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RHEUMATOID ARTHRITIS AND
GLUCOCORTICOIDS: FRAX- ASSISTED
PREDICTION OF HIP FRACTURES

REUMATOIDNI ARTRITIS I
GLUKOKORTIKOIDI: PREDVIĐANJE
FRAKTURA KUKA UZ POMOĆ FRAX-A

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Key words

Fracture risk; Hip fracture; FRAX;
Bone mineral density; Glucocorticoid;
Rheumatoid arthritis;

Ključne reči

Rizik za frakturu; Fraktura kuka; FRAX;
Mineralna koštana gusina;
Glukokortikoidi; Reumatoidni artritis;

Abstract

Introduction: Glucocorticoids play an important role in the treatment of rheumatoid arthritis, but the use of glucocorticoids also increases the risk of osteoporosis and pathological fractures. The aim of this study was to assess and compare the risk of hip fractures in patients with rheumatoid arthritis who use and patients who do not use glucocorticoid therapy, using the FRAX algorithm for the Serbian population. **Material and methods:** This retrospective cross-sectional study included 75 postmenopausal women with rheumatoid arthritis treated at the Special Hospital for Rheumatic Diseases, Novi Sad. Data were collected from patients' medical records, while bone mineral density was measured by osteodensitometry. A FRAX score was calculated separately for each subject to assess the ten-year risk of hip fracture, using an algorithm with and without bone mineral density. **Results:** Of the 75 subjects included in the study, 53 used and 22 did not use glucocorticoid therapy. Subjects who used glucocorticoid therapy had statistically significantly lower bone mineral density of the femoral neck (0.77 vs 0.86), $p = 0.003$. In the group of women who used glucocorticoids 50.94% of women had a high risk of developing a hip fracture, while this percentage in the group of women who did not use glucocorticoids was 9.09%. The statistically significant difference in the distribution of high and low risk for hip fracture existed when the FRAX algorithm was used with bone mineral density, as well when the FRAX algorithm was used without bone mineral density. ($p = 0.001$) **Conclusion:** Subjects with rheumatoid arthritis who was using glucocorticoid therapy had a statistically significantly lower bone mineral density of the femoral neck compared to patients with rheumatoid arthritis who did not use glucocorticoids. In the group of subjects who were using glucocorticoids, there were statistically significantly more women at high risk for developing a hip fracture, whether FRAX scores were calculated with or without the inclusion of bone mineral density.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease associated with progressive disability⁽¹⁾. It is a chronic, erosive, inflammatory arthritis⁽²⁾ characterized by destruction of cartilage and bone^(1,2), morning stiffness, polyarticular pain and swelling. The disease is accompanied by multi-

organ disorders⁽³⁾, and one of the systemic complications is osteoporosis⁽¹⁾. RA usually affects women aged 30-50⁽³⁾, while the prevalence in the total world population is approximately 1%⁽²⁾.

Beside conventional synthetic disease-modifying antirheumatic drugs and biologic therapies, oral glucocorticoids (GC) play an important role in the treatment of RA⁽²⁾. GC

presents a milestone in the treatment of RA, however, long-term use of high doses of GC leads to side effects (2,4,5). The harmful effect of glucocorticoids on bone is manifested by a decrease in bone formation, by increasing bone resorption and damaging bone microarchitecture (4). Patients with RA require fracture risk assessment since the disease itself, immobilization and glucocorticoid use are risk factors for osteoporosis and fragility fractures (1).

The Fracture Risk Assessment Tool (FRAX) is an algorithm for a ten-year risk assessment of major osteoporotic fractures and hip fractures and it was developed by the World Health Organization (6). The probability of fractures varies in different regions (7, 8), which is why the country-specific FRAX tool should be used (9). The FRAX algorithm has been implemented in many national guidelines (1).

This study aimed to assess and compare the risk of hip fractures in patients with RA who use and patients who do not use GC with the FRAX algorithm for the Serbian population.

MATERIAL AND METHODS

This retrospective cross-sectional study was conducted at the Special Hospital for Rheumatic Diseases Novi Sad, Serbia. The study was approved by the Ethics Committee of the Special Hospital for Rheumatic Diseases Novi Sad, and included 75 postmenopausal women with RA, aged ≥ 50 years. Data were collected from the medical records of respondents in the period 2015-2018 and included: age, sex, body mass index, a history of fragility fracture, parental history of hip fracture, use of oral glucocorticoids, the existence of secondary osteoporosis, smoking status, and alcohol consumption of three or more units daily. Bone mineral density (BMD) was measured by osteodensitometry using a GE Lunar Prodigy Primo device. The ten-year risk of hip fracture was calculated for each respondent separately using the FRAX algorithm for the Serbian population (10). FRAX scores were calculated with and without the inclusion of BMD in the algorithm. Subjects were divided into two groups depending on whether they use glucocorticoid therapy.

