Osteoporosis Treatments

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A healthy and active lifestyle is vital for the proper maintenance of all body tissues, including bone. Several studies have highlighted the importance of physical exercise to improve the quality of life of patients with osteoporosis. Diet also plays a fundamental role in bone health. Calcium supplementation is able to decrease the rate of bone mineral density loss in women, presenting even better results in combination with vitamin D. Lately, isoflavones has gain interest as a treatment in osteoporosis but their effectiveness still remains unclear. Therefore, pharmacological therapies have been developed to counteract bone fragility based on molecular targets. Therapies for osteoporosis are focus on restoring the normal balance between bone resorption and bone formation. Bone anti-resorptive therapies focus on the inhibition or reduction of bone resorption process, these are; estrogens, selective estrogen receptor modulators (SERMs), bisphosphonates and monoclonal antibodies. On the other hand, bone formation agents target anabolic pathways to stimulate the osteoblastic activity. This include Teriparatide, a recombinant human parathyroid hormone (PTH), and Romosozumab; an anti-sclerostin monoclonal antibody with dual effect. It increases bone formation and, to a lesser extent, it reduces bone resorption (or bone loss) which translates into a decrease in the risk of fracture. In summary, currently used osteoporosis therapies are not fully effective in all patients and present considerable side effects that seriously compromise their long-term use. Thus, the development of new therapeutic strategies for osteoporosis is necessary in an increasingly aging world population. In this context, cell-based therapeutic strategies based on mesenchymal stem cells are positioning as encouraging possibilities to address osteoporosis.

osteoporosis bone turnover osteoporosis treatments

1. Introduction

A healthy and active lifestyle is vital for the proper maintenance of all body tissues, including bone. Several studies have highlighted the importance of physical exercise to improve the quality of life of patients with osteoporosis[1][2][3].

2. Current Osteoporosis Treatments and Necessities

Recently, Filipović, T. et al 2020[4], has demonstrated that exercising is able to modulate the enzymatic activity of serum matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase 1 (TIMP-1) in postmenopausal osteoporotic patients.

Diet also plays a fundamental role in bone health. Calcium supplementation has been shown to be able to decrease the rate of bone mineral density loss in women, although it does not seem to be enough to prevent fractures[5]. The combination of calcium with vitamin D showed better results, with a reduction of 15% in the risk of total fractures and 30% in the risk of hip fractures[6]. During menopausal transition, the drop of endogenous estrogens enhances bone resorption, at the expenses of the new bone formation, leading to osteoporosis[7]. In consequence, estrogen intake could be an appropriate therapy against osteoporosis. However, estrogen therapy is associated with elevated cancer risk in estrogen receptor (ER)-α rich tissues like the endometrium, breast and ovary. Therefore, alternative molecules have been sought to prevent this unwanted effect of estrogen therapy. In that matter, isoflavones are a type of phytoestrogens that have shown a weak binding to ERα[8] and preferentially bind to ER-β; present in bone, liver, heart and brain. Therefore, they mimic the effects of estrogens in some tissues and at the same time, block the estrogen effects in others. Isoflavones can be absorbed through the diet in legumes (most importantly in soy), nuts and some fruits. Recently, in a randomized clinical trial, isoflavone treatment has achieved a decline in the BMD loss, together with an increased in bone turnover. Moreover, the combination of this phytoestrogens with calcium, magnesium and calcitriol showed even better results[9]. However, its effectiveness remains controversial since a meta-analysis of 10 long term clinical trials concluded that soy isoflavones did not show significant improvement in lumbar spine, total hip or femoral neck BMD of postmenopausal women[10]. Altogether, these approaches are insufficient to prevent the progression of osteoporosis. Therefore, pharmacological therapies have been developed to counteract bone fragility based on molecular targets[11]. Therapies for osteoporosis are focus on restoring the normal balance between bone resorption and bone formation. Currently, the most common therapies are the anti-resorptive ones, focusing on the inhibition or reduction of bone resorption process. These agents include estrogens, selective estrogen receptor modulators (SERMs), bisphosphonates and monoclonal antibodies[12].

