Austin Journal of Orthopedics & Rheumatology

Open Access

Austin Publishing Group

Review Article

What is Missing in the Diagnosis and Treatment of Osteoporosis Including the Impact of the SARS-CoV-2 Pandemic?

Pietrzyk BZ*
Department of Medical Biophysics, Medical University of Silesia, Poland

***Corresponding author:** Pietrzyk BZ, Department of Medical Biophysics, Medical University of Silesia, Faculty of Medical Sciences in Katowice, 18 Medyków Street, 40-752 Katowice, Poland

Received: June 27, 2022; **Accepted:** July 26, 2022; **Published:** August 02, 2022

Abstract

Osteoporosis is a civilization disease characterized by an increased risk of bone fractures as a result of progressive bone loss. The diagnosis of osteoporosis and the assessment of fracture risk are based on a medical examination, imaging diagnostics and laboratory tests. Identifying people at risk is a priority in preventive treatment, and people with already diagnosed osteoporosis require proper treatment. Osteoporotic fractures are the main cause of disability and thus a significant deterioration in the quality of life of patients, which is why the goals of osteoporosis treatment include the prevention of low-energy fractures and the overall improvement of the quality of life. Therefore, a long-term medical care strategy should be planned according to the individual risk of fracture for each patient.

This article is an analysis of selected aspects of the principles of diagnostic and therapeutic procedures in osteoporosis, which due to the SARS-CoV-2 pandemic, were partially or completely omitted, or it was not possible to implement them properly.

Keywords: Osteoporosis; SARS-CoV-2 pandemic; Densitometry; Bone fractures; Health consequences

Introduction

Osteoporosis is a chronic disease of the skeletal system, which is characterized by progressive loss of Bone mineral density (BMD) resulting in an increased risk of pathological fractures and eventually a fracture [1]. Due to the oligosymptomatic puncture, an osteoporotic (low energy) fracture is usually the first serious symptom of the disease [2]. The SARS-CoV-2 pandemic has not changed the diagnostic and therapeutic methods of osteoporosis, but it has contributed to a significant reduction in their availability. Isolation of patients due to the diagnosis of COVID-19, hospitalizations, and the obligation to quarantine, significantly distanced the possibility of a quick diagnosis of osteoporosis and contributed to an increase in the incidence of low-energy fractures [3]. The process of development of the disease is slow, bone tissue degradation occurs over years, so the impact of the two-year SARS-CoV-2 pandemic on the progression of the disease is not yet fully visible. However, we can already notice a significant decrease in the number of medical consultations and diagnostic tests for osteoporosis, including the basic imaging examination – densitometry. The consequence of this is the abandonment of therapy and an increase in the number of osteoporotic fractures. The growing percentage of older people suffering from osteoporosis is associated with surgical treatment, and as a result, an increase in disability after fractures. Using the diagnostic criterion of the World Health Organization (WHO), it has been estimated that currently about 200 million people in the world suffer from osteoporosis, including 22 millionwomen and 5.5 million men in the European Union (EU), of which a total of 2.1 million people are in Poland [4].

Epidemiology and Diagnosis of Osteoporosis

In the current pandemic situation, the leading area is the possibility of performing diagnostic tests in general, as well as gradually increasing the efficiency of densitometric laboratories. It seems that such a scheme will allow earlier and more optimized treatment, and thus minimize the costs of possible hospitalizations. In Poland, the number of medical visits to specialist offices - orthopedists and rheumatologists decreased by 1/3. It was estimated that 74% of the population equal to 1.56 million were undiagnosed, of which about 500,000 patients were over 80 years old. The number of densitometric tests performed also decreased in 2020 by about 36%, and similar numbers apply to hip arthroplasty procedures [5]. In a 2021 global study by Fuggle and colleagues entitled: 'How has COVID-19 affected the treatment of osteoporosis?' the impact of the COVID-19 pandemic on the treatment and diagnosis of patients with osteoporosis was collected and traced. It was found that 7% of specialist clinics covering rheumatology, endocrinology, orthopedics were closed, as was the case in densitometric laboratories – 5% of institutions completely stopped accepting patients. As a result, less than 30% of the assumed densitometric tests were carried out. It was shown that 43% of doctors had limited possibilities of conducting therapy, due to the limitation of patients' access to medical services – only 20% of them held "face to face" medical visits, the remaining advice took place in the form of tele-advice (33%) and videoconferences (21%). On the basis of the collected and analyzed data, a negative impact on the diagnosis and treatment of people suffering from osteoporosis by the COVID-19 pandemic was found, which is associated with a significant increase in morbidity and new low-energy fractures [6]. Immobilization

Citation: Pietrzyk BZ. What is Missing in the Diagnosis and Treatment of Osteoporosis Including the Impact of the SARS-CoV-2 Pandemic?. Austin J Orthopade & Rheumatol. 2022; 9(2): 1112.

of patients after hip fracture and the resulting cardiopulmonary complications are the cause of thousands of deaths every year in the world [7]. Fractures of the proximal end of the femur are a significant health problem in the elderly, affecting about 1.5 million people a year worldwide. It is estimated that this figure is increasing and will affect 2.6 million by 2025 and 4.5 million by 2050, mainly due to the ageing of the population [8].

