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A discussion of the intervention thresholds in osteoporosis treatment in Poland

Głos w dyskusji nad progami terapeutycznymi leczenia osteoporozy w Polsce

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Abstract

Introduction: Epidemiological prognoses regarding the global spread of post-menopausal osteoporosis can prove somewhat nebulous. But it is clear that low-energy fractures and their consequences will become an increasingly serious health problem. Therefore it is crucial to implement prognostic procedures which could more effectively predict the incidence of osteoporosis and its complications.

Material and methods: The study involved 378 female patients aged 40–86 years for whom clinical risk factors of osteoporotic fracture were analysed. Densitometry (DPX) was performed at femoral neck. The 10–year risk of fracture was assessed according to the British model of FRAX calculator.

Results: The study group was divided into two, depending on the history of low-energy fractures. Previous osteoporotic fractures were confirmed in 128 patients. In this group, the mean bone mineral density (BMD) values (0.717 g/cm^2) were lower than in the group without fracture history (0.735 g/cm^2). In 33.3% of patients aged 50–59 years and 17% of women aged 60–79 who required medical treatment for their clinical status (previous fracture), the FRAX value did not meet the criterion of pharmacotherapy administration. Considering BMD in the calculation of FRAX produced an even higher underestimation of the fracture risk. Of women aged 40–49, 25% were qualified for pharmacotherapy of osteoporosis. In that particular age category, BMD did not affect the FRAX value. BMD measurement had a higher discriminatory value among patients aged 50–79, increasing the number of patients requiring therapy by more than 50%.

Conclusions:

1. The FRAX calculator does not always consider the history of low-energy fractures as a criterion sufficient for therapy implementation.
2. Designing a FRAX calculator specifically for the Polish population would be advisable.

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Key words: *osteoporosis treatment, FRAX calculator, intervention thersholds*

Streszczenie

Wstęp: Prognozy epidemiologiczne dotyczące rozprzestrzenienia osteoporozy pomenopauzalnej na świecie są niepokojące. W związku z tym konsekwencje złamań niskoenergetycznych będą stanowiły coraz większy problem zdrowotny społeczeństw. Konieczne staje się zatem wdrożenie postępowań, które będą skuteczniej przewidywały występowanie osteoporozy pomenopauzalnej i powikłań choroby.

Materiał i metody: Występowanie klinicznych czynników złamania oceniano w grupie 378 pacjentek w wieku 40–86 lat. Dodatkowo u wszystkich kobiet przeprowadzono badanie densytometryczne bliższego końca kości udowej. W celu obliczenia 10-letniego ryzyka złamania posłużono się modelem brytyjskim kalkulatora FRAX.

Wyniki: W niniejszej pracy grupę badaną podzielono na dwie części w zależności od wywiadu dotyczącego wystąpienia niskoenergetycznego złamania. U 128 pacjentek stwierdzono w przeszłości złamanie osteoporotyczne. W tej grupie średnie wartości gęstości mineralnej kości (BMD, *bone mineral density*) (0,717 g/cm^2) były niższe niż w grupie bez złamań (0,735 g/cm^2).

W grupie między 50.–59. rokiem życia, która ze względu na stan kliniczny (wcześniejsze złamanie) wymagała leczenia, wartość FRAX w 33,3%, a między 60.–79. rokiem życia w 17%, nie spełniała kryterium włączenia farmakoterapii. Uwzględniając FRAX BMD w grupie między 60.–79. rokiem życia, stwierdzono jeszcze większe niedoszacowanie ryzyka złamań, sięgające 25%.

Wśród kobiet między 40.–49. rokiem życia, bez złamań, 25% kwalifikowała się do farmakoterapii osteoporozy pomenopauzalnej. W tej kategorii wiekowej dodanie informacji BMD nie wpływało na wysokość FRAX-10. Badanie BMD miało większą wartość dyskryminacyjną wśród chorych między 50.–79. rokiem życia, zwiększając liczbę włączonych według wskazań do terapii farmakologicznej nawet o ponad 50%.

