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ORIGINAL ARTICLE

Fractures of vertebrae and peripheral bones in patients with rheumatoid arthritis (based on long-term observation)

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Abstract

Introduction. In rheumatoid arthritis (RA), fractures occur on average 2–3 times more often than in the general population. Data on the incidence of vertebral fractures in RA is controversial and depends on the detection method.

Aim. To determine the incidence of vertebral and peripheral bone fractures in patients with RA during long-term prospective follow-up.

Materials and methods. A prospective multi-year cohort non-interventional study included 120 women with RA (mean age at enrollment 54.3±8.9 years), with a follow-up of 9.5±1.9 years. Initially and then repeatedly, a clinical, laboratory and radiological examination was performed: X-ray morphometry of the spine according to the Genant method, X-ray densitometry of the lumbar spine (L_I-L_{IV}) and femoral neck.

Results. During the follow-up period, there were 104 low-energy fractures in 64 (53%) patients: 69 (66%) vertebral fractures and 35 (34%) peripheral fractures. Two or more fractures occurred in 25 (39%) subjects. In 30 (25%) patients, 52 fractures occurred repeatedly. Among peripheral fractures, the most frequent localization was fractures of the distal forearm and lower leg bones. Patients with fractures during the follow-up period were also more likely to have fractures before enrollment in the study, had an initially longer duration of RA, a mean daily dose, cumulative dose, and duration of glucocorticoid administration, and a lower bone mineral density in the main parts of the skeleton, determined by densitometry. There was no effect of RA activity on DAS-28, rheumatoid factor positivity, or antibodies to cyclic citrullinated peptide on fractures.

Conclusion. More than half of the patients had low-energy fractures during the observation period, the most common being fractures of the vertebrae, distal forearm, and lower leg bones; a high frequency of repeated fractures was reported. The analysis of risk factors showed that a long duration of RA, a mean daily dose, cumulative dose, and prolonged use of glucocorticoids, a history of low-energy fractures, and low bone mineral density were associated with the occurrence of fractures in patients with RA.

Keywords: rheumatoid arthritis, prospective long-term observation, vertebral fractures, peripheral fractures, X-ray morphometry, densitometry, glucocorticoids

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Introduction

Rheumatoid arthritis (RA) is one of the most common chronic autoimmune systemic diseases of the connective tissue. Typical manifestations of RA are erosive polyarthritis, systemic damage to internal organs, local and generalized bone loss with joint destruction, deformation, and dysfunction, as well as osteoporosis (OP) and fractures [1]. The incidence of fractures in RA is 2–3 times higher than in the general population [2, 3]. T. van Staa et al., analyzing data on 30,262 patients of the Brit-ish General Practice Database, found that in patients with RA, the relative risk of a history of verte-bral fractures was 2.4 (95% confidence interval [CI] 2.0–2.8), and 2.0 (95% CI 1.8-2.3) for hip frac-tures compared to patients without RA [4].

A meta-analysis of 13 studies published between 1993 and 2014 confirmed a higher risk of fractures in patients with RA (relative risk 2.25; 95% CI 1.76–2.87); the highest risk of fractures was reported in the spine and proximal hip [5].

Data on the prevalence of vertebral fractures in RA patients is controversial and depends on the as-sessment method (clinical, radiological, or radiomorphometric). According to a Chinese study, the incidence of vertebral fractures in patients with RA was 20.2% [6]; other studies [7, 8] reported 36.4% and 24.1% versus 22.6% and 16.0% in the control group (population control), respectively. Significant risk factors for fractures in RA patients are female sex, elderly age, glucocorticoid (GC) use, low body mass index, long duration of the underlying disease, the onset of RA at a young age, etc. [4, 9, 10].

Most fracture studies in RA patients are cross-sectional retrospective analyses of the data. There are few literature publications on the results of the prospective follow-up of RA patients and the as-sessment of new or repeated fractures, including vertebrae fractures. It should be noted that in these studies, the sample power is low, and the duration of observation is short [11, 12].

The objective of the study is to determine the incidence of vertebral and peripheral bone fractures in patients with RA during long-term follow-up.

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Переломы позвонков и периферических костей у больных ревматоидным артритом (по материалам длительного наблюдения)

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Аннотация

Введение. При ревматоидном артрите (РА) переломы происходят в среднем в 2–3 раза чаще, чем в популяции. Сведения о частоте переломов позвонков при РА противоречивы и зависят от метода, с помощью которого они выявлялись.

