Overview of the pathogenesis and management of postmenopausal osteoporosis

Svetlana Doris Brincat[1], Alison Bincat[2], Jean Calleja Agius[3]

[1]Foundation Doctor - Mater Dei Hospital
Email: svetlana-doris.brincat@gov.mt
[2] Pharmacist - Sir Anthony Mamo Oncology Centre
Email: alison.brincat@gov.mt
[3]Associate Professor, Head of Department Anatomy, Faculty of Medicine and Surgery University of Malta
Email: jean.calleja-agius@um.edu.mt

Educational aims

- To review the pathogenesis of osteoporosis
- To identify risk factors for postmenopausal osteoporosis
- To update healthcare professionals on the management of postmenopausal osteoporosis

Key words
postmenopausal women, osteoporosis, bone density, pharmacological therapy, fracture

Abstract
Postmenopausal osteoporosis is a silent systemic progressive disease characterised by a decrease in bone mass per unit volume, compromising the physical strength of the skeleton and enhancing susceptibility to fractures on minor trauma. The progressive loss of bone tissue occurs as a result of an imbalance between bone formation and bone resorption subsequent to oestrogen deficiency. The aim of this overview is to shed light on the pathophysiology, aetiology and diagnostic techniques for this metabolic bone disorder. It demonstrates current treatment options and evaluates the emerging pharmacological therapies in the management of postmenopausal osteoporosis.

Introduction
Osteoporosis is a silent systemic progressive disease characterised by a decrease in bone mass per unit volume, compromising the physical strength of the skeleton and enhancing susceptibility to fractures on minor trauma.[1, 2]

Osteoporosis can be classified into 2 categories
- **Primary osteoporosis (Type I)** refers to the idiopathic form of osteoporosis occurring as a consequence of the normal process of aging.[3,4] Postmenopausal osteoporosis affects one third of all women and is caused by a decline in sex hormones as a consequence of menopause.[5,6,7]
- **Secondary osteoporosis (Type II)** occurs as a result of chronic conditions such as rheumatoid arthritis and diabetes mellitus, adverse effects of medications or nutritional deficiencies which enhance bone loss and interfere with peak bone mass attained at maturity.[8]

Aetiology
Bone remodelling is a lifelong continuous process whereby bone resorption and bone formation are kept at a balance so as to maintain a normal bone mass. At a cellular level, bone remodelling is dependent on osteoblasts and osteoclasts whilst osteocytes and bone lining cells maintain homeostasis by controlling the bone's microenvironment.[9] Osteoclasts, originating from the monocyte macrophage lineage, are responsible for bone resorption and reside on calcified bone surface.[10] Osteoblasts, originating from precursors of mesenchymal cells, are responsible for bone formation and mineralisation of bone matrix by deposition of the organic matrix called osteoid.[11]

In the presence of stress or microdamage, osteocytes will stimulate the remodelling cycle and start the process of bone repair. Upon stimulation, osteoclasts assemble on the bones' surface held tightly by fimbriated organelles and secrete proteolytic enzymes initiating the process of bone resorption and bone degradation.[10,12] Following resorption, a process known as formation follows whereby osteoblasts secrete both the matrix vesicles which are highly rich in the enzyme alkaline phosphatase, and collagen to produce an unmineralised matrix known as osteoid. Upon osteoid maturation, crystals of hydroxyapatite are deposited on the matrix vesicles leading to bone mineralisation.[12,13] This whole process of bone remodelling occurs every 3 to 6 months.[3,5]

At maturity when peak bone mass is reached, an imbalance exists between bone

resorption by osteoclasts and bone formation by osteoblasts, forming the basis of menopause-related bone loss leading to accelerated bone loss and skeletal fragility.[5] It is proposed that oestrogen deficiency results in a rise in the number of osteoclasts and an increase in the depth of resorption, stimulating more bone turnover sites and thus increasing the number of bone remodelling units.[2,5,14] Oestrogen deficiency results in weakening of the response of osteoblasts to mechanical stimuli hence affecting bone repair.[15] This is known as uncoupling of the bone remodelling process[16] leading to low bone mass and microarchitectural disintegration of bone tissue, with a resultant increase in bone weakness.[17]

Signs and symptoms

Postmenopausal osteoporosis is referred to as a silent epidemic as bone loss itself produces no symptoms until a fracture occurs. Women with osteoporosis have a higher incidence of fractures than non-osteoporotic women when exposed to equal trauma.[18] A fracture is classified as osteoporotic if it occurs in individuals over 50 years of age and is associated with low bone mineral density (BMD) at the fracture site.[15] The most frequent fractures are those occurring at the wrist (most frequently the distal radius), vertebrae and hip (proximal femur).[14,19]

Colles' fracture is a fracture of the distal radius with dorsal displacement producing the "dinner fork deformity". This type of fracture occurs due to a fall on the outstretched hand.[14] Fracture at the wrist is regarded as an early warning sign for the presence of postmenopausal osteoporosis.[2]

Vertebral osteoporotic fractures affect approximately one in four postmenopausal women.[20] These occur when one or more vertebra of the spinal column (most commonly in the T8 to L4 regions) collapse spontaneously with normal activities such as coughing or sneezing.[21] This results in shortening of the length of the spinal column and in the development of the characteristic dorsal kyphosis known as dowager's hump.[3]

Fracture of the neck of the femur is the most severe repercussion of postmenopausal osteoporosis. Pain, disability and hospitalisation are among the consequences of such a fracture.[22] Surgical complications appear in one third of the patients.[2] Hip fractures cause 20% of the affected individuals to die within a year[19], 40% become incapable to carry out their daily needs, 20% bedridden, whilst 20% may require to stay in nursing homes for some period of time.[22]