Wnioski:

1. Kalkulator FRAX nie zawsze uwzględnia wcześniejsze złamanie niskoenergetyczne jako wystarczające kryterium do wdrożenia terapii.
2. Wskazane jest opracowanie kalkulatora FRAX dla polskiej populacji.

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Słowa kluczowe: *terapia osteoporozy, kalkulator FRAX, progi interwencyjne*

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Introduction

Osteoporosis is a medical condition characterised by bone strength reduction and, in consequence, by an increased fracture risk, most often affecting women of post-menopausal age. In men, osteoporosis (OP) is diagnosed mainly in the elderly or may be associated with the prevalence of other diseases disturbing bone tissue metabolism. The available epidemiological data is rather confusing. The life risk for any osteoporotic fracture in women after 50 amounts to 40% [1]. The life risk of femoral neck fracture in women is higher than the total risk for breast, endometrial and ovarian neoplasms [2]. In Europe during the year 2000, 3.79 million low-energy fractures were recorded [3].

Epidemiological data concerning the Polish population may be affected by possible defects in the precise reporting of patient diagnoses to the National Health Fund. The available data shows 17,625 hip fractures in Poland [4]. The rapid progress in medical care has contributed to a significant extension of the average lifespan in developed countries. On the other hand, progress often has unfavourable effects on our lifestyle, including poor dietary habits (with calcium and vitamin D_3 deficiencies), low physical activity and the widespread use of various stimulants. Such trends will contribute to a growing incidence of osteoporosis, unless a more effective screening apparatus is implemented to precisely identify the subjects at risk who will then immediately receive appropriate prophylactic-therapeutic treatment.

In past diagnosis of the disease, BMD was the main parameter of evaluation. The densitometric criteria, as arbitrarily defined by the WHO, identified osteoporosis at a T-score ≤ 2.5 SD, obtained in DPX examination of the femoral neck and/or of the L1-L4 lumbar spine [5]. Recent epidemiological studies have proven, however, that many episodes of low-energy fractures are recorded in patients who, by the above-mentioned WHO criteria, did not qualify for a diagnosis of osteoporosis, which, in consequence, deprived them of appropriate pharmacological therapy. It has now been confirmed that low BMD is an important, but not the **only**, fracture-predisposing factor [6].

Twelve studies, involving a group of approximately 60,000 women, have provided evidence for the effects of other factors on fracture risk [7]. Therefore, osteoporosis diagnosis cannot be derived from BMD measurements alone, but should also take into account history data. The already known clinical risk factors of osteoporotic fractures, treated as reference for the history, obtained from patients, allow the identification of a group of patients predisposed to the disease.

Table I. *Clinical risk factors of low-energy fractures*
Tabela I. *Kliniczne czynniki ryzyka złamań osteoporotycznych*

Clinical risk factors
Low-energy fracture in past
Femoral fracture in parents
Current tobacco smoking
Intake of glucocorticosteroids
Rheumatoid arthritis
BMI (body mass index) < 19
Excess alcohol intake

While performing a subjective study, data should be collected concerning the history of falls during the last 12 months, concomitant diseases and medications, which may predispose to an elevated incidence of fractures. See Table I for the clinical risk factors of osteoporotic fractures.

The risk of low-energy fractures, including those of the femoral neck, increases with age. A low-energy fracture episode may be prognosed in 30–50% of women and 15–30% of men. [8–10]. These numbers transpose into increased mortality rates, especially in patients over 70. Within 12 months of suffering a fracture, 20–45% of patients die of fracture-related complications, while impaired physical ability and considerably diminished life quality are even more frequently observed [11–13]. The decision to start therapy of osteoporosis is made by a doctor on the basis of calculated, individual, 10-year risk assessment for low-energy fracture.

