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The 2024 Guidelines for Osteoporosis - Korean Society of Menopause: Part II

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PHARMACOLOGIC THERAPY OF OSTEOPOROSIS

IV-1. HORMONE REPLACEMENT THERAPY

Key points

Hormone replacement therapy (HRT) is effective in preventing bone loss and reducing the risk of fractures in postmenopausal women. Given its beneficial effects on vasomotor symptoms and osteoporosis, as well as its confirmed protective effect on bones in normal/osteopenic postmenopausal women, it is primarily a drug of choice in women in their 50s. It is also recommended for use in older ages when using other drugs is not feasible and the risk of hormone therapy is not high [1].

1. Effect of HRT on the Musculoskeletal System

Standard-dose oral HRT suppresses bone resorption and regulates bone remodeling, which in turn increases bone mineral density (BMD) in postmenopausal women [2]. However, no study clearly investigated specific changes in BMD based on the type and administration route of estrogen. The response of BMD to estrogen is dose-dependent. The Postmenopausal Estrogen/Progestin Intervention (PEPI) study showed significant increases in lumbar and femoral BMD in postmenopausal women following three years of monotherapy or combined therapy including 0.625 mg of conjugated estrogen (CE) compared to the control group [3,4]. The Women's Health Initiative (WHI) study showed increases of 4.5% and 3.7% in lumbar and femoral BMD, respectively, in the group that used 0.625 mg CE and 2.5 mg medroxyprogesterone acetate for five years compared to the control group [5]. A meta-analysis of 57 studies found 6.8% and 4.1% increases in lumbar and femoral BMD, respectively, in postmenopausal women who underwent two years of oral hormone therapy compared to the control group [2]. Significant increases in lumbar and femoral BMD were also observed in postmenopausal women who received low-dose HRT [6]. However, the bone-protective effect is not sustained after discontinuing hormone therapy [1].

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Postmenopausal HRT reduces the occurrence of all types of fractures, including those of the vertebrae and femur, and these effects are evident even in women with low fracture risk [1]. The WHI study demonstrated reductions of 33% and 35% in vertebral and femoral fractures, respectively, with combined therapy and 38% and 39% reductions, respectively, with monotherapy [5]. A recent meta-analysis also showed significant reductions of 34%, 29%, and 21% in the risk of vertebral, hip, and non-vertebral fractures, respectively, during HRT [7]. Further research is warranted to determine whether low-dose or ultra-low-dose hormone therapy reduces fracture risk.

Tibolone is a synthetic steroid derived from 19-nortestosterone. After administration, tibolone is converted into metabolites that act on estrogen, progestogen, and androgen receptors, simulating their effect [8]. It may also exhibit bone formation-promoting effects via the androgen receptor. BMD increases proportionally to the dose of tibolone used. The Long-term Intervention on Fractures with Tibolone (LIFT) trial, a randomized control study administering 1.25 mg of tibolone for three years to postmenopausal women with osteoporosis, resulted in significant reductions in the risk of new vertebral fracture by 43% and non-vertebral fracture by 26%. The effect on fracture reduction was even more significant in those with pre-existing vertebral fractures [8]. Furthermore, a recent meta-analysis found that the administration of tibolone in postmenopausal women led to reductions in the risk of vertebral and non-vertebral fractures by 44% and 27%, respectively, compared to a placebo group [7].

Tissue-selective estrogen complexes (TSECs) were developed to avoid side effects associated with progestin use in combination therapy by using selective estrogen receptor modulators (SERMs) instead. A TSEC containing 0.45 mg of CE and 20 mg of bazedoxifene showed increases of 2.3% and 1.4% in lumbar and femoral BMD, respectively, after one year of use, compared to a control group. These results were based on an analysis that combined three SMART (Selective estrogen Menopause And Response to Therapy) studies [9]. However, the effect of TSEC on fractures is yet to be determined.

2. Effect of HRT on Other Organ Systems

A detailed analysis of the WHI study revealed that initiating hormone therapy in the 50s significantly reduced the risk of coronary heart disease, while the risk tended to increase when started after the 60s. Venous thromboembolism risk increases initially with the onset of therapy but later decreases to levels similar to the control group; in women in their 50s, who are the main users of hormone therapy, the risk of venous thromboembolism is very low. Furthermore, venous thromboembolism did not increase significantly in the non-oral administration group [1]. On the other hand, the WHI study results showed a decreasing trend in the risk of breast cancer with 7.2 years of monotherapy, while the risk increased with 5.2 years of estrogen and progestin therapy (EPT) [10]. However, even with EPT, no increased risk of breast cancer was observed for up to 7 years in those who had not previously used hormones. The risk of breast cancer occurrence during hormone therapy is related to the type of progestogen used in EPT; micronized progesterone is reported to be relatively safe. Tibolone does not increase breast density and reduces the occurrence of invasive breast cancer, especially estrogen receptor-positive breast cancer [1]. With TSEC use, there was no difference in breast tenderness or density compared to the placebo group, and the incidence of breast cancer did not increase [11].

IV–2. SELECTIVE ESTROGEN RECEPTOR MODULATOR

Key points

SERMs increase BMD in postmenopausal women, particularly by reducing the risk of vertebral fractures, without exerting adverse effects on the breast and endometrium. Although some studies have reported positive findings, the effect on non-vertebral fractures is unclear. Also, the risk of venous thromboembolism may increase with SERM. SERM seems to be a feasible option for patients in their 50s or 60s, considering the benefits and risks of treatment.

1. Effects on the Skeletal System

SERMs are drugs that, while not estrogen themselves, bind to estrogen receptors and selectively act as agonists on the skeletal system.

Raloxifene prevents bone loss in both healthy women and those with osteoporosis [12]. When administered to patients with osteopenia for three years, the rate of BMD improvement compared to baseline was four times higher than in the control group, and the risk of experiencing an initial vertebral fracture decreased by

about 50% [13]. When raloxifene was administered to postmenopausal women with osteoporosis for three years, the increase in vertebral BMD was about 3%, relatively less than other drugs. However, it effectively reduced the risk of vertebral fractures even within the first six months of use. The incidence of vertebral fractures decreased by 30% in women with previous fractures and 50% in those without [13]. However, the incidence of non-vertebral fractures, including hip fractures, did not decrease even when the treatment period was extended to eight years. While the risk of non-vertebral fractures did not decrease significantly, a post hoc analysis of patients with severe vertebral fractures showed a 47% reduction in the risk of non-vertebral fractures.

The improvement in BMD with the use of bazedoxifene is similar to raloxifene, and its effect on reducing fracture risk is also similar [9,14]. The occurrence of new vertebral fractures decreased by 42% in the third year, 35% in the fifth year, and 30% in the seventh year of use. Although there was no significant difference in non-vertebral fractures, a detailed analysis showed a 50% reduction in non-vertebral fracture risk in the high-risk group compared to the control group [14].

2. Effects on Non-Skeletal Systems

Both raloxifene and bazedoxifene do not increase breast density or tenderness [11]. In particular, using raloxifene in postmenopausal women with a high risk of breast cancer significantly reduces the incidence of invasive breast cancer by 72% [6]. The effect of raloxifene on the prevention of breast cancer has been reported to be similar to tamoxifen, which is indicated for hormone receptor-positive breast cancer [15]. While there was no significant overall decrease in coronary artery disease with raloxifene treatment in the general population, there was about a 50% decrease in risk in women under 60s [16]. While there was no overall increase in stroke, there was a 49% and 44% increase in fatal stroke and thromboembolism, respectively [13]. No significant increase in stroke was observed with the use of bazedoxifene. Both raloxifene and bazedoxifene had no stimulatory effect on the endometrium [11]. In a 7-year follow-up study of bazedoxifene users, the incidence of endometrial cancer was significantly reduced. Animal studies also provide support for the relative safety of bazedoxifene compared to raloxifene regarding the endometrium. Based on such rationale, bazedoxifene is included in TSEC as a replacement for the progestin component for EPT.

IV-3. BISPHOSPHONATE

Key points

Bisphosphonates are bone resorption inhibitors. Orally administered forms include alendronate, risedronate, and ibandronate. Injectable forms are available, such as ibandronate and zoledronate. All bisphosphonates, except ibandronate, significantly reduce vertebral and non-vertebral fractures. After 5 years of oral medication or 3 years of injection, in cases where BMD improves to a T-score > –2.5, and the patient is not at high risk, a drug holiday should be considered.