Risk factors

Risk factors for osteoporosis are those which affect peak bone mass, influence bone loss or else interfere in some way with calcium homeostasis.[5] A single risk factor will not cause osteoporosis but in combination these are known to increase the rate of bone loss.[16]

Unmodifiable risk factors include:

- **Age**
  Bone mineral density is on the increase until the mid-twenties when the peak bone density is reached. However, after a period of stability, it starts to decline as from the mid-forties. The rate of bone loss in premenopausal women is less than 1% each year. However, in the early postmenopausal years, a phase of accelerated bone loss ensues in which the rate of bone loss may reach a maximum of 5% each year. Bone mineral density declines with advancing age resulting in a higher risk of osteoporotic fracture.[5,6]
- **Gender**
  Females are at a higher risk for osteoporosis due to smaller bones and consequently lower peak bone mass when compared to males. Additionally, in menopause as a result of a decline in the ovarian hormones, women tend to lose bone at a faster rate than males.[23]
- **Ethnicity**
  Postmenopausal osteoporosis is more common in white or Asian women than among the dark-skinned population.[23]
- **Family history**
  Being a polygenic disorder, several genes are thought to have a role in determining women's rate of bone loss and the inflammatory bone turnover.[5,24]
- **Reproductive History**
  An exponential rate of bone loss occurs after early or surgical menopause which then decreases after 4 years to a rate equal to that of premenopausal women.[5]

Multiple reproductive factors such as parity, age at menarche and menopause, duration of menopause, age at first pregnancy and length of lactation period are known to affect bone mineral density with their effect being debatable. Gur *et al.*, reported that the number of pregnancies is inversely related to BMD and this is correlated with the calcium demands during pregnancy. In contrary to this, other studies reported that high parity is protective against osteoporosis as a result of a rise in circulating level of oestrogen in the third trimester of pregnancy, weight gain and elevated calcium intake. Interpregnancy interval period of less than 2 years, especially if less than 1 year, is associated with increased risk for osteoporosis. Pregnancy before 27 years of age is negatively correlated to BMD as a result of competition between mother and baby for calcium adversely affecting the mother's skeleton. The effect of breastfeeding on BMD is controversial.[25,26]

Potentially modifiable risk factors include:

- **Body mass index**
  Overweight individuals exert more physical stress on the skeleton. However as overweight individuals possess a greater number of fat cells, more oestrone is produced through peripheral conversion of androstenedione in adipose tissue. This elevated oestrogen level may protect such women from postmenopausal osteoporosis by slowing the rate of bone loss.[5] Low body mass index increases the risk for fractures, especially hip fractures. The correlation between BMI and fracture risk is non-linear with BMI <20kg/m^2 linked with higher risk of fractures.[27]
- **Dietary Calcium levels and Vitamin D**
  Diet deficient in calcium results in a decline in bone formation causing low peak bone mass and exerts no effect on the rate of bone loss.[28] Vitamin D aids in calcium absorption and in preserving bone integrity.[5]
- **Caffeine and Alcohol**
  Caffeine and alcohol both promote calcium transfer from bone to plasma.
- **Exercise**
  Sedentary lifestyle increases the risk of osteoporosis. The bone density in the spine and the hip are improved following fast walking exercise by promoting the action of osteoblasts.[28]
- **Smoking**
  Decreased bone mass and higher rate of bone loss are observed in cigarette smokers.[23] Smoking interferes with the hormone calcitonin responsible for calcium metabolism[5] and may also decrease circulating endogenous oestrogen levels.[28,29]

Pathophysiology

Effect of oestrogen on the skeletal system

Low plasma calcium, due to low intake or impaired calcium intestinal absorption, stimulates chief cells of the parathyroid gland to secrete parathyroid hormone (PTH).[9] In order to maintain calcium homeostasis, PTH indirectly stimulates osteoclasts which engage in bone resorption causing calcium mobilisation from bone and thus bone demineralisation. Additionally, PTH upregulates the enzyme 1-alpha-hydroxylase essential for the activation

of the inactive form of Vitamin D to its active form, 1,25-dihydroxycholecalciferol. The latter elevates calcium absorption in the intestine. PTH also acts on the kidneys to increase tubular calcium reabsorption. It has been proposed that sex steroids such as oestrogen, androgens and progesterone inhibit the activity of PTH on bone, decreasing bone resorption.[14,30] Oestrogen has the ability to alter the sensitivity of bone to PTH without changing its sensitivity to other target organs, such as the gut and the kidneys.[16]

During menopause, as oestrogen production decreases, bone becomes more sensitive to PTH. As a consequence, the inhibition of PTH on bone resorption declines and for a certain level of PTH, higher calcium mobilisation from bone occurs. This leads to an increase in plasma calcium which in turn causes a decline in the level of PTH. Renal tubular resorption of calcium decreases causing higher urinary excretion of calcium while the production of 1-alpha hydroxylase decreases, causing a reduction of active vitamin D with less absorption of calcium from gut.[18]

In menopause, a decline in the body's efficiency to make use of dietary calcium together with a decrease in calcium reabsorption from the renal tubule, stimulate bone remodelling in attempt to provide a constant amount of calcium to non-osseous tissues. As the majority of plasma calcium is derived from bone, there is a constant bone loss each year.[18]