The consequences of a hip fracture are severe; a third of patients die within the first postoperative year. The highest population mortality rate in the early postoperative period is recorded, reaching 13.3% within the first 30 days after surgery [9]. Studies indicate numerous risk factors for early mortality after hip fracture, but the results are inconsistent, and the selection of specific risk predictors and their definition sometimes vary significantly [10].

Despite the continuous development of medicine and technology, and thus medical diagnostics, osteoporosis often remains undiagnosed, and is also associated with incomplete and unsatisfactory treatment of patients. Primary osteoporosis, both postmenopausal (PMO) and senile osteoporosis, has been a serious social problem for years and due to its prevalence, it is considered a civilization disease [11]. It occurs in the aging population of women in particular (globally over 30% of postmenopausal women) [12]. More than 40% of them are expected to suffer one or more fractures of fragility over the rest of their lives [13]. Difficulties in the proper conduct of the diagnostic and therapeutic process during the COVID-19 pandemic were noticeable from both doctors and patients. The need for isolation caused by SARS-CoV-2 virus infection, lack of access to facilities, postponement of medical visits, thus abandoning the implementation of therapy in newly diagnosed people, contributed to a decrease in the number of prescribed drugs [14]. Currently, more and more often, the trend for using personalized therapies tailored to a specific patient is being observed. Prolonged restrictions – staying at home, and thus lack of exercise and a sedentary lifestyle, contributed to the increase in risk factors for the development of the disease, while not forgetting about other factors such as, for example, vitamin D3 deficiency and insufficient calcium supply [15]. The goal of osteoporosis treatment is to avoid fracture, and this consists primarily of educational activities aimed at preventing falls, a healthy lifestyle, calcium, and vitamin D3 supplementation. These methods of prevention and treatment should be offered primarily to people that have suffered a low-energy fracture, regardless of the BMD value or any other diagnostic criteria for osteoporosis. The pandemic situation significantly reduced the early and rapid diagnosis of osteoporosis, which disrupted the process of implementing treatment. In the case of patients after a fracture, it partially restricted the prevention of further osteoporotic fractures, while for patients who suffered a fracture before the outbreak of the pandemic, it is associated with a significant deterioration in the long-term quality of life and an increase in the mortality rate [16]. Osteoporotic bone fractures are not only a significant health and psychological problem, but due to disability of the patient, they also generate economic problems [17]. The lifetime risk of hip, vertebral and wrist fractures, estimated at 40%, is similar to the risk of coronary heart disease [18].

Bone densitometry (DXA) is the gold standard in the diagnosis of osteoporosis, although because of a lack of universal access to a densitometric laboratory, its relatively high cost, and a long waiting period for the examination, DXA is not performed on a large scale [19]. If appropriate osteoporosis treatment is needed, the density diagnostic criterion is T-score ≤ -2.5 [20]. The reference locations in the examination are the proximal end of the femur and the lumbosacral spine, although on the basis of an X-ray alone, compression fractures of the vertebrae can be successfully determined due to existing osteoporosis. Studies show a large group of fractures in women whose T-score is in the range from -1.0 to -2.5. i.e., it does not meet the criterion of osteoporosis. The T-score in this range indicate a state of osteopenia, which does not warrant the implementation of full treatment with drugs registered foran indication of osteoporosis according to WHO criteria [21]. Various expert positions are still being presented to try to expand the criteria for the diagnosis of osteoporosis by the T-score range including osteopenia in order to implement treatment and thus prevent fractures in this predisposed group [22]. This problem has been noticed, resulting in refreshed guidelines from the American Association of Clinical Endocrinology (AACE) and the American College of Endocrinology (ACE) [23]. Noting the prevalence of hip fractures in the population, it is important to re-systematize knowledge in the post-pandemic period and optimize the quality of medical care putting a strong emphasis on prevention, which has significantly weakened during the pandemic period [6]. Awareness of the disease and education of sick patients is an indispensable complement to pharmacological treatment conditioning its proper course. Individual diet selection and lifestyle change recommendations should be adjusted according to the degree of diagnosed bone mineralization changes. The problem of educating patients should not only be addressed and left to the discretion of specialist doctors, but also become a basic element of conversation during visits to diagnostic laboratories, in particular after visits to densitometric laboratories. The need to popularize the use of the fracture risk assessment calculator - FRAX® (Fracture Risk Assessment Tool) and to conduct large-scale education in the field of risk factors, basics of pathophysiology of the disease, dietary recommendations, and physical activity, is still relevant [24]. The algorithm of this tool calculates the probability of fracture of the proximal end of the femur or other significant osteoporotic fracture (clinical spine, hip, forearm, and humerus) over the next 10 years, considering risk factors. It is recommended to calculate the individualized risk of fractures in people 40 years of age and older and for women aged 65 years and older to undergo routine screening for osteoporosis [25]. Unfortunately, the pandemic has effectively inhibited the number of and access to doctor's office visits, but also has significantly slowed down the process of estimating the risk assessment of osteoporotic fracture. Research by McCloskey et al. showed that at the beginning of the pandemic in 2020 in Europe, the number of page views on which the FRAX calculator is available decreased by approximately 50%, which may indirectly indicate a probable decrease in the frequency and estimation of fracture risk [26]. In the case of patients after hip fracture and identification of the "weaker" side of the body, it is recommended to carry out an additional advanced assessment: AHA (Advanced Hip Analysis), Hip Axis Length (HAL), Femur Strength System (FIS) and Cross-Sectional Moment of Inertia (CSMI)[27].

