Portuguese recommendations for the prevention, diagnosis and management of primary osteoporosis – 2018 update

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ABSTRACT

Background: Advances in osteoporosis (OP)case definition, treatment options, optimal therapy duration and pharmacoeconomic evidence in the national context motivated the Portuguese Society of Rheumatology (SPR) to update the Portuguese recommendations for the diagnosis and management of osteoporosis published in 2007.

Methods: SPR bone diseases' working group organized meetings involving 55 participants (rheumatologists, rheumatology fellows and one OP specialist nurse) to debate and develop the document. First, the working group selected 11 pertinent clinical questions for the diagnosis and management of osteoporosis in standard clinical practice. Then, each question was investigated through literature review and draft recommendations were built through consensus. When insufficient evidence was available, recommendations were based on experts' opinion and on good clinical practice. At two national meetings, the recommendations were discussed and updated. A draft of the recommendations full text was submitted to critical review among the working

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group and suggestions were incorporated. A final version was circulated among all Portuguese rheumatologists before publication and the level of agreement was anonymously assessed using an online survey.

Results: The 2018 SPR recommendations provide comprehensive guidance on osteoporosis prevention, diagnosis, fracture risk assessment, pharmacological treatment initiation, therapy options and duration of treatment, based on the best available evidence. They attained desirable agreement among Portuguese rheumatologists. As more evidence becomes available, periodic revisions will be performed.

Target audience and patient population: The target audience for these guidelines includes all clinicians. The target patient population includes adult Portuguese people.

Intended use: These recommendations provide general guidance for typical cases. They may not be appropriate in all situations - clinicians are encouraged to consider this information together with updated evidence and their best clinical judgment in individual cases.

Keywords: Portugal; Fragility fracture; Osteoporosis; Recommendations.

INTRODUCTION

Osteoporosis (OP) is characterized by reduced bone mass and micro-architectural deterioration which results in increased bone fragility and propensity to fracture[1]. With the progressive ageing of the population, OP has become one of the most common human diseases worldwide, and a major public health concern. Most individuals are at risk of suffering from OP during their lifetime[2]. Fragility fractures, the main consequence of OP, results in increased morbidity and mortality and represent a major and growing economic burden on health-care systems worldwide[3,4]. European health authorities estimated, in 2011, that 22 million women and 5.5 million men in the European Union had osteoporosis and that 3.5 million suffered new fragility fractures every year, comprising 610.000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures and 1,800,000 other fractures[5]. There is considerable international variability in fracture incidence rate, which has been attributed to age, socioeconomic status and other factors, frequently obscure, related to geography, as some regions have 3 times higher rates than apparently other similar ones[6,7].

In Portugal in 2011-2013, the prevalence of OP in people aged 18+, was estimated at 10.2% (17.0% in women and 2.6% in men)[8]. Altogether, 40,000 osteoporotic fractures are estimated to occur annually in Portugal[9], including over 10,000 hip fractures, the only type of fractures with truly reliable data in Portugal.[10] This number has been increasing steadily in Portugal (5,600 in 1989; 6,718 in 1994; 8,500 in 2000; 9,523 in 2006; 10,124 in 2011) and this is, most probably, accompanied by a proportional increase in other osteoporotic fractures (vertebral, forearm and humerus)[10-12]. Expanding life expectancy is the suggested underlying cause[13]. The incidence of hip fragility fractures in Portugal has been estimated at 154 to 572 per 100,000 women/year and 77 to 232 per 100,000 men[12], one of the lowest in Europe[13]. The social and economic burden imposed by osteoporotic fractures is enormous. The societal cost per each hip fracture in Portugal was estimated at 13,434 euros in the first and 5,985 euros in the second year, following fracture, totalling 216 million euros, taking the incidence and costs of the year 2011. Hip fractures are associated with an absolute excess mortality of 12% in the first year and a sharp drop in quality of life[14]. This individual, social and economic load is bound to increase exponentially over the years to come, unless effective preventive measures are put in place.

Over the last decade, several new therapeutic options that effectively decrease the risk of fracture have become available[15], and new evidence has been gathered regarding treatment duration[16]. The most relevant current clinical challenge consists in accurately identifying and selecting the individuals that will benefit the most from pharmacological treatment: ie, those whose high risk of fracture can be reduced, in order to minimize individual and societal costs. In fact, the need to base the decision to treat on the estimate of absolute fracture risk is now widely accepted[17,18]. Several countries have included validated tools for fracture risk assessment in their OP recommendations[19-24]. The knowledge-based necessary to allow the Portuguese adherence to these modern trends has dramatically increased over recent years: the Portuguese version of the Fracture Risk Assessment Tool (FRAX®) was established[12] and

fully validated to the Portuguese population[14,25]. Furthermore the cost of fractures was studied[14], the cost-effectiveness thresholds for intervention were calculated[26] and multidisciplinary recommendations for dual-energy x-ray absorptiometry (DXA) request and indication to treat and prevent fragility fractures were issued[27]. In light of this new knowledge, the SPR decided to update the 2007 recommendations for the treatment of OP[28], covering the diagnosis, prevention and management of osteoporosis in the adult population.

These recommendations may not be appropriate in all situations and we encourage clinicians to combine this information, with updated knowledge and their best clinical judgment in individual cases.

CORE BACKGROUND CONCEPTS

Some of the major conceptual changes observed in the field of OP in the last decade reside in: 1. The sedimentation of the notion that the sole aim of treating OP is to prevent fragility fractures; 2. The recognition that the risk of fractures is influenced by numerous clinical and environmental risk factors beyond bone mineral density[29-31]. The majority of these factors have been captured in risk prediction tools that are easily accessible and reliable for use in current practice, with emphasis on FRAX®, the most widely validated and adopted fracture risk prediction tool worldwide[32].

This has led to the distinction between two concepts: the diagnostic threshold and the intervention threshold. The diagnosis of OP remains unchanged, based on the threshold of bone mineral density (BMD) T score ≤-2,5, as established by World Health Organization (WHO)[1,33,34]. This, however, does not coincide with the intervention threshold, which should now be based on the absolute risk of fracture, as estimated by the composite consideration of its several determinants, i.e. by the use of fracture risk prediction tools[17,35].

METHODS

To develop these recommendations a working group of 55 participants including rheumatologists and rheumatology fellows and one OP specialized nurse was formed. First, the working group selected pertinent clinical questions for the diagnosis, prevention and management of osteoporosis in clinical practice. A thorough literature review was then performed to address each question. The electronic search was performed in PubMed MEDLINE (2006--2017). The search strategies included the following medical descriptors: “Osteoporosis”, “Fragility fractures”, “Risk assessment”, “Recommendations”, “Guidelines”, ”Treatment”, “Bone mineral density”, “DXA”, “Bone turnover markers” and “Biochemical markers of bone remodelling”. Guidelines and systematic literature reviews regarding the diagnosis and management of OP were also scrutinized and their reference lists were checked to assure completeness. After the literature review, the working group elaborated proposals for recommendations that were presented, discussed and revised in two national meetings, using the nominal group technique, and refined through electronic consultation.

