Assessment of Fracture Risk through Radiofrequency Echographic Multi Spectrometry (REMS) based Bone Mineral Density

Elena Kirilova[1]*, Nikola Kirilov[2] and Iliya Popov[1]

[1]University "Prof. Dr. Assen Zlatarov", Burgas, Bulgaria

[2]Medical University of Sofia, Sofia, Bulgaria

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*Corresponding author: Elena Kirilova, University "Prof. Dr. Assen Zlatarov", Burgas, Bulgaria

Abstract

Introduction: Fracture Risk Assessment Tool (FRAX) was developed by the World Health Organization (WHO) to be applicable to both postmenopausal women and men aged 40 to 90 years. The current National Osteoporosis Foundation Guide recommends treating patients with FRAX 10-year risk scores of > or = 3% for hip fracture or > or = 20% for major osteoporotic fracture, to reduce their fracture risk.

Methods: 189 postmenopausal women with mean age 60 years ± 9 standard deviations (SD), (range 40-86) were included in the study. Women were divided in 2 fracture risk groups: 1st – with FRAX score for major osteoporotic fracture below 20% and for hip fracture below 3%, and 2nd – with FRAX score for major osteoporotic fracture ≥ 20% and for hip fractures ≥3%. Descriptive statistical analysis was used to describe the patients' characteristics in both groups. Independent sample t-test was used to assess the significant association between the quantitative variables and chi-square test – for the qualitative variables.

Results: 77.8% of the women (147/189) had FRAX score for major osteoporotic fracture below 20% and 22.2% (42/189) with FRAX score ≥20%. 62.4% (118/189) of the women had FRAX score for hip fracture below 3% and 37.6% (71/189) had FRAX score ≥3%. Women with FRAX score for major osteoporotic fracture ≥20% and FRAX score for hip fracture ≥3% were significantly older (p=0.000), had significantly lower weight (p=0.000), height (p=0.000) and femoral neck BMD (p=0.000) compared to those with FRAX score for major osteoporotic fracture below 20% and FRAX score for hip fracture below 3%.

Conclusion: Postmenopausal women at older ages, with low femoral neck BMD, low weight and height, who had previous fractures, have diagnosis of Rheumatoid arthritis (RA) and use corticosteroids are at the highest risk of FRAX for major osteoporotic fractures ≥20% and for hip fractures ≥3%.

Introduction

Osteoporosis is a metabolic bone disease, which is characterized by low bone mass and micro-architectural deterioration of the bone tissue, leading to increased fracture risk. But bone mass alone does not explain the risk of fractures in all osteoporosis cases [1]. The existence of patients with osteoporosis and no fractures and those with osteopenia and multiple fractures proves that bone mineral density (BMD) alone is not enough sensitive for predicting fracture risk. Other independent of BMD risk factors should also be added to provide better fracture risk prediction [2]. Greater understanding of these risk factors could be helpful for prevention of the fractures.

Several fracture risk assessment tools have been implemented [3,4]. The most popular tools that are online available are Fracture Risk Assessment Tool (FRAX), Qfracture, FORE 10-Year Fracture Risk Calculator™ (FORE FRC), Canadian Association of Radiologists and Osteoporosis Canada Risk Assessment Tool (CAROC), Garvan fracture risk calculator and Fracture Absolute Risk Assessment (FARA) [5-9]. A novel tool - high resolution peripheral quantitative computer tomography (HR-pQCT) was also introduced to predict fractures using reconstructed three-dimensional images [10].

FRAX algorithm is a web-based tool (www.shef.ac.uk/FRAX), launched by the University of Sheffield in 2008 and designed to calculate the 10-year probability of major osteoporotic fracture and hip fractures based on obtained clinical risk factors and bone mineral density (BMD). Fracture risk prediction tools are designed to improve the decision about the treatment of people at high absolute risk of fractures. According to the National Osteoporosis Foundation (NOF) treatment is recommended for those patients with BMD of lumbar spine, femoral neck and total hip in the osteoporotic range. For osteopenic subjects (with T-score between −1.0 and −2.5, osteopenia), a fixed intervention threshold is recommended for all ages and for both sexes set at 20 % for a major osteoporotic fracture and 3 % for hip fracture

probability [11]. For patients with osteoporosis and increased fracture risk preventive measures such as designing individual therapeutic programs should be adopted [12].