Цель. Определить частоту переломов позвонков и периферических костей у больных РА при длительном проспективном наблюдении.

Материалы и методы. В проспективное многолетнее когортное неинтервенционное исследование включены 120 женщин с РА (средний возраст при включении – 54,3±8,9 года), длительность наблюдения составила 9,5±1,9 года. Исходно и в динамике проведено клиническое, лабораторное и рентгенологическое обследование: рентгеноморфометрия позвоночника по методу Genant, рентгеновская денситометрия поясничного отдела позвоночника (L_I–L_{IV}) и шейки бедра.

Результаты. За период наблюдения произошло 104 низкоэнергетических перелома у 64 (53%) пациентов: 69 (66%) переломов позвонков и 35 (34%) периферических переломов. Два и более перелома произошли у 25 (39%) пациентов. У 30 (25%) больных 52 перелома произошли повторно. Среди периферических переломов наиболее частой локализацией стали переломы дистального отдела предплечья и костей голени. Пациенты, перенесшие переломы за период наблюдения, чаще имели переломы и до включения в исследование, имели исходно большую длительность РА, среднесуточную, кумулятивную дозу и продолжительность приема глюкокортикоидов, меньшую минеральную плотность костной ткани в основных отделах скелета, определенную при денситометрии. Не отмечено влияния активности РА по DAS-28, позитивности по ревматоидному фактору или антителам к циклическому цитруллированному пептиду на переломы.

Заключение. Более чем у 1/2 больных за период наблюдения произошли низкоэнергетические переломы, среди которых преобладали переломы позвонков, дистального отдела предплечья, костей голени; отмечена высокая частота повторных переломов. Анализ факторов риска показал, что большая длительность РА, среднесуточная, кумулятивная доза и длительный прием глюкокортикоидов, низкоэнергетические переломы в анамнезе, низкая минеральная плотность кости ассоциируются с возникновением переломов у больных РА.

Ключевые слова: ревматоидный артрит, проспективное многолетнее наблюдение, переломы позвонков, периферические переломы, рентгеноморфометрия, денситометрия, глюкокортикоиды

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Materials and methods

A prospective multi-year cohort non-interventional study included 120 females with RA living in Moscow. The diagnosis of RA was made following the criteria of the American College of Rheuma-tology / European League Against Rheumatism in 2010 [13]; the OP diagnosis was made according to the guidelines of the Russian Osteoporosis Association 2012 [14]. After signing the informed con-sent form, all patients from 2011 to 2014 were examined at the Research Institute of Rheumatology named after V.A. Nasonova, according to the Program for the Study of Secondary OP in Females with RA. The study did not include pregnant and breastfeeding women and patients who refused fol-low-up observation and examinations.

The study was approved by the local ethics committee of the Research Institute of Rheumatology named after V.A. Nasonova (Minutes No.32 dated 06.12.2012 and No.2 dated 31.01.2013); it is ap-proved and is a fragment of the Fundamental Research No.1021051503137-7.

In all patients, the RA activity (assessed using DAS-28), functional class, health status assessment, extra-articular manifestations and complications of RA, and the number and location of low-energy fractures that occurred during the prospective observation period were assessed. The main hematol-ogy and blood chemistry tests, C-reactive protein, rheumatoid factor (RF), and serum anti-citrullinated protein antibodies (ACPA) were measured. In the study of vertebral fractures, the serial X-ray morphometry of the thoracic and lumbar spine was analyzed using the semi-quantitative Genant method [15]. Vertebral deformities with a decrease in vertebral body height by 20% or more (vertebral body index <0.8) were equated to fractures [16–18]. The serial studies of bone mineral density (BMD) in the lumbar spine (LI–IV) and the femoral neck (FN) were performed using the Ho-logic Discovery device. The obtained history, clinical and instrumental data, and information about the therapy used at baseline and during follow-up were entered into the database.

