УДК 616.71-007.234-055.1:[005.311.11:303.62FRAX]](048.4)

DOI: http://dx.doi.org/10.15674/0030-59872023161-66

Management of osteoporosis in men based Ukrainian version of FRAX

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Objective. The aim of the study was to evaluate the impact of the previous published FRAX thresholds in a male referral cohort from Ukraine. Methods. The cohort comprised 653 men aged 40–88 years (mean age 60.5 ± 11.8). The 10-year probabilities of hip fracture and a major osteoporotic fracture were calculated using the Ukrainian FRAX model. The intervention threshold was set at the age specific fracture probability as first used by the National Osteoporosis Guideline Group for FRAX-based guidelines in the UK and adapted for the Ukraine. Treatment pathways were compared with a previously published female referral cohort from Ukraine. Results. 27 % of men and 51 % of women referred for skeletal assessment had a prior fracture that categorized eligibility for treatment that was more frequent in women than in men. The requirement for BMD testing was also higher in women than in men (18.3 % vs. 4.9 %, respectively). If referral for fracture risk assessment was contingent on the presence of at least one FRAX risk, the proportion of men and women eligible for treatment would rise from 5 % to 89 % in men and from 57 % to 93 % in women. Conclusions. This study demonstrated a higher need for both antiosteoporotic treatment without DXA and additional densitometric examination to further assess the osteoporotic fractures risk in Ukrainian women compared to men and the need for special attention in fracture risk assessment in men with previous fractures. The development of National guidelines together with a validation based on cost-effectiveness would help drive a cohesive national approach to risk assessment in both men and women.

Мета. Оцінити ефективність використання запропонованих межових значень українського алгоритму FRAX у чоловіків. Методи. Обстежено 653 чоловіки віком 40–88 років (середній вік (60,5 ± 11,8)). За допомогою української версії опитувальника FRAX розраховували 10-річну ймовірність основних остеопоротичних переломів й окремо переломів стегнової кістки. Межі втручання встановлювали на підставі вік-залежної ймовірності переломів згідно з методологією National Osteoporosis Guideline Group, застосованої для створення настанов FRAX у Великобританії й адаптованої для України. Оцінювали інформативність визначених раніше критеріїв щодо призначення інструментального обстеження кісткової тканини й ініціації антиостеопоротичої терапії української моделі FRAX за умов використання в чоловіків і порівнювали з оцінками в українських жінок. Результати. Серед чоловіків, скерованих для проведення двофотонної рентгенівської абсорбціометрії (ДРА), переломи в анамнезі, які класифікували як критерій для початку антиостеопоротичного лікування, зареєстровано у 27 % осіб (51 % у жінок). Необхідність визначення мінеральної щільності кісткової тканини також була вищою в жінок, ніж у чоловіків (18,3 та 4,9 %, відповідно). Якби оцінка ризику переломів залежала від наявності принаймні одного фактора ризику FRAX, частка чоловіків і жінок, яким необхідно призначення антиостеопоротичного лікування, зросла б від 5 до 89 % у чоловіків і від 57 до 93 % у жінок. Висновки. Дослідження продемонструвало більшу необхідність призначення антиостеопоротичного лікування й додаткового ДРА–обстеження з метою переоцінки ризику остеопоротичних переломів в українських жінок порівняно з чоловіками, на підставі опитувальника FRAX. Акцентовано увагу на необхідності ретельного оцінювання ризику переломів у чоловіків із переломами в анамнезі. Розроблення національних рекомендацій разом із валідацією на підставі економічної ефективності допоможе запровадити узгоджений національний підхід до оцінювання ризику для чоловіків і жінок. Ключові слова: FRAX, остеопороз, лікування, перелом.

