ORIGINAL ARTICLE

FRAX-based intervention and assessment thresholds for osteoporosis in Iran

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Abstract

Summary We compared the utility of the current Iranian guidelines that recommend treatment in women with a T-score ≤ -2.5 SD with a FRAX-based intervention threshold equivalent to women of average BMI with a prior fragility fracture. Whereas the FRAX-based intervention threshold identified women at high fracture probability, the T-score threshold was less sensitive, and the associated fracture risk decreased markedly with age.

Introduction The fracture risk assessment algorithm FRAX® has been recently calibrated for Iran, but guidance is needed on how to apply fracture probabilities to clinical practice.

Methods The age-specific ten-year probabilities of a major osteoporotic fracture were calculated in women with average BMI to determine fracture probabilities at two potential intervention thresholds. The first comprised the age-specific fracture probabilities associated with a femoral neck T-score of -2.5 SD, in line with current guidelines in Iran. The second approach determined age-specific fracture probabilities that were equivalent to a woman with a prior fragility fracture, without BMD. The parsimonious use of BMD was additionally explored by the computation of upper and lower assessment thresholds for BMD testing.

Results When a BMD T-score ≤ -2.5 SD was used as an intervention threshold, FRAX probabilities in women aged 50 years was approximately two-fold higher than in women of the same age but with an average BMD and no risk factors. The relative increase in risk associated with the BMD threshold decreased progressively with age such that, at the age of 80 years or more, a T-score of -2.5 SD was actually protective. The 10-year probability of a major osteoporotic fracture by age, equivalent to women with a previous fracture rose with age from 4.9% at the age of 50 years to 17%, at the age of 80 years, and identified women at increased risk at all ages.

Conclusion Intervention thresholds based on BMD alone do not effectively target women at high fracture risk, particularly in the elderly. In contrast, intervention thresholds based on fracture probabilities equivalent to a "fracture threshold" target women at high fracture risk.

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Introduction

Bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) is the current reference standard for the diagnosis of osteoporosis. A femoral neck BMD that lies 2.5 standard deviations (SD) or more below the average value for young healthy women (a T-score of < − 2.5 SD) was proposed by the World Health Organization (WHO) as an operational definition of osteoporosis [1–3]. The operational definition was established primarily for descriptive epidemiology. However, since BMD is one of the strongest predictors of fracture risk [4, 5], many agencies worldwide adopted BMD-based criteria for reimbursement and as intervention thresholds. One of the currently accepted criteria for treatment of osteoporosis in Iran is a BMD T-score ≤ − 2.5 SD, which is also the reimbursement threshold for medical intervention [6].

Although low BMD is a strong risk factor for fracture, many studies have shown that half or more of all patients presenting with a fragility fracture have BMD T-scores at the lumbar spine or the hip greater than − 2.5 SD, i.e., are not osteoporotic (WHO 1994). Thus, the current policy can only capture a minority of the population at high risk of fracture. The policy is also problematic in that it assumes that all prospective patients should have a BMD test and the availability of BMD equipment is limited. In a recent survey, there were less than 2 DXA machines per million of the general Iranian population [7], whereas 11 or more is considered appropriate to service the needs of a case-finding strategy [8]. This is while national studies show that about 41% of Iranians suffer from some degrees of bone loss and osteoporotic fractures are experienced in 359.1 cases in every 10,000 person years, which indicates the immediate need for identifying individuals at risk of osteoporosis and its complications [9, 10].

The advent of FRAX® provided a means of assessing fracture probability that is not wholly dependent on BMD. FRAX is a computer-based algorithm (http://www.shef.ac.uk/FRAX) developed by the World Health Organization Collaborating Centre for Metabolic Bone Diseases. The algorithm, intended for primary care, calculates fracture probability from easily obtained clinical risk factors (CRFs) in men and women [11, 12]. The output of FRAX is the 10-year probability of a major fracture (hip, clinical spine, humerus, or wrist fracture) and the 10-year probability of hip fracture. A FRAX model for Iran calibrated to the Iranian population was released in 2016.