Statistical analysis package Statistica 10 for Windows (StatSoft, USA) was used for statistical pro-cessing using generally accepted parametric and non-parametric analysis methods. Quantitative var-iables were described by the number of patients, arithmetic mean (M), and standard deviation from the arithmetic mean (δ) as M±δ, in case of non-normal distribution of the trait, as median (Me), 25th and 75th percentiles. Qualitative variables were described by absolute and relative frequencies (per-centages). Pearson's χ^2-test and Fischer's test were used to compare qualitative indicators; paired and unpaired Student's t-test was used for quantitative indicators. Non-parametric tests were used for quantitative variables with a non-normal distribution: Mann-Whitney and Wilcoxon tests. The dif-ferences were considered statistically significant at $p<0.05$.

Results

At baseline (at enrollment), the average age of patients was 54.3±8.9 years, and the duration of RA was 14.0±9.8 years. The duration of prospective follow-up was 9.5±1.9 years. Eighty-three (69%) patients were diagnosed with OP. Antiosteoporosis treatment (bisphosphonates or denosumab) was recommended in all patients with OP.

During the follow-up, the number of OP patients increased to 95 (79%) subjects. 94% of patients fol-lowed the recommendations for OP treatment, and 36% of them continuously received treatment for more than 3 years. The rest received antiosteoporotic agents in intermittent courses. The mean dura-tion of antiosteoporosis therapy was 43 months (3.5 years).

When assessing the condition of patients, a decrease in RA activity according to DAS-28, an in-crease in the number of patients with Steinbrocker stage IV, and a decrease in the number of patients receiving GCs during follow-up were reported. Table 1 presents a comparative description of the main clinical and radiological parameters of RA patients.

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During the follow-up period, 64 (53%) patients experienced 104 low-energy fractures, including 52 (50%) fractures repeatedly in 30 (25%) patients. Sixty-nine (66%) vertebral fractures (in the tho-racic or lumbar spine) and 35 (34%) fractures of peripheral bones were reported. Fracture localization is shown in Table 2.

During the follow-up period, the number of patients with vertebral fractures increased. At baseline, vertebral fractures were detected in 21 (17%) patients; with a repeated assessment, the number in-creased to 57 (47%) subjects (p<0.001). The index of vertebral deformity in both the thoracic and lumbar regions significantly decreased (worsened). New vertebral fractures were reported in 26 (22%) patients, and repeated fractures in 23 (19%) patients. At the time of re-assessment, deformi-ties in the thoracic spine (ThVI and ThVII vertebrae) were the most common and reported in 13 (11%) and 12 (10%) patients, respectively. No deformations were detected in ThI and ThIII. In the lumbar spine, deformity was most often observed in LIII and LIV (3 [2.5%] patients) and less often in LII and LV (1 [0.8%] patient). The analysis is shown in Table 3.

A comparative analysis of group 1, patients with fractures that occurred during the follow-up peri-od (n=64), with group 2, patients without fractures during this period (n=56), showed that before the enrollment in the study, more group 1 patients had a history of fractures compared to group 2 pa-tients: 30 (47%) vs 12 (21%), respectively (p=0.004). Group 1 patients had a longer duration of RA, a higher mean daily dose of GCs (at baseline and during follow-up), a higher cumulative GC dose, and the duration of GC use was longer than in group 2 patients. According to the serial X-ray mor-phometry, the vertebral deformity index in the thoracic spine in group 1 was significantly lower (worse) than in group 2: 0.73±0.09 vs 0.78±0.06, respectively (p<0.0001). BMD in the studied parts of the skeleton, both at baseline and during follow-up, was lower in group 1. The comparative analy-sis results are shown in Table 4. There was no association of RA activity assessed by DAS-28, RF positivity, or ACPA, both at baseline and during follow-up, and fractures.

Discussion

The incidence of fractures, including vertebrae fractures, in RA patients is higher than in people of the same age and sex in the general population [8, 18–21]. Over the past 20 years, the therapeutic strategy in RA has significantly changed the long-term outcomes of the disease. In addition, several studies have demonstrated that synthetic disease-modifying anti-rheumatic drugs and genetically engineered biological agents (GEBAs) can stop the bone loss associated with systemic inflamma-tion [22]. However, information on bone and vertebral fractures in RA patients, including prospec-tive observations, is limited [12, 23–25]. A Swedish study showed an increased risk of low-energy peripheral fractures in RA in both the 1990s and 2000s, even though patients in the 2000s received powerful pharmacological treatment as early as at the onset of the disease [24]. An upward trend in the incidence of hip fractures in Spanish RA patients was reported between 1999 and 2015, despite a decrease in age-adjusted incidence among the general Spanish population [26, 27].

