EDITORIAL
UVODNIK

University of Novi Sad, Faculty of Medicine Novi Sad
Clinical Center of Vojvodina, Novi Sad
Clinic of Orthopedic Surgery and Traumatology

Uvodnik
Editorial
UDK 616.71 007.234-07/-08
https://doi.org/10.2298/MPNS2006135M

OSTEOPOROSIS

OSTEOPOROZA

Radmila MATIJEVIĆ

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture [1] **(Figure 1).** This definition, developed by international consensus in 1993, accentuates two important characteristics of osteoporosis: its adverse effects on bone mass and microstructure, and fractures as its clinical outcome. In 1994, diagnostic criteria were defined by the World Health Organization (WHO) using standard deviation (SD) scores of bone mineral density (BMD) related to peak bone mass in healthy young women, with osteoporosis being defined as a BMD T score of −2.5 or less and low bone mass (osteopenia) as a BMD T-score between −1 and −2.5 [2]. Low BMD is recognized as an important diagnostic criterion in the pathogenesis of fragility fractures, and a tool that can be used in epidemiological studies to evaluate the prevalence of osteoporosis. However, the benefits of BMD as a clinical benchmark for osteoporosis are limited, because BMD is only one of several important risk factors for fracture, and the majority of fragility fractures occur in persons with BMD values above the defined threshold [3]. Bone density testing by dual energy X-ray absorptiometry (DXA) is a quantitative, non-invasive, comparatively inexpensive, convenient diagnostic procedure for osteoporosis.

Clinical diagnosis of osteoporosis is difficult, because the WHO definition using BMD alone may not take into account other risk factors which independently may cause fragility fracture, whilst fracture-based criteria may exclude populations at risk who also should be treated. More recently, fracture risk calculators, such as the FRAX® algorithm, developed by Professor John Kanis and his team at the University of Sheffield, have facilitated assessment of an individual's fracture risk using clinical risk factors such as age, previous fractures, positive family history, etc. with only partial consideration of BMD. In 2019, FRAX® was available in 65 countries including 10 Asian, 35 European, 9 from the Middle East & Africa, 2 from North America, 7 from Latin America, and 2 from Oceania. Since 2018, Serbia also has a country-specific risk estimator in FRAX®. While it is important to

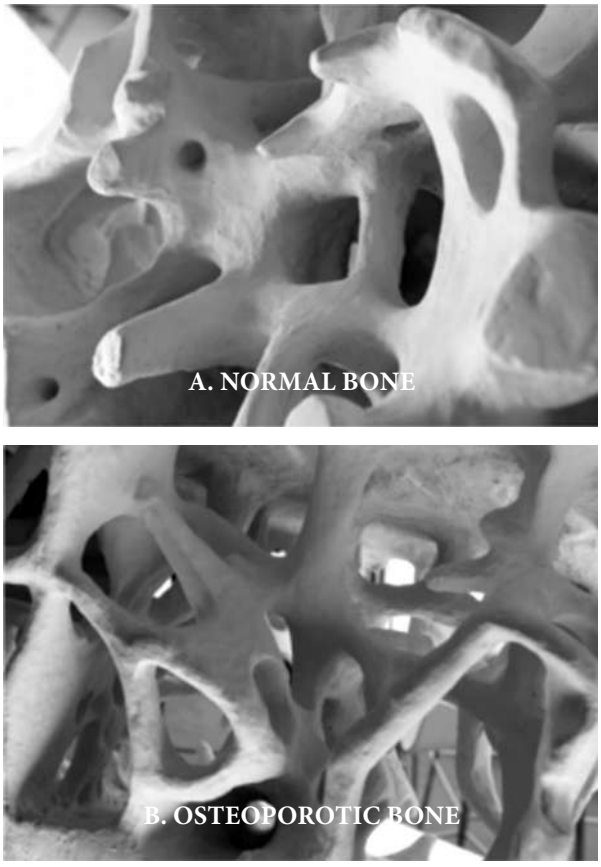


Figure 1. A. Normal vs. **B.** osteoporotic bone
Slika 1. A. *Normalna i* ***B.*** *osteoporotična kost*