In 2008, a team from Sheffield in the UK designed the FRAX calculator, a diagnostic screening tool for fracture risk calculation. It is an easy means of quick risk evaluation and supports individual therapeutic decisions [14, 15]. The therapeutic threshold is defined with regards to the current epidemiological situation and the financial position of the given state. Other available osteoporotic fracture risk calculators can also be used in therapeutic decision making, including OSC Recommendations for Bone Mineral Density Reporting or QFracture Scores [16]. The goal of performed diagnostics in a patient with osteoporosis is to determine an individual 10-year fracture risk, followed by a therapeutic programme, based on accepted therapeutic thresholds.

Because of the difficulties of defining the levels for these thresholds in the Polish population, we accepted age-related therapeutic thresholds, following the algorithm of Kanis et al. [14].

Our study aimed at evaluating the FRAX calculator, regarding its usefulness in qualifying Polish female patients for osteoporosis treatment.

Material and methods

The study group involved 378 female patients of the Endocrinological Outpatient Clinic at the Clinical Hospital in Poznan. Their ages ranged from 40 to 86 years (mean age: 67.4). In all patients, densitometry (by Lunar DPX-L, in which error repeatibility equals max. 1.5%) at the femoral neck was performed. Additionally, following a medical history, including clinical risk factors of osteoporotic fractures, calculation of 10-year risk of fracture was carried out, using the calculator which is available at http://www.sheffield.ac.uk/FRAX (in the version designed for the British population).

The calculations were performed twice. The first series considered the clinical risk factors only (FRAX). The second, verifying, series of calculations additionally accounted for BMD obtained from densitometric examination (FRAX BMD). In the analysis, the major FRAX was used, evaluating the risk level of main osteoporotic fractures (vertebral, antebrachial, femoral and humeral). The study group was divided into five age categories, with 10-year intervals, starting from the age of 40. The thresholds for therapeutic intervention were determined from literature data, as per the study by Kanis et al. [7]. Our research was performed between 2006 and 2009.

Results

The prevalence of recognised clinical risk factors for osteoporotic fractures was evaluated in the studied group of patients. Previous low-energy fractures were recorded in 128 (33.8%) women. An additional family history of hip fracture was obtained in 97 patients (25.7%). See Table II for the prevalence of particular clinical fracture risk factors in the studied group.

Results of densitometry

In the studied group, BMD values from 0.537 g/cm^2 to 0.998 g/cm^2 (mean value: 0.741 g/cm^2) were obtained. In the patients with a history of low-energy fracture, BMD varied from 0.537 g/cm^2 to 0.960 g/cm^2 (mean value: 0.717 g/cm^2 ± 0.1 SD).

BMD in the women without osteoporotic fracture in their history varied from 0.552 g/cm^2 to 0.998 g/cm^2 (mean value: 0.735 g/cm^2 ± 0.12 SD).

Fracture risk evaluation

The analyses were performed separately in groups of patients with and without a history of osteoporotic fracture. Having completed FRAX and FRAX BMD calculations, it was found that the 10-year fracture risk for the patients without a fracture history varied from 6.5% to 54% without BMD consideration, and from 4.5% to 60% for FRAX BMD. See Tables III and IV for the mean values of BMD, T-score and FRAX, with and without BMD in particular age categories.

Table II. *Distribution of low-energy fracture risk factors in the group of 378 women*

Tabela II. *Rozkład czynników ryzyka złamania niskoenergetycznego w grupie 378 chorych*

Risk factor	n	%
Low-energy fracture in patient's history	128	33.8
Parental history of hip fracture	97	25.7
Current tobacco smoking	48	12.7
BMI < 19	5	1.3
Rheumatoid arthritis	0	0
Glucocorticosteroid therapy	0	0

Comparisons of BMD, FRAX and FRAX BMD values between groups with and without fractures in their medical history are presented in Figures 1, 2, and 3.