Currently, a new method called Radiofrequency Echographic Multi Spectrometry (REMS) is developed for osteoporosis diagnosis on axial sites at the Italian Institute of Clinical Physiology of the National Council of Research in Lecce (Echolight project) [13]. It is an innovative non-ionizing sonographic approach, which calculate the same diagnostic parameters provided by a Dual-energy X-ray absorptiometry (DXA) examination (BMD, T-score, Z-score, FRAX). The principle of the method is based on acquired radiofrequency signals during an echographic scan of the lumbar spine or femoral neck. The analysis of these native raw unfiltered ultrasound signals allows to keep maximum information about the investigated tissues, which are filtered out after the B-mode image reconstruction. Consideration about the bone status is given after that acquired signal spectra have been compared with previously derived spectral models for pathological and normal conditions. Collected data provides information about bone quantity and quality, so REMS approach is suitable for the estimation of bone strength and for the prediction of fracture risk [14]. A previous published study showed a high degree of correlation between the T-score values provided by the two techniques - REMS and DXA for both lumbar spine (r = 0.94, p < 0.001) and femoral neck (r = 0.93, p < 0.001), [12]. Furthermore, REMS technology may have some advantages over DXA method - it is non-ionizing approach and it is portable, so this make it possible to do wider screening of osteoporosis and to detect earlier the cases requiring DXA scanning [15-19].

REMS technology is a non-ionizing axial approach for osteoporosis diagnosis. The operating principle is based on the analysis of native raw unfiltered ultrasound signals, the so-called radiofrequency (RF) ultrasound signals, acquired during an echographic scan of lumbar vertebrae and/or femoral neck. The analysis of native unfiltered ultrasound signals allows to retain the maximum information about the characteristics of the investigated tissues, which are normally filtered out during the conventional process of B-mode image reconstruction. The bone health status is assessed through the comparison of the analyzed signal spectra with previously derived reference spectral models for the considered pathological and normal conditions. The large amount of collected data related to internal bone structure provides both quantity- and quality-related information, being thus theoretically suitable for the estimation of bone strength and the prediction of fracture risk. REMS technology is a non-ionizing axial approach for osteoporosis diagnosis. The operating principle is based on the analysis of native raw unfiltered ultrasound signals, the so called radiofrequency (RF) ultrasound signals, acquired during an echographic scan of lumbar vertebrae and/or femoral neck. The analysis of native unfiltered ultrasound signals allows to retain the maximum information about the characteristics of the investigated tissues, which are normally filtered out during the

conventional process of B-mode image reconstruction. The bone health status is assessed through the comparison of the analyzed signal spectra with previously derived reference spectral models for the considered pathological and normal conditions. The large amount of collected data related to internal bone structure provides both quantity- and quality-related information, being thus theoretically suitable for the estimation of bone strength and the prediction of fracture risk. The aim of this study is to assess the characteristics of the patients with FRAX score for major osteoporotic fracture ≥ 20% and for hip fractures ≥3% through REMS technology.

Methods

189 postmenopausal women with mean age 60 years ± 9 standard deviations (SD), (range 40-86) were included in the study. Women were divided in 2 fracture risk groups: 1st – with FRAX score for major osteoporotic fracture below 20% and for hip fracture below 3%, and 2nd – with FRAX score for major osteoporotic fracture ≥ 20% and for hip fractures ≥3%. Descriptive statistical analysis was used to describe the patients' characteristics in both groups. Independent sample t test was used to assess the significant association between the quantitative variables and chi-square test – for qualitative variables. Information about the following risk factors was collected – previous fractures, diagnosis of RA, current smoking, current use of glucocorticoids (GC) and alcohol consumption more than 30 ml per day. Chi-square test was used to assess if there is a significant difference between the risk factors in the both fracture risk groups.

Results

77.8% of the women (147/189) had FRAX score for major osteoporotic fracture below 20% and 22.2% (42/189) had FRAX score ≥20%. 62.4% (118/189) of the women had FRAX score for hip fracture below 3% and 37.6% (71/189) had FRAX score ≥3%. So the majority of the postmenopausal women had FRAX score for major osteoporotic fracture below 20% and FRAX score for hip fracture below 3%. Women with FRAX score for major osteoporotic fracture ≥20% were significantly older - with mean age 72.69 years (yr) ± 8.2 SD compared to those with FRAX score for major osteoporotic fracture below 20% - with mean age 60.84 yr ± 9.7 SD, (p=0.000). Women with FRAX score for hip fracture ≥3% were also significantly older – with mean age 72.37 yr ± 7.6 than those women with FRAX score <3% - with mean age 58.13 yr ± 8.3 SD. The weight of the women with FRAX score for major osteoporotic fracture ≥20% was significantly lower - mean weight 63.6 kilograms (kg) ± 12.9 SD compared to those with FRAX score for major osteoporotic fracture below 20% - with mean weight 73.6 kg ± 16.4 SD, (p=0.000). Women with FRAX score for hip fracture ≥3% had also significantly lower mean weight – 63.6 kg ± 12.4 SD than those women with FRAX score <3% - 76.0 kg ± 16.4 SD, (p=0.000). The group with FRAX score for major osteoporotic fracture ≥20% had significantly lower mean height – 151.8 centimeter (cm) ± 6.6 SD and significantly