In our study, more than half (53%) of patients had 104 low-energy fractures that occurred during the follow-up period (9.5±1.9 years), including 69 (66%) vertebral fractures (in the thoracic or lum-bar spine) and 35 (34%) peripheral fractures. In 30 (25%) patients, fractures occurred repeatedly.

In most studies, age was considered an independent risk factor for fractures; however, we did not find significant differences in age (at baseline and during follow-up) in the group of patients with and without fractures that occurred during the follow-up period. Fractures in the pre-study history were more common in patients in the group with fractures that occurred during the follow-up period. Similar results were obtained in another

Table 1. Main clinical and radiological parameters at baseline and re-assessment (n=120)

Parameter	At baseline	At re-assessment
DAS-28, points M±Δ	4,4±1,2	3,6±1,1*
RF, n (%)	91 (75,8)	80 (66,7)
ACPA, n (%)	45 (37,5)	85 (70,8)
Radiographic stage of RA, n (%)		
I	4 (3,3)	3 (2,5)
II	40 (33,3)	35 (29,2)
III	47 (39,2)	29 (22,2)*
IV	29 (22,2)	53 (44,1)*
Grade of RA activity by DAS-28, n (%)		
0	3 (2,5)	13 (10,8)*
1	15 (12,5)	31 (25,8)*
2	68 (56,7)	59 (49,2)
3	34 (28,3)	17 (14,2)*
GC use, n (%)	61 (51)	52 (43)
Cumulative GC dose, mg, M (min; max)	10339 (0; 79200)	19006 (0; 94500)
GC mean daily dose, mg/day, M (min; max)	3,5 (0; 20)	2,5 (0; 15)
Menopause, n (%)	93 (77)	111 (92)
Patients with OP, n (%)	83 (69)	95 (79)
Patients receiving anti-OP thera-py, n (%)	28 (34)	78 (94)*

* p<0.05

Table 2. Number and location of fractures in patients during the study period

Location of fracture	Number of patients with fracture	Number of fractures
Vertebrae	49	69
Humerus	4	4
Distal forearm	8	9
Lower-leg bones	7	7
Pelvic bones	4	4
Proximal femur	2	2
Ribs	3	3
Other	6	6
Total	–	104

Table 3. Change of spinal deformities during follow-up (n=120)

Parameter	At baseline	At re-assessment	*p*
Thoracic vertebral deformity index, M±Δ	0.78±0.04	0.75±0.08	<0.0001
Lumbar vertebral deformity index, M±Δ	0.79±0.03	0.78±0.03	0.04
Patients with vertebral fracture in at least one re-gion of spine, n (%)	21 (17)	57 (47)	<0.001
Patients with thoracic vertebral fracture, n (%)	16 (13)	53 (44)	<0.001
Patients with lumbar vertebral fracture, n (%)	6 (5)	10 (8)	>0.05

Table 4. The main differences between patients with and without fractures over the study period (n=120)

