of osteoblasts at resorption sites (coupling) ensuring repair of resorbed areas. In turn, osteoblasts are responsible for the formation of new bone at these sites but also for the differentiation of osteoclasts, mostly through the local production of RANKL and OPG, also secreted by osteocytes. Consequently, inhibition of osteoclast differentiation leads to a decrease in both resorption and formation, with suppression of bone remodeling. Denosumab treatment nevertheless allows a continued increase in bone density and reduction in fracture risk over time. The mechanisms by which bone mass continues to increase despite very low remodeling activity appears to involve bone modeling activity, during which bone formation continues independent of bone resorption, particularly in cortical bone. Although not pursued anymore as a therapeutic target, inhibition of cathepsin K in humans decreases bone resorption while maintaining bone formation, allowing cross-talk between osteoclasts and osteoblasts and a robust and prolonged increase in BMD at trabecular and cortical sites. The other, most promising approach involves not the inhibition of resorption but the stimulation of bone formation with osteo-anabolics. Bone formation occurs in the context of bone remodeling or bone modeling, and activation of the PTH and/or Wnt signaling pathways increase bone formation by osteoblasts via both processes. Daily PTH1-34 (Teriparatide) injections increase bone formation but also bone resorption, increasing bone turnover, albeit with a positive balance. Although bone density is efficiently increased, the secondary increase in bone resorption may affect intracortical remodeling and increase cortical porosity, limiting the benefits of PTH treatment. Weekly administration of PTH1-34, the use of PTHrP analogs (Abaloparatide) or the combination of PTH with Denosumab may avoid in part the increase in resorption and increasing bone density further. Other osteo-anabolics target the Wnt signaling pathway, which is a key regulator of the differentiation and function of osteoblasts as well as their ability to cross talk with osteoclasts. Inhibition of endogenous inhibitors such as Sclerostin, secreted locally by osteocytes, leads to massive increases in bone formation and production of OPG, thereby also reducing resorption. Sclerostin antibodies (Romosozumab and Blozosumab) enhance locally, at the level of osteoblasts and osteocytes, Wnt signaling. These compounds have both an anabolic and an anti-resorptive effect that, albeit limited in time, increase very quickly and efficiently bone density at trabecular and cortical sites, in large part via bone modeling. Taken together, these new therapeutic developments provide not only promising prospects for the future treatment of osteoporosis but also important insights into bone biology.

KEYWORDS: osteoporosis, osteoclasts, Denosumab, PTHrP analogs.

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OSTEOPOROSIS: HOW AND HOW LONG TO TREAT

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Osteoporosis is the most prevalent bone disease and a major health-economic problem worldwide. It is defined as a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture. The disease is still underdiagnosed and undertreated in spite of rich armamentarium of different drugs. The aim of treatment is to prevent a fracture. Each patient with osteopenia or osteoporosis should take cholecalciferol 1,000—2,000 IU daily or 7,000—14,000 IU once weekly in addition to food rich in calcium (dairy products) or calcium supplements. Patients who sustained an osteoporotic fracture or those who are at high risk of a major osteoporotic fracture (>20% in next 10 years) or hip fracture (>5%) as assessed by FRAX or other fracture risk assessment algorithm, should receive an antiosteoporotic medication. The most commonly used drugs are antiresorptive medications such as the nitrogen-containing bisphosphonates (BPs) and the receptor activator of nuclear factor kappa B ligand inhibitor denosumab. Whereas both BPs and denosumab inhibit osteoclastic bone resorption (and, to a lesser degree, bone formation), they do so by different cellular and molecular mechanisms. The skeletal effects of denosumab resolve quickly and completely when treatment is stopped while BPs can stay in bone for years. Less commonly used and generally reserved for patients with severe and established osteoporosis are the anabolic agents PTH [PTH-(1—84)] and teriparatide [PTH-(1—34)]. These peptides potently stimulate osteoblastic bone formation but also stimulate bone resorption. The treatment is limited to two years. Immediately after anabolic treatment an antiresorptive medication should be introduced to sustain the benefits. Concomitant teriparatide and denosumab therapy increases BMD more than therapy with either medication alone and more than has been reported with any current therapy. The combination of these agents might be an important treatment option in patients at very high risk of fracture. In case there is a need for prolonged treatment the effect is better when starting with the anabolic drug teriparatide for two years and following with an antiresorptive like bisphosphonate or denosumab. There are new medications in the pharmaceutical pipeline: anti-sclerostin monoclonal antibodies, anti katepsin K monoclonal antibodies, PTHrP analog abaloparatide. How long treatment should last depends on the individual fracture risk assessed by FRAX. This is performed before and every two to three years during the treatment. Continuous long-term therapy with antiresorptive drugs can cause late complications like osteonecrosis of the jaw or atypical femur fractures.

