JMM Journal of Menopausal Medicine
pISSN: 2288-6478, eISSN: 2288-6761
https://doi.org/10.6118/jmm.24000
J Menopausal Med 2024;30:1-23
THE KOREAN SOCIETY OF MENOPAUSE PAGES

The 2024 Guidelines for Osteoporosis - Korean Society of Menopause

Dong Ock Lee[1], Yeon Hee Hong[2], Moon Kyoung Cho[3], Young Sik Choi[4], Sungwook Chun[5], Youn-Jee Chung[6], Seung Hwa Hong[7], Kyu Ri Hwang[8], Jinju Kim[9], Hoon Kim[2], Dong- Yun Lee[10], Sa Ra Lee[11], Hyun-Tae Park[12], Seok Kyo Seo[4], Jung-Ho Shin[12], Jae Yen Song[6], Kyong Wook Yi[12], Haerin Paik[2], Ji Young Lee[13]

[1]Center for Gynecologic Cancer, National Cancer Center, Goyang, Korea, [2]Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, Korea, [3]Department of Obstetrics and Gynecology, Chonnam National University Medical School, Gwangju, Korea, [4]Department of Obstetrics and Gynecology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, [5]Department of Obstetrics and Gynecology, Inje University Haeundae Paik Hospital, Busan, Korea, [6]Department of Obstetrics and Gynecology, College of Medicine, The Catholic University of Korea, Seoul, Korea, [7]Department of Obstetrics and Gynecology, Chungbuk National University Hospital, Cheongju, Korea, [8]Department of Obstetrics and Gynecology, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Korea, [9]Department of Obstetrics and Gynecology, Healthcare System Gangnam Center, Seoul National University Hospital, Seoul, Korea, [10]Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, [11]Department of Obstetrics and Gynecology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, [12]Department of Obstetrics and Gynecology, Korea University College of Medicine, Seoul, Korea, [13]Department of Obstetrics and Gynecology, Konkuk University School of Medicine, Seoul, Korea

FOREWARD

Menopause is a natural biological process that marks the end of a woman's reproductive years. As ovarian function declines, distressing menopausal symptoms such as hot flashes and facial flushing arise. Furthermore, decreased estrogen levels may elevate the risk of chronic conditions, such as osteoporosis and cardiovascular diseases. Currently, South Korean women have been reported to have an average life expectancy of approximately 87–88 years. Considering menopause typically occurs at roughly 50 years old, postmenopausal life spans over 37–38 years, accounting for more than 40% of an individual's lifespan.

Lifestyle modifications and healthy habits during menopause are essential, specifically in preventing and treating osteoporosis. Neglect on this issue not only affects individual postmenopausal women but also results in substantial losses and regrets for society. In an ongoing effort to contribute to the health and well-being of peri-menopausal and postmenopausal women, this guideline has been published to foster a better understanding of osteoporosis.

I. OSTEOPOROSIS: DEFINITION AND EPIDEMIOLOGY

Key points

1. Osteoporosis is defined as a systemic skeletal disease characterized by a decrease in bone mass and abnormal microstructure, ultimately weakening the bones and making them prone to fractures.
2. According to the Korean National Health and Nutrition Examination Survey (KNHANES) conducted from 2008 to 2011, the overall prevalence of osteoporosis in adults over 50 was 22.4%. The prevalence differed by gender, with 7.5% in men and 37.3% in women; women were four times more likely to have osteoporosis than men.

Received: October 27, 2023 **Revised:** December 19, 2023 **Accepted:** January 20, 2024
Address for Correspondence: Ji Young Lee, Department of Obstetrics and Gynecology, Research Institute of Medical Science, Konkuk University School of Medicine, 120 Neungdong-ro, Gwangjin-gu, Seoul 05029, Korea
Tel: 82-2-2030-7643, **E-mail:** jylee@kuh.ac.kr, **ORCID:** https://orcid.org/0000-0002-0682-6685
Dong Ock Lee and Yeon Hee Hong contributed equally to this work.

3. An analysis of health insurance claim data showed that in 2016, there were 212,192 cases of osteoporotic fractures in adults over 50. The overall fracture incidence was 2 to 4 times higher in women than men. Among women, the highest incidence rates of osteoporotic fractures (per 10,000 population in 2016) were in the spine (128 cases), wrist (60 cases), hip (23 cases), and humerus (10 cases), in that order of highest prevalence.

1. Definition

The World Health Organization (WHO) defines osteoporosis as "a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" [1]. The National Institutes of Health in the United States has a similar concept, defining osteoporosis as "a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture" [2]. The term 'bone strength' is a term that reflects both bone density and bone quality.

Bone mineral density (BMD), measured in grams of mineral per area or volume, is determined by an individual's peak bone mass and the degree of bone loss. Osteoporosis occurs as a result of bone loss, typically influenced by aging and decreased estrogen due to menopause in women. However, individuals who fail to reach peak bone mass during childhood and adolescence can develop osteoporosis earlier in their 50s without aging factors and decreased estrogen levels [3,4]. Therefore, failing to achieve appropriate peak bone mass up to adolescence could increase the likelihood of future osteoporosis events. Bone quality is determined by structure, bone turnover rate, accumulation of micro-damage (such as micro-fractures), and mineralization. At present, there are no specific ways to measure bone quality; thus, it could be said that there are no accurate methods to quantify overall bone strength. Consequently, BMD tests are primarily used as a substitute measure for evaluating bone strength. It is known that BMD reflects about 70% of bone strength.

The WHO defines osteoporosis as having a BMD lower than 2.5 standard deviations (SD) (T-score ≤ −2.5) below the average BMD of a young Caucasian female. If osteoporosis is accompanied by fractures related to the disease, it is classified as severe or established osteoporosis. Osteopenia is a condition with a BMD between 1 and 2.5 SD below. However, the aforementioned diagnostic criteria remain controversial, as accurate measurement and standardization in assessing BMD can be challenging. Furthermore, applying these diagnostic standards to men, children, and races other than Caucasians may be an inaccurate assessment. Above all, diagnosing osteoporosis using BMD has low sensitivity in predicting fractures; only about 20% of female fractures are diagnosed as osteoporosis [4].

Osteoporosis is categorized into primary (or idiopathic) and secondary, based on its cause. Primary osteoporosis can occur in men and women of all ages, but it often arises in women after menopause and in older men. Medications such as glucocorticoids or other abnormalities and diseases such as hypogonadism can cause secondary osteoporosis [5,6].

Osteoporosis leads to financial, physical, and psychosocial outcomes that significantly affect individuals, families, and communities. Osteoporotic fractures result from trauma exerted on weakened bones, and their incidence increases with various other risk factors. Osteoporosis is a significant risk factor for fractures. Thus, it is crucial to distinguish between factors that affect bone metabolism and those that increase the risk of fractures.

2. Epidemiology

1) Osteoporosis

Osteoporosis is the most common musculoskeletal disorder and the second most common cause of musculoskeletal symptoms in the elderly after arthritis. There are about 200 million patients diagnosed with osteoporosis worldwide, with the prevalence increasing with age. Over 70% of those in their 80s are known to have osteoporosis.

According to the KNHANES, conducted from 2008 to 2011, the overall prevalence of osteoporosis in adults over 50 was 22.4%, with 7.5% in men and 37.3% in women, showing that the rate is over four times higher in women. The prevalence of osteoporosis by age increased roughly two-fold for every 10-year increase, with 15.4% for women aged 50–59, 36.6% for 60–69, and 68.5% for those over 70.

Data from the claims data of National Health Insurance show that the number of patients over 50 who received medical care for osteoporosis rose from 1.4 million in 2008 to 1.96 million in 2012, an average annual

increase of 7.4%. The medical utilization rate associated with osteoporosis was highest in their 70s and tended to decrease gradually afterwards. The total healthcare costs for osteoporosis patients increased annually by 9.2%, from 4.77 trillion won in 2008 to 6.15 trillion in 2011. This accounts for about one-sixth of the total medical expenses, indicating that the socioeconomic burden will continue to increase. However, only about 60% of osteoporosis patients used medical services, and the treatment rate with medication was 34%. Patient compliance is low, as the continuation rate of medication was only 33% in 1 year and 22% in 2 years.

2) Osteoporotic fracture

Osteoporotic fractures are the most serious complication of osteoporosis. It is more common in women than men; a decrease in BMD due to menopause is known to be a significant factor. The most common osteoporotic fracture sites are the hip, spine, wrist, and proximal humerus. Other sites include distal humerus, rib, tibia, pelvic bone, distal femur, sacrum, and ankle. Of these, hip fractures result in the highest morbidity and account for about 20% of all osteoporotic fractures. Internationally, the economic cost of osteoporotic fractures is significant. In Europe, it is estimated to be around 50 trillion won [7]. In the United States, the cost was about 19 trillion won in 2005 and is projected to rise to around 28 trillion won by 2025 [8]. In South Korea, medical expenses due to osteoporotic fractures increased by 31.6% over three years, from approximately 610 billion won in 2008 to around 800 billion won in 2011 [4].

According to an analysis of health insurance claim data, osteoporotic fractures in adults aged 50 and above were as follows: 146,822 cases in 2008, 155,606 cases in 2009, 190,139 cases in 2010, 205,291 cases in 2011, 208,274 cases in 2012, 214,119 cases in 2013, 209,990 cases in 2014, 207,219 cases in 2015, and 212,192 cases in 2016. This indicates that there was an average annual increase of approximately 15% until 2013, after which the rate of growth showed a tendency to slow down. Women were likely to experience 2–4 times more osteoporotic fractures in all locations compared to men. In 2016, the most common sites of osteoporotic fracture in women (per 10,000 population) were the spine (128 cases), wrist (60 cases), hip (23 cases), and humerus (10 cases), respectively. In women, wrist fractures were most common in their 50s (59.4%), while the rates of femur and spine fractures increased with age [9]. The lifetime risk of experiencing at least one osteoporotic fracture for 50-year-old women was 59.5%, approximately 2.5 times higher than 23.8% for men of the same age. The lifetime risk of experiencing a femur fracture, which has a high mortality rate, was 12.3% for 50-year-old women [10].

However, the 1-year mortality rate following an osteoporotic fracture was lower in women than men. According to the claims data from the Korean National Health Insurance from 2013 to 2015, the 1-year mortality rate after a femur fracture was 20.8% for men and 13.6% for women, and after a spine fracture, it was 9.2% for men and 4.2% for women [11].

In 2015, the prescription rate of osteoporosis medication within 1 year after an osteoporotic fracture was only about 42% of the estimated population with osteoporosis. Of these, only 48% of women and 21% of men received medication. The treatment rate increased with age but decreased after 80 years of age. In terms of fracture type, the 1-year prescription rate after a spine fracture was the highest (53.2%), followed by femur fracture (36.6%), humerus fracture (22.9%), and wrist fracture (22.6%) [11].

3) Secondary fractures (recurrent fractures)

According to data from the National Health Insurance claims data from 2012 to 2016, the cumulative incidence rate of recurrent fractures in osteoporotic fractures was 4.3% in the first year, 12.1% in the second year, 18.8% in the third year, and 24.8% in the fourth year. A comparison of the incidence of osteoporotic fracture in 2013 and recurrent fracture a year later showed that the risk of recurrent fracture was about four times higher in men and about two times higher in women with a previous fracture history. This supports that a past fracture history is an important risk factor for osteoporotic fractures. The spine was the most common recurrent fracture site. The cumulative incidence of recurrent spine fractures in the fourth year was 1,787 per 10,000 patients with fractures, followed by wrist (399 cases), hip (342 cases), and humerus (79 cases) [11].

