

Fracture risk prediction with FRAX in Slovak postmenopausal women

Research Article

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Received 31 January 2013; Accepted 23 April 2013

Abstract: Introduction: Current Slovak treatment thresholds in osteoporosis are based on bone mineral density (BMD) or a previous fracture. Some patients at high risk for fractures may not be identified. FRAX (Fracture Risk Assessment Tool) is based on patient risk profile assessment and calculates 10-year fracture risks. Using FRAX, treatment initiation could be more patient-specific. Aim of study: To evaluate the risk profile with FRAX in Slovak postmenopausal women, to identify those at high risk of fracture according to NOF (National Osteoporosis Foundation) intervention thresholds based on FRAX and to compare this approach to current treatment thresholds. Methods: We measured BMD at lumbar spine, femoral neck, total hip and calculated 10-year absolute fracture risks with the Slovak version of FRAX in 365 patients. Results: Average risk of major osteoporotic fracture was 10,39% and hip fracture 3,00%. 109 patients were eligible for treatment according to actual treatment criteria (88 based on BMD and 21 with previous fracture). In addition, 57 high risk osteopenic patients were identified by NOF thresholds using FRAX, who should be also considered for treatment. Conclusion: Using FRAX and NOF thresholds it's possible to identify high risk patients who don't fulfill current treatment criteria but may profit from treatment.

Keywords: Osteoporosis • Fracture risk • FRAX • Treatment thresholds

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1. Introduction

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. At 50 years of age, one in two women and one in five men will suffer a fracture in their remaining lifetime and the number of fractures is still rising. The highest incidence is observed in Europe and USA - approximately 2.3 millions annually. Often the diagnosis of osteoporosis is set only after the occurrence of a fracture [1]. Direct and indirect costs on treatment and disability represent a severe socio-economic problem. According to European data, 21% of patients die in the first 3 months following a hip fracture, a year later 40% are unable to walk independently, 60% are requiring assistance in common everyday activities as bathing or dressing up and 80% are unable to independently perform at least one everyday activity as shopping or cleaning up [2].

Densitometric measurement at lumbar spine and proximal femur is considered as the gold standard in the diagnostic process of osteoporosis. Decrease in BMD to osteoporotic values (T-scores $\leq -2,5$ standard deviations (SD) - T score describes the number of SDs by which the BMD in an individual differs from the mean value expected in young healthy individuals of the same sex) or a previous fracture are the currently valid interventional thresholds for indication of anti-osteoporotic treatment, also in Slovakia [3].

More than half of osteoporotic fractures occur in patients with osteopenia [1], but these patients do not fulfill the current criteria for treatment initiation. It is therefore important to evaluate the fracture risk factors and identify patients at high risk for a future fracture. The National Osteoporosis Foundation (NOF) published a list of 79 conditions, diseases and medications that cause or contribute to osteoporosis and fractures [4]. They include f.e. a previous fracture, use of glucocorticoids, hypogonadal states, numerous endocrine

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disorders (Cushing's syndrome, hyperparathyroidism, adrenal insufficiency), gastrointestinal diseases as malabsorption or inflammatory bowel disease, also autoimmune and rheumatic diseases as rheumatoid arthritis and others.

To be able to quantify this fracture risk, WHO developed FRAX - Fracture risk assessment tool. FRAX calculates the absolute 10-year fracture risk of a major osteoporotic fracture (femoral neck, clinical spine, proximal humerus, forearm) and hip fracture from 12 independent risk factors and has to be calibrated for each country depending on the epidemiological situation. Mortality data are also incorporated into the algorithm of FRAX, so the absolute fracture risk includes the probability of death before the fracture occurs [5].

Risk factors incorporated in FRAX are independent of BMD and every risk factor has its own weight, its own importance, depending upon age (e.g. a family history), or on the presence or absence of other risk factors. The strongest risk factors in FRAX (except of age and BMD) are a previous fracture, parent fractured hip, rheumatoid arthritis and glucocorticoid treatment [6].

Although the use of FRAX is simple and quick, the interpretation of the fracture risk is difficult. Based on a cost-effectiveness analysis, NOF recommends to use 20% for major osteoporotic fracture and 3% for hip fracture as an intervention threshold for the USA based on FRAX [4].

