Osteoporosis

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Introduction to Osteoporosis

Osteoporosis is a skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to an increase in bone fragility and susceptibility to fracture. An operational definition of osteoporosis has also been defined, based on a value for bone mineral density (BMD) 2.5 standard deviations or more below the young adult mean [1]. The most widely validated technique for the quantitative assessment of BMD is dual-energy X-ray absorptiometry. Bone loss is due to an imbalance between bone resorption by osteoclasts and bone formation by osteoblasts, which are part of the bone remodeling process. This results in a decrease in BMD and alterations of bone geometry and micro-architecture at the cortical and trabecular sites, leading to bone fragility and fractures. Osteoporosis has the potential to alter quality of life and to increase mortality. From the age of 50 years, 50 % of women and 20 % of men will be concerned by fracture during their remaining lifetime. This important public health issue will tend to increase due to the aging of the world population. Beyond aging, many pathological conditions (e.g., endocrine diseases, chronic inflammatory diseases) or treatments (e.g., corticosteroids) interfere with bone metabolism and induce osteoporosis.

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Pathogenesis of Bone Loss

Many factors regulating bone remodeling contribute to osteoporosis (Fig. 1). Both increased bone resorption and decreased formation can contribute to its progression. Significant bone loss occurs in both women and men because of sex steroid deficiency and environmental risk factors, including nutritional intake and lifestyle habits.

Genetic and Lifestyle Habit Risk Factors and Comorbidities

Genetic factors account for 50–80 % of the variation among individuals in bone mass and structure. Peak bone density is achieved at the beginning of the third decade of life. Lower peak bone mass contributes to the risk of osteoporosis and fractures in later life [2]. Lifestyle habits involve excess alcohol intake or tobacco use (because of toxic effects on bone cells but also indirect effects due to endocrine changes and muscle weakness) or physical inactivity. Sporadic causes of bone loss can also be identified in about 20 % of women and 50 % of men and include glucocorticoid therapy (which inhibits bone

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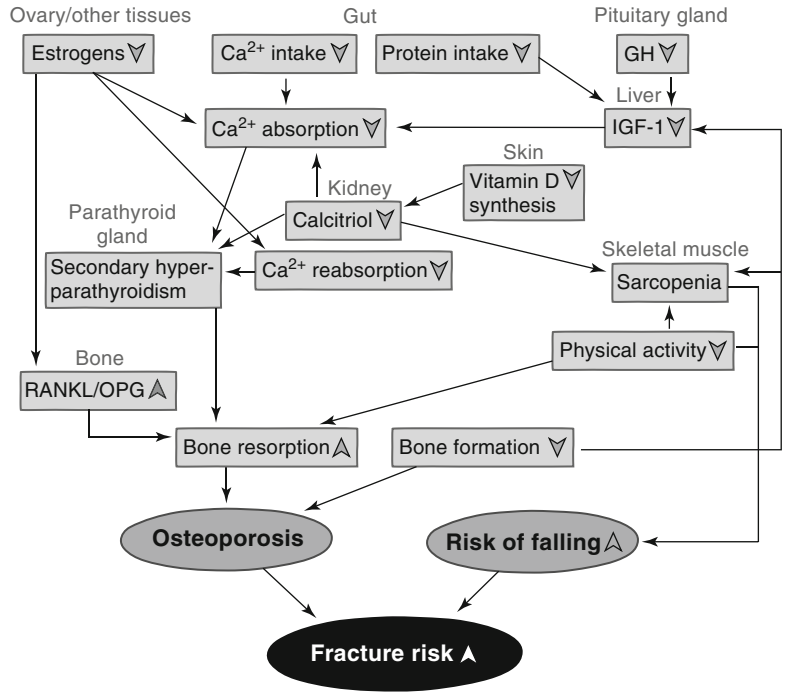

Fig. 1 Metabolic changes in age-related osteoporosis. Multiple metabolic processes in various organs are involved in the imbalance between bone resorption and formation leading to osteoporosis and contributing to the incidence of fractures. *GH* growth hormone, *IGF-1* insulin-like growth factor-1, *RANKL* receptor activator of nuclear factor-κB ligand, *OPG* osteoprotegerin

formation and suppresses calcium (Ca^{2+}) absorption), malabsorption, idiopathic hypercalciuria (excess of urine calcium excretion without an apparent underlying etiology, due to genetic causes), or endocrine diseases, such as primary hyperparathyroidism or hyperthyroidism (all related to an imbalance of hormones affecting bone metabolism).

Endocrine Factors

Ca^{2+} and phosphate (PO_4^{3-}, P_i) are essential components for bone mineral formation and their availability is mainly regulated by parathyroid hormone (PTH, increasing bone resorption) and vitamin D (increasing Ca^{2+} and P_i absorption, see chapter "Overview" under part "Teeth and bones").