In addition to the factors mentioned above, routine laboratory parameters can also predict disease progression and mortality. Low

hemoglobin, total leukocyte, and albumin counts, as well as high creatinine and Parathyroid Hormone (PTH) levels are associated with a higher likelihood of death one year after surgery in patients after hip fracture [28]. The potential effect of vitamin D3 (1,25(OH)2D) on mortality is still quite controversial. Many studies have shown an inverse relationship between (1.25(OH)2D) and mortality [29], while other studies have not shown such an association [30]. It should be noted that in patients infected with the SARS-CoV-2 virus and with vitamin D3 deficiency, an escalation of markers of the inflammatory response was observed, which may indirectly affect the increase in the mortality rate [31]. Only limited information is available on vitamin D3 as a potential risk factor for postoperative medical complications [32], as is the lack of specific information on C-reactive Plaque (CRP) as a potential predictor of annual mortality after hip fracture, while there are data showing no association between CRP and mortality at 3 months after surgery [33].

Patients who have suffered an osteoporotic fracture have a higher mortality rate than people of the same age, without a fracture. However, it is not significant to what extent the fracture is responsible for this and to what extent the patient's state of health before the fracture was responsible for this [34]. Patients with a fracture of the proximal end of the femur, and especially the elderly group, are at high risk of complications, including cardiac ones. Evaluation of brain natriuretic peptide (NT-proBNP) concentrations only partially allows the prediction of cardiac complications in surgical patients. The usefulness of this test in patients after hip surgery is not clear. Thus, it is important to evaluate a more accurate NT-proBNP cut-off value excluding patients with renal insufficiency [35]. There are several tools to help predict complications after hip fracture surgery, including the American Society of Anesthesiologists (ASA) classification [36], American Heart Association (AHA) guidelines [37] and Goldman Heart Risk Index (GCRI) [38] and altered heart risk index (RCRI) [39]. In this case, it seems reasonable for orthopedic doctors and cardiologists who use these tools in practice to cooperate. The role of NT-terminal segment of type B natriuretic pro-peptide (NT-proBNP) as a predictive factor for postoperative cardiac complications and mortality in patients with hip fractures is still being discussed [40]. Elevation of the NT-terminal segment of type B natriuretic pro-peptide (NT-proBNP) proved to be more useful than the ASA classification in independent prediction of postoperative cardiac complications [41]. Studies, however, have also included patients with hip fractures and kidney dysfunction, even though NT-proBNP levels are known to be severely impaired by abnormal kidney function [42]. Therefore, there is a need for further evaluation of the relationship between preoperative NT-proBNP and cardiac complications in the immediate postoperative period after hip fracture surgery. Patients with renal insufficiency may be an additional study group to determine the degree of risk of hip fracture, primarily due to the high prevalence of metabolic bone disease in these patients [43]. Studies indicate that they are several times more susceptible to hip fracture than the general population [44]. Comorbidities such as diabetes, chronic heart disease and cancer are significant risk factors for mortality in all patients after hip fracture surgery. Concomitant bone diseases in patients with renal insufficiency are common and contribute to significant mortality in this group of patients, in addition to an independent risk factor for death, i.e., dialysis therapy [45]. Albumin is a negative protein of the acute phase, a violation of the level of albumin in the plasma disrupts all processes associated with filtration and penetration of water through the walls of blood vessels, such as the formation of urine, extracellular fluid, and lymph. Low levels of albumin occur with age, malnutrition, drugs such as corticosteroids, and also with chronic diseases (e.g., liver, kidneys, rheumatoid arthritis). Most studies indicate albumin is an acute phase reactant in response to severe illness or physiological stress. It is also suggested that low albumin levels are of prognostic importance for morbidity and mortality in patients with hip fracture. Albumin level control is one of the indispensable tools of laboratory diagnostics, facilitating surgical planning and selection of implants with a view to probable survival and the possible need for revision [46]. Most of the literature on the role of albumin in hip fracture comes from small clinical trials without correction for possible infections and disorders from the side of joint mobility. For this reason, the literature lacks definitive findings as to the degree of dependence of albumin on the level of prognosis of mortality in these patients. This ambiguity is reflected in clinical trials. There are some controversial reports of high preoperative albumin levels [47], while others show low levels of albumin readings, particularly in patients with diabetes and hip fracture [48]. Kumar and et al. indicate that albumin levels and lymphocyte counts (TLC) are the only clearly significant predictors of mortality at 12 months, and a delay of up to 4 days after surgery does not significantly increase mortality after a year. Thus, the addition of preoperative albumin measurement to studies is a significant indicator of predicting adverse events (postoperative complications) and mortality in patients with hip fracture [49]. Therefore, it seems reasonable to develop and standardize a model for the precise identification of prognostic factors in patients burdened with risk factors for the development of osteoporosis and those with fracture of the proximal end of the femur. It will also increase the chance of determining a group of patients prone to morbidity and postoperative deaths in the first year after hip fractures.

