MULTIVARIATE ANALYSIS OF RISK FACTORS FOR MAJOR OSTEOPOROTIC FRACTURE RISK ASSESSED WITH RADIOFREQUENCY ECHOGRAPHIC MULTI SPECTROMETRY

S. Vladeva[1], N. Nikolov[2]

[1]Medical Faculty, Trakia University – Stara Zagora
[2]Clinic of Rheumatology, University Hospital "Dr. G. Stranski" – Pleven

Abstract. Aim. *The 10-year probability of a FRAX for a major osteoporotic fracture (MOF) above 20% is considered a high fracture risk based on health and economic estimates. The aim of the current study was to identify the multivariate significant risk factors for FRAX MOF ≥ 20%, calculated by BMD of the femoral neck based on an assessment with the innovative radiofrequency echographic multi spectrometry (REMS) ultrasound technique for axial skeletal scans.* ***Object of the study.*** *For 304 women aged 40-90 years examined by REMS, age, height, weight, body mass index (BMI), menopause and the following risk factors for calculating FRAX were assessed: previous fractures, family history of hip fractures, smoking, alcohol consumption ≥ 3 units daily, use of corticosteroids (CS), diagnosed rheumatoid arthritis (RA) and secondary osteoporosis. Methodology. According to the value of FRAX MOF women were divided into two groups - with FRAX MOF < 20% and with FRAX MOF ≥ 20%. A binary logistic regression analysis was performed to assess the multivariate significant risk factors for FRAX MOF ≥ 20%.R****esults and conclusions.*** *Significant risk factors in the multivariate analysis for FRAX MOF ≥ 20% were previous fracture, use of CS, diagnosis of RA and BMDUS of the left femoral neck. The previous fracture increased the risk of FRAX MOF ≥ 20% by a factor of 38.77. Women who use CS showed about a 13.5-fold higher risk of FRAX MOF ≥ 20% than those who do not use CS. The diagnosis of rheumatoid arthritis increases the risk of FRAX MOF ≥ 20% by 6.92. Any 1% increase in left femoral BMD reduced the risk of FRAX MOF ≥ 20% by 0.29%. This specific model, designed to predict FRAX MOF ≥ 20% with REMS, may be useful for deciding on therapy in women with high risk factors for FRAX MOF ≥ 20%.*

Key words: *FRAX, MOF, risk factors, REMS*

Introduction

Osteoporosis (OP) is defined as a systemic skeletal disease characterized by low bone mass and deterioration of the microarchitectonics of bone tissue with a consequent increase in bone fragility [1]. Thus, the diagnosis of osteoporosis depends on the quantitative measurement of bone mineral density (BMD), considered the main determinant of bone health, which determines bone fragility. This description emphasizes that the importance of the disease OP is rooted in the fractures that occur as a consequence [2].

According to International osteoporosis foundation (IOF) it was projected in 1990 that by 2050, the worldwide hip fracture incidence would increase by 310% in men and 240% in women and it is estimated that 1 in 3 women and 1 in 5 men, over age 50, will experience osteoporosis fractures in their remaining lifetimes [3-7]. In 2010, the number of deaths caused by osteoporotic fractures in Europe was 43,000 and almost 80% of them were due to hip or spinal fractures. Mortality in patients over 65 years of age with a hip fracture averaged 27% within the first year after fracture [8].

There are several tools for assessment of osteoporotic and fracture risk [9,10]. Currently the most popular tool is the fracture risk assessment model FRAX, developed over many years and published on the University of Sheffield website in 2008. The FRAX model provides a framework that improves fracture risk assessment in men and women, integrating clinical risk factors alone or in combination with BMD. FRAX is available for 66 countries, covering more than 80% of the world's population at risk and is included in more than 100 manuals worldwide. The 10-year probability of hip fractures varies more than 15 times between the countries. These large differences may be due to some errors such as duplication of the same fracture, as well as the inability to use a single methodology. Due to the lack of data on major osteoporotic fractures (MOF) in most countries, the probability of MOF is calculated on the basis of data from the Malmö study using a special formula [11, 12].

From the developed FRAX models it is established that BMD as the only criterion for determining treatment becomes more and more inappropriate with age. A similar trend is observed in the likelihood of hip fractures. In the United States, an assessment of FRAX is proposed in women with osteopenia and intervention is recommended for a 10-year probability of MOF above 20% and for a probability of hip fractures above 3% based on the health economic assessments [13-16].

