Taiwan Osteoporosis

Practice Guidelines

Bureau of Health Promotion, Department of Health, Executive Yuan, ROC (Taiwan)

Cherish Life, Promote Health

Taiwan Osteoporosis

Practice Guidelines

Guideline Developers:	:	Bureau of Health Promotion, Department of Health, ROC (Taiwan) National Health Research Institutes The Taiwanese Osteoporosis Association
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Foreword

Osteoporosis, a looming condition without apparent clinical presentation, is one of the most significant health issues in post-menopausal women and elderlies, which may severely threaten the quality of life and the survival of patients because of fracture induced by minor traumas and other complications. According to the Nutrition and Health Survey in Taiwan (NAHSIT 2004-2008), the bone density study showed that the prevalence of femoral neck osteoporosis in individuals aged over 50 was 10.7% for men, and 12.1% for women. The prevalence increased to 22.57% and 41.17% respectively, when osteoporosis was defined as detected in one or more of the following sites: lumbar spine, femoral neck and forearm.

In the developed countries such as the United States (U.S.) and the United Kingdom (U.K.), there were efforts in developing clinical practice guidelines. International Osteoporosis Foundation (IOF) in 2010, National Osteoporosis Society of U.K. in 2008 and Osteoporosis Society of Singapore in 2009 all introduced new clinical practice guidelines for osteoporosis prevention and treatment. They all subject to routine revision based on the most recent medical evidence. Most importantly, modern evidence-based medicine is incorporated into these guidelines to provide references for health care professionals in the prevention, diagnosis and treatment of osteoporosis. To build a trustworthy clinical guideline for osteoporosis, the Bureau of Health Promotion provided funding and guidance to National Health Research Institutes in organizing a multidisciplinary team. The team includes healthcare professionals in orthopaedics, gynecology/obstetrics, family medicine, endocrinology, metabolism, rheumatology and immunology, neurosurgery and rehabilitation. The team conducted literature search, systematic review and appraisal for guideline development, and to furthermore cover wide context from pathophysiology, epidemiology to diagnosis, follow-up, non-medication and medication approaches of prevention and treatment. Practical clinical recommendations and treatments were then inducted for the compilation of credible osteoporosis practice guidelines.

On the eve of printout, I would like to express my sincere gratitude to the compilation team for their diligence and devotion to the project. Lastly, it is expected this guideline will provide good reference to healthcare professionals in the prevention, diagnosis and management of osteoporosis, and ultimately improve quality in prevention of osteoporosis in Taiwan.

Shu-Ti Chiou
Director-General, Bureau of Health Promotion
Department of Health, Taiwan
December 2012

Due to the improvement in healthcare, the patient in Taiwan is experiencing increasing life expectancy. With the transition into an aging society, the policy makers pay attention to healthy aging of the patient. For health authorities, a guideline to address issues of age-related osteoporosis, including the incidence of bone fracture, the care of the aftermath of the events, and the impacts on patients and family, is an essential element of health policy for seniors in clinical and community care. In view of this, the Bureau of Health Promotion (BHP), Department of Health has authorized and corporated with National Health Research Institutes (NHRI) to establish an osteoporosis clinical practice guideline. In order for wide participation we have invited The Taiwanese Osteoporosis Association (TOA) to participate in the project. The project applied strict evidence-based medicine standard as the basic principle. It was done by multidisciplinary approach with more than fifty osteoporosis care experts of different disciplines from major medical centers and accademia. In addition, the experts from industry and health administration were also participated. Many meeting were carried out as well as open hearing for all stakeholders.

To complete this guideline, in addition to the experiences of the participating scholar in their clinical care and prevention, most importantly, we applied the strict international recognized methodology in developing practice guidelines in addition to Taiwan's own published data. With the lead of BHP, NHRI and TOA, the experts had come to the conclusion of this guideline that is most practical for Taiwan. The quality assurance was done with the review and critique from experts, both in osteoporosis and guideline methodology, who did not participate in the development of this guideline. From this project, we realized the necessity of capacity building in guideline development in Taiwan. We hope that this initiative will be able to highlight the importance of the workforce and resources for research in practice to construct a healthy aging society.

Following the publication of this guideline in Chinese, we have realized that it would be mutual beneficial in sharing this guideline internationally because we believe there are certain aspects that are unique or different from the international English publications. We therefore initiated this translation project with the funding of Bureau of Health Promotion, Department of Health with collaboration of Center for Evidence-Based Medicine and The Taiwanese Osteoporosis Association by gathering all contributing members to join the translation effort.

Ken N Kuo

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English editing December 2012

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Chapter 1. Introduction

Editor: Jung Fu Chen

Section 1 The Impact of Osteoporosis on Public Health in Taiwan

The improvement of the osteoporosis related medicine has indicated the need to extend the target patient of osteoporosis management from postmenopausal women to all adults to be in line with the most recent international standards. However, it is essential to take the economic power and policy of each nation into account when considering the coverage of health insurance, and all nations are developing comprehensive approaches in their guidelines that focus on evidence-based medicine and public health, suggesting that insurance coverage is only one of the elements in a guide to current practices. In terms of osteoporosis prevention, appropriate use and interpretation of bone densitometry are crucial, and this is why the new ISCD (International Society for Clinical Densitometry) 2007 consensus[1] was referenced. It highlights the importance of the accurate application and interpretation in bone densitometry.

The objective of this guideline is to provide practical recommendations and approaches based on the systematic review of published literature or guidelines from developed countries and academic groups for practitioners in Taiwan.

Section 2 The Need for the Practice Guidelines for Taiwan Osteoporosis

The goal of this guideline is to provide guidance for clinicians on the prevention, diagnosis and treatment of osteoporosis. Clinicians are strongly encouraged to select the best strategy tailored to the condition of each patient. In creating this guideline, the most recent guidelines on prevention introduced by the International Osteoporosis Foundation (IOF, 2010)[2], National Osteoporosis Foundation (NOF, 2010)[3], NICE Guideline (NHS, 2003)[4], along with Asian guidelines, including the Osteoporosis Society of Singapore guidelines (2009)[5], Asian-Pacific guidelines (2006)[6], and the Consensus and Guidelines on the Prevention of Adult Osteoporosis (The Taiwanese Osteoporosis Association, 2007)[7], were consulted, and the current epidemiologic data of osteoporosis were reviewed in order to establish this guideline for clinical practice in Taiwan.

Section 3 The History of the Practice Guidelines for Osteoporosis in Taiwan

This initiative was started by The Taiwanese Osteoporosis Association as part of a project held by the Bureau of Health Promotion (BHP) and the National Health Research Institutes (NHRI) for consensus building and clinical experience sharing. On January 19, 2010, a preparatory meeting for the "Consensus on the Treatment and Management of Osteoporosis" was held to outline the topics and protocols of development, and Dr. Jung-Fu Chen was assigned as the chairman responsible for this project.

Section 4 The Scope of the Practice Guidelines for Taiwan Osteoporosis

The targets include patients with osteoporosis, meaning this guideline applies to all levels of physicians and healthcare professionals/teams specializing in orthopaedics, obstetrics /gynecology, family medicine, endocrinology, metabolism, rheumatology and immunology, neurosurgery and rehabilitative medicine.

Section 5 Statement of the Organizations in Guideline Development

The application of this guideline is to provide guidance on treatment plans for clinicians, meaning that this guideline does not suggest a standard of care, nor does it discourage approaches that are not included. In this guideline, financial cost is not the main topic because the policies of National Health Insurance and the related coverage are not emphasized. This guideline cannot be used as a substitute for clinician's experience, and proper judgements should be made by clinicians based on the clinical particulars of each patient and other objective factors to select the best treatment.

Section 6 Review and Update of the Practice Guidelines for Taiwan Osteoporosis

It is planned that routine reviews will be performed based on the new information from medical research, newly published literature and regulations inside or outside Taiwan. Expert meetings will be held for the decision and scope of update when new literature is published and its level of evidence warrants update of this guideline before the next planned review.

Section 7 Profile of the Members of Guideline Development

This guideline was created as an objective of the "Project on the Creation of the Guideline" (term: April 1 2010 to December 31 2010), which was conducted by NHRI and sponsored by BHP. This guideline on the clinical treatment of osteoporosis was created by the following fellows convened by the project director, Professor Ken N Kuo:

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※The list contains the title of each member as of December 31, 2010.

■ Section 8 Peer Review and Recommendations for the Guideline Development

The initial draft of this guideline was reviewed by a multidisciplinary peer panel after its completion on July 31, 2010. On October 10, 2010, recommendations were provided by oral comments and in writing, which included format consistency, fluency of translated texts, a pool of reference based on the most recent literature and the addition/removal of chapters and sections. The final draft was approved by the panel on November 10, 2010, and the review by experts who had not participated in the creation of this guideline was coordinated by the National Health Research Institutes.

■ Section 9 The Funding Source of the Guideline Development

The development of this guideline was funded by the Bureau of Health Promotion in support of the “Project on the Creation of the Guideline”, a project held by the National Health Research Institutes.

■ Section 10 Associated Organizations in Guideline Development

Taiwan Orthopaedic Association, The Endocrinology Association of R.O.C., The Radiological Society Republic of China, Taiwan Academy of Physical Medicine and Rehabilitation, Rheumatology Association R.O.C., The Chinese Society of Immunology, Joint Reconstruction Society R.O.C., Society of Nuclear Medicine R.O.C., Taiwan Association of Obstetrics and Gynecology, Taiwan Association of Family Medicine, Taiwan College of Family Physicians, The Taiwan Menopause Society, Taiwan Association of Gerontology and Geriatrics, Taiwan Spine Society, Taiwan Orthopaedic Research Society, Taiwan Neurosurgical Society,

Taiwan Society of Health System Pharmacists.

Section 11 The Statement of Conflict of Interest and Financial Interest

This guideline is created based on the consensus of local experts and evidence from medical research, and there is no conflict of interest and financial interest in individuals or groups.

Section 12 Acknowledgements

We would like to express our sincere gratitude to the following groups that provided consultations during the creation of this guideline: Taiwan Evidence-Based Medicine Association, Taiwan Orthopaedic Association, The Endocrinology Association of R.O.C., The Radiological Society Republic of China, Taiwan Academy of Physical Medicine and Rehabilitation, Rheumatology Association R.O.C., The Chinese Society of Immunology, Joint Reconstruction Society R.O.C., Society of Nuclear Medicine R.O.C., Taiwan Association of Obstetrics and Gynecology, Taiwan Association of Family Medicine, Taiwan College of Family Physicians, The Taiwan Menopause Society, Taiwan Association of Gerontology and Geriatrics, Taiwan Spine Society, Taiwan Orthopaedic Research Society, Taiwan Neurosurgical Society, Taiwan Society of Health System Pharmacists.

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Chapter 2. Methodology

Editors: Ken N Kuo, Chiehfeng Chen, Heng-Lien Lo, Te-Hui Hao

Section 1 Literature Searching

In the preparatory meeting for the "Consensus on the Treatment and Management of Osteoporosis" held on January 19, 2010, it was determined that the contents of this guideline would be arranged in five topics: definition and pathophysiology, epidemiology, diagnosis and follow-up, approaches for prevention and treatment without medication, and with medication.

In each topic, the search included most recent and well recognized clinical guidelines worldwide (for example, the one by International Osteoporosis Foundation), and the clinical study literatures in English and Chinese between 2005 and 2010 by Medline search. The exclusion criteria included animal experiments, description of clinical techniques (technical note and operative nuance), and literatures written in languages other than English and Chinese. The keywords and strategies were decided by each editor of the each chapter.

Section 2 Criteria for Level of Evidence

For the level of evidence, we adopt the recommendations by Scottish Intercollegiate Guidelines Network (SIGN)[1,2] originally used by the National Health Research Institutes. It is classified into eight levels as following:

Level	Type of Evidence
1++	High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias.
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias.
2++	1. High quality systematic reviews of case control or cohort studies. 2. High quality case control or studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2+	Well conducted systematic reviews based on case control or cohort studies (with a low risk of confounding or bias and a moderate probability that the relationship is causal).
2-	Case control or cohort studies with a high risk of confounding or bias (and a significant risk that the relationship is not causal).
3	Non-analytic studies, e.g. case reports.
4	Expert opinion

Table 2-1 Levels of Evidence

Section 3 Forming Recommendation and the Strength of Recommendation

Using classification of levels of evidence according to the criteria in the prior section, we formed the 4 grades of recommendation as the following:

Grade of Recommendation	Properties
A	1. At least one meta-analysis, systematic review or RCT rated as 1++, and directly applicable to the target patient. 2. Systematic reviews, RCTs, or most of the body of evidence consisting principally of studies rated as 1+, directly applicable to the target patient, and demonstrating overall consistency of results.
B	1. A body of evidence including studies rated as 2++, directly applicable to the target patient, and demonstrating overall consistency of results. 2. Extrapolated evidence from studies rated as 1++ or 1+.
C	1. A body of evidence including studies rated as 2+, directly applicable to the target patient, and demonstrating overall consistency of results. 2. Extrapolated evidence from studies rated as 2++.
D	1. Evidence level 3 or 4. 2. Extrapolated evidence from studies rated as 2+.

Table 2-2Grades of Recommendation

It should be noted that recommendations of grade C or D are supported by evidence but their levels of evidence are not as strong as grade A or B. Therefore grade C or D should not be interpreted as negative measures in clinical settings.

Section 4 Application of the Guidelines

This guideline can be used for medical education. It provides clinicians a convenient tip for clinical setting, rather than rigid standards; that is, the management of each patient should be individualized for optimal outcomes.

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Chapter 3. Definition and Pathophysiology

Editor: Rong-Sen Yang

■ Section 1 The Definition of Osteoporosis

According to the World Health Organization (WHO, 1993), osteoporosis is "a disease affecting many millions of people around the world. It is characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to bone fragility and a consequent increase in risk of fracture[1].

The National Institutes of Health (NIH, 2000) defined osteoporosis as "a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength primarily reflects the integration of bone density and bone quality." [2]. Bone density has been used for the diagnosis of osteoporosis because bone quality assessment is still beyond the scope of current clinical technology.

An expert panel, in response to a request from WHO, established the criteria for clinical diagnosis of osteoporosis based on the correlation between bone mass and risk of fracture in Caucasian women[3]. “T-score”, defined as the difference between measured bone density and average bone density of young women divided by standard deviation (SD), was used for the assessment, and the bone density (average and SD) of testees was compared with those of the young individuals using required instruments. Examinations were performed on total hip, femur neck and lumbar spine, and the distal third of radius was used when these parts were not applicable. The T-score of a normal individual is higher than -1, where osteopenia, or low bone mass, is indicated when it is lower than -1 but higher than -2.5, and osteoporosis is defined as a T-score lower than -2.5. This definition has clinical practicability, and it has been widely used by many associations and societies since its introduction.

It is worth noting that the T-score is only applicable to Caucasian women, but not men, premenopausal women or other ethnicities. Similar methodology can be used to establish reference values, but its applicability should be carefully considered. Moreover, osteoporosis-related bone fracture is the consequence of multiple factors, including weakened bone strength and falling. T-score should not be used as the only predictor of bone fracture, and osteopenia is not equivalent to a disease.

In clinical practice, the incidence of fragility fracture (bone fracture caused by minor injuries, falling from standing or a lower height, or unnoticed injuries) justifies the diagnosis of osteoporosis without the T-score data [4], and this was also recognized by many associations and societies, including the North American Menopause Society (NAMS, 2010).

Refer to the subsequent chapters and sections for the epidemiology of the bone fracture risk and the clinical application of measured bone density.

■ Section 2 Pathophysiology

Bone remodeling involves bone formation by osteoblasts and bone resorption by osteoclasts. These two physiological functions are correlated, and interact closely to maintain the dynamic balance in the turnover of bone tissues. Osteoporosis results from loss of bone mass when the rate of bone resorption exceeds that of bone formation[5-11]. Clinically, osteoporosis can be classified as primary and secondary. Primary osteoporosis includes postmenopausal osteoporosis and senile osteoporosis.

Postmenopausal osteoporosis, also known as type 1primary osteoporosis, is common in postmenopausal women, especially those who have been menopausal for 15-20 years. When a woman's estrogen level drops drastically after menopause, followed by increased activity of osteoclasts to promote the resorption of the trabecular bone, causing its thinning, breakdown and disintegration, and, as a consequence, the weakening of bone strength. This condition is associated with compression spine fracture, and wrist fracture as well as intertrochanteric fracture of the femur [5].

Senile osteoporosis (the type 2primary) is usually found in women aged ≥70 years or men aged ≥80 years, and this type of osteoporosis is twice as likely to be found in women than in men. This is related to decreased bone formation caused by diminished function of osteoblasts, insufficient intake of calcium and vitamin D, and poor intestinal absorption. This condition is characterized by porous bone cortex, loss of trabecular bone, significant weakening of bone strength, increased parathyroid activity with normal urine calcium secretion, and is associated with multiple vertebral wedge fracture, and fracture of humerus, tibia and femoral neck (hip)[6,7].

"Secondary osteoporosis" is usually related to bone mass loss from certain conditions such as steroid use, hyperparathyroidism, thyroid disease, hypogonadism, rheumatoid arthritis, kidney disorders, liver disorders, diabetes mellitus, smoking, alcohol abuse, organ transplantation, fracture, and insufficient intestinal absorption. Steroid use is the most significant risk for osteoporosis because it interferes with the intestinal absorption of calcium and phosphorus, and tubular reabsorption of calcium. Both hypercalciuria and accelerated bone loss are followed by affected equilibrium of calcium and triggering of the compensatory mechanism involving the fueling of bone absorption resulting from osteoclast activation through increased level of parathyroid hormone. In addition, it inhibits osteoblasts activity and bone formation, and facilitates bone absorption by affecting the activities of estrogen and calcitonin. This results in osteoporosis related to high incidence of fracture at spine, ribs and hips[8,9].When observing the age distribution of osteoporosis in men, two hikes can be found at ≤40 years and 61-70 years, where the younger cases are usually associated with secondary causes and the older cases are presented as senile osteoporosis. To prevent progression due to improper management, the factors of secondary osteoporosis should be considered when treating male osteoporosis[10,11]. The abovementioned factors have been incorporated into the Fracture Risk Assessment Tool (FRAX)[13].

Accelerated loss of bone mass and deterioration of bone quality originating from aging, menopause, diminished gonad function, increased bone turnover or other clinical risk factors, especially in individuals with lower peak bone mass, may lead to a lower bone density and weakened bone strength. This will increase the risk of fracture when the affected bones encounter forces exceeding the maximum bone strength during the impact of falling in individuals with poor balance, or the stress in certain activities[13,14].

■ Section 3 Clinical Considerations

Unfortunately, as one of the most notorious chronic conditions, there are no typical clinical considerations in patients with osteoporosis. It is usually identified when patients suffer from fracture and the associated complications caused by minor injuries, where the secondary symptoms and impairments lead to poor self-esteem, or even death. Osteoporosis-related fractures, especially spine and hip fractures, severely threaten the quality of life and wellness of patients. Hip fracture is associated with a high one-year mortality rate - 22% for men and 15% for women in Taiwan. Survivors may require long-term care because of the loss of self-care capabilities, and are at imminent risk of further fractures Spine fracture is associated with back pain, hump and loss of height. In severe cases, this can cause pulmonary and digestive disorders, or even death. In patients with wrist fractures, the development of local deformity also affects activities of daily life[13,14]. The prevalence of osteoporosis and related fractures in Taiwan is similar to that of the United States, and the records of National Health Insurance indicate that spine and hip fractures pose a tremendous threat to our society because of the significant cost of acute care, and the resource burden of chronic disabilities that follow.

The definitions of osteoporosis are helpful in diagnosis, but they are not used for defining thresholds of treatment. According to the definition, osteoporosis consists of four distinct characteristics: decreased bone mass, deterioration of microstructure of bone tissues, bone fragility, and an increased risk of bone fracture[1]. In current practice, bone density is the most widely used diagnostic parameter[2]. This assessment is focused on the loss of bone mass and the increased risk of fracture, but it is unable to indicate the changes in bone microstructure and bone fragility. It should be noted that bone strength is determined by bone mass, bone quality and structural integrity, and bone density cannot be used as the only indicator of treatment because it cannot accurately represent the latter two. Currently, there are no applicable non-invasive procedures for determining bone quality and microstructure, and it is recommended to improve accuracy in the prediction of bone fracture by using a risk model based on bone density and clinical factors[13,14]. The inclusion of clinical factors can also explain osteoporosis-related bone fracture in patients with normal bone density. It is expected that the assessments of bone quality and microstructure can uncover more information for providing a better diagnosis and treatment.

Knowledge regarding the pathophysiology of osteoporosis provides precious information for the development of the strategies of treatments. Osteoporosis is the result of imbalance in bone metabolism, indicating a strong relationship with bone cells, which are essential for exercise and the maintenance of normal physiological functions. Bone cells are the targets of many drugs, including bone resorption inhibitors and monoclonal antibodies for the inhibition of osteoclasts, and bone anabolic agents for the activation of osteoblasts are used to rebuild the balance of bone cell activities. Still, osteoporosis is a multi-faceted condition, so considerations must be placed on several aspects. Please refer to the following chapters for more information.

The ultimate goal of osteoporosis treatment is to control the increased risk, i.e. the incidence, of fracture as described in the definition. The prevention for new and recurrent fractures can be achieved with proper diagnosis and adequate treatment; therefore, the keys to prevention include the careful screening of high-risk individuals, and the availability of education, and preventive and/or treatment measures. Non-medicative and medicative approaches can be used as management strategies: establish proper recognition of osteoporosis for the public and healthcare professionals, provide recommendations on a healthier lifestyle, encourage cessation of smoking/alcohol, maintain sufficient intake of vitamin D and calcium, and engage in load-bearing and strengthening exercises. In addition to the maintenance of bone health, preventive measures for falling, bone density monitoring and medicative treatment are also required for controlling the risk of osteoporosis and the related fracture. Refer to other chapters for the keys to the epidemiology, prevention and treatment of osteoporosis and its complications.

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Chapter 4. Epidemiology of Osteoporosis

Editor: Keh-Sung Tsai

Grade of Recommendation	Content of Recommendation	Level of Evidence	Number of Reference
B	Foreign reports showed that spine fracture is associated with a higher mortality rate.	2++	1,2
B	National and foreign reports showed that hip fracture is associated with a higher mortality rate.	2++	1,3
C	The information from the National Health Insurance (NHI) showed that hip fracture leads to higher mortality rate in both men and women.	2++	3
B	The correlation coefficient (r) of the results from dual energy X-ray absorptiometry (DXA) and quantitative ultrasound (QUS) is about 0.6.	2+	4
C	The DXA results of all age groups in Taiwan are similar to those of Caucasians.	2+	7,8,9
C	50% of middle-aged women in Taipei City have insufficient vitamin D intake.	2+	12
C	The bone turnover markers of middle-aged and aged men and women show different senile changes, and a higher level of marker is related to lower bone density.	2+	7
C	The risk of bone fracture is higher in individuals with longer femur necks.	2+	14
B	In Canada, the incidence of femur fracture decreased while the percentage of aged patient remained the same.	2++	18
C	In, 2010, about 15,000 aged individuals in Taiwan experienced hip fracture, and the one-year mortality rate of men was 22%, and it was 15% for women.	2++ 2+	3 19
C	In 1993, compression deformities of vertebral body were noted in 19.5% and 12% of women and men aged ≥65, respectively, in Taiwan.	2+	23

The impact of osteoporosis on patients and society lies in the associated bone fractures, especially the grim outcomes of hip fracture, spine compression fractures and Colle's fracture, where the former two are associated with significant higher mortality rate[1,2]. In Taiwan, the information of the relative mortality risk after spine fracture awaiting further research, yet the data from the NHI in the last 15 years show that the one-year mortality rate of hip fracture in aged men is 22%, and 15% for women, apparently higher than the average mortality rate of the same age group [3]. This indicates that while insufficient bone density is an important factor of bone fracture, the epidemiology should include more than bone parameters, that is, bone mineral density (BMD, "bone density" is used in this guideline) profile and its age-related changes are only parts of the puzzle – the prevalence and mortality rate of bone fracture and their relationship with bone density should also be considered.

Section 1 Epidemiology of Bone Density Disorders

Absorptiometry and quantitative ultrasound (QUS) are the two routine methods for measuring bone density. These two techniques are quite different in their theoretical bases, applicable settings, and the results for the same testee. The correlation coefficient is about 0.6 or less[4]. In the WHO (1994) diagnostic criteria, only DXA values are used and comparisons are made with the average and standard deviation (SD) of young women (aged 20-30). Individuals with values lower than the average by one SD (T score ≤-1.0) or more are defined as osteopenia, and osteoporosis is indicated when the difference between the value and the average exceeds 2.5 SD (T score <-2.5)[5]. For Caucasians, one SD is about 13~15% of the average. A cross-sectional study showed that, at 15 years postmenopause, the average of women aged 65 was about 13~15% lower than those of premenopause, and the difference was 30% for women aged 80. Based on this criteria, about half of women aged 65 have osteopenia, and for women aged 80, the average T score of -2.3 indicates that 40% of this age group is affected by osteoporosis (T score <-2.5) [6]. In a study conducted in several hospitals in Taiwan, the age-related changes of bone density in postmenopausal women was similar to those of Caucasians[9], suggesting that when bone density is used for classification, the distribution of osteopenia (or more severe cases) and osteoporosis in women is similar. The QUS data showed a similar result[10], but the T score and presence of osteopenia or osteoporosis cannot be determined this way as the WHO criteria are not applicable in this case.

