Forum Minireview

Pharmacological Topics of Bone Metabolism:
Recent Advances in Pharmacological Management of Osteoporosis

Atsushi Suzuki1*, Sahoko Sekiguchi1, Shogo Asano1, and Mitsuyasu Itoh1

1Division of Endocrinology and Metabolism, Department of Internal Medicine, Fujita Health University,
1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan

Received November 11, 2007; Accepted January 9, 2008

Abstract. The prevention of osteoporotic fracture is an essential socioeconomic priority, especially in the developed countries including Japan. Estrogen, selective estrogen-receptor modulators (SERMs), and bisphosphonate are potent inhibitors of bone resorption; and they have clinical relevance to reduce osteoporotic fractures in postmenopausal women. However, we can prevent at most 50% of vertebral fractures with these agents. For the better compliance of aminobisphosphonate, the use of a daily bisphosphonate regimen is moving to a weekly or monthly bisphosphonate regimen. Both cathepsin K inhibitors and modulators of the RANK-RANKL system, which can reduce bone resorption, are the candidates for the future treatment of osteoporosis. As well as bone resorption, we need to increase bone formation to prevent osteoporotic fractures, particularly in elderly patients with low bone turnover. In the U.S., Europe, and Australia, they have already started intermittent parathyroid hormone injection and/or oral strontium ranelate to stimulate bone formation. We still need to discover new agents to reduce osteoporotic fractures for the better quality of life without fractures.

Keywords: osteoporosis, bone turnover, fracture risk, antiresorptive agent, bone formation, bone metabolism

Prevalence of osteoporosis

Osteoporosis has clinical and public health importance in many regions of the world because osteoporotic fractures are one of the most common causes of disability in the aged population (1). In developed countries including Japan, the aged population is rapidly increasing, so the prevention of osteoporotic fracture is considered to have an essential socioeconomic priority. About more than 40% of Japanese women experienced vertebral fracture before 80 years of age (2), and the lifetime risk of osteoporotic fractures of the spine in 50-year-old Japanese women is around 37% (3). The number of fractures has been increasing all over the world according to the report from World Health Organization (WHO) (1), but several reports from population-based studies show that recent progress of the diagnosis and treatment of osteoporosis have been effective to reduce the number of hip fractures (4). In this review, the present pharmacological management of osteoporosis and the future perspectives are briefly summarized.

Aging is related to somatopause, menopause (andropause), and adrenopause

From the endocrinological point of view, aging is related to decrease of three major systemic hormones, that is, growth hormone (GH) and sex steroids from both adrenal gland and gonadal glands (Fig. 1). Thus the first strategy to prevent osteoporotic fracture is to modify these hormonal profiles in the aging population. GH secretion and insulin-like growth factor I (IGF-I) levels are reduced in healthy older people and it has been suggested that the somatopause is an age-related GH deficiency state (5). GH deficiency induces the reduction of plasma IGF-I level, resulting in sarcopenia and osteopenia. Although the supplementation of GH ameliorates the bone mineral density (BMD) and muscle strength in the GH-deficient population, additional
supplementation of GH for healthy adults does not seem to have benefit to prevent osteoporotic fractures (5). The treatment with IGF-I for osteoporosis is also considered, but it is not recommended because of the risk of colorectal cancer.