Currently, one of the most common methods for diagnosing OP is dual-energy X-ray absorptiometry (DXA), considered the gold standard for measuring BMD [17]. However, DXA also has its limitations, which make it inappropriate for mass screening of the population, such as exposure to ionizing radiation, high costs, the need for specialized facilities with certified personnel and others [18]. Scoliosis and osteophytes could also affect the accuracy of DXA scan [19,20].

These factors necessitate the development of quantitative ultrasound (QUS) approaches for assessing bone health and diagnosing OP [21,22]. QUS methods have several potential advantages over DXA: non-ionizing radiation, lower costs, better portability, and availability in primary care rooms without the need for special structures [23, 24].

In recent years, an innovative ultrasound approach has been introduced to assess BMDUS of the hip and lumbar spine. This approach is defined as radiofrequency echographic multi spectrometry (REMS) and is established as an innovative in-vivo technique for early diagnosis and monitoring of OP. The study of di Paola et al. compared the T-scores of DXA and REMS and showed promising results that highlighted the high degree of correlation between T-scores obtained by both techniques for both lumbar spine ($r = 0.94$, $p < 0.001$) and femoral neck ($r = 0.93$, $p < 0.001$) [25].

The aim of the current study is to identify the multivariate significant risk factors for FRAX MOF ≥ 20% assessed with REMS technique.

Patients and Methods

304 women aged 40-90 years who underwent REMS scan, were assessed for age, height, weight, BMI, menopausal status and the following risk factors for calculating fracture risk FRAX – previous fracture, family history of hip fracture, smoking, alcohol consumption ≥ 3 units per day, corresponding to 30 ml alcohol daily, use of corticosteroids (CS), rheumatoid arthritis (RA) and secondary OP. The 10-year fracture risk for MOF was assessed on the basis of a specially built-in REMS FRAX risk calculator. A previous fracture is considered to be present only if it occurred spontaneously or more precisely if it is a fracture resulting from trauma that would not lead to a fracture in a healthy individual. There is a special situation with a history of a previous vertebral fracture, because even a morphometric vertebral fracture is reported as a previous fracture. The family history of hip fracture is defined as a history of a parental hip fracture. The use of CS is defined as available if the patient is currently taking oral CS or has taken oral CS in the past for more than 3 months with a dose of prednisolone ≥5 mg daily (or equivalent doses of other CS). RA is noted as a risk factor if the patient has a confirmed diagnosis according to the fulfillment of the criteria for diagnosis. Secondary OP includes diabetes type I (insulin-dependent), osteogenesis imperfecta in adults, untreated long-term hyperthyroidism, hypogonadism or premature menopause (< 45 years), chronic malnutrition or malabsorption, and chronic liver disease. BMDUS measurements with the innovative REMS technology of the left femoral neck were included in the assessment of the FRAX.

Women were divided according to the value of FRAX MOF into two groups – one with FRAX MOF < 20%, the other with FRAX MOF ≥ 20%. The following risk factors were investigated in the univariate and multivariate analyses for FRAX MOF ≥ 20% – previous fractures, use of CS, RA and BMDUS of the left femoral neck (FN). Stepwise binary regression analysis was used as a multivariate analysis of the univariate significant risk factors.

Results

The mean age of the women was 62 ± 12 years (range 40-88 years), with an average weight of 70.5 kg ± 15.7 kg (range 39.4-127 kg), average height 157.1 cm ± 8.8 cm (range 100-182 cm) and average BMI - 28.6 kg/m^2 ± 6.1 kg/m^2 (range 14.9-47.5 kg/m^2), Table 1.

44/304 women (14.5%) were premenopausal and 260/304 women (85.5%) were postmenopausal. Out of a total of 44 premenopausal women, 22 women (50%) had normal BMD of the left FN, 20 women (45.5%) had osteopenia and 2 women – osteoporosis (4.5%). Out of a total of 260 postmenopausal women, 132 women (50.8%) were with osteopenia, 77 women (29.6%) were with osteoporosis and 51 women (19.6%) were with normal BMD of the left FN, Figure 1.

