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OSTEOPOROSIS – FROM HORMONAL REPLACEMENT THERAPY TO BISPHOSPHONATES AND BEYOND: A REVIEW

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ABSTRACT

Objective: To review the old, current, and emerging agents in pharmacological treatment of osteoporosis.

Data sources: Published original research work and reviews from 1993 to 31 December 2006 were searched in English on subjects related to epidemiology, pathophysiology, diagnosis, treatment, and prevention of osteoporosis.

Study Design: Only articles that emphasise on management.

Data extraction: Online and manual library searches done.

Data synthesis: Data added up and summarised.

Conclusion: Osteoporosis is a serious public health issue. The past 10 years has seen great advances in our understanding of its epidemiology, pathophysiology, and treatment, and further advances are rapidly being made. Bisphosphonates represent the biggest advance in the treatment of osteoporosis, and will probably remain the mainstay of therapy. At the same time other diagnostic and therapeutic approaches, including biological agents, are likely to become more widespread. Combination therapy is generally not recommended due to paucity of data concerning antifracture effectiveness, and, there is currently no definitive answer on the length of treatment with antiresorptive agents.

INTRODUCTION

Osteoporosis is a systemic skeletal disorder characterised by a low bone mineral density (BMD) and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequence increase in fracture risk (1,2). The condition is usually painless until a fracture occurs. Because of its association with fractures, osteoporosis is a major public health hazard with high morbidity, mortality and social costs. The aim of prevention and treatment is to improve bone strength, and thus decrease the risk of fracture, with its attendant morbidity and mortality (3). Today there is a wide

range of therapeutic options and several safe and effective pharmacological treatments that have been shown to act quickly (within one year) and to reduce the risk of fracture by up to 50%. It is important that the choice of treatment be tailored to a patient's specific medical needs and lifestyle.

EPIDEMIOLOGY

In the US about ten million people suffer from osteoporosis (80% of whom are women). Another 18 million are at risk (have osteopenia). About 1.5 million fractures occur each year, with an estimated management cost amounting to over 13.8 billion

US dollars/year (4). The international osteoporosis foundation estimates that one in three women and, one in eight men (over the age of 50 years) suffer osteoporosis worldwide (5).

In Kenya prevalence of osteoporosis in post-menopausal women is about 24.3%, as compared to 0.9% in pre-menopausal women. Prevalence of osteopenia is reported to be 32% and 20.5% in post and pre-menopausal women respectively (6). Prevalence is lowest in African women, followed by Asian, and highest in Caucasian women (7).

PATHOPHYSIOLOGY

Bone tissue: Is composed of inorganic (70%), organic (22%), and, water (5-8%). Inorganic matter includes calcium hydroxyapatite (95%) and impurities (5%). Organic matter is composed of type I collagen (85%), other collagens and noncollagenous proteins (osteopontin, fibronectin, peptide growth factors, and osteocalcin), and cells (osteoblasts, osteoclasts, and osteocytes) (8).

Bone macrostructure: Cortical (compact) bone accounts for 80% of bone skeleton, and 20% of bone surface. It is found in shafts (diaphyses) of long bones and outer surfaces of flat bones. Trabecular (spongy or cancellous) bone accounts for 20% of adult skeleton, and 85% of bone surface. It is found in the end of long bones (epiphyses) and inner parts of flat bones, and is made of interconnecting plates within which bone marrow lives. (8).

Bone microstructure: This refers to trabecular thickness, spacing (volume), connectivity, and structural index. Sex hormone deficiency is associated with alteration of the connectivity of trabecular structures, including decreased trabecular number, increased trabecular separation, modification of trabecular shape from plates to rods, and alteration of parameters of connectivity (9, 10). These aspects of bone microarchitecture can be assessed by histomorphometry or by microcomputed tomography (microCT). Early alteration in the microarchitecture include; perforation and/or disappearance of trabeculae, without major effects on BMD.

Determinants of bone strength: These include bone geometry, cortical thickness, porosity, trabecular

bone morphology, intrinsic properties of bone tissue, and rate of bone remodeling (10,11). Increasing the external diameter of a cylinder greatly increases its resistance to flexion. The outer diameter of long bones predicts up to 55% of the variance of bone strength. Increase in cortical thickness also improves bone strength, but to a lesser extent. The combination of increments of outer diameter and cortical thickness results in an additive effect on bone strength.

BMD, which refers to a real density (mass per area rather than mass per volume), corresponds to the ratio between bone mineral content (hydroxyapatite), and bone-scanned area. It is a major determinant of bone strength. (10). Bone strength is indirectly estimated by BMD and by DEXA. In preclinical studies, BMD predicts 50-75% of the variance of ultimate strength (atlas). Degree of mineralization (bone tissue quality) also determines strength.