Sex steroids are the most important hormones to maintain both bone mass and bone quality (6). Women experience the drastic change of the serum levels of estrogen twice in their life, puberty and menopause, which are related to rapid increase of bone mass and its reduction, respectively. At first, hormone replacement therapy (HRT) with estrogen was expected to ameliorate the quality of life (QOL) of postmenopausal women and to decrease the incidence of osteoporotic fractures. Indeed, Women’s Health Initiative (WHI) trial revealed that HRT with oral estrogen and progestin to healthy postmenopausal women reduces hip fracture up to 34% as well as the reduction of the incidence of colorectal cancer (7). However, this trial also revealed that HRT increases breast cancer, venous thromboembolism, and even cardiovascular events. After this “surprising” WHI report, the treatment of osteoporosis with oral estrogen has become extremely restricted, and it is so far not recommended to use estrogen for the general population in order to prevent osteoporotic fracture. As well as estrogen, androgens control a broad range of physiological functions (8). A number of conditions, including osteoporosis, frailty, and sexual dysfunction in both men and women have been improved using androgens. So, testosterone therapy is recommended for symptomatic men with androgen deficiency (8). Although androgen replacement therapy can improve many clinical conditions including sarcopenia and osteoporosis, it is limited by the risk of prostate cancer in healthy men. Also in women, ovarian androgen secretion increases during woman’s peak reproductive years and declines as a woman ages (9). However, it is so far not recommended to use testosterone generally because evidence of safety in long-term studies is lacking (10).

Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) are considered to be important androgen and estrogen precursors in older adults (11). Decline in DHEAS with aging may contribute to physiological changes, which are sex hormone dependent. It has been reported that DHEA replacement therapy in older subjects with low DHEA levels improves hip and spine BMD (11), but it still needs to prove its efficacy to prevent osteoporotic fracture.

**SERMs and SARMs**

As HRT is not a safe enough treatment for osteoporosis in the general population, the compounds that mimic the stimulatory effect of sex steroids on bone are being considered. The selective estrogen-receptor modulators (SERMs) act as estrogen-receptor (ER) agonists in some tissues while acting as an ER-antagonist in others based on conformational change of the receptors (12). Ideally, it is presumed that SERMs should selectively act as an agonist in bone and brain while acting as an antagonist in the breast and uterus. Raloxifene is one of the most commonly used SERMs for the treatment of osteoporosis in postmenopausal women. Raloxifene increases BMD and decreases bone turnover markers, and most clinical trials with fracture outcomes showed that raloxifene reduces approximately 50% in the risk of vertebral fractures specifically (13). The Study of Tamoxifen and Raloxifene (STAR) trial (14) showed that raloxifene reduces the risk of developing invasive breast cancer as well as tamoxifen, which is another SERM designed for the secondary prevention of breast cancer. As for the cardiovascular events, the Raloxifene Use for the Heart (RUTH) Trial (15) showed that among postmenopausal women with cardiovascular disease (CVD) or risk factors for CVD, treatment with raloxifene is not associated with a difference in coronary events compared with placebo. So, nowadays raloxifene is considered to be safe and has several benefits for postmenopausal women with osteoporosis and/or breast cancer. However, there is little evidence that raloxifene can prevent non-vertebral fractures including hip fractures. So, new SERMs, which have enough efficacies to prevent both vertebral and non-vertebral fractures, are considered to be necessary for the better management of osteoporosis with SERM.

How about selective androgen receptor modulators
(SARMs)? An androgen receptor ligand that maintains anabolic activities in bone and muscles with substantially diminished activity in the prostate is expected. Orally active, nonsteroidal SARMs enhance muscle, bone, and sexual function in animal models and may be useful therapeutics in the future (16, 17).

**Bone resorption and bone formation**

Bone metabolism is characterized by two opposite activities, bone formation and bone resorption (18). Once formed, the bones are continuously renovated and modified by the remodeling system in adults, and the remodeling rate is between 2% and 10% of the skeletal mass per year. Bone mass depends on the balance between resorption and formation within a remodeling unit (Fig. 2). As osteoporosis is a disease characterized by a decrease of bone mass and a deterioration in architecture of the bones, the negative bone balance between formation and resorption results in the development of osteoporosis. So, we can expect that the pharmacological modification with an inhibitor of bone resorption and/or stimulator of bone formation will lead to recovery from this negative balance in osteoporotic patients.