FRAX is now incorporated into many clinical guidelines but the manner in which FRAX is used to identify cases for treatment varies widely [13]. Many recent guidance documents have recommended the use of intervention thresholds that are based on age-specific fracture probabilities equivalent to a woman with a prior fragility fracture [13]. The aim of the present analysis was to explore FRAX-based intervention thresholds that might be used to identify Iranian women at high fracture risk.

Methods

Intervention thresholds

In Iran, the current threshold for treatments is based on BMD measurements using DXA with a threshold for reimbursement set at a T-score of − 2.5 SD. The Iranian FRAX model was used to calculate the ten-year probabilities of a major osteoporotic fracture by age (in 5-year increments from the age of 40 to 90 years) in women at the threshold of osteoporosis (T-score = − 2.5 SD). The T-score was based on the NHANES III as a reference for BMD at the femoral neck in Caucasian women aged 20–29 years [14]. Women were assumed to have no other clinical risk factors that might contribute to fracture probability. The calculation of fracture probability was made at a body mass index (BMI) of 24 kg/m². Changes in BMI have little effect on predictive value for fracture risk assessment in the presence of BMD [15].

Since treatment is commonly recommended in women with a previous fragility fracture, a second intervention threshold was calculated over the same age increments in women with a prior fracture but no other clinical risk factors using the Iranian-specific FRAX tool, without BMD and a BMI set at 24 kg/m².

Assessment thresholds for BMD testing

The inclusion of BMD in the calculation of probability improves the accuracy of the assessment [16], but the value of BMD in a clinical context is greatest in individuals in whom fracture probabilities lie close to an intervention threshold [12, 17, 18]. In other words, testing is confined to those in whom there is a reasonable likelihood that individuals at high (or low) risk would be reclassified at low (or high) risk, respectively, on the basis of the BMD test. On this basis, we calculated two assessment thresholds, which were applied to the second intervention threshold described above:

> The threshold probability below which neither treatment nor a BMD test should be considered (lower assessment threshold).
> The threshold probability above which treatment may be recommended without the need for BMD (upper assessment threshold).

The lower assessment threshold was based on the 10-year probability of a major osteoporosis fracture equivalent to women without clinical risk factors (and a body mass index

of 24 kg/m^2 and without BMD). This is consistent with a view in most practice guidelines that individuals without clinical risk factors should not be considered eligible for assessment [19].

The upper assessment threshold was set to optimize the limited access to BMD testing in Iran. As noted above, the risk of changing category from high risk to low risk or vice versa when adding BMD to the estimation of fracture probability is highest close to the threshold. When patients have a fracture probability, that is 20% or more than the intervention threshold, almost no individuals are reclassified when probabilities are recomputed with the addition of BMD to FRAX [17]. For this reason, the upper assessment threshold was set at 1.2 times the intervention threshold.

Results

In women with no clinical risk factors, fracture probability rose with age from 2.2% at the age of 50 years to 10% at the age of 85 years (Fig. 1). At the age of 90 years, the fracture probability was lower than that at age 85 years because of the competing effect of mortality on the fracture hazard.

T-score threshold

In women aged 50 years at the threshold of osteoporosis (a BMD T-score of − 2.5 SD), fracture probability was approximately twofold higher than that in women of the same age but with an average BMD and no risk factors. The 10-year fracture probability rose progressively with age from 4.3% at the age of 50 years to 9.8% at the age of 80 years (see Fig. 1). Thereafter, fracture probability decreased with age and, at the age of 90 years, was comparable to the risk at 60 years. Indeed, at the age of 90 years, the fracture probability for women with a T-score of − 2.5 was lower than in women of the same age but with no risk factors (6.1 vs. 8.6%, respectively), an effect that commenced at the age of 77 years.