Prevention and Treatment

Proper diagnostic of both imaging and laboratory is the first, i.e., the basic step to undertake pharmacological treatment and possibly after the fracture - surgical treatment, as the final stage determining the future quality of life of the patient. Identifying patients at high risk of early mortality is essential and it provides opportunities for better prognosis and adjustment of care. A simple scoring system allows for preoperative identification and should be used on a daily basis in medical practice [50]. An individualized tool for predicting fracture risk is the GARVAN – FRC (Garvan Fracture Risk Calculator), which can be used in people aged 60 years and older, to calculate the 5- and 10-year risk of hip fracture and all low-energy fractures excluding the bones of the fingers and toes. Both tools can be used with or without considering Bone Mineral Density (BMD) [51,1,52]. Studies point to significant differences between practice and guidelines and show that more than 2/3 of patients do not receive optimal treatment as recommended [53,54]. They clearly indicate a high percentage of incorrectly diagnosed or undiagnosed and untreated Postmenopausal Osteoporosis (PMO) [55,56].

Different risk models for mortality of patients after hip fracture in the early postoperative period have been developed and

presented [57]. The Nottingham Hip Fracture (NHFS) scale shows the most promising results so far [58]. However, with the ageing of the population and the increase in fractures, there is still room for its unification and completion [59]. According to the NHFS, more than 87% of patients achieved risk values for 30-day postoperative mortality of 11.8% or less [60]. Precise identification of risk factors increases the chance of identifying patients prone to morbidity and postoperative deaths in the first year after hip fractures. Patient-specific factors such as age, gender, overall health, and concomitant diseases, i.e., heart disease and dementia, have been identified as potential risk factors [9,61].

For many years, pharmacological treatment of osteoporosis has been based on two groups of drugs: the first antiresorption aimed at inhibiting the increased activity of osteoclasts, the second anabolic - stimulating the action of osteoblasts [62]. The gold standard for the treatment of osteoporosis, especially in the population of postmenopausal women, are Bisphosphonate (BPS) drugs, which have antiresorptive effects by inhibiting osteoclast activity and promoting their apoptosis [63]. Currently, Monoclonal Antibodies (mAbs) are increasingly seen as new therapeutic possibilities in the treatment of osteoporosis. The effectiveness of the therapy is assessed primarily by reducing the risk of fractures at the reference locations: the proximal end of the femur and the lumbar spine [64]. The inclusion of biological therapy - monoclonal antibodies, shows higher effectiveness than the standard pharmacological treatment used so far. The recommendations indicate the success of treatment with sequential therapy - first anabolic treatment, followed by treatment with an antiresorptive drug [65]. FRAME was the first study to show that starting treatment with an anabolic drug followed by a potent antiresorptive drug was more effective than starting antiresorption therapy. Patients who received romosozumab followed by denosumab had an 80% greater reduction in the risk of vertebral fractures in the second year of the FRAME study compared to the placebo-denosumab group [66].

Current research confirms the advantage of anabolic drugs over the antiresorption treatment used so far, primarily on their high effectiveness and speed of action [67]. Meanwhile, the SARS-CoV-2 pandemic has very visibly highlighted the lack of access to basic diagnostics. Many patients already using injection treatment may have completely abandoned therapy, and in the case of oral drugs, not taken them regularly [68]. As a consequence, this will contribute to the recurrence of the disease, as well as a real increase in the risk of another fracture [69]. The results of Sharman Moser et al. showed that half of the group of about 18,000 women studied did not take oral antiresorption drugs with the correct frequency, which was clearly associated with a higher risk of low-energy fracture [70]. In the assessment of the 3-year risk of re-fracture, values were indicated to be lower by 44% in people who used systematic antiresorption treatment, compared to patients who did not use pharmacotherapy. In those treated the risk of death decreased by 64% [71].

Pandemic times have limited the availability to patients with osteoporosis of specialists in various fields [6], thus increasing the multidisciplinary problem affecting in particular postmenopausal women with suspicion / and or with metabolic disorders significantly affecting bone metabolism such as, for example: obesity, type 2 diabetes, metabolic syndrome. In these cases, it seems reasonable, in addition to the diagnosis of osteoporosis (primary and secondary) and the assessment of the impact of antiresorption treatment on the risk of osteoporotic fractures, to extend the research to assess the relationship of Bone Mineral Density (BMD) with the levels of markers of bone turnover and particles involved in the control of intracellular signals (sclerostin, OPG, CTX, P1NP) [72]. In the case of imaging diagnostics, it is suggested to use densitometric examination not only to determine bone disorders, but also to diagnose other diseases, including those that are high risk factors for osteoporotic fractures. For example, assessing body composition not only regarding obesity, but also diseases closely related to it, such as type 2 diabetes, metabolic syndrome [73]. It also allows monitoring of many diseases in which significant eating disorders occur (anorexia, wasting syndromes, chronic kidney disease, Cushing's syndrome, sarcopenia). Densitometric examination also allows the assessment of fat, bone, and muscle tissue distribution in individual body compartments. This is important in the assessment of visceral fat, the presence of which is associated with an increased risk of cardiovascular disease, hyperlipidemia, and type 2 diabetes. It allows you to assess the change in body composition during treatment of obesity (depending on the diet used), or autoimmune diseases (lupus, systemic scleroderma, rheumatoid arthritis), and the effectiveness of physical training and treatment of people with type 2 diabetes [74]. The recommendations clearly indicate the importance of introducing broadly understood guidelines around prevention of osteoporosis and the above-mentioned diseases at an early stage of the patient's life. Prevention of osteoporosis should apply not only to middle-aged and elderly people, but also to young and very young people, in line with the 'Capture the fracture' campaign promoted by the International Osteoporosis Foundation (IOF) [75]. Comprehensive osteoporosis prevention should be aimed at essentially all people at different risk groups, including menopausal women and men aged 60 and over [76]. In this group of people especially, there is an urgent need to eliminate modifiable risk factors. It is recommended to have an optimal diet, calcium supplementation (about 1200 mg /d), vitamin D3 (basic dose 1000-2000 IU / d) and physical activity to improve motor skills, as well as in the prevention of falls [77]. It is estimated that 8.9 million osteoporotic fractures occur annually worldwide [78]. Hernlund et al. indicate that the number of fractures in Europe will increase from 3.5 million in 2010 to 4.5 million in 2025 [4]. As a result, it is an absolute necessity to conduct extensive education in all age groups aimed at recognizing and counteracting risk factors for osteoporosis. It seems that the consideration of long-term educational activities in the long term cannot be expected a significant decrease in the number of osteoporotic fractures and deaths. By limiting the possibility of direct contact between patients and doctors, the pandemic caused by the SARS-CoV-2 virus significantly contributed to the disruption of the diagnostic regimen and, as a result, revealed irregularities in proper treatment. Although the introduction of restrictions and limitation of interpersonal contact has significantly minimized the spread of the SARS-CoV-2 virus, the inability to diagnose and treat osteoporosis (in particular the continuation of therapy for previously diagnosed patients) translates directly into an increase in morbidity and number of new low-energy fractures. The lack of medical visits, not to mention diagnostics, will often cause irreversible health consequences, and the cessation of therapy in