Besides gender and age[11], the factors of osteoporosis-related bone fracture also include body length, weight (BMI), parental history of hip fracture, calcium intake (adequacy of vitamin D), falling, chronic steroid use, smoking, alcohol intake, bone length and bone metabolic rate. In Taiwan, studies have been conducted in the community to explore vitamin D intake [12] and the existence of bone turnover marker profiles[7].For middle-aged or aged women in Taipei City, about 50% have inadequate vitamin D intake[12], along with generally higher bone turnover markers and lower bone density[7]. Foreign reports demonstrated that higher metabolic markers are associated with higher risk of bone fracture[13], and individuals with history of hip fracture have longer femur necks[14]. The FRAX software published online by WHO does not count vitamin D intake, bone turnover markers, incidence of falling and length of femoral neck and still requires further development; however, specific FRAX is now applicable to Taiwanese people.

Section 2 Epidemiology of Osteoporosis-Related Fractures

The prevalence and incidence of bone fracture increase with age. However, when observed at the global level, ethnicity, age structure, lifestyle, diet and climate come into play. In general, Caucasians and north Asians are at higher risk of bone fracture than African descendants or Pacific Islanders[15]. Caucasians and Scandinavians are prone to bone fracture because of climate, body length (i.e. bone length) and other unknown factors[16]. In Asia, it is expected that two of the most populous nations, i.e. China and India, are becoming the highest risk zones as the aging patient is growing at a breakneck speed[17]. On the contrary, as a high risk region of osteoporosis and bone fracture, a recent decrease in the incidence of hip fractures in Canada was noted while the growth of aging patient persists[18]. The introduction of National Health Insurance in Taiwan allows accurate statistical recording of the incidence of hip fracture. Based on the survey on the statistical data of two time-lapses (1995~2000[3], 1996~2002[19]), it was estimated that the annual (2009) incidence of hip fracture in Taiwan was about 16,000, where women were twice as likely to experience bone fracture as men. Considering the annual incidence of hip fracture in all age groups, an abrupt increase can be found in women aged ≥60, and 65~70 and above in men. The annual incidence of women aged 75 reaches 1%, and it is 0.5% and 1.5% for 70- and 80-year old individuals, meaning that the incidence of hip fracture of at least one side is about 10% for Taiwanese women in their seventies [3]. The incidence of hip fracture of aged men of all age groups is about half of those of women. When adjusted using the age distribution of Caucasians in the United States, the incidence of hip fracture of Taiwanese women is $450/10^5$, which is higher than for Caucasians in the United States, and the number is $200/10^5$ (equivalent to the incidence of Swedish Caucasians) for men, suggesting that Taiwan is one of the regions with the highest annual incidence. The growth of the aging patient increases the number of cases by 3~5% annually, and the gross one-year death rate of men is 22% and 15% for women, similar to foreign reports [3].

Spine fracture is the compression deformity of the vertebral body, which may or may not have cracks. Patients may not notice its presence because of the degree of deformity, and two terms are used in diagnostic practice: morphometric fracture is defined using the changes in thickness at the anterior edge and central height of the vertebral body in the lateral view images to determine the presence of compression deformity, while clinical vertebral fracture is defined as when patients learn of their spine fracture by any other means. The latter is usually accompanied by back pain, and patients getting medical attention because of the pain would be told of the fracture. Among the cases identified from X-ray screening in the community, only one-third were clinical vertebral fractures[20]. Foreign reports on the prevalence of spine fracture are scarce, and even less explored is its incidence because the follow-up of a large patient is required. For example, in the European Vertebral Osteoporosis Study, a large epidemiology study on Europeans aged ≥65, the prevalence of spine fracture in European men was 10~20% and 18~30% for women[21]. A 2005 study in the United States showed that the annual incidence of spine fracture was nearly twice that of hip fracture (~550,000 cases vs. ~300,000 cases)[22].

In Taiwan, a study was conducted on 3000 individuals aged ≥65 in the cities of Taipei, Kaohsiung, Taichung and Hualien in 1994 by the Taiwan Association of Gerontology and Geriatrics in response to a request from the former Bureau of Health Promotion. X-ray images showed that the incidence rate of vertebral body fracture in women aged 65~70 was 14% and 30% for the group of ≥80. In general, the prevalence in men is about sixty percent of that in women. After adjustment based on age distribution, 19.5% of women and 12% of men aged ≥65

have significant compression deformity in the vertebral body, suggesting that Taiwan is an area of high incidence, and this trend is also present in men[23].

Conclusion: in Taiwan, the incidence of hip fracture or spine fracture of the middle-aged and aged patient is higher than the world average, especially for men, whose adjusted incidence rate is among the highest in the world.

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(2++)

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Chapter 5. Diagnosis of Osteoporosis and Follow Up

Editor: Chih-Hsing Wu

Abstract

Since the introduction of the definition of osteoporosis by the World Health Organization in 1993, various clinical diagnostic methods have been developed in consideration of the convenience and requirements in a clinical setting: physical examination, X-ray bone imaging, quantitative ultrasound (QUS), dual energy X-ray absorptiometry (DXA) and bone turnover markers are just some of the examples, each is based on different clinical evidence, and appropriate interpretation helps in identifying individuals with asymptomatic osteoporosis, or osteoporosis with a high risk of bone fracture. By summarizing related information, it is acknowledged that an approach based on the principles of evidence-based medicine starts with simple physical examination and history taking, or screening of high risk individuals using QUS, and referrals are made for confirmatory examination using DXA.

With most patients being asymptomatic, the patient requiring osteoporosis screening, and the establishment of criteria for classifications to facilitate assessment and follow-up are crucial, but these measures demand assistance in funding and medical insurance plans.

The ultimate goal of osteoporosis management is the prevention of fracture. The Fracture Risk Assessment Tool (FRAX) published by the International Osteoporosis Foundation (IOF) in 2008 provides effective prediction of fracture risk in the following decade, and the FRAX information for Taiwan is already available online. For high risk patients (defined as individuals with a major fracture risk of ≥20% or hip fracture risk of ≥3%), active preventive intervention is recommended. From the point of view of clinical practice and evidence-based medicine, the promotion of the use of Taiwanese FRAX may improve the accuracy of osteoporotic fracture risk assessments.

Section 1 Assessments of Osteoporosis

Editors: Zih-Jie Sun, Chih-Hsing Wu

Grade of Recommendation	Content of Recommendation	Level of Evidence	Number of Reference
Physical Examination (PE) and X-ray			
C	Osteoporosis Self-assessment Tool for Asians (OSTA) is a simple self-assessment tool for women.	2+	2
C	Low body weight (<51 kg) suggests the possibility of osteoporosis or spine fracture in Westerners, but the cutoff value is not yet available for Asians.	2+	1
C	A teeth number of <20 is a predictor of osteoporosis or spine fracture.	2+	1
C	The presence of hump is a predictor of osteoporosis and spine fracture.	2+	1
C	A wall-occiput distance larger than 0 cm is a predictor of osteoporosis and spine fracture.	2+	1
C	A rib-pelvis distance smaller than two fingerbreadths is a predictor of osteoporosis and spine fracture.	2+	1
Bone turnover markers			
C	Bone turnover markers assists in the assessment of bone formation and loss.	2+	3,4
C	Bone turnover markers are predictors of osteoporosis-related fracture.	2+	3,4
C	Bone turnover markers can be used to monitor the response to the treatment of osteoporosis.	2+	3,4
Quantitative Ultrasound (QUS)			
A	Common cutoff points are unable to exclude or confirm the osteoporosis cases diagnosed by DXA.	1+	5
C	Calcaneus QUS can be used to define the risk of osteoporosis-related bone fracture in postmenopausal women or aged men.	2+	6-9
C	There is no difference between men and women when using calcaneus QUS for predicting the risk of hip fracture.	2+	9,10
Dual Energy X-ray Absorptiometry (DXA)			
A	The diagnosis and evaluation based on the lowest T-score from the assessment of lumbar spine and hip bone using DXA is the gold standard in clinical practice.	1+ 1++	11,13 12
A	When lumbar spine and hip bone are not available for DXA assessment, the non-dominant forearm can be used in the diagnosis and evaluation of osteoporosis.	1+ 1++	11,13 12
A	The bone density in the lumbar spine, forearm and hip bone measured with DXA is a predictor of osteoporosis-related fracture.	1+ 1++	11,13, 14,12
A	DXA can be used for the follow-up of osteoporosis treatment, and the interval depends on the therapeutic intervention used.	1+ 1++	11,13,12

Description

Physical Examination (PE)

The physical examinations related to osteoporosis include height, weight, degree of hump, grip strength, thickness of hand skinfold, number of teeth, armspan-height difference, wall-occiput distance and rib-pelvis distance. Individuals with a weight of <51 kg, hump, less than 20 teeth, a wall-occiput distance of >0 cm, and/or a rib-pelvis distance smaller than two fingerbreadths have the highest positive likelihood ratio. However, without further examination, a single PE item is not enough to exclude or confirm the diagnosis of osteoporosis[1].

●Difference between present height and height at youth

A ≥3-cm difference between the present height and the height at youth strongly suggests the possibility of osteoporosis. The changes in height determined each half year also provide information regarding the presence of new osteoporosis-related lumbar spine fracture. Unfortunately, the applicability of this parameter is limited because many people are unable to tell physicians what their exact height was when they were young.

●Weight

Body weight is inversely proportional to bone density, indicating that low body weight is a risk factor of osteoporosis, and this is especially true when body mass index (BMI, calculated by dividing weight [kg] by squared height [m^2]) is lower than 18.5 kg/m^2. The Osteoporosis Self-assessment Tool for Asians (OSTA) is a simple self-assessment tool for women [2]. The observation on the variables of weight and age revealed that "lighter" or older individuals have a higher risk of osteoporosis. To provide a fast, simple understanding for the self-assessment of the risk of osteoporosis, the weight- and age-related risk is summarized below.

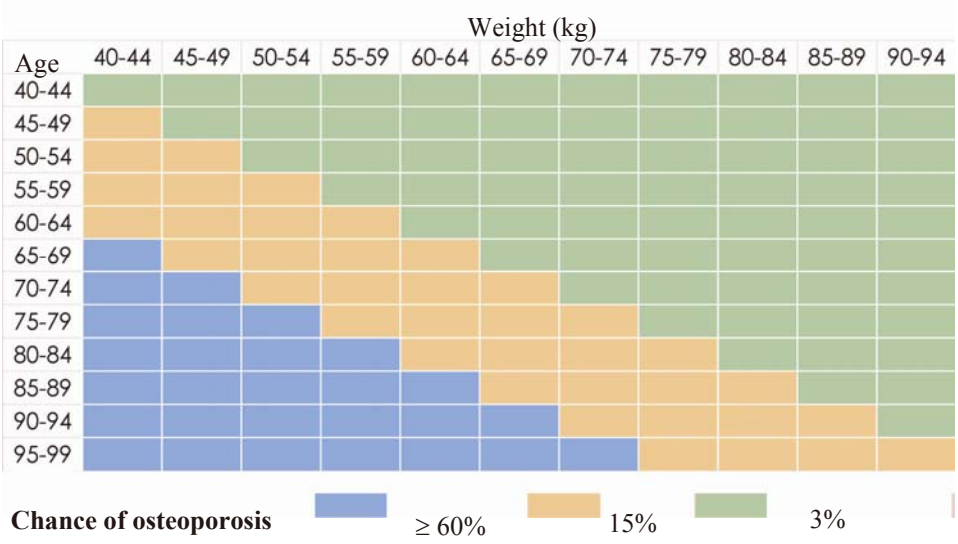

Fig. 5-1Osteoporosis Self-assessment Tool for Asians (OSTA)

●Wall-Occiput Distance (WOD)

This is a quick method for screening subclinical compression fracture of the thoracic spine. Subjects are asked to stand against a wall with both eyes looking ahead at eye level, and the horizontal distance between occiput (back of head) and the wall is measured. A gap of <1 cm (or no gap) is considered normal. When a gap of >3 cm is found, a problem is strongly suggested, and it is confirmed when it is >6 cm (or a fist distance).

• Rib-pelvis distance (RPD)

This is a quick method for screening subclinical compression fracture of the lumbar spine. Subjects are asked to stand with two arms raised to shoulder height, and the vertical distance between the lateral last rib margin and pelvis brim is measured. In normal individuals, it should be 2-3 fingerbreadths or >5 cm. A distance of <2 cm is highly confirmative for a spinal problem.

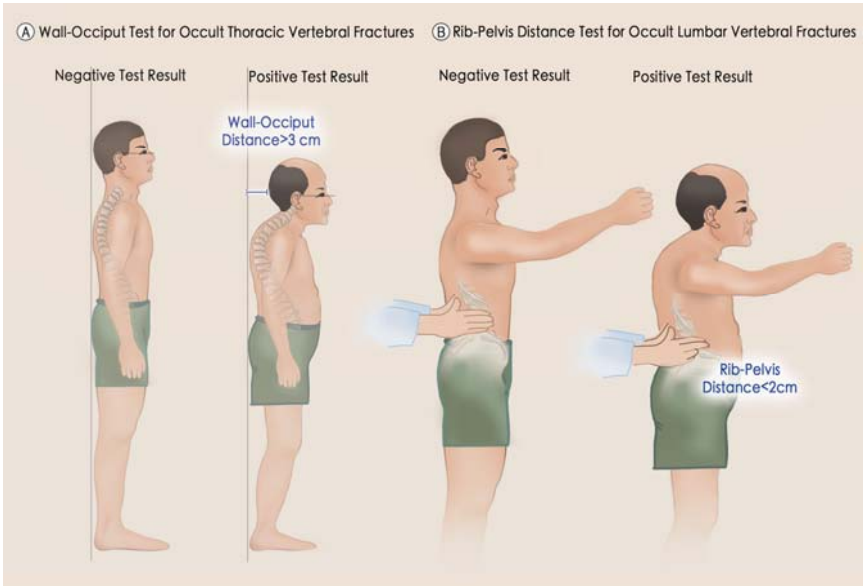

Fig.5-2 WOD and RPD

(Revised from: JAMA 2004; 292: 2890-2900)

●Bone Turnover Markers (BTMs)

Bone turnover can be measured by the biological markers in urine or serum (Table 1), including bone resorption (osteoclast) markers and bone formation (osteoblast) markers [3]. BTMs indicate the speed of bone remodeling, and are used for the dynamic assessment of bone condition and the prediction of bone loss and potential bone fractures. In addition, BTMs can be used to monitor the efficacy of osteoporosis treatment when there is limitation in the bone densitometry measurement, but it should be noted that BTMs cannot be used for the diagnosis of osteoporosis [4].

Bone turnover marker (BTM)
Bone formation marker
Serum Osteocalcin
Serum bone-specific alkaline phosphates
Serum procollagen-I C-terminal peptides (PICP)
Bone resorption marker
Urinary hydroxyproline
Urinary collagen-related substances
Pyridinoline (Pyr)
Deoxypyridinoline (D-Pyr)
N-terminal telopeptide (NTX)
Serum C-terminal telopeptide of type I collagen (ICTP)
Blood tartrate-resistant acid phosphatase (TRAP)

Table 5-1 Common Biomarkers of Bone Metabolism[3]

●Quantitative Ultrasound (QUS)

The speed and attenuation of ultrasound waves in bone have been suggested to be used as a non-invasive approach for the assessment of osteoporosis. Ultrasound can be used to obtain more information about bones to define the resilience and stiffness of bone mass. For the ultrasound densitometry instruments in the market, calcaneus or tibia is the most frequently used for measurement, especially calcaneus (containing 80~90% cancellous bone). Dry and wet systems have been introduced, and the dry system has become the preferred choice. In short, QUS estimates the presence and degree of osteoporosis by ultrasound transmission parameters, including speed of sound (SOS) and broad ultrasound attenuation (BUA). A meta-analysis on twenty five studies was done to identify patients with a T-score of <2.5 in hip or spine DXA using calcaneus QUS data, and it was concluded that QUS lacks a cut-off with sufficient sensitivity and specificity to exclude or confirm the diagnosis of osteoporosis by DXA[5]. However, prospective studies have shown that the calcaneus QUS can be used for the effective evaluation of bone fracture risk in postmenopausal women and aged men[6-9], and the hip fracture risk derived from the data does not show differences between men and women[9,10].

●Dual energy X-ray Absorptiometry (DXA)

Considered the gold standard for diagnostic tool for osteoporosis, DXA can be used for any part of the body, while it is usually used on the lumbar spine and hip bone. It uses X-ray

emitters of two different levels for scanning, and BMD value (g/cm^2) is calculated with the amount of absorption by dorsal bone and soft tissue, and the scanned area. One of its main advantages is that radiation exposure is only one-tenth that of chest X-ray[11,12], and it can also be used for estimation of the risk of bone fracture, the response and efficacy of treatment[12,13].

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■ Section 2 Diagnosis of Osteoporosis

Editor: Chih-Hsing Wu

Grade of Recommendation	Content of Recommendation	Level of Evidence	Number of Reference
Middle-aged or aged individuals (men aged ≥50, or postmenopausal women)			
B	The diagnosis of osteoporosis is suggested when the T-score of any axial bone (lumbar spine or bones in hip or non-dominant forearm) is up to -2.5.	2++	1
B	The diagnosis of osteoporosis is suggested when a patient experienced, or had history of, low impact fracture of bones in hip or non-dominant forearm.	2++ 4	2,8 7
C	The diagnosis of osteoporosis is suggested when compression fracture is found in one or more vertebral bodies, and the patient does not have history of trauma or secondary conditions.	2++ 2-	2 3
B	Quantitative ultrasound or other dual or single photon absorptiometry (peripheral bone densitometer) of other parts of body is better used for reference in screening, and is not recommended to be used as a diagnostic tool.	2++	6
B	Bone turnover marker cannot be used as a diagnostic tool.	2++	4
Adults (men aged 20~49, or premenopausal women)			
B	The diagnosis of osteoporosis is suggested only when the patient has clinical low impact fracture, and the confirmed high risk of bone fracture as determined by the presence of low bone mass (or worse) indicated by the Z-score acquired from DXA.	2++	4

Description

In chapter 3, it has been stated that the definition by the National Institutes of Health (NIH, 2000) defined osteoporosis as a bone condition characterized by affected bone strength and increased risk of bone fracture, where bone strength is determined by bone density and bone quality[9]. Bone density has been used for the diagnosis of osteoporosis because bone quality assessment is still beyond the scope of current clinical technology. Moreover, the diagnosis of osteoporosis is suggested when a patient has a history of low impact fracture[2,7,8], where forearm/wrist, hip or (compression of) spine have the highest risk of involvement. Compression fracture revealed by spinal X-ray[3] or the T-score of axial bone density[1,4,5] can also be used to determine osteoporosis.

●Simple X-ray

Conventionally, the diagnosis of osteoporosis is confirmed by more than 30% loss of bone density, which is visible in standard X-ray images. Spinal fracture is usually overlooked because it may or may not accompany notable symptoms. Unfortunately, for most patients with a T score >-2.5, significant compression fracture and/or deformity of the vertebral body of the thoracic or lumbar spine (from T4 to L5) can be noted in lateral X-ray images, but it is acknowledged that X-rays still play a role in the screening of osteoporosis. The identification of

spinal compression fracture is based on the semiquantitative classification technique by Genant (refer to the figure below). In short, mild (grade I) compression fracture is defined as a difference of ≥4 mm or >20% in the height of the wedge (two sides) or biconcave (central-peripheral) of a vertebra, which indicates the need for aggressive treatment because of the significant increase in the recurrence of bone fracture. When compression fracture at T7 or above is found, it is essential to consider the possibility of other conditions (including tuberculosis, bone metastasis and/or multiple myeloma).

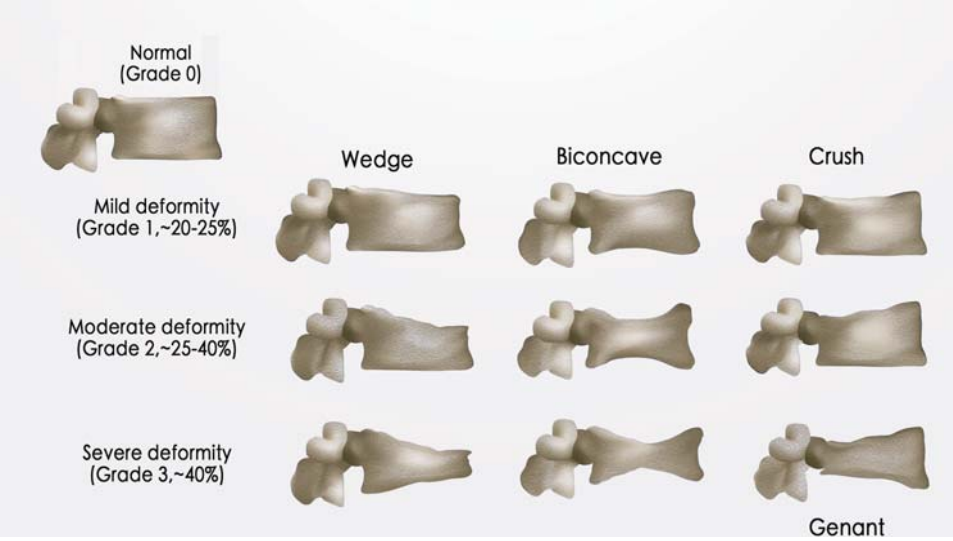

Fig. 5-3 Semiquantitative classification technique
(Revised from: J BoneMiner Res 1993;8:1137–1148.)

Axial dual-energy X-ray absorptiometry (DXA) is a standard tool for the measurement of bone mineral density (BMD). To avoid the confounding higher bone density found in lumbar spine osteoarthrosis in lumbar testing, both the lumbar spine and hip bone should be measured simultaneously. When the correct measurement of these two sites is unavailable, the measurement should be performed on the one-third radius. The lateral vertebral fracture assessment (VFA) based on DXA has attracted much attention, but it can only be used as a reference for the existence of vertebral compression fracture instead of as a basis for the diagnosis of osteoporosis. A least significant change (LSC) should be established for each DXA instrument by technicians. For more details, please refer to the ISCD 2007 consensus (www.iscd.org.tw). The incidence of bone fracture of Taiwanese is similar to those of Caucasians; it is reasonable to apply the WHO diagnostic criteria based on the incidence of bone fracture in postmenopausal Caucasian women on postmenopausal Taiwanese women. Also, after reviewing the guidelines of ISCD and multiple countries, it is believed that this criteria is also applicable to aged men[4]. Individuals with T-score, calculated using the average bone density of individuals aged 20-29 (to date, it is still recommended to use the default data of Asians) as standard, ≧-1.0 are with normal bone mass, where osteopenia (also known as low bone mass or low bone density) is indicated by a T-score falling between -1.0 and -2.5. The diagnosis of osteoporosis is confirmed when the T-score is ≦-2.5, and patients with concomitant bone fractures are defined as cases of severe osteoporosis[1]. For individuals with

T-scores >-2.5, the existence of low traumatic fracture or a decrease of >20% in the height of vertebral body still warrants the diagnosis of osteoporosis [3].

While most instruments adapt the WHO diagnostic criteria based on the T-score from DXA, a consensus is still lacking for the diagnostic criteria derived from evidence-based data, and a consistent cut-off for intervention has yet to be defined. Calcaneus QUS, or dual/single photon absorptiometry (peripheral bone densitometry) of other parts of the body is recommended for screening, but not as an evaluation tool for follow-up. In case of abnormal results, said DXA technique should be used for hip and lumbar examination to confirm the condition. DXA data prevails when there are inconsistencies between the QUS and DXA data. In Taiwan, there are at least 1000 QUS of all types, but consensus on the standards of the consistency of instrumental accuracy and operator quality has not yet been defined. It is expected that The Taiwanese Osteoporosis Association will hold another initiative for the creation of evaluation tools and standards to improve the testing quality and the consistency of results.

For adults aged 20-49, the diagnosis of osteoporosis should be considered only when a patient has low impact fracture events, and the confirmed high risk of bone fracture as determined by the presence of low bone mass shown in the results of DXA, where the DXA results should be interpreted using the Z-score. For children and adolescents under 20, the diagnosis of osteoporosis is not applicable because of the differences in definitions.

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Section 3 Indications for DXA Scan and Recommendations for Follow Up

Editors: Yin-Fan Chang, Chih-Hsing Wu

Grade of Recommendation	Content of Recommendation	Level of Evidence	Number of Reference
Indications for Examinations			
A	Bone density testing using dual-energy X-ray absorptiometry (DXA) should be performed on women aged ≥65.	1++ 2++	1,2 9,11,12
A	Bone density testing using dual-energy X-ray absorptiometry (DXA) should be performed on postmenopausal women aged ≤65 with the risk factors of bone fracture.	1++ 2++	1,2 3,9,11,12
B	Bone density testing using dual-energy X-ray absorptiometry (DXA) should be performed on men aged ≥70.	2++	4-9,11,12
B	Bone density testing using dual-energy X-ray absorptiometry (DXA) should be performed on men aged 50-70 with the risk factors of bone fracture.	2++	4-9,11,12
B	Bone density testing using dual-energy X-ray absorptiometry (DXA) should be performed on individuals aged ≥50 with low impact fracture(s).	2++	3,9,11, 12,13
C	Bone density testing using dual-energy X-ray absorptiometry (DXA) should be performed on individuals with conditions related to loss of bone mass.	2++	9,11,12
B	Bone density testing using dual-energy X-ray absorptiometry (DXA) should be performed on individuals using medications related to loss of bone mass.	2++	3,9,11,12
Follow-up			
B	Bone density should be monitored every 2 years for treated women aged ≥65.	2++	9,11,12
D	Bone density should be monitored every 3 years for untreated postmenopausal women.	2++	9

Description

Dual-energy X-ray absorptiometry (DXA) is used to measure the bone mineral density (BMS) of the hip bone and lumbar spine, and it has become an important element for diagnosing osteoporosis, predicting the risk of bone fracture, and assessing treatment efficacy. In 2002, the recommendations provided by the U.S. Preventive Service Task Force (USPSTF) after systematic review indicated that preventive screening of bone density using DXA should be performed on women aged ≥65 and women aged 60-64 with risk factors[1,2]. In 2003, the American Association of Clinical Endocrinologists (AACE) recommended bone density screening for women aged ≥50 with low impact fractures[3]. Later, the Rotterdam Study and the Osteoporotic Fractures in Men Study (MrOS) suggested the screening for prevention should cover men aged ≥70 and men aged 50-70 with risk factors[4-8]. The International Society of Clinical Densitometry (ISCD) 2007 guideline added that bone density testing should also be

performed on patients with conditions, or medication use, related to loss of bone mass[9]. For healthy men and women aged ≤50, there is no evidence supporting the effectiveness of preventive screening.