A draft document presenting the proposed recommendations and their respective supporting evidence was circulated to the working group of Portuguese rheumatologists, rheumatology fellows and one OP specialized nurse and modifications of format and content were made. Finally, the document circulated among all Portuguese rheumatologists, rheumatology fellows and OP specialized nurse, who anonymously voted online on the level of agreement with each recommendation (total of 88 participants). Agreement was measured on a 10-point numerical rating scale (1=no agreement, 10=full agreement).

RESULTS

To Guide Readers, recommendations are structured around eleven clinically relevant questions:

- *Question 1. When should clinicians think of osteoporosis?*
- *Question 2. How shall clinicians assess the fracture risk of individual patients?*
- *Question 3. When and how should bone mineral density be measured?*
- *Question 4. When and how should secondary osteoporosis be suspected and investigated in adults?*
- *Question 5. Who should be pharmacologically treated for osteoporosis?*
- *Question 6. How should primary osteoporosis be treated?*
- *Question 7. How should osteoporosis in men and secondary osteoporosis be managed?*
- *Question 8. How should the efficacy of osteoporosis*

treatment be monitored?
- *Question 9. When should drug holiday and therapeutic switch be considered?*
- *Question 10. Which are the best strategies to prevent osteoporosis in the general population?*
- *Question 11. When should an osteoporotic patient be referred to a rheumatologist?*

Eleven recommendations were formulated, reaching a high level of agreement among Portuguese rheumatologists (Table I).

RECOMMENDATIONS

QUESTION 1. WHEN SHOULD CLINICIANS THINK OF OSTEOPOROSIS?

- **Recommendation 1a. Clinical risk factors for osteoporosis and fragility fractures should be identified and corrected, if possible, throughout life.**
- **Recommendation 1b. The risk of fracture should be regularly assessed and managed in all women and men over the age of 50.**
- **Recommendation 1c. The risk of fracture does not need to be assessed in people <50 years, unless relevant clinical risk factors are present.**

Although osteoporotic fractures typically occur over the age of 55 (wrist) or 75 (hip, humerus), the underlying OP has its roots, as back in life as, the early childhood. In fact, bone health throughout life can be decisively influenced by events affecting bone mass accrual during infancy and adolescence. Peak bone mass, achieved at 18-25 years of age is a major determinant of bone mineral density and bone fragility later in life. It is largely determined by genetic factors, and also by nutrition, physical activity, endocrine status, health status and medication[36]. The rate of bone mass loss that follows early adulthood and especially the menopause is also influenced by a variety of health and lifestyle dimensions. These clinical risk factors (CRF) have been shown to influence the risk of fracture, independent of the bone mineral density (BMD)[37].

Because OP progresses asymptomatically until a fragility fracture (low trauma fracture) occurs, all modifiable clinical risk factors for low bone mass peak, fast bone loss and fractures should be kept under clinical scrutiny, especially in those with a family history of OP.

The clinical risk factors for fracture include (but are not limited to):
- Age (>65 years)
- Female gender
- Low body mass index (<18.5Kg/m^2)
- Prior fragility fracture
- Parental history of hip fracture
- Long term use of oral glucocorticoids (>5mg of prednisolone per day or equivalent for longer than 3 months)
- Current smoking
- Alcohol intake >3 units/day
- Rheumatoid arthritis and other secondary causes of OP (*diabetes mellitus*, hypogonadism, anorexia nervosa, inflammatory bowel disease, calcium/vitamin D deficiency, hyperparathyroidism), prolonged immobilization and paralysis, medications (anticonvulsants, anticoagulants, proton pump inhibitor and antiretroviral therapy)[19,20,27,38]
- Frequent falls[20,39]

Clinical algorithms for fracture risk estimation, such as the FRAX®, integrate most or all these risk factors, with or without BMD, providing a very convenient and reliable tool to stratify individuals according to risk of fracture and, therefore, to the need of pharmacological intervention[40]. They have only been validated for people age 40+. The typically low fracture risk in generally healthy individuals before the age 50 justifies the age limit indicated in the recommendation for risk fracture assessment.

QUESTION 2. HOW SHALL CLINICIANS ASSESS THE FRACTURE RISK OF INDIVIDUAL PATIENTS?

- **Recommendation 2. Fracture risk assessment for Portuguese individuals should be preferentially based on the use of the FRAX® algorithm, as validated for the Portuguese population.**

A FRAX® algorithm has been established for the Portuguese population and internationally recognized by – FRAX®Port https://www.shef.ac.uk/FRAX/tool.jsp?lang=pt). A recent large-scale population-based study demonstrated that this tool has a high validity and predictive value regarding the subsequent occurrence of fragility fractures in the Portuguese population[25,26]. Evaluation of the clinical risk factors included in FRAX®, should strictly respect the definitions provided by the tool and available at its website[40]. This algorithm is validated for the general

TABLE I. AGREEMENT RATES OF 2017 OP RECOMMENDATION PORTUGUESE SOCIETY OF RHEUMATOLOGY AMONG RHEUMATOLOGISTS

Recommendation	Votes	Agreement Mean (SD) % score ≥ 8
Recommendation 1 1a. Clinical risk factors for osteoporosis and fragility fractures should be identified and corrected, if possible, throughout life 1b. The risk of fracture should be regularly assessed and managed in all women and men over the age of 50 1c. The risk of fracture does not need to be assessed in people <50 years, unless relevant clinical risk factors are present.	88	8.9 (1.3) 90%
Recommendation 2 Fracture risk assessment for Portuguese individuals should be preferentially based on the use of FRAX® algorithm, as validated for the Portuguese population.	88	8.4 (1.8) 75%
Recommendation 3 3a. Bone Mineral Density should be assessed, for clinical purposes, by dual X-ray absorptiometry (DXA) 3b. The decision to perform DXA should be primarily based on the risk of fracture as estimated by clinical risk factors, which can be provided by FRAX®Port. 3c. DXA is warranted in Portugal when FRAX®Port estimates, without DXA, are between 7% and 11% for major osteoporotic fracture AND between 2% AND 3% for hip fracture. 3d. DXA may be, otherwise, justified to evaluate patients with risk factors for osteoporosis not included in FRAX®, to study secondary osteoporosis (table 2) or to evaluate the efficacy of interventions.	88	8.6 (1,2) 85%
Recommendation 4 4a. Secondary Osteoporosis should be suspected in the presence of – conditions known to induce osteoporosis (Table 2) – fragility fractures occurring before the age of 70 for men or before menopause for women – low Z scores in DXA (≤-2.0) 4b. Suspected secondary osteoporosis justifies thorough clinical evaluation and appropriate hypothesis-driven investigations.	88	8.8 (1.7) 86%
Recommendation 5 Pharmacological treatment for osteoporosis should be initiated, unless contraindicated, in all subjects over the age of 50 who satisfy one or more of the following criteria: – ≥ 1 fragility fracture of the hip or ≥ 1 symptomatic vertebral fragility fracture. – ≥ 2 fragility fractures, independently of the site of fracture or the absence of symptoms (e.g. two asymptomatic vertebral fractures). – Estimates of FRAX®Port, without DXA, ≥ 11% for major osteoporotic fracture OR ≥ 3% for hip fracture – Estimates of FRAX®Port, with DXA, ≥ 9% for major osteoporotic fracture OR ≥ 2.5% for hip fracture	88	8.3 (1.7) 79%
Recommendation 6 6.a. Non-pharmacological preventive measures for osteoporosis, designed to correct modifiable relevant clinical risk factors should always be implemented. These include the promotion of healthy diet, regular weight-bearing exercise, adequate calcium intake and sun exposure or supplementation with vitamin D, as well as the prevention of falls, and avoidance of excessive alcohol intake and smoking.	88	8.9 (1.4) 84%