4) Osteopenia

A T-score between −2.5 and −1.0 defines osteopenia. According to KNHANES data from 2008 to 2011, the prevalence of osteopenia in adults aged 50 and above was 46.8% for men and 48.9% for women, corresponding to 47.9% of the total population. A study from

the National Osteoporosis Risk Assessment (NORA), which observed the fracture risk over a year in postmenopausal women, found that those with osteopenia had a 1.73 times higher risk of fracture compared to those with normal BMD [12]. Most of the patients who suffered fractures showed a T-score corresponding to osteopenia. Considering that about 48% of the population falls into the osteopenia category and that the proportion of postmenopausal women among osteoporotic fracture patients is 77%, proactive measures are necessary to prevent fractures in postmenopausal women with osteopenia [13].

3. Conclusion

South Korea is entering a super-aged society at a rapid rate, and the prevalence of osteoporosis is rapidly increasing. Consequently, the treatment costs for osteoporosis and osteoporotic fractures are also sharply rising. Osteoporosis often goes unnoticed and untreated until a fracture occurs since patients have no symptoms before a fracture event. Once a fracture occurs, individuals may suffer from chronic pain, disability, decreased quality of life, and increased mortality rate. Additionally, the opportunity cost to society is substantial; thus, proactive prevention, diagnosis, and treatment are essential. Particularly, patients who have already experienced a fracture are at an increased risk of additional and new fractures. Special attention to a cohort of patients who already experienced fractures is necessary. Moreover, the population corresponding to osteopenia, where actual fractures frequently occur, accounts for 48% of the population over 50 years old. Therefore, it is essential to prepare measures for these patients to establish long-term preventative strategies against future fractures.

II. DIAGNOSIS AND EVALUATION OF OSTEOPOROSIS

1. Radiologic Evaluation and Diagnosis of Osteoporosis

Key points

1. For quantitative assessment of BMD, Dual-energy X-ray absorptiometry (DXA), quantitative computed tomography (QCT), and quantitative ultrasound (QUS) are used.
2. DXA is considered the standard test for BMD measurement. Advantages of DXA include 1) high accuracy, 2) minimal radiation exposure, 3) easy to use and interpret, and 4) easy assessment of response to treatment.

BMD, one of the determining factors for bone strength, is widely implemented for the prediction, diagnosis, and evaluation of treatment efficacy of osteoporosis. Among several tests, DXA is known to provide the most objective and quantitative information. Other quantitative evaluation measures of bone density include QCT and QUS.

1) Dual-energy x-ray absorptiometry

Currently, DXA is the most widely used tool for diagnosing osteoporosis. It reports the results of bone density in the T-score and Z-score. Given the substantial accumulation of clinical research data, DXA is recognized as the standard test for BMD measurement. DXA diagnoses osteoporosis based on the lowest measurement obtained from images of the lumbar spine and the femur, the most frequent sites of osteoporotic fractures. DXA can also measure total body BMD beyond the lumbar spine and femur; it can also evaluate bone density in areas such as the forearm and the calcaneus. In situations where imaging of the lumbar spine and femur is not possible, in cases of hyperparathyroidism or extreme obesity in which the patient cannot get onto the imaging table, DXA captures images of the distal third of the radius [14].

The advantages of DXA include 1) high accuracy, 2) minimal radiation exposure, 3) ease of use and interpretation, and 4) easy assessment of response to treatment.

(1) Measurement and evaluation of lumbar spine BMD

The lumbar spine BMD is measured by capturing images of the L1 to L4 vertebrae and calculating an average value. Regions with fractures, osteophytes (bony outgrowths), scoliosis, or artifacts should be excluded from evaluation. At least 2 or more lumbar vertebrae should be assessed. If this is not feasible, the diagnosis should be made based on the BMD of other regions. The lateral lumbar spine view should not be used for diagnosing osteoporosis.

The imaging should include thoracic vertebrae T12 to lumbar vertebrae L5 and the iliac crest. The top of the

iliac crest corresponds to the interspace between lumbar vertebrae L4 and L5. It is recommended to count the position of the vertebrae from bottom to top. During follow-up observations, it must be confirmed that the lumbar position has been evaluated similarly [14].

Approximately 17% of adults may have variations, such as sacralization of the lumbar spine or lumbarization of the sacral spine, resulting in either fewer than five lumbar vertebrae or the absence of visible ribs at the 12th thoracic vertebra. Therefore, attention should be paid to individual variations. The imaging should include enough soft tissue and exclude artifacts, as it is used for future adjustments; thus, accurate imaging is necessary [15].

Typically, the BMD of the lumbar spine should progressively increase from L1 to L4, and the T-score should not differ by more than 1.0 between the adjacent vertebrae. If the difference exceeds one SD, there is a possibility of lumbar fracture, calcification due to degenerative disc changes, osteophytes, or calcification of the aorta. In such cases, a spine X-ray or vertebral fracture assessment (VFA) should be conducted to evaluate possible vertebral fractures [15].

(2) Measurement and evaluation of femoral BMD

The femur BMD measurement includes both the femoral neck and the total femoral BMD. The femoral neck consists of a higher portion of cortical bone compared to the total femur. The Ward's triangle area, the area with the lowest BMD automatically detected through the device's software, is not used for the diagnosis due to poor reproducibility.

As with lumbar spine BMD measurements, there should be no artifacts. The femoral shaft should be positioned straight, and the lesser trochanter should be visible with a slight internal rotation. Because a very small area is measured, a change in the degree of internal rotation can significantly influence BMD measurement [14].

(3) Measurement and evaluation of forearm BMD

For forearm BMD measurement, the distal one-third of the left radius is used in right-handed individuals if there is no arthritis or fracture. A device is used to maintain position, and there should be no artifacts.

(4) Diagnosis of osteoporosis using DXA

Osteoporosis is diagnosed based on the T-score, which reflects the degree of difference in SDs from the BMD of young women (Table 1). The value of –2.5 is indicative of osteoporosis in postmenopausal Caucasian women; it may not reflect racial and ethnic variations. The T-score is used in postmenopausal women, while the Z-score, which reflects racial differences, is used in premenopausal women. Utilization of the T-score in premenopausal women may not be appropriate; in these women, the terminology "below the expected range for age" is used when the Z-score is –2.0 or lower instead of "osteoporosis" [16].

2) Quantitative computed tomography

QCT measures volumetric BMD and has the advantage of measuring regardless of body size. It can also exclude areas of the spine that influence BMD but not bone strength and can separately measure cortical and trabecular bone. In particular, the trabecular bone is useful because it can evaluate the therapeutic effect of drugs and can exclude degenerative changes in the spine or aortic calcification. The pitfall of QCT is that it exposes the patient to a higher radiation dose than DXA.

QCT can be used effectively to predict fractures as DXA does, but WHO standards cannot be applied. Typically, osteoporosis is diagnosed when the BMD of the L2 and L3 areas is 80 mg/cm^3 or less [14].

3) Quantitative ultrasound

QUS has the advantages of no radiation exposure, being easy to use, and occupying a small space for equipment; thus, it is widely used in many countries. The FDA approved QUS for predicting osteoporosis, and the International Society for Clinical Densitometry (ISCD) consensus recommends measurements only at the heel. The calcaneus, rich in trabecular bone, makes measuring changes in BMD easier than cortical bone.

QUS does not show results that match BMD. In studies that measured BMD and QUS simultaneously, the correlation was moderate. However, it has been reported to predict fracture risk relatively well [14].

Table 1. The World Health Organization diagnostic criteria of osteoporosis

Status	
Normal	T-score ≥ –1.0 SD
Osteopenia	–2.5 SD < T-score < –1.0 SD
Osteoporosis	T-score ≤ –2.5 SD

SD: standard deviation.

Compared to DXA, QUS has issues with reproducibility and accuracy. Due to this, it cannot be used to assess treatment efficacy and is not covered by national health insurance in Korea.

2. Bone Turnover Markers

While BMD is used to decide treatment strategies and assess the rate of bone loss or the response to osteoporosis treatment, it still cannot comprehensively predict the risk of osteoporotic fractures. Furthermore, BMD measurements for assessing treatment response require lengthy measurement intervals of more than a year. Bone turnover, the process of resorbing old bone and forming new bone, is continuously taking place. Changes in the rate of bone turnover may affect bone quality. Considering the limitations of BMD and the characteristics of bone turnover markers that reflect bone quality, the attention given to the potential role of bone turnover markers for predicting fracture risk and monitoring treatment response in the clinical setting is constantly increasing [17].

1) Types of bone turnover markers

It is recommended to use serum C-terminal telopeptide of collagen type 1 (CTX) as a bone resorption marker and serum procollagen type I N-terminal propeptide (P1NP) as a bone formation marker, as they are readily measurable with an automated process with minimal variability.

(1) Bone formation markers

Bone formation markers include osteocalcin (OC), bone-specific alkaline phosphatase (BSALP), Procollagen type I C-terminal propeptide (P1CP), and P1NP [18]. BSALP and OC are released from osteoblasts and play a vital role in bone mineralization. P1CP and P1NP are cleaved from Procollagen type I during collagen synthesis.

(2) Bone resorption markers

Bone resorption markers include CTX, N-terminal telopeptide of collagen type 1 (NTX), free and total pyridinoline (PYD), and free and total deoxypyridinoline (DPD) [18]. In South Korea, CTX is the most commonly used bone resorption marker.

2) Considerations in the analysis process

Various factors, such as biological characteristics and the measurement method, can influence bone turnover marker values. These include age, sex, race, physical activity, diet, medication, liver disease, kidney disease, fractures, and factors related to the technical aspects such as sample handling process, precision and accuracy of measurement, standardization, cross-reactivity with other substances, and inter-laboratory variation. Bone resorption markers exhibit diurnal variation. Especially, serum CTX, the most commonly used, peaks in the early morning (2:00–5:00 am), nadirs around 11:00 am–2:00 pm, and is influenced by meal intake. Therefore, it is recommended that blood samples are collected between 7:30 and 10:00 am after overnight fasting [18]. Bone formation markers can be collected at any time of the day since they have less than 10% diurnal variation; however, they are typically measured along with bone resorption markers. It is important to note that significant variations may be present in the same test depending on the reagent and analysis kits used, which may make direct comparison difficult. Therefore, when monitoring an individual, it is recommended that the same exams are repeated in the same laboratory settings.

3) Clinical utility of bone turnover markers

(1) Prediction of fracture

If the concentration of bone turnover marker is high, rapid bone loss and a high risk of osteoporotic fractures could be expected. According to two major studies based on large cohorts, increased serum BSALP and serum/urine CTX levels were significantly associated with an increased risk of osteoporotic fractures (hip and spine) [19,20]. In these studies, the concentration of bone turnover markers was associated with an increased risk of fractures independent of BMD. This indicates that fracture risk assessment could be supplemented with bone turnover markers in cases where DXA cannot be used. Despite such implications, it is not recommended to routinely use bone turnover markers to assess fracture risk since there is an unresolved uncertainty about the clinical use of bone turnover markers [21,22]. Although there seems to be a positive correlation between bone turnover markers and fracture risk, previous studies have shown inconsistent results with a wide range of variation.