Repeated bone densitometry using DXA is an important method for the assessment of therapeutic efficacy, and the appropriate interval is crucial because the degree of change in bone density may be less than the precision of DXA measurement. The conclusion of the Study of Osteoporotic Fractures suggests that DXA monitoring for women aged ≥65 should be performed every 2 years[10], but the recommended interval for women aged ≤65 and men was not discussed.

So, who requires bone density testing? Based on the USPSTF 2002 recommendations[1,2], ISCD 2007 guideline[9], NOF 2008 recommendations[11] and USPSTF 2010 recommendations[12], we suggest the following patient to be tested:

(1) Women aged ≥65 or men aged ≥70

(2) Postmenopausal women aged ≤65 with risk factors of bone fracture

(3) Women right before cessation of menstruation, and with significant risk factors of bone fracture, including low body weight, history of bone fracture and/or using medication(s) associated with a high risk of bone fracture

(4) Men aged 50~70 with risk factors of bone fracture

(5) Individuals aged ≥50 with low impact fractures

(6) Individuals with conditions that may lead to low, or loss of, bone mass

(7) Using medications associated with low, or loss of, bone mass

(8) Any individual considered for administration of osteoporotic drugs

(9) Individuals getting treatment to monitor efficacy

(10) Individuals with evidence of loss of bone density, and who may be able to receive treatment

- **Bone Density Testing for Follow-Up:**
  (1) Individuals not receiving aggressive treatment are not recommended to receive BMD measurement more than once a year (unless the osteoporosis is secondary to glucocorticoid). Generally, monitoring every 2 years is acceptable.
  (2) It has been suggested that at least one year of treatment is required to control the risk of bone fracture; this means at least one year, preferably two years, of continuous treatment should be administered before the efficacy assessment using DXA.
  (3) A significant change is indicated when the change exceeds least significant change. Take the DXA instrument for example; it is 3~6% for the hip bone, or 2~4% for the lumbar spine[9].

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Section 4 Clinical Risk Factor (CRF) and Fracture Risk Assessment Tool (FRAX)

Editor: Chih-Hsing Wu

Grade of Recommendation	Content of Recommendation	Level of Evidence	Number of Reference
Assessment of Clinical Risk Factors			
B	The One-Minute Osteoporosis Risk Awareness Test by the International Osteoporosis Foundation helps increase the number of individuals for screening, but this test cannot be used to identify osteoporosis.	2++	5
B	The evaluation of clinical risk factors is unable to replace the role of bone densitometry in the diagnosis of osteoporosis.	2++	5,6
Fracture Risk Assessment Tool (FRAX)			
B	For Taiwanese aged 40-90, the Taiwanese FRAX formula can be used to obtain a quick glimpse of the risk of osteoporosis-related fracture.	4 2++	1,2 4
D	DXA and other examinations are recommended for untreated individuals whose ten-year overall risk of osteoporosis-related fracture is 10~20%.	4	1,2
D	DXA and other examinations are recommended for untreated individuals whose ten-year risk of osteoporosis-related hip fracture is higher than 1.5~3%.	4	1,2
D	Intervention is recommended for untreated individuals whose ten-year overall risk of osteoporosis-related fracture is >20%.	4	3
D	Intervention is recommended for untreated individuals whose ten-year risk of osteoporosis-related hip fracture is >3%.	4	3
D	Economic and insurance factors should also be considered when determining the FRAX cut-offs for intervention.	4	3
B	FRAX is unable to replace the role of bone densitometry in the diagnosis of osteoporosis.	2++	6

Description

The screening of osteoporosis should be focused on searching for risk factors, and the One-Minute Osteoporosis Risk Awareness Test (IOF) is a good example in terms of the collection of information regarding lifestyle, family history, medical history and medication history. Bone density testing should be performed on individuals with significant risk factors, especially women aged ≥65. To facilitate early screening and prevention, it is recommended to refer to the Evaluation and Treatment of Osteoporosis in Taiwanese Women published in 2007. As the risk of bone fracture in men aged ≥65 has increased, it is recommended to refer to the Evaluation and Treatment of Osteoporosis in Taiwanese Men published in 2007 to facilitate early screening.

The Fracture Risk Assessment Tool (FRAX) is a practical assessment for the prediction of osteoporosis-related bone fracture [1,3]. The Taiwanese formula based on the incidence of hip fracture [4] and corresponding10-year mortality is already available online: http://www.shef.ac.uk/FRAX/?lang=cht. An estimated major fracture risk of <10% or an estimated hip fracture risk of <1.5% indicates a low risk, where an major fracture risk of 10~20% or a hip fracture risk of 1.5~3.0% means a medium risk, and a high risk is defined as a major fracture risk of >20% or a hip fracture risk of >3.0% [1, 2, 3]. When FRAX is administered on treatment- and evaluation-naive men and women aged 40-90, DXA evaluation or other further examinations are suggested for individuals with medium risk, and intervention is recommended for those with high risk [3].

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Chapter 6. Approaches for Prevention and Treatment of Osteoporosis without Medication

Editor: Keh-Sung Tsai

Abstract

Osteoporosis and related bone fracture can be attributed to various genetic and environmental factors. In the prevention of osteoporosis and bone fracture, these environmental factors can be addressed with safety enhancement and lifestyle modification, and they are essential for preventive measures, although education and a strong will are also required. When compared to medication and surgery, the cost required to overcome the issues related to lifestyle and environmental factors is less likely to impose a burden on society. In this chapter, diet, exercise, lifestyle and fall prevention are discussed, and surgical intervention is also discussed because of its importance in treatment.

Section 1 Diet

Editor: Yi-Chin Lin

Grade of Recommendation	Content of Recommendation	Level of Evidence	Number of Reference
Calcium and Dairy Products			
B	Calcium intake is positively correlated to bone mineral accretion/bone density and decrease of bone mass loss.	1- 2+ 2-	3,4 2,5 1
B	Higher calcium dietary intake is associated with a lower risk of bone fracture.	1- 2+	3,4 5
C	Dairy product intake is positively correlated to bone mineral deposit or bone mineral density (BMD).	2+	5,7, 8
C	Dairy product intake is not associated with the risk of bone fracture/is associated with a significantly lower risk of bone fracture (no related randomized controlled trials to date).	2+	8
Vitamin D			
B	Vitamin D deficiency is one of the main contributors of osteoporosis.	1+ 1-	12 10
C	The normal level of serum 25(OH)D (vitamin D status marker) is positively correlated to BMD.	2++	11
B	Vitamin D supplement has a dose-reaction relationship on the reduction in the risk of non-spinal and hip fractures and the level of serum 25(OH)D (when the serum level ≥75 nmol/L).	1+ 1-	12 10
B	Vitamin D can reduce risk of falls by improving muscle function.	1+2++	13 11
B	For individuals aged ≥65, the 25(OH)D level is suggested to be kept at ≥75 nmol/L to effectively lower the risk of non-spinal fractures and falls.	1+2++ 3	12,13 11 9
Phosphorus			
D	Bone formation may be affected by phosphorus deficiency despite the concomitant administration of bone formation medication and high-dose calcium supplement.	3	16
Protein			
B	Protein intake is positively correlated to bone density, and the use of protein supplement is positively correlated to a higher bone density of lumbar spine.	1+ 2+	15 14
B	There is no significant correlation between the amount of protein intake and the incidence of hip fracture.	1+ 2+	15 14
Vitamin K			
B	Vitamin K supplement helps control the level of undercarboxylated osteocalcin.	2++	17 18

Grade of Recommendation	Content of Recommendation	Level of Evidence	Number of Reference
C	Low vitamin K1 (phylloquinone) intake (about 200-500μg/d) has no significant effect on the bone density change of lumbar spine and femoral neck.	2++	17 18
C	Phylloquinone intake is associated with a lower risk of hip fractures.	1- 2+	19 20
C	The osteoporosis treatment using high dose (45mg/d) of MK-4 (menaquinone-4, vitamin K2) provides protective effect for the bone density or bone fracture risk in lumbar spine or palmar bone.	1- 2+	19 20
Vegetarian			
C	The bone density in the lumbar spine and femoral neck of vegetarians is lower than that of non-vegetarians, and the difference in bone density is statistically significant between vegan and non-vegetarians; a less significant difference is found between lactoovovegetarians and non-vegetarians.	1- 2++	22 21
Table Salt/Sodium			
C	Dietary salt/sodium intake is positively correlated with urinary calcium excretion.	2+ 2-	24,25 23
C	Dietary sodium intake (as indicated by urinary sodium secretion) is negatively correlated with the bone density of hip bone and lumbar spine.	2+	24 25

I. Calcium and Dairy Products

Low blood calcium level caused by insufficient dietary calcium intake induces active vitamin D synthesis with the release of parathyroid hormone (PTH), which elevates blood calcium to the normal level by facilitating intestinal calcium absorption and bone resorption. On the contrary, calcitonin, a hormone released by thyroid gland, controls increased blood calcium with the inhibition of bone resorption and stimulation of bone formation. Sufficient dietary calcium intake provides controlled bone resorption with the inhibition of PTH release, as well as the material required for bone formation.

The association between calcium intake and bone density or loss of bone mass found in the cross-sectional or observational studies is less consistent when compared to those noted in the prospective studies. The analysis in earlier studies, such as Riggs et al. and van Beresteijn et al., did not show association between dietary calcium intake and loss of bone mass in premenopausal and postmenopausal women [1,2]. A meta-analysis on sixteen cross-sectional studies by Cumming (1990) showed consistent low ($r < 0.10$) yet significant positive correlation between calcium intake and bone mineral deposit. In the same article, twelve prospective intervention studies on postmenopausal women were reviewed and a “highly consistent” correlation between calcium supplement and bone mass loss was found: it was estimated that the difference between the supplement group and control group in the average rates of bone mass loss was 0.8%[3]. However, the author also pointed out that the inconsistent quality of the

included studies was one of the concerns. Twenty seven cross-sectional studies (with men and women aged 18-50) were included in a meta-analysis by Welten et al. (1995), where the result showed that, for permenopausal women, a significant positive correlation (r=0.13, 95% C.I.=0.09 – 0.16) was present between calcium intake (average: 436-1086 mg/d) and bone mass. Two long-term follow-up studies (subjects included women aged 18-29, the duration of follow-up was 2 years and 3-4 years) did not show a relationship between calcium intake (average: 820 and 909 mg/d, respectively) and the change of bone mass in the lumbar spine or middle third of radius. An analysis on four intervention studies indicated that intervention with calcium intake (average baseline intake: 651-1000 mg/d; dose of supplement: 550-1500 mg/d) provides prevention of the annual 1% prevention of bone loss in the lumbar spine, radius, humerus or overall (ulna excluded). It should be noted that this review has some important problems such as that too few randomized controlled trials (RCTs) were included, and differences in the evaluation of diet[4]. Also, the accuracy of bone mineral quantification may not be consistent because most studies were conducted when DXA was not available, or had not become a standard tool.

Most intervention studies showed that the use of calcium supplements has a positive effect: of the thirty seven intervention studies (including RCTs, balance studies and bone turnover studies) with adults included in a systematic review by Heaney, thirty five studies showed an association between increased calcium intake and reduced aging-related bone mass loss and a lowered risk of osteoporosis-related bone fractures in at least one body part[5]. The two studies with insignificant results include a study on 77 healthy men where the average calcium intake of control group was high (1159 mg/d), and another study was conducted on early postmenopausal women [5]. A meta-analysis on fifteen intervention studies with postmenopausal women by Shea et al. revealed statistical significance favoring the intervention group in terms of weighted average changes in overall bone density, along with those of the lumbar spine (where supplements had been provided for two years), hip bone and middle third of radius. It should be noted that the bone density changes in the third and fourth years were less significant than the changes in the first and second years [6]. The relative risks (RR) of spinal and non-spinal fractures in the intervention group were 0.77 (95% C.I.: 0.54 - 1.09) and 0.86 (95% C.I.: 0.43 – 1.72), respectively. It was concluded that intervention with calcium intake is associated with minor benefits for the bone density of postmenopausal women, and a trend of lowered risk of spinal fracture [6].

Basically, dairy products are considered the richest and most important dietary source of calcium, where the contained lactose and tyrosine facilitate its absorption, and these are ideal sources of animal proteins that stimulate type 1 insulin-like growth factor (IGF-I). Of the thirty-two observational studies included in the Dietary Guidelines Advisory Committee (DGAC) report, twenty-five showed significant positive correlation between dairy product intake and BMC/BMD values [7], and a positive correlation was noted in four RCTs[8]. Of the eight observational studies exploring the relationship between dairy product intake and bone fracture risk in the 5 DGAC report, significantly lower bone fracture risk was noted in five studies, and no relationship was found between dairy product intake and bone fracture risk in the other three non-RCTs[7].

In Taiwan, the dietary reference intake (DRI) of calcium for adults aged ≥19 is 1000 (the adequate intake [AI]) – 2500 (upper limit) mg/d.

Table 2 provides the main dietary calcium sources listed in the Food Composition Database (Food Industry Research and Development Institute, Department of Health, Executive Yuan), Nutrient Database for Standard Reference (U.S. Department of Agriculture) and information regarding food portion sizes.

Calcium reservoir (mg)	Item	Size
≥350 mg	Hi-iron hi-calcium non-fat milk powder, hi-calcium non-fat milk powder, hi-calcium hi-fiber non-fat milk powder, non-fat instant milk powder	25 g (about 3 tablespoonfuls)
	Hi-calcium non-fat milk	240 c.c. (1 mugful)
300-349 mg	Milk protein, low-fat milk powder, Protison	25 g
	Cheese (Swiss, reduced fat Mozzarella, Cheddar)[2]	1.5 oz (about 40 g)
	Green amaranth	100 g
250-299 mg	Goat milk powder	25 g (about 3 tablespoonfuls)
	Hi-iron hi-calcium non-fat milk, whole-fat milk, low-fat milk, low-fat preserved milk, preserved goat milk	240 c.c.
200-249 mg	High-fiber milk powder, whole-fat (instant) milk	25 g
	Whole-fat preserved milk, high-calcium high-protein milk	240 c.c.
	Cheese (Blue, whole-fat Mozzarella)[2]	1.5 oz
	Black sesame	15 g
	Dried fish	10 g
	Chinese broccoli, black nightshade, honewort	100 g
120-199 mg	Fruit milk powder	25 g
	Strawberry yogurt, high-calcium flavored milk, non-fat preserved fermented milk, plain fermented milk	240 c.c.
	Black sesame powder, sesame paste	15 g
	Shrimp skin	10 g
	Fried marlin floss	35 g
	Red amaranth, amaranth, sprout, gynura	100 g

Source: 1. Food Industry Research and Development Institute [27]

2. Nutrient Database for Standard Reference (U.S. Department of Agriculture) [26]

Table 6-1 Main Calcium Sources in Diet[1]

II. Vitamin D

Vitamin D has a close relationship with bone health because it maintains the balance of calcium and phosphorus in the human body and regulates active calcium absorption in the intestines. With its limited supply in natural foods, sun exposure is the main source of vitamin D other than fortified foods and supplements. Vitamin D deficiency is associated with poor bone calcification, which leads to rickets in children and osteomalacia in adults, and elevates the risk of osteoporosis-related bone fractures.

Serum 25(OH)D (25-hydroxy vitamin D) is used to determine vitamin D status: deficiency is defined as a level of ≤25 nmol/L, while a level of 25-75 nmol/L indicates insufficiency. Adverse reaction may happen when the level comes to >250 nmol/L(9). In a meta-analysis by Bischoff-Ferrari et al. (2005), two of seven RCTs exploring the preventive effect of intervention with vitamin D supplement on bone fracture showed statistically insignificant effect on hip and non-spinal fractures at doses of ≤400 IU/d, while significant decrease of hip (pooled RR=0.74, 95% C.I.=0.61 - 0.88) and non-spinal (pooled RR=0.77, 95% C.I.=0.68 - 0.87) fractures was noted in five other studies using doses of 700-800 IU/d. An inverse linear correlation was found between the decrease of relative bone fracture risk and serum 25(OH)D level[10]. In the twelve RCTs with subjects aged ≥65 included in a meta-analysis published in 2009, significant protective effect on non-spinal fracture was not found in the three using doses ≤400 IU/d. On the contrary, nine with doses >400 IU/d (482-770 IU/d) revealed significant effect (pooled RR=0.80, 95% C.I.=0.72 - 0.89; for hip fracture, pooled RR=0.82, 95%C.I.=0.69 - 0.97). Further analysis showed significant higher protection effect against bone fracture when serum 25(OH)D ≥75 nmol/L[11, 12].

A meta-analysis based on eight RCTs exploring the relationship between intervention with vitamin D supplement and falls showed that the protective effect is dose-related: seven studies based on intervention with higher doses (700-1000 IU/d) showed significant prevention effect against falls (pooled RR=0.81, 95% C.I.=0.71 - 0.92), while it was absent in the two administering doses of <700 IU/d (pooled RR=1.10, 95% C.I.=0.89 - 1.35), and subjects with a serum 25(OH)D level <60 nmol/L (pooled RR=1.35, 95% C.I.=0.98 - 1.84)[13].

The meta-analyses described above suggest a dose-related effect of vitamin D supplement on the reduction of risk of non-spinal or hip fracture and serum 25(OH)D level (at ≥75 nmol/L), indicating that the fall risks may be controlled with the improvement of muscle function by vitamin D supplement. However, this is not the case when serum 25(OH)D level is <60 nmol/L. In the U.S. and Canada, the elderly are recommended to maintain a serum 25(OH)D level of ≥75nmol/L in order to control the risk of non-spinal fractures and falls. Yet, this level of vitamin D3 is difficult for most Caucasian adults with vitamin D synthesis via sun exposure and limited dietary vitamin D intake. It is estimated that an increase of 10 nmol/L in serum 25(OH)D could be achieved by supplement at 700 IU/d, and the increase would come to 25nmol/L when the dose is titrated to 1000 IU/d[9, 11].

The recommended dietary allowance (RDA) of vitamin D for adults aged 19-50 in Taiwan is 200 IU/d (5 μg/d), and 400 IU/d (10 μg/d) for those aged 51-70. The limit is 2000 IU/d (50 μg/d).

III. Protein

Protein is one of the most important components of the bone matrix, but a consensus on the relationship between protein nutritional status/dietary protein intake and bone health is lacking. It is believed that the metabolites of dietary protein, especially animal protein, are the sources of acid load that causes lower blood pH and loss of bone mass because one of the regulatory mechanisms to maintain pH homeostasis in human body is to release acidic hydrogen ion and other alkali ions by accelerating bone resorption. In addition, some claimed that protein intake has a negative effect on calcium retention through elevated urinary calcium excretion. However, many analyses showed that protein intake at 1.0 - 1.5 g/kg is positively correlated to the maintenance of calcium homeostasis without metabolic effects on the skeletal system [14].

In a systematic review and meta-analysis on cross-sectional or cohort studies by Darling et al. (2009), it was shown that BMD is positively correlated to protein intake. The explanatory power of protein intake for BMD is 1-2%. A meta-analysis based on six high-quality RCTs showed that intervention with protein supplement is significantly correlated to bone density of the lumbar spine (weighted mean difference between the supplement group and control group = 0.02, 95% C.I.=0.00 - 0.04), and leads to the decrease of bone resorption indicators. For the reduction of hip fracture risks, significant relationship was not found in cohort studies and intervention with supplements [15].

In Taiwan, the RDAs of protein intake for adults are: 60 (men) and 50 (women) g/d for individuals aged 19-30, 56 (men) and 48 (women) g/d for those aged 31-50, 54 (men) and 47 (women) g/d for those aged 51-70, and 58 (men) and 50 (women) g/d for those aged ≥71.

IV. Phosphorus

Hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$], a molecule formed containing phosphorus and calcium, is the most important mineral that exists in the bone matrix. Also, phosphorus in blood is subject to strict control by the endocrine system, where hypophosphatemia affects bone formation and mineralization, and elevates urinary calcium secretion with the release of PTH. Heaney emphasized the possibility of the combination of unabsorbed dietary calcium with phosphorus and other minerals that leads to lower absorption efficiency. For patients with osteoporosis, especially the elderly, it is crucial to maintain balanced, adequate phosphorus intake so that osteoporotic agents with bone formation and the concomitant high-dose calcium supplement take full effect, and ensure unaffected bone formation [16].

The adequate intake (AI) of phosphorus for adults aged 19-30 or ≥ 51 is 800 mg/d, and 600 mg/d for individuals aged ≥30~50.

V. Vitamin K

Vitamin K is the key cofactor in the carboxylation of osteocalcin, the most abundant non-collagen protein in the bone matrix, and its carboxylation is related to its ability of trapping and fixing hydroxyapatite; it may also play a role in bone formation and the maintenance of bone density and bone strength. Vitamin K status can be judged using the percentage of undercarboxylated osteocalcin (%ucOC).

Natural vitamin K comes from phylloquinone (K1) found in green leaves and vegetable oil, and menaquinones found in animal tissues and gut flora. A systematic review on cross-sectional and observational or cohort studies by Shea and Booth concluded that a negative correlation exists between phylloquinone intake and the risk of hip fracture, whereas higher blood ucOC in aged patient is related to it. Unfortunately, the relationship between phylloquinone intake and bone density was found to be inconsistent, and significant reduction of the risk of hip fracture was not observed in the RCTs based on intervention with phylloquinone supplement. In a review by Cashman et al., vitamin K1 supplement had no significant effect on bone mass loss at major sites (overall, lumbar spine, middle third radius and femoral neck)[18]. In the thirteen intervention studies included in a systematic review and meta-analysis on RCTs using intervention with vitamin K supplement by Cockayne et al., significant reduction of bone loss with the supplement phytonadione (synthetic vitamin K) and MK-4 was observed in twelve studies, and an additional meta-analysis on the seven studies with bone fracture data showed that MK-4 supplement significantly reduces spinal (OR=0.4, 95% C.I.=0.25 - 0.65), hip (OR=0.23, 95% C.I.=0.12 - 0.47) and non-spinal (OR=0.19, 95% C.I.=0.11 - 0.35) fractures. It should be noted that these seven studies were conducted with Japanese subjects [19]. A systematic review on postmenopausal women by Iwamoto et al. showed that vitamin K1 and K2 significantly reduced the percentage of ucOC in blood and the incidence of femoral neck fracture despite inapparent improvement in bone density was noted. It was concluded that vitamin K supplement helps reducing the incidence of fractures because of its benefits for bone strength and bone quality [20].

In summary, higher vitamin K1 intake or vitamin K supplement (MK-4) may improve bone strength and reduce the incidence of bone fracture through the enhancement of bone strength with osteocalcin carboxylation. In Japan, vitamin K2 is classified as an antiosteoporotic agent with bone formation activity, and the highest dose of MK-4 for osteoporosis treatment is 45 mg/d. Recommended or adequate intake level is still unavailable in Taiwan.

VI. Vegetarian

Vegetarians can be classified, according to the limitation on food choices, into lactovegetarian, ovo-vegetarian, lactoovovegetarian and vegan. Most believe that the intake of nutrients related to bone health, such as calcium and vitamin D, of vegetarians may be lower than of non-vegetarians, and vegetarians are at a higher risk of osteoporosis and bone fracture related to lower bone mass and bone density because their consumption of dairy products and animal foods is limited. In fact, the diet pattern of vegetarians, replacing animal foods with large amount of vegetables and fruits, allows higher intake of potassium, magnesium and other minerals, which leads to a higher net base load to promote bone health by reducing acid load caused by standard diets, hence maintaining the reservoir of basic ions and hydrogen ions, and a lower bone resorption rate. After reviewing several large cohort studies, Smith reported that the bone density at the hip of vegans is significantly lower than of non-vegetarians, but a consistent trend of the differences in the intake of calcium and vitamin D is lacking, and the evidence suggesting higher hip fracture risk in vegans than in non-vegetarians is not very convincing [21]. A meta-analysis by Ho-Pham et al. showed that the bone density of the femoral neck and lumbar spine in vegetarians is 4% (95% C.I. = 2% - 7%) lower than in non-vegetarians, and the difference is more significant for vegans (6%, 95% C.I. = 2% - 9%) than lactoovovegetarians (2%, 95% C.I. = 1% - 4%). The incidence of a 5% lower bone density in the femoral neck and lumbar spine is 42% for vegetarians, whereas it is 32% for non-vegetarians, suggesting that the difference in bone density between vegetarians and non-vegetarians has no significant association with the risk of bone fractures [22].