lower mean BMD – 0.567 g/cm2 ± 0.199 SD compared to the group with FRAX score for major osteoporotic fracture< 20% - 157.7 cm ± 7.6 SD and BMD 0.723 g/cm2 ± 0.141 SD, (p=0.000). The group with FRAX score for hip fracture ≥3% had significantly

lower mean height – 152.5 cm ± 7.1 SD and significantly lower mean BMD – 0.579 g/cm2 ± 0.098 SD compared to the women with FRAX score for hip fracture< 3% - height 158.8 cm ± 7.2 SD and BMD 0.735 g/cm2 ± 0.121 SD, (p=0.000), (Table 1).

Table 1: Independent sample t test for comparison of age, weight, height and BMD between the two FRAX risk groups; BMD_{FN} – bone mineral density of the femoral neck.

		FRAX score	N	Mean	Std. Deviation	Std. Error Mean	p-value
FRAX Major osteoporotic	Age (years)	<20%	147	60.84	9.700	.800	0.000
		≥20%	42	72.69	8.188	1.263	
	Weight (kg)	<20%	147	73.567	16.3859	1.3515	0.000
		≥20%	42	63.610	12.8528	2.0073	
	Height (cm)	<20%	147	157.715	7.6493	.6309	0.000
		≥20%	42	151.805	6.5773	1.0272	
	BMDFN (g/cm²)	<20%	147	0.72343	0.1408	0.0345	0.000
		≥20%	42	0.56734	0.1987	0.0345	
FRAX hip fracture	age	<3%	118	58.13	8.300	0.764	0.000
		≥3%	71	72.37	7.581	0.900	
	weight	<3%	118	76.012	16.4217	1.5117	0.000
		≥3%	71	63.614	12.4427	1.4872	
	height	<3%	118	158.771	7.2388	0.6664	0.000
		≥3%	71	152.473	7.1416	0.8536	
	BMDFN (g/cm²)	<3%	118	0.73506	0.1209	0.0115	0.000
		≥3%	71	0.57876	0.0977	0.0116	

In the group with FRAX score for major osteoporotic fracture ≥20%, women with previous fractures (N=32) were about three times more than those without previous fractures (N=10) and in the group with FRAX score for major osteoporotic fracture < 20% the same proportion was observed but in benefit of the women without fractures (111/36 – without fractures/ with fractures). These differences were statistically significant (p=0.000). In the group with FRAX score for hip fractures ≥ 3%, women with previous fractures were also more (N=40) than those women without fractures (N=31) and in the group with FRAX score for hip fractures < 3%, women without previous fractures were about three times more than those with previous fractures, (p=0.000). There were no statistically significant differences between the number of the smoker and non-smoker in the groups with FRAX score for major osteoporotic fracture

and with FRAX score for hip fractures, (p=0.072). The group with FRAX score for major osteoporotic fractures ≥20% and for hip fractures ≥3% showed higher proportion of the women with CS use/without CS use compared to the group with FRAX score for major osteoporotic fractures <20% and for hip fractures <3%, (p=0.009). The proportion of the women with RA/without RA was 0.8 in the FRAX group for major osteoporotic fracture ≥ 20% and about 0.6 in the FRAX group for hip fracture ≥ 3% and these proportions were significantly higher than the proportion 0.3 in the FRAX group for major osteoporotic fracture < 20% and for hip fracture < 3%, (p=0.015). Alcohol consumption more than 30 ml per day was not statistically significant in the groups with FRAX for major osteoporotic fracture and FRAX for hip fractures, (p=0.486), (Table 2).

Table 2: Chi-square test for the significance of the risk factors in both FRAX risk groups.

