prevalence of OP and VOPF was 33.6% and 20.2%, respectively. Patients with OP or VOPF were older, and had longer term use and a larger daily amount and cumulative dose of glucocorticoids (GCs), longer disease duration, and higher Health Assessment Questionnaire (HAQ) scores and Sharp scores than patients without OP or VOPF ($P < 0.05$). OP was also correlated with higher disease activity. The patients treated with GCs had higher incidences of OP and VOPF than the patients without GCs ($P < 0.05$). The cutoff values in the area under curve (AUC) of the daily dose or treatment course of GCs-VOPF were 9 mg and 37.5 days. Older age, female sex, and a higher Sharp score were risk factors for OP in RA patients, while higher BMI was a protective factor. Older age and a high GC daily dose were risk factors for VOPF in RA patients.

Conclusions RA patients have a high prevalence of OP and VOPF. Older age, female sex, lower BMI, and higher activity and severity of RA are closely related with OP. Older age and a higher GC daily dose are risk factors for VOPF in RA patients.

Key Points
- *Older age, female sex, lower BMI, and a higher Sharp score were risk factors for OP in RA patients.*
- *Older age and a high GC daily dose were risk factors for VOPF in RA patients.*
- *OP and VOPF in RA patients were correlated with longer disease duration and higher severity of RA.*

Keywords Glucocorticoid · Osteoporosis · Rheumatoid arthritis · Vertebral osteoporotic fracture

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that typically manifests with symmetric polyarthritis. As a common inflammatory joint disease, RA is characterized by synovitis, which contributes to bone erosion or destruction of joints and systemic bone loss (osteoporosis, OP) [1] and even leads to osteoporotic fracture (OPF). OP is a systemic bone disease, while bone loss and structural deterioration of bone tissue lead to bone fragility and an increased susceptibility to fractures, especially of the hip, spine, and wrist. Several reports have demonstrated that RA patients have a higher probability of OP [1], and the prevalence of vertebral OP in RA patients was twice the prevalence in the healthy population [2]. Bone mass can silently decrease without any discernable symptoms until an OPF occurs, which is the most serious consequence of OP [3]. There are three common sites for fractures: vertebral fractures, fractures of the neck of the femur, and Colles fracture of the wrist. Vertebral osteoporotic fracture (VOPF) can cause severe chronic pain of neurogenic origin and deformity and has adverse impacts on breathing, decreases self-care ability, reduces health-related quality of life, and results in disability.

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Although OPF (hip, vertebral, upper arm, or wrist) in RA patients have been well reported, VOPF and its risk factor were rarely discussed. A large sample study for the prevalence and risk assessment of OP and VOPF in Chinese RA patients is needed. Thus, we analyzed the prevalence rate and risk factors of VOPF and OP in RA patients by conducting anteroposterior and lateral X-ray examinations of vertebral column (T4-L4) and by determining bone mineral density (BMD). The study will provide theoretical evidence for early clinical prediction and intervention in VOPF in RA patients.

Materials and methods

Participants

In this retrospective study, 865 hospitalized Chinese RA patients from the Department of Rheumatology in the First Affiliated Hospital of Anhui Medical University were recruited from January 2010 to June 2018. All patients fulfilled the American College of Rheumatology 1987 and the European League Against Rheumatism 2009 revised classification criteria for RA. The RA patients included 157 men and 708 women, aged from 16 to 86 years, with a disease duration ranging from 1 month to 50 years. A total of 158 age- and sex-matched healthy subjects were recruited from a medical examination center as control group, including 30 males and 128 females, aged from 24 to 81 years. Patients with other secondary osteoporosis (such as chronic obstructive pulmonary disease, endocrine disorders), other causes of vertebral fractures (such as metastasis bone diseases, multiple myeloma, post traumatic fractures), serious liver or kidney disease, and radiological abnormalities (scoliosis, platyspondyly, and others) were excluded. Subjects who had concomitant use of estrogen, androgen, anticonvulsant, or anticoagulant drugs were also excluded. All individuals in the study are Chinese natives. The study protocol was approved by the Ethics Committee of Anhui Medical University and in accordance with the ethical standards laid down in the 1964 Helsinki declaration and its later amendments. Written informed consent was obtained from all the individuals enrolled before measurements were taken.