One major cause of osteoporosis is the decline in estrogens after menopause but also in men, resulting in a negative balance in bone remodeling. Estrogens control bone remodeling by estrogen receptors on osteoblasts and osteoclasts. Estrogen deficiency promotes osteoclastogenesis by upregulating the receptor activator of nuclear factor-κB ligand (RANKL, see chapter "Overview" under part "Teeth and bones") in bone marrow cells, whereas estrogens stimulate the production of its soluble decoy receptor osteoprotegerin in osteoblasts. Estrogen deficiency also stimulates bone resorption by indirect effects, in particular via cells of the immune system and proinflammatory cytokines (see below). Moreover, estrogens modulate Ca^{2+} absorption and excretion.

These effects are often exacerbated by vitamin D insufficiency (calcidiol <50 nmol/l), which induces secondary hyperparathyroidism (meaning increased PTH). Impaired vitamin D synthesis in skin and reduced renal hydroxylation in old age lead to low calcitriol levels.

Renal synthesis of calcitriol is regulated not only by PTH but also by insulin-like growth factor-1 (IGF-1). IGF-1 is produced in the liver in response to growth hormone (somatotropin) from the pituitary (see chapter "Overview" under part "Brain") and dietary animal protein intake, as a diet rich in amino acids is a common inducer of growth. IGF-1 is an important regulator of muscle and bone growth, acting as

an autocrine/paracrine growth factor in multiple tissues through IGF-1 receptor, a classical tyrosin kinase receptor. IGF-1 directly regulates renal tubular reabsorption of P_i and stimulates its transport into osteoblastic cells, resulting in activation of bone mineralization. Furthermore, age-related decrease in IGF-1 levels contributes to sarcopenia by decreasing muscle size and strength, protein synthesis, and increasing muscle cell apoptosis. Sarcopenia reduces muscle loading on the skeleton and is associated with osteoporosis [3]. Consequently, a positive relationship has been found between spontaneous protein intake in both men and women and bone mass at various skeletal sites [4].

More recently, it has been shown that circulating serotonin from the gut is inversely associated with BMD. It inhibits bone mass accrual by decreasing osteoblast proliferation and bone formation [5]. Finally, leptin secreted by adipocytes stimulates bone remodeling directly through increased osteoblast proliferation and differentiation, but indirectly decreases axial skeleton bone formation through a hypothalamic relay via the sympathetic nervous system, independently of its regulation of energy metabolism.

Nutritional Factors

Dietary factors influence bone health, particularly calcium, and protein intakes. Ca^{2+} metabolism is altered in the elderly due to impaired vitamin D levels, reduced intestinal Ca^{2+} absorption, and a lower dietary Ca^{2+} intake[5]. In addition, relative hypocalcemia causes secondary hyperparathyroidism, which stimulates bone resorption to maintain homeostasis in extracellular Ca^{2+} concentration (see chapter "Overview" under part "Teeth and bones").

Immune Factors

Many cytokines, such as interleukin 1, interleukin 6, and tumor necrosis factor-α, are involved in the pathogenesis of osteoporosis. In addition, estrogen deficiency has been associated with an increased production of interleukin 7, leading to T-cell activation in bone. These T cells produce RANKL and tumor necrosis factor-α that stimulate osteoclastogenic activity [6]. The gut microbiota might also increase the frequency of T cells in the bone marrow, thereby promoting the expression of inflammatory cytokines in bone and activating osteoclastogenesis [7].

Osteoporosis Treatment and Influence on Bone Metabolism

The aim of osteoporosis treatment is the prevention of fragility fractures. This includes non-pharmacological interventions, Ca^{2+} and vitamin D supplements, and drugs with proven anti-fracture efficacy. The choice of first-line treatment greatly depends on the patient and his/her personal and disease characteristics, including age, comorbidities, fracture risk, expected adherence and potential adverse effects, and others.

Nutrition and Physical Activity

Reduced intake of Ca^{2+}, proteins, and vitamin D contributes to osteoporosis. Thus, an adequate Ca^{2+} supply is needed to prevent secondary hyperparathyroidism, if necessary with dietary and Ca^{2+} supplements. Vitamin D deficiency is very frequent [8] and hampers the clinical benefits of anti-resorbing therapies [9]. Vitamin D supplements reduce the risk of fracture and propensity to falls by their effect on muscles [10] and prevent secondary hyperparathyroidism. Daily dietary sources (even if rich in oily fish) and sun exposure fail to provide enough vitamin D in patients with vitamin D insufficiency, and supplements are needed to achieve a sufficient circulating level of calcidiol (>50 nmol/l). To improve vitamin D absorption, it should be taken with a fat-rich diet, such as milk, or at the end of the meal.