(2) Evaluation of the treatment effects of osteoporosis

Bone turnover markers can reflect the treatment response to osteoporosis drug therapy earlier than BMD.

① Anti-resorptive agents

Anti-resorptive agents result in a decrease in bone resorption markers, followed by a plateau. Changes in bone turnover markers during the treatment with anti-resorptive agents vary according to the mechanism of action of the drug, the degree of bone resorption inhibition, and the route of administration. The inhibition of bone resorption, through physiological mechanisms that link the activity of osteoclasts and osteoblasts, induces a secondary decrease in bone formation markers.

Bisphosphonates

Bisphosphonates are the most commonly used drugs for the treatment of osteoporosis. The inhibition of bone resorption markers peaks at 8 weeks of treatment, and the inhibition of bone formation markers peaks after 26 weeks [18]. In the TRIO study, alendronate and ibandronate led to a greater reduction of bone turnover markers (CTX-I, NTX-1) than risedronate. In this study, more than 80% of patients showed a response to treatment. In the study, the treatment response was defined as those with a greater decrease than the least significant change (LSC) for CTX-I (56%) and P1NP (38%) after 3 months of treatment [23]. The treatment response group could also be defined as those with a decrease to a value below the median found in healthy young women. Intravenous bisphosphonates inhibit bone resorption and reduce the concentration of bone resorption markers more rapidly than orally administered bisphosphonates [18].

Denosumab

Bone resorption markers (such as CTX-I) decrease within 24 hours of treatment. Denosumab inhibits bone resorption to a greater extent than zoledronic acid [24]. P1NP decreases to a lesser extent over several months than bone resorption markers and maintains this suppressed state with continuous administration for up to 10 years [25]. If the drug is discontinued, bone resorption markers rise sharply, and their concentration increases compared to initial values. This rise in bone turnover markers is associated with accelerated bone loss. One recent study has reported that elevated levels of bone turnover markers are associated with multiple vertebral fractures [26].

Selective estrogen receptor modulators

Selective Estrogen Receptor Modulators (SERMs), such as raloxifene, have a weaker effect on bone turnover rates than bisphosphonates and denosumab. Using an LSC-based approach with CTX-I or P1NP, about 60%–65% of patients with osteopenia demonstrated efficacy with SERM [23].

② Bone-forming agents (osteoanabolic agents)

The connection between osteoclasts and osteoblasts can also work in the opposite direction when combined with bone-forming agents, as opposed to anti-resorptive agents.

Recombinant human parathyroid hormone (PTH) 1-34

Teriparatide is typically characterized as a bone-forming agent, but bone formation and resorption markers increase [27]. Bone formation markers increase within a few days of treatment initiation and peak at three months. P1NP has been demonstrated to be the bone turnover marker that exhibits the most favorable response to teriparatide. If the concentration of serum P1NP increases by greater than 10 pg/mL, a significant increase in BMD could be expected [28,29].

Romosozumab

Romosozumab, an anti-sclerostin monoclonal antibody, also acts in a dose-dependent manner to increase bone formation markers. However, unlike teriparatide, it initially leads to a temporary increase in P1NP levels while serum CTX-I decreases. P1NP levels increase one week after drug administration, peak within a month, and gradually recover to pre-treatment levels within six months. CTX-I initially decreased and remained below the reference value at 12 months [30]. These changes in bone turnover markers are associated with a rapid increase in BMD.

(3) Evaluation of treatment adherence

In postmenopausal women receiving osteoporosis treatment, bone turnover markers could be used to monitor individual treatment adherence. Monitoring bone turnover markers individually may improve patient adherence to osteoporosis treatment [31]. The International Osteoporosis Foundation (IOF) has suggested that bone turnover marker tests, such as P1NP or CTX-I, measured within 3 months of starting treatment, could help identify people with low compliance to osteoporosis treatment [29,32]. If there is no change in the concentration of bone turnover markers during osteoporosis treatment, it may indicate poor compliance. According to a recent Consensus Statement from the Asia-Pacific region, measuring serum CTX-I and/or P1NP levels before treatment initiation and at 3, 6, and 12 months after starting anti-resorptive agent drug therapy can be employed to monitor medication compliance and drug response in patients. In patients

receiving a bone-forming agent, serum P1NP can be used to monitor both drug treatment adherence and treatment response. These measurements should be taken before starting treatment and at 1, 3, 6, and 12 months after treatment initiation [33].

(4) Drug holiday

Monitoring bone turnover markers during a drug holiday could potentially help in deciding when to resume treatment, but the evidence is not sufficient. Long-term use of bisphosphonates is associated with rare but serious side effects such as osteonecrosis of the jaw (ONJ) and atypical femur fractures (AFF) [34]. Therefore, a "bisphosphonate drug holiday" concept has emerged as an alternative option that could circumvent such side effects. Since bisphosphonates remain deposited in the bones for an extended period, the effects of bisphosphonate, including bone resorption inhibition and fracture prevention, are maintained for a prolonged period after the discontinuation of a drug. However, the risk of fractures increases gradually after stopping bisphosphonates, even though they have a long retention period. Therefore, it is necessary to evaluate fracture risk and resume treatment if needed through meticulous monitoring during a drug holiday. Clinical guidelines for monitoring bone turnover markers during a drug holiday are limited. Several meta-analyses have indicated that increased bone turnover is a significant determinant of fracture susceptibility [35-37]. Some guidelines have suggested cessation of the drug holiday if bone resorption markers increase above a certain level compared to pre-treatment levels [38]. A significant decrease in BMD or a substantial increase in bone turnover marker concentration during a drug holiday may indicate that the residual effects of bisphosphonate therapy are diminishing, suggesting that it's time to resume drug therapy [39].

(5) Prediction of side effects such as ONJ and AFF

Although still subject to debate, bone turnover markers could be used cautiously to predict long-term side effects of bisphosphonates, such as ONJ and AFF [40]. Long-term bisphosphonate therapy is associated with rare side effects such as ONJ and AFF. These rare but serious side effects are believed to be associated with a significant suppression of bone turnover. Thus, various bone turnover markers have been investigated as screening methods during the bone remodeling period. Some dentists have proposed CTX-I measurements as a prediction tool for ONJ. If a patient's CTX-I level is less than 0.100–0.150 ng/mL, the risk of ONJ may be high, suggesting the need for a drug holiday or surgery after recovery of CTX-I levels [41]. In one prospective cross-sectional study, bone turnover marker test values, including P1NP, tartrate-resistant acid phosphatase 5b, and undercarboxylated OC, were significantly lower in patients with AFF patients than in patients with a typical osteoporotic femur fracture. They suggested that a severe suppression of bone turnover is associated with AFF [34].

4) Conclusion

Appropriate use of bone turnover markers may assist in predicting fracture risk, monitoring treatment response, and assessing compliance in patients with osteoporosis [31]. However, bone turnover markers have not been widely used in clinical settings due to poor intra-individual and inter-laboratory reproducibility. Efforts to minimize the variability of bone turnover marker tests by automating and standardizing measurements in laboratories are being made. Recently, in the Republic of Korea, bone turnover marker tests have been covered by national health insurance. Thus, bone turnover markers can be used as dynamic indicators reflecting bone quality, supplementing BMD measurements. Further research on the efficacy of BMD will be needed in the near future.

3. Evaluation of Fracture Risk and Treatment Efficacy

Key points

1. To perform an absolute assessment of fracture risk, tools like the Fracture Risk Assessment Tool (FRAX) are employed, considering various fracture risk factors. FRAX calculates the risk of major osteoporotic and hip fractures within a 10-year timeframe.
2. BMD measurements and bone turnover markers are monitored to evaluate treatment efficacy.

1) Risk factors for fracture

Based on large-scale meta-analyses, the independent risk factors for fractures in postmenopausal women are as follows [42]:

(1) Previous fracture history

(2) Low BMD

Low BMD is correlated with fracture risk at all sites, but femur BMD shows the strongest correlation [43]. The risk of hip fracture increases 2.6 times for every 10% decrease in femur neck BMD, whereas for forearm BMD, the risk increases 1.6 times for every 10% decrease.

(3) Age

Elderly women are at a higher risk of fracture than younger postmenopausal women, given the same BMD values [44].

(4) Smoking

In postmenopausal women, smoking increases the risk of fractures by approximately 30%, regardless of BMD. Some studies have suggested that this additional risk is normalized with smoking cessation [45].

(5) Excessive alcohol consumption

The risk of osteoporosis and hip fractures increases by 38% and 68%, respectively, with excessive alcohol consumption of 3 or more drinks per day.

(6) Family history of hip fractures

Parental fracture history is one of the most potent factors in predicting fracture risk.

(7) Medical history and medications

Diseases (such as thyroid diseases, type 2 diabetes, and obesity) and drugs (such as glucocorticoids, antidepressants, and proton pump inhibitors) that cause bone loss have been shown to be associated with increased fracture risk [46].

(8) Falls

Most fractures occur in relation to falls. Therefore, risk factors for falls, including a history of previous falls, visual/hearing impairments, obesity, arthritis, and a decrease in the ability to maintain balance, also serve as risk factors for fractures.

2) Assessment of fracture risk

(1) Fracture risk assessment tool

BMD values measured by DXA are good predictors of fracture risk; the risk of fracture increases by 1.6–2.6 times for every 10% decrease in BMD. However, in order to estimate the absolute risk of fracture rather than the relative risk, it is crucial to consider other major risk factors along with BMD, such as age and a history of previous fractures.

FRAX, based on a meta-analysis of large observational cohorts, incorporates eight risk factors. It is used as a tool to calculate the 10-year risk of major osteoporotic fractures (femur, proximal humerus, distal radius, symptomatic vertebral fractures) or hip fractures [47].

The bone density value used for the calculation of FRAX is limited only to femur-neck BMD, as this was the sole measure of bone density across all cohorts when FRAX was developed. Even when BMD values are unavailable, FRAX could be calculated using factors such as body mass index (BMI). Because the incidence of hip fractures has variations according to race, country-specific FRAX models have been developed and are currently available for use in 63 countries, including South Korea. In the United States, databases for four racial groups (White, Hispanic, Asian, and Black) are being used. Many countries have included FRAX in osteoporosis treatment guidelines, and FRAX is suitable for postmenopausal women with an age range of 40–90 [47].

This computer-based algorithm is available online (www.sheffield.ac.uk/FRAX/) and in standard DXA software. A 10-year risk of major osteoporotic and hip fractures could be calculated by visiting the website and entering the necessary information on the program screen (Fig. 1). According to the meta-analysis of the FRAX large observational cohort, age, gender, BMI, previous fracture history, parental hip fracture, cur-

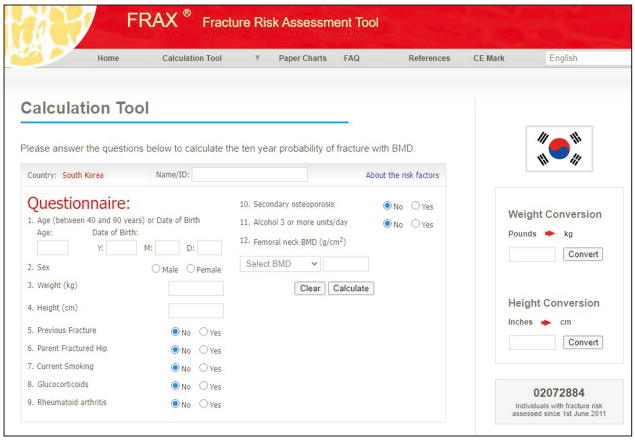

Fig. 1. FRAX, the computer-based algorithm for fracture risk assessment.

rent smoking, steroid use history, rheumatoid arthritis, secondary osteoporosis, femur neck BMD, and alcohol consumption of more than three units per day are included as independent risk factors [47].

