



CHARM issue 5

CARE, HEALTH, ARTHRITIC MANAGEMENT

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EDITOR'S MESSAGE

May I wish you Happy New Year of 2011!

The editorial board of CHARM and the scientific committee of the Hong Kong Arthritis & Rheumatism Foundation would like to greet you with this issue on osteoporosis. This is a condition that not only affects post-menopausal women and is also a major concern of rheumatologists. Osteoporosis is a frequent complication of most rheumatic diseases due to the underlying condition or as a drug related adverse effect. Immobility and long-term corticosteroid use are clinical factors that contribute to osteoporosis that are associated with increased risk of fracture.

In this issue, you'll read about the milestones that lead to the understanding of bone metabolism, definition and treatment of osteoporosis. Our highlight article on osteoporosis provides all you need to know about its diagnosis, risk of fractures, the medical and non-pharmacological approach in the management of this condition. There is an interesting report on the risk of fall and predisposing factors among community dwelling elderly subjects in Hong Kong. We will also learn the various investigative modalities, their clinical usefulness and pitfalls and the interpretation of results in the diagnosis of osteoporosis. Of most concern to rheumatologists, we look forward to reading more about glucocorticoid induced osteoporosis, its pathophysiology, risk assessment and the current available evidence for pharmacological treatment and the 2010 guidelines from the American College of Rheumatology. We also have the privilege of hearing from our pharmacist a comprehensive update on various anti-resorptive agents and anabolic agents approved for prevention and treatment of osteoporosis as well as novel therapies down the pipeline undergoing phase I or II/III clinical trials with promising preliminary results. Last but not the least, our dietician is most helpful to remind us of the importance of adequate daily consumption of calcium and vitamin D, the essential bone building nutrients.

In last October, the scientific committee has organized a second seminar of the "East meets West" educational series on the role of Tai Chi in rheumatic diseases. For those who have missed the event, abstracts on a selection of talks delivered by the speakers can be found in this issue. A video recording of the seminar can also be borrowed from our executive officer and will be uploaded onto our website in due course.

Happy reading!

HISTORY OF OSTEOPOROSIS

Dr. Ng Kam Hung, Daniel

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Osteoporosis is nowadays a major public health issue. However, this condition has actually affected women since the dawn of human history.

Anicent Egypt

Egyptian mummies 4,000 years old have been x-rayed and found to have osteoporosis. The presence of a hump was a tell-tale sign of osteoporosis.

18th century

John Hunter, an English surgeon, found that as new bone was laid down in the body, old bone would be destroyed and absorbed. This process is now known as remodeling.

1830s

Jean Georges Chretien Frederic Martin Lobstein, a French pathologist noticed that some bones in patients had many larger than normal holes. He called osteoporosis, which meant porous bone, to describe it.

1930s

Fuller Albright, an American endocrinologist discovered that postmenopausal women were more susceptible to this condition and to have frail bones.

1940s

Postmenopausal osteoporosis was defined. Estrogen was used to treat women with this condition.

1960s

Densitometer, a more sensitive device was developed for detecting bone loss. Herbert Fleisch, a Swiss Professor, found the compounds known as bisphosphonates that inhibit bone resorption.

1984

The National Institutes of Health of U.S. publicized this disease, citing it as a significant threat to health and emphasizing that bone loss could be reduced by estrogen therapy, calcium, good nutrition and exercise.

1990s

Two bisphosphonates, alendronate and risedronate, were approved by U.S. Food and Drug Administration for prevention and treatment of osteoporosis.

OSTEOPOROSIS HIGHLIGHTS

Dr. IP Tai-Pang

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Introduction

One in three postmenopausal women and one in five elderly men have osteoporosis. Despite its common clinical occurrence, osteoporosis, interestingly, is a relatively new disease entity in the medical literature. Its medical definition was only first defined in 1993, less than 2 decades ago. This article aims to highlight the important fallacies in the understanding and treatment of this important disease. Although majority of osteoporosis-affected persons are asymptomatic, osteoporosis can lead to dreadful complication of fracture. Both spine and hip fractures have been documented to cause significant morbidity, impairment of quality of life and even mortality in affected patients. The 1-year mortality after hip fracture is up to 15-25% and less than half of hip-fractured patients can return to their pre-morbid ambulatory state.

Diagnosis of Osteoporosis & Risk of Osteoporotic Fractures

The initial definition of osteoporosis in 1993 emphasized on bone mass/bone mineral density (BMD). This was revised in 2001 as “a skeletal disorder characterized by compromised bone strength with an increased risk of fracture”. The shift in emphasis from BMD to bone strength is based on the important understanding that bone strength depends not only on BMD but also and even more on bone quality which is determined by the microarchitecture, the structural and material properties of the bone, the level of bone remodeling and the ability to repair microfractures. Bone quality, however, cannot be easily and objectively measured in clinical practice so that the working diagnosis of osteoporosis still relies on the BMD-based World Health Organisation (WHO) definitions (Table 1). On the contrary, the presence of a fragility fracture is already a sufficient clinical indicator of the severity of the disease irrespective of the BMD measurements. Nevertheless, BMD measurements expressed as T-scores still possess very high predictive values for the risk of future fractures even in the absence of prior fracture. On average, the risk doubles for every unity reduction of T-score.