Since 2012, FRAX is available also for Slovakia and its use and future implementation into national guidelines is being considered. The aim of our current study was to evaluate the risk profile in Slovak postmenopausal women using FRAX, to identify those at high risk of fractures and to compare two intervention strategies for treatment initiation - based on low BMD or a previous fragility fracture vs. based on high fracture risk.

2. Materials and methods

This is a prospective study regarding postmenopausal women sent to densitometric testing to the Osteocentre of University Hospital Ružinov, Bratislava, Slovakia. These patients were sent either by their primary practitioner or a specialist to our centre. All patients were anti-osteoporotic treatment-naive.

We measured BMD at lumbar spine, total femur and femoral neck in each patient with dual-energy X-ray absorptiometry (Hologic, Discovery). According to the WHO criteria, the patients were classified by their T-score value at lumbar spine and hip as normal (T-score above -1SD), osteopenic (T-score between -1 and -2,5SD), or osteoporotic (T-score \leq -2,5 SD).

Each patient filled out a questionnaire containing questions about the risk factors included in FRAX. We calculated absolute 10-year major osteoporotic fracture and hip fracture risks with the help of FRAX calibrated to the Slovak national epidemiology data.

3. Results

We assessed a total of 365 women with an average age of 63 years. For the presence of risk factors in study group see Table 1.

Table 1. Presence of risk factors in study group. Previous fractures were assessed by self-report. Treatment with oral glucocorticoids was defined as current or past treatment for more than 3 months with a dose of prednisolone of 5 mg daily or more (or equivalent doses of other glucocorticoids). Alcohol consumption was defined as taking 3 or more units of alcohol daily. (One unit = 8 g of alcohol.)

Risk factor	Number of patients with present risk factor	Proportion of patients with present risk factor
Previous fracture	47	12,8%
Parent fractured hip	25	6,8%
Current smoking	52	14,2%
Treatment with oral glucocorticoids	33	9,04%
Rheumatoid arthritis	46	12,6%
Secondary osteoporosis	99	27,1%
Alcohol consumption	4	1,09%

According to BMD values, 88 patients were osteoporotic, 213 osteopenic and 64 had normal BMD values. Average risk of major osteoporotic fracture based on FRAX was 10,39% and femoral neck fracture 3,00% in the whole group. Results of BMD measurements are summarized in Table 2.

Table 2. BMD measurement results.

Patients subgroups	Average BMD femoral neck		Average BMD lumbar spine	
	Tscore	g/cm ²	Tscore	g/cm ²
Osteoporotic (n=88)	-2,10	0,612	-2,89	0,515
Osteopenic (n=213)	-1,28	0,708	-1,52	0,678
Normal BMD (n=64)	-0,02	0,852	0,02	0,860

According to actual treatment criteria we identified 109 patients suitable for treatment (88 osteoporotic patients based on BMD and 21 osteopenic patients with a previous fracture).

In the osteopenic group, we considered patients to be at high risk if their fracture risks exceeded the NOF criteria (\geq 20 % for major osteoporotic fracture or \geq 3% for hip fracture). This way, we identified 69 patients (32,3%)

at high risk in the osteopenic group (57 (26,7%) after excluding those with a previous fracture), who should be also considered for treatment.

On the other hand in the osteoporotic group, only 46 patients had fracture risks above the NOF criteria (52,3% of the osteoporotic group).

If we use both approaches to treatment indication in our study group (current criteria based on BMD and previous fracture and also NOF thresholds) we would initiate anti-osteoporotic treatment in 166 patients. This would mean a 52,3% increase in the number of treated patients when compared to the current indication criteria.

If we use NOF criteria and FRAX outcomes for treatment indication, we would treat 115 patients, which means a 5,5% increase of treated patients compared to the current criteria.

4. Discussion

In the past years, we observed a tendency to complex evaluation of fracture risk, mostly because high risk osteopenic patients are not identified by current diagnostic methods nor are considered for treatment. Therefore it's important to identify patients with high 10-year absolute fracture risk from this huge and non-homogenous group.