**Bisphosphonates**

Bisphosphonates are the most potent anti-resorptive agents that apparently reduce osteoporotic fractures. In Japan, three types of oral bisphosphonates are so far available for the treatment of osteoporosis. Etidronate was the first bisphosphonate used and there is evidence that it increases lumbar BMD (19), but less evidence that it can prevent clinical fractures compared to the newer aminobisphosphonates, alendronate and risedronate. Both alendronate and risedronate apparently increase BMD and rapidly reduce bone turnover markers (20, 21). The efficacy of these bisphosphonates to prevent vertebral fracture is almost the same as that of raloxifene. Furthermore, both alendronate and risedronate have scientific evidence to prevent non-vertebral fractures including hip fractures, while raloxifene does not seem to work well (20, 21). As hip fracture is one of the most frequent causes of immobility of aged people, these bisphosphonates are useful agents to improve activity of daily life (ADL) and QOL, especially in the older population. Bisphosphonates dramatically increase BMD for the first 3 to 4 years and then reach the plateau (22). Bisphosphonates accumulate in bone matrix, and osteoclast-induced bone resorption is believed to induce the re-use of bisphosphonates released from bone matrix, which explains, at least in part, why anti-resorptive effect of bisphosphonates continues after the cessation of treatment (22). Alendronate maintains the gain of BMD of lumbar spine and anti-fracture efficacy up to 5 years after the cessation (23), while risedronate seems to work for a shorter time period. Nowadays, the efficacy and safety of oral bisphosphonates for the treatment of osteoporosis are well established. However, patient adherence and persistence on treatment are suboptimal. One of the reasons is that their low bioavailability and low potency necessitate frequent administration on an empty stomach. In order to achieve better adherence and persistence, the regimen to prescribe alendronate and risedronate moves from once-daily to once-weekly all over the world. The persistence on treatment seems to be increased in patients receiving once-weekly bisphosphonates compared with daily bisphosphonates. Both once-weekly alendronate and risedronate tablets have been available in Japan from 2006 and 2007, respectively. Furthermore, once-monthly ibandronate, another oral aminobisphosphonate, is commercially available abroad (24), but its efficacy for non-vertebral fracture is still controversial.

For some women with postmenopausal osteoporosis, oral bisphosphonates are not suitable. These women may be unable to take oral bisphosphonate therapy due to upper gastrointestinal tract adverse experiences or they
cannot stay upright for the required length of time. This limits the population in which bisphosphonates can be used and would be addressed by the additional availability of an efficacious intravenous bisphosphonate preparation. Rapid intravenous ibandronate injections, 2 mg (every 2 months) and 3 mg (every three months), are at least as effective as the regimen of 2.5 mg orally daily (25). The U.S. Food and Drug Administration (FDA) has recently approved a quarterly intravenous injection of ibandronate. This is the first ever intravenous injection for the treatment of postmenopausal osteoporosis to be approved by the FDA. Furthermore, a once-yearly infusion of zoledronic acid, the most potent anti-resorptive bisphosphonate, during a 3-year period significantly reduces the risk of vertebral, hip, and other fractures (26). These findings suggest that an intravenous infusion of bisphosphonate might be an effective treatment for postmenopausal osteoporosis, especially for the patients who cannot take oral bisphosphonates. Recently, it was found that use of bisphosphonates may be associated with osteonecrosis of the jaw (ONJ). The risk of ONJ associated with oral bisphosphonate therapy appears to be low (1 in 10,000 – 100,000 patient-treatment years), but it is recommended to minimize surgical procedures in patients taking these drugs, especially for individuals who have been on long-term oral bisphosphonate therapy (empirically defined as, >3 years) (27).