VII. Avoid High Sodium Intake

Dietary sodium intake is positively correlated to urinary calcium excretion, giving rise to a negative calcium balance and accelerated bone resorption as a compensatory measure. A review on the health effect of salt intake by de Wardener and MacGregor (2002) confirmed that high sodium intake is associated with higher urinary calcium secretion, and is positively correlated to the risk of hip fracture. It was hypothesized that halving sodium intake provides reduction of bone mass loss that is equivalent to doubling calcium intake [23]. In a review by Teucher and Fairweather-Tait published in 2003, the urinary secretion of sodium and calcium is positively correlated. An estimation based on three cross-sectional studies showed that the urinary calcium secretion is increased by 1 mmol/d (40 mg) when an additional 100 mmol/d (2300 mg) of sodium is eliminated from the body. However, the relationships between dietary sodium intake, bone turnover marker, bone density or the risk of bone fracture are still unclear [24]. A recent analysis of 1098 Chinese aged ≥65 in Hong Kong by Woo et al. (The Chinese University of Hong Kong) showed that bone density at hip is negatively correlated with the urinary sodium-to-creatinine ratio, and is positively correlated with BMI, urinary potassium-to-creatinine ratio and dietary calcium intake. A similar trend is also observed from the bone density in the lumbar spine - a negative association with urinary sodium-to-creatinine ratio, and a positive association with BMI, dietary calcium intake and systolic pressure. The average dietary calcium intake of this group is 580±282 mg/d, and 78% subjects had average sodium intake of ≥2300 mg/d. It was concluded that high urinary sodium excretion related to high dietary sodium intake facilitates urinary calcium excretion. Decrease of dietary sodium intake is suggested[25].

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Section 2 Exercise and Activity

Editor: Jackson Pui-Man Wai

It is recommended to increase bone density and prevent bone density loss with exercise-based interventions or physical activities.

Grade of Recommendation	Content of Recommendation	Level of Evidence	Number of Reference
A	Low to moderate intensity weight-bearing impact exercise - walking is associated with a consistent and significant improvement for the bone mineral density (BMD) in femoral neck. Brisk walking provides better effect than casual walking, and the effect of longer intervention is longer than those of shorter periods. More significant effect is seen in individuals with lower BMD.	1++ 1+ 2++ 1-	1 3-6 7 2
A	High intensity weight-bearing impact exercise - jogging and running improve the BMD in lumbar spine, femoral neck and calcaneus.	1+ 2++	8,9 10-12
A	Mixed weight-bearing impact exercise - the combination of aerobic exercise including walking, jogging and stair climbing provides notable improvement in the BMD in several vital body parts (lumbar spine, femoral neck, proximal femur).	1+	13-17
A	Special impact exercise - side stepping, jumping rope, stepping and stair stepping with a ground reaction force of ≥2x body weight improve the bone density in lumbar spine and femoral neck in premenopausal and postmenopausal women.	1+	17-22
A	Mixed resistive exercise/weight training provides notable improvement for the BMD in lumbar spine and femoral neck, and the effect is site-specific.	1++ 1+	25,26 23,24
B	Squash and tennis improve the BMD in lumbar spine and limbs (that is, a site-specificity was noted), while long-term high-intensity training is required.	2++	27,28
B	There is no medical evidence supporting the beneficial effect of swimming on the BMD, and long-term swimming training may lead to BMD loss in several body parts.	1+ 2++	29 30,31
B	The medical evidence supporting the beneficial effect of cycling on the BMD is lacking, and long-term cycling training may lead to loss of BMD in lumbar spine.	2++	32-35
A	The medical evidence supporting the effect of Tai Chi on controlling loss of BMD is inadequate.	1++ 1+ 1-	39 36,38 37

Exercise is an activity engaged in the movement of one or more body parts. Studies exploring the bone health benefits of exercise have focused on the "contact" with objects during the movements, i.e. impact exercise. When the reaction force involved in the exercise has no direct relationship with body weight, it is called non-weight-bearing impact exercise, such as punching sandbags, volleyball contact, clapping, board kicking, stepping on the ground (the stepping side does not bear weight). In weight-bearing impact exercise, the reaction force is

directly related to body weight (including the reaction force from the ground). Examples include walking (low intensity), brisk walking (moderate intensity), and jogging, running and jumping rope (high intensity).

●Low to Moderate Intensity Weight-Bearing Impact Exercise - Walking and Brisk Walking

Walking is associated with a more consistent and notable improvement for the bone mineral density (BMD) in the femoral neck. Brisk walking provides better effect than casual walking, and the effect of longer intervention is better than those of shorter periods. More significant effect is seen in individuals with lower BMD.

A systematic review using a meta-analysis [1] on eight eligible RCTs with intervention based on simple walking exercise provided more robust evidence supporting the beneficial effect on the BMD of postmenopausal women from this intervention, but its effect on the BMD loss in the lumbar spine was inconclusive. Derived from five studies, the weighted mean difference of BMD in the femoral neck between the experimental group and controlled group is 0.014 $g \cdot cm^{-2}$ (it was found to be random effects). Several statistical analysis methodology and subgroup analyses were used to define the attrition rate, nutrition supplement, hormone replacement therapy and instruments used in the measurement process. However, the effects of different walking speeds were not compared. The meta-analysis in an earlier systematic review[2] on ten studies (including only five RCTs) with men and women subjects aged ≥50 showed that the intervention plan based on walking exercise provided effective control for the BMD loss in the lumbar spine, but significant effects were not present in the femoral neck or calcaneus. The effects of different walking speeds were not compared.

In studies with the intervention based on brisk walking, it was found that brisk walking has a positive effect on the BMD in the lumbar spine of postmenopausal women. For example, after seven months of walking exercise with an intensity exceeding anaerobic threshold (at 7.2 kph [4.5 mph]), at a duration of 30 minutes and a frequency of three times a week, the BMD of the experimental group increased by about 1%, whereas a decrease of 1.7% was found in the control group[3]. In another study, postmenopausal women were included and were asked to walk 5 km at a speed of 6.1 kph (3.8 mph); a significant increase of overall (+0.4%, +0.005 $g \cdot cm^{-2}$) and foot (+0.08%, +0.001 $g \cdot cm^{-2}$) BMD was observed after 15 weeks, while a decrease of these values was seen in the casual walking group (-1.3% and -1.1%, respectively)[4].

Brisk walking provides minimal alleviation of BMD loss for postmenopausal women, which means the duration of intervention is short. In a two-year brisk walking exercise program[5], a postmenopausal nurse with the history of arm fractures had a 2% net increase in femoral neck BMD when compared to the control group, but no increase was noted in the lumbar spine. However, this apparent effect may be because of two years of intervention and the lower BMD of the subject. The BMD in the lumbar spine of postmenopausal women with osteopenia or osteoporosis in the exercise group (with moderate intensity [at 50% of maximum oxygen uptake] of walking exercise) increased by 1.7% after 12 months, showing a nearly 4% difference when compared to the control group (with a 1.9% decrease of BMD)[6]. This suggests that individuals with low bone mineral density may receive significant benefits from a moderate speed walking exercise program.

Long-term engagement of low- and moderate-intensity exercise, e.g. walking, provides appealing prevention for bone fractures. A cohort study (12 years)[7] showed that the risk of femur fracture of nurses walking four hours a week (no other exercise) is 41% lower than in those walking less than 1 hour a week.

●High Intensity Weight-Bearing Impact Exercise - Jogging and Running

Larger ground reaction forces (GRF) are generated during jogging and running, which translate to larger impact forces to the longitudinal axis of bone and effectively increase the BMD in adults. The BMD loss in men can be controlled by continuous training based on running exercises.

A significant increase (1.3%) of the BMD in the lumbar spine of young women (19.9 years old in average) was noted after an 8-month training session of running with graded loading[8], similar to those who attended strength training (+1.2%). However, no improvement of the BMD in the proximal femur (femoral neck greater, trochanter and Ward's triangle) was found after training. After a 9-month training session, the bone mineral content in the calcaneus of adult men (aged 38-68, with an average age of 48) running 141 km each month increased by 3%[9].

A cross-sectional study showed that the overall BMD (+3.6%) and BMD in legs (+9.6%), femoral neck (+10.0%), trochanter (+9.9%) and Ward's triangle (+11.8%) of athletes engaged in endurance running (aged 19-54, with an average of 32) was significantly higher than in the control group[10]. The BMD in the calcaneus of aged male athletes (aged 70-81, with an average of 74) engaged in long-term running and cross-country skiing (0.186 $g \cdot cm^{-2}$) was significantly higher than in those of the control group (0.165 $g \cdot cm^{-2}$) by 12.7% (11-16%)[11]. The third National Health and Nutrition Examination Survey showed that the BMD in the femur of male joggers jogging ≥9 times a month (1.104 $g \cdot cm^{-2}$) was higher than in those jogging 1-8 times a month (1.071 $g \cdot cm^{-2}$) by 3.1%, and the latter was higher than in individuals going without exercise (1.036 $g \cdot cm^{-2}$) by 3.4%[12].

●Mixed Weight-Bearing Impact Exercise - Walking, Jogging and Stair Climbing

The combination of aerobic exercise including walking, jogging and stair climbing provides notable improvements for the BMD in several vital body parts (lumbar spine, femoral neck, proximal femur) of postmenopausal women.

After a year of exercise intervention started with moderate intensity then graded to high intensity, postmenopausal women benefited in terms of increased overall BMD (+2%), and increased BMD in the lumbar spine (+1.8%), femoral neck (+3.5%), Ward's triangle (+6.1%)[13]. The femoral neck BMD in younger perimenopausal women (aged 52-53) did not show significant loss (increased by 0.00074 $g \cdot cm^{-2}$) after 18 months of moderate-high intensity aerobic exercise (walking, jogging, stair climbing and biking)[14]. The degree of the increase of the overall BMD and BMD in the lumbar spine, femoral neck and Ward's triangle of postmenopausal women (aged 60-72) who received hormone replacement therapy and participated in weight-bearing aerobic exercise (moderate- to high-intensity walking, jogging, and stair climbing) was higher than in subjects with exercise or hormone therapy alone[15]. However, exercise alone not only improves BMD but avoids the risk of the side effects associated with hormone replacement therapy. BMD in the lumbar spine of postmenopausal women (aged 55-70) who received concomitant calcium supplement (1,500 mg/d, 60% of the average calcium intake) and some resistive exercise with high intensity aerobic exercise,

including walking, jogging and stair climbing, at 70-90% of maximum oxygen uptake for three 50- to 60-minute sessions a week was 5.2% at Month 9, and 6.1% at Month 22. Thirteen months after the cessation of training, the difference relative to pre-training was +1.1%, but no significant change of BMD in the lumbar spine was found in the control group receiving the same dose of calcium supplement [16]. Weight-bearing exercise helps improve the BMD in the lumbar spine and femur but the effect is site-specific. Without impact on the upper limbs, these forms of exercise provide very limited prevention effect on the BMD loss in the ultradistal wrist[15] or distal radius[14,17].

●Special Impact Exercises - Heel Jack without a Jump, Climb Stepping, Box Stepping, Jumping and Stepping Exercises

Special high impact exercises produce ground reaction forces of ≥2x body weight, including side stepping, jumping rope, forceful stepping and stair stepping for at least 6 months with a frequency of three days a week may improve the BMD in the lumbar spine and femoral neck of premenopausal and postmenopausal women.

High impact exercises producing ground reaction forces of ≥2x body weight, including jumping jack, running-in-place, knee-to-elbow with jump and low impact exercises producing ground reaction forces ≥1.5x body weight, including casual and brisk walking, heel jack without a jump, for 12 months with a frequency of three days a week and a duration of 20 minutes in each session help maintain the lumbar spine BMD in postmenopausal women. A 2.5% increase of BMD in the lumbar spine and femoral neck was noted in young females (aged 20.5 in average) after 6 months of exercise involving 10 times of jumping with maximal load-bearing in three of seven days in a week. The increase of BMD was not noted in other sites (such as Ward's triangle, trochanter, total hip). Significant improvement of BMD in the lumbar spine, femoral neck and proximal fibula of young premenopausal females (aged 35-45) who attended 18 months of high impact exercises producing ground reaction forces of 2.1-5.6x body weight, including aerobic jumping and high stair stepping[17], for three sessions a week was found. A 3-4% increase of BMD in trochanter, along with a similar increase in femoral neck, was found in young females who attended 6 months of daily exercise including 50 times of jumping or actions of jumping rope, but no change in the lumbar spine was noted[20]. Twelve months of special high-impact exercise including running, jumping, forceful stepping and drops in three of seven days in a week also increased BMD in weight-bearing sites[21, 22].

●Mixed Resistance Exercise Training /Weight Training

Four systematic reviews showed that resistive exercise training/weight training improves BMD in premenopausal or postmenopausal women: a review by Wolff et al.[23] on twenty-five RCTs showed that the weighted overall treatment effect is to prevent or reverse 1% of BMD loss in the lumbar spine or femoral neck every year, similar to the analysis of BMD change in the lumbar spine based on systematic reviews by Wallace and Cumming[24], where the latter showed that resistive exercise training/weight training increases BMD in the lumbar spine by 1.2% for premenopausal women, and 1.0% for postmenopausal women. In a review of fourteen RCTs by Martyn- St James and Carroll[25], resistive exercise training/weight training provided significant BMD increase (0.006 $g \cdot cm^{-2}$, fixed effect p=0.006) in the lumbar spine, and another review on eleven RCTs showed an increase of 0.010 $g \cdot cm^{-2}$ (random effect, p=0.11) in the BMD in the femoral neck. A systematic review by Zehanacker et al.[26] showed that the effect of resistive exercise training/weight training is site-specific - BMD changes only appear in the bones bearing body weight or the pulling forces of muscles. This indicates that this training should be provided in a way that facilitates the balanced development of limbs. Also, Zehanacker et al.[26] summarized effective training prescriptions in different intervention studies and found that the ideal exercise should be performed at an intensity of 70-90% of one-repetition maximum arranged in two or three 8- to 12-repetition sessions a day, and it is recommended to do them 3 days a week.

●Other Exercises - for Enhancing Overall BMD or Providing Site-Specific Effects

Squash and tennis improve the BMD in the lumbar spine and limbs (that is, site-specificity was noted), while long-term high-intensity training is required.

In Finland, the BMD in many body parts, including lumbar spine (+13.8%), femoral neck (+16.8%), distal femur (+11.2%), patella (+6.7%), proximal tibia (+12.6%), sole (+18.5%) and distal radius (+11.3%), of female athletes engaged in tennis and squash is higher than in those of untrained female nurses. For females who attended aerobic dancing training, higher BMD was found in the femoral neck (+8.5%), proximal fibula (+5.5%) and sole (+13.6%), but a significantly lower value was found in the distal radius (-7.8%) when compared to the untrained controls[27]. Higher BMD was found in the forearm of the dominant arm (+6.5%), lumbar spine (+15%), femur (including femoral neck, Ward's triangle, greater trochanter and intertrochanteric zone [+10~+15%]) of male professional tennis players when compared with those without training exercises, but no differences were found in the BMD in the left forearm, left and right leg[28].

●Swimming and Leg Cycling Exercise

There is no medical evidence supporting the beneficial effect of swimming on BMD, and long-term swim training may lead to BMD loss in several body parts. Medical evidence supporting the beneficial effect of cycling on BMD is lacking, and long-term cycling training may lead to loss of BMD in the lumbar spine.

In an animal study, 16 weeks of swim training was provided to prepubertal mice, and the BMD of many body parts (skull, humerus, spine, femur, fibula) was 5-9% lower than in the control group[29]. The overall BMD (-10.4%) and BMD in the lower limbs (-14.8%) of male athletes engaged in long-term non-weight-bearing long-distance swimming was lower than those of untrained controls [30]. When compared to the male athletes engaged in 12 other exercises, the BMD in the lumbar spine and legs of these swimmers was lower than average[31].

For aged male athletes (mean age 51.8) engaged in long-term cycling training, their BMD in the lumbar spine and hip was significantly lower than that of the untrained controls[32], and a similar trend (-4.8% and -10.0%, respectively) was seen in middle-aged (aged 20-59, average: 38.1) cyclists when compared to those engaged in running training[33]. The effect on spinal BMD was measured in anteroposterior and lateral scans, where the BMD was 6.7% and 14.3% lower than for the untrained controls, respectively. In younger (aged 20-30, average: 24.7) male cyclists, BMD in the body parts engaged in the exercise (i.e. lumbar spine, hip and overall) was not different from sedentary controls of the same age[35].

●Tai Chi

A preferred choice of middle-aged and aged individuals to stay fit, Tai Chi involves slower, low-impact movements with lower physical strength demand; however, it does not provide much direct physical pressure on bones. RCTs provide no evidence to include the control of BMD loss as one of the benefits of Tai Chi. A systematic review of five eligible RCTs and two controlled clinical trials (CCTs)[36] showed that most Tai Chi intervention programs do not alleviate BMD loss in the vital parts (lumbar spine, femoral neck and hip) of postmenopausal women. These studies were conducted on middle-aged or aged subjects with 4-12 months of intervention, indicating that further studies are required to explore the effectiveness of longer intervention based on this low impact exercise training. Another systematic review of two RCTs and four non-RCTs[37] concluded that Tai Chi may help alleviate the BMD loss of postmenopausal women, but it is not convincing because only two RCTs were included. Training with Tai Chi may not provide significant benefits for the BMD of postmenopausal women, but it seems to improve physical function, blood pressure control, and lead to a lower risk of falls[38]. Unfortunately, most intervention studies based on Tai Chi are unable to fulfill the requirements of the strict Consolidated Standards for Reporting Trials[39]. We hoped that more robust studies based on this exercise will be conducted to improve internal validity, and explore its scientific value with the backup of evidence-based medicine.

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■ Section 3 Lifestyle

Editors: Yi-Chin Lin, Wen-Ham Pan

Grade of Recommendation	Content of Recommendation	Level of Evidence	Number of Reference
B	A body mass index of ≤18.5 kg/m2 is strongly discouraged.	2++ 2+ 4	1,2 3,4 5
B	Avoid smoking. Smokers are encouraged to quit smoking to avoid the risk of osteoporosis and bone fracture.	2++ 2+	6,7,8,10 9
B	Alcoholism is discouraged - control alcohol intake for better health.	2++ 2+	11 12

●Body Mass Index (BMI)

Lifestyle is a main component of overall health and a key contributor of disease. In this guideline, the relations of smoking, drinking and BMI to osteoporosis and the risk of bone fracture are discussed.

●BMI

To prevent the chronic diseases secondary to being overweight/obese including hypertension, diabetes, stroke, cardiovascular diseases and cancers, healthcare practitioners recommend people maintain a BMI (calculated by dividing weight by height square) of 18.5-24 (kg/m^2). It is especially important for the prevention of cardiovascular diseases s because their risk is associated with higher BMI.

Nevertheless, the relationship of BMI to bone density and the risk of bone fracture is different from that of other chronic diseases, and this issue has attracted much attention. In this guideline, only meta-analyses, systematic reviews and information related to Taiwan are included: A meta-analysis on twelve cohort studies revealed that, when BMI is increased by 1, the risk of hip fracture is decreased by 7%, and by 2% for osteoporotic fracture. The risk of hip fracture in individuals with a BMI of 20 is 95% higher than in those with a BMI of 25, and the risk of hip fracture is decreased by 17% when comparing individuals with a BMI of 30 to 25. A systematic review on one hundred and sixty-seven studies exploring risk factors showed that low body weight (BMI <20) or 10% decrease of body weight is a key risk factor for osteopenia or bone fracture. In a 2009 review, it was concluded that the bone density at the hip and lumbar spine increased by 3-7% for each 10 kg increase of body weight, and the observation holds for Chinese, Americans, and Europeans.

In summary, in terms of the risk of osteoporosis and bone fracture, higher BMI may provide protection, and individuals with lower BMI are at risk. Considering the need of balanced, overall health, the expert panel warns about the risk of low BMI, but does not recommend gaining weight to ensure healthy bone mass. Yet, the threshold of low BMI is hard to define. According to the criteria of obesity from the Department of Health, the ideal range of BMI is 18.5-24. Using the lower boundary as the threshold, the expert panel recommends a BMI of ≥18.5.

In an unpublished study by W.H. Pan et al., the BMI obtained from a cohort of 140,000 individuals who attended health examinations at the MJ Life Health Screening Center in 1994-1996 was used to explore its relationship with medical costs and mortality in 2007, showing that medical costs for bone fractures are similar between all BMI groups. However, when considering non-smokers only, mortality related to bone fracture in BMI <18.5 non-smokers is higher than in those with a BMI of 18.5-19.9 or 20-21.9, where the differences reach only marginal significance. This finding does not contradict the recommendations shown above.

●Smoking

Smoking is a risk factor for cardiovascular diseases, cancers and many clinical conditions, and it is also harmful in terms of bone density and bone fracture. A meta-analysison twenty-nine observational studies (about 16,000 subjects were included) showed that the risk of hip fracture in aged smokers is increased by 41%, and bone density at the femoral neck, radius and calcaneus is lower. A meta-analysis on eighty-six observational studies (about 40,000 were included) and another on ten cohort studies (about 60,000 were included) showed that the lifetime risks of osteoporosis, hip fracture and overall fracture are increased in smokers. In short, the literature provides strong evidence for the benefits of a cigarette-free life. Evidence supporting quitting smoking is scarce. In the 1990s, Hollenbach showed that a dose-effect relationship exists in the bone density of non-smokers, ex-smokers and smokers, and Wong et al. concluded that smoking has a dose-effect relationship with bone mass, where quitting smoking partially reverses lost bone mass. To maintain good bone health, avoid cigarettes, and smokers are encouraged to quit.

●Drinking

Many studies showed that alcoholics have lower bone density and bone formation, and a higher risk of bone fracture, but the effect of moderate alcohol intake on bone density and the risk of bone fracture remains controversial. Five of fifteen observational studies included in a review study showed that moderate alcohol intake is positively correlated to bone density in the hip and lumbar spine, but this was not found in five other studies. To date, no evidence showed that moderate alcohol intake deteriorates bone health. In the dietary guidelines for Taiwanese, the recommended daily alcohol intake is fewer than two drinks(10 g of alcohol per drink) for men and one drink for women. Therefore, the expert panel discourages heavy alcohol consumption –individuals should drink moderately, if at all, for better health. This is consistent with the recommendations on other chronic conditions from the Department of Health.

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Section 4 Fall Prevention and Nursing Care

Editors: Joyce Kee-Hsin Chen, Li-Fen Chao, Hsueh-Erh Liu

Grade of Recommendation	Content of Recommendation	Level of Evidence	Number of Reference
A	No single assessment tool can be universally applied to every institutions and/or different patients. Healthcare professionals must choose a fall assessment tool that is most appropriate for the patient based on the medical conditions.	1+	1
A	Patients with cataracts, glaucoma, or blurred vision should receive special treatment to correct visual acuity.	1+	2,3
A	Hip protectors can be provided to residents live in skill nursing home, but the effect is limited in acute care. Wearing hip protectors may reduce hip fracture rate among nursing home residents. However, it did not show the same results at home or acute care settings.	1++	4-7
B	Pharmacists review and provide a written summary of medications that may lead to falls. Review those medication side effects that could increase the risk of fall such as dizziness, and limb weakness. Educate the patients and caregivers accordingly.	1+	8
B	The use of multiple strategies of fall prevention in medical facilities is associated with lower risk of falling and falling-related injuries.	1++	9-11
B	Primary care, community and acute care settings can use multiple fall-prevention approach to prevent falls and related injuries.	1++	12
B	Heart disease should be treated (for example, pacemaker for arrhythmias).	1++	4
D	Healthcare professionals should be aware of the causes of previous falls, identify individuals at high risk for falls, and provide a fall prevention warning signs to increase staff and caregiver's attention.	4	13
D	Patients who take sedative/hypnotic agents should void the bladder before bedtime and avoid drinking water before going to bed.	4	14
D	Wearing low-heeled, comfortable, covered, non-slip shoes, and the right size clothes. Keep bathroom floors dry and install non-slip facility and hand rails.	4	15
D	Place the aids, glasses, bed pans, or bedside nursing calls in the readily available place.	4	13
D	Make sure that medications are reviewed and adjusted appropriately and gradually reduce sedative/hypnotics and anti-depression medications.	4	14
D	Increase the indoor lighting, allow a unobtrusive aisle at home and avoid protruding furniture. Electrical supplies wire should be attached to the wall. Daily supplies and appliances should be placed at the patient's waist level for easy access.	4	13,14

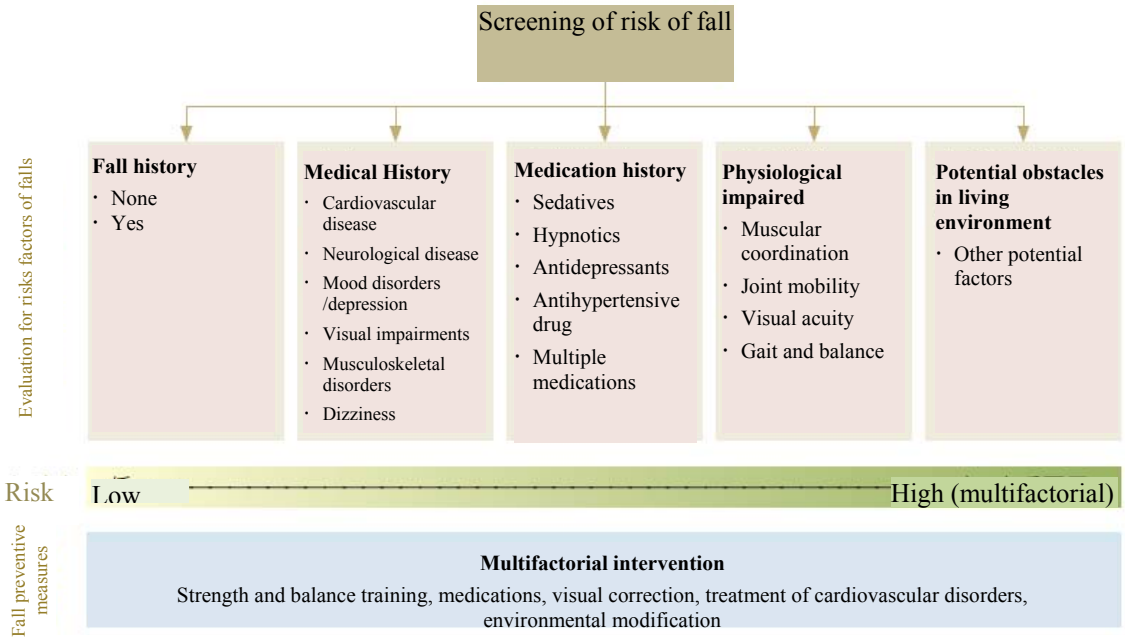

Fig. 6-1Maintain health, improve physical function, ensure safe environment

I. Assessment Tools for Fall Risks

Vassallo, Stockdale, Sharma, Briggs and Allen (2005)[16] compared the benefits of the four assessment tools for fall risks (i.e. STRATIFY, Downton, Tullamore and Tinetti). It was found that STRATIFY is the shortest and easiest tool of all, and it has the highest predictive value but the lowest sensitivity. Kim, Mordiffi, Bee, Devi and Evans (2007)[17] validated the effectiveness of three assessment tools for patients with a high fall risk (MFS, STRATIFY and HFRM) in identifying patients of interest. It was found that Heindrich II Fall Risk Model has the potential of identifying patients with high fall risks. On the contrary, some studies showed that STRATIFY has a high negative predictive value and low positive predictive value and total predictive accuracy, suggesting that it is not an effective tool for the screening of patients with a high fall risk. In addition, the result of STRATIFY may vary when administered to different groups and in different locations[10, 18].