Analysis of therapeutic intervention thresholds

Based on the approved therapeutic decision thresholds, we evaluated how many patients in particular age groups qualified for pharmacotherapy administration. See Tables IV and V for the number of patients with a 10-year probability of fracture exceeding the accepted therapeutic thresholds.

Additionally, for the patients without low-energy fractures in their past history, FRAX and FRAX BMD values were compared, depending on the applied calculator, for the French or the British population, being then referred to the therapeutic thresholds accepted in the reported study (Table VI). We assessed the percentage of women who should have been submitted to anti-osteoporotic therapy, based on the accepted calculator model.

Results from an earlier study at Department of Family Medicine at Medical University in Poznan, were used, introducing the FRAX algorithm, normalised for the Polish population [17].

The highest differences were noted in women aged 60–69, in whom the fracture risk, calculated without BMD consideration, acc. to the French and the British calculators, was 0% and 11.7%, respectively. The FRAX BMD value, acc. to the French model, was 3.3% as against 19.5% obtained from the British calculator (the therapy--demanding group larger by 16.2%). See Table VII for obtained results.

Discussion

Identifying a group of patients who will certainly achieve individual therapy-related health improvement, is a key problem in the decision about pharma-

Table III. *BMD, FRAX and FRAX BMD values in patients without fracture history (n = 250)*
Tabela III. *Wartości BMD, FRAX, FRAX BMD u pacjentek bez złamań (n = 250)*

Age category	n	BMD ± SD	T-score ± SD	FRAX major (%)	FRAX major BMD (%)
40–49	11	0.87 ± 0.1	–0.88 ± 0.77	3 (2.4–3.5)	3.4 (2.5–5.4)
50–59	54	0.82 ± 0.13	–0.72 ± 1.1	5.7 (3.5–14)	7.2 (3.3–19)
60–69	77	0.77 ± 0.11	–1.7 ± 0.9	9.2 (4–20)	11 (3.1–25)
70–79	89	0.72 ± 0.1	–2.2 ± 0.8	15.5 (9.2–35)	17.2 (7.9–49)
> 80	19	0.73 ± 0.1	–1.9 ± 1.4	18.7 (13–32)	16.6 (8.1–38)

Table IV. *BMD, FRAX and FRAX BMD in patients with fracture history (n = 128)*
Tabela IV. *Wartości BMD, FRAX, FRAX BMD u pacjentek ze złamaniami (n = 128)*

Age category	n	BMD ± SD	T-score ± SD	FRAX major (%)	FRAX major BMD (%)
40–49	3	0.94 ± 0.2	–0.9 ± 1.9	8.4 (6.4–15)	8.8 (4.5–11)
50–59	12	0.77 ± 0.1	–1.4 ± 1.6	13.1 (8.7–23)	15.3 (7.7–30)
60–69	34	0.74 ± 0.09	–2.1 ± 0.8	20 (11–33)	21.5 (9.4–38)
70–79	68	0.69 ± 0.09	–2.3 ± 0.8	26.1 (7–46)	27.7 (13–69)
> 80	11	0.68 ± 0.04	–2.5 ± 0.3	34.7 (24–54)	28.9 (21–44)

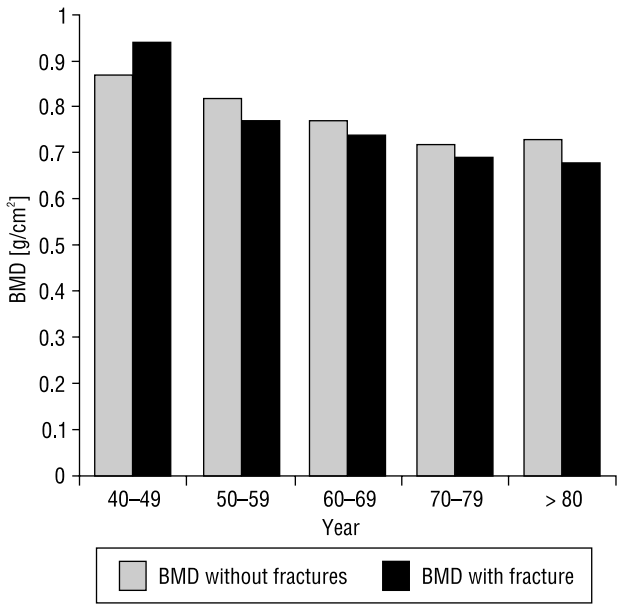

Figure 1. *Comparison of BMD values in group with and without fractures according to age category*
Rycina 1. *Porównanie wartości BMD w grupie z i bez złamań w zależności od kategorii wiekowej*

