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Risk of Fracture and Prevention and Treatment of Osteoporosis

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Introduction

Osteoporosis is presently defined as a systemic skeletal disorder characterized by compromised bone strength with a consequent increase in skeletal fragility and susceptibility to fracture [1]. Currently, there is no accurate measure of overall bone strength, which primarily reflects the integration of bone density determined by peak bone mass and the amount of bone loss, and bone quality including architecture, turnover, damage accumulation, and mineralization [1].

In women, there are four general diagnostic categories, which rely on the quantitative assessment of bone mineral density (BMD) by Dual energy X-ray Absorptiometry (DXA), proposed by the World Health Organization (WHO) and modified by the International Osteoporosis Foundation [2,3], as follows:

Normal: Hip BMD greater than 1 SD below the young adult female reference mean (T score ≥ −1).

Low bone mass (osteopenia): Hip BMD greater than 1 SD below the young adult female reference mean, but less than 2.5 SD below this value (-2.5<T score <−1).

Osteoporosis: Hip BMD 2.5 SD or more below the young adult female reference mean (T score ≥ −2.5).

Severe osteoporosis (established osteoporosis): Hip BMD 2.5 SD or more below the young adult female reference mean in presence of one or more fragility fractures.

In men, the diagnostic standards are dependent on the scales for women or young man [4].

Osteoporosis can be classified into two basic forms: Primary and Secondary osteoporosis. Resulting from cumulative bone loss as people age and undergo sex hormone changes, primary osteoporosis (also known as involutional osteoporosis) is further classified into type (postmenopausal) and type (senile) osteoporosis [5]. Secondary osteoporosis can result from various medical conditions or diseases, or from the use of certain medications that adversely affect skeletal health.

Bone Strength

Osteoporosis is defined as a systemic skeletal disorder characterized by compromised bone strength with a consequent increase in skeletal fragility and susceptibility to fracture [1]. This definition highlights the important role of bone strength and implies that understanding bone strength is the key to understanding fracture risk [6,7]. Bone strength, known as the ability of bone to resist fracture, depends on the quantity of bone as measured by BMD using DXA and the quality of bone, including the spatial distribution of the bone mass (i.e., macro-architecture and micro-architecture of bone) and the intrinsic properties of the materials that comprise the bone (i.e., matrix mineralization, collagen characteristics, microdamage) [8]. Bone macro-architecture refers to whole bone geometry such as bone size and shape. Bone micro-architecture includes cortical micro-architecture described by cortical porosity and thickness, and trabecular micro-architecture described by trabecular scale (i.e., bone volume fraction, trabecular thickness, number and separation), trabecular topology (i.e., trabecular integrity, shape and connectively), and trabecular orientation [9,10].

Although advances in bone imaging techniques have provided tools to assess bone structure at the macro-, micro- and nano-level, use of high-resolution imaging to analyze bone strength is limited by cost, availability, consensus regarding analytical standards, and irradiation [9]. In addition, features of the bone matrix such as the composition of matrix, mineral crystal size and maturation, and the amount and nature of matrix microdamage cannot be assessed non-invasively, and therefore, investigations are also somewhat limited in clinical practice [8]. Areal BMD measurements by DXA can reflect some of the features of bone strength, including bone mass, the degree of mineralization, and to some extent bone size. BMD measurements remain the best available non-invasive assessment of bone strength in routine clinical practice, although BMD measurements do not reflect other features of bone strength, including the three-dimensional distribution of bone mass, trabecular and cortical micro-architecture, and the intrinsic properties of the bone matrix [8].

Risk Factors for Fracture

From mechanical perspective, fractures represent a structural failure of the bone whereby the stress on the bone exceed its load-bearing capacity (known as bone strength). The stress on the bone will depend on the specific activity and will vary with the rate and direction of the applied loads [11]. As mentioned above, the load-bearing capacity of the bone (bone strength) depends on the amount of bone, the spatial distribution of the bone mass, and the intrinsic properties of the materials that form the bone.