Key words. FRAX, osteoporosis, treatment, fracture

Introduction

Osteoporosis and its complications are an important medical and social issue both in Ukraine and worldwide [1]. A recent study in 5 countries of the European Union indicated that the number of fractures will increase from 2.7 million in 2017 to 3.3 million in 2030 (by 23 %), and the annual costs associated with fractures (i. e. 37.5 billion euros in 2017) will increase by 27 % [2]. Osteoporosis affects women more frequently than men due to differences in the attainment of peak bone mass and in bone loss after menopause [3] and relatively few studies have focused on men. However, timely assessment of the risk of osteoporosis and its complication in both women and men is important in the prevention of this severe disease in an aging population.

The web-based tool FRAX® (https://www.sheffield.ac.uk/FRAX) computes the 10-year probability of fragility fractures based on several common clinical risk factors and, optionally, a bone densitometry result obtained from dual energy X-ray absorptiometry (DXA) [4, 5]. FRAX models are available for 73 countries covering more than 80 % of the world population at risk and have been incorporated into more than 100 guidelines worldwide [6].

A country specific FRAX model for Ukraine was launched in November 2016, replacing the Austrian FRAX model previously used [7, 8]. Intervention thresholds for Ukraine have been published and tested in a female referral cohort from Ukraine [9]. The aim of the present study was to evaluate the impact of the published thresholds in a male referral cohort from Ukraine.

Material and methods

Population sample

The cohort comprised 653 men referred as outpatients to the Dmitry F. Chebotarev Institute of Gerontology of the National Academy of Medical Sciences of Ukraine for the evaluation of skeletal status. The study was approved by the local Ethics Committee (protocol № 5 of May 17, 2017) and undertaken from September 2017 to December 2020. All the study participants gave informed written consent for participation.

The baseline characteristics for the calculation of fracture probabilities are given in table 1. Complete information was available in all 653 patients. Bone mineral density (BMD) of the femoral neck was measured by DXA and the BMD was standardised according to the equipment manufacturer [10, 11]. The T-score was calculated using the NHANES III reference values for young Caucasian women [10] as used in FRAX [12].

Fracture probabilities and management thresholds

The 10-year probabilities of hip fracture and a major osteoporotic fracture were calculated using the Ukrainian FRAX model (FRAX version 4.2). Calculations were undertaken with and without the inclusion of femoral neck BMD.

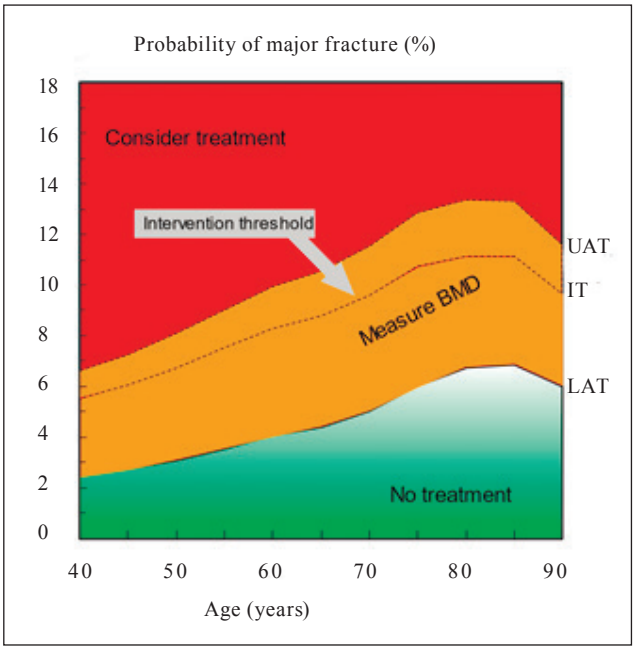

Figure. 10-year probability (%) of a major osteoporotic fracture corresponding to the lower assessment threshold (LAT) and upper assessment threshold (UAT) for Ukraine. The red area is where the treatment would normally be recommended, the orange area shows the limits of fracture probabilities for the assessment of BMD, and the green area is where treatment would not normally be recommended. The dotted line represents the intervention threshold (IT).