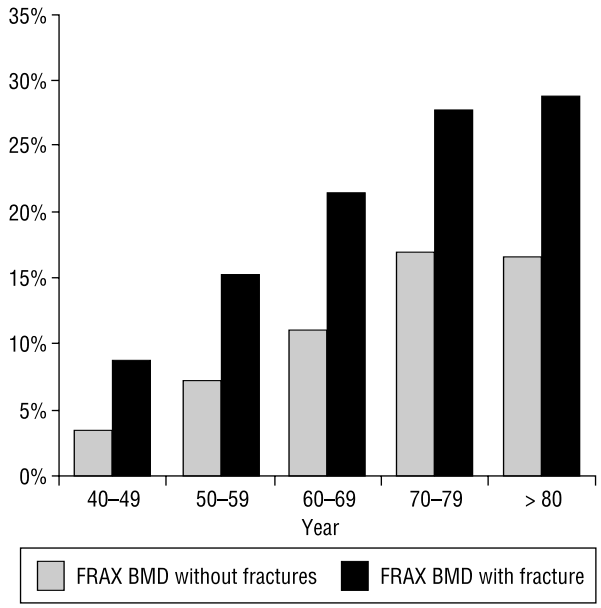

Figure 2. *Comparison of FRAX BMD values in group with and without fractures according to age category*
Figure 2. *Porównanie wartości FRAX BMD w grupie z i bez złamań w zależności od kategorii wiekowej*

cological therapy of osteoporosis, because incurred expenses will then gain social acceptance. It is assumed that an evaluation of the absolute fracture risk in 10-year perspective is, for the time being, an optimal solution.

The cost-effectiveness of osteoporosis therapy has been confirmed for the British population with 10-year fracture risk over 7.5% in 50 year-old women. In subsequent age intervals, the threshold determined for pharmacotherapy onset is gradually getting higher, reaching 30% in the oldest age group.

The acceptance of particular therapeutic thresholds was proposed, following studies of osteoporosis thera-

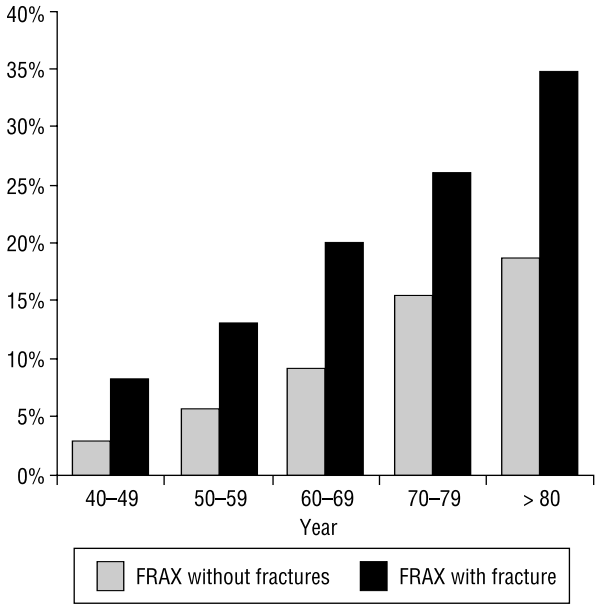

Figure 3. *Comparison of FRAX values in group with and without fractures according to age category*

Figure 3. *Porównanie wartości FRAX w grupie z i bez złamań w zależności od kategorii wiekowej*

py cost-effectiveness, taking into account the funds for osteoporosis treatment vs. the state budget outlays for the treatment of osteoporotic fractures [18]. In those calculations, indirect costs were also accounted for, i.e. those costs associated with periods of absence from work, long-term rehabilitation or the necessity to be covered by disability pension programmes or to receive sickness benefits [19, 20].