In actual clinical settings, more than half of all patients with clinical fragility fractures do not have BMD T-scores in the osteoporotic range. Studies have shown that clinical risk factors would be of important predictive values. These clinical risk factors include age, sex, body mass index, history of prior fracture, parental history of hip fracture, smoking, excessive alcohol consumption, corticosteroid usage and the presence of rheumatoid arthritis or other secondary causes of osteoporosis. These clinical risk factors have been integrated into an algorithm in the WHO fracture risk assessment tool, the FRAX® (<http://www.shef.ac.uk/FRAX/>), which is available as a web-based ethnic-specific tool to compute the absolute 10-year risk of osteoporotic and hip fractures with or without BMD measurements. Many authorities have incorporated the ethnic-specific computed 10-year fracture probability into their guidelines for initiation of anti-osteoporosis treatment.

Pharmacological Treatment of Osteoporosis Reduction in the risk of future fracture is the primary objective of medical treatment for osteoporosis. The last two decades have seen the development of a considerable number of efficacious anti-osteoporosis medications which include bone-forming (anabolic), antiresorptive and dual action agents. They differ in terms of the approved indications, the mode and frequency of administration and the anti-fracture efficacy at the vertebral and non-vertebral sites (Table 2).

It is beyond the scope of this article to review each drug in details. It is suffice to state that prescription of any of the anti-osteoporosis drugs to high risk persons is better than none. Among all the available drugs, hormonal therapy and calcitonin are going out of favour because the former is associated with a potential increase in cardiovascular risk in elderly women and an increase in risk of carcinoma of breast in all postmenopausal women whereas the latter has inconsistent anti-fracture efficacy. In the process of selection of medications, age, severity of osteoporosis, co-morbidities, the anti-fracture efficacy, mode of administration and adverse effects of the drug, in addition to the patient's preference, are important determinants in the individual-based therapy. As a summary, all agents have strong clinical data on both vertebral and non-vertebral fracture risk reduction except raloxifene which has not been proven to reduce non-vertebral fracture risk. Among the bisphosphonates, ibandronate appears to be less effective since data on non-vertebral fracture risk reduction were obtained through post-hoc analysis. Whether bone-forming agent is superior to antiresorptive agents cannot be concluded at this stage since direct head-to-head comparison studies using fracture as the primary endpoint have not been available. However, histological and microarchitectural studies did show a significant improvement in microarchitecture of bone being treated with bone-forming agent. Teriparatide is currently the only pure bone-forming agent available locally. The very high cost of the drug and the need for daily subcutaneous injection have limited its clinical use.

Recent data have also shown that anti-osteoporosis drugs improve survival of fractured patients, in addition to their benefits on fracture risk reduction. The early use of zoledronic acid in hip-fractured patients was associated with a 28% reduction in mortality without any adverse effects on fracture healing. A subsequent meta-analysis involving >40,000 subjects in 10 placebo-controlled randomised studies of 5 agents (alendronate, risedronate, strontium ranelate, zoledronic acid and denosumab) also confirmed that treatment of osteoporosis was associated with a significant 10% reduction in mortality, which corresponded to an absolute mortality benefit ranging from 0.4–7 deaths prevented per 1,000 patient-years of treatment.

Non-Pharmacological Treatment of Osteoporosis Adequate calcium and vitamin D supplements are important to maximise the clinical benefits of the anti-osteoporosis drugs. In general, calcium supplement of 500-1,000 mg and vitamin D supplement of at least 800 IU are considered the daily minimal requirement in the absence of contraindications. Considerably higher dose of vitamin D up to 2,000 IU may be required for obese, institutionalised or home-bound patients. Other non-pharmacological measures include cessation of smoking and excessive alcohol intake, physical exercise and balance training, and fall prevention.

OSTEOPOROSIS HIGHLIGHTS

Conclusions

Osteoporosis has been regarded as a major public health problem worldwide but the local scenario has been far from satisfactory. The level of awareness of the disease is not low but the treatment rate is suboptimal. Medical treatment of osteoporosis has not received much support by the local health authority in the past 20 years. It is only in recent years that fractured patients are funded with anti-osteoporosis medications for secondary prevention. However, there have been a lack of unified treatment guidelines and a limited choice of drugs available in the Hospital Authority. In light of current evidence of the benefits of osteoporosis treatment and notably a survival benefit, high risk patients should be identified and treated early.

Table 1 The World Health Organization criteria for diagnosis of osteoporosis

Diagnostic Category	Definitions
Normal	Bone mineral density (BMD) within 1 standard deviation (SD) of the young adult mean (T-score ≥ -1.0)
Osteopenia	BMD more than 1 SD below the young adult mean but less than 2.5 SD below this value (T-score < -1.0 and > -2.5)
Osteoporosis	BMD being 2.5 SD or more below the young adult mean (T-score ≤ -2.5)
Severe (established) osteoporosis	BMD being 2.5 SD or more below the young adult mean (T-score ≤ -2.5) in the presence of one or more fragility fractures

Table 2 Pharmacological treatment options in postmenopausal osteoporosis.