Clinical variables

General characteristics of research subjects were recorded in detail, including age, height, weight, disease duration, and glucocorticoid use (the daily dose, cumulative amount, and treatment course). The following variables were also collected for RA patients: tender joint count, swollen joint count, time of morning stiffness, erythrocyte sedimentation rate (ESR, mm/h), C-reactive protein (CRP, mg/l), disease activity score in 28 joints (DAS28), visual analogue scale (VAS) of overall pain, clinical disease activity index (CDAI), Health Assessment Questionnaire (HAQ) score, Sharp score, rheumatoid factor (RF, IU/ml), and anti-cyclic citrullinated peptide antibodies (ACPA, IU/ml). The tests of ESR and CRP and the serum levels of RF and ACPA were performed by the laboratory professionals.

BMD measurements

BMD of the lumbar spine 1–4 (L1–4), femoral neck, and total hip was measured by dual-energy X-ray absorptiometry (DEXA) (Lunar Prodigy DF +310504, GE Healthcare, USA). BMD T scores were calculated based on the number of the standard deviation below the mean for young healthy Asian Chinese women (mean = 0.90 g/cm^2; SD = 0.12 g/cm^2) and men (mean = 0.95 g/cm^2; SD = 0.13 g/cm^2). All procedures were performed in accordance with the manufacturer's standardized procedures for spine BMD measurements. Subjects were diagnosed as osteoporosis (T score ≤ -2.5) according to WHO classification [4].

Vertebral fracture assessment

All the RA patients and controls had anteroposterior and lateral spine images from T4 to L4 using the vertebral fracture assessment (VFA) software of the DXA device. VOPFs were diagnosed using the Genant [5] method as a semi-quantitative (SQ) measurement of severity of the fracture: grades 1–3 represent a reduction in anterior, middle, and/or posterior vertebral heights of 20–25%, 25–40%, and over 40%, respectively.

Statistical analysis

The results were expressed as mean ± standard deviation for the parametric data or median (P25, P75) for the non-parametric data. Independent samples *t* test or the non-parametric Wilcoxon rank-sum test was used for analyzing differences between two groups. Chi-square analysis was used to test for differences in OP and VOPF prevalence between two or more groups (Brunden method of multiple comparisons). Analysis of binary logistic regression (backward: LR) was performed to investigate the potential risk factor for OP and VOPF in RA patients. The receiver operating characteristic (ROC) curves were generated to empirically determine the indices' optimal cutoff points, sensitivity, and specificity in the same study sample. Statistical analyses were performed using SPSS version 23.0 statistical software. All significance tests were two-tailed and conducted at the 0.05 significance level.

Results

The demographic and clinical characteristics of the study population are shown in Table 1. No significant difference existed between the RA group and the control group regarding age, sex, and BMI ($P > 0.05$). In our study, 38.0% of RA patients were treated with non-biologic disease modifying antirheumatic drugs (DMARDs) (regularly use csDMARDs for at least 6 months), 2.0% with biological agents (regularly use b-DMARDs for at least 3 months), and 58.7% with GCs.

The prevalence of VOPF

The prevalence of VOPF in patients with RA was 19.2% (166/865), which was 5.1 times the prevalence in the control group (6/158, 3.8%) ($x^2 = 22.634$, $P < 0.001$). The total number of VOPF cases at the thoracic vertebra was 112, and T12 was the most commonly involved fracture site, with a total of 51 cases, followed by T11 with 43 cases. The total number of VOPF cases at the lumbar spine was 100, with 61 cases at L1 and 34 cases at L2 (see Fig. 1). There were 46 patients with fractures in both the thoracic and lumbar vertebrae (46/166, 27.7%), while 72 patients had fractures at more than one site (72/166, 43.4%). One patient was found to have VOPF at 8 vertebral column sites simultaneously, 1 patient had VOPF at 7 vertebral column sites, and 2 patients had VOPF at 6 vertebral column sites. Of the 166 patients with VOPF, patients between the ages of 60 and 69 predominated and accounted for over 1/3 (63 cases) of the cases, followed by patients between 70 and 79 years old with 41 cases (see Fig. 2). In RA patients, prevalence of VOPF was similar between women (19.4%; 137/708) and men (18.5%, 29/157; $x^2 = 0.064$, $P = 0.911$). The incidence of VOPF in premenopausal women patients is 8.3% (15/216), significantly lower than that in those postmenopausal (26.2% (122/492); $x^2 = 30.654$, $P < 0.001$).