Corresponding Author: Doc. dr Radmila Matijević, Univerzitet u Novom Sadu, Medicinski fakultet, KCV - Klinika za ortopedsku hirurgiju i traumatologiju, 21000 Novi Sad, Hajduk Veljkova 1-7, E-mail: radmila.matijevic@mf.uns.ac.rs

Abbreviations

WHO – World Health Organization
SD – standard deviation
BMD – bone mineral density
FRAX – fracture risk assessment
RCT – randomized controlled trial
US – United States

have a reliable screening tool to identify high-risk patients for interventions, it is equally or more important to have intervention thresholds appropriate for the country or populations. FRAX® is now a part of 120 guidelines and many are using it for treatment decision making even without BMD [4].

Osteoporosis has a systemic nature and because of it associated increase in fracture risk is present at all skeletal sites, although hip, wrist and spine are considered as prototypical osteoporotic fractures and they are strongly associated with BMD reduction. However, the incidence of all other fractures (non-hip, non-vertebral) is much higher and collectively these fractures result in more immense economic burden for the society [5].

Hip fractures, associated with pain and an inability to put weight on the affected leg, usually require surgical treatment and are correlated with substantial decline in functional status and quality of life, more than all other types of fractures, high mortality (21% to 30% of patients who experience a hip fracture die within 1 year), and consequent medical costs. An estimated 2.7 million hip fractures occurred in 2010 worldwide, of which 1 364 717 (51%) were calculated to be potentially preventable (264 162 in men, and 1 100555 in women), if osteoporosis (defined as a femoral neck T score of – 2.5 SD or less) could be avoided [6].

Although various treatment modalities for osteoporosis have been shown to be highly effective, there is evidence to suggest that only a minority of patients receive treatment. At the turn of the century, 9 million fragility fractures occurred annually. This included 1.6 million hip fractures which impose a devastating burden on sufferers and their families, and all too often result in premature death. The 1.4 million individuals who sustained vertebral fractures endure back pain, loss of height and many other adverse effects on the quality of their lives. The cost that osteoporosis imposes on healthcare budgets is staggering. In 2010, the European Union countries spent € 37 billion (US$ 40 billion), while in 2015 the United States (US) spent US$ 20 billion [7]. A recent report issued by the US National Osteoporosis Foundation estimated that 2 million Americans had 2.3 million osteoporotic fractures in 2015, with only 9% undergoing BMD testing within 6 months of the fracture. During the first 2 – 3 years after fracture, a succeeding fracture occurred in 307 000 of these individuals incurring a cost of more than 6.3 billion US dollars [8].

This untreated population with osteoporosis is referred to as 'the osteoporosis treatment gap', and recent studies have sought to introduce interventions to reduce it [7]. Despite the introduction of fracture risk assessment tools, and variety of available drugs, there has been a reduction in prescribing treatment for osteoporosis in

Table 1. Anti-fracture efficacy of approved treatments for postmenopausal osteoporosis
Tabela 1. *Antifrakturna efikasnost osteoporotskih lekova*
Available at http://www.worldosteoporosisday.org/sites/default/WOD-2019/resources/compendium/2019-IOF-Compendium-of-Osteoporosis

	Effect on vertebral fracture risk/*Efekat na vertebralne frakture*	Effect on non-vertebral fracture risk/*Efekat na nevertebralne frakture*	Effect on hip fracture risk/*Efekat na prelome kuka*
Alendronate/*Alendronat*	+	+	+
Risedronate/*Risendronat*	+	+	+
Ibandronate/*Ibandronat*	+	–	–
Hormone replacement therapy *Hormonska supstituciona terapija*	+	+	+
Zoledronic acid/*Zolendrična kiselina*	+	+	+
Raloxifene/Bazedoxifene *Raloksifen/Bazedoksifen*	+	–	–
Teriparatide/*Teriparatid*	+	+	–
Abaloparatide/*Abaloparatid*	+	+	–
Denosumab/*Denosumab*	+	+	+
Romosozumab/*Romosozumab*	+	+1	+1