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TABLE I. CONTINUATION

Recommendation	Votes	Agreement Mean (SD) % score ≥ 8
6b. Based on cost-effectiveness considerations, the first line treatment for osteoporosis is oral bisphoshonates (namely oral alendronate). 6c. Intravenous zoledronic acid and subcutaneous denosumab should be considered in case of oral intolerance, malabsorption, dementia and non-compliance. Denosumab can also be preferred in case of renal insufficiency. Teriparatide is an option in patients with very high risk of subsequent fracture.		
Recommendation 7 7a. Osteoporosis in men is more often due to comorbidities: special attention should be paid to secondary causes of OP. 7b. Fracture risk assessment and treatment of male primary osteoporosis is similar to that described in women, except for hormone-based medications.	83	9.0 (1.1) 90%
Recommendation 8 8a. Clinical risk factors, occurrence of fractures, body height, and the adherence to lifestyle interventions and medication should be reassessed annually. Vertebral imaging may be performed if necessary. 8b. DXA assessment should not be repeated within less than 2 years, unless clinical risk factors significantly change. Biochemical markers have little role in evaluating the treatment response/adherence in individual patients. 8c. The absence of a new low trauma fracture, the stability or improvement of BMD over >2 years, and a guaranteed adherence to therapy are consistent with a satisfactory course of treatment.	83	8.7 (1.8) 85%
Recommendation 9 9a. Drug holidays should only be considered for bisphosphonates. An interruption of therapy with these agents, for 2 to 3 years, may be considered if the three following conditions are simultaneously verified – The treatment has been strictly adhered to for at least 5 years with oral or 3 years with intravenous bisphosphonates – No fragility fractures have been observed under treatment – Femoral BMD T Score is >-2.5 9b. Switching anti-osteoporotic therapy should be considered whenever significant adverse events occur or comorbidity emerges that advises reconsideration of the agent being used (eg: newly established renal failure in patients under bisphosphonates). 9c. Stopping anti-osteoporotic therapy should be considered if – it is verified that the criteria to recommend its introduction are not met – significant toxicity contraindicates continuation	83	8.7 (1.2) 85%
Recommendation 10 Healthy diets, adequate sun exposure and regular weight-bearing exercise should be promoted, for bone health, in every stage of life in the general population.	83	8.7 (1.2) 85%
Recommendation 11 A referral to rheumatology should be considered in case of unclear fracture risk assessment, doubts regarding treatment strategies, secondary osteoporosis, inadequate response to therapy or unremitting pain after fracture.	83	9.1 (1.6) 92%

population from 40 to 90 years old who are treatment – naïve for OP.

FRAX® has several limitations, which should be considered for clinical decision in individual cases. Among these, we highlight that FRAX®: 1. Does not take into account the occurrence of falls as a clinical risk factor; 2. Does not consider vertebral bone mineral density; 3. Does not take into account the dose--dependent and time exposure relationships of clinical risk factors (eg: glucocorticoid dose and duration, number of previous fractures) and fractures.[40] In addition, the discriminatory value of the FRAX® algorithm among some sub groups of patients with high risk of fracture, such as those with chronic kidney disease[41], diabetes[42], cancer, mental disorders and related medications[43] is limited.

QUESTION 3. WHEN AND HOW SHOULD BONE MINERAL DENSITY BE MEASURED?

- **Recommendation 3.a. Bone mineral density should be assessed, for clinical purposes, by dual X-ray absorptiometry (DXA)**
- **Recommendation 3.b. The decision to perform DXA should be primarily based on the risk of fracture as estimated by clinical risk factors, which can be provided by FRAX®Port.**
- **Recommendation 3.c. DXA is warranted in Portugal when FRAX®Port estimates, without DXA, are between 7% and 11% for major osteoporotic fracture AND between 2% and 3% for hip fracture.**
- **Recommendation 3.d. DXA may be, otherwise, justified to evaluate patients with risk factors for osteoporosis not included in FRAX®, to study secondary osteoporosis (Table II) or to evaluate the efficacy of interventions.**

These recommendations are rooted on the overarching principles that the decision to make investigations in clinical practice should be based on: 1. The probability that the result will be abnormal; 2. That the result might change subsequent decisions, the decision being, in this case - to treat or not to treat. Prospective studies with DXA have showed that, particularly in old adult women, the risk of fractures approximately doubles for each reduction of one standard deviation (SD) in BMD[44,45]. However, the diagnostic threshold of a T-score ≤ -2.5, defined by WHO in 1994, fails to identify a significant number of those who actually suffer a fragility fracture. BMD values below the osteoporosis diagnostic threshold have high specificity but low sensitivity[34,44,46]. Clinical risk factors for fractures, which are statistically significant independently of BMD, have been identified[47,48]. Considered individually, each clinical risk factor also has poor specificity and sensitivity in predicting fracture risk[47] but combined, they have a performance that is similar to BMD[19,29,46,49,50]. In fact, the validation study of FRAX®-Port[25] demonstrated that the accuracy of this tool was very similar, with and without BMD, at group level.