The prevalence of OP

Compared with the controls, the BMD of all the measured sites in RA patients decreased significantly ($P < 0.001$, shown in Table. 1). The incidences of OP in RA patients were 33.6% (291/865), which was significantly higher than that in controls (12.7%, 20/158) ($x^2 = 27.801$, $P < 0.001$). The prevalence of OP in the lumbar spine in RA was 18.6% (161/865), which was 3.3 times higher than that in the control group (5.7%, 9/158) ($x^2 = 34.439$, $P < 0.001$). The prevalence of OP in women (37.6%; 266/708) was significantly higher than that in men (15.9%, 25/157; $x^2 = 26.97$, $P < 0.001$). The incidence of OP in premenopausal female patients is 7.9% (17/216), significantly lower than that in postmenopausal patients (50.6% (249/492); $x^2 = 116.9$, $P < 0.001$).

All of the six individuals with VOPF in the control group had OP. For RA patients, the percentage of OP in patients with VOPF was 63.3% (105/166), which was higher than that in those without VOPF (26.6%, 186/699) ($x^2 = 80.68$, $P < 0.001$). The percentage of OP at L1–4 in RA patients with VOPF was 36.1% (60/166), which was higher than that in those without VOPF (14.4%, 101/699) ($x^2 = 41.68$, $P < 0.001$).

Table 1 Baseline characteristics of the RA patients and controls in the study population

	RA patients ($n = 865$)	Controls ($n = 158$)	P value
Female, n (%)	708 (81.8)	128 (81.0)	$P = 0.823$
Age (year)	55.6 ± 13.0	53.9 ± 12.5	$P = 0.137$
Menopause age (year)	48.28 ± 4.32	48.69 ± 3.83	$P = 0.406$
BMI (mean + SD)	22.4 ± 3.6	23.0 ± 3.5	$P = 0.098$
Disease duration (years)	9.4 ± 9.1		
Glucocorticoids user (%)	58.7		
DMARDs user* (%)	38.0		
Osteoporosis (%)	291 (33.6%)	20 (12.7%)	$P < 0.001$
VOPF (%)	175 (20.2%)	6 (3.8%)	$P < 0.001$
BMD (mean + SD)			
L1	0.92 ± 0.15	1.03 ± 0.17	$P < 0.001$
L2	0.94 ± 0.19	1.07 ± 0.19	$P < 0.001$
L3	1.01 ± 0.20	1.14 ± 0.20	$P < 0.001$
L4	1.02 ± 0.20	1.14 ± 0.19	$P < 0.001$
Femoral neck	0.80 ± 0.18	0.92 ± 0.15	$P < 0.001$
Total hip	0.82 ± 0.17	0.97 ± 0.15	$P < 0.001$

BMI, body mass index; *BMD*, bone mineral density; *DMARDs*, disease-modifying antirheumatic drugs; *VOPF*, vertebral osteoporotic fracture

*DMARD users refer to the RA patients who has regularly use DMARDs for at least 6 months

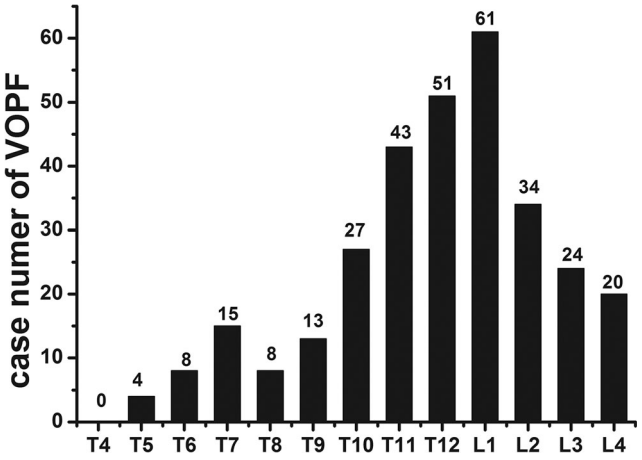

Fig. 1 Case number of VOPF in different site of thoracic and lumbar vertebra (T4-L4) in RA patients