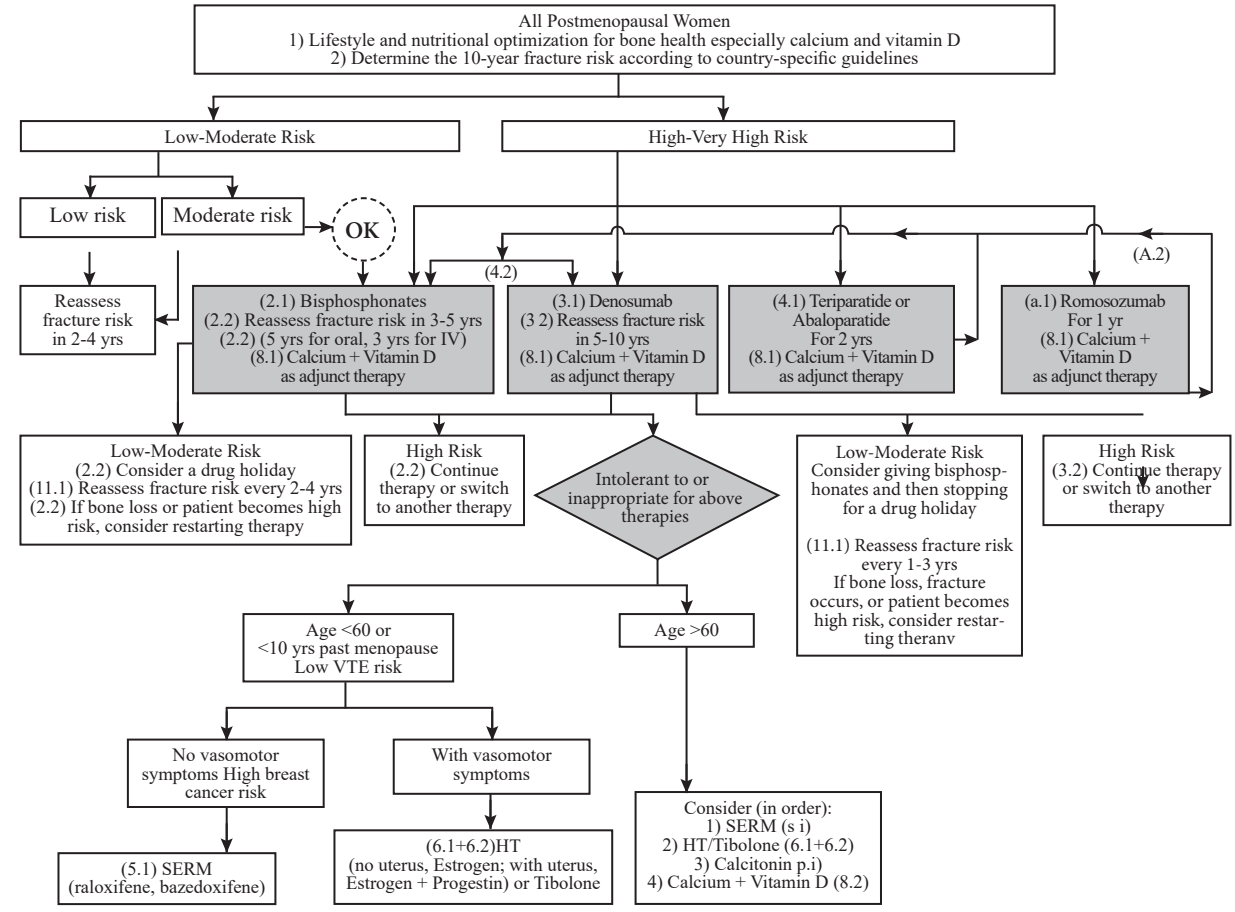
Legend: + significant reduction of fracture in randomized placebo-controlled clinical trials (RCTs) of variable duration (18 months to 6.8 years); - not demonstrated in primary risk; +1 in sequence with alendronate vs alendronate alone
Note: results from subgroup and post-hoc analyses or meta-analyses have not been considered.
As of September 2019, romosozumab has been approved in Australia, Canada, Japan, South Korea and the United States of America. Abaloparatide has been approved in the United States of America.
Legenda: + značajno smanjenje incidence preloma u randomizovanoj placebo kontrolisanim kliničkim studijama (RCT) različite dužine trajanja (od 18 meseci do 6,8 godina); - Nije dokazano u RCT; +1 u sekvenci sa alendronatom u odnosu na primenu samo alendronata
Napomena: rezultati subgrupa i post-hok analiza ili meta-analiza nisu uzimane u razmatranje.
Od septembra 2019. godine Romosozumab je registrovan u Australiji, Kanadi, Južnoj Koreji i Sjedinjenim Američkim Državama. Abaloparatid je registovan u Sjedinjenim Američkim Državama.