Bone fracture is the consequent of multiple risk factors, and this multiplicity should be considered in assessment of fracture risk for an individual [12]. Risk factors for fracture may be divided into those that impair the load-bearing capacity of the bone (bone strength), and those that cause excessive loads on weakened bone from falls, or in some cases ordinary activities of daily living [13]. Risk factors related to impair bone strength include low BMD, age, sex, low body-mass index, high bone turnover, hormonal abnormalities, nutritional deficiency, previous fracture, parental history of fracture, active cigarette smoking, excessive alcohol consumption, glucocorticoid treatment, or a specific pathological disease associated with changes in bone [13,14]. Risk factors that lead to excessive loading of the bone include falls and propensity to falls, and fall mechanics [13]. The

pathogenesis of falls is complex and multiple factors including age-related deficits in visual, proprioception, and vestibular systems; medical conditions and comorbidity burden; use of psychotropic medications such as antidepressants and benzodiazepines; and environmental factors are associated with the increased likelihood of fall [15,16].

Assessment of Fracture Risk

Although low BMD is among the strongest risk factors for fracture and the ability to predict hip fracture risk from BMD alone is at least as good as the ability to predict stroke risk from blood pressure readings, several clinical studies have demonstrated the limitations of BMD measurements in assessing fracture risk [8,17]. In order to better predict fracture risk in clinical management process, the WHO has developed and introduced a country-specific Fracture Risk Assessment Tool (FRAX), based on information collected from all international cohort studies in which clinical risk factors, BMD, and incident fractures were evaluated. FRAX is a fracture risk assessment tool for the prediction of fractures in men and women with use of clinical risk factors with or without femoral neck BMD [18]. These clinical risk factors include age, sex, race, height, weight, body mass index, previous fractures, history of hip fracture in one or both parents, glucocorticoids therapy, current smoking, alcohol abuse, rheumatoid arthritis, and other secondary causes of osteoporosis. The FRAX algorithms combine BMD measurement and clinical risk factors to derive the 10-year probability of a hip fracture or the 10-year probability of a major osteoporotic fracture (hip, shoulder, forearm, or clinical spine fracture, but not radiological spine fracture without symptoms), thereby allowing identification of individuals at high risk of fracture [12,19]. FRAX is currently universally accessible free of charge on the Internet (www.shef.ac.uk/FRAX).

Prevention and Treatment of Osteoporosis

It is well know that osteoporosis is a silent disease without any symptoms or increased morbidity until the first fracture occurs. The key aim of osteoporosis prevention and treatment should be the prevention of the first and subsequent fractures rather than the treatment of a single risk factor, such as low BMD. General management for the prevention and treatment of osteoporosis includes assessment of the risk of falls and their prevention; maintenance of activity and exercise, such as weight-bearing exercise and walking; lifestyle changes, such as cessation of smoking and reduction of alcohol consumption; and correction of nutritional deficiencies, particularly of calcium, vitamin D and protein [14]. In all therapeutic management strategies for the prevention and treatment of osteoporosis, the use of combined calcium and vitamin D supplementation is recommended as baseline treatment in each patient with osteoporosis. It is recommended that patient should have at least a calcium intake of 1000 mg and a vitamin D intake of 800 IU per day [14]. In addition to increase BMD and reduce fractures, calcium and vitamin D supplementation can improve muscle strength, function and balance and reduce the risk of falling [20].

National Osteoporosis Foundation (USA) guidelines recommend osteoporosis pharmacological intervention not only the presence of a fragility fracture irrespective of BMD or with T-scores ≤ –2.5 at hip or spine, but also in osteopenic postmenopausal women and men aged ≥ 50 with a FRAX-based 10-year risk of hip fracture of ≥ 3% or a major osteoporotic fracture risk of ≥ 20% [21]. Osteoporosis pharmacological therapies are divide into two classes, those which inhibit bone resorption, antiresorptive agents including bisphosphonates, denosumab, and the Selective Oestrogen Receptor Modulators (SERMs) raloxifene and toremifene, and those which stimulate bone formation, anabolic agents including Parathyroid Hormone (PTH 1-84), teriparatide (PTH 1-34), and strontium ranelate. All these drugs have been shown to reduce the risk of vertebral fracture, and some have also been shown to reduce the risk of non-vertebral and hip fracture. In clinical practice, drug choice will depend on availability, cost, disease severity, reimbursement criteria, side-effects and co-morbidities.