Taken together, the available evidence suggests that, the most efficient way of screening individuals at risk of a fragility fracture, resides in using FRAX tool without BMD[25,50]. BMD measurement may be justified when the risk estimate is in the vicinity of the lower cost-effective intervention thresholds previously calculated for Portugal (9% for major and 2,5% for hip fractures)[26] because, in such cases, the dichotomous decision to treat/not to treat may be changed by consideration of DXA values. For this reason, the Portuguese multidisciplinary recommendations[27] endorsed by the SPR, established an uncertainty margin of 2% and 0.5 % around the stated intervention threshold, for major fracture and hip fractures, respectively, which demands the performance of DXA to support the final decision to initiate treatment. It is estimated that the probability that the decision to treat/not to treat, will be changed by DXA, in patients whose prior estimated fracture risk is either above or below the uncertainty margin, is too small to make DXA warranted for these purposes. The width of this uncertainty margin was, however, based solely on expert opinion (Figure 1).

BMD should also be assessed to determine the individual risk of fracture in cases of suspected secondary OP, in the presence of risk factors not included in FRAX tool, and in patients treated with anti-osteoporotic drugs (Table II and Figure 1)[22,51,52].

QUESTION 4. WHEN AND HOW SHOULD SECONDARY OSTEOPOROSIS BE SUSPECTED AND INVESTIGATED IN ADULTS?

- **Recommendation 4.A. Secondary osteoporosis should be suspected in the presence of conditions known to induce osteoporosis (Table II) fragility fractures occurring before the age of 70 for men or before menopause for women low Z scores in DXA (≤-2.0)**

TABLE II. RISK FACTORS FOR BONE FRAGILITY AND SECONDARY CAUSES OF OSTEOPOROSIS

Inflammatory conditions
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Ankylosing spondylitis
- Crohn's disease, ulcerative colitis
- Sarcoidosis
- HIV infection

Endocrinopathies or metabolic causes
- Hypercortisolaemia (Cushing's syndrome)
- Hyperthyroidism
- Primary hyperparathyroidism
- Hyperprolactinaemia
- Premature menopause (auto-immune, surgical, drugs)
- Male hypogonadism
- Acromegaly
- Growth hormone defficiency
- Diabetes mellitus type I and II
- Porphyria
- Hypophosphatasia
- Pregnancy

Liver and GI conditions/Nutrition
- Chronic liver disease
- Primary biliary cirrhosis
- Gastrointestinal resection or bypass
- Celiac disease
- Malabsorption
- Lactose intolerance
- Pancreatic insufficiency
- Total parental nutrition
- Alcoholism
- Anorexia Nervosa
- Calcium deficiency

Haematological conditions
- Multiple myeloma and monoclonal gammopathy of unknown significance
- Myeloproliferative disorders
- Systemic mastocytosis
- Thalassemia
- Hemophilia
- Sickle cell anaemia

Kidney diseases
- Chronic kidney disease
- Kidney transplantation
- Idiopathic renal hypercalciuria
- Renal tubular acidosis

Genetic disorders
- Osteogenesis imperfecta
- Marfan's syndrome
- Ehlers–Danlos syndrome
- Homocystinuria
- Pseudoxanthoma elasticum
- Gaucher disease
- Hypophosphatasia
- Haemochromatosis

Drugs
- *Glucocorticoids*
- *Antiepileptics:*
- *Hypoglycaemiants* (thiazolidinediones)
- *Lipase inhibitors*
- *Selective serotonin reuptake inhibitors*
- *Excess thyroxine supplementation*
- *Aromatase inhibitors*
- *Gonadotropin-releasing hormone agonists*
- *Depot medroxyprogesterone acetate*
- *Tamoxifen*
- *Chemotherapy*
- *Immunosuppressants:* cyclosporine, tacrolimus
- *Furosemide*
- *Lithium*
- *Heparin*
- *Proton pump inhibitors*
- *Aluminium-containing antacids*
- *Antipsychotics*
- *Anti-retroviral drugs*

Adapted from Sheu A *et al*, Hofbauer LC and Camacho[22,51,52]

- **Recommendation 4.B. Suspected secondary osteoporosis justifies thorough clinical evaluation and appropriate hypothesis-driven investigations.**

The reader should be aware that most European and American guidelines for the management of postmenopausal osteoporosis recommend that secondary causes and contributory factors to OP should be

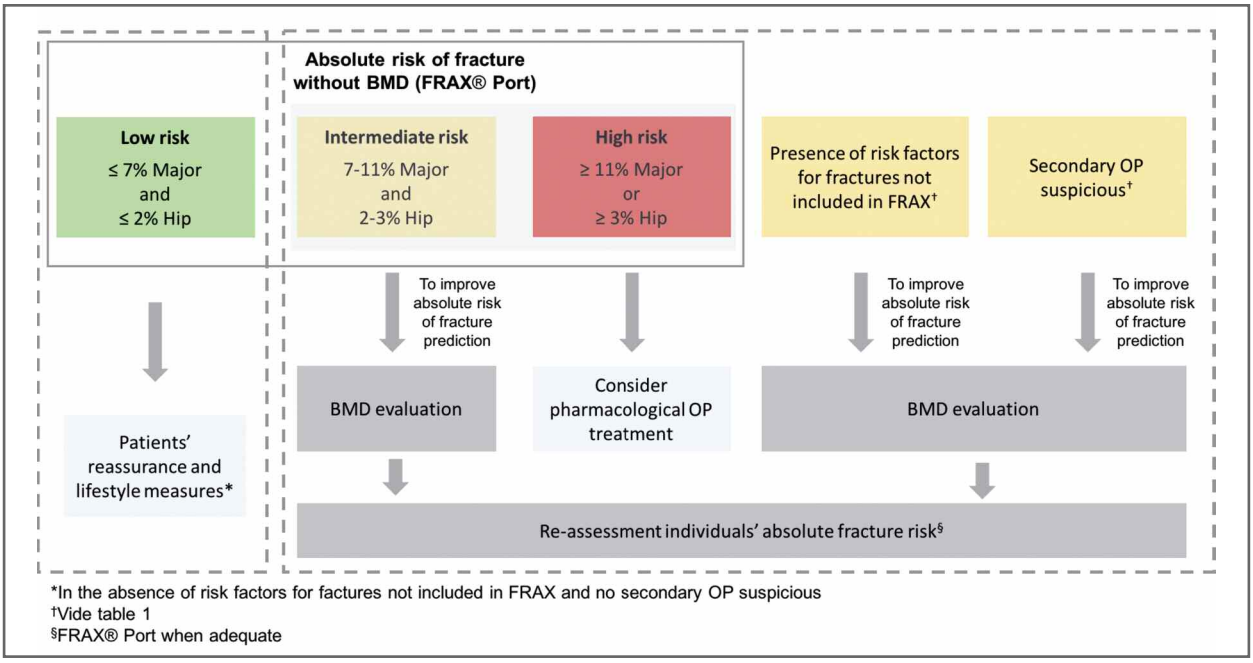

FIGURE 1. Flowchart of fracture risk assessment

searched in every patient with OP, irrespective of the presence or absence of fragility fractures[19,20,24,53]. Some scenarios are highly suspicious for secondary OP, like fragility fractures occurring in men with less than <70 years old[54], or in premenopausal women without obvious risk factors for osteoporosis; or multiple low-impact fractures, very low bone mineral density, Z-score ≤–2.0, atypical fractures or occurrence of fractures despite anti-osteoporotic therapy[51,52].