Bone remodeling process: This is a surface-based phenomenon that involves the removal of a quantum of bone by osteoclasts, followed by the deposition of new bone by osteoblasts, within the cavity formed. Knowledge of remodeling is essential to understanding pathophysiology of osteoporosis. The primary function of bone remodeling is repair of microdamage and supply of calcium, to maintain serum calcium levels. (12). The end result is that damaged bone is replaced by new bone.

Stimulators of bone remodeling include systemic hormones (parathyroid hormone, vitamin D, growth hormone, parathyroid hormone related peptide, and thyroid hormone), and locally acting factors [interleukin 1, tumor necrotic factor α , insulin-like growth factor, IL 6, IL 11, prostaglandins, monocyte colony stimulating factor, and receptor activated nuclear factor kappa b ligand (RANKL)] (12,13).

Inhibitors of bone remodeling include systemic hormones (estrogens, androgens, progesterone, and calcitonin), and locally acting factors (osteoprotegerin, interferon gamma, interleukins 4, 10, 13, and 18, transforming growth factor β , and mechanical loading).

The remodeling cycle has four phases, namely; resorption, reversal, formation, and quiescence. (13). Resorption phase takes 10-14 days while formation phase 150 days. During resorption (phase I remodeling), osteoclast recruitment, differentiation, activation and attraction to site of resorption occurs.

Early differentiation is under transcription factor PU-1, while late phase is under MCSF, NFkB, RANK, RANKL, and C-fors. Mature osteoclasts form tight seal over bone surface, secrete hydrochloric acid which dissolves hydroxyapatite, while proteolytic enzyme (cathepsin K) degrade bone matrix. After resorption is completed, osteoclasts undergo apoptosis.

During bone formation (phase 3 remodeling), osteoblasts undergo recruitment, differentiation and activation. They produce osteoid (bone matrix), which later becomes calcified to mature bone. Some osteoblasts become trapped within the matrix and differentiate into osteocytes. Others differentiate into flattened lining cells that cover the bone surface, while the rest undergo apoptosis (12,13).

Estrogen inhibits osteoclasts (OCL), and stimulates osteoblasts (OBs). OBs produce many growth factors and cytokines that mediate estrogen action, some of which regulate the OCL indirectly. Estrogen deficiency stimulates Osteoblast production of IL-1, IL-6, IL 11, RANKL and, TNF α , inhibits apoptosis and extends the lifespan of OCLs.

Estrogen deficiency also decreases production of TGF- β and osteoprotegerin ligand (OPG-L), factors that mediate osteoclast apoptosis. The net result of estrogen deficiency is increased osteoclast recruitment and perhaps activity (9). Glucocorticoids increase bone loss by multiple mechanisms (12,14). The predominant effect is reduction in bone formation owing to reduced generation of osteoblast precursors, and increased apoptosis of osteoblasts. Increased bone resorption can also occur. This may be due to impaired calcium absorption across the intestines (via a vit D independent effect), increased urinary calcium loss, and induction of some degree of secondary hyperparathyroidism. Increased resorption could also be due to decreased estrogen and androgen production. Induction of glucocorticoid myopathy may exacerbate effects on skeletal and calcium homeostasis, as well as increase the risk of falls.

DIAGNOSIS

In the absence of methods of measuring bone quality, Bone mineral density (BMD) using dual energy X-ray absorptiometry (DEXA) is the standard diagnostic test for osteoporosis (15,16). BMD is one of the most important risk factors for fracture of

substantial importance (17) Central (hip and spine) measurement by DEXA should be used for both risk assessment, and follow-up, as they provide the most accurate and precise measurement of BMD. Hip is the preferred site in most individuals. Spine BMD may be the most sensitive indicator of bone loss, in young individuals.

The second way of measuring bone density is by quantitative computed tomography, which is primarily used to the spine. Unlike (DEXA), it can provide a true density (mass of bone per unit volume) since it is three dimensional and it specifically analyses trabecular bone in vertebrae, eliminating posterior cortical elements of the spine. Due to cost and greater radiation dose, it is not widely used as a screening tool. It also has a lower reproducibility at least for the central assessment of the axial skeleton.

Bone density in peripheral sites can be measured using DEXA, single energy X-ray absorptiometry (SXA), quantitative computed tomography, ultrasonometry, and, single photon absorptiometry. The role of peripheral (radius, phalanx, heel) BMD measurement in clinical practice is not clear.

Who should be done BMD?