	Approved Indications ^a		Documented Fracture Reduction		
	Prevention	Treatment	Vertebral	Non-Vertebral	Hip
Anti-resorptive Agents					
HRT	+	-	+	+	+
Raloxifene	+	+	+	-	-
Calcitonin	-	+	+	-	-
Alendronate	+	+	+	+	+
Risedronate	+	+	+	+	+
Ibandronate	+	+	+	+ ^b	-
Zoledronic Acid	+	+	+	+	+
Denosumab	+	+	+	+	+
Bone-Forming Agent					
Teriparatide	-	+	+	+	-
Dual Action Agent					
Strontium ranelate	-	+	+	+	+ ^b

^a Approved either by the United States Food & Drug Administration (FDA) or the European Medicines Agency (EMA)

^b post-hoc analysis in high risk subgroups

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STERIOD INDUCED OSTEOPOROSIS UPDATE

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Introduction

Bone loss is one of the most important side effects of glucocorticoid use, even in low doses. Glucocorticoid-induced osteoporosis (GIO) is the most common form of secondary osteoporosis. Fractures, which are often asymptomatic, may occur in as many as 30-50% of patients receiving chronic glucocorticoid therapy. Vertebral fractures occur early after exposure to glucocorticoids, at a time when bone mineral density (BMD) declines rapidly. BMD declines rapidly in the first 3 months, peaks at 6 months and followed by slower steady loss when steroid is continued. Steroid induced osteoporotic fracture is characterised by fractures occurring at higher BMD levels compared with postmenopausal osteoporosis. Bone loss is predominantly found in bone with high trabecular content, such as ribs and vertebrae but also at other sites.

STERIOD INDUCED OSTEOPOROSIS UPDATE

Pathophysiology

Glucocorticoids have direct and indirect effects on bone with primary effects on osteoblasts and osteocytes. Glucocorticoids impairs replication, differentiation and function of osteoblasts. These effects lead to suppression of bone formation, a central feature in the pathogenesis of GIO. Moreover, it induces apoptosis of mature osteoblasts and osteocytes resulting in rapid weakening of bone architecture and increase in fracture risk. These account for occurrence of fracture at higher BMD. Glucocorticoids also favor osteoclastogenesis and, as a consequence, increase bone resorption. Non-genomic effects (mediated by glucocorticoid interactions with biological membranes, either through binding to membrane receptors or by physicochemical interactions) may have a role in the pathogenesis of GIO.

Management

Increased risks of vertebral and nonvertebral fractures have been reported with dosages of prednisolone or equivalent as low as 2.5–7.5 mg daily. This risk may be related more strongly to daily rather than to cumulative doses of glucocorticoids.

There are two treatment approaches to reduce fracture risk. Because most rapid bone loss often occurs in the first 6 months after starting glucocorticoid, the approach of primary prevention involves management of patients who are to be started on glucocorticoid therapy i.e. who have not yet lost bone. On the other hand, treatment (or secondary prevention) involves managing patients receiving long term glucocorticoid, who have existing bone loss to a certain extent. Therefore, it is never too early or too late to treat.

Important approaches to avoid glucocorticoid induced osteoporosis:

- Use lowest possible dose of glucocorticoid
- Lifestyle modification including adequate calcium intake (1200 to 1500 mg/day), healthy diet, avoid smoking and excessive alcohol, weight bearing exercise and fall prevention
- Medical therapy to prevent or reverse bone loss.

Risk assessment

Patient's overall clinical risk instead of T-scores alone

Bone density alone may not be the sole reliable diagnostic guide for treatment for some patients receiving glucocorticoids, because fracture in these patients may occur independent of a reduction in bone mass. There are other factors in addition to BMD, such as age and weight, that contribute to fracture risk.

- The updated American College of Rheumatology (ACR) guideline (2010) classify patients into three fracture risk categories -- high, medium and low risk -- based on gender, age, race/ethnicity, and femoral neck bone-density T scores.
- Using the FRAX calculator, the Expert Advisory Panel defined a 10-year risk of a major osteoporotic fracture of 10% or less as low risk, 10-20% as medium risk, and greater than 20% or a T score of less than or equal to -2.5 or a history of a fragility fracture as high risk (which is the threshold for cost-effective treatment recommended by the National Osteoporosis Foundation).
- There are additional clinical factors that increase fracture risk. (Table 1)

Pharmacological treatment

Management recommendations take into consideration the dosage and anticipated duration of glucocorticoid therapy. Based on a systematic review of therapies currently approved for the treatment of postmenopausal osteoporosis or GIO, the ACR guideline provides algorithms outlining the recommended approaches for postmenopausal women and men aged over 50 years and for premenopausal women not of child bearing potential as well as men aged under 50 with a history of fragility fracture. Bisphosphonates (alendronate, risedronate, or zoledronic acid) are currently the preferred treatment for GIO with evidences from several randomised controlled trials. Zoledronic acid, a single infusion yearly, has been shown to improve BMD as the primary end point and favourable effect on fracture reduction in the high risk group of postmenopausal women. There are insufficient data in the recommendation of use of ibandronate, etidronate, calcitonin, estrogen, testosterone and raloxifene. Hormonal therapy such as estrogen replacement and testosterone use is no longer recommended. There is no good evidence that one specific bisphosphonate is superior to another bisphosphonate due to a lack of good head-to-head studies on GIO.

Teriparatide (TPT), which has stimulatory effect on osteoblasts, has received US Food and Drug Administration (FDA) approval for treatment of GIO. The use of TPT is supported by physiologic ground because GIO is mostly due to decreased osteoblast function. Calcium and plain vitamin D3 supplementation are considered important support for prevention and treatment of GIO. For older patients, the stepwise approach in management begins with counseling and risk factor assessment, followed by determination of the level of fracture risk. If the risk is high, treatment with alendronate, risedronate, or zoledronic acid is recommended. For younger subjects, there is inadequate evidence to make recommendations if there is no prevalent fragility fracture. If the risk is present, treatment recommendations again depend the duration and dosage of glucocorticoid therapy, as well as the childbearing potential for women.