FRAX is the most widely used tool worldwide and can enhance the sensitivity of fracture prediction without decreasing specificity by combining BMD with age and clinical risk factors. If there is a probability of 3% or more for hip fractures or 20% or more for major osteoporotic fractures occurring within 10 years, pharmacological treatment should be considered (Refer to Box 1. Case study) [48].

(2) Other risk assessment methods

Bone density can also be assessed by technologies including QUS and QCT.

Biomechanical CT is a method of quantitatively assessing the lumbar spine and hip to estimate the bone strength of an individual patient. The advantage of this method is that it is unaffected by the patient's spinal deformities or individual body size. However, the clinical utility of biomechanical CT is still limited, considering the comparative advantages of DXA over biomechanical CT.

The trabecular bone score (TBS) is a method of indirectly evaluating the distribution of bone density by analyzing two-dimensional (2D) DXA images and representing them in 3D. It correlates with the microstructure of trabecular bone and can predict fracture risk independent of BMD. It has been integrated into FRAX [49,50]. Recently, in the United States, a program that adjusts FRAX using TBS after a BMD evaluation has been commercialized. In women with a high risk of fracture, integration of TBS could be helpful. This method is useful for predicting osteoporotic fractures not only in postmenopausal women but also in men over 50.

(3) Limitations of fracture risk assessment

There are limitations to FRAX, including the possibility of underestimating fracture risk in cases of a fall history, diabetes, or patients with a low BMD only limited to the lumbar spine. Furthermore, responses for some FRAX items are dichotomized only as "yes" or "no," thus making it impossible to quantify risk factors such as dosage of glucocorticoids, number and type of previous fractures, and recent occurrence. This could limit its ability to reflect the weights of each risk factor accurately. Despite these limitations, FRAX has been validated and widely used as a predictor of fracture risk in the United States and Canada [51,52]. Until another practical and economical method to accurately measure bone strength emerges, FRAX will continue to be used as a useful tool to estimate fracture risk.

(4) Indications for BMD testing

According to guidelines from the National Osteoporosis Foundation (NOF), the North American Menopause Society (NAMS), and the American Association of Clinical Endocrinologists (AACE), all postmenopausal women at risk of low BMD are recommended to undergo BMD measurements [53]. This includes all women over 65 and younger postmenopausal women with one or more risk factors for low BMD, such as a history of fractures, family history, being underweight (international standard: 127lb [57.7 kg], and BMI < 21, Korean standard: BMI < 18.5). The US Preventive Service Task Force (USPSTF) guidelines, less commonly referred, recommend BMD testing for women over 65 or women aged 60 to 64 with a FRAX estimate of osteoporotic fracture risk of 9.3% or more (similar to the risk in 65-year-old women without other risk factors). According to the updated guidelines by the USPSTF, BMD testing is recommended for women aged 60 to 64 with low BMD results and a high fracture risk, as well as for women over 65, based on screening tools such as FRAX or the Simple Calculated Osteoporosis Risk Estimation (SCORE) [54].

3) Evaluating treatment response

For postmenopausal women who are receiving osteoporosis treatment due to low BMD and high fracture risk, it is recommended to measure the BMD of the spine and femur every 1–3 years to evaluate the response to treatment [55]. For bone turnover markers, serum CTX, a bone resorption marker, and P1NP, a bone formation marker, could be used to assess the response to treatment [33]. The efficacy of drug treatment for osteoporosis patients ultimately depends on demonstrating a reduction in fracture risk, with a typical treatment reducing the risk of spinal fractures by 30%–70%, femoral fractures by 40%–50%, and nonvertebral fractures by 15%–20%. However, assessing fractures can be challenging due to their low occurrence rate, extended time to occurrence, and susceptibility to multiple influencing factors.

The Committee of Scientific Advisors of the IOF has suggested that treatment responses could be evaluated

using fractures, changes in BMD, and bone turnover markers. Although the evidence is limited, it could be considered a treatment failure if two or more fractures occur during treatment, bone turnover markers are not suppressed, or BMD continues to decrease [32].

When evaluating treatment response and selecting non-responsive groups, it is essential to consider whether the patient is adhering to the medication regimen, taking appropriate doses of calcium and vitamin D, not experiencing gastrointestinal absorption disorders, or having an underlying condition contributing to secondary osteoporosis.

(1) Fractures

In clinical trials, secondary or tertiary fractures were shown to decrease significantly by 80%–90% compared to the placebo treatment group [32]. Osteoporosis treatment may reduce the risk of fractures but cannot completely eliminate the possibility of occurrence. Hence, a new fracture doesn't necessarily imply a lack of response to treatment. Thus, the patient is considered non-responsive to treatment if two or more fractures occur [32]. Even if a single fragility fracture occurs, a decrease in BMD and an increase in bone turnover markers may lead to the case being classified as non-responsive. Moreover, fragility fractures occurring within the first 6 months of treatment should not be regarded as a treatment failure. Not all fracture sites are associated with osteoporosis; fractures of the skull, hands, fingers, feet, and ankles are not considered fragility fractures [32].

(2) Bone mineral density

Osteoporosis is characterized by progressive bone loss, and BMD is used as a predictor of fracture risk. However, the decrease in femoral neck BMD in postmenopausal women with osteoporosis who are not receiving treatment is generally 1%–2%, nearly the same as the precision error of BMD measurement at this site. BMD measured using Central DXA should be compared in g/cm^2, not T-scores. To evaluate whether the change in BMD during treatment exceeds the error range of the measuring device in actual clinical settings, it is necessary to calculate the LSC for the measurement site, which can be checked on the ISCD website (www.iscd.org). A minimum confidence level of 95% is required when inferring changes in BMD during follow-up examinations, and a decrease in BMD greater than the LSC at 95% confidence can be considered an indicator of non-response to treatment.

Different standards for defining non-responders using BMD apply across societies. Generally, a patient could be classified as non-responsive if there is a difference greater than the LSC in at least two consecutive BMD measurements (roughly 2% or more) or if an overall decrease in BMD of 5% in the spine and 4% or more in the femur is observed.

(3) Bone turnover markers

Generally, it was predicted that the fracture risk would be reduced to a greater degree if the bone turnover markers decreased further after treatment with antiresorptive drug therapy. Several clinical studies have shown a strong correlation between the change in P1NP levels after 1 month and 3 months of using the anabolic drug and the increase in spine BMD after 12 and 18 months [33].

When evaluating bone turnover markers, it is important to consider secondary causes of osteoporosis. For example, bone resorption markers and bone formation markers appear to be lower in diabetic patients. They can fluctuate in patients with chronic kidney disease and endocrine disorders, which may lead to secondary osteoporosis [46]. CTX levels may be high in adult patients with congenital hypophosphatemia who need long-term phosphate supplementation. Moreover, OC titers could be high in postmenopausal women deficient in vitamin D.

Among various bone turnover marker tests, serum CTX and P1NP are predicted to be more accurate in reflecting the remodeling speed of bones. When monitoring adherence and drug response, they can be measured at baseline, 3 months, 6 months, and 12 months after treatment begins. In the case of using an antiresorptive agent, CTX can be measured 3–6 months after the start of treatment. In the case of bone-forming agents, P1NP can be evaluated 1–3 months after treatment to monitor adherence and drug response. When CTX or P1NP are applied clinically, the clinical characteristics are listed in the table below (Table 2) [33].

The treatment response for these markers is considered significant if they decrease by more than 25% compared to baseline in antiresorptive drug treatment or increase by more than 25% in anabolic drug treatment, such as PTH. The IOF-IFCC (International Federation of Clinical Chemistry and Laboratory Medicine) also deems it significant if P1NP decreases by more than 38% and CTX decreases by more than 56%

Table 2. Clinical characteristics of serum CTX and P1NP in short-term monitoring of osteoporosis treatment

	CTX	P1NP
Drugs for monitoring response	Anti-resorptive drug	Anti-resorptive drug Anabolic drug
Monitoring Frequency (follow-up intervals)	• Baseline • 3–6 months after 1st treatment • 12 (or 6) months follow-up	• Baseline • 3–6 months after 1st treatment • 12 (or 6) months follow-up
Threshold for efficacy	• > 30% or 100 ng/L	• > 20% or 10 μg/L
Possible interfering factors	• Diurnal variations • Food intake • Diabetes • Renal failure	• Diurnal variation • Minimal variation caused by food intake • Renal failure

CTX: C-terminal telopeptide of collagen type 1, P1NP: procollagen type I N-terminal propeptide.

3 months after treatment. If the baseline levels of bone turnover markers are not available, it can be interpreted as a response to treatment if it decreases below the median of young, healthy premenopausal adult women. The median P1NP of premenopausal women is roughly 30–40 ng/mL, and the median CTX is 0.22–0.30 ng/mL, although variations depending on studies exist. The median P1NP of premenopausal Korean women is roughly measured as 35–42 ng/mL, and for CTX, it is 0.279–0.573 ng/mL.

(4) Clinical evaluation of treatment response

If adherence does not improve further and the response criteria are not met within 1 year after starting treatment, it is recommended to consider changing treatment in the following situations [56].

① When two or more fragility fractures occur,

② When a single fracture is accompanied by an increase in CTX or P1NP or no significant reduction of either two markers,

When a single fracture is accompanied by a significant decrease in BMD,

When a single fracture is accompanied by a significant increase in bone turnover markers and a decrease in BMD,

③ When CTX and P1NP do not decrease significantly while BMD decreases significantly.

There is ongoing research regarding the effects of different treatment modalities in various routes of administration. Oral medications can be replaced with injectable drugs or switched to stronger anti-resorptive or anabolic agents. Combination therapy could be considered as well.

III. LIFESTYLE MODIFICATION FOR BONE HEALTH: EXERCISE AND NUTRITION

1. Calcium and Vitamin D

Key points

1. The best route of calcium intake in postmenopausal women is through a calcium-rich diet. Calcium supplements are secondary to a healthy diet when consumption is deemed insufficient.
2. Vitamin D deficiency in postmenopausal women is diagnosed by testing the blood concentration of 25-hydroxyvitamin D, and vitamin D intake is recommended at 800 IU/day to maintain bone health and general health.

Calcium and vitamin D supplements are commonly recommended to postmenopausal women for the prevention and treatment of osteoporosis. However, recent research results suggest that high-dose calcium supplement intake can cause cardiovascular disease. Further studies on the efficacy of vitamin D have also highlighted the need to revisit the importance of appropriate daily intake.

1) Calcium

Adequate calcium intake is essential for maintaining bone health and preventing osteoporosis regardless of age. Calcium is abundant in dairy products, fish, and green vegetables. If calcium intake is insufficient with a regular diet, calcium supplements may be considered. The 2021 NAMS (position statement) recommended that all postmenopausal women should have a balanced diet containing calcium and vitamin D, maintain overall health, including bone health, by quitting

unhealthy substances such as cigarettes, and exercise regularly, regardless of their BMD, clinical risk factors, or fracture risk [42]. Nonetheless, lifestyle changes are insufficient to inhibit BMD reduction in women who undergo premature menopause, nor can they enhance BMD or offer a satisfactory therapeutic substitute for postmenopausal women suffering from osteoporosis. Therefore, calcium supplementation is recommended for postmenopausal women as a strategy for the prevention and management of osteoporosis and bone fractures [57]. The Institute of Medicine (IOM) in the United States stated that the recommended daily allowance (RDA) of calcium needed to maintain bone health, including overall health, is 1,000 mg for adults aged 19–50 and 1,200 mg for women over 51.