Risk factors for OP and VOPF

As shown in Table. 2, RA patients with OP were older and had a lower BMI, longer treatment course of GC usage, larger daily dose and cumulative amount of GCs, longer disease duration, and higher HAQ scores, DAS28, Sharp scores, and CDAI compared with the group without OP ($P < 0.05$). The results in Table 3 showed that compared with RA patients without VOPF, patients with VOPF were older and had a longer treatment course of GC usage, higher daily amount and cumulative amount of GCs, longer disease duration, and higher HAQ and Sharp scores ($P < 0.05$). The serum levels of RF and ACPA and the systemic inflammation indicators were not associated with OP or VOPF.

The incidence of OP in patients treated with GCs (37.0%, 188/508) was higher than that in patients without GCs (28.8%, 103/357; $x^2 = 6.248$, $P = 0.013$). Patients treated with GCs also had a higher incidence of VOPF (23.2%, 118/508) than patients without GCs (13.4%, 48/357; $x^2 = 12.94$, $P < 0.001$). The incidence of OP in patients treated with DMARD (31.0%, 102/329) was similar with that in patients without DMARD (35.3%, 189/536; $x^2 = 1.656$, $P = 0.208$). The incidence of VOPF also showed no significant difference between patients treated with DMARD (20.1%, 66/329) and patients without DMARD (18.7%, 100/536; $x^2 = 0.259$, $P = 0.657$). In GC user, the incidence of OP in patients treated with DMARD (31.8%, 83/261) was lower than that in patients without DMARD (42.5%, 105/247; $x^2 = 6.243$, $P = 0.013$). In non-GC user, the incidences of OP in patients treated with or without DMARD have no significant difference. Compared with non-GC users, GC users are older, mostly women, have longer disease duration, higher RF, Sharp score, and HAQ ($P < 0.05$). Compared with non-DMARD users, DMARD users have lower ESR, CRP, DAS28, and CDAI ($P < 0.05$). Detailed presentation of the study parameters in terms of glucocorticoid users and DMARD users was shown in the supplementary material.