In the UK, the prevalence of hip fracture is 372/ /100,000 subjects vs. the average number of 224/100,000 subjects for the Polish population [21, 22]. A particular model of the FRAX calculator, designed for the population of a given country, is based on the epidemiological data, concerning the incidence of proximal femur and extravertebral fractures. However, no Polish version has thus far been created, one of the obstacles being divergent epidemiological data concerning the hip fracture incidence in Poland. Depending on a given region of the country, the researcher and the accepted method of calculations, the figures vary from 165/100,000 to 283/100,000 [10, 19, 20]. At present, the British model of the calculator is recommended to be used for Polish patients.

Low-energy fracture is a recognised risk factor for the occurrence of subsequent fractures. The FRAX calculator is not an ideal tool, partly because one of the FRAX-determining factors is the information on previous osteoporotic fracture(s); although, as a rule, all those patients should already have been treated, thus questioning the sense of FRAX calculation at the time of the reported study.

Table V. *Patients without fractures (n = 250) who met the FRAX- and FRAX BMD-related criteria for starting therapy*

Tabela V. *Liczba pacjentek bez złamań (n = 250) spełniających warunki włączenia terapii przeciwosteoporotycznej na podstawie FRAX i FRAX BMD*

Age category	Therapeutic threshold (%)	Patients in a given age group	Patients above FRAX-related threshold	Patients above FRAX BMD--related threshold
40–49	5	11	3 (27.3%)	3 (27.3%)
50–59	10	54	5 (9.3%)	10 (18.6%)
60–69	15	77	9 (11.7%)	15 (19.5%)
70–79	20	89	17 (19.1%)	25 (28%)
> 80	30	19	1 (5.3%)	1 (5.3%)

Table VI. *Patients with fractures (n=128), who met the FRAX- and FRAX BMD-related criteria for starting therapy*

Tabela VI. *Liczba pacjentek ze złamaniami (n= 128) spełniających warunki włączenia terapii przeciwosteoporotycznej na podstawie FRAX i FRAX BMD*

Age category	Therapeutic threshold (%)	Patients in a given age group	Patients above FRAX--related threshold	Patients above FRAX BMD--related threshold
40–49	5	3	3 (100%)	2 (66.7%)
50–59	10	12	8 (66.7%)	8(66.7%)
60–69	15	34	28 (82.4%)	26 (76%)
70–79	20	68	56 (83.6%)	50 (74.6%)
> 80	30	11	5 (45.4%)	4 (36.4%)

Table VII. *Percentage of patients qualifying for therapy by obtained results, regarding earlier analyses for the Polish population, following the French and the British FRAX model*

Tabela VII. *Porównanie odsetka pacjentów kwalifikujących się do leczenia na podstawie uzyskanych wyników z wcześniejszymi analizami dla populacji polskiej według modelu francuskiego i brytyjskiego*

	FRAX		FRAX BMD	
	France	UK	France	UK
50–59	0%	9.3%	6.3%	18.6%
60–69	0%	11.7%	3.3%	19.5%
70–79	9%	19.1%	17%	28%
> 80	23%	5.3%	23%	5.3%

FRAX — calculations based on clinical risk factors; FRAX BMD — calculations with an additional consideration of DPX

The study group was divided according to fracture history. The highest incidence of osteoporotic fractures in the studied group (46.6%) was noted in the age group of 70–79, while the lowest (18.2%) was observed in the group with subjects between the 50th and the 59th years of life. Loss of height over 4cm was not, however, considered in those analyses. While it is true that, usually, this is evidence of other, clinically silent fractures of vertebral bodies, it is striking how height loss often passes totally unnoticed, either by the patients themselves or their physicians. At the root of this peculiar lack of perception is the relatively high number of undiagnosed compressive vertebral fractures. Since loss of height was in the reported study only communicated by the patients, the parameter was not taken into account, fearing the lack of precise data in the calculations.