Scott et al. (2007)[1]conduct a systematic review of published English researches that test the validity and reliability of fall-risk assessment tools for use among elderly in community, home-support, long-term and acute care settings. Searches were conducted in EbscoHost and MEDLINE between 1980 and July 2004, where the primary or secondary purpose was to test the predictive value of one or more fall assessment tools on a patient primarily 65 years and older. Thirty-four articles met the inclusion criteria. The community setting represents the largest number of studies (14) and tools (23) tested, followed by acute (12 studies, 8 tools), long-term care (LTC) (6 studies, 10 tools) and home-support (4 studies, 4 tools). Eleven of the thirty-eight options are multifactorial assessment tools (MAT) covering a wide range of risk factors of falls. Twenty-seven functional mobility assessment (FMA) tools are gait-related assessments focused on physical activities, stretching or balance. It was concluded that the tools assessing fall risks for most healthcare settings have moderate to good validity and reliability. It should be noted that only a few tools have been used more than once, or tested in more than one facility, indicating that there is no single tool applicable to all facilities or different patients. Morse Fall Scale requires complex calculation, and Hendrich II Fall Risk Model has too many

items and is too complex in structure, so these two are not extensively used in the automated nursing records in hospitals[19, 20].

A 12-month, clustered RCT by Meyer, Köpke, Haastert and Mühlhäuser (2009)[21] included residents of 29 nursing homes (experimental: 574; control: 551; 1,125 in total) to assess the effectiveness of standardized assessment tools for fall risks and clinical judgements of nurses and compared with those with clinical judgements of nurses alone. Structured education for fall prevention was provided to all residents before randomization. Monthly assessment with Downton Index was conducted for the experimental group but not in the control group. It was revealed that these two groups are similar in the proportion of residents who experienced at least one fall (experimental: 52%; control: 53%; mean difference - 0.7; 95% CI=10.3~8.9, P=0.88) and the number of events (n = 1,016 and n = 1,014), showing that the use of assessment tools of fall risks in nursing homes does not provide better clinical outcome[21].

Dynamic Gait Index (DGI) is a tool for the assessment of gait, balance and risks of falls, and it can be used for the assessment of walking on flat ground and more challenging tasks. Herman, Inbar-Borovsky, Brozgol, Giladi and Hausdorff (2009)[22] assessed the balance and transfer function of 278 healthy elderly, where Dynamic Gait Index (DGI), Berg Balance Test (BBT), Timed Up and Go (TUAG), Mini Mental State Exam (MMSE), the motor exam of Unified Parkinson's Disease Rating Scale (UPDRS), Activities-specific Balance Confidence (ABC scale) and annual incidence of falls were assessed. The study showed that, when compared with non-fallers, the DGI score of fallers is worse (p=0.029). Despite the high possibility of ceiling effects, this seems to be a suitable choice for the evaluation of health function in the elderly.

The observation by Melzer, Benjuya and Kaplanski (2004) [23] showed that the elderly with a history of falls tend to have worse balance function, and are more "shaky" when standing on a narrow base. This might be a useful method for the identification of falls in aged individuals. In the static two-point discrimination (TPD) test, the performance of the elderly with a fall history is worse (14.93±1.1 mm vs. 12.98±0.3 mm). Easy and safe to use, these tests can be used to determine if the elderly are at high risk of falls, and can become a choice for the screening of high risk individuals.

Mackenzie, Byles and D'Este (2009)[24] included 727 legionnaires and war widows aged ≥70 in a prospective study validating The Home Falls and Accidents Screening Tool (HOME FAST). The baseline tests for enrolled subjects included the assessment of the risk factors of falls, and the risk at home using "HOME FAST". The changes in "HOME FAST" scores were used to predict the incidence of falls in the next three years based on a logistic regression model, and it was found that the incidence of fourteen risk items in "HOME FAST" was lower than baseline ($p \leq 0.05$). The incidence of falls had a significant correlation with the baseline "HOME FAST" score (odds ratio [OR] 1.016, 95% CI=1.004 - 1.098, $p = 0.006$), and a lower risk at home was noted in follow-up (OR 0.984, 95% CI=0.973 - 0.996, $p = 0.02$). This indicates that HOME FAST is able to predict falls in the elderly and discriminate. The items of "HOME FAST" include: bedside lamp, grab rail in bathroom, well-lit outside path, identifiable stair edges, toilet in close proximity to the bedroom, grab rail extending along the full length of outdoor steps, flat carpet/mat, safe transfer from chairs, slip resistant mats in bathroom, safe transfer before/after shower, adequate lighting, safe use of entrance door(s), safety transfer before/after toilet, safety transfer to/from bed, safe use of stairs, flat floor, accessibility of cupboards, walkway free of clutter, safe attendance to pets, dry floor, safe shoes, safe transfer into bathroom, and safe handling of meals

By summarizing the published assessment tools for the risk of falls, Currie (2006)[25] introduced a universal scale for acute and chronic care, which includes:

1. General Scale
   (a) Tinetti Performance Oriented Mobility Assessment (POMA): an easy task-oriented assessment for the gait and balance function of adults. The ability of maintaining balance is assessed when the patient attends to activities of daily living (ADLs); the test items include balance, and the strength of limbs. This assessment takes 10-15 minutes, but examiner's training is required.
   (http://web.missouri.edu/~proste/tool/Tinetti-Balance-Gait--POMA.rtf)
   (b) Berg Balance Scale (BBS): The ability of maintaining balance in adults is assessed with 14 clinical items when the patient attends to activities of daily living (ADLs); the tests include balance, and upper and lower limb strength. This assessment takes about 15-20 minutes, but examiner's training is required.
   http://www.strokecenter.org/trials/scales/berg.pdf)

(c) Elderly Fall Screening Test (EFST): a screening tool for falls in the elderly, and used as an algorithm for screening and referral.
(http ://www. saskatoonhealthregion.ca/pdf/05_Elderly%20Falls%20Test%20 procedure.pdf)

(d) Dynamic Giant Screening Test: define the possibility of falls in adults by assessing the ability to correct gait pattern in a changing working setting. Eight dimensions of gait are tested. This assessment takes about 15 minutes, but tester training is required. (http://web.missouri.edu/~proste/tool/Dynamic-Gait-Index.rtf)

(e) Get Up and Go Test: assess the functional gait and balance of the elderly. The testee is asked to stand up without the assistance of arms, walk forward 10 feet, turn around and walk back to the chair and sit down; observation is made to confirm if there is a possibility of losing balance. To maintain sensitivity, the testee should complete the test in 16 seconds.
(http://www4.va.gov/ncps/SafetyTopics/fallstoolkit/
media/timed_up_and_go_test-07-15-04.pdf)

(f) Time Get Up and Go Test: a simple test used to confirm the risk of falls associated with balance or gait problems. The testee is asked to stand up from a straight back chair without the assistance of arms. Cane/walker can be used for assistance, and put on his/her shoes. The testee is then asked to walk forward 10 feet, turn around and walk back to the chair and sit down. The time required to finish a cycle is recorded. Adults without balance problems can complete the test within 10 seconds, while adults with difficulties in movement or ADL-dependent individuals may require more than 30 seconds completing it.
(http://www.fallpreventiontaskforce.org/pdf/TimedUpandGoTest.pdf)

(g) Functional Mobility Assessment (FMA) tools (functional mobility assessment tools, FMA)

2. Assessment tools for acute care facilities

(a) St. Thomas Risk Assessment Tool in Falling Elderly Inpatients (STRATIFY): a tool supported by strong evidence, and a risk score is generated by risk factor checking. This can be used to confirm the clinical risk factors of falls in the elderly, and predict the incidence of falls.
(http://www.bmj.com/content/315/7115/1049.full)

(b) Morse Falls Risk Assessment Tool (MFS): this is recommended by the National Center for Patient Safety to evaluate the risk factors of falls in hospitalized patients. MFS is extensively used in acute care units of hospitals and long-term care centers, and it is a systematic, reliable and validated option to be used at admission, after falls, change in condition, discharge or referral.
http://www4.va.gov/ncps/SafetyTopics/fallstoolkit/ notebook/05_FallsPolicy.doc)

(c) Hendrich Falss Risk Model I (HFRM-I) and Hendrich Falss Risk Model II (HFRM-II): Risk assessment tools for patients during hospitalization and/or receiving long-term care, and are recommended by the National Center for Patient Safety (http://www4.va.gov/ncps/ SafetyTopics/fallstoolkit/notebook/05_FallsPolicy.doc)

(d) Mini-Mental State Exam (MMSE): a versatile, validated, short screening tool to test the orientation, immediate callback, short term verbal memory, calculation, language and construction ability.
(http://neurologynerd.com/pictures/MMSE.jpg)

(e) Geriatric Depression Scale (GDS): a basic tool for the screening of depression in adults.
(http://www.stanford.edu/~yesavage/GDS.html)

3. Assessment tools for chronic care facilities

(a) Mobility Interaction Fall Chart (MIF chart)
(http://www.ncbi.nlm.nih. gov/pubmed/10998775)

(b) Downtown Instrument
(http://stroke.ahajournals.org/cgi/content/ full/27/10/1821; Downton JH. Falls in the Elderly. London, UK: Edward Arnold; 1993:64-80, 128-130)

II. Fall Prevention

(i) General principle for Fall Prevention:

To prevent falls and fall-related injuries, a multifactorial assessment should be administered to confirm potential risk factors of falls. Healthcare providers should be provided an individualized nursing care plan.

1. Assess the risk factors of falls:

(1) Physical and psychological assessment: risk factors included: age of ≥65 years old, history of falls, dizziness and/or weakness, weak limbs, unbalanced gait, poor coordination or balance, irritable behavior, requiring assistance in transfer or walking, frequent toilet visits or depression.

(2) Medication review: elderly using sedatives, hypnotics, antidepressants, or benzodiazepines tend to have a higher risk of falls[26]. Also, the use of antiepileptics, muscle relaxants, diuretics, laxatives, antihypertensives, analgestics, mydriatics as well as alcohol intake may be associated with an increased risk of falls. Patients should be told of side effects such as dizziness and weak lower limbs[8]. A survey by Zermansky et al. (2006)[8] on 661 subjects showed that the incidence of falls in patients provided with written information from medication review before the referral of family physicians was significantly lower than in the control group (95% CI 0.53 - 0.72). In a study by Crotty, Rowett, Spurling, Giles & Phillips (2004)[27], 110 nursing home residents referred from hospitals for the first time were included. Written summary of drugs for referral was provided by pharmacists, and medication review and case discussion were conducted by community-based physicians and pharmacists. However, this study did not indicate the number of subjects. By comparing the summarized data from these two studies, no statistically significant difference was found in the incidence of falls (random effects 0.90, 95% CI 0.62 - 1.32: I2 = 51%).

2. Assessment and Management of Visual Acuity[14]:

(1) For patients with poor vision, home environment safety help decrease the incidence and risk of falls[28]. However, the effect is not confirmative in other patients.

(2) Use glasses wisely: clean glasses regularly to maintain sharp vision. Do not wear presbyopic glasses when walking, and wear sunglasses when attending outdoor activities. Cumming (2007)[2] suggested that the most common measure for visual correction is to obtain a new pair of glasses, and it was found that weak elderly may require a relatively long time to adapt to new glasses, and the risk of falls is more profound during this period.

(3) Give eyes enough time to adapt to changes of light intensity.

(4) Achieve good diabetes control and attend annual visual examination.

(5) Elderly who completed cataract surgery is lower fall incidence than those on a waiting list (Harwood, 2005)[3], but individuals with early cataract surgery of the second eye have a postsurgical fall risk similar to those who received regular scheduled procedure [2,29]. Patients with cataract, glaucoma or blurred vision should receive treatment.

3. Assessment and Management of Bladder and Bowel[14]:

(1) Empty the bladder before bedtime or going out.

(2) Avoid intake of caffeine or alcohol.

(3) Maintain adequate dietary fiber and water intake and physical activity. Avoiding sit on toilet too long because of constipation. Individuals with bladder (e.g. polyuria) or bowel problems (e.g. constipation, diarrhea) should be treated as soon as possible.

(4) Maintain adequate blood sugar control as high blood sugar increases the risk of bladder inflammation.

(5) Wear loose or modified clothes (e.g. replace buttons with velcro, and replace belts with zipper or elastic waist band) to easily handle clothing before/after toilet use.

(6) Use elevated toilet seat when necessary. Bedpans are recommended for patients using diuretics, laxatives, sedatives and/or hypnotics.

4. Assessment and Management of Pain[14]:

(1) Maintain good posture when standing, sitting or walking to prevent injuries.

(2) Complete a pain diary: record pain score based on a numerical scale of 0-10, and the factors associated with deterioration or alleviation.

(3) Learn relaxing techniques to help lessen the emotional reaction caused by pain.

5. Sleep Hygiene[14]:

(1) The normal sleep pattern of the elderly is six hours each day with two interruptions each night. It is normal to fall asleep within 20 minutes after the interruption. When the interruption lasts for more than 20 minutes, activities such as reading or listening to music are recommended.

(2) Avoid caffeine-containing foods before sleep; warm milk is recommended. Alcohol intake should also be limited: it helps individuals fall asleep but affects sleep quality.

(3) Arrangement of more activities in daytime (e.g. walking for 20 minutes) is recommended, and sleeping in the evening is discouraged.

(4) Keep the room quiet.

(5) Learn relaxation techniques.

6. Foot care[14]

(1) Wear low-heel shoes with slip-resistant (for example, rubber) design.

(2) Buy slippers that provide support and cover the sole.

(3) Use sock aids and shoe helpers to assist in putting on socks and shoes to avoid body tilting.

7. Strategies for safe transfer (Fig 1 on the right page):

(1) Progressive postural change is suggested to avoid secondary hypotension.

(2) When performing postural changes, slow down the movement of getting up, and remain sitting for 1-2 minutes before standing up.

(3) For individuals with spinal or knee injuries, the higher mobile commode can be considered.

(4) Avoid carrying heavy objects. The use of assistive devices is recommended to improve balance.

(5) Understand the safe procedures of transferring to/from bed (wheelchair) and using assistive devices. (Refer to Fig 2 on the right page)

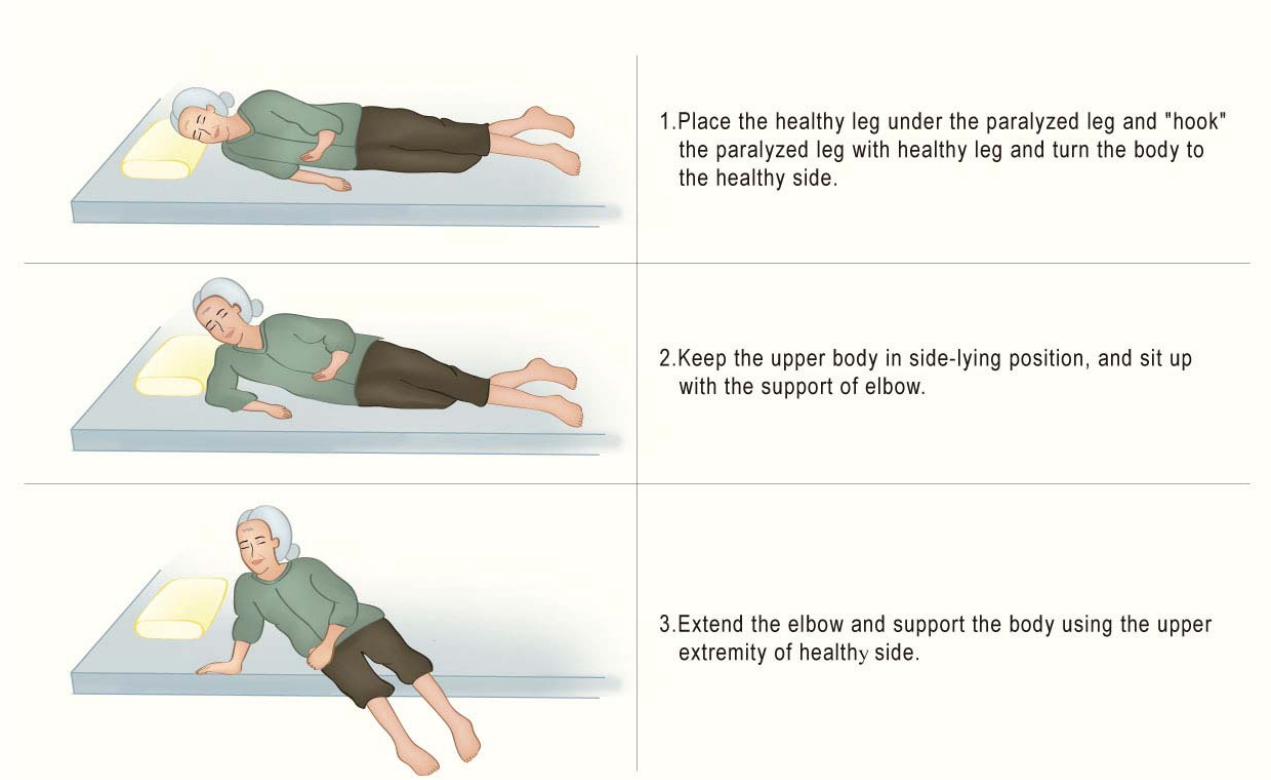

Fig. 6-2Get practice in changing position from lying to sit up

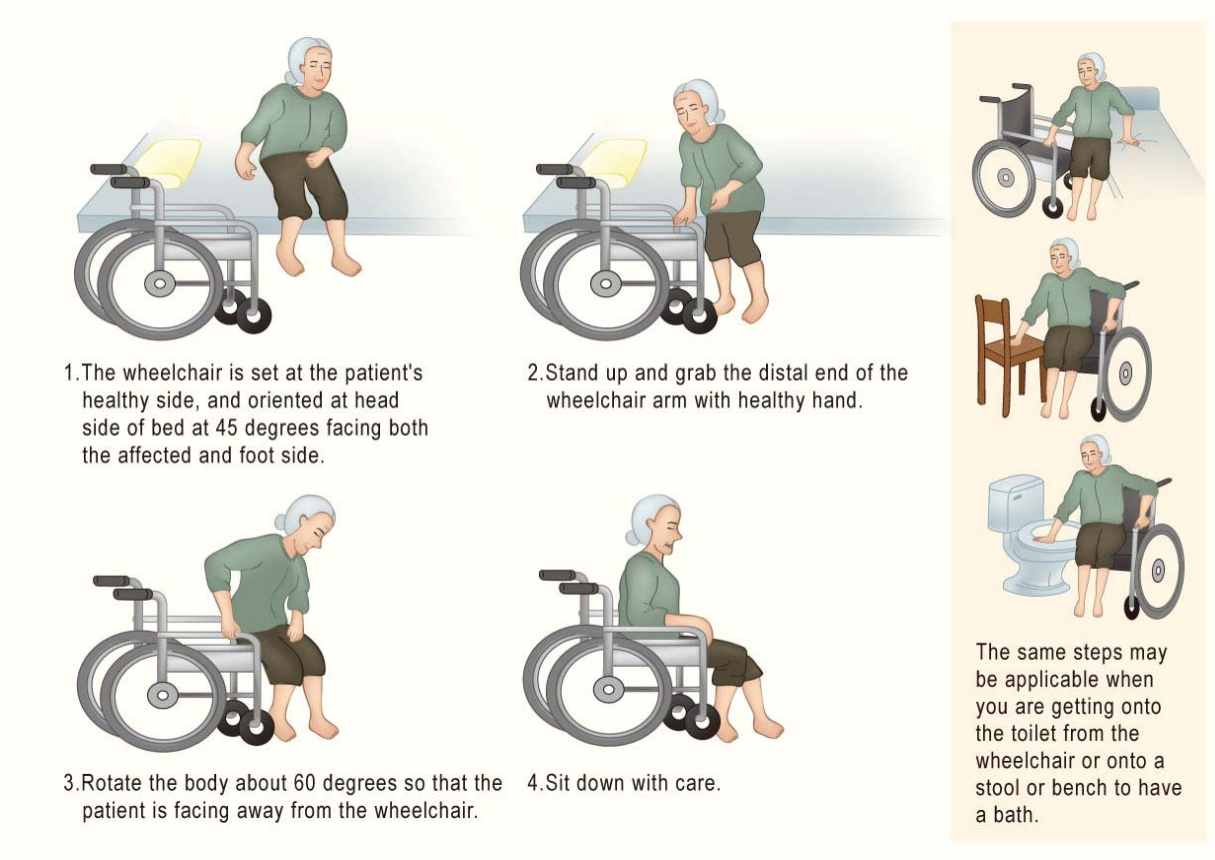

Fig.6-3Safe Procedures of Transferring to/from Bed (wheelchair) and Using Assistive Devices

(6) Avoid showering in the bathtub, or use walk-in bathtub to minimize the risk of falls when entering into/leaving it.

8. Environmental safety checking[14]:

(1) Indoor:

(a) Wireless or mobile phone should be provided to the elderly with risk factors living alone to ensure timely assistance after falling.

(b) Maintain cleanliness and avoid tripping by remove clutter or cords in walkways (e.g. cords of electric appliances should be kept against the wall).

(c) Label doorsills and stair edges with high contrast colors to avoid missing steps. To provide support during transfer, the installation of rails in corridors is suggested.

(d) Keep floor dry and use appropriate cleaner. Avoid over-waxing floors.

(e) Floor in bathroom and toilet should be kept dry and assistive grab bars and slip-resistive appliances should be provided. A "bathing chair" can be used for sitting baths. Do not shower when sitting at the edge of bathtub or on toilet.

(f) Provide adequate lighting in the lobby, stairs and bathroom, especially bedside or night lighting for the toilet.

(g) Avoid using furniture that may tilt or move when used as support. Rearrange the positions of furniture (especially for walker or wheelchair users).

(h) To ensure easy access, housewares and kitchen wares should be placed at waist height, and use a reacher to retrieve objects instead of reaching on a mobile stair.

(i) Install "emergency calls" to allow the elderly to ask for assistance.

(2) Outdoor

(a) Install automatic or scheduled lighting system.

(b) When going out, avoid slippery ground or crowded places. Using a cane or walker is a good way to remind others to preserve space for the elderly.

(c) Keep the center of gravity around the legs, and avoid straining while walking or standing

(d) Use waist packs, backpacks or bendable shopping carts instead of carrying heavy bags by hands.

(3) Environmental safety checklist:

(a) Centers for Disease Control and Prevention Check for Safety: A Home Fall Prevention Checklist for Older Adults (http://www.cdc.gov/ncipc/duip/fallsmaterial.htm#BRochures)

(b) Minnesota Safety Council Home Safety Checklist
(http://www.minnesotasafetycouncil.org/SeniorSafe/fallcheck.pdf)

(c) Taking Action to Prevent Falls
(http://www.stopfalls.org/files/ProgramExpansion-HomeAssessmentTool.pdf)

(ii) Fall Preventive Measures in Medical Facilities

The residents of a nursing home affiliated with Caulfield General Medical Centre were included in a three-year quality promotion program by Fonda, Cook, Sandler and Bailey (2006)[9]. A multi-strategy prevention approach was provided, and its effect on controlling the incidence of falls and fall-related injuries was discussed. Introduced in September 2001, this approach included information collection, fall risk screening, proper management, modification of environment and equipment, staff education, and the subjects were followed for 2 years. A 19% decrease in the number of falls (12.5 vs. 10.1, $p = 0.001$) and a 77% decrease in the number of severe injuries caused by falls (0.73 vs. 0.17, $p < 0.001$) were noted after this two-year program. In addition, the rate of staff's adherence to fall risk assessment increased from 42% to 70%, and 60% of staff indicated that they modified their working patterns to prevent the falls of residents. This suggests that a multi-strategy prevention approach plays an important role in the prevention of falls and fall-related injuries, and the incorporation of the program as a part of routine nursing practice is crucial for the success and sustainability of fall prevention.

Thirteen studies included in a systematic review by Oliver et al. (2007)[6]showed that the control of the incidence of falls can be facilitated by a multifaceted intervention program based on risk assessment, risk factor assessment, nursing plan, medical/diagnostic methodology, modification of physical environment, educational program, medication review, use of hip protector, removal of body restraint and exercise, and the incidence of falls and bone fracture is 0.82 (95% CI: 0.68 – 0.997) and 0.59 (95% CI: 0.22 – 1.58), respectively. The relative risk is 0.95 (95% CI: 0.71 – 1.27. However, eight nursing home studies did not provide enough evidence to prove the effectiveness of single- or multi-faceted intervention program, where the incidence of falls and bone fracture is 0.80 (95% CI: 0.59 – 1.09) and 0.91 (95% CI: 0.54 – 1.53), respectively. The relative risk is 0.92 (95% CI: 0.82 – 1.03. [6].