Of 304 women, about one third of them had a history of a previous fracture (107/304 patients), and

Table 1. Age, height, weight and BMI of the women

	Mean value	Minimum	Maximum	Standard deviation
Age (years)	62	40	88	12
Height (centimeters)	157.1	100	182	8.8
Weight (kilograms)	70.5	39.4	127	15.7
BMI (kg/m^2)	28.6	14.9	47.5	6.1

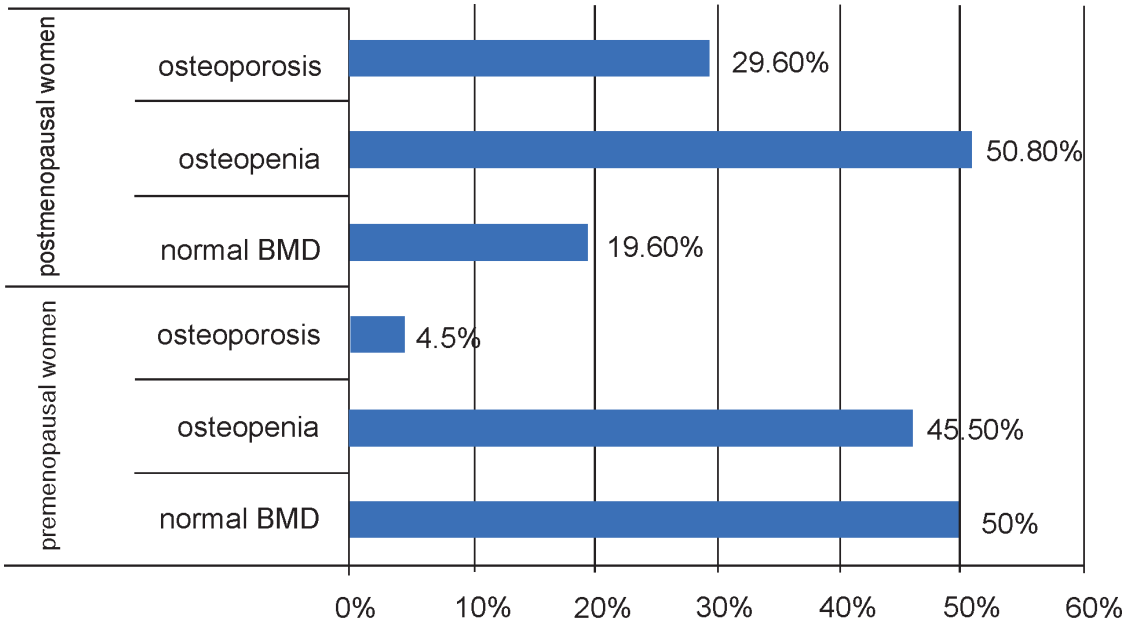

Fig. 1. Distribution of the normal left FN BMD (US), osteopenia and osteoporosis in the groups of premenopausal and postmenopausal women

3.3% (10/304) had a history of a parental fracture of the femoral neck. Current smokers were about 22.7% (69/304 patients), and the number of those consuming hard alcohol more than 3 units per day was 6.6% (20/304). The incidence of RA among women was about 22.4% (68/304 patients) and about 12.8% (39/304) used CS at the time of the study. 70/304 women (23%) had premature menopause and were accordingly included in the group of patients with secondary OP, Table 2.

In the univariate analysis, we found that previous fractures (p = 0.000), current use of CS (p = 0.003), diagnosis of RA (p = 0.000) and BMD (US) of the left FN (p = 0.012) were significant risk factors for FRAX MOF ≥ 20%. Alcohol consumption more than 3 units or 30 ml. daily, current smoking, parental fracture of the FN and secondary osteoporosis did not show any significant difference between the groups with FRAX MOF< 20% and FRAX MOF ≥ 20%.

Univariate significant risk factors for FRAX MOF were included in the multivariate analysis. The multivariate model was correctly predicted for 93% of cases as 97% were correctly predicted women with FRAX MOF < 20% and 81.9% were correctly predicted women with FRAX MOF ≥ 20%. Overall, the model was significant (p = 0.006) in the fourth step. Table 3 presents the results of step 4 of the binary logistic regression analysis.