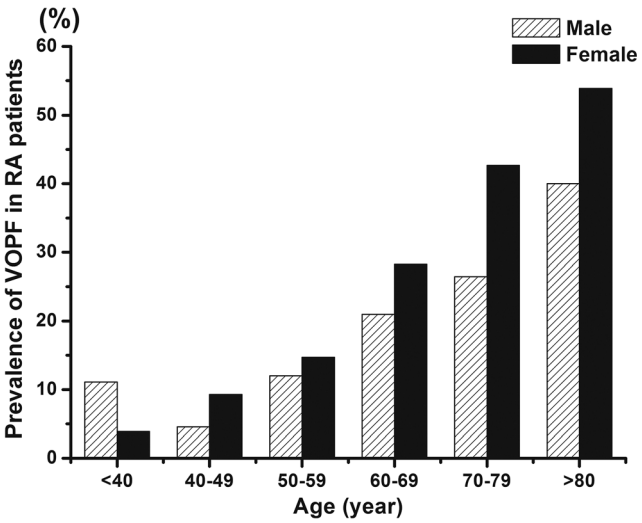

Fig. 2 Prevalence of VOPF in male and female RA patients of different age group

Analysis of binary logistic regression was performed to investigate the potential risk factors for OP and VOPF in RA patients. Whether or not one RA patient was accompanied with OP or VOPF was defined as dependent variable (0 = No, 1 = Yes). Age, sex, disease duration, BMI, GC usage, DMARD usage, RF, ACPA, DAS28, CDAI, Sharp score, and HAQ were defined as independent variables. The results showed that older age (OR = 1.094, $P < 0.001$, 95% CI 1.074–1.114), female sex (OR = 6.237, $P < 0.001$, 95% CI 3.478–11.184), and higher Sharp score (OR = 1.008, $P < 0.001$, 95% CI 1.005–1.011) were risk factors for OP in RA patients, while higher BMI was protective factor (OR = 0.865, $P < 0.001$, 95% CI 0.818–0.915). Older age (OR = 1.063, $P < 0.001$, 95% CI 1.041–1.084) and higher GC daily dose (OR = 1.057, $P = 0.003$, 95% CI 1.019–1.096) were risk factors for VOPF in RA patients. OP was the risk factor for VOPF (OR = 2.844, $P < 0.001$, 95% CI 1.845–4.382), while adjusted with age, gender, BMI, and treatment. RA was also an independent risk factor for VOPF (OR = 4.347, $P < 0.001$, 95% CI 1.845–10.369), while adjusted with age, gender, and BMI. Then, we analyzed the risk factor of OP and VOPF according to GC or DMARD usage; the results were similar with that in all RA patients. In GC user, older age (OR = 1.085, $P < 0.001$, 95% CI 1.058–1.112), female sex (OR = 2.431, $P = 0.016$, 95% CI 1.184–4.993), and higher GC daily dose (OR = 1.072, $P = 0.011$, 95% CI 1.016–1.131) were risk factors for VOPF. In non-GC user, older age (OR = 1.104, $P < 0.001$, 95% CI 1.048–1.162) and longer disease duration (OR = 1.056, $P = 0.021$, 95% CI 1.008–1.106) were risk factors for VOPF. In patients without DMARD, older age (OR = 1.072, $P < 0.001$, 95% CI 1.048–1.097), higher GC daily dose (OR = 1.050, $P = 0.018$, 95% CI 1.008–1.094), and higher Sharp score (OR = 1.006, $P = 0.001$, 95% CI 1.003–1.010)

Table 2 Comparison of clinical characteristics and GC usage between RA patients with or without osteoporosis

Parameters	RA without OP ($n = 574$)	RA with OP ($n = 291$)	t/z	P value
Age (year)	51 (45, 62)	63 (56, 69)	10.549	< 0.001
Female, n (%)	442 (77)	266 (91)	26.974	< 0.001
Menopause age (year)	48.67 ± 4.10	47.93 ± 4.41	1.936	0.053
BMI (kg/m^2)	22.4 ± 3.6	20.9 ± 3.3	28.878	< 0.001
Disease duration (year)	5.0 (1.5, 12)	10.0 (4, 20)	5.823	< 0.001
ESR (mm/h)	58 (31, 83)	61 (36, 85)	1.585	0.113
CRP (mg/l)	29.18 (10.95, 57.05)	26.40 (9.37, 61.94)	0.122	0.903
RF (IU/ml)	119 (32, 167)	126 (34.3, 172.3)	1.244	0.214
ACPA (RU/ml)	395 (86.75, 967.25)	383 (86, 1045)	0.827	0.408
DAS28	5.22 ± 1.31	5.47 ± 1.24	7.702	0.006
CDAI	27 (17, 40)	30 (20, 44)	2.115	0.034
Sharp score	20 (5, 73)	76 (15.5, 150)	7.688	< 0.001
HAQ	1.25 (0.6, 1.85)	1.60 (1.1, 2.1)	5.325	< 0.001
Daily amount of GCs (mg)	5 (0, 10)	5 (0, 10)	2.490	0.013
Treatment course of GCs (day)	30 (0, 500)	180 (0, 1012)	3.781	< 0.001
Cumulative amount of GCs (mg×day)	182.5 (0, 3650)	1425 (0, 7875)	3.928	< 0.001

ACPA, anti-cyclic citrullinated peptide antibodies; *BMI*, body mass index; *CDAI*, clinical disease activity index; *CRP*, C-reactive protein; *DAS28*, disease activity score in 28 joints; *ESR*, erythrocyte sedimentation rate; *RF*, rheumatoid factor; *GCs*, glucocorticoids; *HAQ*, Health Assessment Questionnaire score; *VAS*, visual analogue scale of overall pain

were risk factors for VOPF in RA patients. In women RA patients, neither menopause age nor menopause state was the independent risk factor for OP or VOPF ($P > 0.05$).