Parameter	Group 1, patients with frac-tures (n=64)	Group 2, patients without frac-tures (n=56)	*p*
Age at baseline, years, M±Δ	55.3±7.1	53.2±10.5	>0.05
Age during follow-up, years, M±Δ	64.3±6.8	62.9±9.7	>0.05
Duration of RA at baseline, years, M (min; max); Me [25%; 75%]	16.4 (2.0; 44.0); 14.0 [10.0; 21.5]	11.2 (0.1; 37.0); 10.0 [5.0; 15.0]	0.001
Duration of RA at baseline, n (%)			
>10 years	46 (72)	24 (43)	0.002
>5 years	57 (89)	40 (71)	0.02
>3 years	62 (97)	47 (84)	0.03
DAS-28 score at baseline, points, M±Δ	4.3±1.2	4.6±1.2	>0.05
DAS-28 score during follow-up, points M±Δ	3.6±1.1	3.7±1.2	>0.05
Remission at baseline by DAS-28, n (%)	2 (3.1)	1 (1.8)	>0.05
Remission by DAS-28 during follow-up, n (%)	8 (12.5)	5 (8.9)	>0.05
High activity at baseline by DAS-28, n (%)	16 (25)	18 (32.1)	>0.05
High activity during follow-up by DAS-28, n (%)	11 (17.2)	6 (10.7)	>0.05
DMARD use at baseline, n (%)	51 (79.7)	46 (82.1)	>0.05
DMARD use during follow-up, n (%)	43 (67.1)	39 (69.6)	>0.05
GEBA use at baseline, n (%)	7 (10.9)	16 (28.6)	0.015
GEBA use during follow-up, n (%)	17 (26.5)	22 (39.2)	>0.05
GC mean daily dose for a year before the enrollment, mg, M (min; max), Me [25%; 75%]	3.9 (0; 20.0); 5 [0; 5]	3.1 (0; 20.0); 0 [0; 5]	0.04
GC mean daily dose for a year before the follow-up assessment, mg, M (min; max), Me [25%; 75%]	3.1 (0; 10.0); 3.1 [0; 5]	1.8 (0; 15.0); 0 [0; 2.5]	0.01
GC cumulative dose at baseline, mg, M (min; max)	13,140 (0; 79,200)	7,137 [0; 37,800]	0.02
GC cumulative dose during follow-up, mg, M (min; max)	23,742 (0; 94,500)	13,594 (0; 70,200)	0.006
Total duration of GC therapy, months, M (min; max), Me [25%; 75%]	132 (0; 420); 133 [14; 228]	81 (0; 264); 43 [0; 144]	0.008
Thoracic vertebral deformity index over time, M±Δ	0.73±0.09	0.78±0.06	<0.0001
LI–LIV BMD at baseline, g/cm^2, M±Δ	0.88±0.15	0.93±0.15	0.04
FN BMD at baseline	0.66±0.10	0.72±0.13	0.009
Overall hip BMD at baseline	0.75±0.12	0.84±0.14	0.002
FN BMD during follow-up	0.60±0.10	0.66±0.11	0.006
Overall hip BMD during follow-up	0.72±0.11	0.80±0.15	0.007

prospective study. S. Kerkeni et al. [28] showed that the number and severity of vertebral fractures influence the further risk of vertebral fractures in post-menopausal women with OP.

Our data on the effect of RA duration on the risk of fractures are consistent with the findings by T. van Staa et al. [4]. In our study, an increased risk of fractures was found in patients with a RA du-ration of >10 years, significant differences were observed between patients with and without frac-tures with a RA duration of >5 and >3 years. However, no association with the RA activity accord-ing to DAS-28 was found.

In patients with fractures that occurred during the follow-up period, the mean daily dose of GCs and the cumulative dose of GCs were higher, and the duration of GC use was longer than in patients without fractures, which confirms the negative impact of GCs on bone in RA patients [29, 30]. BMD in LI–LIV, in the FN area and the proximal femur at baseline and during follow-up in patients with fractures was lower. Of note, in the study by B. Buehring et al., 26.3% of RA patients with vertebral fractures had normal BMD in the lumbar spine [7]. South Korean researchers found no significant difference in BMD in RA patients with and without fractures [31].

Attention is drawn to the non-compliance with the recommendations for antiosteoporosis therapy by the majority of patients in the long term. Only a third of them followed the recommendations and continuously received bisphosphonates or denosumab for more than 3 years.

Conclusion

The results of long-term prospective follow-up of patients with RA showed a high incidence of vertebral and peripheral bone fractures, including recurrent fractures. There were 104 low-energy fractures in 64 (53%) patients: 69 (66%) vertebral fractures and 35 (34%) peripheral fractures, and 52 fractures in 30 (25%) patients were repeated. It was found that in patients with fractures, BMD was lower in LI–LIV, in the proximal femur part, and the FN, and the mean daily and cumulative doses of GCs were higher, and the duration of GC use was longer. Prolonged RA was a risk factor for fractures. No association of fractures with RA activity assessed DAS-28 was found. Note the low ad-herence of patients with RA and OP to long-term antiosteoporosis therapy.

Disclosure of interest. The authors declare that they have no competing interests.

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Authors' contribution. The authors declare the compliance of their authorship according to the international ICMJE criteria. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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Compliance with the ethics principles. The study protocol was approved by the local ethics committee of the Nasonova Research Institute of Rheumatology (Minutes No. 32 dated 06.12.2012, No. 2 dated 31.01.2013). Protocol approval and procedure were obtained according to the principles of the Declaration of Helsinki.

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