Introduction

Osteoporosis is a common disease where bone mass is reduced, leading to an increased risk of bone fracture. Half of Caucasian women and a fifth of men experience osteoporosis-related bone fracture in the course of lifetime [1]. Treatment of osteoporosis-related fracture causes enormous socio-economic burden, costing nearly $17 billion in 2005 in the U.S.; it is expected to double or triple in the next four decades due to rapidly aging population [2].

Osteoporosis is caused by an imbalance of osteoblastic bone formation and osteoclastic bone resorption. Thus, anti-osteoporosis medications aim to reduce the risk of bone fracture either by increasing osteoblastic bone formation or suppressing bone resorption. Currently, four classes of anti-resorptive agents and one class of anabolic agent are approved by the U.S. Food and Drug Administration for the treatment of osteoporosis (Table 1). However, these medications have failed to increase bone formation or decrease bone resorption in isolation due to the closed coupling of osteoblasts and osteoclasts whereby changes in differentiation or activity of one eventually affects the other [3]. This phenomenon not only limits the therapeutic efficacy but also threatens the safety of osteoporosis drugs. This review will discuss the biological mechanisms of action of currently approved medications for osteoporosis treatment, focusing on the osteoblast–osteoclast coupling.

Anti-resorptive Drugs

1. Bisphosphonates

Bisphosphonates (BPs) are the most common class of medications for the treatment of osteoporosis. They are analogues of pyrophosphate and become highly concentrated in mineral-
ized tissues because the oxygen atoms in the phosphonate groups have a high affinity for divalent cations such as calcium. This leads to the osteoclast-specific effect of BPs, since they are released from bone tissue by osteoclastic bone resorption and internalized by adjacent osteoclasts. Although the mechanism by which BPs inhibit osteoclastic bone resorption is not fully understood, they block farnesyl diphosphate synthase (FPPS) in the mevalonate pathway [5]. Disruption of FPPS prevents formation of farnesol and geranylgeraniol for prenylation of multiple proteins, including small guanosine triphosphatases (GTPases) [6], that are critically involved in the differentiation and survival of osteoclasts [7]. The anti-osteoclastogenic effect of BPs is rescued by the addition of geranylgeraniol, but not farnesol, in vitro [8], supporting the view that interference with protein prenylation may be the underlying mechanism of BP action. Recently, cholesterol has been found to be the endogenous ligand for the estrogen-related receptor alpha (ERRα), originally known as an orphan nuclear receptor [9]. BPs exert their anti-osteoclastogenic effect by blocking the mevalonate pathway and decreasing intracellular cholesterol levels, leading to decreased activation of ERRα. Consequently, hypercholesterolemia-induced bone loss and the osteoprotec-
tive effect of BPs are abolished in ERRα knockout mice [9].

BPs effectively reduce the risk of vertebral, non-vertebral, and hip fractures by suppression of osteoclastic bone resorption [10]. Although there is some in vitro evidence that BPs may have an anabolic effect on osteoblasts [11], BPs decrease not only osteoclastic bone resorption but also osteoblastic differen-
tation in vivo [12]. This is primarily due to the coupling of osteoblasts and osteoclasts: inhibition of osteoclast differentiation and bone resorption decrease production and/or release of osteoblast–stimulating osteoclast–derived growth factors, such as Wnt10a and sphingosine-1-phosphate, and matrix–derived growth factors, such as transforming growth factor–β1 and insulin–like growth factor–1 [4,13]. The excessively low bone turnover caused by BPs has been associated with some rare but serious side effects, such as atypical femoral shaft fracture and medication–related osteonecrosis of the jaw (MRONJ), although the mechanisms of pathogenesis of these are still poorly understood [14].

2. Receptor activator of nuclear factor kappa–B ligand antibody (Denosumab)

Denosumab is a fully humanized monoclonal antibody that targets receptor activator of nuclear factor kappa–B ligand (RANKL) [15]. RANKL, which belongs to the tumor necrosis factor family, binds to the RANK (receptor activator of nuclear factor kappa–B) receptor on myeloid lineage cells and this binding interaction is a key step for the differentiation of osteocl-
clast precursors into mature osteoclasts. Denosumab binds to RANKL and prevents RANKL from binding to RANK, inhibiting differentiation, activation, and survival of osteoclasts.

Denosumab reduces the risk of vertebral, non-vertebral, and hip fractures by suppressing bone resorption [16]. Due to os-
teoblast–osteoclast coupling, denosumab also decreases os-
teoblastic bone formation, similarly to BPs, and has also been associated with atypical femoral shaft fracture and MRONJ [17]. With regard to the MRONJ, however, denosumab has an advantage over BPs due to its shorter half–life. BPs are accumu-
lated in bone minerals and slowly released by osteoclastic bone resorption, even years after stopping treatment. In con-
trast, denosumab reversibly inhibits RANKL, such that bone turnover markers are rapidly recovered within a few months after discontinuation [14,18]. Denosumab increases the risk of infections such as cellulitis, probably due to the inhibition of RANKL in the immune system, although the pathogenesis of this is not fully understood [19].