Many factors, which affect the results of DXA testing (f.e.: osteoarthritis at lumbar spine and proximal femur, inborn vertebral deformities or fractures, severe scoliosis) [3] are often not taken into account in clinical practice and can lead subsequently to falsely high BMD results and no treatment even in a high risk patient.

Previous fracture is considered as osteoporotic when following a low intensity trauma. The assessment of vertebral fractures has also its limitations, which can contribute to no treatment initiation in a high risk patient (up to 2/3 of vertebral fractures are asymptomatic and patients are not sent to X-ray. Often mild or moderate vertebral fractures are not described by radiologists and even if they are, they're evaluated as posttraumatic and not osteoporotic) [7].

For this purpose, FRAX was developed by WHO, but despite its simple and clear form it has also multiple limitations. For example, it's not recommended to use FRAX in patients receiving anti-resorptive drugs nor for treatment efficiency monitoring, the dose of glucocorticoids can't be entered. The diagnosis of rheumatoid arthritis is also a problematic risk factor, because many patients confuse this disease with various forms of arthropathies. FRAX doesn't incorporate BMD at lumbar spine, mostly because of the pitfalls in interpretation of its measurement and the lack of information about lumbar spine BMD in the source cohorts used to construct

FRAX. In addition, femoral neck BMD is associated with a higher gradient of risk (increase in fracture risk/unit decrease in BMD) for hip fracture than BMD measurements at the lumbar spine [6]. FRAX doesn't contain biochemical markers of bone turnover. They have a wide range of biological variability and laboratory methods of their assessment are not uniform. These were one of the reasons International Society for Clinical Densitometry (ISCD) and International Osteoporosis Foundation (IOF) published official positions regarding each risk factor and their limitations, for example if a patient takes glucocorticoids in a higher or lower dose as it is regarded in FRAX, the final risk will be under or overestimated. Similar positions were published regarding also multiple previous fractures or degree of disability in patients with rheumatoid arthritis [8].

Predicted and observed fracture risks may differ. The prediction accuracy of FRAX was examined in several studies and FRAX may underestimate the risk of fractures [9,10]. When compared to other risk assessment methods, FRAX performs similarly or better than other simpler methods (based on age, previous fracture or BMD), outcomes on comparison with other calculators are inconsistent [11-18]. However, construction on multiple population cohorts, external validation, applicability to various countries, output as absolute risk and inclusion of risk factors amenable to treatment are major advantages of FRAX compared to other risk assessment tools [19,20].

FRAX has also received some unpopularity, some authors doubt the methodology and complexities in both the original derivation and validation [21]. Nevertheless, assessment of risk factors is considered for diagnosis and treatment of osteoporosis in various countries. In Switzerland, a FRAX-based intervention threshold of 15% for a major osteoporotic fracture for both women and men is considered to be cost-effective in patients at high fracture probability based on clinical risk factors [22]. In the UK, patients are identified opportunistically, using a case-finding strategy based on the presence of a previous fragility fracture or significant clinical risk factors. The intervention threshold at each age is set at a risk equivalent to that associated with a prior fracture. In the presence of other risk factors than a previous fracture, the ten year probability of a major osteoporotic fracture should be determined using FRAX. According to the resultant fracture risk, patients at high risk are considered for treatment, patients with moderate risk are considered for BMD testing and fracture probabilities are recomputed with FRAX. Patients at low risk can be reassured [23]. A similar approach with age-adjusted fracture risks is practiced also in Belgium [24]. In Japan, a 10-year probability of 10% for osteoporosis-

related fracture was set as an acceptable intervention threshold based on the fracture probability at which intervention is currently considered to be worthwhile [25]. Swedish national guidelines also include FRAX in the diagnostics and treatment decision making process [26]. In Germany and Poland, national guidelines allow to consider the presence of risk factors in treatment decision making [27,28].

Considering the risk profile and 10 year absolute fracture risk assessed by FRAX in treatment initiation in osteopenic patients could be a more sensitive way to identify patients at high risk (compared to treatment indication based on BMD and a previous fracture), but it would also lead to an increase in the number of treated patients [29]. During the implementation of FRAX into national guidelines on treatment of osteoporosis, its necessary to consider also the economic burden associated with the increased number of treated patients. Implementing intervention thresholds of other countries, for example USA, could be economically unbearable, for the NOF thresholds were set according to a cost/benefit analysis regarding US economy. Therefore it's important to evaluate the cost/benefit of intervention thresholds based on fracture risk for every country.