KEYWORDS: osteoporosis, antiresorptive drugs, denosumab, PTHrP analogs.

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DIABETES AND BONE

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Diabetes mellitus type 1 and 2 (T1DM and T2DM) are associated with increased fracture risk in both male and female individuals. The relative risk (RR) of hip fractures in patients with T1DM ranges from 1.7 to 12.3, and increases with age, particularly after the age of 40. The outcome of a single study showed that the prevalence of morphometric vertebral fractures was higher in young (30 year old) patients with T1DM (24%) than in a control population (6%). Patients with T2DM in general have a moderately increased risk of hip fractures (RR 1.7, 95% CI 1.3—2.2). However, when restricting the analysis to the cohorts with more than 10 years of follow-up observation, the RR of hip fractures increased to 2.7 (95% CI 1.7—4.4). Fractures of the wrist and the foot also appeared to be more frequent in patients with T2DM than in healthy individuals. A single study conducted in Japan found that T2DM was associated with an increased risk of vertebral fractures in women (OR 1.9; 95% CI 1.11—3.12) and men (OR 4.7; 95% CI 2.19—10.20). Drs. Albright and Reifenstein first suggested that there was a link between BMD loss and T1DM over 50 years ago. Nowadays, it has been proven that individuals with T1DM have 22—37% less BMD than the non-diabetic control. The effects of T2DM on bone metabolism have remained less clear. Many studies have found a 5-10% increase in BMD above an age-matched non-diabetic population. By contrast, the trabecular bone score (TBS) at the lumbar spine decreased in patients with T2DM. It appeared that fracture risk in T2DM is higher for a given BMD T-score and age or for a given FRAX score (a web-based tool for estimating the 10-year probability of bone fracture risk). Both MRI and high-resolution peripheral quantitative CT revealed an increase in cortical porosity and trabecularization of the bone cortex. Bone material strength (assessed by *in vivo* microindentation) appeared to be lower in T2DM patients compared with non-diabetic controls, which is consistent with the alteration in collagen structure induced by hyperglycemia. The cellular and molecular mechanisms of increased bone fragility are rather complicated and probably not fully understood yet. At the tissue level, a decreased number of osteoblasts and diminished quantities of osteoid have been documented in patients with T2DM. The activation frequency of the bone remodeling units is decreased in diabetic patients. At the same time, the degree of bone mineralization and of non-enzymatic collagen crosslinking by pentosidine increased and positively correlated with HbA1c levels. These findings are consistent with a relatively low bone turnover state. Other determinants of bone fragility include Wnt dysregulation and increased marrow fat, adipokine alterations, oxidative stress, inflammation, use of thiazolidinediones or some SGLT2 inhibitors. Complications of diabetes mellitus increase the risk of falls and risk of fracture. In addition to this, recent investigations have identified the crucial role of osteocalcin in regulating insulin metabolism in a hormonal manner. The use of osteoblast-specific knockout mice produced a strong body of evidence that glucose homeostasis is controlled by the amount of osteocalcin in the circulation. Observational data in humans has provided strong evidence of a link between the levels of circulating osteocalcin and type 2 diabetes mellitus, although clinical trials of osteocalcin have not been initiated. In conclusion, patients with diabetes have an increased risk of low-traumatic fracture, particularly with hip fractures, yet the common approach to osteoporosis diagnostics appears to be inefficient. The mechanism of bone fragility in patients with diabetes is not fully understood, but it certainly related to hyperglycemia and the consequent changes in bone tissue and bone remodeling regulation. The role of osteocalcin on glucose metabolism and its potential therapeutic advantages in diabetic patients remains to be investigated.

KEYWORDS: FRAX score, bone fragility, vitamin D deficiency.

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RARE BONE DISEASE WITH ABNORMAL BONE MASS

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The group of genetic skeletal disorders comprises a total of almost 500 entities. Obviously this a very heterogeneous group with a clinical picture ranging from lethal over (very) severe to almost asymptomatic. Also the mechanisms that are disturbed vary, depending on the time, the skeletal sites as well as the cell types being affected. Despite the fact that these monogenic conditions are in general very rare, they can provide us with nice models for more complex, multifactorial diseases that are more common in the population. This is definitely the case for osteoporosis and a subset of the genetic skeletal disorders. For many of the latter, the disease causing genes have been identified and the underlying pathogenic mechanisms provided novel insights with relevance towards understanding and treatment of osteoporosis. Some monogenic conditions present with an increased fracture rate as seen in osteoporosis. This can be due to structural abnormalities within the bone matrix as is the case in some forms of osteogenesis imperfecta or osteopetrosis. But in other conditions the increased fracture risk is simply caused by a reduced bone mass, as seen in osteoporosis pseudoglioma syndrome. Also the pathogenic mechanisms of sclerosing bone dysplasias associ-