the case of people already diagnosed, in the near future will lead to permanent disability and a significant deterioration in their quality of life. However, it is worth remembering that abandoning therapy will not immediately translate into an increased current number of fractures. It will be a long-term process, gradually spread over time. It seems that during the pandemic an important aspect was primarily the attempt to maintain the applicable standards of patient care, which are updated on a regular basis. A strategic point in the updated guidelines is to propose a therapeutic treatment based on an assessment of fracture risk, with particular emphasis on postmenopausal osteoporosis [23]. In the current situation, it is crucial to re-implement the correct treatment procedures while maintaining the sequence of actions continuing the care of patients with osteoporosis. In turn, screening tests dedicated to undiagnosed people from high-risk groups of fractures to still current and growing problem [79].

Conclusions

1. The COVID-19 pandemic has significantly affected the quality of treatment of chronic diseases such as osteoporosis. Identifying people at risk of osteoporosis, especially postmenopausal osteoporosis, is a priority in preventive treatment. The easing of the current pandemic does not necessarily mean the disappearance of the SARS-CoV-2 virus, and thus the end of these infections. Over time, the acquired immunity in the population will decrease, so further outbreaks of COVID-19 can be expected in the future [80].

2. This phenomenon should be taken into account when sealing diagnostic and therapeutic systems for chronic diseases, including osteoporosis.