Bone resorption is highly determined by hormone levels, such us estrogens. As mentioned above, unopposed estrogen can increase the risk of breast and uterine cancers, deep vein thrombosis and stroke[13]. Therefore, in order to reduce the side effects of estrogens, SERMs have taken a step forward. Although they demonstrate selectivity toward estrogen receptors in the bone and are able to maintain bone mineral density (BMD), they lack the efficacy of traditional estrogens[14]. Many clinical trials with postmenopausal osteoporotic women using different types of SERMs have shown that their benefit for fractures prevention is anatomically limited (present certain limitations in preventing non-vertebral fractures). In addition, SERMs are also associated with detrimental extra-skeletal effects such as an increased risk of a cardiovascular event and endometrial cancer risk[15], as well as related side effects such as thromboembolic events and, in some cases, carcinogenesis[16].

Among anti-resorptive drugs, the most used are bisphosphonates. Bisphosphonates are pyrophosphate analogues that bind to hard bone through their affinity for hydroxyapatite[17]. They are incorporated into bone matrix and taken up by osteoclasts, suppressing their activity in bone remodeling[18]. This way, the bone density increases but the quality of the bone is compromise since the old bone is prone to have microfractures that negatively affect its function. Moreover, the prolonged use of bisphosphonates may lead to adverse events, such as gastrointestinal problems, osteonecrosis of the jaw, atrial fibrillation and musculoskeletal pain[19][20].

Denosumab is a monoclonal antibody that binds with high affinity to receptor activator of nuclear factor kappa-B ligand (RANKL), preventing the binding between RANKL and receptor activator of nuclear factor kappa-B (RANK) and thus inhibiting the differentiation and activity of the osteoclasts[21]. Unlike bisphosphonates, Denosumab is not incorporated into bone, yielding a much shorter terminal half-life[22]. Consequently, Denosumab presents a potential advantage for the patients who have a side effect for the therapy, due to the fact that it will be no longer active six months after the last dose. A big concern regarding Denosumab treatment is the regular adhesion to this treatment, because the patient's fracture risk might increase after the dose "wears off"[23].

Although anti-resorptive osteoporosis medications reduce fractures, they have rare and serious adverse effects that may limit their safety for medium and long-term use, so new safe therapies capable of restoring skeletal structure and integrity are needed. In fact, current pharmacologic attempts for osteoporosis aim to prevent fractures through stimulation of bone formation. These agents target anabolic pathways to stimulate the osteoblastic activity, increasing the bone volume without inhibiting its resorption.

The first approved agent to accomplish this was teriparatide. Teriparatide is a recombinant human parathyroid hormone (PTH), known to be the only available therapeutic agent that increases the formation of new bone tissue[24]. PTH regulates the amount of calcium in bone; therefore this treatment is used to stimulate osteoblasts to create new bone[25][26]. Toxicological studies revealed osteosarcoma in treated rats; nonetheless this problem has not been detected in treated patients. As a consequence, the approved lifetime duration of treatment with teriparatide is 24 months; but it is recommended only for patients for whom potential benefits outweigh potential risk[27][28].

Romosozumab, is another monoclonal antibody recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of osteoporosis in postmenopausal women. The registered trade name of Romosozumab is Evenity. It is the first humanized anti-sclerostin monoclonal antibody that has been shown to increase bone formation with dual effect: on one hand, it increases bone formation and, on the other, although to a lesser extent, it reduces bone resorption (or bone loss) which translates into a decrease in the risk of fracture[29]. However, according to the prescribing information; it may increase the risk of myocardial infarction, stroke and cardiovascular death. Therefore, it should not be administered to patients who have had a myocardial infarction or stroke within the preceding year.

Sclerostin, expressed by osteocytes and articular chondrocytes, is the product of SOST gene. It is an endogenous inhibitor of the Wingless-type mouse mammary virus integration site (Wnt) signaling pathway. Wnt signaling has been described as a positive regulator of bone formation and regeneration[30]and thus, Wnt signaling could be modulated to treat osteoporosis and other skeletal diseases associated with low BMD and increased facture risk[31]. Therefore, anti-sclerotin compound would inhibit sclerostin (an inhibitor of Wnt signaling) and in consequence, promote Wnt signaling and stimulate bone formation by osteoblasts[32]. Another two anti-sclerostin monoclonal antibodies are being developed by other companies; blosozumab (Eli Lilly and Company, Indianapolis, IN, USA) and BPS804 (Novartis, Basel, Switzerland).

In summary, currently used osteoporosis therapies are not fully effective in all patients and present considerable side effects that seriously compromise their long-term use. Thus, the development of new therapeutic strategies for osteoporosis is craved in an increasingly aging world population with a longer life expectancy.

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