Table 2. Distribution of the women according to the risk factors

Risk factors		Count
Previous fracture	yes	107
	no	197
Parental fracture of the FN	yes	10
	no	294
Current smoker	yes	69
	no	235
Currently using CS	yes	39
	no	265
RA	yes	68
	no	236
Secondary OP	yes	70
	no	234
Consuming alcohol more than 30 ml daily	yes	20
	no	284

From the stepwise binary regression analysis we found that the independent risk factors significant for FRAX MOF ≥ 20% were previous fracture, use of CS, RA and BMD (US) of the left femoral neck. After calculating the Odds ratios for the independent risk factors, we found that the previous fracture increased the risk of FRAX MOF ≥ 20% by a factor of 38.77. This means that women with a previous fracture have about 38.8 times higher risk of future major osteoporotic fracture than women without a previous fracture. Odds ratio for women who use CS was 13.49, i.e., women who use CS showed about a 13.5-fold higher risk for future major osteoporotic fracture than those who do not use CS. Rheumatoid arthritis increased the risk by 6.92 for FRAX MOF ≥ 20%. Odds ratio for BMD (US) of the left FN was 0.710, i.e., each 1% increase in left FN BMDUS decreased the risk for FRAX MOF ≥ 20% by 0.29%. Graphically, all odds ratios are shown in Figure 2.

Therefore, the previous fracture increases the fracture risk associated with a future major osteoporotic fracture, followed by a reduction in the strength of prediction, respectively, the use of CS, RA and BMD (US) FN.

Table 3. Indicators of the 4th step of the binary regression analysis for prediction of FRAX MOF ≥ 20%

Independent risk factors		Regression coefficient	Standard error	Wald	P value	Odds ratio
Step 4	Previous fracture	3.658	.649	31.73	.000	38.770
	CS	2.602	.861	9.14	.003	13.494
	RA	1.934	.722	7.17	.007	6.918
	BMD (US) FN	-.342	.053	41.85	.000	.710
	Constant	17.330	2.857	36.79	.000	33606359.7

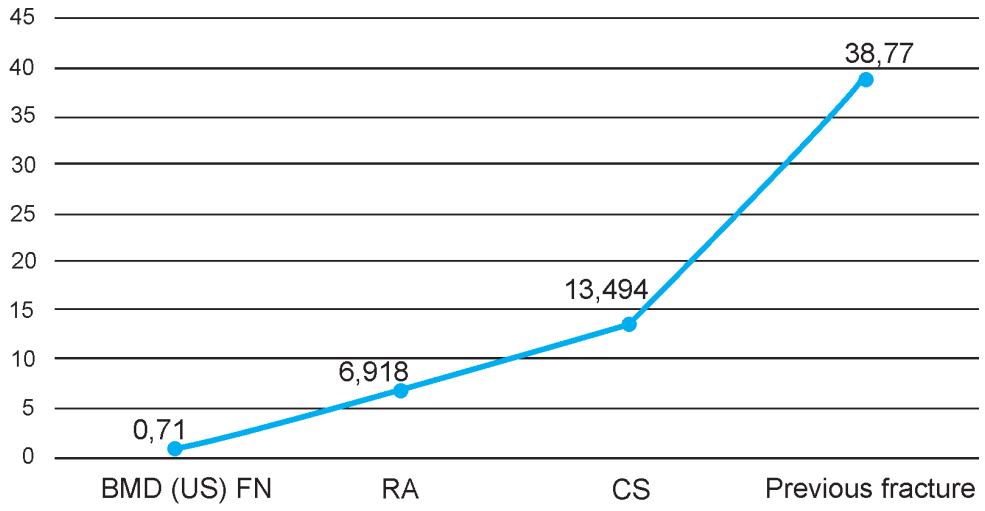

Fig. 2. Odds ratios of the independent risk factors for prediction of FRAX MOF ≥ 20%

Discussion

After conducting univariate analysis, we found that previous fracture, use of CS, diagnosis of RA and BMD (US) of the left FN assessed with REMS were significant risk factors for FRAX MOF ≥ 20%. Consumption of alcohol more than 30 ml daily, as well as current smoking, parental hip fracture and secondary OP did not show any significant difference between the groups with FRAX MOF < 20% and FRAX MOF ≥ 20%.

Previous fracture is a known risk factor for a future fracture. In a study published by Kanis and co-authors fracture risk was assessed based on previous fractures, age, gender, and BMD in 15,259 men and 44,902 women in 11 cohorts. The effect of the previous fracture on the risk of a MOF as well as on the femoral fracture was investigated using a Poisson model for each sex of each cohort. The studied covariates were age, sex and BMD. Individuals with a history of a previous fracture had a significantly

higher fracture risk than individuals without a history of a previous fracture (R = 1.86; 95% CI = 1.75-1.98). The history of a previous fracture increased the risk of MOF and the risk of hip fracture with similar force. There was no significant difference in the risk ratio between men and women. Low BMD increased the fracture risk of MOF by 8% and the fracture risk of hip fracture by 22%. In conclusion, in the study of Kanis et al. a history of a previous fracture led to an increased risk of future fracture, independent of BMD [26].

