

Risk factors and Management of Osteoporotic Fractures: An Update

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Abbreviations

OP: Osteoporosis; IOF: International Osteoporosis Foundation; NOF: National Osteoporosis Foundation; FRAX: Fracture Risk Assessment Tool

Osteoporosis (OP) is a common skeletal disorder characterized by low bone mass predisposing to an increased risk of fracture. It is a serious health problem with a progressive prevalence worldwide. Most cases of OP occur in postmenopausal women and according to the International Osteoporosis Foundation (IOF) there are 200 million osteoporotic women in the world [1,2].

Fractures of the proximal femur, proximal humerus and vertebrae are considered major osteoporotic fractures. They are the most important clinical outcome of osteoporosis as they have greater consequences in terms of morbidity (deformities, chronic pain, disability) and mortality. Most patients with hip fractures require hospitalisation and surgery, suffer from depression, decreased quality of life and social isolation.

Despite many advances in the diagnosis, the development of therapies and the production of best practice guidelines of osteoporosis, it has been shown that a minority of women and men at high risk of fracture receive treatment. Thus, it is important to identify patients who have low bone mass and high fracture risk to provide preventive and pharmacologic therapy.

This editorial provides a brief update on risk factors and management of osteoporotic fractures.

In 2014, the National Osteoporosis Foundation (NOF) published Clinician's Guide and recommendations regarding prevention, risk assessment, diagnosis, and treatment of osteoporosis in postmenopausal women and men age 50 and older [3].

In 2016, The American Association of Clinical Endocrinologists/American College of Endocrinology provided AACE/ACE Guidelines for the diagnosis and treatment of post-menopausal OP with the hopes of reducing the risk of osteoporosis-related fractures [4].

The guidelines recommend that all postmenopausal women aged 50 and older should be evaluated for osteoporosis risk including a detailed history, physical exam and clinical fracture risk assessment.

Risk factors for osteoporotic fractures

Measurement of Bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA)

Measurement of BMD by dual X-ray absorptiometry (DXA) is currently the gold standard for the diagnosis of osteoporosis based on the World Health Organization (WHO) criteria. Osteoporosis is present when T-score of <-2.5 SD (BMD is 2.5 SD or more below the average value for young healthy women). Severe osteoporosis is defined by T score at or below -2.5 with one or more documented fragility fractures. When T score is between -1.0 and -2.5, it defines osteopenia [5].

The development of fracture is closely correlated to a reduced BMD. However, the BMD measurement does not provide information on bone quality and reduced BMD alone indicated only a modest increase in fracture risk. In fact, other features independent of BMD, such as trabecular microarchitecture, accumulation of microfractures, or influence of many individual's clinical risk factors contribute to increase the risk of fracture in the population.

Clinical risk factors and Fracture risk assessment tools

A number of tools have been developed to calculate an individual's risk based on clinical risk factors and or in combination with BMD.

Clinical risk factors (CRF)

There are many recognized clinical risk factors (CRF) associated with increased risk of fragility fracture and a list of these CRF has been determined [3]:

- Age is a major risk factor.
- Sex
- Low body mass index (BMI ≤ 19 kg/m²): low BMI is well recognized as an important risk factor for hip fracture.
- A history of a previous fragility fracture, particularly of the hip, wrist and spine: the presence of a prior fracture is significant as a predictive factor for subsequent fractures
- Secondary causes of osteoporosis including:
 - Parental history of hip fracture
 - Current glucocorticoid treatment (any dose, by mouth for three months or more)
 - Current smoking Alcohol intake of three or more units daily
 - Rheumatoid arthritis
 - Untreated hypogonadism in men and women
 - Anorexia nervosa (and other hypogonadal states)
 - Prolonged immobility
 - Organ transplantation
 - Type I diabetes
 - Vitamin D insufficiency
 - Aromatase inhibitor for breast cancer treatment
 - Hyperthyroidism
 - Inflammatory Bowel Diseases (IBD) and other gastrointestinal diseases
 - Chronic liver disease
 - Chronic obstructive pulmonary disease
 - Frequent falls are an important risk factor for osteoporotic fractures.

Fracture Risk Assessment Tool or FRAX tool

The World Health Organization (WHO) has developed a risk-assessment survey Fracture Risk Assessment Tool (FRAX) that calculate the 10-year probability of hip fracture or other major osteoporosis-related fracture (clinical spine, forearm, hip, or proximal humerus).

The FRAX tool integrates an individual's risk factors (11 variables: age, sex, weight, height, previous fracture as an adult, parental hip fracture, smoking, current (or 3 months prior) use of glucocorticoids, diagnosis of rheumatoid arthritis, consumption of ≥ 3 units of alcohol daily, and secondary osteoporosis) and can be calculated with or without hip BMD. The WHO FRAX tool is considered as one of the most accurate methods for assessing the risk of fractures for individuals between the ages of 40-90 years [6].

Trabecular Bone score (TBS)

Trabecular bone score (TBS) is a FDA-approved method to assess the texture of trabecular bone using a conventional DXA image [7]. TBS was shown to be a risk factor for osteoporotic fracture and also for risk of death independent of FRAX clinical risk factors and femoral neck BMD. In clinical practice, TBS should not be used alone to determine treatment recommendations.

Vertebral Fracture Assessment (vertebral imaging)

Vertebral Fracture Assessment (VFA) is a densitometric spine imaging performed for the purpose of detecting asymptomatic vertebral fractures in older patients.

Lateral Spine imaging with Standard Radiography or Densitometric VFA is indicated when T-score is < -1.0 and of one or more of the following is present: women age ≥ 70 years or men age ≥ 80 years; Historical height loss > 4 cm (>1.5 inches), Self-reported but undocumented prior vertebral fracture, Glucocorticoid therapy equivalent to ≥ 5 mg of prednisone or equivalent per day for ≥ 3 months [3].