Prior fracture threshold

The fracture probabilities equivalent to women with a previous fragility fracture are shown in Fig. 1. The probability rose with age, from 4.9% at the age of 50 years to 17% at the age of 80 years and decreased thereafter. Fracture probabilities using this threshold were consistently higher than in women with no clinical risk factors.

BMD assessment thresholds

The lower assessment threshold, below which BMD tests are of limited value, is shown in Table 1, representing the age-specific probabilities in women with no clinical risk factors.
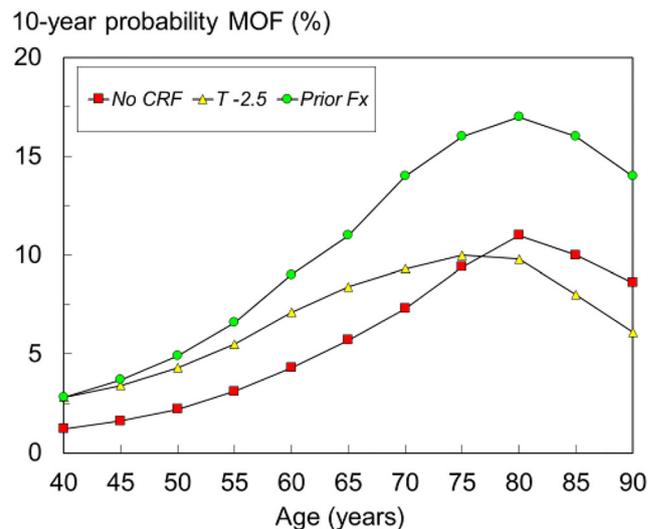

Fig. 1 10-year probabilities of a major osteoporotic fracture (MOF; hip, clinical spine, humerus, and forearm) calculated with the Iranian FRAX model for women

The upper assessment was set at 1.2 times the intervention threshold. The intervention threshold together with the two assessment thresholds is shown in Table 1.

Discussion

In this study, we have examined two scenarios for the assessment and treatment of women at high fracture risk based on the Iranian FRAX tool. The first examined the current Iranian guidelines—namely that intervention and reimbursement can be recommended with a BMD T-score of − 2.5 SD or less. A fixed threshold based on the T-score of − 2.5 SD has the advantage of simplicity and universality, but it also has important limitations. The present study showed that fracture risk is approximately doubled in women age 40–50 years with a T-score of − 2.5 compared with women of the same age with no clinical risk factors (see Fig. 1 and Table 2) but, with advancing age, the difference is attenuated. Indeed, from the age of 80 years, a T-score of − 2.5 SD is protective, in the sense that the fracture probability is lower than that of the general population at that age. Thus, the BMD criterion for intervention using a fixed T-score became less and less appropriate with advancing age.

A similar phenomenon is reported in the use of FRAX models elsewhere [20–22]. The explanation is that the average T-score in the elderly is less than − 2.5 since the T-score of the general population decreases with age. Thus, at the age of 50 years, the relative risk (RR) of hip fracture in a woman at the threshold value for osteoporosis (T-score = − 2.5 SD) = 2.9. At the age of 75 years, the RR is < 1.0 [23]. Also, a low BMD is associated with increased mortality which decreases fracture probability. A further impediment to the use of BMD

Table 1 Ten-year fracture probabilities for a major osteoporotic fracture (%) in women by age at the intervention threshold and the upper and lower assessment thresholds

Age (years)	Lower assessment threshold	Intervention threshold	Upper assessment threshold
40	1.19	2.75	3.30
45	1.64	3.68	4.42
50	2.23	4.90	5.88
55	3.07	6.58	7.90
60	4.29	8.97	10.76
65	5.67	11.49	13.79
70	7.32	13.96	16.75
75	9.40	16.48	19.78
80	10.65	17.34	20.81
85	10.06	16.28	19.54
90	8.55	13.84	16.61

alone as an intervention threshold is that access to BMD testing is limited in Iran [7]. These considerations suggest that reimbursement criteria based on the T-score alone do not effectively target treatment.