Table 1

Summary description of the referral population

Parameters	M ± SD (range) or % (n)
Baseline age (years)	60.5 ± 11.8 (40–88)
Height (cm)	175.2 ± 7.5
Weight (kg)	83.9 ± 15.2
BMI (kg/m^2)	27.3 ± 4.5 (15.0–51.9)
Previous low-energy fracture	26.6 % (174)
Parental hip fracture	6.4 % (42)
Current smoking	16.2 % (106)
Glucocorticoids	4.9 % (32)
Rheumatoid arthritis	3.1 % (20)
Secondary osteoporosis	3.7 % (24)
Alcohol 3 or more units per day	1.2 % (8)
Femoral neck BMD T-score, SD	–0.8 ± 1.2 (–4.3–3.8)
No clinical risk factors (FRAX)	53.4 % (349)

Notes. BMI — body mass index, BMD — bone mineral density, Data presented in M ± SD and Range (Min-Max) or in % (n).

The intervention threshold was set at the age specific fracture probability equivalent to women with a prior fragility fracture as first used by the National Osteoporosis Guideline Group for FRAX-based guidelines in the UK [12] and adapted for the Ukraine [8, 9].

Management pathway

The management pathway explored was identical to that previously described in a female referral population. In brief, men with a prior fragility fracture were considered eligible for treatment. In those without a prior fracture, FRAX would be calculated without BMD. Fracture probability could thereafter be categorised as low, intermediate, or high (green, amber or red areas in figure). Patients categorised as low risk would not normally be given bone-specific intervention. Those at high risk would be eligible for treatment without necessarily having a BMD test (other than to provide a baseline to monitor treatment). Those at intermediate risk would be offered a BMD test and FRAX recomputed with the addition of BMD. Patients would then be re-categorized to low or high risk if the fracture probability fell below or above the intervention threshold, respectively.

Data derived for men were compared with that derived from a female referral population (3179 women, age 40–90 years) to the same institute [9].

Statistical Analysis

We performed the statistical analysis using Statistica 10.0 software. The relevance of sample in terms of the normal distribution principle was checked by Shapiro-Wilk's test and demonstrated abnormal distribution of FRAX parameters. The data were presented as n (%), mean values (M) and standard deviation (SD) or median (Me) and the lower and upper quartiles (25Q÷75Q) according to data distribution.

Table 2

Ten-year probability (%) for hip fracture and a major osteoporotic fracture calculated with and without bone mineral density

Ten-year probability	n	Median	25Q ÷ 75Q	Range
MOF calculated without BMD	653	2.3	2.0 ÷ 4.1	0.9–11.9
Hip fracture calculated without BMD	653	0.5	0.2 ÷ 1.1	0.0–7.8
MOF calculated with BMD	653	2.7	2.0 ÷ 4.4	0.9–28.1
Hip fracture calculated with BMD	653	0.6	0.2 ÷ 1.3	0.0–20.0

Notes. MOF — 10-year probability of major osteoporotic fractures, BMD — bone mineral density.

Results and their discussion

Probabilities of hip fracture and a major osteoporotic fracture (with and without BMD) are given in table 2. The mean probability of a major fracture was 3.8 % and, for a hip fracture was 1.3 % when BMD was used in the FRAX model (the same indexes without BMD consisted 3.1 and 0.8 %). Fracture probability calculated with BMD was higher than that without BMD. The probable reason for this is the preferential referral of men with lower-than-average BMD.

Table 3

Disposition of the Ukrainian male and female cohort according to National Osteoporosis Guideline Group guidance

Category	Number	%	10-year probability with BMD	
			MOF	HIP
Men				
Entire cohort	653	100	3.8	1.3
Prior fracture	174	26.6	6.5	2.6
Eligible for treatment	183	28.0	6.8	2.9
For treatment by FRAX alone	9	1.4	11.6	7.5
Low risk	470	72.0	2.6	0.6
BMD tests	32	4.9	6.4	2.7
Women				
Entire cohort	3719	100	8.8	3.3
Prior fracture	1906	51.3	11.6	4.7
Eligible for treatment	2134	57.4	11.8	4.9
For treatment by FRAX alone	228	6.1	13.1	6.5
Low risk	1585	42.6	4.7	1.2
BMD tests	681	18.3	6.9	2.5

Notes. MOF — 10-year probability of major osteoporotic fractures, HIP 10-year probability of hip fractures.