In South Korea, calcium is one of the least consumed nutrients. According to the National Health and Nutrition Survey, the average daily calcium intake for individuals over 1-year-old was 68.4% of the recommended amount, which continues to decrease with age. Specifically, the daily calcium intake for women between 50 and 64 is 486.5 mg (60.8%), and for those aged 65 and above, it is 392.0 mg (49.0%). This is relatively low compared to the average daily calcium intake in the United States and Canada, which is between 700 and 800 mg. Patients with malabsorption or calcium metabolism disorders, such as hyperparathyroidism, require a greater amount of calcium and vitamin D supplementation.

However, recent studies have found that a high intake of calcium supplements may contribute to the calcification of blood vessels, leading to myocardial infarction and increasing the risk of kidney stones and colon polyps [58]. This has sparked ongoing discussions about whether it is really beneficial to supplement with calcium and what the appropriate intake amount should be. According to a meta-analysis by the NOF, calcium intake reduced the risk of all fractures by 15% and the risk of hip fractures by 30%. However, other studies did not reach a consensus on the efficacy of calcium in preventing fractures [59,60]. A meta-analysis of the effects of calcium intake on cardiovascular disease found that long-term prescription of calcium supplements increased the risk of myocardial infarction by 31% compared to the control group, and prescribing high-dose calcium supplements of 1,200 mg or more increased the cardiovascular risk by 5%, with an additional 10% increase for dosages above 1,400 mg. However, contrary to these findings, another study found that a group consuming 700 mg of calcium daily had a higher incidence of cardiovascular disease than a group consuming 1,400 mg. The study concluded that there was no consensus on the impact of the duration and amount of calcium intake on cardiovascular disease. According to a prospective longitudinal cohort in Sweden, a total daily calcium intake exceeding 1,500 mg, including dietary calcium, increased the all-cause mortality rate (hazard ratio, 1.4; 95% confidence interval, 1.17–1.67) [61]. However, another study found that a group of 9,000 postmenopausal women who were given 500–1,000 mg of calcium over a 10-year period showed a statistically significant increase in survival rate compared to a non-supplementation group, but there was no change in mortality among those who took more than 1,000 mg of calcium compared to those who did not.

In many research findings, there is no consensus on the additional health benefits of calcium intake, such as its impact on cardiovascular diseases and overall mortality, beyond its effects on bone health. Due to the risk of kidney stones, calcium supplements should not be recommended indiscriminately, with vague expectations. As reported studies consistently noted, caution should be exercised when considering high-dose calcium supplementation [62]. Calcium is a threshold nutrient. BMD decreases below a certain intake level, but consuming more than the threshold provides no additional benefit. Consequently, since substantial calcium supplementation offers no clear benefit, healthy postmenopausal women and women diagnosed with osteoporosis are advised to prioritize dietary calcium intake. The AACE, the NOF, the IOM, and the Endocrine Society recommend a total daily calcium intake of 1,200 mg from food and supplements for women over 51 [62]. Before recommending calcium supplements, it is important to assess the amount of calcium that could be consumed through diet. Half of the daily required calcium intake in the United States may be fulfilled with a regular diet alone. Thus, the actual recommended dose of calcium supplements would be 600 mg. For individuals with low dietary calcium intake, the approach should not be to increase the dose of calcium supplements but to correct dietary habits first by encouraging the consumption of calcium-rich foods such as dairy and nuts. Calcium supplements should be recommended only when dietary intake is insufficient. A daily calcium intake of 600 mg or less is known to have no serious side effects, but consuming more may

lead to constipation or bloating.

There are various types of calcium supplements. Calcium carbonate, which contains 40% calcium, is inexpensive and convenient; however, it may cause constipation or gastrointestinal disorders. It should be taken with food to maximize absorption since gastric acid secretion facilitates it. Calcium citrate contains 21% calcium, is more expensive and requires more pills for the same dose as calcium carbonate. However, the absorption is not affected by stomach acid, and it causes fewer gastrointestinal disorders. Some calcium supplements are available in forms that can be chewed, which can be easier to swallow for some patients. For optimal absorption, regardless of the type of supplement, calcium should be taken in doses not exceeding 500–600 mg at a time. If more than 600 mg of calcium supplementation is needed, it should be taken in divided doses.

2) Vitamin D

Vitamin D plays a crucial role in the absorption of calcium in the intestines, bone health, muscle function, body balance, and reducing the risk of falls. Adequate levels of vitamin D can enhance the response to bisphosphonate therapy in patients with osteoporosis, increase bone density, and prevent fractures. As a result, numerous societies have recommended that adults over 50 intake daily at least 1,000 IU of vitamin D. In healthy women with an average age of 63 and a baseline serum concentration of 25-hydroxyvitamin D at 27.6 ng/mL, administering omega-3 and vitamin D at a dosage of 2,000 IU for 24 months did not raise the serum concentration above 30 ng/mL, despite the high dosage being administered [63]. This could be attributed to vitamin D being a threshold nutrient, meaning that severe deficiency can be harmful, but beyond the threshold necessary to avoid deficiency, there may be no additional benefits from further supplementation. The IOM in the United States has recommended a daily intake of 600 IU/day for vitamin D up to age 70, and 800 IU/day for those aged 71 and above [64]. These dosages are deemed necessary to maintain an appropriate blood concentration of 25-hydroxyvitamin D, at 20 ng/mL, in postmenopausal women. The potential benefits of vitamin D supplementation for bone health in healthy adults are unclear, and multiple meta-analyses have not reached a consensus regarding its effect on fracture risk [65]. While some research suggests that taking 700–800 IU of vitamin D supplements daily reduce femoral fractures by 26% and non-vertebral fractures by 23% [38], others indicate that taking high doses of vitamin D, such as 500,000 IU annually (approximately 1,370 IU/day), increases the risk of fractures by 26% and the risk of falls by 16% [66]. These findings have prompted a paradigm shift in recommended daily intake. In 2021, the USPSTF raised issues when they released guidelines against the routine use of calcium and vitamin D supplements to prevent fractures in community-dwelling adults without a history of osteoporosis or fractures, and who do not have a vitamin D deficiency [67]. According to a meta-analysis of 11 systematic clinical trials involving 51,419 community-dwelling adults without prior history of vitamin D deficiency, osteoporosis, or fractures, vitamin D supplementation in isolation did not significantly alter the risk of hip fractures [59]. Combined supplementation of vitamin D and calcium also showed no effect on vertebral and hip fractures but increased the risk of kidney stones. The beneficial effects of vitamin D on fractures were primarily observed in older adults with vitamin D deficiency or those in care facilities. Consequently, the USPSTF concluded that there is insufficient evidence to evaluate the benefits and harms of supplementing postmenopausal women residing in communities with 400 IU of vitamin D or more than 1,000 mg of calcium, or monitoring and supplementing vitamin D deficiencies through blood tests for the primary prevention of fractures [67]. Similarly, the Endocrine Society in the US also stated that there is a lack of sufficient evidence for screening serum vitamin D levels in adults without a risk of deficiency.

In conclusion, although calcium and vitamin D supplementation appears to have no preventive effect on osteoporotic fractures in healthy adults without risk of fractures, a daily intake of 800 IU of vitamin D is recommended to maintain bone health [68,69]. While the conventional practice has been to co-administer calcium and vitamin D with medications for osteoporosis in women with the condition to enhance their effect, there is insufficient evidence to support this. Thus, it is advised not to take large amounts of vitamin D and calcium routinely and to stay within recommended doses [70]. Vitamin D can be synthesized in the skin through sunlight exposure, or it could be obtained from food sources such as fatty fish like mackerel, tuna, salmon, egg yolks, and cheese.

2. Other Dietary Management and Exercise

In dietary management for the prevention of osteo-

porosis, it is crucial to consume appropriate levels of calcium and vitamin D, or use supplements if there is a deficiency. This section will explore other dietary management strategies and exercises for the prevention of osteoporosis, excluding calcium and vitamin D. It is generally recommended to maintain an appropriate weight as low body weight is a risk factor for osteoporosis and fractures.

Key points

1. Consume a low-salt diet with sufficient protein intake, avoiding excess beyond recommended levels.
2. Adequately consume soy and tofu, which are rich in magnesium and plant estrogens.
3. Ensure ample intake of fresh vegetables and fruits for vitamins such as vitamins C, K, and minerals like potassium and magnesium.
4. Maintain a healthy weight, avoiding excessive weight loss.
5. Limit the intake of carbonated drinks and coffee. Opt for tea (green or black) when a caffeinated beverage is required.
6. Avoid smoking and limit alcohol consumption to 1–2 drinks, if possible.

1) Other dietary management

Bones are composed of both inorganic and organic components, and in the deposition, maintenance, and repair of bone tissue, minerals such as calcium and vitamin D, as well as inorganic minerals like vitamin C, K, phosphorus, magnesium, zinc, play important roles.

Among various etiologies of osteoporosis, nutrition not only influences bone mass and quality but also the occurrence and healing of fractures. Bone mass is determined by genetic factors, but adequate nutrition during adolescence, which is the period for acquiring maximum bone mass, especially through the intake of calcium, vitamin D, and protein, plays a crucial role in maintaining high bone density throughout life. An increase of 10% in maximum bone mass can reduce the risk of fracture by 50%. After achieving maximum bone density, the absorption of bone exceeds deposition, which in turn leads to bone demineralization. The extent and speed of this process are influenced by the intake of calcium, vitamin D, fluoride, magnesium, zinc, and vitamin K. Furthermore, adequate muscle or fat around the hip can cushion the bone during falls, enabling faster recovery after a fracture. Therefore, sufficient nutrient intake affects not only fracture prevention but also recovery [71].

(1) Protein

Protein, along with calcium, forms the fundamental structure of bones. It accounts for half of the total bone volume and a third of its weight. Protein intake, when sufficient, determines about 2%–4% of adult bone density [72]. Therefore, adequate protein intake is essential for bone health. In elderly patients with osteoporosis, a daily protein intake of more than 0.8 g per kg of body weight increases BMD, slows bone loss, and reduces the risk of hip fracture [73]. However, recent studies suggest that this amount may be insufficient, and Korean research also advocates for an intake of not less than 0.9 g [11]. Adequate protein supplementation after a hip fracture has been reported to shorten the hospital stay and aid functional recovery [74-76]. In patients with chronic kidney disease, a high-protein diet can affect kidney function; therefore, the American National Kidney Foundation limits protein intake to approximately 0.6–0.75 g per kg of body weight per day for non-dialysis patients with chronic kidney disease.

Excessive protein intake (> 2 g/kg) can increase calcium excretion in the kidneys, thus underlining the importance of appropriate protein intake [73]. This is especially significant when the daily calcium intake is below 600 mg.

