New Strategies for the Prevention and Treatment of Bone Loss

Editorial

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Human skeletons physiologically hold the dynamic balance of bone formation and bone resorption for whole life. Any time bone resorption is faster or more active than bone formation, bone loss occurs. It would lead to low bone mineral density (BMD), bone weakness, and finally osteoporosis. With an increase in life expectancy worldwide, the prevalence of osteoporosis is expected to rise. Traditional anti-osteoporosis drugs can be classified as anti-resorptive agents (such as bisphosphonates, raloxifene), anabolic drugs (such as parathyroid hormone), and bone mineralization drugs (such as calcium agents). These therapies have been shown to increase BMD and reduce the risk of fractures, which are the primary characteristics of osteoporosis. But their long-term safety, efficacy and side-effects are ongoing concerns. Moreover, drugs for osteoporosis treatment remain costly.

Following the promising progress in the modulation of bone turnover and pathogenesis of bone loss, possible new targets appear for controlling osteoclast and osteoblasts formation and activity. Thus, new, safe, effective, low-cost modalities are desired to ameliorate osteoporotic conditions. Recently, new targeted small molecules, new medical components from natural plants and combined or sequential application of various therapies are proposed as the promising strategies for the prevention and treatment of bone loss. Generally, for the relatively young patients with osteoporosis, the first choice is anti-resorptive drugs. Once the treatment fails, the anabolic drugs should be added. When patients treated with bisphosphonates had a hip fracture or decreased BMD, human PTH 1-34 and more powerful anti-resorptive should be chosen. For the patients only with the vertebral fracture or BMD decreased, the bone forming agent, then sequentially anti-resorptive treatment may be appropriate. For the patients with severe osteoporosis which never been treated, the early combined treatment of human PTH 1-34 and Denosumab would maximize their BMD. This special issue will review the frontier therapy of osteoporosis, current research consensus and point out the future direction from different professional aspects.

Fassio et al. comprehensively summarized the most promising new drugs in the treatment of systemic and local osteoporosis including the RANKL antibody (denosumab, DMAb), the monoclonal antibodies against sclerostin, parathyroid hormone-related protein analogue, calcilytics, cathepsin K inhibitor, Bazedoxifene, and the combination or the sequential use of the above drugs, briefly from the mechanisms of Wnt canonical pathway and RANKL-RANK-OPG system [1].

Liu et al. overviewed the sequential and combination therapies of bone-forming agents and anti-resorptive agents, or two kinds of anti-resorptive agents, or strontium ranelate and other anti-osteoporosis agents [2]. Possible regimens were in sequential or combined use, given concurrently or in sequence. According to the “Activation-Depress-Free-Repeat” (ADFR) theory proposed by Frost, the sequential and combination treatment was found to have the advantages on BMD compared with monotherapy.

Picca A et al. overviewed the pathophysiology of osteoporosis by the ways of epigenetics, cell biology and osteoimmunology [3]. In the light of the bone-muscle interconnection, their review also discussed the relevant pathways that may be dissected for identifying new therapeutic targets for age-related musculoskeletal degeneration. The osteo-sarcopenia concept highlighted the close relationship between bone and muscle as well as the pathophysiologic communibilities between them. Clinically, the early recognition and timely treatment of osteo-sarcopenia was crucial for preventing bone loss.

Since mechanical loading provides an essential stimulus for bone remodeling, it can be used as a strategy to prevent and treat bone loss. Prof. Sun et al. described the effects of mechanical loading on bone [4]. The data suggested that an appropriate exercise (including magnitude, direction, rate, cycle, etc.) would prevent or decrease the rate of bone loss. Therefore, more physical activities at an earlier age in life will have lasting benefits when getting older.

The immune system, including T cells, B cells and inflammatory cytokines, regulates bone homeostasis, which is termed as Osteoimmunology. Prof. Guo and his co-authors presented the involved molecular pathways and their applications in the prevention and treatment of bone loss [5]. T cells play a key role during inflammatory induced bone resorption mainly through inflammatory cytokines including interleukin, tumor necrosis factor, and interferon-γ etc. B cells are the active regulators of the RANK/RANKL/OPG axis in osteoporosis and human immunodeficiency virus-associated bone loss. In fact, existing drugs for countering bone loss have been shown to regulate bone remodeling at least partly through the immuno-skeletal interactions. In addition, new targets for the treatment of various forms of pathological bone loss, including arthritis, periodontitis and OP, will be developed from the perspective of osteoimmunology.

Ivanova S and Vasileva L proposed that the treatment strategies of osteoporosis included non-pharmacological treatment (such as diet rich of calcium and vitamin D, healthy lifestyle, proper exercise plan) and pharmacological therapy [6]. Combination of non-pharmaceutical and pharmacological strategies has to be considered for the prevention of osteoporosis and minimization of the risk of fractures. The prevention strategies should be initiated early in life. Lifestyle changes must be popularized among healthy young patients. Nutrition that maintains normal bone homeostasis and regular physical activity are crucial for the prevention of bone loss. Given the heterogeneity of osteoporosis syndrome and lack of significant comparative studies, the choice of a pharmacological agent should be individualized depending on the combination of several factors: severity of bone loss and the number of the risk factors, profile of the patient, efficacy, tolerance (side effects and contraindications), the presence of accompanying diseases.

Bone marrow stromal cells and hematopoietic stem cells are multi-potential cells that can differentiate into bone, cartilage, tendon, adipose tissue and fibrous tissue. They would potentially be applied for treating bone loss diseases. Xiao N outlined research and technique in the role of stem cells from bone, blood, periosteum, adipose, dental pulp stem cells, and fetal mesenchymal stem cells in bone repair, and highlighted the current and potential stem cell based treatment for bone loss diseases in the future [7].

Xia WB and Pang R reviewed the advantages, disadvantages and side-effects of various managements to bone loss [8]. Anti-resorptive agents including hormone replacement therapy, bisphosphonates, selective estrogen receptor modulators and DMAB are commonly applied in the treatment of bone loss, but can lead to overall decrease of bone turnover rate. Moreover, jaw osteonecrosis related with systemic application of bisphosphonates is a severe problem that can not be ignored. Anabolic agents, mainly PTH, are usually combined with other anti-resorptive drugs, and PTHrP might be a promising pure anabolic agent for osteoporosis. Future drug targets such as cathepsin K inhibitors,
sclerostin inhibitors and integrin antagonists will mainly come from RANK-RANKL-OPG system and Wnt/β-catenin signaling pathway. Moreover, the pre-existing drugs could be explored in new patterns.

Yang YQ et al. introduced the important role and its signaling pathways of Interleukin-17 (IL-17) in inflammatory bone disease including periodontitis, rheumatoid arthritis (RA) and spondyloarthritis (SpA), and forecasted that it could be an attractive therapeutic target to inflammation-mediated bone loss [9]. There was a variety of options targeting IL-17: an IL-17 directly inhibitor, an IL-23 inhibitor on the differentiation of Th17 cells which acting upstream, an inhibitor of receptor signaling which acting downstream, or in combination with blocking other inflammatory factors (using TNF, IL-1 and IL-6 inhibitors).

Although great progress has been achieved in the prevention and treatment of bone loss, above mentioned drugs unfortunately have little effect on cortical bone, non-vertebral fracture, and glucocorticoid induced osteoporosis in men. However, there are still many problems and issues which need to be discussed further. More precision has become an inevitable trend and has far-reaching significance.

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REFERENCES