1. Mechanism of Bisphosphonates

Bisphosphonates are stable derivatives that have the P-C-P structure by substituting oxygen with carbon in the P-O-P structure of pyrophosphate. Initially, developed substances not only inhibited bone resorption but also inhibited the calcification process of the bone. Their mechanism of action involves binding with farnesyl pyrophosphate synthase (FPPS), which is crucial for cholesterol synthesis, thereby blocking the mevalonate pathway and inhibiting the prenylation of proteins essential for the function and survival of osteoclasts, which leads to osteoclast apoptosis. Each type of bisphosphonate has a different ability to bind to the bone and inhibit FPPS, which results in different levels of bone resorption inhibition [17].

2. Bisphosphonates Available in South Korea

There are both oral and injectable forms of bisphosphonates. Commonly used oral medications include alendronate, risedronate, and ibandronate. As for the intravenous form, pamidronate, ibandronate, and zoledronate are available. Oral formulations show good efficacy but can lead to side effects such as gastrointestinal disorders and osteonecrosis of the jaw (ONJ) due to long-term usage. Injectable medications have a higher patient compliance rate. They are particularly useful for elderly patients with comorbid conditions such as hypertension and diabetes, thus susceptible to polypharmacy. Notably, only about 0.6%–1.0% of oral medications are absorbed after administration, while injectable drugs have high bioavailability, nearly 100%, and minimal gastrointestinal side effects [17,18].

1) Oral bisphosphonate formulations

(1) Alendronate

For the prevention of osteoporosis, a daily dose of 5 mg or a weekly dose of 35 mg is recommended. For treatment purposes, 10 mg daily or 70 mg weekly doses are advised. Weekly dosages have been reported to have fewer gastrointestinal side effects with a similar increase in BMD [19].

Studies involving postmenopausal osteoporosis patients showed that administering 10 mg daily of alendronate for three years resulted in an 8.8% increase in vertebral BMD and a 5.9% increase in femoral BMD. Additionally, alendronate could reduce the occurrence of new fractures or decreases in height by about 48%. According to prospective studies investigating the effect of alendronate in fracture prevention, a 3-year administration in women with vertebral fractures resulted in a 47% and 51% decrease in new vertebral and femoral fractures, respectively [20]. In women without vertebral fractures, administration of alendronate resulted in a 44% decrease in vertebral fractures and a 36% decrease in femoral fractures after four years [21]. In another study, all types of clinical fractures were reduced by 30% through alendronate administration, and the significant effect was observable 12 months after starting the medication [22].

(2) Risedronate

Risedronate has been approved for the prevention and treatment of postmenopausal osteoporosis at a daily oral dose of 5 mg or weekly oral dose of 35 mg. It is known to have relatively few gastrointestinal side effects. When administered to postmenopausal women with osteoporosis for three years, lumbar BMD increased by 4.3%, femoral neck BMD increased by 2.8%, and incidences of vertebral and non-vertebral fractures decreased by 41% and 39%, respectively [23]. A study on the preventive effect of vertebral fractures showed that administering 5 mg of risedronate for three years reduced the incidence of new vertebral fractures by 41% and non-vertebral fractures by 39%. This effect was observed within six months of medication use [24].

(3) Ibandronate

Ibandronate has been approved for the prevention and treatment of postmenopausal osteoporosis, with a daily oral dosage of 2.5 mg or a monthly oral dosage of 150 mg. In early postmenopausal women without osteoporosis, treatment with ibandronate for two years led to a 1.9% increase in vertebral BMD and a 1.2% increase in femoral BMD. For postmenopausal women with low BMD, three years of treatment resulted in an increase in vertebral BMD by 5.3%, femoral neck BMD by 4.1%, and a 49% reduction in vertebral fractures [25].

2) Intravenous bisphosphonates

(1) Ibandronate

Ibandronate is approved for the treatment of postmenopausal osteoporosis at a dosage of 3 mg administered intravenously every three months. After two years of treatment, the increase in vertebral and femoral BMD was higher than in the oral administration group, with excellent compliance. The incidence of adverse reactions was similar to that of the oral formulation [26].

(2) Zoledronate

Zoledronate is an approved medication for treating bone-destructive lesions such as hypercalcemia in cancer patients, multiple myeloma, and metastatic bone tumors. For osteoporosis treatment, 5 mg is given once every 12 months over 15 minutes [27]. In major phase 3 clinical trials involving postmenopausal women, treatment with Zoledronate for three years led to a 70% reduction in vertebral fractures, a 41% reduction in hip fractures, and a 25% reduction in non-vertebral fractures. The most common adverse reactions were immediate post-infusion symptoms, including fever, myalgia, flu-like symptoms, headache, and bone pain. The majority of these occurred within the first three days after administration, and the incidence rate of adverse reactions significantly decreased in subsequent administrations [28].

3. Drug Holiday

Bisphosphonates have proven effective in reducing fractures after 3–5 years of use, but long-term use leading to strong bone metabolism suppression has reported side effects such as jaw necrosis and atypical femur fractures. Thus, a "drug holiday" concept has emerged to reduce the risk of these side effects. For non-high-risk patients, a drug holiday is considered after 5 years of therapy with an oral route or 3 years of intravenous administration [29]. Even with sufficient treatment duration with bisphosphonates, if the T-score is still –2.5 or lower, the patient has a history of hip or vertebral fractures, or if there is a high risk of fractures due

to chronic disease or drug-induced secondary osteoporosis, continuous treatment without a drug holiday, or a switch to another treatment may be considered. Restarting the therapy is considered if there is a significant change in BMD after the drug holiday, if a new osteoporotic fracture occurs, or if the T-score decreases to –2.5 or lower.

IV–4. DENOSUMAB

Key points

1. Denosumab is recommended as a primary treatment for postmenopausal women with osteoporosis at high risk of fractures, with a subcutaneous injection of 60 mg administered every six months.
2. Denosumab significantly reduces vertebral and non-vertebral fractures and shows a persistent increase in vertebral and femoral BMD over ten years of administration.
3. If denosumab treatment is discontinued, a switch to another type of antiresorptive agent (bisphosphonates, HRT, SERMs, etc.) is necessary to maintain the beneficial effect on BMD and fracture prevention associated with denosumab treatment.

1. Mechanism of Action and Characteristics

Denosumab is a human monoclonal antibody against *RANKL* (nuclear factor kappa B ligand) and was approved in 2010 for the treatment of osteoporosis. *RANKL* is synthesized in osteoblasts, bone marrow stromal cells, and activated T cells and promotes bone resorption by enhancing the formation, differentiation, activation, and survival of osteoclasts through the activation of its receptor, *RANK*, present on progenitor osteoclasts and osteoclasts. Osteoprotegerin (OPG) is a soluble receptor synthesized in osteoblasts, which binds to circulating *RANKL* and prevents *RANK*-mediated activation of osteoclasts. In the absence of *RANK* signaling, osteoclasts undergo apoptosis. Denosumab acts like OPG, binding with high affinity to *RANKL* to prevent *RANK* activation. As a result, it inhibits the formation and activation of osteoclasts, suppresses bone resorption, and increases BMD. The anti-resorptive effect of denosumab is different from bisphosphonates and estrogen, as it not only inhibits the maturation and survival of osteoclasts but also suppresses active bone resorption by osteoclasts.

2. Clinical Efficacy

1) Effects on BMD

In a randomized phase II trial of denosumab, postmenopausal women (n = 412, under 80 years) with a lumbar vertebral T-score of –1.8 to –4.0 or total hip or femoral neck T-score of –1.8 to –3.5 were randomly assigned to denosumab, alendronate, or placebo groups for two years. An increase in BMD was reported at all sites in the denosumab group compared to the placebo group [30]. After two years, patients in the denosumab group received an additional two years of denosumab (60 mg every six months), while one subgroup discontinued treatment for a year before resuming, and another discontinued for two years. A total of 262 women completed the study. Long-term denosumab treatment increased BMD in the lumbar vertebrae and hip, while the placebo group consistently decreased. When treatment was discontinued after two years, BMD decreased, but when treatment was resumed after a year, BMD recovered to levels similar to those seen after the initial two years of treatment and in the group treated for four years [31]. In a phase III study with 332 postmenopausal women with a lumbar vertebral T-score of –1.0 to –2.5, all sites showed increased BMD after two years of denosumab treatment compared to the placebo group [32]. In phase III, a double-blind, randomized DECIDE (Determining Efficacy: Comparison of Initiating Denosumab vs. alEndronate) study, 1,189 postmenopausal women with lumbar or total hip T-scores of –2.0 or less were given denosumab or alendronate and observed for one year. Compared to the alendronate group, the denosumab group had a greater increase in BMD and a significant reduction of bone turnover markers [33]. In phase III, double-blind, randomized STAND (Study of Transitioning from AleNdronate to Denosumab) study, 504 postmenopausal women aged 55 and over, who had been receiving alendronate treatment for at least six months with a T-score of –2.0 to –4.0, were followed up for 12 months. The group that switched to denosumab had a greater increase in BMD (1.90% vs. 1.05%) and a greater reduction in bone turnover markers compared to those who continued with alendronate treatment [34].