No evidence was found in a meta-analysis by Coussement, Paepe, Schwendimann, Denhaerynck, Dejaeger & Milisen (2008)[30] showing that the number of falls can be effectively controlled by fall prevention programs. These individual studies suggested the beneficial effect of these approaches when adapted in long-term care facilities. Kerse, Butler, Robinson and Todd (2004)[31] discussed systematic, individualized fall prevention approaches with existing resources, including administrating assessment tools for patient with a high fall risk, using watchout signs for high-fall-risk individuals, and provided solutions for identified risks. Unfortunately, these measures did not cut down the number of falls and fall-related injuries, and the effectiveness of low-intensity intervention may be worse than that of routine care. A study by Gates, Lamb, Fisher, Cooke, Carter (2007)[12] revealed that multifactorial fall prevention programmes in primary care, community-based, emergency care facilities provide limited control on fall and injury events.

Cameron et al. (2010)[11] conducted a systematic review of fall prevention programmes adapted in nursing facilities and hospitals. This included 41 studies with 25,422 subjects in total, where 3/4 were women and the average age was 83. Many of the participants had documented cognitive problems. The result showed that: (1) multifactorial fall prevention programmes in nursing facilities did not provide effective fall control, unless presented in an integrated form by a coordinated team; (2) the administration of vitamin D-containing drugs and the review of current medications by pharmacists may help reduce falls, yet there is no evidence showing that single-factorial measures including exercise are associated with a lower incidence; (3) multifactorial programmes in combination with exercise under supervision reduce the incidence of falls. However, it was unable to explore the effectiveness of each program as only a few hospital-based studies were included, with the adaptation of different elements.

- **Special attention should be placed on the following environmental/assistive factors:**

1. It has been shown that the use of carpet[32], fall alert bracelet[33] and bed alarm system[34] fails to provide effective control over the incidence of falls in hospitals.
2. Educate patients and caregivers about the method of transferring from the bed, notifying medical staff when caregivers are out of sight of patients, and provide training for the proper use of bedrails and bedpans. Assessment of the understanding of the patients and caregivers is required, and a consensus on fall prevention should be established.
3. Arrange beds based on patients' condition or care needs. For example, patients with right hemiplegia are better assigned to a bed that allows transfer at the left side, or minimize their distance from the nursing station to facilitate care.
4. Sensor of bed-leaving alarm should be used for patients with dementia, no family members aside, old age or who have experienced multiple fall events
5. Patients with high risk of fall should be clearly described in notes, and educational instructions and leaflets should be provided to patients and caregivers.
6. Objects used by patients, including assistive devices, glasses, urinal or bedside caller, should be within reach.
7. Bed wheels should be locked and routine checks are required to ensure functionality. Bed height should be kept at the lowest point between each treatment to allow patients to step onto the ground during their transfer.
8. Adequate restraints, such as safety belts, should be provided to wheelchair users.
9. Warning signs are suggested to be used as a remainder for staff and caregivers who take care of the high-risk patients, identified by screening tools.
10. Increase the frequency of visit to the high-risk patients.

(iii) Fall Prevention Measures at Home

In a systematic review by Gillespie, Robertson, Gillespie, Lamb, Gates, Cumming and Rowe (2009) [4], one hundred and eleven RCTs (55,303 subjects in total) were included. The findings are as follows: (1) Some studies indicated that referrals following the assessment in multifactorial intervention effectively control the incidence of falls, while some didn't. As a whole, it is believed that these measures decrease the incidence of falls, but the effectiveness factor was not confirmed because of their high complexity; (2) Interventions focused on home

safety are not effective unless provided to known high-risk patients; (3) Effective control of the incidence of falls may be achieved by the review and adjustment of certain medications that increase the risk of falls, such as those used to improve sleep quality or alleviate anxiety and/or depression; (4) Cataract surgery helps prevent falls related to poor vision, and the implantation of pacemakers is associated with a lower incidence of falls related to the changes of heart rate and blood pressure secondary to hypersensitivity of the carotid sinus.

III. Managements and Equipment for Minimizing Fall-Related Injuries

(i) Strategies for minimizing injuries and bone fractures

In an 18-month follow-up on 1200 elderly in community by Liang, Ji, Hu, Lin (2005)[35], 145 fall events were recorded, and the determination factors of the severity of fall-related injuries were analyzed. It was found that the severity of falls is determined by the movement of the victim's center of gravity, the direction of falls, and the landing body parts, where the fall injuries tend to be more severe when the victim's center of gravity moves vertically or horizontally than when there is no movement. This is also true for falling forward and sideward as compared to falling backward, and landing on the arm, forearm, shoulder (or higher body parts) and lower limbs when compared to landing on the gluteus.

(ii) Related risk factors and equipment

In the prevention of bone fractures, considerations include not only bone health, but other risk factors such as muscle strength and coordination, balance, use of medications that may induce hypotension, hyperglycemia or dizziness, cluttering of the environment, vision. When required, canes, walkers and hip protectors may be used (The Taiwanese Osteoporosis Association,http://www.toa1997.org.tw/index.php?page_id=9bf31c7ff062936a96d3c8bd1f8f2ff3&mod=bulletin_edit&id=35).

A hip protector is a plastic shield or foam pad placed close to the underwear to decrease the impact on the hip joint during a fall, and the corresponding risk of bone fracture. In facilities with higher incidence of falls, using hip protectors is able to secure a lower risk of bone fractures[5]. Earlier studies showed that a safe and reliable hip protector cuts down on the number of hip fracture events[7], and provides a promising control over the incidence of bone fractures in nursing homes[6]. However, the effect was challenged by new evidence: Sawka et al. (2005)[36] analyzed the effectiveness of hip protectors in nursing home residents and showed that more evidence is required to confirm the potential benefits. No evidence showed benefits when hip protectors are used by the elderly living at home, and most individuals are reluctant to use it because of discomfort[5].

A systematic review of fifteen clinical studies relating to the effectiveness of hip protectors in the prevention of hip fractures in the elderly by Cochrane showed that: (1) by summarizing the information gained in eleven studies conducted in nursing homes or institutions, it was found that hip protectors reduce the incidence of hip fractures (RR = 0.77, $p < 0.05$); (2) by summarizing three community-based studies, no significant decrease of the incidence of hip fractures was noted in subjects using hip protectors (RR = 1.16, $p < 0.05$); (3) hip protectors are not associated with severe side effects, but long-term adherence is poor; (4) the effectiveness of hip protectors against the incidence of hip fractures remains controversial [5].

IV. Immediate Assessment and Emergency Management

Education should be provided so that patients better understand protective strategies, especially those who are younger and in better physical condition with more activity and better reaction ability: reduce severity by allowing landing on the gluteus, which involves keeping the center of gravity to the rear[35].

In case of falls, they should not panic, and should not immediately move/get on their feet to avoid more serious injury due to another fall. They should get up slowly when it is okay to do so. They should use the emergency caller to ask for assistance from institutional staff or call "911" to reduce the risk of hospitalization or death [14]. Remind the patients: "Don't be shy! Use it!"

When the rescue team arrives, if the patient still lying on the ground, don't move, check his/her conscious level and vital signs first. Resuscitation and medical attention must be acquired if consciousness, breath and heartbeat are gone. For patients with stable vital signs, assessment should focus on bleeding, head trauma, any severe pain caused by falls, or swelling, deformity or immobility of limbs. If bone fracture is suspected, immobilization should be provided before medical management, which is strongly recommended even if injuries are not found in the initial assessment. By confirming that no injuries or fractures are present, patient safety is guaranteed [37, 38]. It is recommended to perform the initial assessment and subsequent actions in reference to the following procedures (refer to Fig 3).

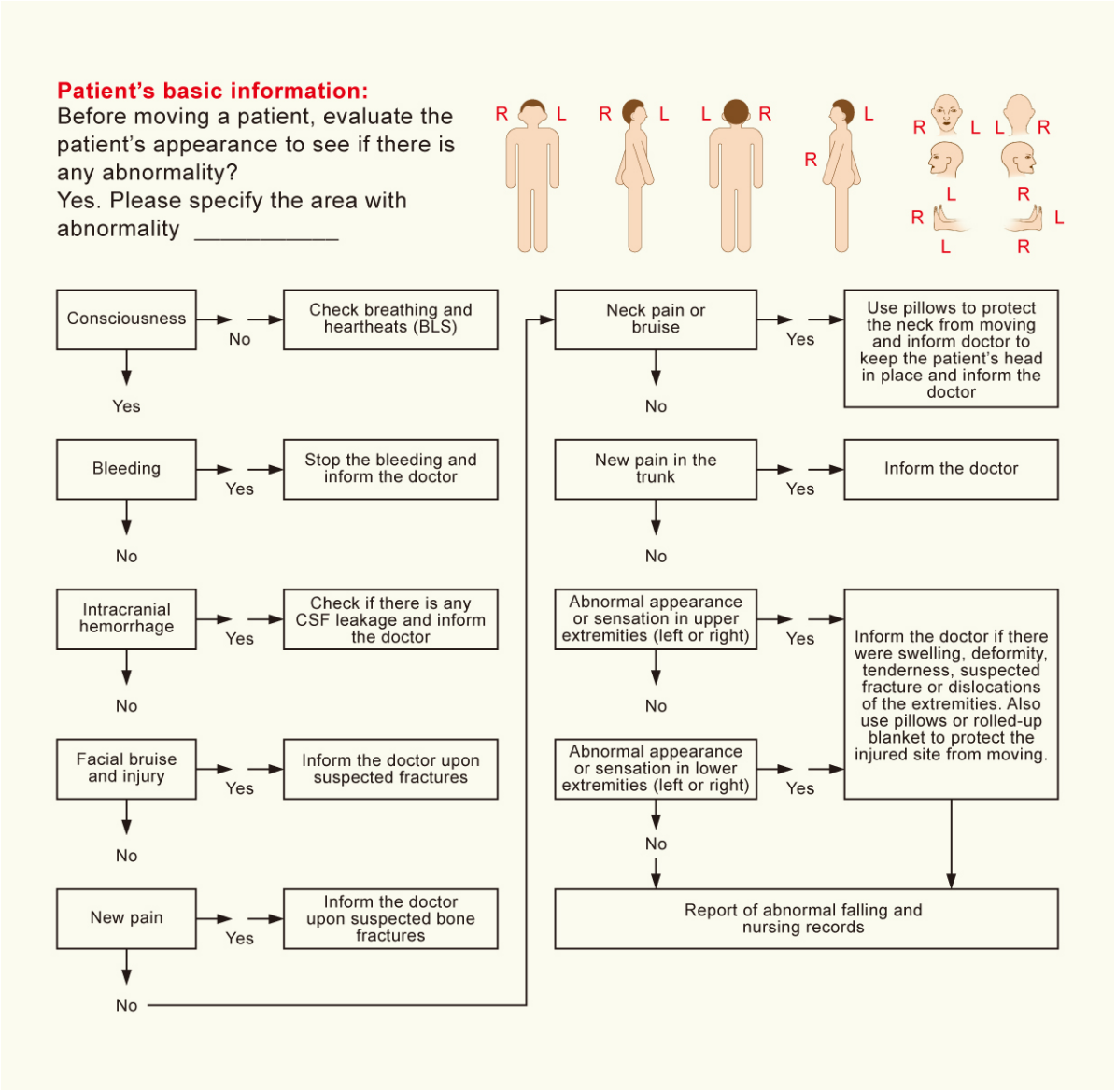

Fig. 6-4Procedures of post fall accidence

(Revised from: Fenton, W. (2008).Introducing a post-fall assessment algorithm into a community rehabilitation hospital for older adults. Nursing Older People, 20 (10), 36-39.)

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Section 5 Surgical Management of Osteoporosis Related Problems

Editor: I-Jan Kao

Grade of Recommendation	Content of Recommendation	Level of Evidence	Number of Reference
A	Early surgical intervention, typically hip arthroplasty, should be provided to patients with hip fractures to facilitate early rehabilitation.	1+	1
B	The rationale of early surgical intervention for spinal fracture patients without neural damage is inconclusive.	1	2
C	Vertebroplasty provides immediate pain relief to patients with acute spinal fractures. Please note that the patients should be told of the potential risks of the treatment.	3	3
C	Assistive device-based approach is effective in patients with non-weight-bearing limb fractures.	3	4

Osteoporosis is nearly asymptomatic until the development of pain, deformity or physical impairment because it lacks typical signs and symptoms. Therefore, bone fracture and the following changes are the key focuses of the current model. The use of antiosteoporotics provides a significant decrease of the risk of primary or secondary fractures. In consideration of secondary prevention, surgical intervention in combination with medication may play an active role. The healing of bone fracture includes three phases: inflammation, reparative and remodeling. Local necrotic inflammation and formation of spaces and hematoma may occur at the fracture site after the event. In the reparative phase, increased bone formation and the formation of woven bone take place, and in the latter remodeling stage, it is transformed into lamella bone and strength is reestablished. The goals of surgical intervention include pain relief, bone healing, function recovery. The expedient procedures (shortened surgical time, decreased bleeding volume, and less patient's physical and physiological stress) are crucial to achieve the goals.

Clinically, the four common sites of osteoporotic fractures include spine, hip, wrists and shoulder region. Spinal fracture, a common condition in patients 60 or older, leads to severe pain in the acute phase, indicating for efficient pain management. For osteoporotic patients, surgical intervention for spinal fracture, including vertebroplasty, kyphoplasty, decompression and internal fixation, is followed by a periodic use of a back brace. In the last decade, percutaneous vertebroplasty, based on bone cement infusion that requires only local anesthesia, has become popular because of the preference for simplified procedures, and has been used as an efficient approach to achieve pain management and regain activity. However, recent studies revealed that the efficacy of vertebroplasty is not significantly better when compared with controls. Considering the risk of bone cement leakage, infection and neural damage, this invasive procedure is recommended for patients with poor response to conventional treatments, and who suffer from persistent pain for more than a month.

The incidence of hip fractures is prevailing in the aged patient, especially those aged 70-80, because the hip is a key weight-bearing joint for the trunk. Longer bedridden time and complications may result if timely reduction and hip activities are not provided. Unless contraindicated due to underlying medical comorbidity, hip fractures are typically managed with surgical intervention (either internal fixation or arthroplasty): displaced femoral neck fracture

with partial hip arthroplasty, and internal fixation in non-displaced femoral neck fractures and intertrochanteric fractures because these tend to have better blood supply. Possible complications include displacement of fixators and infection. Rehabilitative approaches include pain relief, and training programmes for lower limb muscle strength, transfer and walking.

As a low-impact injury, wrist fracture is mostly found in women aged about 50, where the risk of distal radius involvement is the highest. In the wrist fractures in patients with osteoporosis, significant displacement is less observed, and closed reduction and cast immobilization are the favored approaches. The combination of internal fixation with external fixators may be considered for cases with severe displacement or deformity.

Loosening of the fixators or implants in osteoporotic fracture patients is common because their fragile bone mass causes a low predictability of the management of such with internal fixation. The goal of surgical intervention is to anatomical reduction and stable fixation of the fracture site, where bone healing is facilitated by effective reduction that depends on stable fixation - an "intervention cascade". Currently, how to decrease complications and recurrent fracture rate is the key issue for successful surgical intervention.

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Chapter 7. Prevention and Treatment of Osteoporosis with Medication

Editor: Keh-Sung Tsai

Abstract

In the prevention of osteoporosis and bone fractures, despite maximum support from medical staff, patients still face a high risk of bone fracture because of their age, neurological and muscular disabilities, low bone density and defective bone strength. For these patients, concomitant use of medications should be considered. Medications for the prevention of osteoporosis and bone fracture are classified by their mechanisms: anti-osteoclast/anti-resorptive activities, osteoblast and bone formation activators, or mixed activities.

Anti-osteoclast medications include calcium supplements, vitamin D, calcitonin, bisphosphates, selective estrogen receptor modulators (SERMs), sex hormones, osteoclastic enzyme inhibitors, and RANKL monoclonal antibodies, whereas parathyroid hormone and its active fragments are considered osteoblast activators, and strontium salts are the only one with mixed activity. These medications are discussed in this chapter.

As with all medications, side effects may occur after using medications for osteoporosis. Published clinical trials show that concomitant medication use does not present additional anti-fracture effects, but causes unwanted interactions that affect the benefits and elevated risk and severity of side effects; therefore, the concomitant use of two medications with anti-resorptive activity, or one anti-resorptive plus osteoblast activators, other than vitamin D and calcium is not recommended in many osteoporosis prevention guidelines. With their anti-resorptive activity, the concomitant use of vitamin D and calcium supplements is strongly recommended to ensure the material supply for bone formation and bone and muscle protection by vitamin D. Evidence has shown that a 40-65% decrease in the cases of spinal body fracture can be achieved by these medications, but not all are proven effective against hip fractures. In practice, these medications are identified as different lines of medications in osteoporosis prevention guidelines based on their price and ability to reduce the risk of bone fractures. Generally, medications that are cheaper and/or provide prevention against bone fractures at multiple sites are recognized as first-line choices, while others are sorted as second or further lines.

This classification is not used in this guideline. Readers are advised to make decisions based on the description in this guideline and the price. Medications for osteoporosis prevention, including bisphosphates, strotium salts, parathyroid hormone, SERMs, and estrogen, are recognized as effective because they are associated with a ≥40% decrease of the incidence of bone fracture. When compared to the effectiveness of anti-hypertensives for cerebrovascular accidents and/or cholesterol-reducing drugs for coronary heart diseases, the cost-effectiveness of these osteoporosis prevention drugs is more promising.

■ Section 1 Calcium

Editors: Ming-Chun Kuo, Jung-Fu Chen

Grade of Recommendation	Content of Recommendation	Level of Evidence	Number of Reference
C	Calcium supplement is associated with a lower risk of bone fracture in adults aged ≥50.	2+	3
D	Calcium supplement is associated with a lower risk of low traumatic fractures.	2-	4
C	Calcium supplement alone may provide effective control over the risk of bone fractures in postmenopausal women.	2++ 2-	5 6
D	Evidence regarding the beneficial effect of the concomitant use of calcium supplement and vitamin D on the risk of bone fracture remains controversial.	2-	
C	Calcium supplement (1000 mg) and vitamin D (400 IU/day) for healthy postmenopausal women provide little effect, and these may cause a higher risk of renal stones.	2+	11
B	Calcium supplement alone, or in combination with vitamin D, is ineffective in the prevention of secondary bone fractures.	1-	12
D	Calcium-fortified food is more effective in improving bone density than calcium supplement.	3	13
D	Concomitant use of calcium supplement and vitamin delays bone loss in men aged ≥65.	3	
D	Calcium supplement provides little benefit to bone density of healthy children.	3	9
D	The benefits of calcium supplement on the bone density of prepubertal girls remain unknown.	3	9

I. Physiological Role of Calcium

The normal growth and maintenance of healthy bones are based on a balanced diet with macronutrients (protein, fat and sugars) and micronutrients (vitamins and minerals). The calcium in bones is bound to collagen in the form of hydroxyapatite ($Ca_{10}[PO_4]_6[OH]_2$). Of all the nutrients we require, calcium and vitamin D are known for their key roles in bone health. Low dietary intake may lead to negative calcium balance. Low blood calcium induces the release of parathyroid hormone (PTH) that activates 25-(OH)D3 in kidney to transform into its active form, 1,25-(OH)2-D3, which acts with PTH to change the bone cells and the ionic valence of hydroxyapatite, transforming orthophosphate into pyrophosphate. This makes hydroxyapatite more likely to dissociate and release calcium to elevate blood calcium, which is also known as bone resorption. This mechanism maintains the equilibrium of blood calcium level, but sacrifices bone mass. Continuous loss of bone mass will result in osteoporosis.

II. Adequate Calcium Intake

Daily calcium intake of<250-500 mg is associated with a higher risk of bone fracture. However, women with low calcium intake (<500 mg/day) may be able to maintain bone density with milk. High calcium intake is associated with a lower risk of bone fracture.

An investigation by W.H. Pan (Institute of Biomedical Sciences, Academia Sinica) with sponsorship from the Department of Health showed that, in 1999 to 2000, the aged patient (defined as age ≥65) in Taiwan had inadequate calcium intake: the mean calcium intake of aged men was 622 mg, and 635 mg in women, about 60% of the intake recommended by Department of Health.[1]

In the 2002 Dietary Reference Intakes, the recommended adequate daily calcium intake for children aged 3-9 was 300-800 mg, 1000-1200 mg for children aged 10-18, and 1000 mg for adults aged >19. According to the International Osteoporosis Foundation, the recommended daily calcium intake of postmenopausal women and elders aged >65 is 1300 mg.[2]

The daily tolerable upper intake level (UL) of calcium is 2500 mg, but there is no evidence showing the benefits of a calcium intake higher than 2000 mg/day. Calcium carbonate is the most common and cheapest form of calcium supplement and reaches maximum absorption at 500 mg doses. To achieve better absorption, calcium citrate is recommended for individuals with inadequate gastric acid secretion, constipation, bloating or a history of kidney stones.

III. Calcium intake required for the treatment of osteoporosis

A meta-analysis of seventeen randomized studies (including 52625 adults aged >50) showed that the relative risk of bone fracture in subjects taking calcium supplements alone or in combination with vitamin D is 12% lower than in the control group, and bone loss in the hip joint and spine is decreased by 0.54% and 1.19%, respectively ($p < 0.001$).[3]

In a secondary RCT, 821 colorectal adenoma patients were included to compare the daily calcium supplement of 1200 mg and placebo. After a follow-up period of 10.8 years, it was found that the incidence of any bone fracture (0.9% vs. 3%, $p<0.05$, NNT 48), as well as mild traumatic fracture (fall below standing height, 0% vs. 1.9%, $p<0.05$, NNT 53), was significantly lower in the daily calcium supplement (1200 mg) group.[4]

A systematic review of fifteen randomized studies (including 1806 subjects) showed that calcium supplements cause a slight increase of bone density and decreased incidence of spinal fractures.[5]

A randomized study with 1460 postmenopausal women aged >70 compared the effectiveness of calcium carbonate supplement at 600 mg/day to placebo, and showed that 821 highly compliant patients who received calcium supplement at 600 mg/day had a lower incidence of bone fracture (10.2 vs. 15.4 had any fracture; NNT 20).[6]

Another randomized study with 1471 healthy postmenopausal women (mean age: 74) compared the effectiveness of calcium supplement at 500 mg to a placebo. Five years of observation showed that the calcium supplement group gained bone density (1.8% in spine, 1.6% in total hip and 1.2% overall) but the incidence of bone fracture did not decrease.[7]

A systematic review of nineteen randomized studies (including 2859 healthy children, where 1367 received calcium supplements and 1426 received placebo) showed that calcium supplements do not improve bone density in the femoral neck and spine (bone density in upper limbs is slightly increased).[8]

In an 18-month study providing calcium supplements to prepubertal girls, the overall bone density of girls in the calcium supplement group increased by 1.3%, and spinal bone density increased by 2.9%.[9]

IV. The Effect of Calcium Supplements in Combination with Vitamin D on Osteoporosis

Evidence regarding the beneficial effect of the concomitant use of calcium supplements and vitamin D on the risk of bone fracture remains controversial: a systematic review of forty five randomized or non-randomized studies showed that this intervention controls the incidence of non-spinal fractures in the elderly prone to falls (a subgroup analysis of two studies [including 3853 subjects] showed that the incidence of new hip fractures was 8.1 vs. 10.7% [p=0.0049, NNT 36], and the incidence of new non-spinal fractures was 16% vs. 18.7%, p = 0.025, NNT 37). [10]

In a study with 36282 healthy postmenopausal women aged 50-79, concomitant use of calcium supplement at 1000 mg and vitamin D3 at 400 IU daily significantly increased bone density at the hip joint (1.6%) and the risk of kidney stones (2.47% vs. 2.1%), but it was found to be ineffective to reduce the incidence of bone fracture. [11]

Ineffective secondary bone fracture prevention was found when 1000 mg calcium supplement alone or in combination with 800 IU vitamin D3 daily was provided to 5292 patients aged ≥70 who had history of low impact fractures.[12]

In a study, 101 postmenopausal women were randomized into a calcium-fortified diet group (1200 mg calcium supplement in combination with 300 IU vitamin D3, and dietary instruction was given once every two weeks), 1200 mg calcium supplement group or control group, and significant improvement of hip, spinal and total body bone density was noted in the women of the calcium-fortified diet group. [13]

A hundred and ninety-nine elderly living at home were included in an RCT exploring the benefits of calcium supplements and vitamin D3 and randomized into a group provided with 500 mg calcium citrate and 700 IU vitamin D3 or control group. After three years of observation, the incidence of bone fracture was too low to reach a conclusion.[14]

V. Conclusion

Daily calcium intake of <250-500 mg is associated with a higher risk of bone fracture. However, women with low calcium intake (<500 mg/day) may be able to maintain bone density with milk. High calcium intake is associated with a lower risk of bone fracture. The concomitant use of calcium supplements and vitamin D is associated with a lower risk of bone fractures, especially in women with inadequate intake of calcium and vitamin D. This effect was not found in women with adequate intake. The recommended daily calcium intake for men is 1000 mg, and 1500 mg for women.