Banefelt and co-authors reported the incidence of subsequent fractures within the first and second years after an initial fracture in women ≥ 50 years in Sweden. The highest risk of subsequent fractures was observed in women with vertebral fracture. A previous fracture was an independent risk factor for a future fracture, taking into account other risk factors such as age and co-morbidities. In this study, the incidence of subsequent fractures within 12 months after the first fracture was 7.1% and increased to 12% at 24 months [27].

Use of CS affects the strength and structure of bones, which leads to an increased fracture risk. Glucocorticoid-induced OP is the leading cause of fractures with approximately doubling the risk of fracture, regardless of the BMD [28]. Epidemiological studies have shown that the risk of fracture increases with the use of CS despite the reduction in BMD and therefore, in addition to BMD, clinical risk factors must be taken into account in the fracture risk assessment. Several randomized controlled clinical trials have shown a significant reduction in the risk of fracture with the use of various pharmacological therapies in individuals using CS [29, 30]. Guidelines have been developed for the use of pharmacological agents for fracture prevention in patients using CS [31-34]. It is now recommended that even low-risk patients who start CS therapy, albeit for a short period of time, have to be treated for fracture prevention [34]. Kanis and co-authors found that exposure to CS significantly affected the likelihood of fracture. Subsequently, they formed the following rule: exposure to low doses (< 2.5 mg daily prednisolone or equivalent) reduced the likelihood of FRAX MOF by about 20% depending on age. For moderate doses of CS (2.5-7.5 mg daily), the final value of FRAX may not be adjusted relative to the dose of CS. For high doses (> 7.5 mg daily), FRAX MOF should be adjusted by increasing its value by about 15% [35].

In studies published to date, it has been found that patients with RA have a higher risk of OP and osteoporotic fractures than those without RA [36-38]. Papers have shown that the incidence of OP among patients with RA is about 1.9 times higher than among patients without RA [39]. Bone loss in RA patients is associated with many factors, including chronic inflammation, use of CS and immobilization. The release of proinflammatory cytokines such as interleukin-1 (IL-1), IL-6 and tumor necrosis factor-α (TNF-α) can cause abnormal osteoclast production, thus upsetting the balance between bone resorption and bone formation [40-42]. RANKL secretion by T-lymphocyte activation induces synovial macrophage differentiation in osteoclasts, leading to bone loss [43, 44]. At the same time, immobilization due to pain associated with RA leads to muscle weakness and increases fracture risk [45, 46]. A published meta-analysis, summarizing 13 studies, showed similarly increased fracture risk in both men and women with RA, suggesting that RA is an independent risk factor for fracture risk. Although several studies have identified specific fracture sites in RA patients, some reporting more femoral fractures and others more spinal fractures, the meta-analysis showed comparable risks of vertebral and femoral fractures in RA patients, suggesting no specificity in the location of the fracture with respect to RA [47]. Because fractures often reduce quality of life and increase costs, their prevention is crucial for patients with RA. The risk of fracture in these patients must first be assessed. Although RA is an independent risk factor for fracture risk, chronic inflammation and the use of CS may further increase fracture risk [48-50]. Therefore, the assessment of BMD as well as the risk factors that are needed to calculate the risk of fracture using the FRAX tool should be performed for early detection of OP in patients with RA [51, 52]. For patients at high fracture risk and especially for those taking CS, additional replacement with calcium, vitamin D3 and, according to the BMD, bisphosphonates, denosumab or parathyroid analogues at low BMD is required. Additionally, chronic inflammation in patients with RA should be controlled. Disease-modifying anti-rheumatic drugs such as methotrexate did not show an increased risk for OP and osteoporotic fractures in patients with RA [53]. Studies with TNF-α inhibitors such as etanercept and adalimumab have also shown that they don't impair bone remodeling [54, 55]. Patients with RA should also be assessed for risk of falls, as falls are the leading cause of fractures. More than 95% of femoral fractures are the result of falls. Taking certain preventative measures such as regular physical activity and minimizing objects at home that can cause falls can help reduce the risk of fractures [56].