STERIOD INDUCED OSTEOPOROSIS UPDATE

Conclusion

Despite increased knowledge on bone loss and fracture risk during glucocorticoid use, there is a need to optimize management in terms of prevention and treatment of GIO. Education of health care workers in the pathophysiology, general measures and pharmacological intervention for prevention and treatment of GIO is needed.

Table 1 Clinical factors predisposing to a greater fracture risk in glucocorticoid-induced osteoporosis.

- Low body mass index
- Parental history of hip fracture
- Current smoking
- 3 or more alcoholic drinks per day
- Higher daily glucocorticoid dose
- Higher cumulative glucocorticoid dose
- Intravenous pulse glucocorticoid usage
- Declining central bone mineral density measurement that exceeds the least significant change

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ASSESSMENT AND INVESTIGATIONS OF OSTEOPOROSIS

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Introduction

A comprehensive clinical history and physical examination are the cornerstones to the diagnosis and assessment of osteoporosis, similar to many other diseases. In addition, biochemical indices may reveal the cause of skeletal disease or the results of changes in skeletal metabolism. Radiological assessment can detect asymptomatic skeletal abnormalities. Measurement of bone mineral density is the gold standard in the diagnosis of osteoporosis. These techniques and their applications are reviewed briefly in this article.

Osteoporosis is known as a silent epidemic in the elderly population. However, its complications are often overlooked by both patients and clinicians. Progressive loss in body height, fragility fractures, kyphosis and back pain are common symptoms and signs of osteoporotic fractures. Osteoporosis can be secondary to systemic illnesses and treatment such as rheumatoid arthritis, multiple myeloma, use of long term steroids or aromatase inhibitors, which may be picked up by clinical history or physical examination. It is also important to delineate an individual's risk factors of osteoporosis and its dreadful complication of fragility fracture. The Osteoporosis Self-Assessment Tool for Asians (OSTA) is a simple clinical tool, which incorporates age and weight only, that provides clinicians with a rough estimate of the risk of osteoporosis in an individual patient. More sophisticated tool with compilation of risk factors has been developed and is readily available for clinical use. The WHO Fracture Risk Assessment Tool (FRAX) generates an individual's absolute risk of fragility fracture and hip fracture. In general, a person who has parental history of fracture and personal history of fragility fracture are at a significantly higher risk of subsequent fragility fractures.

Biochemical assessment

Bone markers

At present, the most sensitive markers for bone formation in postmenopausal osteoporosis include serum total osteocalcin, a small protein almost specific to bone, the bone isoenzyme of alkaline phosphatase (bone ALP), and procollagen type I N-terminal propeptide (PINP), which reflects the rate of synthesis of the main constituents of bone tissue. For the evaluation of bone resorption, most currently available assays are based on the detection in serum or urine of breakdown products of type I collagen fragments. These include the inter-molecular crosslinkspyridinoline (PYD) and deoxypyridinoline (DPD), the cathepsin K (CTX, NTX) and matrix-metalloproteases (MMP) - generated (CTX-MMP or ICTP) telopeptides and fragments of the helical portion of type I collagen molecule (helical peptide). These bone markers have been proven useful in fracture risk assessment and monitoring of treatment efficacy in osteoporosis. However, there are significant individual variations in the level of these markers and even throughout the day. Their roles in routine clinical use are yet to be defined.

ASSESSMENT AND INVESTIGATIONS OF OSTEOPOROSIS

Vitamin D assay

It is not surprising to know that more than 80% of patients suffered from hip fractures are deficient in Vitamin D, partly because of lack of outdoor activities in the elderly, concern about sun exposure related skin changes and impaired ability in vitamin D synthesis in the elderly, etc. Elderly individuals should be advised on adequate daily intake of vitamin D (1000 IU/day) and adequate sunlight exposure. The severity of vitamin D deficiency are generally defined based on serum 25(OH)D levels, for which less than 12.5 nmol/L is considered severe deficiency, a level between 12.5 and 25 nmol/L as deficiency, and a level of 25 to 50 nmol/L as inadequacy.

Radiological assessment

Plain radiograph

Despite its widespread availability, plain X-ray is not a desirable tool to diagnose osteoporosis. Features of osteoporosis will only be shown in plain XR with bone loss over 50%. It is a convenient tool for the diagnosis of fragility fractures, but it is worth to note that half of the vertebral fractures in plain XR are not documented in clinical reports.



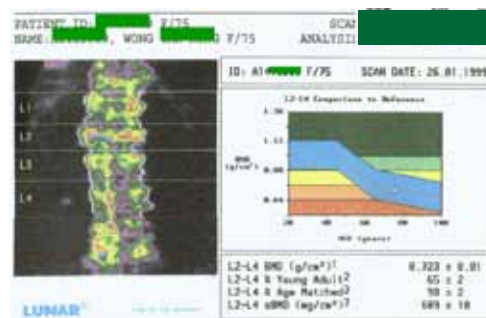
Hip Fracture



DEXA machine

Dual Energy X-Ray Absorptiometry (DEXA)

Bone mineral density (BMD) measurement by DEXA remains the gold standard for the diagnosis of osteoporosis. A patient's BMD is often expressed by its relationship with the expected BMD for 'young normal' adults of the same sex (T score), and the expected BMD for the patient's age and sex (Z score). The difference between patient's score and the norm is expressed in terms of standard deviations (SD) above or below the mean. Osteoporosis is defined as a BMD T score of less than or equal to -2.5, and osteopenia as a T score between -2.5 and -1. The lumbar spine (L1-4) and hip are the preferred sites for DEXA measurement. It is important to note that the BMD measured by DEXA reflects an areal density, instead of a volumetric density, which can be influenced by other factors. Degenerative changes with osteophytosis, aortic calcification, severe kyphoscoliosis and vertebral collapse can all factitiously increase the BMD. Interval BMD measurement should be carried out with the same machine, usually at least 1 year apart, to maximize the chance of detecting a "least significant change".