References

1. van der BurghAC, de KeyserCE, ZillikensMC, StrickerBH. The Effects of Osteoporotic and Non-osteoporotic Medications on Fracture Risk and Bone Mineral Density. Drugs. 2021; 81: 1831-1858.
2. Cosman F, Beur SJD, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporosis International. 2014; 25: 2359-2381.
3. Hall AJ, Clement ND, MacLullich AMJ, White TO, Duckworth AD. IMPACT-Scot 2 report on COVID-19 in hip fracture patients. The bone & joint journal. 2021; 103-B: 888-897.
4. HernlundE, SvedbomA, Ivergård M, CompstonJ, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: medical management, epidemiology, and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch. Osteoporos. 2013; 8: 136.
5. National Health Fund, Department of Analysis and Strategy - about health: Osteoporosis. 2019. Warsaw, ISBN: 978-83-944 034-5-4
6. FuggleNR, SingerA, GillC,Patel A, Medeiros A, MlotekAS, et al. How has COVID-19 affected the treatment of osteoporosis? An IOF-NOF-ESCEO global survey. Osteoporos Int. 2021; 32: 611-617.
7. GerberY, Melton LJ3rd, McNallanSM, Jiang R, Weston SA, Roger VL. Cardiovascular and noncardiovascular disease associations with hip fractures. Am J Med. 2013; 126: 169.
8. AbrahamsenB, van Staa T, Ariely R, Olson M, CooperC. Excess mortality following hip fracture: a systematic epidemiological review. Osteoporos Int. 2009; 20: 1633–1650.
9. Hu F, Jiang C, Shen J, Tang P, Wang Y. Preoperative predictors for mortality following hip fracture surgery: a systematic review and meta-analysis. Injury. 2012; 43: 676-685.
10. IrelandAW, Kelly PJ, Cumming RG. Risk factor profiles for early and delayed mortality after hip fracture: analyses of linked Australian Department of Veterans. Affairs databases. Injury. 2015; 46: 4–11.
11. Handoll HHG, Elliott J. Rehabilitation for distal radial fractures in adults. The Cochrane database of systematic reviews. 2015; 9: CD003324.
12. Kanis JA, CooperC, Rizzoli R, Reginster JY. Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) and the Committees of Scientific Advisors and National Societies of the International Osteoporosis Foundation (IOF). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2019; 30: 3-44.
13. Lems WF, Raterman HG. Critical issues and current challenges in osteoporosis and fracture prevention. An overview of unmet needs. Therapeutic Advances in Musculoskeletal Disease. 2017; 9: 299-316.
14. García-Sempere A, Hurtado I, Sanfélix-Genovés J, Rodríguez-Bernal C, Peiró S, Sanfélix-Gimeno G. Improving the accuracy of medication adherence measures using linked prescription and dispensation data: findings from the ESOSVAL cohort of patients treated with osteoporosis drugs. Current Medical Research and Opinion. 2019; 35: 1535-1544.
15. Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, et al. National Osteoporosis Guideline Group (NOGG). UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos. 2017; 12: 43.
16. Hampson G, Stone M, Lindsay JR, Crowley RK, Ralston SH. Diagnosis and Management of Osteoporosis During COVID-19: Systematic Review and Practical Guidance. Calcified Tissue International. 2021; 109: 351-362.
17. UpadhyayaGK, IyengarK, JainVK, Vaishya R. Challenges, and strategies in management of osteoporosis and fragility fracture care during COVID-19 pandemic.J Orthop. 2020; 21: 287-290.
18. Broussard DL, Magnus JH. Coronary heart disease risk and bone mineral density among U.S. women and men. Journal of women's health. 2008; 17: 479-490.
19. NayakS, Edwards DL, SalehAA, Greenspan SL. Systematic review, and meta-analysis of the performance of clinical risk assessment instruments for screening for osteoporosis or low bone density. Osteoporos. Int. 2015; 5: 1543-1554.
20. Kanis JA, CooperC, Rizzoli R, Reginster JY. Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) and the Committees of Scientific Advisors and National Societies of the International Osteoporosis Foundation (IOF). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2019; 30: 3-44.
21. Kanis JA, Harvey NC, McCloskey E, Bruyère O, Veronese N, Lorentzon M, et al . Algorithm for the management of patients at low, high, and very high risk of osteoporotic fractures. Osteoporos Int. 2020; 31: 1-12. Erratum in: Osteoporos Int. 2020; 31: 797-798.
22. EliakimA, Litmanovitz I, NemetD. The Role of Exercise in Prevention and Treatment of Osteopenia of Prematurity: An Update. Pediatr Exerc Sci. 2017; 29: 450-455.
23. Camacho PM, Petak SM, Binkley N, Diab DL, Eldeiry LS, Farooki A, et al. American Association of Clinical endocrinologists/ American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis— 2020 update. Endocr Pract. 2020; 26: 1-46.
24. Samelson EJ, Broe KE, Xu H, Yang L, Boyd S, Biver E, et al. Cortical and trabecular bone microarchitecture as an independent predictor of incident fracture risk in older women and men in the Bone Microarchitecture International Consortium (BoMIC): a prospective study. The lancet. Diabetes & endocrinology. 2019; 7: 34-43.
25. Bergh JPWVD, Geel TACMV, Lems WF, Geusens PP. Assessment of Individual Fracture Risk: FRAX and Beyond. Current Osteoporosis Reports. 2010; 8: 131-137.
26. McCloskey EV, Harvey NC, Johansson H, Lorentzon M, Vandenput L, Liu E, et

al. Global impact of COVID-19 on non-communicable disease management: descriptive analysis of access to FRAX fracture risk online tool for prevention of osteoporotic fractures. Osteoporosis International. 2020; 32: 39-46.

27. Nuti R, Brandi ML, Checchia G, Munno OD, Dominguez L, Falaschi P, et al. Guidelines for the management of osteoporosis and fragility fractures. Internal and Emergency Medicine. 2018; 14: 85-102.

28. LaulundAS, Lauritzen JB, Duus BR, Mosfeldt M, Jørgensen HL. Routine blood tests as predictors of mortality in hip fracture patients. Injury. 2012; 43: 1014–1020.

29. Amrein K, Zajic P, Schnedl C,Waltensdorfer A, Fruhwald S, HollA, et al. Vitamin D status and its association with season, hospital, and sepsis mortality in critical illness. Crit Care. 2014; 18: 47.

30. Formiga F, Ferrer A, Megido MJ, Boix L, Contra A, Pujol R. Low Serum Vitamin D is Not Associated with an Increase in Mortality in Oldest Old Subjects: The Octabaix Three-Year Follow-Up Study. Gerontology. 2013; 60: 10-15.

31. Jain A, Chaurasia R, Sengar NS, Singh M, Mahor S, Narain S. Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers. Scientific Reports. 2020; 10.

32. Mosfeldt M, Pedersen OB, Riis T, Worm HO, Mark SV, Jørgensen HL, et al. Value of routine blood tests for prediction of mortality risk in hip fracture patients. Acta Orthopaedica. 2012; 83: 31-35.

33. Vacanti CJ, VanHouten RJ, Hill RC. A Statistical Analysis of the Relationship of Physical Status to Postoperative Mortality in 68,388 Cases. Anesthesia & Analgesia. 1970; 49: 564-566.

34. Schousboe JT. Mortality After Osteoporotic Fractures: What Proportion Is Caused by Fracture and Is Preventable?. Journal of Bone and Mineral Research. 2017; 32: 1783-1788.

35. Nordling P, Kiviniemi T, Strandberg M, Strandberg N, Airaksinen J. Predicting the outcome of hip fracture patients by using N-terminal fragment of pro-B-type natriuretic peptide. BMJ Open. 2016; 6: e009416.