This is the first study which assessed multivariate significant risk factors for FRAX major osteoporotic fracture risk (MOF) ≥ 20% through radiofrequency echographic multi spectrometry (REMS).

In a previous study with REMS there was found in the univariate analysis that women with a previous fracture had higher mean values of FRAX MOF and FRAX for hip fracture than women without a previous fracture [57]. Another study showed also in the univariate analysis that postmenopausal women at older ages, with low femoral neck BMDUS, low weight and height, who had previous fractures, had diagnosis of RA and used corticosteroids were at the highest risk for FRAX MOF ≥ 20% and for hip fractures ≥ 3% [58].

From the stepwise binary regression analysis in the current study it was found that the independent risk factors significant for FRAX MOF ≥ 20% are previous fracture, use of CS, RA and BMDUS of the left FN. After calculating the probability ratios for the independent risk factors, we found that women with a previous fracture had about 38.8 times higher risk of future major osteoporotic fracture than women without a previous fracture. Patients who use CS have a risk of FRAX MOF ≥ 20% 13.5 times higher than those who do not use CS. RA increases the risk by a factor of 6.92 for FRAX MOF ≥ 20%. Each 1% decrease in BMDUS of left FN increase the risk for FRAX MOF ≥ 20% by 0.29%.

In conclusion, from the stepwise binary regression analysis in the current study it was found that the independent significant risk factors for FRAX MOF ≥ 20% were previous fractures, use of CS, diagnosis of RA and BMDUS of the left femoral neck. This specific model created for predicting FRAX MOF ≥ 20% with REMS could be useful to make decision about the therapy in women with risk factors with a high probability ratio for FRAX MOF ≥ 20%.

Библиография / References:

1. Sözen T, Özışık L, Başaran NÇ. An overview and management of osteoporosis. Eur J Rheumatol. 2017;4(1):46-56.
2. National Institute for Health and Care Excellence. NICE clinical guideline 146. Osteoporosis: assessing the risk of fragility fracture. London, UK: 2012. https://www.nice.org.uk/guidance/ cg146.
3. Gullberg B, Johnell O, Kanis JA. World-wide projections for hip fracture. Osteoporos Int. 1997; 7(5): 407-13.
4. Odén A, McCloskey EV, Kanis JA, Harvey NC, Johansson H. Burden of high fracture probability worldwide: secular increases 2010-2040. Osteoporos Int. 2015;26(9):2243-8.
5. Melton LJ 3rd, Atkinson EJ, O'Connor MK et al. Bone density and fracture risk in men. J Bone Miner Res. 1998;13(12):1915-23.
6. Melton LJ 3rd, Chrischilles EA, Cooper C et al. Perspective. How many women have osteoporosis? J Bone Miner Res. 1992;7(9):1005-10.
7. Curtis EM, Van der Velde R, Moon RJ et al. Epidemiology of fractures in the United Kingdom 1988-2012: Variation with age, sex, geography, ethnicity and socioeconomic status. Bone. 2016;87:19-26.
8. Hernlund E, Svedbom A, Ivergård M et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos. 2013;8(1):136.
9. Kirilova E, Kirilov N. Osteoporotic fracture risk prediction tools. Revmatologiia/Rheumatology. 2019; 27(3): 55-65.
10. Kirilova E, Kirilov N, Bischoff F. Predictive ability of the osteoporosis self-assessment tool for assessing the risk of osteoporosis. Revmatologiia/Rheumatology. 2019; 27(3): 3-9.
11. Kanis JA, Dawson A, Oden A et al. Cost-effectiveness of preventing hip fracture in the general female population. Osteoporos Int. 2001a; 12:356-61.
12. Lam A, Leslie WD, Lix LM et al. Major osteoporotic to hip fracture ratios in Canadian men and women with Swedish comparisons: a population-based analysis. J Bone Miner Res. 2014; 29:1067-73.
13. Ettinger B, Black D, Dawson-Hughes B et al. Updated fracture incidence rates for the US version of FRAX®. Osteoporos Int. 2009; 21:25-33.
14. Kanis JA on behalf of the World Health Organization Scientific Group. Assessment of osteoporosis at the primary healthcare level. Technical Report. WHO Collaborating Centre, University of Sheffield, UK. 2008. Available at. http://www.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf.
15. National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. National Osteoporosis Foundation; Washington, D C: 2008. 1-36.
16. Tosteson AN, Melton LJ. 3rd, Dawson-Hughes B et al. Cost-effective osteoporosis treatment thresholds: The United States perspective. Osteoporos Int. 2008; 19:437-47.
17. Morgan SL, Prater GL. Quality in dual-energy X-ray absorptiometry scans. Bone. 2017;104:13-28.
18. Choksi P, Jepsen KJ, Clines GA. The challenges of diagnosing osteoporosis and the limitations of currently available tools. Clin Diabetes Endocrinol 2018; 4, 12.
19. Kirilova E, Kirilov N, Todorov S et al. Evaluation of scoliotic women with osteoporosis of the lumbar spine through DXA. Osteoporosis Int. 2020; 31(1): 482-482.
20. Kirilova E, Kirilov N, Nikolov N et al. DXA for assessment of bone mineral density of women with lumbar scoliosis. Osteoporosis Int. 2020; 31(1): 479-480.
21. Hopkins SJ, Welsman JR, Knapp KM. Short-term precision error in dual energy X-ray absorptiometry, bone mineral density and trabecular bone score measurements; and effects of obesity on precision error. J Biomed Gr Comput 2014; 4:8-14.
22. Tuna F, Yavuz S, Demirbağ Kabayel DD, Sarıkaya A. Effects of clinical reanalysis in dual energy X-ray absorptiometry reports. Turk J Phys Med Rehabil. 2017;63(3):201-206.
23. Binkovitz LA, Henwood MJ. Pediatric DXA: technique and interpretation. Pediatr Radiol. 2007;37(1):21-31.
24. Mazess RB. Bone density in diagnosis of osteoporosis: Thresholds and breakpoints. Calcif Tissue Int. 1987; 41:117-118.
25. DiPaola M, Gatti D, Viapiana O et al. Radiofrequency echographic multispectrometry compared with dual X-ray absorptiometry for osteoporosis diagnosis on lumbar spine and femoral neck. Osteoporos Int. 2019;30(2):391-402.
26. Kanis JA, Johnell O, DeLaet C et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone. 2004; 35:375-382.