some developed countries, United Kingdom and United States of America included [9, 10]. This trend may reflect inadequate spotlighting in the mass media of rare adverse events associated with bisphosphonate use, such as osteonecrosis of the jaw and atypical femoral fractures [7]. There is, however, little evidence to suggest that the risk of these adverse events is significantly higher in individuals taking bisphosphonates for 10 years, compared to age-matched controls [11].

In order to increase identification of individuals at risk of fracture, prescribing rates of osteoporosis drugs, and thus reduce the osteoporosis treatment gap, vigorous screening programs are required. The WHO recommends that individuals be identified as either at high, medium or low risk of fracture. Following this, they recommend that high-risk individuals be considered for treatment, low-risk individuals not be recommended for treatment and medium-risk individuals be further assessed with a measurement of BMD [2]. Studies and trials from different countries and regions (Aberdeen, COSHIBA, ROSE and SCOOP) had major findings pointing out that allocation to screening increased the prescription of osteoporosis medications, reduced fracture incidence and risk of fracture (any site) in the screened groups [12–15].

The role of calcium supplementation, with or without vitamin D, has been the subject of considerable scientific debate in the literature during the last years. In the 2019 Compendium, on the basis of the current evidence, the International Osteoporosis Foundation and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases recommended that calcium and vitamin D supplements are generally appropriate for those with a high risk of calcium and vitamin D insufficiency and those who are receiving treatment for osteoporosis [7]. The objective of treating osteoporosis is to reduce the likelihood of fragility fractures by strengthening the skeleton and decreasing the fall frequency, or both. Healthy life style (good nutrition, regular physical activity, unfavorable lifestyle habits avoidance) are recommended for all patients at risk of osteoporosis. During the last three decades, a broad range of therapeutic options have become available to reduce risks of fragility fractures. These medicines are available in a uniquely flexible array of dosing regimens,

Scheme 1. Endocrine Society Guideline Update
Shema 1. *Dopunjeni vodič Endokrinološkog društva*



Available at https://academic.oup.com/jcem/article/104/5/1595/5418884

which includes daily, weekly or monthly oral tablets, daily, three-monthly and six-monthly injections, or annual infusions [7]. The anti-fracture efficacy of the most commonly used agents for postmenopausal osteoporosis is summarized in **Table 1.**

The Endocrine Society has updated treatment guidelines for osteoporosis in postmenopausal women to include or alter treatments with romosozumab, selective estrogen receptor modulators, menopausal hormone therapy and tibolone, calcitonin, and calcium and vitamin D. The update was published in February this year in *The Journal of Clinical Endocrinology &Metabolism*. It was issued, in part, due to the recent approval of romosozumab, a monoclonal antibody targeting sclerostin. The treatment was approved by the United States Food and Drug Administration, the European Medicines Agency, and Health Canada [16] **(Scheme 1).**

References

1. Kovacev Zavisić B, Ristanović V, Tijana I, Novakovic Paro J. Efficacy of ibandronat 150 mg given once a month in the treatment of postmenopausal osteoporosis on the basis of biochemical bone markers – adhero study. Med Pregl. 2012;65(9-10):379-82.

2. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. World Health Organ Tech Rep Ser. 1994;843:1-129.

3. Schuit SC, van der Klift M, Weel AE, de Laet CE, Burger H, Seeman E, et al. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. Bone. 2004;34(1);195-202.

4. Kanis JA, Harvey NC, Cooper C, Johansson H, Odén A, McCloskey EV. A systematic review of intervention thresholds based on FRAX: a report prepared for the National Osteoporosis Guideline Group and the International Osteoporosis Foundation. Arch Osteoporos. 2016;11(1):25.

5. Compston JE, McClung MR, Leslie WD. Osteoporosis. Lancet. 2019;393(10169):364-76.

6. Oden A, McCloskey EV, Johansson H, Kanis JA. Assessing the impact of osteoporosis on the burden of hip fractures. Calcif Tissue Int. 2013;92(1):42-9.

7. Cooper C, Ferrari S, Mitchel P. IOF compendium of osteoporosis. 2nd ed. Nyon: International Osteoporosis Foundation; 2019.

8. Compston J. Reducing the treatment gap in osteoporosis. Lancet Diabetes Endocrinol. 2020;8(1):7-9.

9. Solomon DH, Johnston SS, Boytsov NN, McMorrow D, Lane JM, Krohn KD. Osteoporosis medication use after hip fracture in U.S. patients between 2002 and 2011. J Bone Miner Res. 2014;29(9):1929-37.

10. van der Velde RY, Wyers CE, Teesselink E, Geusens PPMM, van den Bergh JPW, de Vries F, et al. Trends in oral anti-osteoporosis drug prescription in the United Kingdom between 1990 and 2012: variation by age, sex, geographic location and ethnicity. Bone. 2017;94:50-5.

11. LeBlanc ES, Rosales AG, Black DM, Genant HK, Dell RM, Friess DM, et al. Evaluating atypical features of femur fractures: how change in radiological criteria influenced incidence and demography of atypical femur fractures in a community setting. J Bone Miner Res. 2017;32(11):2304-14.

12. Barr RJ, Stewart A, Torgerson DJ, Reid DM. Population screening for osteoporosis risk: a randomised control trial of medication use and fracture risk. Osteoporos Int. 2010;21(4):561-8.

13. Clark EM, Gould V, Morrison L, Ades AE, Dieppe P, Tobias JH. Randomized controlled trial of a primary care-based screening program to identify older women with prevalent osteoporotic vertebral fractures: Cohort for Skeletal Health in Bristol and Avon (COSHIBA). J Bone Miner Res. 2012;27(3):664-71.

14. Rubin KH, Rothmann MJ, Holmberg T, Høiberg M, Möller S, Barkmann R, et al. Effectiveness of a two-step population-based osteoporosis screening program using FRAX: the randomized Risk-stratified Osteoporosis Strategy Evaluation (ROSE) study. Osteoporos Int. 2018;29(3):567-78.

15. McCloskey E, Harvey N, Johansson H, Lorentzon M, Vandenput L, Kanis JA. Screening for high fracture risk. Osteoporos Int. 2020;31(6):1179-80.

16. Shoback D, Rosen CJ, Black DM, Cheung AM, Murad MH, Eastell R. Pharmacological management of osteoporosis in postmenopausal women: an endocrine society guideline update. J Clin Endocrinol Metab. 2020;105(3):dgaa048.

Rad je primljen 23. IX 2020.
Prihvaćen za štampu 23. IX 2020.
BIBLID.0025-8105:(2020):LXXIII:5-6:135-138.