**Other anti-resorptive agents**

Calcitonin is a naturally occurring peptide that acts via specific receptors to strongly inhibit osteoclast function. A randomized trial of nasal spray salmon calcitonin in postmenopausal women showed the risk reduction of vertebral osteoporotic fractures, but there is insufficient and/or inconsistent evidence of an effect on osteoporotic fractures for calcitonin (28). On the contrary, there is mounting evidence to show that calcitonin diminishes bone pain in osteoporotic vertebral fractures, which may have clinical utility in vertebral crush fracture syndrome (29). Nowadays in Japan, once-weekly intramuscular administration of calcitonin is recommended not to prevent osteoporotic fracture but to relieve bone pain with vertebral fracture. The receptor activator of nuclear factor-kappaB ligand (RANKL), its cognate receptor RANK, and its natural decoy receptor osteoprotegerin have been identified as the final effector molecules of osteoclastic bone resorption (30). This has provided an ideal target for therapeutic interventions in metabolic bone disease. Denosumab is a fully human monoclonal antibody against RANKL, and denosumab given every 3 or 6 months is well tolerated, increases BMD, and decreases bone resorption markers for up to 24 months (30, 31). Cathepsin K is a lysosomal cysteine protease expressed abundantly in osteoclast cells, and a new target to prevent the osteoporotic fracture by osteoclast-induced bone resorption (32). Several compounds are on the way, but still under investigation.

**Stimulator of bone formation**

Parathyroid hormone (PTH) has long been considered to increase bone resorption because of the clinical experience of secondary osteoporosis due to primary hyperparathyroidism. Continuous elevation of serum PTH induces ostitis fibrosa at cortical bones, but intermittent administration of PTH is revealed to stimulate bone formation both in vitro and in vivo. In the United States, treatment with PTH for one and a half years for osteoporosis was approved by the FDA and shows good efficacy to increase BMD (33). As PTH is a biological agent, like estrogen and SERM, the gain of BMD with PTH treatment will be lost soon after cessation of the treatment. So, it is considered to be better to use anti-resorptive agents such as bisphosphonates after PTH treatment. Strontium ranelate is a heavy metal that is absorbed and accumulated in bone (34). Recent findings suggest that strontium ranelate modulates Ca-sensing receptor (CaSR) activity of bone cells by increasing Ca concentration in the microenvironment (35). The signal from CaSR in osteoblasts acts as an activator of bone formation, while it suppresses osteoclasts activity, resulting in the reduction of bone resorption (36). Strontium ranelate leads to a 41% reduction in vertebral fracture risk during three years, while there is a 16% reduction in nonvertebral fractures (34). Furthermore, strontium ranelate is the only treatment proven to be effective at preventing both vertebral and nonvertebral fractures in women aged 80 years and older. Strontium ranelate is now available in Australia and Europe.

**Others**

**Vitamin D and its analogues:** Vitamin D is an essential nutrient for the absorption of Ca from the intestine, and evidence supports the use of calcium, or calcium in combination with vitamin D supplementation, in the preventive treatment of osteoporosis (36). Although the efficacy to prevent osteoporotic fracture is less than anti-resorptive agents such as bisphosphonates and SERM, recent findings suggest that the high prevalence of hypovitaminosis D in adults becomes a new issue in accordance with the increase of aged individuals all over the world including Japan (37, 38). There are several reports saying that hypovitaminosis D attenuates the
effect of bisphosphonates, and well controlled-randomized trial of combination therapy of alendronate and active vitamin D is on going in Japan. As a candidate for active vitamin D analogs that have selective effects on bone, 1α,25-dihydroxy-2β-(3-hydroxypropoxy)vitamin D₃ (ED-71) has been synthesized and is currently under clinical trials. ED-71 increases BMD regardless of serum 25-hydroxy vitamin D level, which is postulated to reflect most accurately vitamin D stores in osteoporotic subjects (39).

**Vitamin K:** Vitamin K functions as cofactor for the post-translational carboxylation of glutamate residues. Incomplete carboxylation of γ-carboxy glutamic acid (Gla)-residues of osteocalcin due to vitamin K deficiency results in an increased risk for developing osteoporosis (40). Undercarboxylated osteocalcin is frequently found in postmenopausal women, and the supplementation with extra vitamin K seems to increase the markers for bone formation and reduces bone fractures.

**Conclusion**

Recent progress of diagnosis and treatment with new drugs seems to have some efficacy to reduce osteoporotic fractures, but we still need newer and more potent agents, which can reduce both vertebral and non-vertebral fractures. In addition, better adherence and persistence and long-term safety are needed for the ideal management of osteoporosis.

**References**

Management of Osteoporosis 535