Calcitonin is a hormone synthesised by the parafollicular cells of the thyroid gland in response to an increase in plasma calcium. Calcitonin has opposite effects to PTH. It suppresses both the production of new osteoclasts and it also inhibits their activity. Calcitonin causes less calcium tubular reabsorption in the kidneys and elevates urinary excretion of calcium.[14] Oestrogen elevates calcitonin levels needed to prevent bone loss.[18]

Effect of oestrogen on fibrocartilage

Twenty percent of the spinal column height is attributable to the intervertebral disc. The roles of the intervertebral disc in permitting mobility of the spine and acting as a "shock absorber" are most compromised in osteoporotic compression fracture.[31,32]

In pre-menopausal women, the nucleus pulposus and annulus fibrosus of the intervertebral disc contain collagen type IV, II and IX, elastin, glycosaminoglycans and water. These constituents provide visco-elastic properties and a discoid anatomy to the intervertebral discs.[30,32] As the woman advances in her postmenopausal years, a more pronounced difference in collagen types is observed.[31]

Menopause has an effect on connective tissue.[31] Aging causes diminished circulation to the nucleus pulposus leading to a series of modifications in discs' components. These variations include a decrease in glycosaminoglycans and elastin content, dehydration and formation of collagen types I, III and VI replacing previous collagen types. Disc fibrosis and degeneration cause loss of intervertebral disc height interfering with its function as a vital tissue pump.[33]

Diagnostic techniques for bone mass measurement

Radiographic techniques

In postmenopausal women, bone mineral density can vary according to the skeletal site. Postmenopausal women may present with normal bone mineral density in one part of the body and low bone mineral density in another body part. The primary site where bone loss occurs is the spine (L1 or L2-L4) as it is the region where the greatest trabecular bone remodelling occurs. In women up to 65 years of age, the ideal body region to measure bone mineral density should be the spine as it is the first site of bone loss.[34,35]

BMD testing is advised in patients with dual-energy X-ray absorptiometry (DXA) in women aged 65 years of age and older and in postmenopausal women younger than 65 years of age but with clinical risk factors for fracture. Patient should then have BMD testing at least every 2 years as follow-up.[36,37]

Several direct methods for measuring bone mineral densities are available.[16] Dual-energy X-ray Absorptiometry (DXA) is mainly used to determine bone mass in the spine (mainly in the lumbar regions), the hip or the total skeleton. Dual-Photon Absorptiometry (DPA) uses a beam of photons with discrete energy peaks in which one of them is absorbed by soft tissue and the other by bone. DXA uses an X-ray beam with discrete energy peaks in which one of them is absorbed by soft tissue and the other by bone DXA is regarded as the gold standard for diagnosing postmenopausal osteoporosis as it provides both accurate and precise measurements.[2,35]

Interpreting a DXA bone density result

The different bone mineral density tests are generally reported in the form of a T-score or Z-score. The T-score, is the number of standard deviations (SD) by which the bone mineral density (BMD) of the patient (Equation 1) varies when compared to that of the average young adult (30 years old) of the same gender and ethnicity. The Z-score is the number of standard deviations the bone mineral density measurement varies when compared to a mean bone mineral density of the same age, gender and ethnicity (Equation 2). This score determines whether a secondary underlying cause is actually contributing to bone loss.[6,35] In accordance to the International Society for Clinical Densitometry (ISCD), the WHO classification shall only be recommended to be used in clinical practice for postmenopausal women and in men 50 years and older.[38]

Quantitative ultrasonography (QUS) is used to assess skeletal status of the calcaneous and the phalanges. As QUS makes use of ultrasound waves, no radiation load is involved, making it a safe and a non-invasive technique. QUS can also be used in conjunction with DXA to provide a better prediction of fracture risk.[23,34,39]

Biochemical markers of bone turnover

Biomarkers are sensitive tools to assess bone resorption and formation. These are actually used to monitor treatment of osteoporotic patients rather than to diagnose osteoporosis itself. The level of biochemical markers fluctuate within few months following initiation

Table 1: World Health Organisation (WHO) classification[11]

T-score is equal or greater than -1 SD	Normal
T score between -1 SD to -2.4 SD	Osteopenia
T-score is equal or lower than -2.5 SD	Osteoporosis

$$\text{T score} = \frac{\text{BMD} - \text{population peak}}{\text{SD of population peak BMD}}$$

Equation 1: T-score[6]

$$\text{Z score} = \frac{\text{Patient's BMD} - \text{population age-related}}{\text{SD of population age-related BMD}}$$

Equation 2: Z-score[6]

of treatment. Postmenopausal women are characterised by an increase in bone resorption markers and a decline in bone formation makers indicating the extent of uncoupling of bone formation and resorption present in postmenopausal osteoporosis.[6,40,41]

Biomarkers of bone formation represent osteoblastic activity and these are by-products of collagen synthesis, matrix proteins or osteoblastic enzymes.[40] These biomarkers include serum total alkaline phosphatase, osteocalcin and procollagen type I. These markers can be measured directly from circulation by a serum or plasma sample.[42]

Biomarkers of bone resorption represent osteoclastic activity and are mainly degradation products of type I collagen.[40] Fragments resulting from osteoclastic degeneration of bone as well as from disintegration of the organic matrix are used as biochemical markers for bone resorption. These fragments generally possess post-translational modifications of collagen which make them useless for utilisation by the body.[42] Disintegrated products resulting from enzymatic hydrolysis of type I collagen are among the most effective markers for bone resorption.[41] These collagen degradation products are released in circulation and then excreted in urine.[6] N-telopeptide, C-telopeptides and related pyridinoline cross-links of bone type I collagen are used as markers of bone resorption in osteoporosis.[41]