(2) Magnesium

Approximately 60%–70% of magnesium is present in the skeleton or teeth, where it combines with calcium and phosphorus, altering the surface characteristics of calcium and phosphorus. Magnesium also plays a crucial role in facilitating intestinal calcium absorption [77]. Rich sources of magnesium include green leafy vegetables, legumes, nuts, and less refined grains due to its role as a component of chlorophyll. While the necessity of magnesium supplementation has been questioned, no randomized studies have yet confirmed its influence on fracture risk or BMD. Adequate amounts of magnesium could be found in a regular diet [38]. However, magnesium supplementation could be beneficial in the circumstances suspected of magnesium deficiency, for instance, malabsorption, chronic liver diseases, alcohol consumption, loss through kidneys, and long-term use of proton-pump inhibitors or diuretics. Magnesium can also be helpful in relieving

constipation caused by calcium intake.

(3) Sodium

Consuming salt increases calcium excretion in the kidneys. In menopausal Korean women, higher sodium intake was associated with lower femoral BMD and increased osteoporosis risk. The Korean Dietary Reference Intakes recommends a sodium intake of less than 2,000 mg (5 g of salt), yet the national health and nutrition survey shows actual intake exceeding 3,200 mg [78].

(4) Phosphorus

Phosphorus, combined with calcium, is essential for bone and teeth formation. Phosphorus deficiency may lead to osteomalacia, bone pain, and muscle weakness. However, it is contained in various types of foods, making deficiency rare among those who maintain a regular diet. The optimal phosphorus intake ratio to calcium is 1:1, yet the KNHANES indicates a 2:1 ratio [79]. Excessive phosphorus intake can negatively affect calcium metabolism; thus, there is a need to limit the consumption of high-phosphorus beverages such as carbonated soda [80].

(5) Vitamin A, K, phytoestrogen, omega-3

Vitamin A plays a role in the differentiation of osteoblasts and osteoclasts; thus, deficiency may impair bone formation. However, chronic consumption of large amounts of vitamin A (over 10,000 IU per day) can negatively impact bone health and should be avoided [38].

Vitamin C is essential for collagen synthesis, osteoblast stimulation, and calcium absorption. It is advisable to meet the Korean Dietary Reference Intakes' recommendation of 100 mg and not to exceed the upper intake level of 2,000 mg [81].

Vitamin K is required for the synthesis of osteocytes, calcium attachment to the bone matrix, and fracture healing. There are reports suggesting that supplementing about 1 mg of vitamin K per day can reduce bone turnover and increase bone loss in postmenopausal women [38]. However, further research is needed in order to confirm these benefits and consider their inclusion in the standard recommendations for the prevention of osteoporosis. Vitamin K stimulates the synthesis of OC, and the deficiency caused by coumarin anticoagulant therapy can impact OC, potentially harming bone health [82].

Vitamin A is found in animal products such as liver and egg yolk, while vitamins C and K are abundant in plant-based foods such as green vegetables and fruits. Bacteria in the colon also synthesize vitamin K, and they are absorbed via the intestines. This implies a relationship between intestinal health and the nutritional status of vitamins.

A diet rich in isoflavones, also called "phytoestrogens," which act on estrogen receptors, has been reported to prevent bone loss and reduce fracture risk [83]. However, the overall evidence supporting the benefit of isoflavone supplementation in enhancing BMD or reducing fracture risk remains inconclusive [38].

Omega-3 fatty acids, abundant in fish and seafood, positively affect bone density. They can promote calcium absorption in the duodenum by regulating ATPase. A study of postmenopausal Korean women showed a positive correlation between blood levels of omega-3 fatty acids and BMD. Yet, there are insufficient data to confirm the benefits of omega-3 supplementation for bone health.

(6) Other trace elements

In addition to calcium, trace elements such as zinc, copper, and manganese are also required for bone formation. For zinc, about 2–3 g is present in our body; about 28% is distributed in the bones and teeth. With advancing age, the concentration of zinc in urine elevates, a process that is further intensified in the presence of osteoporosis and decreased upon the administration of estrogen in postmenopausal women. Zinc is abundant in animal-derived food sources such as red meat and oysters.

(7) Caffeine

Caffeine consumption may reduce intestinal calcium absorption and increase excretion through urine. Drinking more than four standard cups (1 standard cup = 240 mL) per day could decrease BMD, but moderate consumption does not seem to be associated with osteoporosis. Therefore, limiting caffeine intake to 1–2 cups per day or switching to decaffeinated options is recommended [84]. Although tea, including black and green, contains caffeine, it also contains fluoride, plant estrogen, and manganese; thus, limiting the intake is unnecessary. One report stated that consuming tea for over 10 years, regardless of the type, has increased BMD [85].

(8) Alcohol

Excessive alcohol intake increases the risk of fractures. This is primarily due to its negative impact on bone formation. In most studies, OC, a bone formation marker, increases when alcohol consumption is ceased. Moreover, alcohol consumption increases the risk of falls, exacerbates calcium deficiency, and may elevate the risk of liver disease and subsequent vitamin D deficiency due to chronic liver disease [86]. Therefore, it is recommended that postmenopausal women who are at high risk for osteoporosis limit their daily alcohol intake to no more than two drinks. Here, one drink is defined as 120 mL of wine, 30 mL of spirits, or 260 mL of beer [87].

(9) Smoking

Numerous studies have established an increased risk of osteoporotic fractures associated with smoking [38]. The precise mechanism remains uncertain but could be due to reduced calcium absorption in the gut, increased metabolism of endogenous estrogen, or the direct impact of cadmium on bone metabolism [86]. Although no prospective studies confirm that quitting smoking reduces fracture risk, some meta-analyses reported a higher fracture risk in current smokers compared to those who have quit. Therefore, all smokers should receive cessation counseling. The use of alternative tobacco products is also detrimental to overall health and bone integrity.

2) Exercise strategies for the prevention of osteoporosis

Key points

1. Weight-bearing and strength-training exercises should be incorporated into daily routines.
2. High-intensity aerobic exercise is more effective than low-intensity exercises such as walking.
3. Patients with severe osteoporosis should avoid exercises that require sit-ups, excessive spinal flexion, or heavy weightlifting.
4. For osteoporotic patients, safety should be prioritized over efficiency during exercise.
5. Exercise prevents fractures from falls. Exercises aimed at maintaining balance and preventing falls are as important as using osteoporotic drugs to prevent fractures.

(1) Exercise and bone

Numerous studies on exercise and bone health exhibit a range of results, yet they all conclude that exercise can, to some extent, affect BMD. According to a meta-analysis of 16 studies, exercise has been reported to increase lumbar BMD by about 2%. The mechanical stress applied during exercise imposes tension on the bone, triggers morphological changes, provokes localized bone responses, suppresses bone resorption, and promotes bone formation. Exercise also stimulates the secretion of growth hormones. Moreover, metabolic acidosis induced by exercise is reported to stimulate bone remodeling. In addition to the direct load on the bone, strengthening muscles through exercise can also increase bone density [86]. The effect of commencing and continuing exercise before adolescence on bone density and volume is significant, approximately 1%–6%, much higher than the 0.3%–2% effect of exercise after adolescence. Therefore, high-intensity sports such as gymnastics, badminton, tennis, volleyball, and basketball can be beneficial, providing tension in bones during adolescence.

Whether exercise can increase bone strength remains uncertain, mainly because methods for measuring and predicting bone strength are not as well established as those for bone density. Though evidence is scarce, exercise has been reported to cause a small but significant increase in the strength of bones in the lower extremities in young adults who have not reached peak height. Interestingly, this effect was not observed in women of the same age. Once growth is complete, exercise does not significantly impact bone strength in either sex.

Muscle weight is a critical factor in determining bone mass. Both muscle weight and bone mass decline with age. Bone mass is closely related to exercise and strength training. In elderly individuals, increasing muscle mass through strength training can reduce the rate of bone loss.

(2) Exercise and decreased fracture rate

Published studies investigating the incidence of fractures indicate that exercise reduces fracture risk, as it helps maintain adequate muscle strength and aids in maintaining walking speed and posture control, thereby preventing falls [88]. However, it has also been reported that the group that exercised only showed a reduction in fractures by about 4%, which was not statistically significant. The UK National Osteoporosis Guideline Group (2017) summarized that weight-bearing exercise

benefits BMD but doesn't reduce actual fracture risk [74]. Nevertheless, it concluded that periodic weight-bearing exercises should be recommended, tailored to meet each individual's needs [74].

There is a need for careful consideration and counseling about the potential drawbacks of exercise, as excessive encouragement may increase the risk of falls in elderly patients. Moreover, excessive exercise may be associated with joint pain, back pain, or headaches, which in turn results in reduced activity and muscle loss.

(3) Practical exercise for osteoporosis

So, what is the ideal exercise for osteoporosis prevention? It's challenging to present a standardized program, but weight-bearing and strengthening exercises should be in the mainstream of exercise. Weight-bearing exercises include activities such as running, walking, jogging, Tai Chi, stair climbing, dancing, tennis, etc. Exercise that applies a strong weight-bearing load on targeted areas of bone is reported to stimulate bone formation more effectively than applying a constant but tolerable load throughout the body. The intensity of weight-bearing exercise should be safely adjusted, considering each individual's cardiovascular endurance and joint function. The intensity, once adjusted, should be gradually increased [4].

Strength exercises are beneficial for BMD in both pre- and post-menopausal women. Progressive resistance strength training performed under non-weight-bearing conditions significantly reduced postmenopausal femoral neck BMD loss and decreased total hip bone density loss by about 1%. Strength exercises include equipment-based exercises (dumbbells, weights, etc., most equipment in fitness clubs) and body-weight exercises (push-ups, squats, etc.), as well as yoga and Pilates. Strength exercises should begin within a safe range and gradually increase in intensity. The same action should be repeated 8–20 times, followed by a 1–2 minutes break, then another 8–20 repetitions. After 10–18 weeks of strength training, muscle strength increases by about 20%, but when exercise is discontinued, 70% of the gained strength is lost after 12 weeks [5].

High-intensity aerobic exercise is more effective than low-intensity exercises such as walking. A year of persistent low-intensity weight-bearing exercise, like walking three to 5 times a week, has been reported to have minimal effect on BMD in postmenopausal women [89]. Some studies even indicate that walking alone has no significant impact on BMD [90]. Higher BMD increases have been reported for moderate to high-intensity aerobic exercises (climbing stairs, brisk walking, weighted walking, running) sustained over 1–2 years than for low-intensity exercises like simple walking.

Combining two or more exercises is more effective for increasing BMD than individual exercises. According to a meta-analysis, in postmenopausal women, a combination of resistance exercises (a method of combining resistance exercises with high-impact or weight-bearing exercises) significantly increased lumbar and femoral BMD more than resistance exercises alone [90]. Furthermore, a combination of aerobic and anaerobic exercises is reported to be the most effective approach to prevent spine BMD.

Combining exercise with calcium or hormone replacement therapy in women enhances BMD to a greater degree than exercise therapy alone. The overall benefit of exercise on BMD appears to be around 0%–2%. Considering that about 1% of bone loss occurs annually in a non-exercising control group, this effect can be considered substantial [89]. However, if exercise is not sustained, its effect diminishes. While exercise can maintain bone mass or alleviate bone loss, it cannot replace bone resorption inhibitors.

(4) Precautions and exercises to avoid

Patients with severe osteoporosis should avoid exercises that require sit-ups, excessive spinal flexion, heavy weightlifting, or bending the torso sideways. These movements can exert pressure on the spine, potentially leading to fractures.