27. Banefelt J, Åkesson KE, Spångéus A et al. Risk of imminent fracture following a previous fracture in a Swedish database study. Osteoporos Int. 2019;30(3):601-609.
28. Van Staa TP, Laan RF, Barton IP et al. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. Arthritis Rheum 2003; 48(11): 3224-3229.
29. Saag KG, Zanchetta JR, Devogelaer JP et al. Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial. Arthritis Rheum 2009; 60(11): 3346-3355.
30. Saag KG. Prevention of glucocorticoid-induced osteoporosis. South Med J 2004; 97(6):555-558.
31. Eastell R, Reid DM, Compston J et al. A UK Consensus Group on management of glucocorticoid-induced osteoporosis: an update. J Intern Med. 1998;244(4):271-92.
32. Grossman JM, Gordon R, Ranganath VK et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care Res (Hoboken). 2010;62(11):1515-26.
33. Manolagas SC, Weinstein RS. New developments in the pathogenesis and treatment of steroid-induced osteoporosis. J Bone Miner Res 1999; 14:1061.
34. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on GlucocorticoidInduced Osteoporosis. Arthritis Rheum 2001;44(7):1496-1503.
35. Kanis JA, Johansson H, Oden A, McCloskey EV. Guidance for the adjustment of FRAX according to the dose of glucocorticoids. Osteoporos Int. 2011; 22:809-816.
36. Kim D, Cho SK, Choi CB et al. Incidence and risk factors of fractures in patients with rheumatoid arthritis: an Asian prospective cohort study. Rheumatol Int 2016;36:1205-14.
37. Wang Y, Hao YJ, Deng XR et al. Risk factors for bone mineral density changes in patients with rheumatoid arthritis and fracture risk assessment. Beijing Da Xue Xue Bao 2015;47:781-6.
38. Wright NC, Lisse JR, Walitt BT et al. Women's Health Initiative Investigators. Arthritis increases the risk for fractures--results from the Women's Health Initiative. J Rheumatol. 2011 Aug;38(8):1680-8.
39. Lee SG, Park YE, Park SH et al. Increased frequency of osteoporosis and BMD below the expected range for age among South Korean women with rheumatoid arthritis. Int J Rheum Dis. 2012 Jun;15(3):289-96.
40. Le Goff B, Blanchard F, Berthelot JM et al. Role for interleukin-6 in structural joint damage and systemic bone loss in rheumatoid arthritis. Joint Bone Spine 2010;77:201-5.
41. Polzer K, Joosten L, Gasser J et al. Interleukin-1 is essential for systemic inflammatory bone loss. Ann Rheum Dis 2010;69:284-90.
42. Van den Berg WB. Uncoupling of inflammatory and destructive mechanisms in arthritis. Semin Arthritis Rheum 2001;30(5):7-16.
43. Romas E, Gillespie MT, Martin TJ. Involvement of receptor activator of NF kappa B ligand and tumor necrosis factor-alpha in bone destruction in rheumatoid arthritis. Bone 2002;30:340-6.
44. Sasaki N, Kusano E. Bone and bone related biochemical examinations. Bone and collagen related metabolites. Measurement and clinical role of OPG. Clin Calcium 2006;16:956-62.