Management pathway

174 of 653 men (26.6 %) had a prior fragility fracture and would be eligible for treatment on this basis. At the initial assessment (FRAX without inclusion of BMD), no men were eligible for treatment. Of these, 447 low risk individuals (68.5 % of whole cohort, 93.3 % of males without previous fractures) would not normally be eligible for further assessment in that their fracture probability lay below the lower assessment threshold. The intermediate category of risk comprised 32 men (4.9 % of whole cohort) in whom FRAX would be recalculated with the inclusion of femoral neck BMD. Of these 23 were categorized at low risk (3.5 %) and 9 at high risk (1.4 % of whole cohort). The overall disposition of the cohort is shown in table 3 and compared to that of women.

The disposition of the cohort in men was markedly different to that for women. Those eligible for treatment was 28 % of men and 57 % of women. For both sexes, eligibility was primarily determined by the presence of a prior fragility fracture but eligibility for treatment by FRAX alone was higher in women than in men (6.1 % vs. 1.4 % of whole cohort, respectively). The requirement for BMD testing was also higher in women than in men (18.3 % vs. 4.9 % of whole cohort, respectively). As might be expected, fracture probabilities were lower in men than in women (see table 3).

Not all men and women had a FRAX clinical risk factor. In the low-risk categories, 1442 of 1585 women and 349 of 470 men (n = 349; 53.4 % of whole cohort; 73 % of males without previous fractures) had no FRAX-based clinical risk factor. Thus, if referral for fracture risk assessment w as contingent on thepresence of at least one FRAX risk, the proportion of men and women eligible for treatment (amongst those with at least one FRAX risk factor) would rise from 5 % to 89 % in men and from 57 % to 93 % in women.

In a historical context, osteoporosis has been viewed as a disorder of women rather than men, and the majority of studies covering assessment and treatment have focused on women [1]. In recent years, it is increasingly recognized that osteoporosis and fragility fractures are also common in men. In 2019 there were estimated to be 32 million individuals in Europe with osteoporosis as defined by densitometry of whom 6.5 million (20 %) were men. In the same year, there were 4.2 million fragility fractures of which one third were in men [13]. Of 29 countries in Europe surveyed, all but four provided for men in guidelines for the assessment of osteoporosis.

According to the State Statistics Service of Ukraine data (01.01.2020 [14]) there were 19 343 440 men (46.4 % of the total population) and 10.17 % of males aged 50 years and older. According to the Ukrainian Research and Medical Center for Osteoporosis, 28.4 % of men in this age group have low BMD according to the DRA, and 6.7 % — osteoporosis. Thus, our calculations indicate that in Ukraine more than 123 thousand men aged 50 years and older have osteoporosis and almost 560 thousand — osteopenia.

The impact of fragility fracture is similar in men and women, in terms of fracture site, associated comorbidity and reduced survival [13, 15–18]. This raises the question of whether there are intrinsic differences between men and women, which impact on the assessment of fracture risk with the use of FRAX. In the case of clinical risk factors, no systematic sex differences have been observed in the strength of the clinical risk factors (apart from age) [4]. With regard to BMD, at any given age the average BMD is higher in men than in women. However, the gradient of risk (increase in fracture risk/SD decrease in BMD) is the same in men as in women [19]. Moreover, the absolute incidence of hip fracture and of all fractures by femoral neck T-score also appears similar in men and women [20, 21]. These data support the view that FRAX can be applied equally to men as to women.

In the present study, we have examined the assessment of fracture risk in a referral population of men and compared their disposition with that of a referral population of women. Many men and women referred for skeletal assessment had a prior fracture that categorized eligibility for treatment, a characteristic that, as might be expected was more frequent in women (51 % of referrals) than in men (27 %). Of the remaining men, very few men were eligible for treatment under the current management pathway, principally because the majority of men with no prior fracture had no clinical risk factors. These findings suggest that referral for fracture risk assessment should be recommended in men with at least one clinical risk factor. Alternatively, intervention thresholds should be made less conservative. The various options might be optimally explored by health economic assessment.