DEXA result on lumbar spine

Bone quality assessment

Despite the good predictive ability of BMD assessment, other aspects of bone properties are equally important. The term bone quality, encompassing various biomechanical concepts and properties of bone, is often used to explain those changes which cannot be explained by BMD. Qualitative ultrasound (QUS) is one of the many methods to assess bone quality, its mechanical property and response. Speed of sound and ultrasound attenuation reflects the mechanical property of the segment of bone measured when ultrasound wave passes through. These measurements are independent risk factors in predicting fragility fracture, but it is important to remember that QUS could not replace DEXA assessment, which remains the gold standard in the diagnosis of osteoporosis.

Summary

Patients with osteoporosis warrant a throughout evaluation of underlying etiologies predisposing to the condition. DEXA scan remains the gold standard in diagnosis of osteoporosis. Other clinical risk factors, bone markers assessment and bone quality assessment carry similar significant clinical importance.

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UPDATE ON DRUGS USED IN THE TREATMENT OF OSTEOPOROSIS

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An increase in the prevalence of developing osteoporosis world-wide has been predicted due to improved life expectancy. In recent years, initiatives of researching possible new treatment for osteoporosis have been studied. Revised guidelines from the Osteoporosis Guideline Group (NOGG) and the National Institute for Health and Clinical Excellence (NICE) have issued guidelines in regard to treatment strategies in the prevention and treatment of osteoporosis. Bone loss occurs with advancing age. Osteoporosis develops when there is an imbalance in the bone remodelling process, where bones are removed faster than they are replaced i.e. a high bone turnover. Based on this pathology, treatment of osteoporosis is divided into two categories, antiresorptive agents (that slow bone remodelling and increase bone density), and anabolic agents (that build new bones).

Current pharmacological treatments

Antiresorptive agents

Bisphosphonates

Bisphosphonates are the first line treatment for both prevention and treatment of osteoporosis in both men and women. Alendronate, ibandronate, risedronate and zoledronate are all approved by the FDA for this indication. They decrease osteoclast activity and induce osteoclasts apoptosis. Bisphosphonates do not work optimally when there is underlying vitamin D deficiency. Thus, there are combination preparations of bisphosphonates with calcium carbonates e.g. Didronel PMO (licensed in the UK) or vitamin D e.g. Fosamax Plus to optimise the bone developing and remodelling processes. Studies have reported significant reductions in both vertebral and non-vertebral fracture rates in postmenopausal women with established osteoporosis following a year's treatment. The main concern of bisphosphonates is its low oral bioavailability (approximately 5% of the dose) even with proper administration method. It is advised to take the tablet with an overnight fast and remain in upright position for 30 minutes after ingestion. This improves bioavailability as well as reduces the risk of developing oesophageal ulceration. Bisphosphonates have been linked with osteonecrosis of the jaw (ONJ) and atrial fibrillation. ONJ may be precipitated by recent dental procedures. However, the evidence is insufficient to warrant any specific advice on the prescription in regard to these issues.

Selective Oestrogen Receptor Modulators (SERMs)

Menopause is a strong risk factor for osteoporosis. Hormone replacement therapy (HRT) may be beneficial but it is a less attractive treatment option because of its long term risks. Thus, HRT should only be considered as an alternative in women when other treatments have failed. Raloxifene is approved by the FDA for both prevention and treatment of osteoporosis in postmenopausal women, and it is the only licensed SERMs for treatment of osteoporosis. The drug binds selectively to oestrogen receptors with resultant agonistic effect on bone. Raloxifene 60mg daily compared to placebo¹, has been shown to reduce vertebral fractures by 55% in women who have osteoporosis with no prior vertebral fracture, or by 30% who have a previous fragility fracture. However, its efficacy in preventing non-vertebral or hip fractures has not been demonstrated. It may cause hot flashes and predispose to deep vein thrombosis with comparable risk to oestrogen replacement therapy. Newer SERMs are currently being studied. Arzoxifene shows promising results in increasing bone mineral density² in early clinical trials. Lasofoxifene has been reported to be associated with lower risk of vertebral fractures³. Other SERMs agents such as Bazedoxifene and droloxifene are currently in phase III clinical trials.

Calcitonin

Calcitonin is a hormone produced by the thyroid gland. Salmon Calcitonin is FDA-approved for the treatment of osteoporosis in women who are at least 5 years postmenopausal. It possesses dual mechanisms of action involving inhibition of bone resorption by osteoclasts and stimulation of bone formation by osteoblasts. It is available in injection and intranasal forms. It has been shown to reduce the risk of vertebral fractures in osteoporosis and that there is no evidence for reduction of other types of fracture. The side effect profile of intranasal calcitonin is mild with rhinitis or occasional epistaxis.