Fracture risk calculators

New diagnostic techniques have been devised to assess the absolute risk of developing an osteoporotic fracture. FRAX® algorithm and the Garvan nomogram are web-based tools which integrate the clinical risk factors with BMD measured at the neck of the femur. FRAX® algorithm can predict a 10-year risk of hip fracture and other major osteoporotic fractures. The latter refers to a clinical spine, forearm, hip or humerus fracture. The fracture risk is calculated based on clinical risk factors with or without femoral neck BMD.[35]

Treatment

The primary goal of treating postmenopausal osteoporosis is to mediate bone repair, alleviate bone strength and decrease the frequency of both vertebral and non-vertebral fractures which account for significant morbidity and mortality.[43,44,45]

The management of postmenopausal osteoporotic women involves both pharmacological and non-pharmacologic treatments.[43]

Pharmacological interventions

Table 2: Pharmacological agents[48]

Anti-resportive	Anabolic	Anti-resorptive & anabolic
HRT Calcitonin Bisphosphonates SERMs Cathepsin K inhibitor (odanacatib) Denosumab	Teriparatide Parathyroid hormone	Strontium ranelate

Pharmacological therapy shall be considered in postmenopausal women and men aged 50 years and older with history of hip or vertebral fracture, T-score of -2.5 or lower at the femoral neck or spine without any secondary causes and in patients with T-score between -1 and -2.5 at femoral neck or spine who have a 10 year probability of hip fracture of ≥3 or any osteoporotic fracture of ≥20% based upon the United states using the WHO FRAX.[46]
As displayed in table 2, treatment can be categorised into antiresorptive drugs which delay bone resorption and anabolic drugs which promote bone formation.[47]

- **Hormone Replacement Therapy (HRT)**
  Hormone replacement therapy involves the administration of physiologic levels of oestrogen and progestin to replace and artificially boost the hormones which decline during menopause.[14]

  Epidemiology shows that a short time frame with HRT decreases the occurrence of osteoporotic fractures.[14] It has been determined that undergoing oestrogen therapy for 5 years reduces vertebral fracture by 60% whilst hip fracture can decline by 50%.[2,49]

  Generally by oestrogen treatment, bone turnover is reduced by half, decreasing postmenopausal bone loss and lowering the incidence of an osteoporotic fracture.[50] However, once treatment with HRT stops, oestrogen level declines and protection against osteoporosis is lost again. Most studies suggest that bone loss will progress at the same rate as before HRT treatment. Thus the accelerated bone loss during menopause is postponed by the duration of HRT treatment.[2,14]

  As long term duration of therapy is needed for the prevention of postmenopausal osteoporosis, HRT has been associated with various risks which limit its attraction as treatment option.[19]

  The long term adverse effects implicated for HRT include carcinoma mainly of the breast, endometrium and colorectal as well cardiovascular diseases such as coronary heart disease, cerebrovascular accident and pulmonary embolism.[51,52]

  Regulatory authorities state that HRT should not be used as first-line treatment in prophylaxis as long term risks may outweigh the potential benefits.[6,40,45] Thus HRT should only be considered when other treatment options have proved to be unsuccessful.[45,53,54]
- **Teriparatide**
  Teriparatide is a recombinant synthetic form of the natural human hormone, PTH which is administered subcutaneously. It is known to enhance bone formation by activating osteoblasts and increase bone mineral density.[14,55] Teriparatide enhances calcium intestinal absorption as well as calcium reabsorption from the kidney. With its anabolic action, it decreases significantly vertebral and non-vertebral fractures but not hip fracture.[56] Teriparatide is used mainly in severe osteoporotic patients with a high fracture risk.[2]
- **Bisphosphonates**
  Bisphosphonates are anti-resorptive drugs[2] which act by adsorbing onto hydroxyapaptite crystals in bone and exert a potent inhibitory effect on bone resorption rate maintaining BMD. Bisphosphonates can be used both as a prophylaxis and as treatment for osteoporosis as they decrease the rate of bone loss and fracture risk in osteoporotic patients.[53] In fact, bisphosphonates decrease both vertebral and non-vertebral fractures up to 50% while hip fractures are decreased by 20%. Bisphosphonates also enhance BMD at both the hip and the spine in a dose-dependent way.[57]

  Bisphosphonates can be divided into two main groups: non-nitrogen containing bisphosphonates and nitrogen containing

bisphosphonates. Etidronate is a non-nitrogen containing bisphosphonate. The nitrogen containing bisphosphonates include alendronate, risedronate and ibandronate. Alendronate, risedronate and etidronate are most clinically used in corticosteroid-induced osteoporosis to decrease both vertebral and non-vertebral fractures.[6, 55] Osteonecrosis of the jaw [53] and gastro-intestinal damage are among the adverse effects which limit the use of oral bisphosphonates.[19,56] Administering bisophosphonates such as ibadronate and zoledronic acid intravenously enhance their potency in inhibiting bone remodelling however they are linked to transient flu-like symptoms and self-limited myalgia.[57]