The area under curve (AUC) of GC daily dose-VOPF was 0.613 ($P < 0.001$), and the cutoff value of GC daily dose was 9 mg. The cutoff value for age especially in women was still 53.5 years (the AUC of age-VOPF was 0.733, $P < 0.001$). The AUC of GC treatment course-VOPF was 0.609 ($P < 0.001$), and the cutoff value was 37.5 days. The AUC of age-VOPF was 0.722 ($P < 0.001$), and the cutoff value of age was 53.5 years.

Table 3 Comparison of clinical characteristics and GC usage between RA patients with or without VOPF

Parameters	RA without VOPF ($n = 690$)	RA with VOPF ($n = 175$)	t/z	P value
Age (year)	52 (47, 64)	64 (56, 71)	8.553	< 0.001
Female, n (%)	571 (82)	137 (83)	0.065	0.911
Menopause age (year)	48.25 ± 4.38	48.35 ± 4.16	0.218	0.828
BMI (kg/m^2)	22.01 ± 3.59	21.62 ± 3.66	1.216	0.224
Disease duration (year)	6 (2, 13)	10 (4, 20)	4.663	< 0.001
ESR (mm/h)	59 (33, 83)	60 (31, 86)	0.720	0.472
CRP (mg/l)	27.88 (10.21, 57.21)	30.08 (9.80, 67.14)	0. 447	0.655
RF (IU/ml)	124 (35, 168.9)	98.5 (28, 168)	1.042	0.297
ACPA (RU/ml)	394.5 (86.5, 989)	363 (86.5, 1041.5)	0. 448	0.654
DAS28	5.29 ± 1.29	5.37 ± 1.32	0.767	0.443
CDAI	27 (18, 40)	28 (18, 44)	0.617	0.537
Sharp score	29 (6, 95)	57 (11, 136)	3.884	< 0.001
HAQ	1.35 (0.65, 1.85)	1.53 (1.1, 2.1)	3.502	< 0.001
Daily amount of GCs (mg)	5 (0, 10)	7.5 (0, 10)	4.698	< 0.001
Treatment course of GCs (day)	30 (0, 700)	300 (0, 1440)	4.461	< 0.001
Cumulative amount of GCs (mg×day)	166.3 (0, 3650)	1825 (0, 10,000)	4.741	< 0.001

ACPA, anti-cyclic citrullinated peptide antibodies; *BMI*, body mass index; *CDAI*, clinical disease activity index; *CRP*, C-reactive protein; *DAS28*, disease activity score in 28 joints; *ESR*, erythrocyte sedimentation rate; *RF*, rheumatoid factor; *GCs*, glucocorticoids; *HAQ*, Health Assessment Questionnaire score; *VAS*, visual analogue scale of overall pain

Discussion

RA is a heterogeneous autoimmune disease characterized by chronic synovitis and progressive damage of the joint structure, including local bone erosion/damage and systemic osteoporosis. Bone tissue continuously undergoes a tightly regulated remodeling process that can be disturbed by many factors, such as hormonal changes, chronic diseases, and inflammation. An imbalance between bone formation and bone resorption can lead to osteopenia, which may ultimately turn into OP with consequent increased bone fragility. RA is a common cause of secondary OP. If not effectively controlled, OP can easily lead to VOPF as RA progresses and results in a poor prognosis. Moreover, GC-induced OP is also a very common form of secondary OP irrespective of the presence of RA.

In this study, the incidence of OP was 33.6% in the RA group, which was much higher than in the control group (12.7%). In addition, RA patients with OP were older and had longer GC use with larger doses, longer disease duration, and higher HAQ scores, DAS28, Sharp scores, and CDAI than the group without OP. Older age, female sex, and higher Sharp scores were risk factors for OP in RA patients. Higher BMI was a protective factor. The risk of OP increased 9.4% for every 1-year increase in age. These findings are consistent with a variety of studies. In the study by Seung-Geun et al. [6] in Korea, the incidence of OP in RA patients (22.1%) was approximately twice that in healthy people (11.4%). Older age, lower BMI, and higher RF level were associated with a decrease in lumbar spine BMD. Avouac et al. [7] reported similar findings that the incidence of OP at the lumbar spine was 21% in RA patients. Patients with OP group were older, had higher accumulated doses of GCs, and received more calcium supplementation than patients without OP. Haugeberg et al. [8] reported that rate of OP was 14.7% at femur neck and 16.8% at lumbar in RA patients, and the overall OP incidence was approximately twice that of the reference population. OP is associated with a variety of factors, including age, menopausal status, course of disease, and GC use. These studies revealed that OP in RA and primary OP share the same risk factors (such as older age, female sex, and underweight) [4]. In our study, females had a significantly higher OP prevalence than males in RA patients over 50 years old. In patients less than 50 years old, females and males have a similar prevalence of OP. This might be due to estrogen deficiency after menopause. Estrogens are protective against bone resorption by decreasing RANKL expression and increasing osteoprotegerin production in osteoblasts [9].