3. Hormone replacement therapy: estrogen therapy

Menopause is one of the most important risk factors for osteoporosis in middle–aged women [20]. This is because estrogen positively regulates bone and mineral homeostasis,
4. Selective estrogen receptor modulators

Selective estrogen receptor modulators (SERMs) are a class of compounds that bind to the estrogen receptor (ER) and act as an agonist or antagonist depending on the target tissue. Raloxifene and bazedoxifene, for example, are estrogenic for the bone and liver, but anti–estrogenic for the breast and endometrium (raloxifene is neutral for the endometrium) [33]. Thus, they have the beneficial effects of estrogen therapy on bone, but may even reduce the risk of invasive breast cancer, although they still increase the risk of venous thromboembolism due to anabolic effects on coagulation factors in the liver [34]. The tissue–selective agonistic or antagonistic effect of SERMs is presumed to be associated with several factors as follows: 1) ligand–dependent promotion or inhibition of recruitment of transcriptional coregulators to the SERM–ER complex and tissue–specific enrichment of those coregulators; 2) regulation of coactivator stability or activity by SERM; and 3) preferential affinity of SERM to ERα over β and differential tissue distribution of these ER isoforms [35].

Both raloxifene and bazedoxifene reduce the risk of vertebral fractures, but not non–vertebral or hip fractures [36,37]. Thus, these SERMs are recommended for younger postmenopausal women, who have low risk of hip fracture, especially for those who are concerned about the risk of breast cancer [17].

**Anabolic Drugs**

1. Parathyroid hormone receptor agonists

Currently, the only class of anabolic drug approved for the treatment of osteoporosis is parathyroid hormone (PTH) receptor agonists, which include teriparatide and abaloparatide. Teriparatide is a recombinant protein containing the first 34 amino acids of human PTH, which retain the essential anabolic effect of native PTH. Abaloparatide is a synthetic analogue of parathyroid hormone–related protein with 76% homology. Both drugs bind to the parathyroid hormone 1 receptor (PTH1R), primarily present in the bone and kidney.

The primary physiological function of PTH is to raise the plasma calcium concentration in response to low plasma calcium levels by acting primarily on the bone and kidney. Although conflicting results regarding the direct effect of PTH on the osteoclasts have been reported, it is now widely accepted that PTH binds to PTH1R in osteoblasts and increases RANKL expression to indirectly stimulate osteoclastic bone resorption, thereby liberating calcium into the plasma [38]. PTH, however, also simultaneously increases osteoblastic bone formation by promoting osteoblast differentiation and survival. Thus, PTH has both catabolic and anabolic effects on bone, and the balance is determined by the duration for which PTH remains available to the PTH1R in osteoblasts. While the continuous...
elevation of PTH levels in hyperparathyroidism results in increased bone resorption being dominant over increased bone resorption and net bone loss, a brief elevation (1 to 3 hours) of PTH levels by therapeutic intermittent injection primarily stimulates bone formation and increases bone mass [38]. The mechanism of this biphasic effect of PTH (continuous vs. intermittent) is not fully understood, but longer exposure of osteoblasts to PTH seems to be necessary for increasing RANKL expression, in contrast to cell-autonomous anabolic effects [39].

Both teriparatide and abaloparatide reduce the risk of vertebral and non-vertebral fractures [40,41]. However, the use of these drugs is limited to 18 to 24 months for two reasons. First, there is a theoretical concern about increased risk of osteosarcoma because treatment with PTH for two years greatly increased the risk of osteosarcoma in rats [42], although there is no evidence that PTH increases the risk of osteosarcoma in humans. Second, because of osteoblast–osteoclast coupling, the osteoclastic bone resorption slowly begins to increase after several months of PTH treatment. During the first 24 months of treatment, the rate of bone formation is greater than that of bone resorption, making the so-called 'anabolic window', but eventually the increasing rate bone resorption equals that of bone formation and there is no net gain in bone mass [43].

Conclusions

Bone fractures from osteoporosis can be life-threatening in older people. Current anti-osteoporosis drugs are being successfully used to reduce the risk of these fractures. However, all medications are subject to the effects of osteoblast–osteoclast coupling, limiting treatment efficacy and safety. The recently developed sclerostin antibody, Romosozumab, may be the first medication to uncouple the activities of osteoblasts and osteoclasts and exert simultaneously anabolic and anti-catabolic effects, although there are concerns about the increased risk of cardiovascular disease [44]. Future anti-osteoporosis drugs may target the osteoblast–osteoclast coupling process to develop more effective and safe medications.

Acknowledgements

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2016R1D1A1B03931522).

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

References