- **Strontium ranelate**
  Strontium ranelate is a dual action bone agent as it has an anti-resorptive and anabolic action.[56] It inhibits the osteoclasts recruitment and augments osteoblasts proliferation and differentiation.[58] Thus, with strontium ranelate therapy bone resorption is suppressed while bone formation is stimulated. Both hip and vertebral fractures are decreased with such a treatment.[56]
- **Selective oestrogen receptor modulators (SERMs)**
  SERMs are non-steroidal compounds with tissue-specific activity having oestrogenic effects in certain tissues and anti-oestrogenic effects in others. They bind to oestrogen receptors within the bone and change the receptor conformation to aid in the binding of co-regulatory proteins and activate target genes.[59] Raloxifene is an anti-resorptive agent which prevents osteoporosis-related vertebral fracture. It decreases vertebral fractures by 30-50% and increases bone mineral density at the hip and the spine by 0.5% to 1.0% respectively.[6,34,45]
- **Calcitriol**
  Calcitriol (1,25-dihydroxycholecalciferol) is an active vitamin D metabolite used to treat low calcium levels in postmenopausal women. Conflicting data has emerged regarding the effect of calcitriol on bone.[6] Studies have shown that calcitriol aids in calcium intestinal absorption and reduces the rate of vertebral fracture whereas it has no effect on hip fracture.[45]
- **Vitamin D and calcium supplementation**
  During infancy, childhood and adolescence calcium intake is of utmost importance as calcium is required for peak bone mass to be achieved. Postmenopausal women have the highest calcium requirements with a recommended daily intake of at least 1000-1200mg. Providing adequate amount of dietary or supplemental calcium and vitamin D to postmenopausal women particularly the elderly serves as a baseline treatment of postmenopausal osteoporosis[56] as a decrease in intestinal calcium absorption is noted with advancing age.[60]

  Calcium supplementation may lower the rate of bone loss following two years of treatment however during the initial 5 years of menopause, it exerts little effect on bone loss as it can be attributed to the decline in oestrogen synthesis.[18,47] Calcium supplementation is regarded as an adjunct to other treatment regimens unless sufficient dietary intake is ensured.[56]

  Institutionalised or housebound patients who are rarely exposed to the natural sunlight and persons who chronically use sunscreen products particularly with high sun protection factors may possess vitamin D deficiency. Thus Vitamin D supplementation is essential in these patients. Vitamin D may decrease the risk of hip and non-vertebral fractures in ambulatory elderly patients only if an oral supplementation of 700-800IU is administered each day.[6,61]

  Vitamin D and calcium supplementation increase BMD and decrease the risk of fracture. The latter is negated by some randomised controlled clinical trials.[57] In additional to calcium, other elements including copper, boron, magnesium, manganese, phosphorus, potassium and zinc are associated with improving bone health. Aluminium, cadmium and lead appear to affect BMD negatively.[62]
- **Fluoride**
  The use of fluoride in the treatment of osteoporosis is argumentative.[2,63] Fluoride treatment activates osteoblasts resulting in bone formation in trabecular part of bone while long term treatment enhances the mass of the central skeleton.[16]
- **Denosumab**
  Denosumab is a Receptor Activator of Nuclear Factor kappa-β ligand (RANKL) - targeted monoclonal antibody.[64] By binding with high affinity and high-specificity to RANK, it suppresses the binding of RANKL to receptor Activator of Nuclear Factor kappa-**β** (RANK) [64,65] and hence, blocks the development, differentiation, activation and survival of osteoclasts. This leads to a decline in bone resorption and promotes BMD. Its fast onset of action and its constant prolonged reversible activity make denosumab a better therapeutic agent than the current treatment options.[65-68]

  Administration of denosumab subcutaneously once every 6 months for 36 months decreases the risk of vertebral, non-vertebral and hip fractures in osteoporotic women.[68] However, two major drawbacks of using denosumab as a treatment of postmenopausal osteoporosis are the potential formation of infections and higher risk of malignancy.[69]
- **Calcitonin**
  Calcitonin is a peptide hormone synthesised by the thyroid gland. Calcitonin has been withdrawn for the treatment of osteoporosis as it has been found that long term use increases the risk of cancer.[70]

Potential novel pharmacological agents

- **Cathepsin K inhibitors**
  Cathepsin K is an acid activated cysteine protease,[71] required for the degradation of the organic matrix.[72] It exerts its function specifically on bone type I collagen under acidic conditions.[73,74]

  Odanacatib is the most advanced cathepsin K inhibitor undergoing clinical trials.[47] It decreases bone resorption not by decreasing the presence of osteoclasts or their activity but by selectively suppressing the degradation of matrix protein. Substantial dose-related increase in BMD was observed in lumbar spine, total-hip, femoral neck and one-third of the radius during the second year of treatment. Headaches, flu-like symptoms and abdominal discomfort are amongst the adverse effects of odanacatib.[74,75]

  The novel cathepsin-K inhibitor, ONO-5334 is still undergoing clinical investigation. It seems to enhance BMD in the lumbar spine with an improved effect on the femur and induces no severe side effects.[47,76,77]
- **Calcilytic drugs (MK-5442)**
  MK-5442 is a calcilytic drug which targets calcium sensing receptors (CaSR antagonist) of the parathyroid glands. It provokes a hypocalcaemic environment hence stimulating pulsed PTH secretion resulting in a net anabolic situation. MK-5442 is still currently undergoing clinical trials.[47,78,79] MK-5442 has not been shown to improve BMD in patients already on bisphosphonates therapy and hence should not be considered to be used in combination with bisphosphonates.[80]
- **Wnt /β-catenin pathway antagonists**
  Osteoblastic differentiation and subsequently bone formation can be induced by Wnt-dependent nuclear accumulation of **β**-catenin.