Statistical processing and analysis were performed in the statistical package SPSS ver. 20. The distribution of numerical variables did not meet the normality criteria, which was confirmed by the Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous data were shown

as medians and ranges, and the Mann-Whitney U test was used to test the differences. Categorical data were presented as absolute frequencies, and the differences between them were tested by the Chi-Square test. A value of $p < 0.05$ was considered statistically significant.

RESULTS

The study involved 75 postmenopausal women with RA aged 50 to 77 years. Subjects were divided into two groups depending on whether they used corticosteroid therapy, where 53 subjects used and 22 did not use corticosteroid therapy. A statistically significant difference between the two groups was observed in relation to the age of the subjects, frequency of previous fractures, frequency of hip fractures in parents, smoking status, frequency of secondary osteoporosis and in relation to BMD of the femoral neck. Subjects who used corticosteroid therapy were statistically significantly older than subjects who did not use corticosteroid therapy ($p=0.000$), they had a higher frequency of previous fragility fractures ($p=0.000$), and median BMD of the femoral neck was statistically significantly lower in a group of women who used GC (Me=0.77 vs. Me=0.86), $p=0.003$. On the other hand, the prevalence of secondary osteoporosis was higher in a group of women who did not use GC. In the group of women who did not use GC, there were more smokers and the frequency of parental hip fracture was higher. (Table 1).

Table 1. Demographic characteristics of patients

	RA+GK (n = 53)	RA-GK (n = 22)	p Value (n = 75)	All
Age (years), median (range)	59.00 (51 - 77)	53.50 (50 - 65)	0.000^a	58 (50 - 77)
BMI (kg/cm ²), median (range)	25.7 (15.40–34.30)	26.60 (19.30–36.40)	0.515 ^a	26.00(15.40–36.40)
BMI category, n (%)				
underweight (< 18.5)	2 (3.77%)	0 (0%)	0.009^b	2 (2.67%)
normal weight (18.5 - 25)	23 (43.40%)	6 (27.27%)		29 (38.67%)
overweight (25 - 30)	19 (35.85%)	12 (54.55%)		31 (41.33%)
obese (>30)	9 (16.98%)	4 (18.8%)		13 (17.33%)
Previous fractures, n (%)			0.000^b	
Yes	7 (13.21%)	1 (4.55%)		8 (10.67%)
No	46 (86.79%)	21 (95.45%)		67 (89.33%)
Hip fracture in parents, n (%)			0.000^b	
Yes	7 (13.21%)	7 (31.82%)		14 (18.67%)
No	46 (86.79%)	15 (68.18%)		61 (81.33%)
Smoking status, n (%)			0.000^b	
Yes	9 (16.98%)	8 (36.36%)		17 (22.67%)
No	44 (83.02%)	14 (63.64%)		58 (77.33%)
Alcohol consumption, n (%)			-	
Yes	0 (0.00%)	0 (0.00%)		0 (0%)
No	53 (100%)	22 (100%)		75 (100%)
Secondary osteoporosis			0.000^b	
Yes	47 (88.68%)	21 (95.45%)		68 (90.67%)
No	6 (11.32%)	1 (4.55%)		7 (9.33%)
BMD of femoral neck, median (range)	0.77 (0.59 - 0.94)	0.86 (0.65 - 1.09)	0.003^a	0.80 (0.59 - 1.09)

^aMann-Whitney U test, ^b χ^2 - chi-square test.

RA+KS= patients with rheumatoid arthritis who used glucocorticoid therapy

RA-KS= patients with rheumatoid arthritis who used glucocorticoid therapy

Among women who used GC, 50.94% had a high ten-year risk of developing a hip fracture ($\geq 3\%$) (11) while the high risk in a group of women who did not use GC had 9.09% respondents. The difference was statistically significant ($p=0.000$). Likewise, the difference in the distribution of high and low fracture risk was statistically significant even when FRAX scores were calculated without BMD ($p=0.000$). (Table2).