In order to check the FRAX calculator sensitivity, fracture risk levels were also calculated for the patients in whom therapy had already been continued due to low-energy fracture in the past. Interestingly, having completed the calculations for those patients, the 10-year fracture risk was either not the same in all of them or exceeded the already established therapeutic thresholds. In the group aged 50–59, having completed FRAX and FRAX BMD calculations, as many as one in three of the women did not meet the pharmacotherapy starting criterion. It is important to note that the women were usually very active at the time of the reported study, thus any experienced fracture could have significantly decreased their quality of life, while on the other hand, if FRAX calculations had rigidly been followed, those women would have been deprived of any therapy. In the group of patients between the 60th and the 79th year of life, the FRAX index eliminated 17% of those patients from therapy. Having taken into account additional BMD measurements, even higher underestimation was confirmed. Following FRAX BMD results, the therapy starting criterion was not met in approximately one quarter of the patients, despite its clinical necessity.

Even higher divergencies were observed in women aged > 80, but the rather small number of patients in that age group makes it unsafe to draw conclusions.

Regarding patients aged 40–49 with no history of fractures, the results of FRAX calculations qualified only 25% of those patients for therapy. Neither did FRAX BMD change in any way the obtained values of the 10-year risk of fracture. Hip BMD measurements were more significant in the patients between the 50th and the 79th year of life, substantially increasing the number of patients to be treated (in the age group of 50-59 years, the number of those patients grew by 100% and, in the group aged60–70 by 50%). In patients over 80 years, for whom the therapeutic threshold was set at > 30%, densitometry examination had no effect on the therapeutic decision. It seems then that, with older patients, DPX influences fracture risk evaluation less than with younger patients and that the obtained results are in line with earlier observations [18].

Due to the different, population-related incidence of hip fractures in the UK population vs. the Polish population, FRAX calculations, performed in earlier studies of the team of authors, were based on the French pattern. This selection was dictated by the incidence of fractures in France, the closest to the Polish data published at that time [19]. Comparing the percentages of therapy-qualifying patients in the results of the French and the British calculator, considerable differences were demonstrated for each age catergory. Using the FRAX calculator for the French population, the number of patients qualified for treatment was distinctly lower. The biggest differences concerned women aged 50–69, in whom the fracture risk was evaluated on the basis of clinical data, as well as BMD values. In turn, FRAX, calculated according to the French model for patients aged 60–69 and with no history of fractures, was 0% vs. 11.7% for the British model. Having added the results of proximal femoral bone densitometry, the divergence of results was even higher, amounting to 3.3% vs. 19.5%, respectively.

By contrast, in the group of patients aged > 80, calculations in the British version demonstrated lower percentage values of the patients qualifying for therapy vs. those in the French version (5.3% vs. 23%); but, as has already been mentioned, the small number of patients in the group does not allow the drawing of any conclusions.

Taking into account the differences in the published data concerning the incidence of fractures in Poland, any application of a calculator designed for another

population bears a risk of error. This suggests the need to precisely determine the number of hip fractures for the entire population of Poland, and then use the results to design a calculation tool specifically for the Polish data. Otherwise, any intervention, based on fracture risk calculation with a FRAX calculator in a version designed for other populations, could be biased and, in consequence, affect patients with compromised results of applied therapy.

Conclusions

1. FRAX calculator does not always account for previous low-energy fracture as a therapy starting criterion.
2. The use of the British FRAX model increased the number of patients qualifying for osteoporosis pharmacotherapy compared to the French FRAX model.
3. It is necessary to design a Polish version of the FRAX calculator.

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