Strontium Ranelate

Although Strontium Ranelate is not FDA-approved, it is licensed in Europe for risk reduction of vertebral and hip fractures in postmenopausal women. Like calcitonin, Strontium ranelate has dual mechanisms of action. Its effectiveness⁴ has been demonstrated by clinical studies which have also shown a slight increased risk of venous thromboembolism compared with placebo. Strontium ranelate remains as a second line treatment option for osteoporosis due to its cost implication. Strontium ranelate is not currently licensed for men.

UPDATE ON DRUGS USED IN THE TREATMENT OF OSTEOPOROSIS

Anabolic agent

Parathyroid Hormone (PTH)

Teriparatide is approved by the FDA for the treatment of osteoporosis in postmenopausal women and men at high risk of fracture. Teriparatide (Forsteo), a recombinant human PTH, promotes bone growth. It is the first licensed anabolic drug used to reduce the risk of vertebral fractures in established osteoporosis. PTH produces greater increase in BMD than antiresorptive drugs and improves bone microarchitecture. Teriparatide in a subcutaneous dose of 20 microgram daily, was shown to decrease risk of vertebral fractures by 65% and non-vertebral fractures by 53% in patients with osteoporosis, after an average of 18 months of therapy. Studies also demonstrated its superiority over alendronate in the treatment of steroid-induced osteoporosis⁵. The safety and efficacy of Teriparatide has not been demonstrated beyond 2 years of treatment. It is recommended that antiresorptive drugs be stopped during PTH therapy and restarted after the course of PTH is complete. Teriparatide is well tolerated with mild side effects such as leg cramps and dizziness. It should not be used in those having prior radiation therapy of the skeleton, bone metastases, hypocalcaemia or a history of skeletal malignancy because of its increased risk of osteosarcoma.

Novel therapies

Receptor activators of NF- κ B ligand (RANKL) is a cytokine that modulates bone resorption through the osteoclastic receptor, RANK⁶. Preliminary data has suggested a favourable effect of osteoprotegerin, a ligand that binds to RANKL, in the treatment or prevention of osteoporosis in postmenopausal women⁷. In line with such research, a human monoclonal antibody that targets RANKL has been developed. To date, Denosumab, administered subcutaneously twice a year, has been shown to reduce over 50% in risk of vertebral fracture in postmenopausal osteoporosis⁸. A smaller phase III trial demonstrated its effect on risk reduction of vertebral fracture in men with non-metastatic prostate cancer undergoing androgen deprivation therapy⁹. Denosumab has been officially launched in the treatment of osteoporosis since May 2010. Other potential agents such as sclerostin inhibitors, integrin antagonists and therapies that involve the inhibition of cathepsin K (an enzyme expressed in osteoclasts which is involved in the degradation of bone matrix)¹⁰ have also been reported to be associated with favourable outcome and warrant further clinical studies.

Although current treatment strategies of osteoporosis are efficacious, they are associated with variable limitations. Research effort is on-going with novel therapeutic options to add to the current array of osteoporosis drugs.

Appendix I (online version only) - Common drugs used in the prevention and treatment of osteoporosis, their indications and side effect profiles.

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DIETARY ADVICE ON OSTEOPOROSIS

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Bone health is a major concern among the elderly. Nevertheless, proper bone-building diet and regular physical activity are important at any age. Calcium and vitamin D are vital for bone health and are prime nutrients needed for bone building.

Calcium

Foods that are good sources of calcium include milk, dairy products such as cheese, yoghurt, fish containing soft bones such as tinned sardines, vegetables of the cruciferous family including Chinese kale and pak choy, beans and pulses, nuts such as almonds, Brazil nuts, hazelnuts, sesame seeds and calcium fortified foods such as breakfast cereals and soy milk (Table 1).

DIETARY ADVICE ON OSTEOPOROSIS

Dishes with high calcium ingredients



Broccoli with bean curd in casserole



Fried celery with dried bean curd and shrimp

Table 1 Approximate amount of calcium per serving of food

Foods with average 300 mg calcium per serving:		Foods with average 200 mg calcium per serving:	
Food	Serving	Food	Serving
Milk	240 ml	Cheese	1 slice
Calcium fortified soy milk	240 ml	Tinned sardine	1 piece
Tofu	1 cube	Choi sum	4 taels
Yoghurt	1 cup	Pak choy	4 taels
Chinese kale	4 taels		

Individual requirements for calcium are difficult to quantify because of variability in both the bioavailability of calcium from different foods and its rate of absorption. The bioavailability of calcium from different kinds of food highly varies. Calcium absorption is also enhanced by lactose and there is higher bioavailability of calcium for milk and milk products. On the other hand, calcium absorption is inhibited by phytates (in many cereal foods) and oxalates (in spinach). Calcium absorption is enhanced by 1,25-dihydroxyvitamin D, the bioactive form of vitamin D. Calcium absorption decreases with age as vitamin D metabolism becomes less efficient. In 2000, the Chinese Nutrition Society has provided recommendation for daily dietary reference intake of calcium (Table 2).

Table 2 Dietary Reference Intakes considered sufficient to meet the needs of most of the population.