The risk of OP in RA was also related to the disease itself, as indicated by the positive correlations with longer disease course, higher disease activity, and poorer ability to engage in daily activities. Chronic inflammation in RA can disturb bone metabolism, leading to excessive bone resorption as well as impaired bone formation [10, 11]. The activation of B cells, T cells, and macrophages can activate osteoclasts in inflammatory diseases via receptor activator of NF-κB ligand (RANKL) expression and RANK activation, and via the release of inflammatory cytokines [12]. The pro-inflammatory cytokines TNF, IL-1, and IL-6 all enhance osteoclastogenesis and inhibit osteoblast function [11, 13]. The degree of disease activity and inflammatory response is closely linked to the extent of local and systemic bone loss. In our study, RA patients with OP had higher HAQ scores, DAS28, Sharp scores, and CDAI than patients in the non-OP group. Serum inflammatory indicators were similar between patients with and without OP. Therefore, serum inflammatory indicators do not necessarily reflect the changes in BMD in patients with RA. In addition to the systemic bone changes, local events including erosive changes and juxta-articular bone loss occur in RA. When assessing hand and wrist joints by the Sharp score, our study showed that a higher Sharp score was a risk factor for OP, and indicated that severe local events in hand and wrist joints are linked to systemic OP in RA.

OPF is a serious complication of RA, affecting the survival and life quality of RA patients. The spine is the most common and the earliest site for OPF to occur in the elderly with primary OP, but there have been few reports about VOPF in RA patients. Our study showed that the incidence of VOPF in RA patients was 19.2%, which was 5.1 times the rate in the healthy group. The VOPF occurred most commonly in the first and second lumbar and the twelfth and eleventh of the thoracic vertebrae. In addition, the OPF at more than one site was more common in RA. The incidence of VOPF was 19.4% (137/708) in female RA patients and 26.2% (122/469) in female RA postmenopausal patients. Ghazi et al. [14] reported a 21.7% incidence of VOPF in female RA patients, and found that RA patients with VOPF were older and had a lower BMI. They also found that 25% of all RA patients and 63.6% of RA patients with VOPF had OP. The study by Avouac et al. [7] reported that 33% of 139 RA patients had OPF in various sites, including vertebral and non-vertebral sites. They identified that the age, OP, and low 25(OH)D levels (< 30 ng/ml) were independent risk factors for fractures and that treatment with biological DMARDs was protective against fractures.

Our study also found that RA patients in the VOPF group were older and had a longer disease course and higher HAQ scores and Sharp scores than patients in the non-VOPF group. The disease activity indicated by DAS28 and CDAI and the systemic inflammation indicators were not associated with the presence of fractures. When we analyzed the RA disease activity according to DMARD usage, we found the DAS28 and CDAI were lower in RA patients with DMARDs. Thus, the disease activity might be affected by the treatment. The results also

indicated that VOPF might not be directly related with disease activity of RA. Multiple regression analysis confirmed that age was a risk factor for VOPF in RA patients; the risk of VOPF increased 7.2% in RA patients for each 1-year increase in age. Through the ROC curve analysis, we found that the cutoff value for age was 53.5 years. Our results showed that VOPF was closely related with age, GCs daily dose, OP, and RA (including disease duration and joint function). RA itself was also an independent risk factor for VOPF. In RA patients, OP and VOPF shared common risk factors, including not only age, but also longer disease course, and higher Sharp score. As higher HAQ scores and Sharp scores indicated worse joint function, we concluded that the severity of RA would increase susceptibility to VOPF. Therefore, effective control of RA and prevention of OP are both important measures to avoid VOPF.