36. Chen L, Liang J, Chen M, Wu C, Cheng H, Wang H, et al. The relationship between preoperative American Society of Anesthesiologists Physical Status Classification scores and functional recovery following hip-fracture surgery. BMC Musculoskeletal Disorders. 2017; 18.

37. Eagle KA, Brundage BH, Chaitman BR, Ewy GA, Fleisher LA, Hertzer NR, et al. Guidelines for perioperative cardiovascular evaluation for noncardiac surgery: report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Committee on Perioperative Cardiovascular Evaluation for Noncardiac Surgery. Circulation. 1996; 93: 1278–1317.

38. Devereaux P, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. Canadian Medical Association Journal. 2005; 173: 627-634.

39. Vasireddi SK, Pivato E, Soltero-Mariscal E, Chava R, James LO, Gunzler D, et al. Postoperative Myocardial Injury in Patients Classified as Low Risk Preoperatively Is Associated with a Particularly Increased Risk of Long-Term Mortality After Noncardiac Surgery. J Am Heart Assoc. 2021; 10: e019379.

40. Ushirozako H, Ohishi T, Fujita T, Suzuki D, Yamamoto K, Banno T, et al. Does N-terminal Pro-brain Type Natriuretic Peptide Predict Cardiac Complications After Hip Fracture Surgery?. Clinical Orthopaedics and Related Research®. 2017; 475: 1730-1736.

41. Luo Y, Jiang Y, Xu H, Lyu H, Zhang L, Yin P, et al. Risk of post-operative cardiovascular event in elderly patients with pre-existing cardiovascular disease who are undergoing hip fracture surgery. International Orthopaedics. 2021; 45: 3045-3053.

42. TakaseH, Dohi Y. Kidney function crucially affects B-type natriuretic peptide (BNP), N-terminal pro-BNP and their relationship. Eur J Clin Invest. 2014; 44: 303–308.

43. Hsu C, Chen L, Chen K. Osteoporosis in Patients with Chronic Kidney Diseases: A Systemic Review. International Journal of Molecular Sciences. 2020; 21: 6846.

44. Guzon-Illescas O, Fernandez EP, Villarias NC, Donate FJQ, Peña M, Alonso-Blas C, et al. Mortality after osteoporotic hip fracture: incidence, trends, and associated factors. Journal of Orthopaedic Surgery and Research. 2019; 14.

45. Lin JC, Liang WM. Mortality, and complications after hip fracture among elderly patients undergoing hemodialysis. BMC Nephrol. 2015; 16: 100.

46. Kieffer W, Rennie C, Gandhe A. Preoperative albumin as a predictor of one-year mortality in patients with fractured neck of femur. Annals of The Royal College of Surgeons of England. 2013; 95: 26-28.

47. Gunnarsson AK, Akerfeldt T, Larsson S, Gunningberg L, Scand J. Increased energy intake in hip fracture patients affects nutritional biochemical markers. Scand J Surg. 2012; 101: 204-210.

48. Pimlott BJ, Jones CA, Beaupre LA, Johnston DWC, Majumdar SR. Prognostic impact of pre-operative albumin on short-term mortality and complications in patients with hip fracture. Archives of gerontology and geriatrics. 2011; 53: 90-94.

49. Kumar V, Alva A, Akkena S, Jones M, Murphy PN, Clough T. Are albumin and total lymphocyte count significant and reliable predictors of mortality in fractured neck of femur patients?. European Journal of Orthopaedic Surgery & Traumatology. 2013; 24: 1193-1196.

50. LiX P, Zhang P, Zhu SW, Yang MH, Wu XB, Jiang XY. All-cause mortality risk in aged femoral intertrochanteric fracture patients. J Orthop Surg Res. 2021; 16: 727.

51. Cosman F. ANABOLIC THERAPY AND OPTIMAL TREATMENT SEQUENCES FOR PATIENTS WITH OSTEOPOROSIS AT HIGH RISK FOR FRACTURE. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2020; 26: 777-786.

52. Sandhu SK, Nguyen ND, Center JR, Pocock NA, Eisman JA, Nguyen TV. Prognosis of fracture: evaluation of predictive accuracy of the FRAX algorithm and Garvan nomogram. Osteoporos Int. 2010; 21: 863–871.

53. Nguyen TV. Individualized fracture risk assessment: State-of-the-art and room for improvement. Osteoporosis and Sarcopenia. 2018; 4: 2-10.

54. BollandMJ, SiuAT, Mason BH, HorneAM, AmesRW, GreyAB, et al. Evaluation of the FRAX and Garvan fracture risk calculators in older women. J Bone Miner Res. 2011; 26: 420–427.

55. Kanis JA, Oden A, Johansson H, Borgstrom F, Strom O, McCloskey E. FRAX and its applications to clinical practice. Bone. 2009; 44: 734–743.

56. Andrade SE, Majumdar SR, Chan KA, Buist DS, Go AS, Goodman M, et al. Low frequency of treatment of osteoporosis among postmenopausal women following a fracture. Arch Intern Med. 2003; 163: 2052-2057.

57. Marufu TC, Mannings A, Moppett IK. Risk scoring models for predicting peri-operative morbidity and mortality in people with fragility hip fractures: Qualitative systematic review. Injury. 2015; 46: 2325-2334.