Age (years)	Calcium (mg) (Adequate Intakes)	Vitamin D (ug) (Recommended Nutrient Intake)
11 - 17	1000	5
18 - 49	800	5
> 50	1000	10

Vitamin D

Vitamin D regulates plasma calcium concentrations by stimulating active intestinal absorption of calcium and bone resorption. In younger individuals, the primary source of vitamin D comes from endogenous synthesis in the skin from sunlight exposure. Cutaneous synthesis is reduced in elderly people. Vitamin D deficiency is more commonly found in individuals who have little sunlight exposure, such as institutionalised subjects, those with dark skin and those who wear fully concealing clothings outdoors. The most common natural and fortified sources of vitamin D include fatty fish such as tuna and salmon, egg yolk, liver, fortified margarine and breakfast cereals.

Other essential bone building nutrients

Sufficient protein intake is also important for bone health. However, excessive protein intake may be harmful because products of protein metabolism increase calcium excretion from the kidney. Food with high sodium content and preserved food should be avoided. There is an association between high dietary sodium intake and increased calcium excretion. Phosphorus, in the form of phosphate, constitutes more than half of bone mineral mass. However, excessive phosphorus intake relative to calcium may result in bone loss. Phosphate is added to many fizzy drinks. Foods containing phytic acid (cereal bran, beans and grains) and oxalates (rhubarb and spinach) can bind calcium in the gut and decrease its absorption. This should not cause major calcium loss with regular consumption.

In conclusion, a healthy balanced diet which provides vitamins, minerals and protein from a variety of food contributes to healthy bone and reduce risks of other diet related diseases.

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MONITORING FALLS IN COMMUNITY-LIVING ELDERLY IN HONG KONG

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Falls are very common domestic accidents among the elderly around the world. In Hong Kong, about 26% of community-living elderly people have suffered a fall; the one-year prevalence rate of falls is 17-19% in a representative sample^{1,2}. The mean number of falls was 1.4/person who had a fall³. A study in Hong Kong found that 9.9% of falls resulted in bone fractures and 31.3% resulted in soft tissue injuries⁴. Falls are clearly a common danger for the elderly and may have both intrinsic and extrinsic causes. For example, falls can be a result of syncope or diseases such as strokes, or due to home hazards such as poor lighting, inadequate grab rails support, uneven floor or poor footwear. A comprehensive review of 16 studies showed that falls were associated with the following risk factors. They are listed in descending order of their relative risk ratios [RR] – the risk given the condition of falls versus the risk given the condition of no falls. The risk factors are muscle weakness (RR 4.4), history of falls (RR 3.0), gait deficits (RR 2.9), balance deficits (RR 2.9), use of assistive devices (RR 2.6), visual deficits (RR 2.5), arthritis (RR 2.4), impaired Activities of Daily Living (ADL) (RR 2.3), depression (RR 2.2), cognitive impairments (RR 1.8) and advanced age (RR 1.7)⁵. In addition, there is strong evidence that psychotropic medications are linked to falls^{6,7}. Many of these factors involve personal conditions, so it is still unclear just how much environmental hazard have on the risk of fall among the elderly.

Recently, the Department of Rehabilitation Sciences have conducted a study in collaboration with the Elderly Resources Centre of the Hong Kong Housing Society. A sample of 592 participants aged 65 years and above, living independently in the community in Hong Kong, was recruited by convenience sampling at the Centre over a year. To obtain a more representative sample, we stratified the study participants by five age groups according to the distribution of the Hong Kong Population Census of 2007. The participants were followed-up monthly by telephone calls for a period of 12 months. Home visits by occupational therapists for environmental inspection would be conducted within 3 days for those who reported falls in an indoor environment. Results showed that the subject group was quite healthy with 78.4% independent in walking without walking aids, and 97.1% could ambulate independently outdoors. Furthermore, 46.8% were found independent undertaking heavy household duties. 77 participants reported history of falls (indoor:outdoor - 1:2) over the preceding 12 months. The fall rate was 24.8%, and the one-year prevalence of falls (persons with at least one fall) was 16.7%; for two or more falls it was 3.9%. Logistic regression analysis showed that a history of previous falls in the preceding 12 months (OR 2.88, CI 1.67-7.17), female gender (OR 8.91, CI 0.27-0.47), and self-reported diabetes mellitus (OR 3.55, CI 1.10-3.55) were independent predictors for subjects with at least one episode of fall. Previous falls in the preceding 12 months (OR 3.48, CI 1.16-10.41), self-reported arthritis (OR 3.10, CI 1.04-9.26) and self-reported diabetes (OR 6.00, CI 1.46-24.49) were independent predictors for fallers with two or more episodes of falls. We also compared the domiciliary environments and found significant differences between the homes of fallers and non-fallers in the number of hazards with respect to seating ($p = .011$), toilets ($p = .018$), kitchens ($p = .026$) and the number of steps and stair railings ($p = .009$). Our findings suggest that elderly who reported previous falls over the preceding 12 months were the major factor associated with the occurrence of one or more falls (2.88 times greater than those without previous falls) and repeated falls (3.48 times greater than those without previous falls) among our sample of older people. Other comorbidities like diabetes or arthritis may contribute to falls and should not be overlooked, although the causal relationship could not be found in this study. In fact, some studies show no association between environmental hazards and falls^{8,9}, and the existence of home hazards alone is insufficient to cause falls except among those older people with only fair balance and limited mobility, or with a history of falls. So it is still unclear how much effect environmental hazards have on the risk of fall among older people. Obviously, older persons with arthritis may give ways or lose protective action because of knee pain or weakness whenever there is any external hazards. Some elderly who are more mobile, may also over-estimate their ability to overcome obstacles or underestimate the risks of familiar environments. Local authorities should identify older persons living in community with a previous history of falls or other intrinsic factors so that they may consider improving the environment for fall prevention.