45. Kaz Kaz H, Johnson D, Kerry S et al. Fall-related risk factors and osteoporosis in women with rheumatoid arthritis. Rheumatology (Oxford) 2004;43:1267-71.
46. Van den Bergh JP, Van Geel TA, Geusens PP. Osteoporosis, frailty and fracture: implications for case finding and therapy. Nat Rev Rheumatol 2012;8:163-72.
47. Xue AL, Wu SY, Jiang L et al. Bone fracture risk in patients with rheumatoid arthritis: A meta-analysis.Medicine (Baltimore). 2017;96(36):6983.
48. Güler-Yüksel M, Allaart CF, Goekoop-Ruiterman YP et al. Changes in hand and generalised bone mineral density in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis. 2009;68(3):330-6.
49. Haugeberg G, Conaghan PG, Quinn M, Emery P. Bone loss in patients with active early rheumatoid arthritis: infliximab and methotrexate compared with methotrexate treatment alone. Explorative analysis from a 12-month randomised, double-blind, placebo-controlled study. Ann Rheum Dis 2009;68:1898-901.
50. Vis M, Guler-Yuksel M, Lems WF. Can bone loss in rheumatoid arthritis be prevented? Osteoporos Int 2013;24:2541-53.
51. Mullen MB, Saag KG. Evaluating and mitigating fracture risk in established rheumatoid arthritis. Best Pract Res Clin Rheumatol 2015; 29:614-27.
52. Siris ES, Adler R, Bilezikian J et al. The clinical diagnosis of osteoporosis: a position statement from the National Bone Health Alliance Working Group. Osteoporos Int. 2014; 25:1439-43.
53. Buckley LM, Leib ES, Cartularo KS et al. Effects of low dose methotrexate on the bone mineral density of patients with rheumatoid arthritis. J Rheumatol. 1997;24(8):1489-94.
54. Genovese MC, Bathon JM, Martin RW et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum. 2002;46(6):1443-50.
55. Wijbrandts CA, Klaasen R, Dijkgraaf MG et al. Bone mineral density in rheumatoid arthritis patients 1 year after adalimumab therapy: arrest of bone loss. Ann Rheum Dis. 2009;68(3):373-6.
56. Gillespie LD, Robertson MC, Gillespie WJ et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 2012;9:CD007146.
57. Kirilov N, Kirilova E. Fracture risk assessment (FRAX) in women through radiofrequency echographic multispectrometry, Osteoporosis Int. 2019; 30(2): 436-S437.
58. Kirilova E, Kirilov N, Popov I. Assessment of Fracture Risk through Radiofrequency Echographic Multi Spectrometry (REMS) based Bone Mineral Density. Ortho & Rheum Open Access J. 2019; 15(1): 555905.

Постъпила за печат: 4.03.2022 г.

✉ *Адрес за кореспонденция:*
Проф. Стоянка Георгиева Владева
Тракийски университет – Стара Загора
ул. Армейска 11
6000 Стара Загора
тел. 0884623614, e-mail: drvladeva@abv.bg
ORCID: 0000-0001-6457-5178

Submitted: 4.03.2022

✉ *Correspondence address:*
Prof. Stoyanka Georgieva Vladeva
Trakia University – Stara Zagora
11 Armeyska St.
6000 Stara Zagora
tel. 0884623614, e-mail: drvladeva@abv.bg
ORCID: 0000-0001-6457-5178