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■ Section 2 Vitamin D

Editors: Jung-Fu Chen, Ming-Chun Kuo

Grade of Recommendation	Content of Recommendation	Level of Evidence	Number of Reference
Vitamin D testing			
B	Blood 25(OH)D level is a good indicator of adequate vitamin D in the body.	2+	1,2
B	A blood [25(OH)D] level of >30 ng/ml is considered physiologically adequate.	2+	3
C	Vitamin D level should be determined for osteoporosis patients or individuals with a high risk of vitamin D deficiency, and it can be tested after three months of supplement of ≥800 IU.	2+	1,2
A	Vitamin D [25(OH)D] insufficiency (< 30ng/ml) is a common disorder in many regions worldwide, including Asia.	2+	4
Vitamin D supplement and its effect on the prevention of osteoporosis			
B	The recommended daily supplement of vitamin D is 800-1000 IU.	2+	1,2
A	Concomitant supplement of vitamin D and calcium is associated with increase of bone density in postmenopausal women and men aged ≥50.	2+ 1-	8 11
A	Daily supplement of 800 IU vitamin D and 1000 mg calcium is associated with a lower incidence of hip and non-spinal fractures in the aged patient living in long-term care facilities.	2+ 1-	10 12
B	Daily supplement of vitamin D at 800 IU is associated with a lower incidence of falls in the aged patient.	1-	15, 16
A	Clinical trials of medications with proven efficacy for treating osteoporosis and bone fractures are all provided with sufficient supplement vitamin D and calcium.	1++	17,18

●Section 1 Introduction of Vitamin D

Vitamin D plays an important role in the development of the musculoskeletal system and calcium/phosphorus metabolism. Blood [25(OH)D] level is a good indicator of vitamin D level in the body[1]. With a half-life of 15-20 days, its blood level is stabilized after 3-4 months of supplement intake, and the adequacy of vitamin D supplement is also confirmed then[2]. A [25(OH)D] level of >30 ng/ml is considered an indicator of physiologically adequate level because it provides effective control of PTH level[3].

●Section 2 Inadequate Vitamin D Intake is Common around the World

Vitamin D [25(OH)D] intake of <30 ng/ml is considered inadequate, and it is a generalized phenomenon around the world, including Asia[4]. For example, about 75% of U.S. residents have inadequate vitamin D intake, whereas it's 50% in Thailand and Malaysia, and as high as 90% in Japan and South Korea. Of the adults aged 19-64 included in the "Investigation on the Dietary Nutrition Intake of Taiwanese" in 2005-2008[5], up to 75% of women had inadequate vitamin D intake, similar to North Americans.

●Section 3 Vitamin D and the Prevention of Osteoporosis

The affected calcium absorption and bone density secondary to inadequate vitamin D intake is one of the most important risk factors for osteoporosis-related bone fractures[6]. An observational study showed that 25(OH)D level is positively correlated with bone density[7], whereas a 1.06% higher total hip bone density was noted in a study by the Women's Health Initiative[8] in which 2,341 postmenstrual women were provided with supplement of vitamin D and calcium. Lower 25(OH)D level is considered a risk factor for bone fracture events as an observational study concluded that significantly lower incidence of bone fracture was noted in subjects with a higher vitamin D level[9]. A meta-analysis of five studies (including 9,829 subjects) showed that a 23% decrease in the incidence of non-spinal fractures after intake with vitamin 800 IU, especially in those with blood 25(OH)D level≥30 ng/ml.

Adequate intake of calcium and vitamin D is crucial for the prevention of osteoporosis. A meta-analysis of sixth studies (including 45,509 subjects) showed that the supplement of vitamin D at 400-800 IU in combination with calcium is associated with a lower incidence of bone fractures (RR = 0.82)[11].

It has been shown that providing the elderly living in long-term care facilities with 800 IU vitamin D plus 1000 mg calcium is associated with a significant lower incidence of hip and non-spinal fracture[10, 12], but this effect was found to be less significant when applied to those living in the community[13]. This may be related to their unstable compliance with drugs. 800 mg vitamin D is considered the minimal effective dose in the prevention of bone loss[14].

●Section 4 Vitamin D and Falls

Lower incidence of falls can be achieved by vitamin D supplement because it improves muscle strength and lower limb function[15]. A meta-analysis of five studies showed that a significant decrease (22%) in the incidence of falls is associated with vitamin D intake, but the dose should be at least 800 IU/day[16].

●Section 5 Summary and Recommendation

Adequate vitamin D (at least 800 IU/day) and calcium intake is a basic and important element in the prevention of osteoporosis. All clinical trials of medication with proven efficacy for treating osteoporosis and reducing bone fractures are must provided with critically sufficient vitamin D and calcium nutrition.[17, 18]

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Section 3 Bisphosphonates

Editors: Shan-Fu Yu, Chung-Jen Chen, Tien-Tsai Cheng

Grade of Recommendation	Content of Recommendation	Level of Evidence	Number of Reference
A	Reduction of the risk of spinal, non-spinal and hip fractures in postmenopausal women with osteoporosis can be achieved by the administration of bisphosphates such as alendronate, risedronate and/or zoledronic acid.	1++	1-8
A	Reduction of the risk of spinal fractures in postmenopausal women with osteoporosis can be achieved by bisphosphates such as ibandronate and/or etidronate.	1++ 1+	10,13 11,12
A	Osteoporosis-related hip fractures can be treated with zoledronic acid because its use is associated with lower incidence of bone fractures and lower mortality.	1++	9
A	Reduction of bone fractures in men with osteoporosis can be achieved by the administration of bisphosphates such as alendronate, risendronate and oledronic acid.	1++ 1+	15 14
A	For osteoporosis secondary to steroid use, bisphosphates are effective in increasing bone density in the lumbar spine and femoral neck and minimizing bone loss, but evidence of its effect in the prevention of bone fractures is lacking.	1++	16
A	The effectiveness of bisphosphates on the secondary osteoporosis in children and adolescents is not established.	1++	17
B	The increased risk of esophageal or gastric cancer related to bisphosphates has not been established.	2++	18
B	Long-term bisphosphate use may lead to an increased risk of atypical femoral head fractures (including subtrochanteric fractures and femoral shaft fractures), which have a low absolute risk. More studies are required to confirm this relationship.	2++	19, 20
B	The relationship between bisphosphate use and jaw bone necrosis in osteoporosis patients lacks supporting evidence, but attention as well as preventive measures should be exercised when high-dose injective bisphosphates are used in cancer patients considering the risk of jaw necrosis.	2++	21, 22
B	Atrial fibrillation may be a complication of bisphosphate use, but the evidence of their relationship is lacking.	2++	23-25
A	Continuous bisphosphate use is recommended for high fracture risk patients who have used it for at least 5 years. For patients with stable bone density, no fracture history and a low risk of bone fracture, cessation of bisphosphates may be considered.	1+	26, 27

I. Introduction:

While the choices for osteoporosis treatment are increasing, bisphosphates remain the preferred medication. The mechanism of bisphosphates involves the inhibition of osteoclast activity and bone resorption. Oral bisphosphates have an extremely low bioavailability (about 1-3% of dose administered) and should be taken with 200ml water. When taken with food, calcium supplements, iron supplements, coffee, tea or orange juice, its absorption is likely to be

affected. When entering the human body, its high plasma clearance is associated with rapid elimination through urine, but still allows about 50% of the administered dose to accumulate in bone, where the half-life in bone is much longer. Different dosage forms and administration routes can be found on the market, and bisphosphates approved by Food and Drug Administration include alendronate (Fosamax, Alendronate Sandoz), zoledronic acid (Aclasta) and ibandronate (Boniva). It has been shown that bisphosphatesare effective in improving spinal and hip bone density.

II. Insights of Bisphosphates:

1. Alendronate (Fosamax®: oral 10 mg QD [once a day] or 70 mg QW [once a week]; Alendronate Sandoz®: oral 70 mg QW): In a review by Cochrane (2010), oral alendronate administered to postmenopausal women with osteoporosis complicated with its related bone fractures (as a secondary prevention measure) at 10 mg QD provided effective prevention against secondary spinal, non-spinal, hip and carpal fractures and minimized risks[1]. When provided to postmenopausal women with osteoporosis (as a primary prevention measure), it is only associated with a lower incidence of spinal fractures, but does not prevent fractures of other sites. In the Fracture Intervention Trial, it was observed that the risk of spinal and hip fracture in postmenopausal women with history of spinal fractures was decreased by 47% and 51%, respectively, after three years of alendronate use[2], the risk of spinal fractures in patients with low bone mass but without history of spinal fracture was deceased by 44%[3], and the risk of symptomatic and hip fractures in patients without history of spinal fractures was decreased by 36% and 56%, respectively[3].
2. Risedronate (Actonel®: oral 5 mg QD, 35 mg QW or 150 mg once each month): This medication has not been introduced into Taiwan. In a review by Cochrane (2010), oral risedronate administered to postmenopausal women with osteoporosis (as a secondary prevention measure) at 5 mg QD is associated with a lower risk of spinal, non-spinal and hip fractures[4], but clinical or statistically significant benefits were not found when used for primary prevention. In the VERT trials, it was observed that the risk of spinal and non-spinal fractures in postmenopausal women with osteoporosis complicated with clinical spinal fracture was decreased by 40-50% and 30-36%, respectively, after risedronate use[5,6]. Another large study on aged women[7] showed that a 30% decrease in the risk of hip fracture can be achieved with risedronate, and the decrease was as high as 40% in osteoporotic women aged 70-79. However, the prevention effect was not found in non-osteoporotic women aged >80.
3. Zoledronic acid (Aclasta®: injective 5 mg once each year): In the HORIZON trials, it was observed that the administration of zoledronic acid was followed by significant decrease in the risk of spinal, non-spinal and hip fracture in postmenopausal women (aged 65-89) with osteoporosis or bone deficit plus history of spinal fracture (by 70%, 25% and 41%, respectively)[8]. The decreased risk of spinal fracture was found in the first year of administration, while the effect on the risk of non-spinal and hip fractures was not observed until the second year. Zoledronic acid should be provided to patients experiencing their first episode of osteoporosis-related hip fracture as soon as possible because its use is associated with a 35% decrease of the incidence of symptomatic bone fractures and a 28% decrease of mortality[9]. Zolendronic acid is the only effective bisphosphate molecule against spinal, non-spinal and hip fractures, but long-term (>3 years) safety data is lacking.

4. Ibandronate (Boniva®: oral 2.5 mg QD, oral 150 mg once each month, and injective 3mg once each three months): In the BONE trial, it was observed that the risk of spinal fracture in postmenopausal women with osteoporosis was decreased by 62% after the administration of oral ibandronate at 2.5 mg QD for 2 years[10]. In Taiwan, the intravenous (IV) ibandronate was used because it provides better reaction in terms of increase of bone density[11] and better adherence[12]. Oral 150 mg once each month or injective 3 mg once each three months is associated with increased bone density, lower risk of spinal fractures and improved adherence, but its effectiveness against the risk of hip or non-spinal fractures still lacks direct evidence[10,11].
5. Etidronate (Didronel®: oral 400 mg QD or 14-day regimens once each three months): This medication has not been introduced into Taiwan. In a review by Cochrane (2010), oral etidronate administered to postmenopausal women with osteoporosis (as a secondary prevention measure) at 400mg QD is associated with a lower risk of spinal fractures, but not for non-spinal, hip and carpal fractures[13]. Also, clinical or statistically significant benefits were not found when used for primary prevention.

III. Special Patient:

1. Men with osteoporosis (aged ≥50): alendronate improves bone density in the spinal column and femoral neck, and is associated with a lower incidence of spinal fractures[14]. Risedronate improves bone density, and is associated with a lower incidence of spinal and non-spinal fractures[15].
2. Steroid-induced osteoporosis: daily steroid use of >7.5 mg is associated with a higher incidence of clinical osteoporosis. In a review by Cochrane (2010)[16], bisphosphates provide effective control over steroid-induced osteoporosis. When compared with the control group, the bone density in the lumbar spine and femoral neck of patients treated with bisphosphates is 4.3% and 2.1% higher, respectively; however, its effectiveness in the prevention of bone fractures still lacks evidence.
3. Secondary osteoporosis in children and adolescents: Evidence regarding the efficacy of bisphosphates in the treatment of secondary osteoporosis in children remains inadequate.[17]

IV. Adverse Events:

1. Esophageal cancer: oral bisphosphates may induce gastrointestinal discomfort (e.g. acid reflux, nausea and vomiting, esophagitis or esophageal ulcer), but the evidence regarding the relationship between bisphosphates and the risk of esophageal or gastric cancer is inadequate[18].
2. Atypical femoral head fractures including subtrochanteric fractures or diaphyseal fractures: Long-term bisphosphate use may lead to an increased risk of these fractures, which have a low absolute risk[19,20]. More studies are required to confirm this relationship.
3. Osteonecrosis of the jaw: cases of jaw bone necrosis have been reported since 2003, while the relationship between osteonecrosis and bisphosphate use awaits further exploration. Attention should be exercised on the risks when high-dose injective bisphosphates are administered to cancer patients[21, 22]. As the relationship between cessation of bisphosphates and lower risk of jaw bone necrosis has not been established, these medications should be used with care.
4. Atrial fibrillation: In a clinical trial of zoledronic acid (HORIZON Pivotal Fracture Trial), a few cases of atrial fibrillation were reported, but similar risk was not observed in other clinical trials. No evidence was identified in the long-term monitoring report from the U.S. Food and Drug Administration (FDA), registered studies of marketed drugs and Taiwanese studies showing the association of bisphosphate with an increased risk of atrial fibrillation.

V. Recommended Regimen and Long-Term Safety:

Discussion regarding the proper length of regimens remains inconclusive. Notably, evidence supporting patients with high fracture risk (e.g. history of bone fractures, elderly, with a high risk of falls) who have used bisphosphates for five years to continue treatment because of the benefit of osteoporosis medications after cessation is unclear, and it is believed that continuing treatment may provide benefits that outweigh the risk of jaw bone necrosis. For patients with stable bone density, no fracture history and a low risk of bone fracture, cessation of bisphosphates may be considered [26,27].

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Section 4 Hormone, Tibolone, SERM

Editors: Yung-Kuei Soong, Fan-Ping Chen, Hong-Yuan Huang

Grade of Recommendation	Content of Recommendation	Level of Evidence	Number of Reference
A	Hormone replacement therapy (HRT) is a preferred choice in the prevention of bone loss in postmenopausal women.	1++	5, 6, 7
A	Conjugated equine estrogen (Premarin) at 0.625 mg QD, 17β-estradiol at 1-2 mg or equivalent transdermal or transvaginal estrogen. Concomitant use with progesterone (e.g. medroxyprogesterone acetate [Provera] at 2.5-5 mg QD) is suggested. Estrogen alone should be provided to individuals who underwent hysterectomy.	2++ 1++	10, 11 5, 6, 7
A	HRT is associated with a lower incidence of spinal compression or hip fractures in individuals aged ≤60. First-line therapies are not recommended for individuals aged ≥60.	1++	4, 12, 13, 14, 15
A	HRT is contraindicated for postmenopausal women with risk factors of endometrial cancer, breast cancer and/or thrombosis.	1++	4, 5, 6, 20
A	Tibolone is a tissue-selective estrogenic activity regulator (STEAR), where its selective tissue estrogenic or progestogenic activity comes from its metabolite.	4	21
A	Tibolone is associated with significant decrease of spinal and non-spinal fractures, along with lower risk of breast and colon cancer.	2++ 1++ 4	25 22,23,24, 26
A	Tibolone is associated with a significantly increased risk of stroke related to cardiovascular diseases. Postmenopausal women aged ≥60 should be aware of the risk of cardiovascular diseases and stroke episodes.	1++	24
B	The incidence of bleeding, breast pain and headache is low in women using tibolone to control postmenopausal syndrome.	2++ 4	25 27
A	Raloxifene hydrochloride, a selective estrogen receptor modulator (SERM), acts differently from estrogen because it binds with estrogen receptors on the bone cells to achieve lower bone loss, improve bone density and effectively control the incidence of bone fractures without the concern of breast and uterine side effects. The maximum daily dose is 60 mg.	1++	29, 30, 31, 32, 33,
A	National Health Insurance coverage is provided to raloxifene hydrochloride administered to postmenopausal women with osteoporosis-related spinal compression or hip fractures (and documentation in the medical records should be made).	2++	37
A	Raloxifene hydrochloride should not be used with bisphosphates, calcitonin, active vitamin D3 and estrogen.	2++	37

●Section 1 Hormone Therapy

Mechanism: In the postmenopausal phase of a woman's life, the lower estrogen level is associated with the rapid loss of bone density (15-30% decrease in 5-7 years following menopause) [1]. Postmenopausal osteoporosis is related to increased bone resorption caused by the activation of osteoclasts and deactivation of osteoblasts. Estrogen inhibits the bone resorption rate by controlling the proliferation and maturation of pre-osteoclasts[2]. For postmenopausal women, hormone therapy based on estrogen and progesterone is an effective first-line therapy in the prevention and treatment of osteoporosis[3]. The analysis of the large, double-blind WHI study showed that 5.6 years of treatment with estrogen and progesterone is associated with a 33% decrease in the risk of hip fractures[4].

Clinical bone benefits: The large Women's Health Initiative (WHI)[5,6] and Postmenopausal Estrogen/Progestin Interventions (PEPI)[7] RCTs showed that estrogen therapy is associated with slower bone loss and increased bone density in postmenopausal women, while in the WHI studies[5,6], statistically significant decrease of the risk of spinal or non-spinal fractures, especially hip fractures, can be achieved by the administration of estrogen alone or in combination with progesterone (33% decrease in a mean follow up of 5.6 years). The U.S. Food and Drug Administration (FDA) approved the use of estrogen as a hormone therapy in the prevention of osteoporosis, but not for treatment, while clinical studies showed that using estrogen as a hormone therapy in postmenopausal women provides positive outcome in terms of improved bone density and lower risk of bone fractures, but the effect of hormone therapy disappears after its cessation. The National Osteoporosis Risk Assessment study[8] showed that, more than five years after the cessation of hormone therapy, the bone density of the subjects who had hormone therapy was similar to those of the naïve subjects. Moreover, the benefits of hormone therapy, i.e. lower risk of hip fractures, were gone after the cessation of hormone therapy. A two-year RCT[9] showed that low-dose estrogen (conjugated estrogen 0.3, 0.45 mg/day) is associated with improved bone density and prevention of bone loss in postmenopausal women, while some studies showed that the delivery of low doses of estrogen (oral E2 0.25 mg/day, conjugated estrogen 0.3 mg/day, transdermal E2 0.014 and 0.025 mg/day) in combination with calcium and vitamin D is also associated with a significant increase of bone density[10,11]. The WHI study, exploring the effect of the combination of estrogen and progesterone on the prevention and treatment of bone fractures, did not show aged-related differences[4], while some studies indicated that hormone therapy only provides effective prevention against bone losses and fractures in postmenopausal women aged ≤60, but the effect is minimal or none in those aged ≥60[12,13]. Consensus has been made that the choice of medication for postmenopausal women with osteoporosis should be determined based on age[14,15].

Clinical non-bone benefits: estrogen is effective for symptoms related to vasodilation/vasoconstriction (including hot flushes, night sweats), and is the only drug approved by the U.S. FDA for the treatment of these symptoms. In a database systematic review by Cochrane[16], it was shown that hormone therapy provided effective control over hot flushes and night sweats: the incidence of hot flushes was cut down by 75%, and the events were found to be milder. In addition, hormone therapy is effective against urogenital atrophy. A database systematic review by Cochrane[17] showed that vaginal atrophy can be treated with the administration of estrogen in the vagina.

An epidemiological study[18] declared that hormone therapy is associated with a 50% decrease in the risk of heart disease in postmenopausal women, while WHI[5,6] showed the relationship of hormone therapy with estrogen and progesterone with an increased risk of coronary heart disease (CHD, 7/10,000), stroke (8/10,000), venous thromboembolism (VTE, 8/10,000) and breast cancer (8/10,000). Estrogen alone is associated with slight increased risks of stroke and VTE, but does not affect, or even lower, the risk of CHD and breast cancer. The main differences between said epidemiological study[16] and WHI studies[5,6] are the age of postmenopausal women (30-55 vs. a mean of 63) and years after menopause (<5 years vs. 14 years). Agreement has been reached that hormone therapy may be associated with heart benefits when provided to women without history of CHD during perimenopause phase or within 10 years after menopause (i.e. 50-59), and is supported by WHI[19]: postmenopausal women provided with estrogen alone for 7 years had a lower risk of calcification of coronary arteries when compared to the control group. Estrogen alone may be associated with a higher risk of endometrial cancer, but concomitant use with progesterone is able to minimize this risk[20].

Side effects: Breast pain, temporary nausea, mild edema, abnormal vaginal spotting. The result of the double blinded study in the large WHI showed that more than 5 years of hormone therapy may increase the risk of breast cancer, and elderly postmenopausal women (>65 y/o) may also be associated with a higher risk of CHD.[4].

• Section 2 Selective Tissue Estrogenic Activity Regulator (STEAR) Tibolone

Mechanism: STEARs are synthetic steroid hormones that follow a pathway different from the action of the selective estrogen receptor modulator (SERM) by modulating hormone receptors on body tissues. Tibolone, a STEAR, is metabolized in the liver and intestines, and the metabolites from different enzymatic activities act as estrogen analogs and/or antagonists and progesterone in various tissues: it acts as estrogen in bone, the central nervous system and vagina, but acts as progesterone elsewhere because its estrogenic activity is inhibited in the breast and endometrium. The metabolites include 3α-hydroxy tibolone, 3β-hydroxy tibolone and △4-isomer[21], where the first two have estrogenic activity, and the last acts as progesterone and androgen.

Clinical bone benefits: Tibolone may be used in the prevention of osteoporosis because of its estrogenic effect of improving bone density.
An analysis of a large double-blind study revealed the effectiveness of tibolone in the prevention of osteoporosis in postmenopausal women: spinal bone density increased by 2.6% after a year of tibolone treatment at a dose of 2.5 mg QD. Similar effect was also found in the hip region, and its effectiveness is similar to other medications used for the prevention of osteoporosis, i.e. bisphosphates and SERMs[22]. A study showed that bone density in the spine and femoral neck of postmenopausal women with a history of bone fractures increased by 6.9% and 4.5% from tibolone at 2.5 mg QD[23]. A ten-year prospective study showed that bone density in the spine and femoral neck increased by 4.5% and 3.7%, respectively, with the administration of tibolone at 2.5 mg QD. Another large RCT discussed the efficacy of three years of tibolone 2.5 mg QD on the bone deposit rate of the vertebral body in aged postmenopausal women (mean age: 68), showing that the incidence of vertebral body and non-vertebral body fracture was decreased by 45% and 26%, respectively. However, the risk of CHD is doubled after three years of treatment[24].

Clinical non-bone benefits: tibolone can be used for postmenopausal syndrome (symptoms include hot flushes and night sweats) because its actions are similar to estrogen and progesterone, and it is associated with a lower risk of uterine bleeding than the hormone therapy with progesterone[25] and the increased breast density is milder than in conventional hormone therapy using concomitant estrogen and progesterone[26] because it does not have estrogenic activity on the endometrium and breast. The risk of invasive breast and colon cancer in aged women (mean age: 68) was decreased by 68% and 69%, respectively[24], after three years of treatment of tibolone at 1.25 mg QD, while this is accompanied with a significant higher risk of stroke[24].

Side effects: The incidence of bleeding, breast pain and headache related to estrogen and progesterone is lower in individuals treated with tibolone because it does not have estrogenic activity on the endometrium and breast[27]. Other side effects including dizziness, pruritis, mild nausea and slight weight gain may be more significant.

Section 3 Selective estrogen receptor modulator (SERM)

Mechanism: SERM is a non-estrogenic medication that induces estrogenic or anti-estrogenic activity by binding with estrogen receptors on the cells, which can be explained with three interrelated mechanisms[28]: (1) the tissue-specific expression status of estrogen modulator/ receptors α and β, (2) the formation of different ratio of α ftioa estrogen receptor-ligand complex in that tissue/cell, and (3) the different expression and binding pattern with the coregulator proteins (including coactivators and corepressors). Raloxifene is a drug approved by the U.S. FDA for the prevention and treatment of osteoporosis in one tablet (60 mg) QD. The tablet can be taken with food, drinks, vitamin D and calcium supplements. Raloxifene has estrogenic activity on the bone and fat metabolism, but anti-estrogenic activity on the breast and uterus. SERMs under development, including ospemifene, lasofoxifene, bazedoxifene and arzoxifene, were proven effective against osteoporosis in animal models and phase III clinical trials have been completed, but are pending approval from the U.S. FDA.

Clinical bone benefits: raloxifene can be used as a means of osteoporosis prevention because it is associated with increased bone density in postmenopausal women[29]. In a large RCT, Multiple Outcomes of Raloxifene Evaluation (MORE)[30], the effect of raloxifene against bone fracture was tested in postmenopausal women with osteoporosis. It was shown that the incidence of new spinal fractures in postmenopausal women with a history of osteoporosis-related spinal fractures was significantly decreased (by 30%), where the incidence was decreased by 50% in those without history of osteoporosis-related spinal fractures. However, the change in the incidence of non-spinal fractures remained insignificant. When compared to the control group, raloxifene was associated with increased bone density in the lumbar spine and femoral neck. The benefit of raloxifene in terms of significant decrease of the incidence of new spinal fractures was persistent during the four-year duration of the MORE study[31].

Clinical non-bone benefits: A significant decrease (84%) of the incidence of estrogen-receptor-positive (ER+) invasive breast cancer was observed in the four-year duration of the MORE study[32]. In the Continuing Outcome Relevant to Evistat (CORE) trial[33], the extended study of MORE, the significant decrease of the incidence of ER+ invasive breast cancer was found to be persistent for 8 years (66% in 4 years, 76% in 8 years).