Notably, denosumab leads to a sustained increase in BMD in both vertebral and hip over a decade of administration. In contrast, bisphosphonate administration leads to only a constant increase in vertebral BMD, not hip BMD, which plateaus after a certain period. The

persistent increase in BMD observed with denosumab is attributed to its systemic action through the bloodstream on both trabecular and cortical bone, affecting both bone remodeling and modeling, unlike bisphosphonates which are absorbed onto the bone surface and predominantly increase trabecular BMD.

2) Effects on fractures

In the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) trial, a randomized phase III clinical trial evaluating the efficacy of denosumab, 7,868 women aged 60–90 years with a T-score of –2.5 to –4.0 in the vertebrae or femur were given 60 mg of denosumab or placebo every six months to compare the occurrence of new vertebral fractures. The FREEDOM study reported that denosumab reduced the incidence of new radiographic vertebral fractures by 68% and clinical fractures by 61% compared to placebo. For secondary outcome variables, hip fractures decreased by 40% and non-vertebral fractures by 20%. The effect emerged after two doses, significantly reducing vertebral fractures by 61% within the first year of administration [35]. After the 3-year FREEDOM study, an open-label extension study was conducted for 7 years. The incidence of fractures was maintained similarly to the FREEDOM study, and BMD continued to increase over 10 years of denosumab treatment [36].

A recent meta-analysis reported that compared to the placebo group, denosumab reduced the risk of vertebral fractures by 68% (hazard ratio [HR], 0.32; 95% confidence interval [CI], 0.26 to 0.40), hip fractures by 39% (HR, 0.61; 95% CI, 0.37 to 0.98), and non-vertebral fractures by 19% (HR, 0.81; 95% CI, 0.69 to 0.95) [37].

The American Association of Clinical Endocrinology (AACE) recommends denosumab as a primary treatment along with alendronate, risedronate, and zoledronate in most osteoporotic patients with high fracture risk and in those with a very high fracture risk [38]. Similarly, denosumab is recommended as a first-line treatment by the Endocrine Society [7], the International Osteoporosis Foundation [39], and the National Osteoporosis Foundation (NOF) [40].

3. Adverse Reactions

In many clinical trials of denosumab, no major adverse reactions such as cancer, infection, cardiovascular disease, and ONJ were observed. In the FREEDOM study, the incidence of eczema and cellulitis was significantly higher than in the control group. However, it is thought not to be causally related to denosumab treatment. There was also no increase in these conditions observed in patients receiving high-dose denosumab for long-term osteoporosis treatment or progressive cancer. As a bone resorption inhibitor, there may be a risk of ONJ and atypical femoral fractures, but this risk is very low. Such risks are mainly identified when used at high concentrations in cancer patients, but no results suggest a greater risk compared to bisphosphonates.

Denosumab, due to its rapid and potent effect, may potentially cause hypocalcemia, necessitating appropriate supplementation with calcium and vitamin D concurrently with the treatment. In patients with hypocalcemia, it is contraindicated as hypoparathyroidism or osteomalacia may occur. In two clinical studies, the risk of hypocalcemia when using denosumab was reported to be less than 0.05%, and it was reported to be between 14%–25% in patients at risk of hypocalcemia. The frequency of clinically important side effects was not reported to be significantly high, but monitoring of calcium levels is necessary for patients with decreased renal function or chronic kidney disease.

4. Considerations

In patients who demonstrated poor adherence to therapy or no improvement in BMD while on bisphosphonates, switching to denosumab improved adherence and increased BMD. However, if denosumab treatment is discontinued after an increase in BMD, there is a rapid rise in bone turnover markers and a decrease in BMD. Twelve months after discontinuation, the BMD remains slightly higher than pre-treatment levels. After stopping denosumab, the preventive effect on vertebral fractures also rapidly disappeared. Multiple vertebral fractures after discontinuation of denosumab have been reported. A “drug holiday” during denosumab treatment is not recommended. In order to prevent a sudden increase in fracture risk after discontinuation, it is recommended to continue using anti-resorptives such as bisphosphonates to maintain the increased BMD and fracture prevention effects achieved during denosumab treatment. Switching from denosumab to parathyroid hormone (PTH) analogue may cause a rapid decrease in hip BMD, which could increase the risk of fractures. Thus, sequential therapy with PTH analogue in patients using denosumab is not recommended.

IV–5. PARATHYROID HORMONE ANALOGUES

Key points

1. PTH acts as a bone formation stimulant when administered intermittently.
2. PTH analogues, when administered, has a specific period known as the 'anabolic window', during which bone formation occurs without absorption.
3. Teriparatide reduces vertebral fractures by 65% and non-vertebral fractures by 53% compared to the placebo group and reduces new vertebral fractures by 54% compared to risedronate.

PTH analogues, such as teriparatide and abaloparatide, have been developed as treatments for osteoporosis. Currently, only teriparatide is available in the Republic of Korea. Endogenous PTH is composed of a total of 84 amino acids. Among them, teriparatide is a synthesized peptide hormone with the same sequence as the 34 amino acids on the biologically active N-terminal side. Domestically, teriparatide is available in two regimens: daily subcutaneous and weekly.

1. Mechanism of Action and Characteristics

PTH is a bone-forming agent. When the calcium concentration in the blood decreases, the endogenous PTH induces the secretion of calcium stored in the bones to maintain a constant concentration of calcium in the blood. Therefore, if the endogenous PTH continually increases, bone absorption will occur, leading to bone loss or osteoporosis. However, intermittent administration of PTH analogues promotes bone formation. This results in a specific period known as the 'anabolic window', during which bone is formed without absorption. Both teriparatide and abaloparatide are considered "anabolic" agents.

Teriparatide directly promotes the differentiation of mesenchymal stem cells into osteoblasts and indirectly promotes their differentiation by regulating various factors involved in the process. It also increases the function of osteoblasts through various pathways, including inhibiting apoptosis of osteoblasts, which results in increased bone mass.

2. Clinical Efficacy

The bone mass-increasing effect of bone formation stimulants is superior to bone resorption inhibitors. In the Fracture Prevention Trial (FPT) involving 1,637 women who had experienced menopause for at least five years and had a previous fracture, the group receiving 20 μg teriparatide for 19 months had a decrease in vertebral and non-vertebral fractures by 65% and 53%, respectively, compared to the placebo group, and the BMD of the lumbar and femoral neck increased by 9.7% and 2.8% respectively [41,42].

In a randomized controlled trial comparing the fracture prevention effect of teriparatide with risedronate, teriparatide reduced new vertebral fractures by 54% in postmenopausal women with fractures at 24 months of administration compared to risedronate [43]. In a meta-analysis published in 2020, teriparatide reduced non-vertebral fractures by 35% compared to bisphosphonates [44]. The effect of PTH is pronounced in cases with previous fractures or very high-risk fracture groups (e.g., high fall risk, a T-score BMD below –3.0, over 65 years old, femur fracture risk over 4.5% in Fracture Risk Assessment Tool (FRAX), major osteoporotic fracture risk over 30%).

It is important to consider a sequential treatment involving the use of antiresorptive agents because bone mass decreases sharply after discontinuation of teriparatide.

3. Adverse Reactions

During the use of teriparatide, symptoms such as nausea, headache, dizziness, leg cramps, and orthostatic hypotension may occur [42,45]. However, these symptoms are typically mild and transient, and new side effects are rare. After injection, the calcium concentration in the blood may increase, but this is also a mild and temporary change. Teriparatide administration has been reported to induce osteosarcoma in rats. Therefore, it is not used in patients with a high risk of osteosarcoma, including those with Paget's disease, skeletal malignancies, bone metastasis, or previously received radiation therapy to the bone. However, a study in 2018 reported no increased incidence of osteosarcoma in teriparatide users after following up on side effects after 240,000 person-years of use since 2009 [46].