  Possible future therapeutic agents include BHQ-880 which suppress Wnt pathways by Dickkopf-1 antibodies and Romosozumab

and blosozumab by targeting sclerostin antibodies. These medications are still under study as potential therapeutic agents for postmenopausal osteoporosis.[47,80]

Alternative and complementary therapy

- **Phytoestrogens**
  As some women have fear of the adverse effects produced by some drugs, alternative methods to prevent and treat postmenopausal osteoporosis are sought. Phytoestrogens are plant-derived compounds which function like oestrogen. Classes of phytoestrogens include isoflavones present in soy beans and soy products, lignans present in oilseeds and coumestans found in alfalfa and red clover. These phytoestrogens exert a protective effect on bone by retarding bone resorption and maintaining skeletal integrity. Phytoestrogens promote osteogenesis when taken at low concentrations and suppress osteogenesis at higher doses.[6]

Conclusion

A high index of clinical suspicion of postmenopausal osteoporosis is required as it may go unnoticed until a fracture occurs. Lifestyle measures that include the adequate intake of calcium and vitamin D, 30-minutes exercise at least three times a week and smoking cessation and limit alcohol intake aim to reduce bone loss in postmenopausal women. Counseling on fall prevention to women at risk shall be employed. The choice of pharmacological therapy depends on multiple factors including the severity of the osteoporosis and the risk for fractures. Preventing and treating post-menopausal osteoporosis decreases the social, emotional and financial burden of an osteoporotic fracture.[46]

Key points

- Post-menopausal osteoporosis is a silent progressive disease until a fracture occurs
- Bone mineral density is helpful in assessing bone health in women. Timely intervention can prevent bone loss and its associated complications
- BMD testing is advised in women aged 65 years of age and older and in postmenopausal women younger than 65 years of age with clinical risk factors for fracture
- Prevention of osteoporosis involves proper nutrition, exercise, lifestyle and early screening
- The management of postmenopausal osteoporotic women involves both pharmacological and non-pharmacologic treatments

References

1. World Health Organisation. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Switzerland: WHO Library Cataloging in Publication Data; 1994.
2. Abernethy K. The menopause and HRT. 2nd ed. China: Bailliere Tindall; 2002.
3. Tanna N. Osteoporosis and its prevention. Pharm J. 2005;275:521-524.
4. Skugor M. Osteoporosis. In: Carey W, editor. Current Clinical Medicine. USA: The Cleveland Clinical Foundation; 2010.
5. Lindsay R. Pathogenesis, detection and prevention of postmenopausal osteoporosis. In: Studd JW, Whitehead MI, editors. The menopause. London: Blackwell Scientific Publications; 1988.
6. Rees M, Purdie D, editor. Management of the menopause: the handbook. 4th ed. The Netherlands: Royal Society of Medicine; 2006.
7. Holloway D. An overview of the menopause: assessment and management. Nursing Standard. 2011;25(30):47-57.
8. International Osteoporosis Foundation. About osteoporosis. 2015. Available from: http://www.iofbonehealth.org/what-is-osteoporosis; Accessed 18 February 2016.
9. Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG. Williams Gynecology. China: McGraw Hill; 2008.
10. Cosman F, Dempster D. Clinical and mechanistic insights into novel agents in development for osteoporosis. Current Medical Evidence. 2009;2(5):1-11.
11. Lentle B, Worsley D. Osteoporosis Redux. J Nucl Med. 2006;47(12):1945-1959.
12. Lerner UH. Bone remodelling in post-menopausal osteoporosis. J Dent Res. 2006;85(7):584-596.
13. Young B, Lowe JS, Stevens A, Heath JW. Wheater's functional histology: a text and colour atlas. 5th ed. China: Churchill Livingstone Elsevier; 2006.