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The scientific committee of the Hong Kong Arthritis and Rheumatism Foundation has organized an “East meets West” educational series since 2009. This educational series aim to promote interflow of knowledge and experience on patient management between health care professionals practicing western medicine and traditional chinese medicine in the field of rheumatology.

To celebrate the 10th Anniversary of Hong Kong Arthritis & Rheumatism Foundation and support the World Arthritis Day (12 October) established in 1996 as part of a global awareness initiative by the United Nations endorsed Bone and Joint Decade 2000-2010, the symposium on “The role of Tai Chi in the management of rheumatic diseases” was held on 30 October 2010 at the Hong Kong Hospital Authority. Dr. William Tsang from the Hong Kong Polytechnic University delivered a talk on “The “mystery” behind Tai Chi in health”. Dr. Mason Leung from the Hong Kong Polytechnic University shared his clinical experience with the audience in his session on “The many facets of Tai Chi - What is the recommendation for arthritis patients?”. Besides, a patient expert in Tai Chi, Ms Chung Ngan-ching, demonstrated Tai Chi style suitable for patients with arthritis and also shared how Tai Chi helped to improve her health and her life. The symposium was well received.



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APHK-RIS-10.12

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Appendix I. A summary of common drugs used in Osteoporosis in Hong Kong

Drug	Hong Kong licensed Indications	Dose	Common Side Effects
Bisphosphonates			
Alendronic acid	<p>Fosamax[®] (70mg tablet)¹ Treatment of osteoporosis in postmenopausal women to prevent fractures, including those of the hip & spine (vertebral compression fractures). Treatment of osteoporosis in men to increase bone mass. Treatment of glucocorticoid-induced osteoporosis in postmenopausal women not receiving estrogen who are receiving glucocorticoids equiv to ≥7.5 mg prednisone daily & with low bone mineral density.</p> <p>Fosamax PLUS[®] (Alendronate Na 70mg + Cholecalciferol 2800iu tablet)² Treatment of osteoporosis in postmenopausal women to increase bone mass & reduce incidence of fractures, including those of the hip & spine (vertebral compression fractures). Treatment of osteoporosis in men to increase bone mass.</p>	<p>10mg or 70mg once weekly</p> <p>1 tablet once weekly</p>	<p>Severe oesophageal reactions, Gastrointestinal side effects, headache³</p>
Ibandronic Acid	<p>Bonviva[®] (150mg tablet or 3mg injection)⁴ Treatment of osteoporosis in postmenopausal women to reduce the risk of vertebral fractures</p> <p>Bondronat[®] (50mg tablet)⁵</p>	<p>PO 150mg once a month</p> <p>IV 3mg every 3 months</p> <p>PO 50mg daily⁵</p>	<p>Headache, dyspepsia, nausea, Gastrointestinal side effects, rash, arthralgia, myalgia, muscular-skeletal pain, bone pain,</p>

¹ Fosamax package insert

² Fosamax PLUS package insert

³ British National Formulary electronic version accessed via www.medicinescomplete.com on 16 SEP 2010

⁴ Bonviva package insert

⁵ Bondronat Package Insert

	<p>Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone.</p> <p>Treatment of hypercalcaemia of malignancy (HCM)⁷</p> <p>Aclasta[®] (solution for infusion 5mg/100ml)⁸</p> <p>Treatment of osteoporosis in postmenopausal women and in men. Prevention of clinical fractures after hip fracture in men and women. Treatment and prevention of glucocorticoid-induced osteoporosis in women and men⁸.</p> <p>Treatment of Paget's disease of the bone (osteodystrophia deformans)</p>	5mg once a year	<p>fatigue, rigors, arthralgia, myalgia⁷.</p> <p>Fever, flu-like symptoms, arthralgia and headache⁸.</p>
Selective Oestrogen Receptor Modulators (SERMs)			
Raloxifene (Evista [®])	Treatment & prevention of osteoporosis in postmenopausal women ⁹	60mg daily.	Hot flushes, flu syndrome, leg cramps, peripheral oedema, venous thromboembolic events e.g. DVT, pulmonary embolism, retinal vein thrombosis, superficial vein thrombophlebitis ⁹ .
Calcitonin (Miacalcic [®])	Postmenopausal osteoporosis to reduce risk of vertebral fractures ³	Intranasally 200 iu/day (1 spray) into one nostril, alternating nostrils everyday ¹⁰ .	Rhinitis, sinusitis, epistaxis ¹⁰

⁸ Aclasta package insert

⁹ Evista package insert

¹⁰ Miacalcic package insert

Strontium Renelate (Protelos®)	Treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures ¹¹	PO 2g once daily in water, preferably at bedtime ³	Nausea, diarrhoea; venous thromboembolism; headache; dermatitis, eczema ¹¹
Parathyroid Hormone (PTH)			
Teriparatide (Forteo®)	Treatment of established osteoporosis in postmenopausal women. A significant reduction in the incidence of vertebral, but not hip fractures has been demonstrated. ¹²	SC 20mg once daily ¹²	Nausea, pain in limb, headache, dizziness, muscle cramps, fatigue ¹²
<p>Note: Postmenopausal osteoporosis, PMO</p> <p>Oral, PO</p> <p>Intravenous injection, IV</p> <p>Subcutaneous injection, SC</p>			

¹¹ Protelos package insert

¹² Forteo package insert