Many practice guidelines recommend that women with a prior fragility fracture should be considered for treatment [13]. In Iran, as in the USA, this eligibility clause is confined to individuals with a recent fracture of hip or vertebra (clinical or morphometric). If women with a prior fragility fracture merit intervention, then women with a fracture probability that equals or exceeds that of women with a prior fracture should also be eligible for treatment.

In line with guidelines for the UK and Europe, we examined an intervention threshold based on the ten-year probability of a major osteoporotic fracture for a woman with a previous fracture. The intervention threshold is age-specific and ranged from 2.8% at the age of 40 years up to 17% at the age of 80 years. At all ages studied, a prior fracture was associated with a marked increase in fracture probability compared with women with no CRFs (see Fig. 1). This increase in risk over all relevant ages contrasts markedly with intervention thresholds based on BMD alone.

The use of intervention thresholds based on such a "fracture threshold" permits more women at high risk to be considered for treatment and avoids treatment in women at low risk, thereby targeting interventions more appropriately than intervention thresholds based on BMD alone. By way of an example, a woman aged 65 years from Iran whose mother had a hip fracture and has a T-score of − 2.0 SD has a fracture probability of 12% which exceeds the risk in a woman of the same age with a prior fracture and no other clinical risk factors (10%; BMI set at 25 kg/m^2). Thus, this woman would be eligible for treatment even in the absence of a fracture history and a BMD test. Conversely, a woman aged 80 years with a T-score of − 2.5 SD has a fracture probability (10%) that is well below the intervention threshold for that age (17%). She would not be eligible for treatment despite the presence of densitometric osteoporosis.

Although the use of BMD tests poses some problems as a gateway to intervention, the categorization of patients at high or low risk is improved by the use of BMD. For this reason, the present study provided assessment thresholds for the use of BMD tests. Assessment thresholds for the measurement of

Table 2 10-year probabilities of a major osteoporotic fracture (hip, clinical spine, humerus and forearm) calculated with the Iranian FRAX model for women

	Age (years)										
	40	45	50	55	60	65	70	75	80	85	90
Major fracture											
No clinical risk factors	1.2	1.6	2.2	3.1	4.3	5.7	7.3	9.4	11	10	8.6
BMD T-Score − 2.5 SD[a]	2.8	3.4	4.3	5.5	7.1	8.4	9.3	10	9.8	8.0	6.1
Previous fracture[a]	2.8	3.7	4.9	6.6	9.0	11	14	16	17	16	14
				Ratios between probabilities							
No CRF, T-score − 2.5 vs. no BMD	2.3	2.1	2.0	1.8	1.7	1.5	1.3	1.1	0.9	0.8	0.7
Previous fracture vs. no CRF	2.3	2.3	2.2	2.1	2.1	1.9	1.9	1.7	1.5	1.6	1.6

[a] No other clinical risk factors

BMD followed a current practice where individuals were considered to be eligible for assessment in the presence of one or more CRF. An upper assessment threshold (i.e., a fracture probability above which patients could be treated without recourse to BMD) was based on optimization of the positive predictive value of the assessment tool [24].

The concept of assessment thresholds can be illustrated in terms of a management pathway. The management process begins with the assessment of fracture probability and the categorization of fracture risk on the basis of age, sex, BMI, and clinical risk factors. On this information alone, some patients at high risk may be offered treatment without recourse to BMD testing. For example, as noted above, most guidelines in Europe and North America recommend treatment in the absence of BMD in women with a previous fragility fracture. Many would perform a BMD test, but frequently this is for reasons other than to decide on intervention (e.g., as a baseline for monitoring treatment). There will be other instances where the probability will be so low that a decision not to treat can be made without BMD. An example might be the well woman at menopause with no clinical risk factors. Thus, not all individuals require a BMD test.

The use of assessment thresholds in the context of the Iranian population is illustrated in the management algorithm outlined below in conjunction with Fig. 2.