Anti-resorptive drugs

Bisphosphonates: Currently bisphosphonates are the most commonly prescribed drugs for the treatment of osteoporosis and are likely to remain in the immediate future because they are inexpensive and used across a broad spectrum of osteoporosis, including postmenopausal, male, and glucocorticoid-induced osteoporosis [22]. They are administered either orally (daily, weekly, or monthly tablets) or intravenously (quarterly or yearly infusions), and are divided into two classes, the low potency non-nitrogen containing bisphosphonates (etidronate and clodronate) and the potent nitrogen-containing bisphosphonates (alendronate, pamidronate, risedronate and zoledronate). Bisphosphonates avidly bind to hydroxyapatite on bone surfaces and are released as bone is resorbed, then are internalized by osteoclasts to inhibit resorption [23,24]. These two classes have different intracellular targets and molecular mechanisms of action that inhibit the activity of osteoclasts and bone resorption [25]. All bisphosphonates have a common phosphate-carbon-phosphate structure with different side chains. Alendronate is the first line treatment in the majority of cases, and other bisphosphonates are recommended for patients who are intolerant of alendronate [14].

Although bisphosphonates have been shown their impressive antifracture efficacy for patients with osteoporosis, there are certain limitations and side effects in using them. Bisphosphonates are retained in bone for long periods of time and their duration of physiological effect is still unclear, but the level of suppression of bone turnover can remain for at least 5 years after cessation of therapy [26]. This may lead to a potential risk of oversuppresion of bone turnover with possible increased risk of fracture [27]. The optimum duration of bisphosphonate therapy remains unclear. Based on the results of Fracture Intervention Trail Long-term Extension study, it has been suggested that for some women, alendronate should be stopped after 5 years therapy for a drug-free holiday [28]. Moreover, oral bisphosphonates are poorly absorbed and have very strict and specific guidelines for dosage, such as alenIdronate must be taken fasting with water and patient must remain upright and fasting for at least 30 minutes to decrease the risk of ulcer formation. Despite the strict guidelines, oral bisphosphonates are often associated with upper gastrointestinal side-effects, such as erosions and ulcers in the stomach and small intestine [29]. These side-effects may cause patient noncompliance with oral bisphosphonates. Intravenous administration of bisphosphonates avoids the gastrointestinal side-effects and overcomes this patient non-compliance, and the most commonly side-effects is mild self-limiting flu-like symptoms for a few days after dosing [24]. Finally, long-term use of bisphosphonates may cause osteonecrosis of the jaw and atypical femoral fractures, but these complications are rare.

Selective Estrogen Receptor Modulators (SERMs): Because the long-term oestrogen replacement therapy has been documented to have

several sever adverse effects on extra-osseous tissues, including increased risk of venous thromboembolism, stroke, and uterine and breast cancers, it is no longer recommended for the treatment of osteoporosis [30].

To avoid the potential side-effects of oestrogen, SERMs were investigated for a estrogen-like activity in bone. SERMs are nonsteroidal molecules that bind to the estrogen receptors to exert selective agonist or antagonist effects on different oestrogen target tissues. They remain the beneficial effects of oestrogen on bone and overcome the adverse effects of oestrogen on extra-osseous tissues. Currently raloxifene is the only SERM available for prevention and treatment of postmenopausal osteoporosis. Raloxifene was confirmed to significantly reduce the risk of vertebral fracture in clinical trails [31]. However, there was no significant reduction in the risk of non-vertebral fractures or hip fractures [23]. Given the potential effect of prevention the development of oestrogen-receptor-positive breast cancer, raloxifene is typically used in patients at high risk of vertebral fracture and breast cancer [23]. Other new SERMs including lasofoxifene, bazedoxifene, and arzoxifene are in late-stage treatment studies.