When considering fracture risks and NOF thresholds in treatment initiation parallel with current criteria in our study, the number of treated patients would rise by 52,3%. In the osteopenic group, we identified 32,3% of patients, who are at high risk of fracture in the next 10 years. This relatively high proportion of high risk osteopenic patients is caused by the frequent presence of risk factors in our study. The majority of patients was sent to DXA measurement because of the presence of these risk factors. Our Osteocentre specializes in secondary osteoporosis, which is the reason for the high percentage of secondary causes of osteoporosis in our study group. However, if BMD value is considered in the FRAX calculation, the presence of a secondary cause doesn't change the resultant risk [30].

Although the presence of risk factors may seem frequent in our study, we suppose that specifically these osteopenic patients at high risk are discriminated by their BMD value and may benefit from fracture risk assessment and potential treatment initiation.

In the osteoporotic group, 52,3% didn't meet the criteria for being at high risk according to FRAX and NOF threshold. These patients were osteoporotic at lumbar spine, which is not considered in the FRAX algorithm. BMD values at hip were in osteopenic or normal range and spine-hip discordance was greater compared to the high risk osteoporotic patients (average T-score spine-hip discordance 0,98SD compared to 1,72SD).

When using the threshold proposed as cost-effective in Switzerland in our study group (15% for a major osteoporotic fracture), 30 patients in the osteoporotic group (34%) and 30 patients in the osteopenic group (14%) would be eligible for treatment. This threshold identifies even less osteoporotic patients as NOF criteria, although it doesn't consider femoral neck fracture risk.

Our results share similarities with some previously published studies. In a retrospective study of 1000 randomly selected women from an outpatient hospital specialized in bone metabolism in Belgium, 167 women had access to drug reimbursement according to current Belgian criteria (which are equal to those applied in Slovakia), but only 38,9% would be potentially reimbursed if FRAX criteria supposed for Belgium were used (corresponding to a woman with a prior fragility fracture with an average BMD) [31]. In a UK study, national guidelines based on FRAX were compared to clinician determined treatment intervention thresholds in 288 patients. Discordance in treatment indication was observed in 25% of subjects and the primary source of this discrepancy was the absence of spine BMD from FRAX [32]. Also when comparing UK and US osteoporosis treatment guidelines (both incorporate fracture risk assessment), a difference of 27% was observed between the proportion of patients indicated for treatment when UK and US guidelines were applied [33].

BMD still remains a strong factor in risk prediction. We are inclined to agree with NOF recommendations, that FRAX should be used when the decision to treat or not to treat is uncertain [4]. Treatment initiation in patients with osteoporosis according to BMD values or a previous fracture is not questionable. We suggest that a combined intervention threshold based on BMD and FRAX could allow us to target treatment to patients at high risk of future fracture and would be more sensitive compared to current thresholds. This combined approach will need to be supported by appropriate health economic analyses.

Properly chosen therapeutic thresholds would suppose not only a more targeted but also an economically bearable treatment (with regards to treatment cost/benefit and local economy).

In summary, with the help of FRAX, it is possible to identify patients at high fracture risk in the next 10 years who are currently not considered for anti-osteoporotic treatment. This allows us to individualize treatment in patients according to their risk profile and not only according to a quantitative parameter as BMD or a previous fracture.

In our study, we identified with help of FRAX and NOF thresholds 32,3% of our osteopenic patients be-

ing at high risk of fracture in the next 10 years despite their BMD not meeting the criterion for osteoporosis. An increase in the number of treated patients could partly burden the national economy, but treatment would be patient-specific and could save direct and indirect costs resulting from fractures. Therefore, each country be-

sides having its own FRAX model has to review its economic situation and the suitability of NOF intervention thresholds for treatment initiation. Further research on a greater amount of patients in Slovakia including also men is needed to be able to set intervention thresholds based on fracture risk.

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