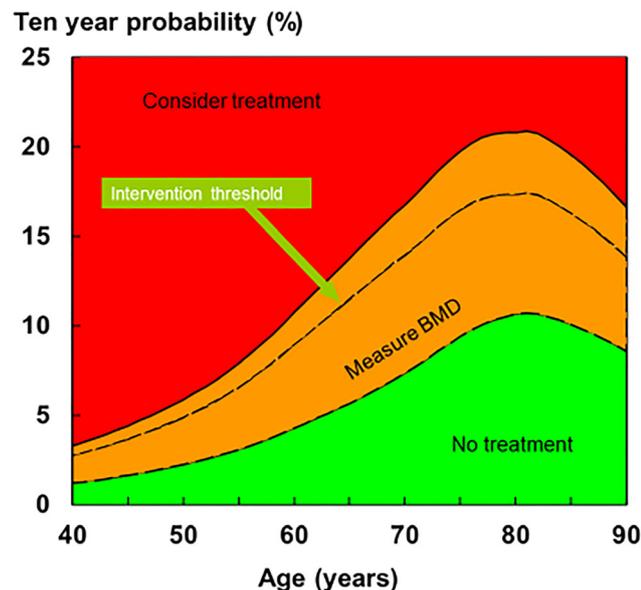1. Women with a prior fragility fracture should be considered for treatment.

Fig. 2 Intervention thresholds for Iran as set by FRAX-based 10-year probabilities (%) of a major osteoporotic fracture. The red area is where treatment could be recommended, the green area is where treatment would not be recommended, and the orange area is where BMD could be measured (where available) to enhance the estimation of fracture risk. The dashed line designates the intervention threshold

2. Postmenopausal women with a clinical risk factor should have fracture probability assessed using the FRAX tool without measurement of BMD.
3. Individuals with probabilities of a major osteoporotic fracture below the lower assessment threshold given in Fig. 2 can be reassured. A further assessment may be recommended in 5 years or less depending on the clinical context.
4. Women with probabilities of a major osteoporotic fracture above the upper assessment threshold or with probabilities of a hip fracture above the upper limit given in Fig. 2 can be considered for treatment without BMD testing.
5. Individuals with probabilities of a major osteoporotic fracture within the limits of the assessment thresholds given in Fig. 2 should have a BMD test and probabilities recomputed. If probabilities exceed the treatment threshold, intervention should be considered.

The intervention thresholds proposed above are not without limitations. The consequences of assessment and intervention thresholds on the requirements for BMD testing have not been explored in Iran. It will also be important to explore the cost-effectiveness of intervention and the budget impact of any changes in reimbursement policy. Despite these gaps, intervention strategies based on fracture probabilities are more effective than strategies reliant on the use of BMD alone in identifying high-risk individuals for treatment and avoiding intervention in those at low risk. An added advantage is that BMD testing is not a prerequisite for assessment or treatment. This feature would be particularly useful in some provinces of Iran with limited access to DXA. Moreover, the reimbursement for DXA is less than the cost of DXA, which imposes its own financial constraints on individuals.

In summary, there is almost universal agreement that individuals with a prior fragility fracture should be considered as candidates for osteoporosis-specific treatments, though the fractures that qualify for this criterion differ somewhat between countries. In individuals without a prior fracture (however defined), there is a case to be made for assessment of fracture risk in individuals with risk factors for osteoporosis. The use of BMD as a gateway to fracture risk assessment presents difficulties, particularly in the elderly in whom fracture risk is high. Some of these difficulties are overcome by the use of FRAX since the tool is designed for the assessment of fracture risk rather than for the detection of osteoporosis. Moreover, the tool is widely available at no or little cost and can be used with or without the inclusion of BMD. The intervention threshold explored in the present study was the age-specific fracture probability in women equivalent to those with a prior fracture but no other clinical risk factors using the Iranian-specific FRAX tool without BMD. The same approach,

first adopted in the UK [25], is now incorporated in many national and European guidelines [19].

Compliance with ethical standards

Conflicts of interest None.

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