4. Considerations

1) Duration of administration

The occurrence of osteosarcoma in rats treated with teriparatide [47], combined with the fact that the FPT study was terminated before completing two years,

led to a recommendation of administration of teriparatide for a maximum of two years due to unproven safety and effects of long-term use. Re-administration after the completion of teriparatide for two years has not been recommended as well. However, reports of osteosarcoma after teriparatide use were from rats, not human subjects. Also, a study showed that BMD in the lumbar vertebrae and femur remained elevated up to the third year in patients with glucocorticoid-induced osteoporosis who were treated with teriparatide for three years [48]. These facts led the Food and Drug Administration (FDA) to remove the warnings about osteosarcoma and the treatment duration limitation to two years in November 2020. Patients with high fracture risk may be candidates for long-term teriparatide use over two years. These include high-risk patients who need to continue using glucocorticoids and those who still maintain high levels of procollagen type 1 amino-terminal propeptide (P1NP), or those who had multiple compression fractures before treatment but did not relapse while using teriparatide [49].

2) Effect of transition from bone resorption inhibitors to teriparatide

When transitioning from bisphosphonates to teriparatide and completing a 24-month treatment, femoral BMD increases. However, the extent of the increase in femoral BMD is significantly lower compared to using teriparatide from the beginning of the treatment [45]. Furthermore, femoral BMD decreases in the first 6–12 months after transitioning from bisphosphonates to teriparatide, which is not observed when teriparatide is used from the start. Thus, the risk of fractures increases in the first year after transitioning from bisphosphonates to teriparatide [50]. This decrease in BMD could be prevented if bisphosphonate is continued along with teriparatide, or if switched to romosozumab, a medication with both anti-resorptive and bone-forming properties.

The BMD decreases even after switching from denosumab, a strong anti-resorptive agent, to teriparatide. This is because many osteoclast precursors, which had been dormant due to the effect of denosumab, become active.

IV-6. ROMOSOZUMAB

Key points

1. Romosozumab is a monoclonal antibody against sclerostin, which has dual effects of promoting bone formation and inhibiting bone resorption.
2. Romosozumab enhances BMD and reduces the incidence of vertebral and non-vertebral fractures.
3. In postmenopausal women at risk of fracture, it demonstrated a significantly greater reduction in fracture rates compared to alendronate.
4. When transitioning from long-term bisphosphonate use (over three years) to romosozumab, a greater increase in BMD was observed compared to transitioning to teriparatide.
5. After administering for 12 months, transition to a bone resorption inhibitor for maintenance is recommended.

1. Mechanism of Action, Characteristics

Romosozumab, a monoclonal antibody against sclerostin, promotes bone formation and inhibits bone resorption, thus increasing BMD. Sclerostin, primarily in osteocytes, inhibits the Wnt signaling pathway, critical to bone homeostasis and osteoblast function, as it suppresses bone formation [51]. Moreover, sclerostin augments the expression of *RANKL* in osteocytes, promoting bone resorption. Romosozumab inhibits these actions of sclerostin, stimulating bone formation by activating the Wnt signaling pathway and inhibiting bone resorption by modulating *RANKL* expression. After 12 months of romosozumab use, an increase in BMD was observed in all sites. Currently, it is possible to use it for the treatment of postmenopausal osteoporosis patients at high risk of fractures and for increasing BMD in male osteoporosis patients at high risk of fractures.

2. Clinical Efficacy

1) Fracture risk

Regarding clinical effects, one of the notable phase 3 clinical trials for romosozumab, the FRAME (Fracture Study in Postmenopausal Women with Osteoporosis) study, involved 7,180 postmenopausal women with osteoporosis. For the initial 12 months, the trial was divided into a group receiving 210 mg of romosozumab via subcutaneous injection every month and a placebo group, after which both groups were administered

denosumab for the following 12 months. The results demonstrated a 73% decrease in vertebral fractures in the romosozumab group compared to the placebo at 12 months and a 75% decrease at the 24-month analysis. Clinical fractures, including non-vertebral fractures, decreased by 36% at 12 months and 33% at 24 months in the romosozumab group compared to placebo. However, non-vertebral fractures decreased by 25% in both groups at 12 and 24 months compared to placebo, but this was not statistically significant [52]. In the FRAME extension study, which analyzed fracture risk 36 months after starting treatment with 12 additional months of denosumab, vertebral and clinical fractures decreased by 66% and 27%, respectively, compared to placebo. Non-vertebral fractures also significantly decreased by 21% [53].

Another phase 3 clinical trial, the ARCH (Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk) study, targeted 4,093 postmenopausal women with osteoporosis with a history of fractures. The trial was divided into a group that received 210 mg of romosozumab via subcutaneous injection every month for the initial 12 months and a group that took 70 mg of alendronate orally every week. After this period, both groups were transitioned to alendronate for comparative analysis. The results showed a 37% reduction in vertebral fractures in the romosozumab group compared to the alendronate group at 12 months, and even after transitioning to alendronate, a significant 48% reduction was observed at 24 months compared to continuous use of alendronate. Clinical fractures were also 27% less in the romosozumab group at 12 months, and non-vertebral fractures and hip fractures were significantly reduced by 19% and 38%, respectively [54].

2) BMD and bone turnover markers

As mentioned previously, the FRAME study showed significant increases in BMD at the lumbar vertebrae, total hip, and femoral neck by 13.3%, 6.9%, and 5.9%, respectively, in the romosozumab group compared to the placebo group at 12 months [52]. This increase in BMD persisted even after transitioning to denosumab, with the FRAME extension study showing significant increases of 10.5%, 5.2%, and 4.8% in these areas, respectively, at 36 months. This change in BMD was corroborated by a rapid increase in the bone formation marker P1NP and a decrease in the bone resorption marker β-CTX after the initiation of romosozumab [53].

Similarly, the ARCH study, which compared the group transitioning from romosozumab to alendronate and the group that consistently used only alendronate, also demonstrated significant increases in BMD in the romosozumab group. At 12 and 24 months, the lumbar vertebrae, total hip, and femoral neck BMDs in the romosozumab group were 3%, 5%, and 10% higher, respectively, compared to the alendronate group. Particularly in the case of the lumbar vertebral BMD, a rise of more than 10% was observed compared to baseline levels in the romosozumab group at both 12 and 24 months. Using romosozumab led to increased P1NP and decreased β-CTX, which continued to decrease after transitioning to alendronate, remaining below baseline levels at 36 months. On the other hand, in the group only using alendronate, P1NP, and β-CTX decreased within a month and remained below baseline levels at 36 months [55].

Lastly, the STRUCTURE study (An Open-label Study to Evaluate the Effect of Treatment With Romosozumab to Teriparatide in Postmenopausal Women), an open-label phase 3 trial comparing romosozumab and teriparatide, included 436 postmenopausal women with osteoporosis who had experienced fractures and had been taking oral bisphosphonates for at least three years. The study compared BMD at 12 months in a group receiving monthly subcutaneous injections of 210 mg romosozumab and a group receiving daily subcutaneous injections of 20 μg teriparatide. The results demonstrated that the lumbar vertebral BMD increased by 9.8% in the romosozumab group, significantly higher than the 5.4% increase in the teriparatide group. Notably, the total hip BMD increased by 2.9% in the romosozumab group, while the teriparatide group showed a 0.5% decrease. Femoral neck BMD also increased by 3.2% in the romosozumab group and decreased by 0.2% in the teriparatide group, although this was not statistically significant [56].

In conclusion, all three FRAME, ARCH, and STRUCTURE studies showed increased BMD in postmenopausal women with osteoporosis using romosozumab. The following table summarizes the results of the major phase 3 studies related to BMD (Table 1) [52,53,55,56].