Denosumab: Denosumab, a fully human monoclonal antibody with affinity and specificity for RANKL, is an anti-resorptive drug that acts by binding to RANKL to prevent the RANKL/RANK interaction on the osteoclast precursor cells which inhibits the differentiation, function and survival of these cells. This reduces bone resorpion and improves bone mass and strength. It have been demonstrated that denosumab was associated with increasing BMD and reducing the risk of fractures at multiple sites including vertebral, hip, and other nonvertebral sites [32]. Denosumab was approved for treatment of osteoporosis in both women and men with high risk of fracture. Potential adverse outcomes of denosumab include hypocalcaemia, osteonecrosis of the jaw, atypical fractures, delayed fracture healing, and infections [33].

Anabolic Drugs

Parathyroid hormone (1-84 PTH) and teriparatide (1-34 PTH): Although hyperparathyroidism contributes to loss of bone mineral content and increase skeletal fragility, intermittent administration of PTH has an anabolic effect on bone remodeling [34]. The full-length molecule PTH (1-84) and teriparatide (1-34 PTH) are currently the only pure anabolic drugs available for the prevention and treatment of osteoporosis in many European countries. Teriparatide, 1-34 amino acid peptide, is a recombinant N-terminal fragment of human PTH which stimulates new bone formation on trabecular and cortical bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity and prevention of osteoblast apoptosis [23,35]. Teriparatide was shown to significantly reduce vertebral and non-vertebral fracture risk in postmenopausal women and men with primary osteoporosis or GIOP [36]. Continuous treatment with teriparatide is not recommended and the maximum accepted treatment duration is limited to 24 months followed by maintenance therapy with an antiresorptive drug. The anabolic effect of PTH is blunted by prior treatment with bisphosphonates and simultaneous therapy with anti-resorptives is also not recommended in recent guidelines. In generally, side-effects of teriparatide are mild and include hypercalcaemia, leg cramps, nausea, and headaches [23].

Strontium Ranelate (SR): Unlike other available treatments for osteoporosis, SR has a unique dual mode of action. It increases bone formation by stimulating the differentiation and function of osteoblast, while simultaneously decreasing bone resorption by inhibiting the activity and differentiation of osteoclast [37]. Although the exact mechanism of action of SR remains unclear, several mechanisms are thought to involve, including the calcium sensing receptor (CaSR) and the OPG/RANKL system as well as ERK1/2 and AKT signaling and PGE2 production [38,39]. Clinical studies have demonstrated the efficacy of SR in significant reduction the risk of vertebral and non-vertebral (including hip) fractures in postmenopausal women with osteoporosis or a prevalent vertebral fracture or both [40]. SR is available in EU and many non-European countries and is recommended to use in patients in whom bisphosphonates therapy has failed or is contraindicated [24]. Common adverse effects include nausea, diarrhea, headache, dermatitis and venous thrombosis.

The future

Recent new insights into bone physiology and pathophysiology and improved knowledge on the mechanisms involved in the development of osteoporosis have exploited new therapeutic targets and led to the development of new anti-resorptive and anabolic drugs to treatment osteoporosis. Odanacatib, a new anti-resorptive drug, is a selective, reversible nonpeptidic biary1 inhibitor of cathepsin K. It has been shown to suppress bone resorption markers and increase BMD of the lumbar spine and total hip in patients with postmenopausal osteoporosis [41]. Odanacatib can suppress bone resorption whilst maintaining bone formation, an uncoupling effect in contrast to other anti-resorptive drugs [22]. Phase 3 clinical trails of odanacatib are now underway. Although most existing treatments focus on anti-resorptive drugs, anabolic drugs are undoubtedly of interest. Current focuses of interest include inhibitors of naturally occurring Wnt-pathway antagonists, such as sclerostin antibody and Dickkopf-1 (Dkk-1) antibody, and calcilytic agents, which act as antagonists of the CaSR and mimic hypocalcaemia, thereby evoking a short pulse of PTH secretion.

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