Limitation. These findings are relevant for the referral population to the present institute and may not reflect practice elsewhere in the Ukraine. The development of National guidelines together with a validation based on cost-effectiveness would help drive a cohesive national approach to risk assessment in both men and women.

Conclusions

The fragility fracture was the most frequent (26.6 %) risk factor for osteoporotic fractures in

Ukrainian males (the corresponding index in females was 51.3 %), and it was the reason for antiosteoporotic treatment initiating. Only 6.7 % of men without previous fractures were found to require additional DXA examination according to FRAX and none had a high fracture risk. 73 % of men without fractures did not have any risk factor included in the FRAX algorithm. This study showed a greater need for both antiosteoporotic treatment without DXA assessment and additional densitometric examination for the osteoporotic fracture risk assessment for the Ukrainian women rather than men, and necessity of special attention to the presence of previous fractures in males, and consideration of other osteoporosis risk factors which are not included in this FRAX.

Declaration of conflicting interests. The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding. The authors received no financial support for the research and/or authorship of this article.

References

1. Management of endocrine disease: Male osteoporosis: diagnosis and management — should the treatment and the target be the same as for female osteoporosis? / T. Porcelli, F. Maffezzoni, L. C. Pezzaioli [et al.] // European Journal of Endocrinology. — 2020. — Vol. 183 (3). — P. 75–93. — DOI: 10.1530/EJE-20-0034.
2. Fragility fractures in Europe: burden, management and opportunities / F. Borgström, L. Karlsson, G. Ortsater [et al.] // Arch Osteoporos. — 2020. — Vol. 15(1) — Article ID: 59. — DOI: 10.1007/s11657-020-0706-y.
3. Kaufman J. M. Management of osteoporosis in older men / J. M. Kaufman // Aging clinical and experimental research. — 2021. — Vol. 33 (6). — P. 1439–1452. — DOI: 10.1007/s40520-021-01845-8.
4. Assessment of osteoporosis at the primary healthcare level. Report of a WHO Scientific Group / World Health Organization Scientific Group. — WHO Collaborating Centre, University of Sheffield, UK 2007. — Available from : http://www.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf.
5. FRAX and the assessment of fracture probability in men and women from the UK / J. A. Kanis, O. Johnell, A. Oden [et al.] // Osteoporosis international. — 2008. — Vol. 19 (4). — P. 385–397. — DOI: 10.1007/s00198-007-0543-5.
6. A systematic review of intervention thresholds based on FRAX: A report prepared for the National Osteoporosis Guideline Group and the International Osteoporosis Foundation / J. A. Kanis, N. C. Harvey, C. Cooper [et al.] // Archives of osteoporosis. — 2016. — Vol. 11 (1). — Article ID : 25. — DOI: 10.1007/s11657-016-0278-z.
7. Epidemiology of hip fracture and the development of FRAX in Ukraine / V. V. Povoroznyuk, N. V. Grygorieva, J. A. Kanis [et al.] // Archives of osteoporosis. — 2017. — Vol. 12 (1). — Aricle ID : 53. — DOI: 10.1007/s11657-017-0343-2.
8. Application of FRAX to determine the risk of osteoporotic fractures in the Ukrainian population / V. V. Povoroznyuk, N. V. Grygorieva, J. A. Kanis [et al.] // International Journal of Osteoporosis and Metabolic Disorders. — 2018. — Vol. 11 (1). — P. 7–13. — DOI: 10.3923/ijom.2018.7.13.