FRAX Major osteoporotic		FRAX Major osteoporotic		FRAX hip fracture		p-value
		<20%	≥20%	<3%	≥3%	
		Count	Count	Count	Count	
Previous fracture	yes	36	32	28	40	0.000
	no	111	10	90	31	
smoking	yes	38	5	32	11	0.072
	no	109	37	86	60	
Corticosteroid use	yes	17	14	13	18	0.009
	no	130	28	105	53	

Rheumatoid arthritis	yes	34	19	26	27	0.015
	no	113	23	92	44	
Alcohol consumption more than 30 ml	yes	12	2	10	4	0.486
	no	135	40	108	67	

Discussion

Osteoporosis is a highly prevalent metabolic bone disease, which leads to bone fragility and subsequent fractures, most of them with social and economic impact. The necessity of adequate treatment for individuals at high risk of fractures brought about the need for new risk prediction models. FRAX algorithm, released in 2008 by WHO, is a fracture risk assessment tool, which gives 10-year probability for major osteoporotic fractures and hip fractures [20,21]. The clinical risk factors in the FRAX model are on one hand easily accessible and on the other hand highly validated from an evidence-based assessment [22]. Furthermore, FRAX tool has been incorporated into the software of some DXA scanners [23,24]. In the current study, the opportunity to assess the 10-year fracture risk with REMS technology, which has integrated Fracture Risk Assessment Tool (FRAX) [25], motivated us to describe the patients' characteristics in the different FRAX risk groups with this novel method.

We found out that the incidence of FRAX for major osteoporotic fractures was 22.2% and the incidence of FRAX for hip fractures ≥3% was 37.6%. FRAX score was calculated using the following risk factors - age, weight, height, BMD, previous fractures, current smoking, diagnosis of RA, current use of corticosteroids and alcohol consumption more than 30 ml per day. We observed statistically significant differences for age, weight, height, BMD, current use of corticosteroids, previous fractures and diagnosis of RA between the groups with FRAX for major osteoporotic ≥20% and with FARX for major osteoporotic <20%. The same results were observed in the groups with FRAX score for hip fracture ≥3% and with FRAX score for hip fracture <3%.

Results in the current study showed that age is a very important risk factor for FRAX major osteoporotic and for hip fractures due to statistically significant differences in the age between the women in the both FRAX groups. The influence of the FRAX risk assessment by the age is in accordance with the data provided by the National Osteoporosis Group [11]. In the study of Gadam et al. age was the only risk factor in postmenopausal women that was significantly different between those with identical and different predictions [26-29]. The indicators - weight and height are significant risk factors for FRAX major osteoporotic ≥20% and for hip fractures ≥3% in our study. Similar results are observed in the other FRAX studies. Body mass index (BMI), an indicator compounded of weight and height, showed negative association with FRAX-based fracture probabilities in the previous studies. This association was especially significant in subjects with a BMI less than 19 kg/m², while for subjects with a BMI greater than 19 kg/m², the fracture risk remained relatively stable [30-32].

According to the World Health Organization (WHO) criteria, BMD measured by dual-energy X-ray absorptiometry (DXA), is the most widely used in the diagnosis of osteoporosis [33]. Although a low BMD is a determinant of osteoporotic fracture, some fracture cases did not have a BMD in the osteoporotic range [34-36]. According to Kanis et al. the prediction of fractures with the use of clinical risk factors alone in FRAX is comparable to the use of BMD alone to predict fractures. In the current study patients with lower BMD showed significantly higher FRAX score for major osteoporotic fractures and for hip fractures, which is in accordance with the previous studies [37-39].

According to our study presence of previous fracture was significant for FRAX major osteoporotic ≥20% and for hip fractures ≥3%. It is beyond controversy that previous fractures increase the risk of future fractures [20,37]. In the study of Morin et al. non-traumatic fractures in women were associated with osteoporosis at the femoral neck and the authors showed that the site of previous fractures impacts future fracture risk, independent of the BMD value [40].

RA has been incorporated as a dichotomous predictor in the WHO FRAX algorithm for predicting the 10-year risk of hip or major osteoporotic fracture. In our study RA was significant for FRAX major osteoporotic and FRAX for hip fractures. Several studies showed in alignment with our study that the incidence of fracture is higher in RA patients than in controls [41-44]. FRAX could be underestimated due to the lack of information about the severity of RA and on the contrary it may overestimate fracture risk due to higher mortality among patients with RA [45]. The use of corticosteroids (CS) has been incorporated as one of the clinical risk factors for calculating the 10-year fracture risk in the Fracture Risk Assessment Tool (FRAX). CS can have impact on the fracture risk independent of bone density [46]. According to Kanis et al. the exposure to glucocorticoids was found to be significant for fracture probability. Fracture probabilities increased with 15% for high doses of CS (> 7.5 mg daily).

Conclusion

Postmenopausal women at older ages, with low femoral neck BMD, low weight and height, who had previous fractures, have diagnosis of RA and use corticosteroids are at the highest risk of FRAX for major osteoporotic fractures ≥20% and for hip fractures ≥3%.

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