The causes of secondary OP are numerous, (Table II) but the prevalence of undiagnosed secondary causes of osteoporosis is not well established[55]. In an observational retrospective study from a Fracture Clinic, secondary causes were found to be infrequent (17/499, 3.4%)[56]. The clinical evaluation is aimed to exclude diseases that can mimic osteoporosis (eg osteomalacia) and to elucidate potential causes of OP that may influence management[19]. A complete medical history should be collected focusing on endocrine, metabolic and inflammatory disorders associated with altered bone metabolism (including malabsorption syndromes), personal habits (diet, exercise patterns, sun exposure, tobacco and alcohol consumption) and past and present medications capable of interfering with bone metabolism. A family history of bone fragility provides a hint for genetic contributions towards OP. The clinical factors included in FRAX® provide a general, although not exhaustive, guide for these explorations[40]. Special attention should be given to common medications whose association with OP and fragility fractures is frequently ignored, such as proton pump inhibitors, selective serotonin reuptake inhibitors, anticonvulsants, thiazolidinediones (diabetes), aromatase inhibitors, tamoxifen, luteinizing hormone releasing hormone (LHRH) analogues (breast cancer) and gonadotropin-releasing hormone (GnRH) agonists and antiandrogens (prostate cancer).

Physical examination should pay special attention to low height and/or low body mass index (<18.5 Kg/m^2), signs of hypogonadism and presence of kyphosis, joint inflammation, blue sclera and poor dentition.

A basic lab screening for secondary causes of OP should include serum calcium, phosphate, protein electrophoresis, alkaline phosphatase, creatinine, full blood counts, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver enzymes (alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transpeptidase (GGT)), fasting glucose, thyroid (thyroid-stimulating hormone (TSH)) and parathyroid (parathyroid hormone (PTH) function tests. Depending on clinical findings or previous

investigations results, other laboratory tests can be considered with emphasis on serum 25(OH)vitamin D, 24-hour urine calcium , total and free testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH) (suspected hypogonadism in men), cortisol levels, and anti-transglutaminase (suspected malabsorption).

Primary hyperparathyroidism in one of the most common causes of secondary OP. The diagnosis is primarily biochemical, based on the finding of hypercalcemia together with PTH levels that are high or inappropriately normal relative to serum calcium levels. The clinician should keep in mind that near-normal calcium levels may be found in mild primary hyperparathyroidism: calcium levels should be measured several times and corrected for albumin.[57]

QUESTION 5. WHO SHOULD BE PHARMACOLOGICALLY TREATED FOR OSTEOPOROSIS?

- **Recommendation 5. Pharmacological treatment for osteoporosis should be initiated, unless contraindicated, in all subjects over the age of 50 who satisfy one or more of the following criteria:**
  - **≥1 fragility fracture of the hip or ≥1 symptomatic vertebral fragility fracture.**
  - **≥2 fragility fractures, independently of the site of fracture or the absence of symptoms (e.g. two asymptomatic vertebral fractures).**
  - **Estimates of FRAX®Port, without DXA, ≥ 11% for major osteoporotic fracture OR ≥ 3% for hip fracture**
  - **Estimates of FRAX®Port, with DXA, ≥ 9% for major osteoporotic fracture OR ≥ 2.5% for hip fracture**

The decision to (not) prescribe anti-osteoporotic medications should be based on the individual's ten-year risk of subsequent osteoporotic fracture as estimated by the FRAX®Port tool. The risk-based thresholds for intervention indicated above are based on cost-effectiveness analysis and are applicable to the most affordable treatment scheme: generic alendronate (Figure 2). More expensive medications have higher cost-effective thresholds of intervention (Table III)[26]. Patients with prior fragility fractures (particularly hip) will have a significantly cost-effective reduction on the risk of subsequent fragility fracture with pharmacologic therapy, independently of their BMD[58-66]. It also noteworthy that some international recommendations advice that treatment should be started in the presence of a vertebral deformity grade 2 (ie height loss >25-40%) even if asymptomatic[67]. The reader is made aware that many international recommendations indicate that patients with a DXA T score ≤ -2.5 should also be treated, irrespective of FRAX® and age[19-23]. These recommendations were based on the principle that the elevated risk of fracture associated with a T score of -2.5 or less at femoral neck or lumbar spine has showed to be reduced with pharmacological treatment [61,63,64,66,68-77].The SPR, in accordance with the

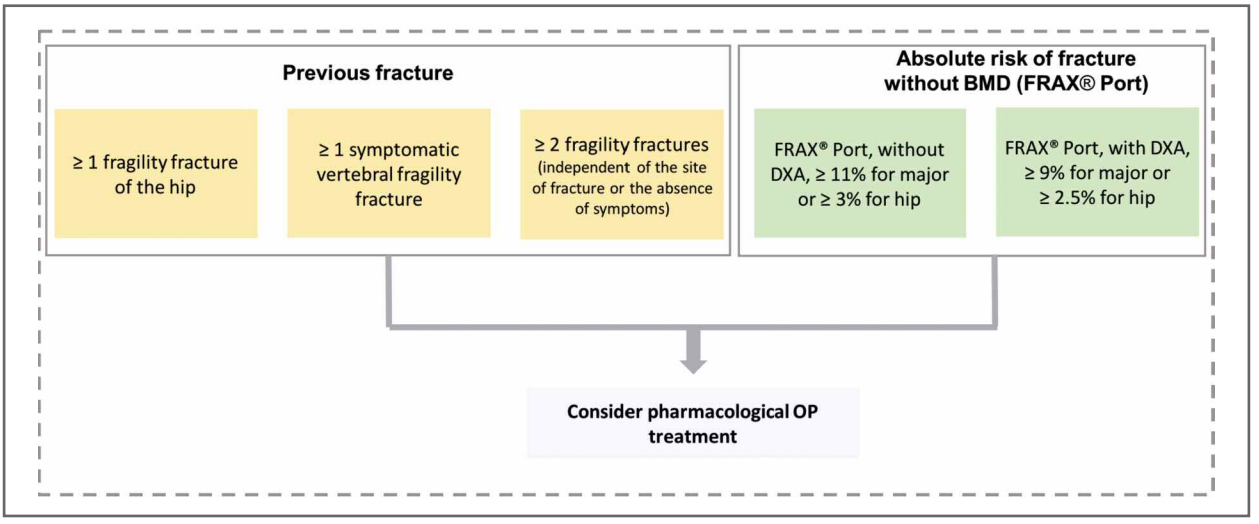

FIGURE 2. Criteria for pharmacological OP treatment

TABLE III. COST-EFFECTIVENESS THRESHOLDS FOR INTERVENTION WITH SEVERAL MEDICATIONS IN PORTUGAL, BASED ON THE FRAX®PORT TEN-YEAR OSTEOPOROTIC FRACTURE RISK ESTIMATE, FOR DIFFERENT MEDICATIONS, BASED ON A WILLINGNESS TO PAY OF 32.000€/QALY AND CURRENT COST OF MEDICATION

		Without DXA		With DXA	
	Cost basis/year (€)	Major %	Hip %	Major %	Hip %
Generic alendronate	99	11	3	9	2.5
Zoledronic acid	347	22	12	20	10
Denosumab	552	37	25	35	23
Teriparatide	4234	80	65	78	63

Adapted from Marques *et al*[26].