Spinal fractures can occur not only from strenuous exercise but also in daily life, especially when bending forward to lift objects, which can exert pressure on the spinal bones 10–20 times higher than the normal position. A 2-year study tracking women aged 49–60 with spinal osteoporosis found that 67% of those who did not exercise experienced fractures, compared to 89% of those who performed exercises involving excessive spinal flexion.

For patients with osteoporosis, safety should take precedence over efficiency. Preparation and cool-down exercises must always be included before and after workouts. Comprehensive assessments of balance, gait, vision, orthostatic blood pressure, medication therapy, environment, cognitive function, and mental health in elderly patients should be made in advance of working out. For those with functional limitations, alternative

methods of exercise should be suggested to reduce the risk associated with such limitations.

For postmenopausal women with osteoporosis, the following precautions should be considered during exercise:

The intensity of the exercise should be gradually increased.

Safety should be prioritized, and strenuous exercises should be avoided.

Exercises that cause excessive torso bending should be avoided.

Individualized exercise protocols should be prescribed based on the patient's BMD and physical ability.

Sustainable exercise environment should be fostered with ongoing education and observation.

(5) Fall prevention

Approximately one-third of individuals aged 65 and over, and about half of those aged 80 and over, experience falls each year. Of these, 20%–30% suffer from moderate to severe injuries. While osteoporosis is a risk factor for fractures, 90% of fractures are caused by falls. The risk of femoral fractures increases 2.5 times with a decrease of 1 SD in BMD, but it increases more than five times due to falls. In particular, about 95% of hip fractures occur due to falls. In individuals aged 75 and over, the risk of fractures is solely attributed to the incidence of falls, not a decrease in BMD [89].

Exercise has a preventive effect on falls and fall-induced fractures by improving agility, balancing sense, muscle strength, and BMD. Recent studies have reported that exercise reduces incidences of fractures by reducing falls [91]. Therefore, exercise is as important as the use of osteoporosis medication for fracture prevention [92]. Exercises that enhance muscle strength, coordination, and balance, such as dancing, Tai Chi, and walking, are recommended. Long-term participation in such balance exercises is effective in preventing falls. According to a meta-analysis, these exercises not only reduce fall frequency by 10% but also lessen the severity of injuries when falls occur [93]. Tai Chi, for instance, has been reported to decrease the frequency of falls by 47% and reduce the risk of femoral fractures to a quarter [94]. Exercising using gym balls can also improve balance. It is also important to identify fall risk factors, such as aging, history of stroke, visual and muscular conditions, underlying diseases, medication use that can induce dizziness or reduced alertness, and environmental factors (for instance, furniture and electric cord placements, dim indoor lighting, slippery floors or tiles). Necessary measures should be taken accordingly [95].

3) Conclusion

Management of lifestyle factors such as calcium, protein, and vitamin D intake, physical activity, smoking cessation, moderate alcohol consumption, nutritional management, and fall prevention are crucial for osteoporosis and fracture prevention. Such lifestyle modifications are recommended, regardless of the current intake of osteoporosis drug treatments. The FRAX developed by the WHO classifies certain lifestyle-related factors as risk factors for fractures. The NOF and the IOF have included lifestyle management in their osteoporosis treatment guidelines. It is imperative to quit smoking and avoid excessive alcohol consumption, maintain a healthy weight, limit caffeine and carbonated beverages, and avoid excessive salt intake.

Exercise helps maintain BMD and reduce the risk of falls. It helps prevent fractures and shortens the recovery period post-fracture. A combination of weight-bearing and resistance exercises is recommended as long as they are performed safely. The AACE strongly advises lifelong physical activity for cardiovascular health, osteoporosis prevention, and overall health. The recommended 150 minutes of moderate aerobic exercise per week and strength exercises at least twice a week should be initiated. The duration and intensity should be gradually increased over time and maintained for over a year with the goal of integrating exercise into a healthy lifestyle.

Most risk factors for osteoporosis and fractures are related to lifestyle habits. Rather than focusing on medication, paying attention to each risk factor and making efforts to correct them through lifestyle modification can help patients prevent fractures and lead a healthier life.

ACKNOWLEDGMENTS

We express sincere appreciation to Prof. Hee Dong Chae, the former president of the Korean Society of Menopause (KSM), Prof. Mee-Ran Kim, the current president, as well as advisory committee member Prof. Weon Hoi Kim, Tak Kim, Ki Hyun Park, Jung-Gu Kim, Jin-Hong Kim, Hyoung Moo Park, Hoon Choi, Hong Gyun Lee, Byung-Koo Yoon, and Byung Seok Lee for their support on behalf of KSM.

REFERENCES

1. Kanis JA, Melton LJ 3rd, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res 1994; 9: 1137-41.
2. Osteoporosis prevention, diagnosis, and therapy. NIH Consens Statement 2000; 17: 1-45.
3. Riggs BL, Khosla S, Melton LJ 3rd. Sex steroids and the construction and conservation of the adult skeleton. Endocr Rev 2002; 23: 279-302.
4. Guideline for osteoporosis with fractures. The Korean Society of Osteoporosis, Korea Women's Health and osteoporosis foundation; 2021.
5. Physician's guide for osteoporosis. The Korean Society for Bone and Mineral Research; 2020.
6. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. World Health Organ Tech Rep Ser 1994; 843: 1-129.
7. Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 2013; 8: 136.
8. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res 2007; 22: 465-75.
9. Choi SH, Kim DY, Koo JW, Lee SG, Jeong SY, Kang CN. Incidence and management trends of osteoporotic vertebral compression fractures in South Korea: a nationwide population-based study. Asian Spine J 2020; 14: 220-8.
10. Lee YK, Yoon BH, Koo KH. Epidemiology of osteoporosis and osteoporotic fractures in South Korea. Endocrinol Metab (Seoul) 2013; 28: 90-3.
11. The Korean Society for Bone and Mineral Research (KSBMR). Osteoporosis and osteoporotic fractures fact sheet. KSBMR; 2019.
12. Siris ES, Miller PD, Barrett-Connor E, Faulkner KG, Wehren LE, Abbott TA, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. JAMA 2001; 286: 2815-22.
13. Siris ES, Chen YT, Abbott TA, Barrett-Connor E, Miller PD, Wehren LE, et al. Bone mineral density thresholds for pharmacological intervention to prevent fractures. Arch Intern Med 2004; 164: 1108-12.
14. The Korean Society of Osteoporosis. Manual of bone densitometry. The Korean Society of Osteoporosis; 2018.
15. Licata AA, Williams SE. A DXA primer for the practicing clinician: a case-based manual for understanding and interpreting bone densitometry. Springer Science & Business Media; 2013.
16. Saag KG, Morgan SL, Clines GA. Diagnosis and management of osteoporosis. Professional Communications; 2013.
17. Garnero P, Cloos P, Sornay-Rendu E, Qvist P, Delmas PD. Type I collagen racemization and isomerization and the risk of fracture in postmenopausal women: the OFELY prospective study. J Bone Miner Res 2002; 17: 826-33.
18. Park SY, Ahn SH, Yoo JI, Chung YJ, Jeon YK, Yoon BH, et al. Position statement on the use of bone turnover markers for osteoporosis treatment. J Bone Metab 2019; 26: 213-24.
19. Garnero P, Hausherr E, Chapuy MC, Marcelli C, Grandjean H, Muller C, et al. Markers of bone resorption predict hip fracture in elderly women: the EPIDOS Prospective Study. J Bone Miner Res 1996; 11: 1531-8.
20. Vergnaud P, Garnero P, Meunier PJ, Bréart G, Kamihagi K, Delmas PD. Undercarboxylated osteocalcin measured with a specific immunoassay predicts hip fracture in elderly women: the EPIDOS Study. J Clin Endocrinol Metab 1997; 82: 719-24.
21. Marques EA, Gudnason V, Lang T, Sigurdsson G, Sigurdsson S, Aspelund T, et al. Association of bone turnover markers with volumetric bone loss, periosteal apposition, and fracture risk in older men and women: the AGES-Reykjavik longitudinal study. Osteoporos Int 2016; 27: 3485-94.
22. Melton LJ 3rd, Crowson CS, O'Fallon WM, Wahner HW, Riggs BL. Relative contributions of bone density, bone turnover, and clinical risk factors to long-term fracture prediction. J Bone Miner Res 2003; 18: 312-8.
23. Naylor KE, Jacques RM, Paggiosi M, Gossiel F, Peel NF, McCloskey EV, et al. Response of bone turnover markers to three oral bisphosphonate therapies in postmenopausal osteoporosis: the TRIO study. Osteoporos Int 2016; 27: 21-31.
24. Miller PD, Pannacciulli N, Brown JP, Czerwinski E, Nedergaard BS, Bolognese MA, et al. Denosumab or zoledronic acid in postmenopausal women with osteoporosis previously treated with oral bisphosphonates. J Clin Endocrinol Metab 2016; 101: 3163-70.
25. Bone HG, Wagman RB, Brandi ML, Brown JP, Chapurlat R, Cummings SR, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. Lancet Diabetes Endocrinol 2017; 5: 513-23.
26. Lamy O, Gonzalez-Rodriguez E, Stoll D, Hans D, Aubry-Rozier B. Severe rebound-associated vertebral fractures after denosumab discontinuation: 9 clinical cases report. J Clin Endocrinol Metab 2017; 102: 354-8.
27. Finkelstein JS, Leder BZ, Burnett SM, Wyland JJ, Lee H, de la Paz AV, et al. Effects of teriparatide, alendronate, or both on bone turnover in osteoporotic men. J Clin Endocrinol Metab 2006; 91: 2882-7.
28. Glover SJ, Eastell R, McCloskey EV, Rogers A, Garnero P, Lowery