3. Clinical Use

Romosozumab has been approved in various countries, including Canada, Japan, Europe, and the United States, as a treatment for osteoporosis in postmeno-

Table 1. Least-squares mean changes in BMD with subcutaneous romosozumab in postmenopausal women with osteoporosis in phase III trials

Timepoint	Treatment (no. of pts)	LSM % change from BL in BMD (mean BL BMD T-score)		
		Lumbar spine	Total hip	Femoral neck
FRAME [52][a]				
Month 12	ROM (3,169–3,237)	+13.1* (–2.7)	+6.0* (–2.5)	+5.5* (–2.8)
	PL (3,176–3,256)	+0.4 (–2.7)	+0.3 (–2.5)	+0.3 (–2.7)
Month 24	ROM→DEN (3,169–3,237)	+16.6*	+8.5*	+7.3*
	PL→DEN (3,176–3,256)	+5.5	+3.2	+2.3
FRAME extension [53][a]				
Month 36	ROM→DEN (3,169–3,237)	+18.1*	+9.4*	+8.2*
	PL→DEN (3,176–3,256)	+7.5	+4.2	+3.4
ARCH [55][ab]				
Month 12	ROM (1,750–1,826)	+13.7*(–2.9)	+6.2* (–2.8)	+4.9* (–2.9)
	ALE (1,757–1,829)	+5.0 (–3.0)	+2.8 (–2.8)	+1.7 (–2.9)
Month 24	ROM→ALE (1,750–1,826)	+15.3*	+7.2*	+6.0*
	ALE→ALE (1,757–1,829)	+7.2	+3.5	+2.3
Month 36	ROM→ALE (1,750–1,826)	+15.2*	+7.2*	+6.0*
	ALE→ALE (1,757–1,829)	+7.8	+3.5	+2.4
STRUCTURE [56]				
Month 6	ROM (206)	+7.2**†† (–2.8)	+2.3**†† (–2.3)	+2.1**†† (–2.5)
	TER (209)	+3.5†† (–2.9)	–0.8† (–2.2)	–1.1* (–2.4)
Month 12	ROM (206)	+9.8**††	+2.9**††	+3.2**††
	TER (209)	+5.4††	–0.5†	–0.2

All pts received daily calcium and vitamin D in addition to the study drug.
ALE: oral alendronate 70 mg once weekly, ARCH: Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk, BL: baseline, BMD: bone mineral density, DEN: subcutaneous denosumab 60 mg once every 6 months, FRAME: Fracture Study in Postmenopausal Women with Osteoporosis, LSM: least squares mean, PL: placebo, pts: patients, ROM: subcutaneous romosozumab 210 mg once monthly, STRUCTURE: An Open-label Study to Evaluate the Effect of Treatment With Romosozumab to Teriparatide in Postmenopausal Women, TER: subcutaneous teriparatide 20 μg once daily.
*$P < 0.001$, **$P < 0.0001$ vs. comparator group for the specific timepoint.
†$P < 0.05$, ††$P < 0.0001$ vs. STRUCTURE BL.
[a]P values were nominal in these studies.
[b]BMD changes in ARCH are based on an ANCOVA model using last-observation-carried-forward adjusting.

pausal women at high risk of fractures. It is administered via a subcutaneous injection of 210 mg monthly for 12 months. It is given in two divided doses; 105 mg of romosozumab is injected into one of three potential sites - the abdomen, thigh, or upper arm - followed by an immediate injection of another 105 mg into a different site. If a dose is missed, it should be administered as soon as possible, and subsequent doses should follow a monthly schedule. Supplemental calcium and vitamin D are essential during treatment. If osteoporosis treatment is still necessary after 12 months of romosozumab use, anti-resorptive drugs should be continued. It is not indicated for use in pregnant women or women of childbearing age.

4. Adverse Effects and Considerations

The adverse reactions of romosozumab were not significantly different from those of placebo, alendronate, or teriparatide. Injection site reactions occurred in 4%–8% of patients, which is higher than the 3% seen in control groups, but these were mostly mild injection site pain and erythema. Rarely, hypocalcemia occurred in less than 0.1% of patients. Romosozumab is contraindicated in patients with hypocalcemia, which must be corrected before initiating treatment. In patients with severe renal dysfunction (eGFR 15–29 mL/min/1.73 m^2) or undergoing dialysis, serum calcium levels must be monitored.

There have been concerns about cardiovascular side

effects with romosozumab use due to sclerostin's protective effects against aortic aneurysms and arteriosclerosis, aside from its role in bone resorption. However, studies show that the likelihood of cardiovascular side effects from romosozumab use is relatively low, as no difference in the incidence of cardiovascular side effects was found compared to placebo.

In the FRAME study, the incidence of severe cardiovascular disease after romosozumab administration was 1.2%, compared to 1.1% for placebo. Mortality rates were 0.8% for romosozumab and 0.6% for placebo, showing similar results in both groups. In contrast, the ARCH study showed a higher incidence of serious cardiovascular diseases such as myocardial infarction or stroke after romosozumab administration (2.5%) than alendronate (1.9%). The mortality rate was also higher in the romosozumab group (1.5%) than in the alendronate group (1.0%).

While the mechanism linking cardiovascular disease and romosozumab is not well understood, care should be taken when using romosozumab in patients with cardiovascular diseases, as there may be an increased risk of myocardial infarction, stroke, and cardiovascular mortality [57]. In Europe, romosozumab is contraindicated in patients with a history of myocardial infarction or stroke. In the United States, treatment with romosozumab should not be initiated in patients with a history of myocardial infarction or stroke within the past year. If a myocardial infarction or stroke occurs during romosozumab treatment, treatment should be stopped. The benefits and drawbacks of romosozumab treatment should be carefully considered for patients with other cardiovascular risk factors. Taking these side effects into consideration, it would be best for patients with a history of myocardial infarction or stroke to refrain from using it for the time being.

Hypersensitivity reactions to romosozumab, such as angioedema, erythema multiforme, dermatitis, rash and urticaria, have been reported. If these hypersensitivity reactions occur, the treatment should be discontinued.

While the compliance of romosozumab, which requires a once-monthly subcutaneous injection, is better than that of daily-injection teriparatide, it does not offer any advantage over denosumab, which requires an injection every six months. Regarding the duration of treatment, romosozumab is treated for a maximum of one year, compared to two years of abaloparatide and teriparatide and five years of bisphosphonate. After the completion of bone-forming agents, switching to antiresorptive agents such as bisphosphonate and denosumab is necessary to prevent BMD loss and osteoporotic fractures.

In summary, in postmenopausal women with osteoporosis who are at high risk of fracture or who cannot use oral bisphosphonates due to compliance or safety issues, romosozumab treatment for 12 months significantly reduces new vertebral and clinical fractures. This reduction in fracture risk is sustained for 1–2 years after switching to an antiresorptive drug after romosozumab treatment. Additionally, romosozumab is associated with significantly improved BMD compared to placebo or alendronate, observed after 6 and 12 months.

V. SEQUENTIAL AND COMBINATION THERAPY IN OSTEOPOROSIS

Key points

1. There is insufficient evidence regarding the effect of combined administration in its actual fracture prevention effects, and it may be associated with increased medical costs. Thus, a combination of drugs for osteoporosis is not recommended.
2. When treating osteoporosis, the patient's clinical status, underlying conditions, and potential side effects from long-term medication use should be considered. Medications can be discontinued if necessary, and sequential treatment can be considered to maintain/increase BMD and reduce fracture risk.
3. Terminating denosumab treatment without replacing it with another drug could expose patients to an increased risk of fracture due to rapid bone loss. Therefore, upon discontinuing denosumab, other antiresorptive drugs, such as bisphosphonates, should be administered.
4. Sequential treatment with PTH following denosumab administration is not recommended as it may induce rapid bone loss.

1. Combination Therapy

1) Menopausal hormone therapy and bisphosphonates

Studies comparing combined alendronate and menopausal HRT with HRT alone revealed significant increases in BMD at the vertebrae (3.6% vs. 1.0%) and

trochanter (2.7% vs. 0.5%) in the combination group [58]. Another study demonstrated that after two years, vertebral BMD increased by 6.0% with 10 mg alendronate monotherapy and 8.3% with combination therapy. Femur BMD increased significantly, with 2.9% in alendronate monotherapy, 2.6% in estrogen monotherapy, and 4.2% in the combination therapy group [59].

2) Menopausal HRT and PTH analogues

In a randomized study involving 34 postmenopausal women, the results of comparing a group receiving estrogen alone (CEE 0.625 mg) with a group receiving a combination of estrogen and PTH over a period of three years indicated that the combination therapy group reported continuous increases in BMD and a reduction in vertebral fractures [60].

In another randomized study involving 52 postmenopausal women, comparing HRT alone with a combination of HRT and PTH (25 μg/day) injection for 3 years, following two years of hormone therapy, it was concluded that the anti-resorptive effect of estrogen does not interfere with the anabolic action of PTH [61].

3) Bisphosphonates and SERM

In a study of 331 postmenopausal women who underwent one year of treatment with a placebo, raloxifene, alendronate, and combination therapy, a significant increase in vertebral BMD in the combination therapy group was observed. Femur BMD was significantly increased in the combination therapy group compared to the alendronate-only group (3.7% ± 0.5% vs. 2.7% ± 0.5%) [62]. In a study that compared the effect of raloxifene, alendronate, or a combination of raloxifene and alendronate on BMD after 12 months, BMD increased compared to basal levels in all three groups. The combination group had higher BMD compared to raloxifene-only or alendronate-only group with significance [63].