14. Christiansen C. Menopausal osteoporosis: impact of sex steroid replacement. In: Adashi EY, Rock JA, Rosenwaks Z, editor. Reproductive endocrinology, surgery, and technology. USA: Lippincott-Raven; 1996.
15. McNamara LM. Perspective on post-menopausal osteoporosis: establishing an interdisciplinary understanding of the sequence of events from the molecular to whole bone fractures. J. R. Soc. Interface. 2010;7:353-372.
16. Notelovitz M. Menopause and climacteric. In: Philipp E, Barnes J, Newton M., editor. Scientific foundations of obstetrics and gynaecology. 3rd ed. London: William Heinemann Medical Books; 1986.
17. Bethel M. Osteoporosis. 2016. Available from: http://emedicine.medscape.com/article/330598-overview; Accessed 18 February 2016.
18. Mishell DR. Menopause - Endocrinology, Consequences of Estrogen deficiency, Effects of hormonal replacement therapy, Treatment regimens. In: Mishell RD, Stenhever MA, Droegemueller W, Herbst A, editor. Comprehensive Gynecology. 3rd ed. USA: Mosby; 1997.
19. Baqir W, Copeland C. Current and future drug treatments for the management of osteoporosis. Pharm J. 2010;284: 345-346.
20. Brincat M, Muscat Baron Y, Calleja-Agius J. Vertebral disc health: Effect of hormone replacement therapy and osteoporosis [powerpoint]; 2009.
21. Brincat M, Muscat Baron Y, Galea R. The menopause. In: Shaw RW, Soutter WP, Stanton SL, editors. Gynaecology. London: Churchill Livingstone; 1997.
22. Mayes SL. Review of Postmenopausal Osteoporosis Pharmacotherapy. Nutr Clin Pract. 2007;22(3):276-285.
23. Scottish Intercollegiate Guidelines Network. Management of osteoporosis. 2003;71.
24. Raisz LG. Pathogenesis of postemenopausal osteoporosis. Reviews in Endocrine and Metabolic Disorder. 2001;2:5-12.
25. Ersoy GS, Giray B, Subas S, Simsek E, Sakin O, Turhan OT, et al. Interpregnancy interval as a risk factor for postmenopausal osteoporosis. Maturitas. 2015;82(2):236-240.
26. Cavkaytar S, Seval MM, Atak Z, Findik RB, Tre S, Kokanali D. Effect of reproductive history, lactation, first pregnancy age and dietary habits on bone mineral density in natural postmenopausal women. Aging Clin Exp Res. 2015;27(5):689-94.
27. Compston JE, Flahive J, Hosmer DW, Watts NB, Siris ES, Silverman S et al. Relationship of weight, height, and body mass index with fracture risk at different sites in postmenopaual women: The global longitudinal study of osteoporosis in women (GLOW). J Bone Miner Res. 2014;29(2):487-493.
28. Parvez T. Postmenopausal osteoporosis. JK-Practitioner. 2004;11(4):281-283.
29. The Cleveland Clinic Foundation. Menopause and osteoporosis. 1995-2015. Available from: https://my.clevelandclinic.org/health/diseases_conditions/hic-what-is-perimenopause-menopause-postmenopause/hic_Menopause_and_Osteoporosis; Accessed 3 February 2016.
30. Harvey RA, Ferrier D, editor. Lippincott's illustrated reviews: Biochemistry. 5th ed. China: Lippincott Williams & Wilkins; 2011.
31. Calleja-Agius J, Brincat M. The effect of menopause on the skin and other connective tissues. Gynecol Endocrinol. 2012;28:273-277.
32. Brincat MP, Calleja-Agius J, Muscat Baron Y. The skin, carotid and intervertebral disc: making the connection! Climacteric. 2007;10(2):83-87.
33. Muscat Baron Y, Brincat MP, Galea R, Calleja N. Intervertebral disc height in treated and untreated overweight post-menopausal women. Hum Reprod 2005;20(12):3566-3570.
34. Brincat M, Calleja-Agius J, Vujovic S, Erel T, Gambacciani M, Lambrinoudaki I et al. EMAS position statement: Bone densitometry screening for osteoporosis. Maturitas. 2011;68 (1): 98-101.
35. American Academy of Orthopaedic Surgeons. Osteoporosis tests. 2007. Available from: http://orthoinfo.aaos.org/topic.cfm?topic=A00413#Dual-Energy%20Xray%20Absorptiometry. Accessed 28 February 2016.
36. Cosman F, De Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporosis Int. 2014;25(10):2359-2381.
37. Kleerekoper M. Screening for osteoporosis. In: UpToDate, Rosen CJ, Schmader KE (Ed), Available from: http://www.