9. FRAX-Based Intervention Thresholds for Osteoporosis Treatment in Ukraine / V. V. Povoroznyuk, N. V. Grygorieva, H. Johansson [et al.] // Journal of Osteoporosis. — 2021. — Article ID: 2043479. — DOI: 10.1155/2021/2043479.
10. Updated data on proximal femur bone mineral levels of US adults / A. C. Looker, H. W. Wahner, W. L. Dunn [et al.] // Osteoporosis international. — 1998. — Vol. 8 (5). — P. 468–489. — DOI: 10.1007/s001980050093.
11. Standardization of bone mineral density at femoral neck, trochanter and Ward's triangle / Y. Lu, T. Fuerst, S. Hui, H. K. Genant // Osteoporosis international. — 2001. — Vol. 12 (6). — P. 438–444. — DOI: 10.1007/s001980170087.
12. Case finding for the management of osteoporosis with FRAX® assessment and intervention thresholds for the UK / J. A. Kanis, E. V. McCloskey, H. Johansson Dunn [et al.] // Osteoporosis international. — 2008. — Vol. 19 (10). — P. 1395–1408. — DOI: 10.1007/s00198-008-0712-1.
13. SCOPE 2021: a new scorecard for osteoporosis in Europe / J. A. Kanis, N. Norton, N. C. Harvey [et al.] // Archives of osteoporosis. — 2021. — Vol. 16 (1). — Article ID : 82. — DOI: 10.1007/s11657-020-00871-9.
14. State Statistics Service of Ukraine. Portal "Population of Ukraine". Thematic section "Distribution of the permanent population by sex, separate age groups and type of locality" / Electronic resource. Available from: http://database.ukrcensus.gov.ua/MULT/Dialog/statfile_c.asp. Accessed 27 Jun 2021.
15. Economic burden of osteoporosis-related fractures in the US Medicare Population / S. A. Williams, S. G. Daigle, R. Weiss [et al.] // Annals of Pharmacotherapy. — 2021. — Vol. 55 (7). — P. 821–829. — DOI: 10.1177/1060028020970518.
16. Burden of hip fracture using disability-adjusted life-years: a pooled analysis of prospective cohorts in the CHANCES consortium / N. Papadimitriou, K. K. Tsilidis, P. Orfanos [et al.] // Lancet Public Health. — 2017. — Vol. 2 (5) — P. 239–246. — DOI: 10.1016/S2468-2667(17)30046-4.
17. Mortality in older adults following a fragility fracture: real-world retrospective matched-cohort study in Ontario / J. P. Brown, J. D. Adachi, E. Schemitsch [et al.] // BMC Musculoskeletal Disorders. — 2021. — Vol. 22 (1). — Article ID: 105. — DOI: 10.1186/s12891-021-03960-z.
18. Sex differences in recovery of quality of life 12-months post-fracture: analyses of the Australian Arm of the International Costs and Utilities Related to Osteoporotic Fractures Study (AusICUROS) / J. Talevski, K. M. Sanders, J. J. Watts [et al.] // Osteoporosis international. — 2021. — Vol. 33 (1). — P. 67–75. — DOI: 10.1007/s00198-021-06058-3.
19. Does bone mineral density improve the predictive accuracy of fracture risk assessment? A prospective cohort study in Northern Denmark / P. Dhiman, S. Andersen, P. Vestergaard [et al.] // BMJ Open. — 2018. — Vol. 8 (4). — Particle ID: e018898. — DOI: 10.1136/bmjopen-2017-018898.
20. Hip fracture prediction in elderly men and women: validation in the Rotterdam study / C. E. De Laet, B. A. Van Hout, H. Burger [et al.] // Journal of bone and mineral research. — 1998. — Vol. 13 (10). — P. 1587–1593. — DOI: 10.1359/jbmr.1998.13.10.1587.
21. Bone density variation and its effects on risk of vertebral deformity in men and women studied in thirteen European centers: the EVOS Study / M. Lunt, D. Felsenberg, J. Reeve [et al.] // Journal of bone and mineral research. — 1997. — Vol. 12 (11). — P. 1883–1894. — DOI: 10.1359/jbmr.1997.12.11.1883.

Стаття надійшла до редакції 27.12.2022

МЕНЕДЖМЕНТ ОСТЕОПОРОЗУ У ЧОЛОВІКІВ ЗА ДОПОМОГОЮ УКРАЇНСЬКОЇ ВЕРСІЇ FRAX

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