Correction of poor protein intake can restore an altered growth hormone–IGF-1 axis and improve BMD as well as muscle mass and strength. Promotion of physical activity has a positive impact on bone loss and prevention of

falls, mechanical stimuli targeting osteocytes, and muscle strength. Mechanical loading also prevents the expression of sclerostin, a negative regulator of bone formation produced by osteocytes, inducing new bone formation.

Anti-osteoporotic Drugs

The primary objective of all anti-osteoporotic drugs is to reduce fracture risk, by improving bone strength. Except for hormone replacement therapy (HRT), the efficacy of all drugs was tested in patients receiving a combination of Ca^{2+} and vitamin D (Table 1) [11]. HRT was commonplace in the treatment or prevention of osteoporosis, but its indication is now reduced because of an increased risk of breast cancer (see chapter "Breast cancer"), cardiovascular disease (see chapter "Atherosclerotic heart disease"), and stroke (see chapter "Stroke") induced by the estrogens [12].

Most of the more recent drugs (Table 1) decrease bone resorption: bisphosphonates, denosumab, and SERMs (selective estrogen-receptor modulators).

Bisphosphonates were the first of these and are still the most common treatment. They inhibit osteoclastic resorption. Selective estrogen-receptor modulators, nonsteroidal agents that bind to estrogen receptors (see chapter "Breast cancer"), act as estrogen agonists on bone. More recently, denosumab was developed, a humanized monoclonal antibody that selectively inhibits the RANKL. The only bone anabolic agent (promoting bone formation) for the treatment of osteoporosis is truncated or full-length PTH. Teriparatide, the first 34 amino acids of human PTH, was the first anabolic agent based on the effects of PTH on bone turnover that depend on the pattern and duration of its elevation. While hyperparathyroidism is associated with increased bone resorption, daily administration of teriparatide results in upregulation of bone formation on the skeleton. Strontium ranelate reduces fracture risk both by inhibiting bone resorption and stimulating bone formation, through various mechanisms not yet fully elucidated.

Perspectives

Osteoporosis is a common disorder associated with high morbidity and increased mortality, which can be easily diagnosed based on clinical risk factors and BMD assessment. Its prevention is feasible by cost-effective strategies targeting risk factors or drugs modifying bone turnover. With population aging and increased life expectancy, long-term treatment of osteoporosis needs to consider sequential therapeutic strategies. Promising drugs currently under investigation include an oral drug that inhibits the bone resorption enzyme cathepsin K (odanacatib) and anti-sclerostin monoclonal antibodies (romosozumab) that stimulate bone formation by osteoblasts.

Table 1 Pharmacological agents preventing fracture risk used in postmenopausal osteoporosis

Drug class	Drug molecules	Bone targets and mechanism of action	Effects on Bone remodeling		Side/off-target effects and adverse effects
			Bone resorption	Bone formation	
Bisphosphonates	Alendronate, risedronate, ibandronate, zoledronate,	*Inhibitors of bone resorption:* Inhibit osteoclast activity Induce osteoclast apoptosis	⩛⩛⩛	⩛⩛⩛	Oral: low bioavailability due to low absorption in gastrointestinal (<1 %) Long-lasting remanent protection of bone Oesophageal irritation Flu-like symptoms after intravenous injection Osteonecrosis of the jaw in patients receiving high doses Atypical fractures of the femur with long-term use
SERMs	Raloxifene, bazedoxifene	*Inhibitors of bone resorption:* Nonsteroidal agents that bind to the estrogen receptor and act as estrogen agonists on bone	⩛⩛	⩛⩛	Risk of invasive breast cancer due to estrogen antagonist effects⩛ Deep venous thromboembolism⩓
Anti-RANKL monoclonal antibodies	Denosumab	*Inhibitors of bone resorption:* Humanized monoclonal antibodies binding to RANKL. Prevent the effect of RANKL on osteoclasts differentiation, activation, and survival	⩛⩛⩛	⩛	Possible adverse immune effects (dermatological side effects and skin infection) Hypocalcemia Possibly associated with osteonecrosis of the jaw and atypical fractures of the femur
PTH	Teriparatide	*Activators of bone formation:* Number and activity of osteoblasts⩓	⩓⩓	⩓⩓⩓	Contraindicated in conditions with abnormally increased bone turnover, in patients with prior radiation therapy to the skeleton, skeletal malignancies, or bone metastases Limited to 24 months (risk of osteosarcoma)
Strontium ranelate		*Mixed effect on bone resorption and formation:* Inhibits bone resorption and stimulates bone formation	⩛	⩓	Venous thromboembolism risk⩓ Isolated cases of drug rash with eosinophilia and systemic symptoms

SERM selective estrogen-receptor modulator, *RANKL* receptor activator of nuclear factor-κB ligand

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