4) Bisphosphonates and PTH analogues

A study of 238 women with osteoporosis showed increased vertebral BMD in all treatment groups (PTH monotherapy [100 μg/day], alendronate monotherapy [10 mg/day], and combination therapy) after 12 months. There were no significant differences between the PTH monotherapy group and the combination therapy group. Bone formation was significantly higher in the PTH monotherapy group than in the combination therapy group, suggesting no synergistic effect of combination therapy [64]. Meta-analyses have reported no significant differences between vertebral and femoral BMD and no differences in vertebral and non-vertebral fracture risk between groups [65]. In contrast, a recent meta-analysis suggested the benefits of additional BMD increase in the hip and femur in the short (6–12 months) and long term (18–24 months) with combination therapy [66]. Another randomized study of 12 months of combination therapy versus monotherapy using zoledronate and teriparatide showed similar results, stating that combination therapy is associated with a faster increase in BMD and additional improvement in hip BMD [67].

5) PTH analogues and SERM

A study comparing teriparatide monotherapy with combination therapy of teriparatide and SERM demonstrated the positive effects of combination therapy. After six months, vertebral BMD increased by 5.19% ± 0.67% in the monotherapy group, while the combination therapy group showed significant increases in the vertebral (6.19% ± 0.65%), femur (2.23% ± 0.64%), and hip (2.31% ± 0.56%) BMD, suggesting an additional benefit of combined therapy [68].

2. Sequential Therapy

1) SERM after bisphosphonates therapy

A randomized controlled study with 99 postmenopausal women who underwent alendronate therapy (average duration: 43 months) examined the effects of a placebo, raloxifene, and extended alendronate. After 12 months, the group that discontinued alendronate showed decreased vertebral BMD. However, in groups that replaced their treatment with either raloxifene or alendronate, vertebral BMD did not decrease [69].

2) Denosumab after bisphosphonate therapy

In a study comparing 504 postmenopausal women who continued alendronate and those who switched to denosumab, the group that switched to denosumab demonstrated significantly higher BMD in the vertebra, hip, and femur after 12 months [34]. Similarly, a cohort study examining 215 women who had previously received bisphosphonate therapy (median duration: 7 years) and subsequently received either denosumab or teriparatide also found a significant increase in BMD in the vertebra, hip, and femur after switching to denosumab [70]. Another study examining 643 women

who had received oral bisphosphonate and were then administered either intravenous zoledronate or denosumab showed that the denosumab group experienced a significantly greater increase in BMD in the vertebra, hip, and femur after 12 months, alongside a greater inhibitory effect on bone remodeling [71].

3) PTH analogues after bisphosphonate therapy

Several studies have reported that the administration of anabolic agents after bisphosphonate treatment results in a blunting of the increase in BMD.

The pharmacological properties of bisphosphonates lead to their long-term deposition in bone, resulting in the inhibition of both bone resorption and bone formation. This is suggested to reduce the bone-forming effects of PTH. This phenomenon is more pronounced with bisphosphonates that have a longer skeletal half-life. Results from several studies support this fact. In a study of 59 postmenopausal women who had previously received raloxifene or alendronate and were then administered teriparatide, vertebral BMD increased by 10.2% in the raloxifene group and by 4.1% in the alendronate group after 18 months, indicating a greater increase in the raloxifene group. However, while the hip BMD significantly increased compared to the baseline in the raloxifene group, no significant increase was observed in the group that previously received alendronate [72]. The EUROFOS (European Study of Forsteo) study involved 503 postmenopausal women, some of whom had received anti-resorptive agents previously and others had not. After 24 months of administering teriparatide, it was observed that the group with no previous anti-resorptive therapy experienced a greater increase in BMD, although an increase was also observed in the group that had received prior anti-resorptive therapy. Thus, it is suggested that BMD increment may be delayed when PTH therapy is given after anti-resorptive therapy [73].

4) Bisphosphonate after denosumab therapy

In a study involving 120 women who received denosumab treatment, the group which did not receive any treatment afterward and the group which received alendronate or zoledronate after cessation of denosumab were compared in terms of vertebral fractures and morphometric fractures. A significant difference was noted with the vertebral fracture rate; the rate was 21.1% in the untreated group, compared to 5.5% in the group continuing with bisphosphonate treatment [74]. Further studies also observed the effect on BMD maintenance when zoledronate was continued after treatment with denosumab. Thus, bisphosphonate may be primarily considered as sequential therapy when discontinuing denosumab [54,75,76].

5) PTH analogues after denosumab, and denosumab after PTH analogues

In the DATA-Switch study involving 94 postmenopausal osteoporotic women, the group which received both teriparatide and denosumab for two years was given denosumab for additional 24 months. The group which received only teriparatide for two years was given denosumab for the next two years, and the group with denosumab for two years was given teriparatide for the next two. The highest increase in vertebral and hip BMD was noted when both drugs were co-administered, and an increase was also noted when teriparatide was replaced with denosumab. However, temporary but rapid bone loss was induced when teriparatide was administered after denosumab treatment. The exact mechanism of this effect is not clearly understood, but it is thought that teriparatide may stimulate quiescent osteoclast precursors. Therefore, sequential teriparatide therapy following denosumab should be avoided [50].

6) SERM after PTH analogues

Rapid bone loss may occur when discontinuing PTH analogs. Several studies have reported on the use of sequential therapy with anti-resorptive agents. It has been reported that replacing with raloxifene is effective in preventing bone loss and maintaining vertebral and hip BMD after cessation of PTH analogues [77].

7) Bisphosphonate after PTH analogues

Multiple studies have reported that administering oral alendronate after PTH analogues increases vertebral and femoral BMD. Specifically, it has demonstrated higher efficacy in vertebral BMD than raloxifene [78-80].

3. Summary

Studies have reported that the combination of osteoporosis medications leads to additional increases in BMD and improvement in bone microarchitecture. However, the combined use of multiple drugs can increase the medical costs and there is still insufficient data regarding their actual effectiveness in preventing fractures. Even in the 2020 AACE/American College

of Endocrinology (ACE) guidelines, the combination therapy of osteoporosis drugs is not recommended due to the lack of evidence supporting a reduction in fracture risk.

During osteoporosis treatment, the patient's clinical status, underlying diseases, and potential side effects from long-term drug use should be taken into account, which may lead to the discontinuation of the current drug. In such cases, sequential therapy may be considered to maintain/increase BMD and reduce fracture risk.

Discontinuing denosumab treatment without switching to another drug may expose patients to a fracture risk due to rapid bone loss. Therefore, it is necessary to administer another anti-resorptive agent when discontinuing denosumab. Bisphosphonates have been reported to maintain BMD after denosumab, while evidence on the effects of other anti-resorptives remains limited.

Sequential therapy with PTH analogues after denosumab is not recommended as it may induce rapid bone loss.

VI. CLINICAL SIGNIFICANCE OF OSTEOPENIA AND THE MANAGEMENT

Key points

1. The current diagnostic criteria for osteoporosis, which solely rely on BMD T-scores, often overlook the treatment of osteoporotic fractures that frequently occur in elderly patients with osteopenia.
2. It is recommended to initiate treatment in patients with osteopenia when the fracture risk is high, as determined by fracture risk assessments considering factors such as age and risk elements for fracture.
3. To date, HRT, zoledronic acid, raloxifene, and risedronate have been reported to have fracture prevention effects in patients with osteopenia.

1. Definition of Osteopenia

According to World Health Organization (WHO) standards, osteopenia refers to cases where the T-score from a BMD measurement falls between –1.0 and –2.5. T-scores of –1.0 and above are classified as normal, while those below –2.5 are classified as osteoporosis. Instead of using the term "osteopenia," it is also referred to as "low bone mass," "low BMD," or "reduced bone mass."

2. Clinical Importance of Osteopenia

The BMD follows a normal distribution curve based on age, moving progressively towards lower values as age advances. When T-scores below –2.5 are defined as osteoporosis, the proportion of women diagnosed with osteoporosis in each age group gradually increases, eventually leading to approximately 21% of women over 50 years being diagnosed with osteoporosis. This proportion parallels the lifetime risk of hip fracture in white women and thus has been chosen as the diagnostic criteria for osteoporosis.

The problem with this diagnostic criteria is that it fails to reflect changes in fracture rates that occur with the same BMD at different ages. Even at the same BMD T-score of –2.5, the rate of hip fractures within 10 years is less than 3% in women in their 50s, but it exceeds 10% in women in their 80s.