J, et al. Rapid and robust response of biochemical markers of bone formation to teriparatide therapy. Bone 2009; 45: 1053-8.
29. Eastell R, Krege JH, Chen P, Glass EV, Reginster JY. Development of an algorithm for using PINP to monitor treatment of patients with teriparatide. Curr Med Res Opin 2006; 22: 61-6.
30. McClung MR, Grauer A, Boonen S, Bolognese MA, Brown JP, Diez-Perez A, et al. Romosozumab in postmenopausal women with low bone mineral density. N Engl J Med 2014; 370: 412-20.
31. Delmas PD, Vrijens B, Eastell R, Roux C, Pols HA, Ringe JD, et al. Effect of monitoring bone turnover markers on persistence with risedronate treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab 2007; 92: 1296-304. Erratum in: J Clin Endocrinol Metab 2007; 92: 2285.
32. Diez-Perez A, Adachi JD, Agnusdei D, Bilezikian JP, Compston JE, Cummings SR, et al. Treatment failure in osteoporosis. Osteoporos Int 2012; 23: 2769-74.
33. Wu CH, Chang YF, Chen CH, Lewiecki EM, Wüster C, Reid I, et al. Consensus statement on the use of bone turnover markers for short-term monitoring of osteoporosis treatment in the Asia-Pacific region. J Clin Densitom 2021; 24: 3-13.
34. Iizuka Y, Iizuka H, Kaneko T, Mieda T, Takechi R, Suzuki H, et al. Bone turnover markers and the factors associated with atypical femur fractures among Japanese patients. Injury 2016; 47: 2484-9.
35. Bonnick SL, Shulman L. Monitoring osteoporosis therapy: bone mineral density, bone turnover markers, or both? Am J Med 2006; 119(4 Suppl 1): S25-31.
36. Wasnich RD, Miller PD. Antifracture efficacy of antiresorptive agents are related to changes in bone density. J Clin Endocrinol Metab 2000; 85: 231-6.
37. Cummings SR, Karpf DB, Harris F, Genant HK, Ensrud K, LaCroix AZ, et al. Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. Am J Med 2002; 112: 281-9.
38. Camacho PM, Petak SM, Binkley N, Diab DL, Eldeiry LS, Farooki A, et al. American Association of Clinical Endocrinologists/American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update. Endocr Pract 2020; 26(Suppl 1): 1-46.
39. McClung M, Harris ST, Miller PD, Bauer DC, Davison KS, Dian L, et al. Bisphosphonate therapy for osteoporosis: benefits, risks, and drug holiday. Am J Med 2013; 126: 13-20.
40. Lee CY, Suzuki JB. CTX biochemical marker of bone metabolism. Is it a reliable predictor of bisphosphonate-associated osteonecrosis of the jaws after surgery? Part I: biological concepts with a review of the literature. Implant Dent 2009; 18: 492-500.
41. Lee CY, Suzuki JB. CTX biochemical marker of bone metabolism. Is it a reliable predictor of bisphosphonate-associated osteonecrosis of the jaws after surgery? Part II: a prospective clinical study. Implant Dent 2010; 19: 29-38.
42. Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society. Menopause 2021; 28: 973-97.
43. Cummings SR, Black DM, Nevitt MC, Browner W, Cauley J, Ensrud K, et al. Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. Lancet 1993; 341: 72-5.
44. Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. Osteoporos Int 2001; 12: 989-95.
45. Kanis JA, Borgstrom F, De Laet C, Johansson H, Johnell O, Jonsson B, et al. Assessment of fracture risk. Osteoporos Int 2005; 16: 581-9.
46. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes--a meta-analysis. Osteoporos Int 2007; 18: 427-44.
47. Kanis JA, McCloskey EV, Johansson H, Oden A, Ström O, Borgström F. Development and use of FRAX in osteoporosis. Osteoporos Int 2010; 21 Suppl 2: S407-13.
48. Watts NB, Lewiecki EM, Miller PD, Baim S. National Osteoporosis Foundation 2008 Clinician's Guide to Prevention and Treatment of Osteoporosis and the World Health Organization Fracture Risk Assessment Tool (FRAX): what they mean to the bone densitometrist and bone technologist. J Clin Densitom 2008; 11: 473-7.
49. Nassar K, Paternotte S, Kolta S, Fechtenbaum J, Roux C, Briot K. Added value of trabecular bone score over bone mineral density for identification of vertebral fractures in patients with areal bone mineral density in the non-osteoporotic range. Osteoporos Int 2014; 25: 243-9.
50. McCloskey EV, Odén A, Harvey NC, Leslie WD, Hans D, Johansson H, et al. Adjusting fracture probability by trabecular bone score. Calcif Tissue Int 2015; 96: 500-9.
51. Leslie WD, Berger C, Langsetmo L, Lix LM, Adachi JD, Hanley DA, et al. Construction and validation of a simplified fracture risk assessment tool for Canadian women and men: results from the CaMos and Manitoba cohorts. Osteoporos Int 2011; 22: 1873-83.
52. Papaioannou A, Morin S, Cheung AM, Atkinson S, Brown JP, Feldman S, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ 2010; 182: 1864-73.
53. The North American Menopause Society. Menopause practice: a clinician's guide. 6th ed. The North American Menopause Society; 2019.
54. U.S. Preventive Services Task Force. Screening for osteoporosis: U.S. preventive services task force recommendation statement. Ann Intern Med 2011; 154: 356-64.
55. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society* clinical practice guideline. J

Clin Endocrinol Metab 2019; 104: 1595-622.
56. Kanis JA, Johansson H, Odén A, Harvey NC, Gudnason V, Sanders KM, et al. Characteristics of recurrent fractures. Osteoporos Int 2018; 29: 1747-57.
57. Chlebowski RT, Johnson KC, Kooperberg C, Pettinger M, Wactawski-Wende J, Rohan T, et al. Calcium plus vitamin D supplementation and the risk of breast cancer. J Natl Cancer Inst 2008; 100: 1581-91.
58. Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, O'Sullivan MJ, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med 2006; 354: 684-96. Erratum in: N Engl J Med 2006; 354: 1102.
59. Kahwati LC, Weber RP, Pan H, Gourlay M, LeBlanc E, Coker-Schwimmer M, et al. Vitamin D, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults: evidence report and systematic review for the US preventive services task force. JAMA 2018; 319: 1600-12.
60. Viswanathan M, Reddy S, Berkman N, Cullen K, Middleton JC, Nicholson WK, et al. Screening to prevent osteoporotic fractures: updated evidence report and systematic review for the US preventive services task force. JAMA 2018; 319: 2532-51.
61. Michaëlsson K, Melhus H, Warensjö Lemming E, Wolk A, Byberg L. Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study. BMJ 2013; 346: f228.
62. Osteoporosis prevention, screening, and diagnosis: ACOG clinical practice guideline no. 1. Obstet Gynecol 2021; 138: 494-506.
63. Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. N Engl J Med 2019; 380: 33-44.
64. Rabenberg M, Scheidt-Nave C, Busch MA, Thamm M, Rieckmann N, Durazo-Arvizu RA, et al. Implications of standardization of serum 25-hydroxyvitamin D data for the evaluation of vitamin D status in Germany, including a temporal analysis. BMC Public Health 2018; 18: 845.
65. Guirguis-Blake JM, Michael YL, Perdue LA, Coppola EL, Beil TL. Interventions to prevent falls in older adults: updated evidence report and systematic review for the US preventive services task force. JAMA 2018; 319: 1705-16.
66. LeBoff MS, Murata EM, Cook NR, Cawthon P, Chou SH, Kotler G, et al. VITamin D and OmegA-3 TriaL (VITAL): effects of vitamin D supplements on risk of falls in the US population. J Clin Endocrinol Metab 2020; 105: 2929-38.
67. Krist AH, Davidson KW, Mangione CM, Cabana M, Caughey AB, Davis EM, et al. Screening for vitamin D deficiency in adults: US preventive services task force recommendation statement. JAMA 2021; 325: 1436-42.
68. Sempos CT, Vesper HW, Phinney KW, Thienpont LM, Coates PM. Vitamin D status as an international issue: national surveys and the problem of standardization. Scand J Clin Lab Invest Suppl 2012; 243: 32-40.
69. Binkley N, Sempos CT; Vitamin D Standardization Program (VDSP). Standardizing vitamin D assays: the way forward. J Bone Miner Res 2014; 29: 1709-14.
70. Scragg R, Khaw KT, Toop L, Sluyter J, Lawes CMM, Waayer D, et al. Monthly high-dose vitamin D supplementation and cancer risk: a post hoc analysis of the vitamin D assessment randomized clinical trial. JAMA Oncol 2018; 4: e182178.
71. The Korean Society for Bone and Mineral Research (KSBMR). Textbook of osteoporosis. 5th ed. KSBMR; 2016.
72. Rizzoli R, Biver E, Bonjour JP, Coxam V, Goltzman D, Kanis JA, et al. Benefits and safety of dietary protein for bone health-an expert consensus paper endorsed by the European Society for Clinical and Economical Aspects of Osteopororosis, Osteoarthritis, and Musculoskeletal Diseases and by the International Osteoporosis Foundation. Osteoporos Int 2018; 29: 1933-48.
73. Bonjour JP. Protein intake and bone health. Int J Vitam Nutr Res 2011; 81: 134-42.
74. Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, et al. UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos 2017; 12: 43.
75. Heaney RP, Layman DK. Amount and type of protein influences bone health. Am J Clin Nutr 2008; 87: 1567S-70S.
76. Myint MW, Wu J, Wong E, Chan SP, To TS, Chau MW, et al. Clinical benefits of oral nutritional supplementation for elderly hip fracture patients: a single blind randomised controlled trial. Age Ageing 2013; 42: 39-45.
77. Movassagh EZ, Vatanparast H. Current evidence on the association of dietary patterns and bone health: a scoping review. Adv Nutr 2017; 8: 1-16.
78. Kwon SJ, Ha YC, Park Y. High dietary sodium intake is associated with low bone mass in postmenopausal women: Korea National Health and Nutrition Examination Survey, 2008-2011. Osteoporos Int 2017; 28: 1445-52.
79. Korea Centers for Disease Control and Prevention. National health survey: The 7th Korea National Health and Nutrition Examination Survey. Korea Centers for Disease Control and Prevention; 2019.
80. Tucker KL, Morita K, Qiao N, Hannan MT, Cupples LA, Kiel DP. Colas, but not other carbonated beverages, are associated with low bone mineral density in older women: The Framingham Osteoporosis Study. Am J Clin Nutr 2006; 84: 936-42.
81. The Korean Nutrition Society. Dietary reference intakes for Koreans. Ministry of Health and Welfare; The Korean Nutrition Society; 2015.
82. Shearer MJ. Role of vitamin K and Gla proteins in the pathophysiology of osteoporosis and vascular calcification. Curr Opin Clin Nutr Metab Care 2000; 3: 433-8.

83. Lagari VS, Levis S. Phytoestrogens for menopausal bone loss and climacteric symptoms. J Steroid Biochem Mol Biol 2014; 139: 294-301.
84. Hallström H, Wolk A, Glynn A, Michaëlsson K. Coffee, tea and caffeine consumption in relation to osteoporotic fracture risk in a cohort of Swedish women. Osteoporos Int 2006; 17: 1055-64.
85. Chen Z, Pettinger MB, Ritenbaugh C, LaCroix AZ, Robbins J, Caan BJ, et al. Habitual tea consumption and risk of osteoporosis: a prospective study in the women's health initiative observational cohort. Am J Epidemiol 2003; 158: 772-81.
86. Abrahamsen B, Brask-Lindemann D, Rubin KH, Schwarz P. A review of lifestyle, smoking and other modifiable risk factors for osteoporotic fractures. Bonekey Rep 2014; 3: 574.
87. Maurel DB, Boisseau N, Benhamou CL, Jaffre C. Alcohol and bone: review of dose effects and mechanisms. Osteoporos Int 2012; 23: 1-16.
88. Kemmler W, Häberle L, von Stengel S. Effects of exercise on fracture reduction in older adults: a systematic review and meta-analysis. Osteoporos Int 2013; 24: 1937-50.
89. Korean Society of Menopause. Management of menopausal women. Korean Society of Menopause; 2020.
90. Howe TE, Shea B, Dawson LJ, Downie F, Murray A, Ross C, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database Syst Rev 2011; (7): CD000333.
91. Granacher U, Gollhofer A, Hortobágyi T, Kressig RW, Muehlbauer T. The importance of trunk muscle strength for balance, functional performance, and fall prevention in seniors: a systematic review. Sports Med 2013; 43: 627-41.
92. Sherrington C, Whitney JC, Lord SR, Herbert RD, Cumming RG, Close JC. Effective exercise for the prevention of falls: a systematic review and meta-analysis. J Am Geriatr Soc 2008; 56: 2234-43.
93. Choi M, Hector M. Effectiveness of intervention programs in preventing falls: a systematic review of recent 10 years and meta-analysis. J Am Med Dir Assoc 2012; 13: 188.e13-21.
94. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 2012; 2012: CD007146.
95. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 2014; 25: 2359-81. Erratum in: Osteoporos Int 2015; 26: 2045-7.