GC therapy is widely used in RA. As GC decreases the inflammation and disease activity, inflammation-related bone erosion in RA patients could be alleviated. However, glucocorticoid-induced osteoporosis, one of the adverse events associated with GCs, is the most common secondary OP. Long-term treatment with GCs contributes to decreased osteogenesis and osteoporosis by promoting osteoclast-mediated bone resorption and collagen and bone matrix decomposition and by inhibiting the activity of osteoblasts [15]. Therefore, the overall effect of GCs on BMD or on the risk of OPF in RA patients is widely debated.

Van Staa et al. [16] reported a dose-dependent fracture risk. The relative rate of vertebral fractures increased from 1.55 in the low dose group (less than 2.5 mg/day) to 2.59 in the medium group (2.5–7.5 mg/day) and to 5.18 in the high dose group (7.5 mg/day or more) relative to the control and decreased after the cessation of GCs. Michel et al. [17] reported that in 395 patients taking GCs (< 20 mg/d) followed up for 6.7 years, the risk of fracture was 10% and was related to the dose and duration of GCs. According to the study by Suzuki [18], the administration of GCs significantly reduced the BMD of RA patients, and the effect on the axial skeleton was the most obvious. A meta-analysis of GC-induced osteoporosis showed strong correlations between the cumulative GC dose and a decline in BMD and between the daily dose and the risk of fracture [19]. Oral GC therapy more than 5 mg (of prednisolone or equivalent) daily leads to decreased BMD and a rapidly increased risk of fracture [19]. However, in the study by Ghazi et al., the prevalence of VOPF was negatively correlated with the use of DMARDs and GCs, indicating that controlling RA disease activity could be protective against bone fragility [14]. In a randomized controlled 2-year trial, the addition of 10 mg prednisone daily to a methotrexate-based strategy did not lead to bone loss in early RA patients receiving preventive treatment (calcium, vitamin D, and bisphosphonates) for osteoporosis [20].

Our study found that the OP group or VOPF group had longer durations of GC treatment and higher daily doses and cumulative amounts than the group without OP or VOPF. The incidences of OP and VOPF in RA patients using GCs were 1.28 times and 1.73 times higher than those in the non-GC group. When the average daily dose of GCs was over 9 mg/day or the duration of use exceeded 37.5 days, RA patients were more susceptible to VOPF. This undoubtedly suggested that the risks of OP and VOPF in RA patients were closely related to GCs.

Thus, an important measure to prevent VOPF in RA patients is to minimize the daily dose and treatment course of GCs. The use of DMARDs, including biological agents, may offset the bone loss caused by GCs and RA itself to some extent [21]. In the EULAR recommendations for the management of rheumatoid arthritis, it is highly recommended that short-term glucocorticoids should be considered when initiating or changing conventional synthetic DMARDs, and the dose should be tapered as rapidly as is clinically feasible [22]. The administration of anti-OP medicine is crucial for the prevention of OP and VOPF in RA patients [19]. In our study, in GC users, the incidence of OP in patients treated with DMARDs was lower than that in patients without DMARDs. The results indicated that DMARDs might alleviate OP in RA patients who had been treated with GCs. However, the prevalence of VOPF showed no significant difference between patients treated with or without DMARDs. In China, biological agents were not covered by medical insurance. Due to the high cost of biological agents, only a small number of RA patients can regularly use b-DMARDs. The low proportion of b-DMARD users may explain the insignificant correlation between DMARD usage and VOPF.

In conclusion, RA patients have a higher incidence of OP and VOPF. Older age, female sex, lower BMI, use of GCs, longer disease duration, higher activity, and severity of RA are related to OP. Our study also suggests that aging and GC therapy are risk factors for VOPF in RA patients. To improve joint function and survival in RA patients to the utmost, we should evaluate the risk factors, reach better treatment decisions with GCs, and institute early interventions to prevent the occurrence of OP and VOPF in RA patients.

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Compliance with ethical standards

Disclosures None.

Ethical approval All procedures performed in our study had been approved by the ethics committee of Anhui Medical University and had therefore been performed in accordance with the ethical standards laid down in the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

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