Portuguese Multidisciplinary Recommendations, does not endorse this policy, because a low BMD is not necessarily associated with a significant risk of fracture, especially in young people[45,46] .

QUESTION 6. HOW SHOULD PRIMARY OSTEOPOROSIS BE TREATED?

- **Recommendation 6a. Non-pharmacological preventive measures for osteoporosis, designed to correct modifiable relevant clinical risk factors should always be implemented. These include the promotion of a healthy diet, regular weight-bearing exercise, adequate calcium intake and sun exposure or supplementation with vitamin D, as well as the prevention of falls, and avoidance of excessive alcohol intake and smoking.**

Adequate nutrition with a well-balanced diet, sufficient sun exposure and regular weight-bearing exercise are important measures that promote bone health, not only in the general population, but especially in patients with osteoporosis[79]. Several studies have shown that excessive alcohol intake and smoking are deleterious for bone[80-83] and increase the risk of fragility fractures[48,49]. If adequate intake of calcium cannot be assured through diet, supplementation is indicated up to the recommended daily intake of 1000-1200 mg/day[20]. The side effects of calcium supplementation include kidney stones and gastrointestinal symptoms. The cardiovascular risk increase due to calcium supplementation is controversial and is considered negligible if associated to vitamin D within the recommended doses[84-88]. Adequate vitamin D status must be assured in patients with OP and serum 25 (OH) vitamin D should be measured in patients considered at risk of severe vitamin D deficiency: advanced age, obesity, renal insufficiency, malabsorption, chronic liver failure and exposure to medications that increase breakdown of vitamin D (anticonvulsants, highly active antiretroviral therapy (HAART) and glucocorticoids)[89].Vitamin D supplementation (800-2000UI/day or equivalent) should be considered in patients with serum 25(OH)Vitamin D levels below 30ng/ml[90,91]. All clinical trials with pharmacological therapies for OP were performed while guaranteeing adequate calcium and vitamin D levels through diet, sun exposure or supplementation[61,63,64,66,68-77].

- **Recommendation 6b. Based on cost-effectiveness considerations, the first line treatment for osteoporosis is oral bisphoshonates (namely generic oral alendronate).**
- **Recommendation 6c. Intravenous zoledronic acid and subcutaneous denosumab should be considered in case of oral intolerance, malabsorption, dementia and non-compliance. Denosumab can also be preferred in case of renal insufficiency. Teriparatide is an option in patients with very high risk of subsequent fracture.**

The current evidence does not allow a clear distinction between available treatments in terms of their relative efficacy in the prevention of fractures, as demonstrated by network meta-analyses designed to overcome the lack of head-to-head comparisons[92,93].

Bisphosphonates are considered the first line of therapy for osteoporosis in several countries[19,20,23,94,95]. In Portugal, generic oral alendronate is the most cost-

-effective drug available (Table III). The decision to start an anti-osteoporotic treatment with agents other than generic alendronate should be informed by their respective cost-effectiveness thresholds in Portugal (see Table III)[26]. Alendronate[58] and risedronate[60] are oral bisphosphonates that have demonstrated a broad anti-fracture efficacy (for vertebral, non-vertebral and hip fractures), generic alendronate being the less expensive in Portugal. The other available oral bisphosphonate, ibandronate, reduces the incidence of vertebral fractures but its ability to reduce the rate of nonvertebral fractures has not been robustly documented[59]. Annual intravenous infusions of zoledronic acid have also been shown to significantly reduce the incidence of vertebral, non-vertebral and hip fractures[74]. Moreover, zoledronic acid has also been demonstrated to prevent new fractures and decrease mortality after a recent hip fracture[65].

Denosumab, a monoclonal anti-RANKL antibody, has proven efficacy in the prevention of vertebral, non-vertebral and hip fractures when administered as 6-montly subcutaneous injections. Unlike bisphosphonates, denosumab has no renal excretion and its use in chronic renal disease seems to be safe and effective [96-99].The use of bisphosphonates in osteoporosis patients does not seem to have renal toxicity, but their use in chronic renal insufficiency should be cautious [100].In fact, there is insufficient data about the efficacy of bisphosphonates, raloxifene and teriparatide in preventing fractures in patients with renal insufficiency [101-104]. Osteonecrosis of the jaw and atypical femoral fractures are extremely rare with the usual doses of bisphosphonates and denosumab[100,105,106].

Teriparatide, the N-terminal 34 aminoacids of PTH, stimulates bone formation and is administrated subcutaneously, on a daily basis, for 18 to 24 months. The efficacy of teriparatide in reducing the incidence of vertebral and non-vertebral fractures is well established but not in hip fractures[107]. Overlapping teriparatide with bisphosphonates or denosumab and continuing an antiresorptive agent after teriparatide therapy seems to optimize the increase of BMD[108-111]. Due to its high cost and daily subcutaneous administration, teriparatide is usually reserved for subjects at very high risk of fragility fractures, namely with several previous fractures [112]. Unlike the bisphosphonates, both denosumab and teraparatide are followed by an abrupt and rapid bone loss when discontinued, thus requiring careful management of long-term therapy[113,114].

Raloxifene is a selective oestrogen receptor modulator that reduces the incidence of vertebral fractures but not hip or non-vertebral fractures. It has been demonstrated to reduce the risk of invasive breast cancer in postmenopausal women but to increase the risk of stroke and venous thromboembolism[115-118]. The recent recommendations of the American College of Physicians explicitly recommend against the use of hormone replacement therapy or raloxifene for the treatment of osteoporosis [119].

QUESTION 7. HOW SHOULD WE MANAGE OSTEOPOROSIS IN MEN AND SECONDARY OSTEOPOROSIS?