Raloxifene was associated with a significant decrease of total cholesterol and low density cholesterol (LDL) during the four-year duration of the MORE study[34]. While raloxifene does not provide significant effect on the incidence of cardiovascular diseases, it is associated with a significant decrease of cardiovascular events in patients with cardiovascular disease or who have a high risk.

Side effects: Raloxifene is associated with a higher risk of hot flushes and leg cramps when compared to the control group[31,35]. Considered a severe side effect, increased incidence of VTE was noted in raloxifene users (3.5/1,000) in the first two years when compared to the control group (1.7/1,000). This difference became insignificant in the long term[32,36].

Safety: The risk of myocardial infarction, stroke, uterine cancer, endometrial hyperplasia, ovarian cancer or postmenopausal bleeding related to raloxifene is similar to those of the control group[33].

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Section 5 Parathyroid Hormone (PTH)

Editors: Jawl-Shan Hwang, Jung-Fu Chen

Grade of Recommendation	Content of Recommendation	Level of Evidence	Number of Reference
Taiwanese and Asian studies			
A	Parathyroid hormone (PTH) is associated with increase of lumbar spine BMD in Taiwanese women with severe osteoporosis.	1++	1
A	PTH is associated with increase of lumbar and hip BMD in Asian women with severe osteoporosis.	1++	2,3
A	PTH is associated with increase of bone formation markers in Taiwanese and Asian women with severe osteoporosis.	1++	1-3
Other studies			
A	PTH is associated with increased of lumbar spine and hip BMD in men and women with osteoporosis.	1++ 1+	4-8 12
A	PTH is associated with a significantly reduced the risk of vertebral spinal and non- vertebral fractures in women with osteoporosis.	1++ 1+	4,7,8 12
A	PTH is associated with increased bone formation markers in patients with osteoporosis.	1++	4-8,12
A	PTH is associated with pain relief and quality of life of osteoporosis-related bone fractures.	1++	9-11
A	PTH is associated with increased of lumbar spine and hip BMD in steroid induced osteoporosis.	1+	13,14
A	No addition of effects was observed when PTH combined with other drugs for osteoporosis.	1++	15,16
A	Other drugs for osteoporosis should be administered following PTH.	1++	17-20

I. Introduction:

Parathyroid hormone (PTH) regulates calcium homeostasis by promoting bone metabolism, renal calcium reabsorption and intestinal calcium absorption. When chronic or continuous exposure as seen in hyperparathyroidism, which causes higher osteoclastic activity and rapid progression of osteoporosis. When exogenous administered once a day, the risk of bone fractures is lower because intermittent use is associated with higher osteoblastic activity, which elevates bone markers, promotes formation of trabecular and cortical bone, and reinforces bone microstructure, mass and strength.

II. Medications:

1. Parathyroid hormone 1-34, teriparatide (Forteo®), injective 20μg QD.

Manufactured with genetic engineering technology, teriparatide is a bio-synthetic human parathyroid hormone fragment (1-34 amino acids at N-terminus). Once-daily injections is

associated with the activation of osteoblasts and bone formation (to patient: please kindly check the Chinese description, I cannot understand what it means). Teriparatide has been approved in the United States and Europe for the treatment of osteoporosis in men and postmenopausal women, and its approval in Taiwan for the treatment of osteoporosis since June 2004. It is administered 20 mg daily subcutaneously at thigh or abdominal wall. With a bioavailability of 95% and a plasma half-life of 1 hour, peak blood level is reached 30 minutes after injection and became undetectable 3 hours after injection.

In a Taiwanese efficacy study, it was found that six months of treatment with teriparatide is associated with an increase of bone turnover markers and a mean increase of 4.5% of the lumbar spine BMD[1]. In Asian women with severe osteoporosis was increased by 5% lumbar spine BMD after six months of treatment[2], and the lumbar spine and femoral BMD in Japanese osteoporosis patients was increased by 10% and 2.7% at month 12, respectively, and 14% and 3.7%, respectively, at month 24[3]. The Fracture Prevention Trial compared the effect of teriparatide with placebo in a duration of 19 months. It has been shown that teriparatide is associated with 65% and 53% decrease of the risk of vertebral and non- vertebral fractures, respectively, and 9% and 3% increase of the lumbar and femoral neck BMD, respectively. Increased bone turnover markers were identified[4]. For men with osteoporosis, 9.5% and 1.5% increase of the lumbar spine and hip BMD were noted in osteoporosis after 11 months of teriparatide treatment[5-8]. Also, teriparatide relieves the pain of osteoporosis-related bone fractures and improves the quality of life[9-11].

2. Parathyroid hormone 1-84, teriparatide (Preotact® ,PREOS®), injective 100 μg QD

In the Treatment of Osteoporosis with Parathyroid Hormone (TOP) study, women with osteoporosis were included to compare parathyroid hormone 1-84 with placebo for 19 months. It has been shown that bone density of the lumbar spine and femoral neck was increased by 6.9% and 2.5%, respectively[12], and the risk of vertebral fractures in subjects with and without spinal fractures was reduced by 53% and 68%, respectively[12]. Parathyroid hormone 1-84 was approved in Europe for the treatment of osteoporosis in men and postmenopausal women, but it has not been approved in Taiwan.

III. Special Patient:

PTH is associated with increased of lumbar and hip BMD, and a reduced the risk of vertebral fractures in steroid induced osteoporosis.[13,14]

IV. Drug Adverse Reactions:

Adverse reactions include hypercalcemia, hypercalciuria, nausea, headache, leg cramps and orthostatic hypotension, and usually temporary and mild[4-6,12,13]. Teriparatide is not recommended for patients with history of metastatic bone tumors or bone malignancy because its long-term use at high doses has been associated with a higher risk of osteosarcoma in the animal model. It is not recommended to be used on patients with Paget's disease or metabolic bone diseases.

V. Recommended Duration and Concomitant Use:

The used for treatment, PTH should not exceed 24 months, and concomitant use with anti-resorptives is not suggested because there is no evidence showing the addition of benefits and effectiveness in fracture risk reduction, as well as because of the concerns of cost and side effects.

The use of PTH following bisphosphate regimen in patients with osteoporosis may blunting the increase of bone density[17-18].

The bone density decline after the cessation of teriparatide, which means that other medications should be followed when the regimen is discontinous.

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■ Section 6 Strontium Ranelate

Editors: Jawl-Shan Hwang, Jung-Fu Chen

Grade of Recommendation	Content of Recommendation	Level of Evidence	Number of Reference
Taiwanese and Asian studies			
A	Strontium ranelate is associated with increased of lumbar spine and hip BMD in Taiwanese and Asian women with osteoporosis.	1++	1,2
A	Strontium ranelate is associated with increased of bone formation markers in Taiwanese women with osteoporosis.	1++	1
Other studies			
A	Strontium ranelate is associated with increased of lumbar spine and hip BMD in men and women with osteoporosis.	1++ 1+	3-5,7,8 6
A	Strontium ranelate is associated with reduced risk of vertebral and hip femoral fractures in women with osteoporosis.	1++	3-5
A	Strontium ranelate is associated with increased the markers of bone formation and reduced bone resorption markers in women with osteoporosis.	1++	3-5, 7,8

I. Introduction:

Being classified into the same group (alkali earth metal) with calcium in the periodic table, strontium (Sr) acts similarly to calcium and has the highest affinity to bone and teeth. The bioavailability of strontium element is low (about 1-3%), but is increased to 27% when bound with ranelic acid, an organic acid. Strontium ranelate is a medication with anti-resorptive and stimulate osteoblastic activities because it promotes bone formation through the stimulation of calcium sensing receptors (CaSRs) that activates pre-osteoblasts to osteoblasts, while the inhibition of bone resorption is achieved by interfering with the binding of the receptor activator of NF-kB (RANK) with RANK ligand (RANKL) that strontium ranelate stimulate to secrete osteoprotegerin (OPG). These make strontium ranelate a medication for the inhibition of bone resorption as well as the increases of bone formation.

II. Medications:

Strontium ranelate (Protos®): one package (2 grams) QD

One package (2 grams) of strontium ranelate added to water to prepare oral suspension taken once a day. For adequate absorption, at least two hours should be kept between strontium ranelate and the use of calcium, antacids and antibiotics (e.g. tetracycline, quinolone). When orally administered at a dose of 2 grams, the peak blood level of strontium ranelate is reached after 3-5 hours and becomes stable at day 14. It has a half-life of 60 hours and a bioavailability of 27%, but the bioavailability is affected by 60-70% when it is used with calcium. Strontium ranelate has been approved in Europe for the treatment of osteoporosis in men and postmenopausal women, and it has been approved by the Taiwan Department of Health for patients with osteoporosis.

Efficacy studies in Taiwan showed increase of lumbar spine and hip BMD by 5.9% and 2.7%, respectively and increased bone formation markers after 12 months of treatment in Taiwanese women with osteoporosis[1], and increased 4.7% and 3.2% of the lumbar spine and hip BMD for Asian women with osteoporosis[2]. In two large foreign studies, SOTI and TROPOS and decreased bone resorptive marker s-CTX, increased bone formation marker Bs-ALP[3-5], that bone density is increased by 14% in lumbar spine. For men with osteoporosis, lumbar spine and hip BMD is increased by 5.8% and 3.5%, respectively[6].

III. Drug Adverse Reactions:

The side effect is similar to those of placebo. Most are temporary mild adverse reactions, including diarrhea, nausea, headache and dermatitis, may occur at the start of treatment. Precaution is advised in patients, e.g. phenylketouria (PKU) and venous thromboembolism (VTE). Cessation is recommended for patients experiencing drug rash with eosinophilia.

IV. Recommended Duration:

An eight-year study on bone density and safety showed that it is associated with decreased bone loss and improved bone density, the recommended length of used remains inconclusive.

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■ Section 7 Calcitonin

Editor: Chen-Tung Yu

Grade of Recommendation	Content of Recommendation	Level of Evidence	Number of Reference
Other studies			
A	Calcitonin is associated with improved bone density in postmenopausal individuals with osteoporosis.	1++	1,9
A	Calcitonin is associated with a lower risk of vertebral fracture in postmenopausal individuals with osteoporosis.	1++	1,9
A	Calcitonin is associated with decreased bone turnover markers in postmenopausal individuals with osteoporosis.	1++	9
A	Calcitonin directly acts on central nervous system to achieve analgesic effect, which can be used to relieve pain caused by osteoporosis-related fractures and improve quality of life after event.	1++	1,7-9, 13-14, 25-27
A	Calcitonin significantly improves the microstructure, volume and number of trabecular bone and minimizes the space between bone materials.	1++	1,2
A	Calcitonin is associated with improvement of lumbar BMD and pain relief.	1++	1,10-11
A	Calcitonin is associated with improvement of lumbar and femoral BMD in individuals with steroid induced osteoporosis.	1++	31, 32

●Medication treatment

Calcitonin - Calcitonin is a hormone existing in the human body to maintain calcium balance. High blood calcium (due to the migration of calcium from bone into blood) may result in osteoporosis, hypercalcemia, or even death. Miacalcic® is calcitonin analogue extracted from salmon that is readily absorbed and its strength is 50 times that of human calcitonin. It is effective against osteoporosis-related fractures, possessing analgesic properties, and most importantly, has a good safety profile and the experience of long-term use. Available in injective and nasal spray, it is indicated for osteoporosis, hypercalcemia related to malignancy and Paget's disease. Future researches are focused on the development of oral administration dosage and further application on osteoarthritis[1].

Mechanism: By binding with the calcitonin receptors on osteoclasts, calcitonin reversibly inhibits osteocalst activity to control bone resorption, improve bone density, and minimize the risk of osteoporosis-related fractures with its strengthening effect on the microstructure of trabecular bone. Also, salmon calcitonin binds with the receptors in the central nervous system to achieve pain relief[1-8].

Clinical benefits: Miacalcic is proven to be effective in the first year and persists for 5 years, and the increase of lumbar bone mineral density (BMD) reaches statistical significance (1.0-2.0%), maintaining lumbar BMD effectively. Compared to placebo group (vitamin D and calcium supplement alone), the incidence of new spinal fractures in individuals who with concomitant miacalcic nasal spray 200 IU QD was clinically and statistically lower (by 36%) ,

and the risk of multiple vertebral fracture was lower than placebo by 35%. Despite the study design rendering the difference insignificant, the prevention effect of Miacalcic against hip and non-vertebral fractures was observable, and it is also associated with improvement of lumbar BMD and pain relief[9-13].

When compared to placebo, significant improvement on microstructure, volume and number of trabecular bone and minimization of the space between bone materials were observed after two years of treatment with nasal spray[2]. Miacalcic directly acts on the central nervous system to relieve pain, especially the pain related to acute vertebral fractures as shown in the pain VAS score, and in concomitant use of analgesics and mobility after spinal fractures. In the patients who experienced acute vertebral compression fracture, the VAS of the Miacalcic group was significantly lower than that of the control group (by 3.08 at week 1 and by 4.03 at week 4). Injective was found to be effective against the pain related to metastatic bone malignancy and complex regional pain syndrome (CRPS)[14-27].

Side effects: Since its introduction, more than 20 years of clinical experience has shown that Miacalcic has an excellent safety profile. Side effects are usually mild and are associated with dose level and first use. Temporary flush, nausea and vomiting may occur at the start of treatment with injective, and these side effects can be minimized by switching to subcutaneous doses, using at a lower dose, or using nasal spray at night. Nasal spray may be associated with local side effects such as nasal discomfort, nasal congestion and sneezing. To avoid the risk of allergic reactions to polypeptides, the main component of salmon calcitonin, skin test is suggested for patients with suspected hypersensitivity[1, 28-30].

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Section 8 Receptor Activator of Nuclear Factor kappa-B Ligand (RANKL) Inhibitor

Editors: Jawl-Shan Hwang, Jung-Fu Chen

Grade of Recommendation	Content of Recommendation	Level of Evidence	Number of Reference
Other studies			
A	RANKL inhibitor is associated with increased of lumbar spine, hip and radial BMD in women with low bone density and osteoporosis.	1++	1-4
A	RANKL inhibitor is associated with a significantly reduced the risk of hip, vertebral spinal and non- vertebral fractures in women with osteoporosis.	1++	4
A	RANKL inhibitor is associated with reduced bone turnover markers in patients with osteoporosis.	1++	1-4
A	RANKL inhibitor is associated with increased lumbar spine, hip and radial BMD in osteoporosis patients treated with bisphosphates.	1++	5,6

I. Introduction:

In the cell differentiation process of bone remodeling, receptor activator of NF-kB (RANK) binds with RANK ligand (RANKL) to activate the differentiation of osteoclasts, while osteoprotegerin inhibits osteoclastic activity. RANKL inhibitors act on RANKL to block activation, which inhibits osteoclastic activity, and is followed by decreased bone loss, increased bone density and a decreased risk of bone fractures.

II. Medications:

RANKL inhibitor (denosumab, Prolia®): 60 mg subcutaneous injection every 6 months.

Denosumab is a human monoclonal antibody administered 60 mg subcutaneously. With a bioavailability of 61% and a half-life of 26 days, peak blood level is reached 10 days after administration. It has been approved in the United States and Europe for the treatment of osteoporosis in postmenopausal women.

Studies on European and American patients with low bone density and osteoporosis showed that a 24-month regimen of denosumab is associated with a 6.5% increase in lumbar spine BMD, and 3.4% in hip, 1.4% in radius, and 2.4% in total body. Improvement of bone structure and bone turnover markers (CTX, TRAP, P1NP) were also noted[1-3]. The three-year FREEDOM trial showed that compared to placebo, subcutaneous denosumab 60 mg once every six months reduces fracture risk as 68% vertebral fractures, 40% fewer hip fractures and 20% non- vertebral fractures, decreased bone turnover markers, as well as increased 9.2% and 6% of lumbar spine and hip BMD relative to placebo[4]. The DECIDE study compared subcutaneous denosumab 60 mg Q6M (once every six months) or alendronate 70 mg QW in postmenopausal women with low BMD, and it showed that BMD was increased 1.1% in the lumbar spine, and 0.6% in the hip and the radius in favor of denosumab after a year of treatment[5]. In the STAND study, postmenopausal women with low BMD who had been treated with bisphosphates were included to compare subcutaneous denosumab 60 mg Q6M with alendronate 70 mg QW. The

BMD was increased 1.2% in thelumbar spine, and 0.9% in the hip in favor of denosumab after a year of treatment[6].

III. Drug Adverse Reactions:

In clinical trials comparing denosumab with placebo, side effects identified include infection, constipation, sore throat, rash and diverticulitis that are usually mild[1-4].

IV. Recommended Regimen and Long-Term Safety:

A six-year study on bone density and safety showed that it is associated with decreased bone loss and improved bone density, but the recommended length of used remains inconclusive[7,8].

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Section 9 Traditional Chinese Medicine

Editor: Hwa-Chang Liu

Grade of Recommendation	Content of Recommendation	Level of Evidence	Number of Reference
C	"Kidney-nourishing" Chinese herbs are associated with lower serum estrone as well as increased estradiol level and BMD, suggesting its effectiveness in the prevention and treatment of osteoporosis.	2-	1
C	Prescriptions for bone strengthening and kidney nourishment are associated with increased estrogen level, BMD and bone formation, especially in postmenopausal women with osteoporosis.	2-	2
C	Concomitant use of the prescriptions for bone strengthening and kidney nourishment, prescriptions for blood and qi replenishment and vitamin D supplement is associated with significant differences in BMD, estradiol level, testosterone level and tartrate-resistant acid phosphatase after treatment. This is an effective approach for the prevention of osteoporosis as it inhibits bone resorption and promotes bone formation.	3	3
C	The combined Chinese-Western prescription based on six flavor rehmanni (liu wei di huang wan), a prescription for kidney nourishment, and anti-resorptives including nilestriol has been used for the treatment of primary osteoporosis in postmenopausal women and showed significant improvement of pain and BMD.	3	4
C	The ingredients and their effects of the decoction of kidney- and spleen-nourishment and blood circulation-activating are: herba epimedii and fortune's drynaria rhizome for kidney warming, bone strengthening and nourishment of liver and kidneys. Chinese yam rhizome, the rhizome of *Atractylodes macrocephala* and the root of *Pilose Asiabell* for spleen nourishment and qi replenishment. Chinese angelica root, rhizoma corydalis, red paeony root, penoy root peel and the rhizome of *Szechwan Lovage* for enriching blood and promoting blood circulation, relaxing muscle/tendon/joints, removing meridien obstruction and blood stasis, and relieving pain. The rhizome of rehmannia, the root of rehmannia and the fruit of medicinal cornel as tonic for the liver and kidney and essence enrichment. These ingredients are combined to nourish the kidney and enrich vital essence, strengthen bone, muscle and ligaments, expel wind and dampness, activate blood circulation, dissipate blood stasis, promote qi circulation and relieve pain. Pharmacological studies showed that herba epimedii and fortune's drynaria rhizome possess sex hormone-like activities, while spleen-strengthening herbs are associated with enhancement of digestive function as well as better absorption and distribution of nutrients. Decoction of kidney- and spleen-strengthening and blood circulation-activating is associated with improved BMD in postmenopausal women with osteoporosis and relieves back and bone pain.	2-	5
C	Strong Bone capsule is a reasonable treatment for osteoporosis because it is effective against clinical symptoms in patients with osteoporosis, and it is associated with increased bone density. In terms of safety, no adverse cardiac, hepatic and/or renal reactions were observed in all subjects. Strong Bone capsule is safe and effective in the treatment of primary osteoporosis (kidney deficiency syndrome).	2-	6
C	The decoction of kidney- and spleen-invigoration and bone strengthening is safe, free of side effects, and is effective against the clinical symptoms of osteoporosis.	3	7
C	Clinical studies showed that: flavones fortune's drynaria rhizome is associated with increased overall bone mass in elderly with osteoporosis, back pain relief, better bone strength at proximal femur and hip fracture prevention because of the promotion of collagen synthesis, bone turnover, bone formation, and the reduction of bone resorption.	2-	8
C	Water extract of fortune's drynaria rhizome is expected to be provided to subjects with osteoporosis at clinical doses in clinical trials. Bone marker analysis, including bone density, blood alkaline phosphatase, and urine deoxypyridinoline and N-telopeptide of type I collagen (NTx) showed that the water extract of fortune's drynaria rhizome is associated with improvement of bone density and clinical symptoms.	2-	9

The management of osteoporosis in Chinese medicine differs from its western counterpart because of the differences in basic philosophy. The hormone therapies, vitamin D3 and calcium supplement used in western medicine, in the philosophy of Chinese medicine, are measures for "managing the signs" instead of real solutions. Osteoporosis does not exist in the glossary of Chinese medicine. Instead, this disorder is described as "bone bi syndrome", "bone wilting/bone atrophy", "bone desiccation" and/or "bone shrinkage"[10]. Its pathological mechanism in Chinese medicine includes kidney deficiency, spleen deficiency and blood stasis, which are managed mainly with prescriptions for kidney and spleen nourishment, bone strengthening and qi replenishment, and supplemented with prescriptions for blood circulation-activating and the dissipation of blood stasis[11]. Modern Chinese medicine professionals consider Chinese herbs as real solutions, although this requires more evidence and observation.

For osteoporosis, Chinese medicine provides two dimensions of treatment, including single-herb prescription such as psoralea fruit, fortune's drynaria rhizome, eucommia bark, himalayan teasel root, herba epimedii, two tooth achyranthes root and mulberry mistletoe stem[10,12], and traditional Chinese herb pills such as six flavor rehmanni, huqian pills and psoralea pills for kidney yin deficiency[10,12], whereas kuei-lu-erh-hsien-chiao (KLEHC) decoction of si wu (four substance) plus ginseng and eucommia is for facilitation of calcium absorption. Herba epimedii, KLEHC and fortune's drynaria rhizome are the most frequently used prescriptions for osteoporosis[10,12]. Herba epimedii is the dried aerial part or whole plant of Epimedium brevicornum Maxim., a member of the family *Berberidaceae*, and members of the same genus. Warm in nature and sweet in flavor, it is used for liver and kidney invigoration and the strengthening of bone, tendon, muscle, bursa, ligament and some of the cartilage. Researches showed that flavone is associated with effective control of bone loss and acceleration of bone formation[13-14]. *Ex vivo* studies showed that the flavones in the extract of herba epimedii promote the proliferation of osteoblasts, increase its synthesis of OPG mRNA and inhibit the expression of RANKL mRNA[15]. However, large multicenter RCTs are required to provide clinical evidence for these laboratory findings. Kuei-Lu-Erh-Hsien-Chiao (KLEHC), made from turtle shell, deer antler, ginseng and wolfberry (goji berry), is a preferred prescription for the strengthening of bone, tendon, muscle, bursa, ligament and some of the cartilage. Fortune's drynaria rhizome, one of the common Chinese herbs in folk medicine, is prepared from dried Drynaria forunei (Kunze) J. Sm. It is used for the treatment of bone fractures, kidney deficiency, tinnitus and diarrhea because it contains davallic acid, hesperidine and naringin that can be used for the treatment of kidney deficiency, back pain, sudden sprain and contusion due to trauma, and the sprain of extremities[10,12]. Experiments have shown that fortune's drynaria rhizome is associated with increased glycoprotein in the bone formation process, and provides osteoblasts with antioxidant activity[16]. Its relationship with increased bone density was observed in controlled clinical trials[9]. However, this requires more research to establish its validity.

Conclusion: The knowledge base of Chinese medicine is different from that of western medicine because it is based on minimal knowledge of human physiology, which is a relatively new subject in the development of Chinese medicine. Meanwhile, western medicine provides a sound pathological mechanism, but the treatment effect is limited to the inhibition of osteoclastic activity when PTH is not counted. Today, as the knowledge base of Chinese medicine is growing at a breakneck speed, it is expected that new evidence regarding the treatment of osteoporosis based on Chinese medicine may become more fruitful.

Prescription	Reference	Materials
Six flavor rehmanni	Precious Mirror of Health[17]	Rehmanniae radix et rhizoma (8 taels), penoy root peel, Indian buead and oriental water plantain rhizome (3 taels each), fruit of medicinal cornel and Chinese yam (4 taels each). The abovementioned materials are better ground into fine powder and made into honey pills as large as phoenix tree seeds (about 0.5-1 cm in diameter). Fifty pills should be taken with warm rice wine before meals. When Chinese magnoliavine, cinnamon and prepare aconite root (1 tael each) are added, it is called “shenqi pill” (kidney qi pill or pill for invigorating kidney energy).
Huqian pill	Danxi's Mastery of Medicine[18]	Amur corktree bark, turtle shell, common anemarrhea rhizome, rehmanniae radix et rhizoma, dried tangerine peel, white peony root, herba cynomorii, tiger bone and dried ginger
Huqian pill	Classified Treatment[19]	Amur corktree bark, turtle shell, common anemarrhea rhizome, rehmanniae radix et rhizoma, dried tangerine peel, white peony root, herba cynomorii, tiger bone, dried ginger, Chinese angelica root and two tooth achyranthes root
Kuei-Lu-Erh-Hsien-Chiao (KLEHC)	Variorum of Medical Recipes (Yi Fang Ji Jie)[20]	Deer antler (10 catties), turtle shell (5 catties), wolfberry (2 catties) and ginseng (1 catty)
Psoralea pill	Standards for Diagnosis and Treatment (Zhengzhi Zhunsheng)[21]	Psoralea (2 taels) soaked in liquor for one night, then stir fried with bran into powder. Almond scalded to remove the seed coat and radicle, then ground; peach seed stir-heated to remove the seed coat and radicle and ground (1 tael each). Mix well, add to herb liquor and boil until it becomes slurry, then make into pills as large as phoenix tree seeds (about 0.5-1 cm in diameter). Fifty pills should be taken with salt soup or rice wine before meal.

Table 7-1 Common drugs and materials

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