Table 2. Low / high risk distribution for hip fracture

	RA+GK (n = 53)	RA-GK (n = 22)	p Value	All (n = 75)
FRAX HIP + BMD, median (range)	3.40 (0.60–21.00)	0.70 (0.10 – 4.70)	<0.001	2.20 (0.10 – 21.00)
high risk	27 (50.94%)	2 (9.09%)	–	29 (38.67%)
low risk	26 (49.06%)	20 (90.91%)		46 (61.33%)
FRAX HIP - BMD, median (range)	2.60 (0.50-18)	0.70 (0.3-4.50)	<0.001	4 (0.30-18)
high risk	25 (47.17%)	1 (4.55%)	–	26 (34.67%)
low risk	28 (52.83%)	21 (95.45%)		49 (65.33%)

Mann-Whitney U test;

Note: For hip fracture High risk is classified as a 10-year fracture probability $\geq 3\%$.

FRAX HIP + BMD= FRAX algorithm with mineral bone density

FRAX HIP - BMD= FRAX algorithm without mineral bone density

RA+GK= patients with rheumatoid arthritis who used glucocorticoid therapy

RA-GK= patients with rheumatoid arthritis who did not use glucocorticoid therapy

The graph shows the ratio of high and low risk calculated with and without the inclusion of BMD in the FRAX algorithm. (Graph1) No statistically significant difference was observed between the FRAX scores calculated with and without BMD. (Table3)

Graph 1. The ratio of high and low risk with and without bone mineral density

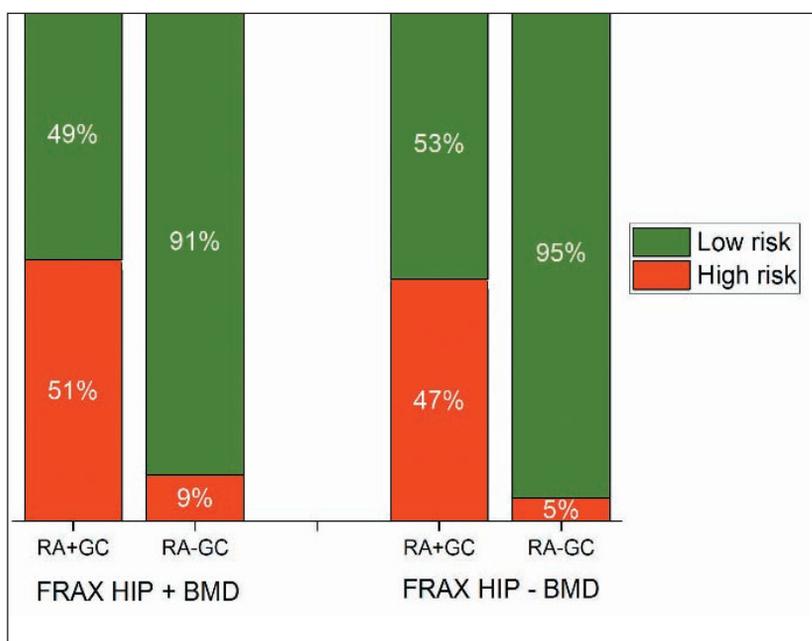


Table 3. Median values of FRAX scores with and without bone mineral density

	RA+GK	RA-GK	p Value
FRAX HIP + BMD, median (range)	3.40	0.70	0.87
FRAX HIP - BMD, median (range)	2.60	0.70	0.98

Mann-Whitney U test;

DISCUSSION:

Analyzing 66 publications, Andre et al. reported that the percentage of RA patients using prednisone varies from 34-93% depending on the biological therapy the patient use (12). In our study, the percentage of patients who used GC was 70.67%. Patients with RA who used GC had statistically significantly lower BMD which was in line with previous studies (5,13). Reduced bone density results in fragility fractures (14) and it is associated with disease activity, immobility, and long-term use of corticosteroids (1). Patients who used GC had statistically significantly more previous fractures compared to patients who did not use GC ($p= 0.000$).

Increased incidence of fragile fractures among patients with autoimmune rheumatic diseases is well established (15). In our study, the percentage of patients who had a previous fracture was 10.67%, while Ghazi et al. reported the frequency of previous vertebral fractures was 21.7% (16). This difference in the frequency of previous fractures may stem from the discrepancy between patient self-reported previous fractures and physician-detected fractures. Patients with autoimmune disease, and especially those using GC, may have a high incidence of asymptomatic vertebral fractures (15).