- **Recommendation 7a. Osteoporosis in men is more often due to comorbidities: special attention should be given to secondary causes of OP.**
- **Recommendation 7b. Fracture risk assessment and treatment of male primary osteoporosis is similar to that described in women, except for hormone-based medications.**

Osteoporosis in men is more often secondary than in women, approximately two thirds of all cases of male osteoporosis, according to some studies [120]. The most common secondary causes of OP in men include hypogonadism, alcohol abuse, multiple myeloma, hyperparathyroidism, malabsorption and glucocorticoid use[120]. For this reason, investigation of secondary causes of osteoporosis is especially warranted in males, as they may significantly influence the treatment strategy.

The overall management strategy for primary osteoporosis in men does not differ from that recommended for women: all risks factors for osteoporosis, fractures and falls should be corrected, as described above. The decision to start anti-osteoporotic medications is based on the same criteria and cost-effectiveness thresholds. Regarding the choice of treatment, data that specifically apply to men are scarce and expectations are extrapolated from studies in females, as the efficacy is expected to be similar in men and women[121]. One study demonstrated that treatment with zoledronic acid reduced vertebral fractures in osteoporotic men[122].

Treatment of secondary osteoporosis largely exceeds the scope of these recommendations, given the variety of conditions and nuances that need to be considered. Interested readers are advised to consult

the most relevant literature to the case at hand[123] . The recent Italian Guidelines for the diagnosis, prevention and management of osteoporosis[23] provide a wide scope review of numerous conditions. The prevention and treatment of glucocorticoid induced osteoporosis are the object of several dedicated recommendations[124,125].

QUESTION 8. HOW SHOULD THE EFFICACY OF OP TREATMENT BE MONITORED?

- **Recommendation 8a. Clinical risk factors, occurrence of fractures, body height, and the adherence to lifestyle interventions and medication should be reassessed annually. Vertebral imaging may be performed if necessary.**
- **Recommendation 8b. DXA assessment should not be repeated within less than 2 years, unless clinical risk factors significantly change. Biochemical markers have little role in evaluating the treatment response/adherence in individual patients.**

Periodic follow-up is important to ensure the adherence to treatment and life-style interventions, monitor adverse events and evaluate the response to treatment[112,126]. OP patients have a low/moderate adherence to anti-osteoporotic drugs, which leads to a loss of efficacy in fracture prevention[127,128]. Regular clinical evaluations have demonstrated to increase treatment adherence[129]. During clinical appointment, patients should also be inquired regarding new clinical risk factors, new onset of secondary OP and adverse events related to OP drugs, which may require adjustment of the treatment plan[20]. To evaluate treatment efficacy, subjects should be asked regarding the occurrence of new fragility fractures. Vertebral imaging should be performed if a new vertebral fracture is suspected[20,126].

DXA testing can be advocated to monitor OP treatment efficacy. In fact, pilot studies with anti-osteoporotic drugs have shown a small to moderate relationship between the increase of BMD and the reduction of fracture risk in different trials. However, several studies demonstrate that women treated with bisphosphonates, raloxifene, and teriparatide benefited from reduced rate of fractures even if the BMD did not increase[130-132]. Accordingly, many experts consider that medication can be expected to be efficient and that the most important task of the clinician in this respect resides in guaranteeing adherence to evidence-based treatment. The recent recommendations of the American College of Physicians explicitly recommend against bone mineral density monitoring during pharmacologic treatment in women[119]. In any case, the time interval to repeat DXA must be sufficiently long to allow for detectable changes, which means that DXA assessment should not be repeated within less than 2 years[19,20,112].

Bone turnover markers (BTM), namely serum levels of procollagen I N-terminal extension peptide (P1NP) and C-telopeptide break (CTX) are typically reduced after 3-6 months of anti-resorptive therapy and increase after 1-3 months of anabolic therapy[19,20,112,126,133,134]. Studies have showed that short--term decrease in markers of bone turnover is associated with gains in BMD and with a reduction in the rate of fragility fractures [135-140]. The International Osteoporosis Foundation and the European Calcified Tissue Society[141] proposed that BTM should be used as a screening strategy to detect a lack of adherence to bisphosphonates based on the Trio study results[142]. However, the serum levels of these markers are extremely variable, depending on several factors not related to bone metabolism, such as diet, time of the day and of the year, concomitant medications, etc. This strongly reduces their value in individual patients, despite the sensitivity to change at the group level. Altogether, we consider that their use in clinical practice is rarely justifiable in agreement with the recent Italian Guidelines explicitly state that "bone markers cannot be used for routine clinical evaluations at present"[23].

- **Recommendation 8c. The absence of new low trauma fractures, the stability or improvement of BMD over >2 years, and a guaranteed adherence to therapy are consistent with a satisfactory course of treatment.**

The available evidence does not support a clear definition of the success or failure of OP treatment. Even the occurrence of a new fragility fracture cannot be taken as a demonstration of treatment failure: another one may have been prevented, as no medication has been shown to prevent all fractures. Despite this, treatment failure was defined by the International Osteoporosis foundation (IOF), based on expert opinion, as the occurrence of an incident fracture after at least 6 months of anti-osteoporotic treatment and/or a decrease in BMD greater than the least

significant change (approximately 5 % at the spine 4% at the femoral neck) over 2 years of treatment[133].

QUESTION 9. WHEN SHOULD DRUG HOLIDAY AND THERAPEUTIC SWITCH BE CONSIDERED?

- **Recommendation 9a. Drug holidays should only be considered for bisphosphonates. An interruption of therapy with these agents, for 2 to 3 years, may be considered if the three following conditions are simultaneously verified**
  - **The treatment has been strictly adhered to for at least 5 years with oral or 3 years with intravenous bisphosphonates**
  - **No fragility fractures have been observed under treatment**
  - **Femoral BMD T Score is >-2.5**

This recommendation is similar to that of the American Society for Bone and Mineral Research, which proposes that, in patients who have received bisphosphonates for ≥5 years if oral or for ≥3 years if intravenous, treatment with bisphosphonates or alternative therapy should be continued for up to ten years in those with hip, spine or multiple other osteoporotic fracture before or during therapy, a hip T-score ≤-2.5 or FRAX fracture risk score that is above country specific thresholds.[16]

Evidence for additional benefit of long-term bisphosphonates is provided by extensions of pivotal studies with alendronate (FLEX study)[68] and zoledronate (HORIZON extension study) [143].These studies verified that an additional 5 years treatment with alendronate or additional 3 years with zoledronate was associated with, respectively, fewer clinical vertebral fractures and fewer morphometric spine fractures. The risk of atypical femoral fracture is increased with prolonged therapy, but these events remain rare and are clearly outweighed by vertebral fracture risk reduction in high-risk patients[144]. On the other hand, the effects of bisphosphonates on bone persist for at least 2 years after discontinuation of long-term therapy. This allows for the consideration of bisphosphonate holiday in individuals not at high risk[68,143,145-149].