Fractures occur in the elderly, even in patients with osteopenia. Since the proportion of postmenopausal women with osteopenia is high, most patients who visit the hospital for fractures are those with osteopenia. In the National Osteoporosis Risk Assessment (NORA) study, 82% of patients who visited the hospital for osteoporotic fractures had a T-score higher than –2.5 in DXA (dual-energy X-ray absorptiometry) from the previous year. While the rate of fracture occurrence increases as BMD decreases, the high portion of patients classified with osteopenia implies that the absolute number of fracture occurrences predominantly arises from osteopenic cases [81,82].

In the Rotterdam study, it was found that 43.3% of women who visited the hospital with nonvertebral fractures had osteopenia, while 12.6% had normal BMD. Among women diagnosed with hip fractures, 31.3% had osteopenia, and 5.2% had normal BMD [83].

This phenomenon is due to the current method of diagnosing osteoporosis, which only considers BMD and not fracture risk factors such as age, fracture history, and family history. To address this, FRAX, a tool designed to identify osteopenic patients who require treatment, was developed. FRAX calculates the risk of fracture over the next 10 years by considering the patient's age, height, weight, history of fractures, parents' hip fracture history, smoking, steroid use, rheumatoid arthritis, secondary osteoporosis, and the consumption of 3 or more units of alcohol per day, along with BMD [84-86]. Many countries, including the United States

NOF, recommend initiating treatment when the calculated fracture risk exceeds 3% for hip fractures and 20% for major osteoporotic fractures. It is recommended to establish the criteria for initiating treatment based on the specific circumstances of each country.

The prevalence of osteopenia in Korea was studied between 2008 and 2011 through the Korean National Health and Nutrition Survey, which performed BMD testing on all subjects. It found that among women over 50, 48.7% had osteopenia and 38.0% had osteoporosis, while among men, 46.5% had osteopenia and 7.3% had osteoporosis [87].

In the 2005–2006 NHANES (National Health and Nutrition Examination Survey) conducted in the United States, the data analysis showed that based on femoral neck BMD, 50% of women over the age of 50 had osteopenia, 10% had osteoporosis, 30% of men over the age of 50 had osteopenia, and 54% of men over 60 had osteopenia [88].

Given the definition of osteopenia, approximately 50% of any population will be diagnosed with osteopenia. Therefore, it is important to identify patients with a high risk of fractures among those with osteopenia.

3. Treatment of Osteopenia

The current problem with diagnosing osteopenia is that the diagnosis is based solely on BMD, which means that even those with osteopenic BMD may not be treated if they are at high risk of fractures. In order to overcome such pitfalls, FRAX have been developed which consider fracture risk factors, and the most important factors are the patient's age and previous fracture history.

The same BMD may indicate a higher fracture risk as age increases, and patients with a history of fracture and osteopenic BMD have a higher fracture rate than patients with osteoporotic BMD and no fracture history. Other factors such as the patient's height, weight, presence of secondary osteoporosis, smoking, and alcohol consumption are also considered. The most commonly used tool for this is FRAX and a version of FRAX reflecting Korean hip fracture data has been developed. In the United States and other countries, treatment is recommended when the 10-year risk of a major osteoporotic fracture, calculated via FRAX, is over 20% and the risk of a hip fracture is over 3%.

In patients with osteopenia, it is crucial to maintain or improve BMD through appropriate intake of calcium and vitamin D and exercise. If a fracture is confirmed through a vertebral fracture assessment, they should be reclassified as patients with osteoporosis and receive the corresponding treatment. Treatment should be initiated if the risk of fractures is high as determined through fracture risk assessments.

There have been ongoing studies on the effect of drug treatments for osteopenia. In a study where 5 mg of zoledronate was administered at 18-month intervals to patients diagnosed with femoral neck or pelvic osteopenia over six years, significant reductions in frailty fractures, symptomatic fractures, vertebral fractures, and nonvertebral fractures were observed [89].

Risedronate, when administered to postmenopausal women with osteopenia but without previous vertebral fracture history for three years, resulted in a 73% decrease in frailty fractures [90].

Raloxifene, when used over three years in women with osteopenia with an average age of 65.2, resulted in a 47% decrease in new vertebral fractures and a 75% decrease in new clinical vertebral fractures [91]. The use of estrogen in the WHI study showed a 34%–36% decrease in vertebral fractures and a 34%–35% decrease in hip fractures in postmenopausal women whose prevalence rates of osteoporosis was 4%–6% [5].

4. Conclusion

The current diagnostic approach for osteoporosis, which relies solely on BMD, poses a serious issue as it prevents patients with osteopenia with a high fracture risk from receiving appropriate treatment. It is advised to evaluate and treat patients based on their fracture risk, even in cases of osteopenia. One of the available tools for assessing fracture risk and determining treatment candidates is FRAX. To effectively reduce fractures through aggressive treatment, insurance coverage policies should be modified accordingly, such as expanded insurance coverage for those with osteopenia. Continued attention and awareness from the medical community are necessary as well.

VII. SARCOPENIA

Key points

Sarcopenia is a progressive systemic skeletal muscle disorder encompassing the loss of muscle mass and function associated with detrimental health outcomes. It is diagnosed by evaluating muscle mass, strength, and performance.

Currently, there are no approved pharmacological treatments, and improvements in sarcopenia can be made through exercise.

1. Definition

Sarcopenia refers to the state of muscle mass loss, diminished muscle strength, or functional decline related to aging. It manifests as a progressive systemic skeletal muscle disorder associated with falls, functional deterioration, frailty, and increased mortality. Sarcopenia is influenced by genetics and lifestyle; it can arise due to the aging process or various causes in midlife. Muscle mass and strength, along with BMD, peak during young adulthood, then enter a period of stability and gradual decrement. In old age, muscle mass and strength decline rapidly. Sarcopenia may occur not only in lean individuals but also in obese individuals; weight loss in obese individuals can lead to muscle loss, potentially increasing the risk of death and disability [92].

2. Epidemiology

The prevalence of sarcopenia in Asia ranges from 7.3% to 12.0%. The prevalence varies with environmental factors and is more frequently seen in hospital inpatients, post-acute treatment settings, and nursing homes than in the community. The risk factors for sarcopenia primarily include advanced age, and other contributing factors include lifestyle, physical inactivity, nutritional status, poor dental health, and disease conditions (diabetes, hypertension, dyslipidemia, etc.).

3. Causes

Sarcopenia could be classified into primary (idiopathic) sarcopenia caused by aging and secondary (acquired) sarcopenia resulting from medications or diseases. Sarcopenia can be manifested acutely in situations such as the onset of an acute illness or hospital admission that limits mobility or may manifest gradually as a chronic condition.

Key points

Causes of sarcopenia

Nutrition
1. Decreased protein intake
2. Reduced energy intake
3. Micronutrient deficiency
4. Malabsorption and other gastrointestinal disorders
5. Anorexia (aging, oral cavity and gingival issues)

Decreased activity
1. Bed rest, immobilization, deteriorating condition
2. Low physical activity, sedentary lifestyle

Diseases
1. Bone and joint diseases
2. Cardiopulmonary diseases, including chronic heart failure and chronic obstructive pulmonary disease
3. Metabolic disorders (e.g., diabetes)
4. Endocrine disorders (e.g., androgen deficiency)
5. Neurological disorders
6. Cancer
7. Liver and kidney disorders

Iatrogenic
1. Hospitalization
2. Drug-related issues

4. Diagnosis

There are no internationally agreed-upon criteria for diagnosing sarcopenia, and the criteria presented by each international society may vary slightly. However, it is generally diagnosed by evaluating muscle mass, muscle strength, and muscle performance (Table 2) [93-97].

1) Muscle mass

Various methods have been utilized to measure muscle mass; however, limitations exist, as they report inconsistent results, have vague standards, and have a low correlation between muscle mass and health. The most effective current method for muscle mass measurement is DXA, although BIA (bioelectrical impedance analysis), computed tomography (CT), and magnetic resonance imaging (MRI) can also be used. Typically, muscle mass is quantified as the sum of the appendicular lean mass (ALM) of the limbs divided by the square of the height (height^2).