uptodate.com/contents/screening-for-osteoporosis; Accessed 10 June 2016.
38. Rosen HN, Drezner MK. Clinical manifestations, diagnosis and evaluation of osteoporosis in postmenopausal women. In: UpToDate, Rosen CJ, Schmader KE (Ed). Available from: http://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-evaluation-of-osteoporosis-in-postmenopausal-women; Accessed 10 June 2016.
39. Gluer CC. Quantitative ultrasound technique for the assessment of osteoporosis: expert agreement on current status. J Bone Miner Res. 1997;12(8):1280-1288.
40. Eastell R , Hannon RA. Biomarkers of bone health and osteoporosis risk. Proceedings of the Nutrition Society; 2007 July 16-19; Coleraine, Ireland. Amsterdam: Elsevier; 2008.
41. Talwar SA. Bone markers in osteoporosis. 2014. Available from: http://emedicine.medscape.com/article/128567-overview. Accessed 23 February 2016.
42. Bonde M, Christiansen C. Value of bone markers in osteoporosis and related diseases.The management of the menopause - annual review. London: The Parthenon Publishing Group; 1998.
43. Murphy FT, Kivitz AJ, Sands EE. Management of postmenopausal osteoporosis. J Am Osteopath Assoc. 2003;103(10) Supp 6: S6-S11.
44. Delmas PD. Treatment of postmenopausal osteoporosis. Lancet. **2002**;359(9322):2018-26.
45. Tanna N. Osteoporosis and its treatment. Pharm J. 2005;275:581-584.
46. Rosen HN, Drezner MK. Overview of the management of osteoporosis in postmenopausal women. In: UpToDate, Rosen CJ, Schmader KE (Ed). Available from: http://www.uptodate.com/contents/overview-of-the-management-of-osteoporosis-in-postmenopausal-women; Accessed 10 June 2016.
47. Rachner TD, Khosla S, Lorenz C Hofbauer LC. Osteoporosis: now and the future. Lancet 2011;377:1276–87.
48. Lin X, Xiong D, Peng YQ, Sheng ZF, Wu XY, Wu XP et al. Epidemiology and management of osteoporosis in the People's Republic of China: current perspectives. Clin Inter Aging. 2015;10:1017-1033.
49. Torgerson DJ, Bell-Syer SEM. Hormone replacement therapy and prevention of vertebral fractures: a meta-analysis of randomised trials. BMC Musculoskeletal Disorders. 2001;2:7-10.
50. Eriksen EF, Kassem M. The clinical problem of treating osteoporosis with estrogen. In:Studd J, editor. The management of the menopause - annual review. London: The Parthenon Publishing Group; 1998.
51. Beral V, Banks E, Reeves G. Evidence from randomized trials on the long-term effects of hormone replacement therapy. Lancet. 2002;360:942-944.
52. Calleja-Agius J, Brincat MP. Hormone replacement therapy post Women's Health Initiative study: where do we stand? Curr Opin Obstet Gynecol. 2008;20(6):513-518.
53. Bryan J. Benefits versus risks – the rise and fall of hormone replacement therapy. Pharm J. 2011;286:110-111.
54. European Medicines Agency, HMA Management Group. Pharmacovigilance working party – monthly report. 2010.. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500069737.pdf; Accessed 10 June 2016.
55. European Medicines Agency. Forsteo. 2014. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000425/human_med_000798.jsp&mid=WC0b01ac058001d124; Accessed 7 February 2016.
56. Baqir W, Copeland C, Worsley A. Osteoporosis treatment and risk assessment. Clin Pharm. 2009;1:216-223.
57. Lewiecki EM. Current and emerging pharmacologic therapies for the management of postmenopausal osteoporosis. J Womens Health. 2009;18(10):1615-26.
58. Cole Z, Dennison E, Cooper C. Update on the treatment of post-menopausal osteoporosis. Br Med Bull. 2008;86:129-143.
59. Osborne CK, Zhao H, Fuqua SAW. Selective estrogen receptor modulator: structure,t function, and clinical use. JCO 2000;18(17):3172-3186.
60. Tai V, Leung W, Grey A, Reid IR, Bolland MJ. Calcium and bone mineral density: a systematic review and meta- analysis. BMJ 2015;351:h4183-4197.
61. Norval M, Wulf HC. Does chronic sunscreen use reduce vitamin D production to insufficient levels? Br J Dermatol. 2009;161(4):732-736.
62. Rizzoli R, Stevenson JC, Bauer JM, van Loon LJC, Walrand S, Kanis JA et al. The role of dietary protein and vitamin D in maintaining musculosketetal healh in postmenopausal women: A consensus statement from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Maturitas 2014;79(1):122-132.
63. Aaseth J, Boivin G, Andersen O. Osteoporosis and trace elements – An overview. J Trace Elem Med Biol. 2012;26:149-152.
64. Rizzoli R. Targeting RANKL in post-menopausal osteoporosis. Eur Musculo Rev. 2009:25-28.
65. Mensah KA, Li J, Schwarz EM. The emerging field of osteoimmunology. Immunol Res. PMC 2010;7:1-15.
66. Rachner TD, Khosla S, Lorenz C Hofbauer LC. Osteoporosis: now and the future. Lancet. 2011;377:1276–87
67. Sampaio Lacativa PG, Fleiuss de Farias ML. Osteoporosis and inflammation. Arq Bras Endocrinol Metab. 2010;54(2):123-132.
68. Rizzoli R. Targeting RANKL in post-menopausal osteoporosis. Eur Musculo Rev. 2009:25-28.
69. Cummings SR, Martin JS, McClung MR, Siris ES, Eastell R, Reid IR et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361(8):756 -765.
70. European Medicines Agency. Calcitonin. 2013. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Calcitonin/human_referral_000319.jsp&mid=WC0b01ac05805c516f. Accessed 10 June 2016.
71. Vega D, Maalouf NM, Sakhaee K. The role of receptor activator of nuclear factor-KB (RANK)/RANK Ligand/Osteoprotegerin: clinical implications. J Clin Endocrinol Metab. 2007;92(12):4514-4521.
72. Salari P, Abdollahi M. A Comprehensive Review of the Shared Roles of Inflammatory Cytokines in Osteoporosis and Cardiovascular Diseases as Two Common Old People Problem - Actions Toward Development of New Drugs. Int J Pharm. 2011;7(5):552-567.
73. Troen BR. Molecular mechanisms underlying osteoclast formation and activation. Exp Gerontol. 2003;38:605-614.
74. Akesson K. New approaches to pharmacological treatment of osteoporosis. Bull World Health Organ. 2003;81(9):657-663.
75. Stoch SA, Zajic S, Stone JA, Miller DL, van Bortel L,Lasseter KC et al. Odanacatib, a selective cathepsin K inhibitor to treat osteoporosis: safety, tolerability, pharmacokinetics and pharmacodynamics-results from single oral dose studies in healthy volunteers. Br J Clin Pharmacol. 2012;75(5):1240-1254.
76. Bone HG, McClung MR, Roux C, Recker RR, Eisman JA, Verbruggen N et al. Odanacatib, a cathepsin-K inhibitor for osteoporosis: a two-year study in postmenopausal women with low bone density. J Bone Mineral Res. 2010;25(5):937-947.
77. Engelke K, Nagase S, Fuerst T, Small M, Kuwayama T, Deacon S et al. The effect of the cathepsin K inhibitor ONO-5334 on trabecular and cortical bone in postmenopausal osteoporosis: The Ocean study. J Bone Miner Res. 2014;29(3):629-638.
78. Behrendt N. Matrix Proteases in Health and Disease. Germany: Wiley-VCH Verlag & Co; 2012.
79. Cosman F, Gilchrist N, McClung M, Foldes J, de Villiers T, Santora A et al. A phase 2 study of MK-5442, a calcium-sensing receptor antagonist, in postmenopausal women with osteoporosis after long-term use of oral bisphosphonates. Osteoporos Int. 2016; 27(1):377-386.
80. Cairoli E, Zhukouskaya VV, Eller-Vainicher C, Chiodini I. Perspectives on osteoporosis therapies. J Endocrinol Invest. 2015;38(3):303-311.