Teriparatide is not licensed to use for longer than 24 months, due to fears of osteosarcoma [110].

- **Recommendation 9b - Switching anti-osteoporotic therapy should be considered whenever significant adverse events occur or comorbidity emerge that advises reconsideration of the agent being used (eg: newly established renal failure in patients under bisphosphonates).**
- **Recommendation 9c -Interruption of anti-osteoporotic therapy should be considered if**
  - **it is verified that the criteria to recommend its introduction are not met**
  - **significant toxicity contraindicates continuation**

Evidence supporting the switch from bisphosphonate to teriparatide or denosumab is limited to the effect on BMD and bone turnover markers, there being no evidence regarding fracture incidence[110,150]. Teriparatide should be stopped after 18 to 24 months of treatment[110] and should be followed by bisphosphonate or denosumab[109,111,151]. Age, is not a reason to stop anti-osteoporotic therapy given that the risk of fractures steadily increases with age[2].

QUESTION 10. WHAT ARE THE BEST STRATEGIES TO PREVENT OSTEOPOROSIS IN THE GENERAL POPULATION?

- **Recommendation 10. Healthy diet, adequate sun exposure and regular weight-bearing exercise should be promoted, for bone health, in every stage of life, in the general population.**

Genetic factors account for 60 to 80% of the peak bone mass, but there is evidence that lifestyle factors, like adequate nutrition and regular weight-bearing exercise, are essential to achieve the genetic potential and have a positive effect in bone mass accrual in childhood and adolescence[36]. A 10% increase in peak bone mass has been predicted to delay the development of osteoporosis by 13 years[36,152]. The same lifestyle factors are advocated to prevent premature or accelerated bone mass in adults and old adults, although the evidence that these interventions will reduce fracture risk at any age is limited[152].

A well-balanced diet should provide adequate amounts of calcium, vitamin D and proteins, as well as other elements that are important for bone health (e.g. zinc, manganese, vitamin A, vitamin C, vitamin K, complex B vitamin, potassium and sodium)[152].

Recommended dietary allowances for calcium and vitamin D vary according to age group, gender and special situations. National recommendations for a healthy nutrition have been issued by the Direc-

torate-General of Health of the European Union and should be followed[9,153]. Dairy products are the main dietary source of calcium due to their high calcium content and bioavailability, providing also other important nutrients. Three servings of dairy products per day (milk, cheese or yogurt) deliver most of the recommended calcium intake for the general population[9]. Bioavailability of calcium provided by non-dairy sources is reduced and it may be impossible to meet recommendations in a dairy-free diet[9]. Calcium supplements may be an alternative if dietary intake is insufficient. Head-to-head studies have shown that increments in bone mass are higher with dietary calcium than with supplements[9]. There is an ongoing debate over the negative role of calcium (dietary or supplements) in cardiovascular diseases, hypertension, kidney stones and prostate cancer, as well as its positive effect in hypertension, colorectal cancer, preeclampsia and weight management [84]. For these reasons, we recommend that calcium intake should be mostly dietary and within recommended allowances. Supplements should only be considered for patients with OP under pharmacologically treatment or subjects unable to have an adequate calcium intake through diet.

Vitamin D is essential for bone development and maintenance throughout life, and it also has an important role in muscle, improving strength and function [89]. Vitamin D is obtained primarily from sun exposure, as the relevant dietary sources are very few (fresh or canned oily fish, cod liver oil, egg yolk)[89]. Skin mediated production varies greatly with age, skin type, latitude, time of day and season and use of sunscreen products. Supplementation of vitamin D may be considered in special situations (namely OP subjects under pharmacological treatment) and is recommended by the Directorate General of Health for those over 65 years of age[9,90]. The currently recommended intake of vitamin D in adults varies from 600 to 6000 UI/day, according to age, gender and body mass index[89,154].

There is strong evidence that exercise begun early in life contributes to higher peak bone mass. The importance of physical exercise in adults lies not only in the potential to reduce bone loss and improve muscle strength, but also in helping to prevent falls by enhancing coordination, balance and posture. Resistance training and weight-bearing exercises are the most beneficial for bone mass (ie, dancing, jogging, climbing stairs)[155,156].

Finally, excessive alcohol intake (more than 3 units/day for men and 2 units /day for women) and smoking are deleterious for bone and considered clinical risk factors for fractures. Excessive alcohol intake and smoking should be avoided in order to prevent osteoporosis[40,155].

QUESTION 11. WHEN SHOULD AN OSTEOPOROTIC PATIENT BE REFERRED TO A RHEUMATOLOGIST?

- **Recommendation 11.** ***A referral to rheumatology should be considered in case of unclear fracture risk assessment, doubts regarding treatment strategies, secondary osteoporosis, inadequate response to therapy or unremitting pain after fracture.***

Rheumatologists provide care for patients with OP in a cost-efficient, evidence-based and patient centered approach. The main aim in the treatment of an OP patient is to prevent a fragility fracture, improve quality of life and prevent disability. Rheumatologists work in a variety of settings in the hospital, namely outpatient office, infusion center and inpatient clinic. In addition, they are intensively trained and experienced in the diagnosis and management of complex cases of osteoporosis. OP patients should be referred to a rheumatologist when there is an inadequate response to therapy, which is indicated by significant loss of BMD or occurrence of fragility fracture in patients with good compliance to appropriate therapy, as defined in recommendation 8c.

In selected cases, referral may also be indicated if the caring physician is uncertain about the absolute risk of fracture, about the secondary nature of osteoporosis or the most appropriate treatment. This may also be justified to reassure patients who feel anxious or disturbed by the diagnosis or its management.

Referral should be based on appropriate information, including a clear expression of the questions to be addressed and all clinically pertinent information, such as current and previous medications, FRAX® estimates and relevant medical history, imaging and lab results.

AREAS WHERE EVIDENCE IS LACKING

In the present OP recommendations, the SPR recommends FRAX® algorithm to evaluate individuals absolute risk of fracture. A recent randomized controlled trial revealed that FRAX® algo-

rithm is a feasible and effective screening tool in reducing hip fractures[157]. However, it is important to note that evidence linking FRAX® scores to treatment efficacy is lacking[158]. In addition, comparative effectiveness trials evaluating pharmacologic treatments for low bone density or osteoporosis and high risk of fracture patients are also lacking[119].

CONCLUSION

This article presents the 2018 update of the Portuguese recommendations for diagnosis and management of OP in adults. They are meant to provide a valid guide on OP diagnosis, fracture risk assessment, pharmacological treatment decision, therapeutic options and duration, informed by national evidence and circumstances. These recommendations may not be appropriate in all situations and we encourage clinicians to use this information together with their best clinical judgment in the individual case.

CONFLICTS OF INTEREST

None of the authors report conflicts of interest

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