2) Muscle strength

Both grip strength and lower limb strength could be evaluated. Grip strength is commonly used as a stan-

Table 2. Diagnostic criteria for sarcopenia

	Muscle mass	Muscle strength	Physical performance
EWGSOP-2 (2019) [93]	DXA Men: < 7.0 kg/m^2 Women: < 5.5 kg/m^2	Handgrip strength Men: < 27 kg Women: < 16 kg	Gait speed : ≤ 0.8 m/s (4 m) Timed up and go test[a]: ≥ 20 s
AWGS-2 (2020) [94]	DXA Men: < 7.0 kg/m^2 Women: < 5.4 kg/m^2 BIA Men: < 7.0 kg/m^2 Women: < 5.7 kg/m^2	Handgrip strength Men: < 28 kg Women: < 18 kg	Gait speed : < 1.0 m/s (6 m) 5-time chair stand test: ≥ 12 or SPPB ≤ 9
FNIH (2014) [95]	DXA (ALM[b]) Men: < 19.75 kg Women: < 15.02 kg	Handgrip strength Men: < 26 kg Women: < 16 kg	Gait speed: ≤ 0.8 m/s (4 m)
IWGS (2011) [96]	DXA Men: < 7.23 kg/m^2 Women: < 5.67 kg/m^2		Gait speed: ≤ 1.0 m/s (4 m)
SDOC (2020) [97]		Handgrip strength Men: < 35.5 kg Women: < 20.0 kg	Gait speed: ≤ 0.8 m/s (4 m)

EWGSOP: European Working Group on Sarcopenia in Older People, AWGS: Asian Working Group on Sarcopenia, FNIH: Foundation for the National Institutes of Health, IWGS: International Working Group on Sarcopenia, SDOC: The Sarcopenia Definitions and Outcomes Consortium, DXA: dual-energy X-ray absorptiometry, BIA: bioelectrical impedance analysis, SPPB: Short Physical Performance Battery, ALM: appendicular lean mass.
[a]A test that measures functional mobility in the elderly, it records the time taken to complete the test. The test involves a patient getting up from a chair, walking three meters, turning, walking back to the chair, and sitting down again.
[b]The total amount of lean or muscle mass in the arms and legs.

dard test due to its convenience.

3) Muscle performance

The most commonly used measure of muscle performance is walking speed (over 4 m or 6 m). The Short Physical Performance Battery (SPPB) is also used, which scores the balance test, walking speed, and chair rise test results.

5. Treatment

1) Non-pharmacologic treatment

(1) Exercise

Its efficacy in improving sarcopenia has been confirmed in both elderly and obese sarcopenia patients.

(2) Increased protein intake in the elderly

There is still insufficient evidence regarding nutritional supplementation.

Many studies have investigated the effects of exercise with or without nutritional supplementation, and the beneficial effects of exercise have been confirmed irrespective of nutritional supplementation.

2) Pharmacological treatments

While no drug therapies have been approved for sarcopenia, various substances such as vitamin D, estrogen-progesterone combination therapy, dehydroepiandrosterone, and growth hormone have been proposed as potential treatment candidates. Phase II clinical trials are ongoing for therapeutic agents for sarcopenia, such as myostatin antibodies and bimagrumab [94,98].

VIII. MEDICATION-RELATED OSTEONECROSIS OF THE JAW

Key points

Drug-related ONJ, while rare, is a serious complication. The risk is highest with prolonged use of bisphosphonates. It is necessary to identify and mitigate risk factors and attempt to avoid them. For individuals on long-term anti-resorptive agent therapy, considering a drug holiday or switching to an alternative medication may be advantageous.

1. Overview

Medication-related Osteonecrosis of the Jaw (MRONJ)

is a rare but severe condition that first appeared in reports in the early 2000s. It primarily affects patients using anti-resorptive agents, and it involves the exposure of the jawbone, often accompanied by necrosis in severe cases. Initially, it was identified as a side effect associated with bisphosphonates, leading to the name "Bisphosphonate-Related Osteonecrosis of the Jaw" (BRONJ). However, as cases were reported in patients using various anti-resorptive agents and angiogenesis inhibitors, the term was broadened to MRONJ in 2014. The incidence varies, but it is generally reported at around 0.3–0.4 cases per 100,000 [99].

2. Diagnosis

The diagnostic definition established by the American Association of Oral and Maxillofacial Surgeons (AAOMS) is widely used. A diagnosis of MRONJ is established if all of the following criteria are met: 1) the jawbone is exposed, or a fistula persists for more than 8 weeks, 2) the patient is using or has a history of using anti-resorptive agents or angiogenesis inhibitors, and 3) the patient has no history of receiving radiotherapy in the surrounding area. In addition to clinical examinations, imaging diagnostics such as panoramic radiography, CT, and MRI can be helpful [100].

Staging for MRONJ was proposed by Ruggiero et al. [100] in 2014. Nowadays, an updated staging by the AAOMS in 2014 is widely used (Table 3) [100].

3. Cause

The exact cause and process of MRONJ are not yet clearly known. However, it is believed that the inhibition of bone regeneration by osteoporosis treatments, such as anti-resorptive agents (bisphosphonates, denosumab, etc.), may be a potential cause. Angiogenesis inhibitors used in cancer patients (vascular endothelial growth factor [VEGF] inhibitors like bevacizumab, tyrosine kinase inhibitors like sunitinib, etc.) are also considered causative due to the inhibition of mucosal or bone regeneration. It seems to occur when medication risks overlap with factors such as dental treatments or inflammation in the temporomandibular joint. Therefore, in cases where an individual belongs to a high-risk group, it is necessary to mitigate the compounding of risk factors by avoiding risk factors, addressing dental issues before starting osteoporosis treatment, or considering a drug holiday [101].

Oral bisphosphonates have been reported to increase the risk by approximately four times after five years of use; therefore, the duration of use is an important factor to consider. In the case of denosumab, ONJ has been reported when used in high doses as part of cancer treatment [101,102]. The known risk factors for ONJ are listed in Table 4 below.

4. Prevention

Identifying risk factors and minimizing their overlap is necessary. Maintaining good oral hygiene helps, and regular dental check-ups are recommended. The treatment period of anti-resorptive agents such as oral

Table 4. Risk factors for osteonecrosis of the jaw

Systemic risk factors	1) Types and duration of use of anti-resorptive agents or angiogenesis inhibitors 2) Use of steroids 3) Advanced age 4) Diabetes 5) Smoking 6) Genetic predisposition
Local risk factors	1) Dental treatments involving the jawbone, such as tooth extraction 2) Denture use 3) Accompanying dental diseases (periodontal disease, tooth periapical abscess) 4) Local anatomical factors

Table 3. Staging of the MRONJ (AAOMS, 2014)

Stage	Clinical condition
Stage 0	No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes and symptoms
Stage 1	Exposed and necrotic bone or fistulas that probe to the bone in patients who are asymptomatic and have no evidence of infection
Stage 2	Exposed and necrotic bone or fistulas that probe to bone associated with infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage
Stage 3	Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in mandible maxillary sinus, and zygoma in maxilla) resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor

MRONJ: Medication-related Osteonecrosis of the Jaw, AAOMS: American Association of Oral and Maxillofacial Surgeons.

alendronate and risedronate is 5 years, and zoledronic acid injection is 3 years; problems arise if the treatment period is prolonged. Before the treatment period ends, the risk of MRONJ after undergoing dental treatment is not high, and the necessity for a drug holiday is relatively low. General treatments such as dental scaling are well tolerated, but if the drug has been used for longer than 3–5 years and dental treatment such as extraction or implants is required, it is recommended to have a drug holiday period for anti-resorptive agents [99].

The AAOMS recommends discontinuing associated drugs 3 months prior to the treatment and resuming them 3 months after the completion of the treatment. However, the adequate duration for this is still unclear due to insufficient data and further research is needed. As bisphosphonates remain absorbed in the bone for a considerable period even after cessation, a drug holiday could be considered after usage of 3–5 years. If a high risk of fractures persists even during the drug holiday, it may be worth considering switching to a SERM regimen, which has reported very low risk of ONJ [100].

5. Treatment

Systemic risk factors should be identified and treated accordingly. Optimal blood sugar levels should be maintained, consumption of alcohol and smoking should be stopped, and the use of medications that increases the risk of ONJ should be minimized or discontinued. The treatment strategies set by stage are as follows [103]:

Stage 1: Enhance oral hygiene and treat periodontitis with local antibiotic gargles.

Stage 2: When pain is accompanied by inflammation and infection, a conservative approach, antibiotic treatment, and surgical intervention are carried out.

Stage 3: If pathological fractures, fistulas, or extensive lesions are observed, surgical treatment is necessary, and selective mandibular bone resection may be required.

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