58. Karres J, Heesakkers NA, Ultee JM, Vrouenraets BC. Predicting 30-day mortality following hip fracture surgery: evaluation of six risk prediction models. Injury. 2015; 46: 371-377.

59. Tarazona-Santabalbina FJ, Ojeda-Thies C, Figueroa-Rodríguez J, Cassinello-Ogea C, Caeiro JR. Orthogeriatric Management: Improvements in Outcomes during Hospital Admission Due to Hip Fracture. Int J Environ Res Public Health. 2021; 18: 3049.

60. Marufu TC, White SM, Griffiths R, Moonesinghe SR, Moppett IK. Prediction of 30-day mortality after hip fracture surgery by the Nottingham Hip Fracture Score and the Surgical Outcome Risk Tool. Anesthesia. 2016; 71: 515–521.

61. Raheman FJ, Rojoa DM, Nayan –Parekh J, Berber R, Ashford R. Meta-analysis and metaregression of risk factors associated with mortality in hip fracture patients during the COVID-19 pandemic. Sci Rep. 2021; 11: 10157.

62. Siris ES, Adler R, Bilezikian J, Bolognese M, Dawson-Hughes B, Favus MJ, et al. The clinical diagnosis of osteoporosis: a position statement from the National Bone Health Alliance Working Group. Osteoporosis International.

2014; 25: 1439-1443.

63. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clinic proceedings. 2008; 83: 1032-1045.

64. Qaseem A, Forciea MA, McLean RM, Denberg TD. Clinical Guidelines Committee of the American College of Physicians, et al. Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update from the American College of Physicians. Ann Intern Med. 2017; 6: 818-839.

65. Cosman F, Nieves JW, Dempster DW. Treatment Sequence Matters: Anabolic and Antiresorptive Therapy for Osteoporosis. Journal of Bone and Mineral Research. 2017; 32: 198-202.

66. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, et al. Romosozumab. treatment in postmenopausal women with osteoporosis. N Engl J Med. 2016; 375: 1532–1543.

67. McClung MR. Role of bone forming agents in the management of osteoporosis. Aging Clinical and Experimental Research. 2021; 33: 775–791.

68. Torres-Naranjo F, Peña-Rodríguez PDL, López-Cervantes RE, Morales-Torres J, Morales-Vargas J, Gutiérrez-Hermosillo H, et al. Joint position statement on management of patient with osteoporosis during COVID-19 contingency from the AMMOM, CONAMEGER, FELAEN, FEMECOG, FEMECOT, and ICAAFYD. Archives of Osteoporosis. 2021; 16.

69. Silverman S, Gold DT. Medication Decision-making in Osteoporosis: Can We Explain Why Patients Do Not Take Their Osteoporosis Medications?. Current Osteoporosis Reports. 2018; 16: 772-774.

70. Moser SS, Yu J, Goldshtein I, Ish-Shalom S, Rouach V, Shalev V, et al. Cost and Consequences of Nonadherence With Oral Bisphosphonate Therapy. Annals of Pharmacotherapy. 2016; 50: 262-269.

71. Degli Esposti L, Girardi A, Saragoni S, Sella S, Andretta M, Rossini M, et al. Use of antiosteoporotic drugs and calcium/vitamin D in patients with fragility fractures: impact on refracture and mortality risk. Endocrine. 2019; 64: 367–377.

72. NohJY, YangY, Jung H. Molecular Mechanisms and Emerging Therapeutics for Osteoporosis. Int J Mol Sci. 2020; 21: 7623.

73. Salamat MR, Salamat AH, Janghorbani M. Association between Obesity and Bone Mineral Density by Gender and Menopausal Status. Endocrinology and Metabolism. 2016; 31: 547.

74. Kärnsund S, Lo B, Bendtsen F, Holm J, Burisch J. Systematic review of the prevalence and development of osteoporosis or low bone mineral density and its risk factors in patients with inflammatory bowel disease. World Journal of Gastroenterology. 2020; 26: 5362-5374.

75. Akesson K, Marsh D, Mitchell PJ, McLellan AR, Stenmark J, et al. Capture the Fracture: A Best Practice Framework and global campaign to break the fragility fracture cycle. Osteoporos Int. 2013; 24: 2135-2152.

76. Kanis JA, Johnell O, Oden A, Jonsson B, De Laet C, Dawson A. Risk of hip fracture according to the World Health Organization criteria for osteopenia and osteoporosis. Bone. 2000; 27: 585–590.

77. Méndez-Gallegos E, Caire-Juvera G, Astiazarán-García H, Méndez-Estrada RO. Comparison of Measurements of Bone Mineral Density in Young and Middle-Aged Adult Women in Relation to Dietary, Anthropometric and Reproductive Variables. Nutrients. 2018; 10: 1669.

78. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporosis International. 2006; 17: 1726-1733.

79. Hachuła M, Pietrzyk B, Gruszka W, Cedrych I, Chudek J. High rates of undiagnosed and untreated osteoporosis in postmenopausal women receiving medical services in the area of Upper Silesia. Menopausal View. 2020; 19: 72-79.

80. Robinson E, Jones A, Lesser I, Daly M. International estimates of intended uptake and refusal of COVID-19 vaccines: A rapid systematic review and meta-analysis of large nationally representative samples. Vaccine. 2021; 39: 2024-2034.