Biochemical bone turnover (or remodeling) marker (BTM)

Biochemical markers of bone turnover (BTM) are divided to formation markers [serum bone-specific alkaline phosphatase, osteocalcin, aminoterminal propeptide of type I procollagen] and resorption markers [serum C-telopeptide (CTX) and urinary N-telopeptide (NTX)]. The use of bone markers is not systematically recommended but they may provide information on fracture risk and may predict the rapidity of bone loss in untreated patients. They can be performed to determine if treatment is producing expected effect after 3 - 6 months of treatment. They also may help determine adequacy of patient compliance with osteoporosis therapy.

Management of osteoporotic fractures

Strategies to prevent and to treat osteoporosis-related fractures include several interventions with non-pharmacologic measures (lifestyle modification such as nutritional advice with an adequate intake of calcium and vitamin D, weight-bearing, muscle strengthening exercise, avoidance of bone-toxic drugs, fall prevention). They are universally recommended for all patients.

Pharmacological treatment are classified into anabolic or antiresorptive agents: menopausal hormone therapy, selective estrogen receptor modulators (SERMs: Raloxifene, Tamoxifene, Lasofoxifene, Bazedoxifene, Arzoxifene), bisphosphonates, denosumab, strontium ranelate, teriparatide. Bisphosphonates and denosumab are the most efficient osteoporosis therapies. They reduce the risk of vertebral fracture by 70%, hip fracture by 40 - 50% and all non-vertebral fractures by about 20 - 30% [8].

Bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid) represent first-line agents for the prevention and treatment of postmenopausal osteoporosis based on safety and proven efficacy in reducing fractures (vertebral and non-vertebral fractures). According to the American Association of Clinical Endocrinologists (AACE), the initial therapy should be guided by the patient's fracture risk and the presence or absence of prior fragility fractures. Bisphosphonates are always recommended as the first-line medications for OP and for reduction of the fracture risk. In a meta-analysis, zoledronic acid (an annual infusion of 5 mg of zoledronic acid for 3 consecutive years with a great antiresorptive potency) was the most effective bisphosphonate in the prevention of fracture at any sites in primary OP.

Denosumab (human monoclonal Antibody -RANKL inhibitor) is the first biological drug approved for the treatment of osteoporosis [9]. Denosumab (60 mg as a subcutaneous injection every 6 months) is approved for the treatment of osteoporosis in postmenopausal women at high risk of fracture, for men at high risk of fracture, for women with breast cancer on aromatase inhibitor therapies, and for men receiving gonadotropin-releasing hormone treatment for prostate cancer who are at high risk for fracture. This treatment can be initiated as a first-line treatment in patients who have renal failure or have shown intolerance to oral Bisphosphonate.

Teriparatide (recombinant human parathyroid 1- 34) is approved for the treatment of osteoporosis in postmenopausal women and men at high risk for fracture and for osteoporosis induced by glucocorticoid therapy. It is the only class of anabolic drugs currently used in the treatment of menopausal women with prior vertebral fractures (20 µg daily subcutaneous injection for a duration of 18 to 24 months therapy). Several studies have shown show effective anabolic response to teriparatide after previous treatment with bisphosphonates for an average period of 36 months show effective anabolic response to teriparatide after previous treatment with bisphosphonates for an average period of 36 months.

Several other drugs have been developed for the prevention of fracture and for the treatment of OP. Romosozumab (anti-sclerostin monoclonal antibody) and abaloparatide (selective activator of the parathyroid hormone type 1 receptor) are 2 new drugs in phase-3 development [10].

The development of odanacatib (an oral inhibitor of cathepsin K, protease of the osteoclast involved in the degradation of organic bone matrix) has been discontinued in 2016 because of increased risk of stroke events in the odanacatib group compared to placebo [10].

A recent onset fracture at any major skeletal site in an adult older than 50 years with or without trauma, should suggest the diagnosis of osteoporosis and needs urgent diagnosis and treatment. A vertebral fracture is consistent with the diagnosis of osteoporosis, even in the absence of a bone density diagnosis; it is an indication for pharmacologic treatment to reduce subsequent fracture risk.

Patients with low bone mass (T-score between -1.0 and -2.5 at the femoral neck or lumbar spine) and a 10 - year probability of a hip fracture $\geq 3\%$ or a 10-year probability of a major osteoporosis-related fracture $\geq 20\%$ should also be treated.

The role of orthopedic surgeons is important in the investigation and treatment of osteoporosis after fragility fractures. In the other hand, osteoporosis-related fractures are always challenging the orthopaedic surgeons. The priority objective of the treatment of an acute osteoporotic vertebral fracture is to achieve appropriate control of symptoms and prevent muscular atrophy and other complications. In cases of vertebral fracture, surgical treatment can be considered when there is neurological damage or when conservative treatment has failed. Vertebroplasty and kyphoplasty have been used for pain relief in particular.

The main objective of treatment of an acute osteoporotic non-vertebral fracture (proximal femur, proximal humerus, wrist) is to recover function as soon as possible with a solid fixation of the fracture which is not always easy for those advanced age and polymedicated patients.

Conclusion

Because osteoporotic fracture causes a huge financial burden on societies across the world, osteoporosis must be prevented, diagnosed, and treated before a fracture occurs. Attention must be focused on the identification of high fracture risk among osteoporotic patients. The main goal of treatment is to reduce the prevalence of fractures, maintain stable or increasing bone mineral density. The International Osteoporosis Foundation (IOF) website lists osteoporosis guidelines from around the world.

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