In the group of respondents who did not use GC, there were more smokers, the prevalence of parental hip fractures was higher, and unexpectedly there were more subjects who had secondary osteoporosis (95.45% vs 88.68%). This result may be due to the fact that associated diseases have not been considered (e.g. diabetes mellitus (17) and hyperthyroidism (18)) and they may also contribute to secondary osteoporosis. Also, we could not calculate the trabecular bone score, for risk stratification in osteoporosis (19).

In the group of women who used GC, a high ten-year risk of developing a hip fracture had 50.94% of women when the FRAX score was calculated with the inclusion of BMD in the algorithm. This percentage was 47.17% when BMD was not included in the FRAX algorithm. There was no statistically significant difference in the values of FRAX scores calculated with and without BMD in the group of women who used GC ($p=0.87$), nor in the group of women who did not use GC ($p=0.98$). The results of the Danish study showed that the FRAX scores calculated without the inclusion of BMD were slightly overestimated compared to the FRAX scores calculated with the inclusion of BMD at the group level (1). In the present study, there was no statistically significant difference between the 10-year risk of hip fracture cal-

culated with or without BMD ($p=0.98$). It should be emphasized that no comparison was made at the individual level in our study. In the mentioned Danish study, a difference was noted between the estimated fracture risks with and without BMD in individual patients with RA ⁽¹⁾, while Egsmose et al. showed deviation at the individual level in women with a fragile fracture of the distal radius ⁽²⁰⁾.

Our study has some limitations such as a small number of respondents and inhomogeneity of groups. Also, the duration of the disease was not considered, as well as the period of use and the dose of glucocorticoids.

CONCLUSION

Subjects with rheumatoid arthritis who was using glucocorticoid therapy had a statistically significantly lower bone mineral density of the femoral neck compared to patients with rheumatoid arthritis who did not use glucocorticoids. In the group of respondents who were using glucocorticoids, there were statistically significantly more women at high

risk for developing a hip fracture, whether FRAX scores were calculated with or without the inclusion of BMD. There was no statistically significant difference between FRAX scores calculated with and without BMD in group level.

Abbreviations:

RA- Rheumatoid arthritis

GC- Glucocorticoid

FRAX- Fracture Risk Assessment Tool

BMD- Bone mineral density

Sažetak

Uvod: Glukokortikoidi imaju važnu ulogu u lečenju reumatoidnog artritisa, ali upotreba glukokortikoida povećava rizik za nastanak osteoporoze i patoloških fraktura. Cilj ove studije bio je da se proceni i upoređi rizik za nastanak preloma kuka kod pacijenata sa reumatoidnim artritismom koji koriste i pacijenata koji ne koriste glukokortikoidnu terapiju, uz pomoć FRAX algoritma za srpsku populaciju. **Materijal i metode:** U ovu retrospektivnu studiju preseka uključeno je 75 postmenopauzalnih žena obolelih od reumatoidnog artritisa lečenih u Specijalnoj bolnici za reumatske bolesti, Novi Sad. Podaci su prikupljeni iz medicinskog kartona pacijentkinja, dok je mineralna koštana gustina merena osteodenzitometrijom. Za svaku ispitanicu je posebno izračunat FRAX skor za procenu desetogodišnjeg rizika za prelom kuka, koristeći algoritam sa i bez mineralne koštane gustine. **Rezultati:** Od 75 ispitanice koje su bile uključene u studiju, 53 su koristile, a 22 nisu koristile glukokortikoidnu terapiju. Ispitanice koje su koristile glukokortikoidnu terapiju imale su statistički značajno nižu mineralnu koštanu gustinu vrata butne kosti (0,77 vs 0,86), $p=0,003$. Visok rizik za nastanak frakture kuka u grupi žena koje su koristile glukokortikoide imalo je 50,94% žena, dok je ovaj procenat u grupi žena koje nisu koristile glukokortikoide iznosio 9,09%. Statistički značajna razlika u distribuciji visokog i niskog rizika za nastanak frakture kuka postojala je i pri korišćenju FRAX algoritma sa i FRAX algoritma bez mineralne koštane gustine. ($p=0,001$) **Zaključak:** Ispitanice sa reumatoidnim artritismom koje koriste glukokortikoidnu terapiju imaju statistički značajno nižu mineralnu koštanu gustinu na vratu butne kosti u odnosu na pacijentkinje sa reumatoidnim artritismom koje ne koriste glukokortikoide. U grupi ispitanica koje koriste glukokortikoide bilo je statistički značajno više žena sa visokim rizikom za nastanak frakture kuka, bilo da su FRAX skorovi računati sa ili bez uključivanja mineralne koštane gustine.

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