According to guidelines (5) from the National Osteoporosis Foundation, BMD should be measured in the following people:

- Postmenopausal women (PMW) older than 65 years
- PMW younger than 65 years who have 1 or more risk factor, in addition to postmenopausal status.
- PMW who present with fragility fractures.
- Women who are considering therapy in which BMD will affect that decision.
- Women who have been on hormone replacement therapy (HRT) for prolonged periods.
- Men who experience fractures after minimal trauma.
- People with osteopenia apparent on X-ray film (radiographic lucency).
- People with disease known to place them at risk for osteoporosis.
- Other risk factors that may warrant screening include: Women with weight less than 57.6 kg, Family history of fracture, Current cigarette smoking, and use of glucocorticoid or anticonvulsant drugs.

FDA approved indications for BMD tests:

- Estrogen deficient women at clinical risk of osteoporosis.
- Vertebral abnormalities on X-ray suggestive of osteoporosis (fractures, osteopenia).
- Glucocorticoid treatment equivalent to 7.5 mg or more of prednisone or duration of more than three months.
- Primary hyperparathyroidism.
- Monitoring treatment.

WHO Diagnostic Categories for BMD in postmenopausal Caucasian Women (1)

- Normal: BMD not more than 1 SD below the peak bone mass or young adult mean (T-score above -1)
- Osteopenic: T-score between -1 and -2.5
- Osteoporosis: T-score at or below -2.5
- Severe osteoporosis (established osteoporosis): T-score at or below -2.5 and the presence of one or more fragility fractures.

MONITORING

Depending on the clinical situation, central DEXA scans (lumbar spine and hip) may be repeated in one to three years, to monitor response to pharmacological therapy or to document the stability of bone density in untreated patients at risk of bone loss and to improve adherence to therapy (5,18)

Further evidence should be collected to determine the role of peripheral BMD measurements (e.g., ultrasound or DEXA measurements in the radius, phalanx, or heel) in clinical practice.

Measurement of height loss is a good clinical indicator of vertebral fracture. (19) Postmenopausal women with historical height loss of greater than 6 cm, prospective height loss greater than two din, kyphosis, or acute incapacitating back pain syndrome should be sent for spine radiographs with specific request to rule out vertebral fractures. AP and lateral projections of both the thoracic and lumbar spine radiographs remain the best method of assessing the presence of vertebral fractures. For follow-up, only the lateral radiographs are required, as these are the most effective in the detection of osteoporotic fractures.

Bone turnover markers have emerged as powerful tools to help in the management of osteoporosis since they provide information that is

different and complementary to BMD measurement. (20) The ability to monitor treatment with bone turnover markers to rapidly assess adherence and effectiveness of pharmacological interventions represents the most promising clinical application.

Bone formation markers include serum osteocalcin, bone alkaline phosphatase, and the C- and N- terminal propeptides of type 1 collagen (PICP, PINP)

Bone resorption markers include urinary hydroxyproline, urinary pyridinoline (PYR), urinary deoxypyridinoline (D-PYR), as well as urinary collagen type I cross-linked Ntelopeptide (uNTx), and urinary and serum collagen type 1 cross-linked C-telopeptide (uCTx and sCTx)

Currently approved osteoporosis therapies are mostly antiresorptives and produce a rapid reduction of bone turnover that reaches nadir levels in 3 to 6 months, followed by a plateau. The optimal threshold of bone marker change that will lead to the maximal fracture reduction is yet to be defined.

TREATMENT

The goals of osteoporosis management should be fracture risk assessment and prevention of fracture (21). BMD should not be viewed as the only indicator for management success because therapy may or may not be associated with significant increase in BMD.

NON-PHARMACOLOGICAL THERAPY

Risk factors reduction: Counsel patient about interventions that decrease the risk of fractures and bone loss e.g., smoking cessation, decreasing or eliminating alcohol consumption, environmental safety, ensuring glucocorticoids are truly indicated, and using the lowest dose possible.

Nutritional recommendation: Optimal bone health requires good overall nutrition. Malnutrition is associated with an increased risk of osteoporosis. BMI \leq 20 kg/m² is associated with increased risk of fracture.

Calcium and vitamin D recommendation: Although it might not be sufficient as the sole therapy for osteoporosis, routine supplementation with calcium (1,000 mg) and vitamin D3 (800 mg) is still

recommended as mandatory adjunct therapy to the main pharmacological interventions (22). Calcium and vitamin D3 act to reduce parathyroid hormone and so may preserve bone mass.

Preventive measures should begin in childhood and adolescence. Adequate dietary intake of calcium is necessary for mineralization and attainment of peak bone mass. In PMW, calcium supplements slow bone loss and improves BMD (12,23).

The aim of vitamin D3 supplementation should be to maintain serum 25OHD consistently at above 50 umol/l (20 ng/ml).

Exercise: Physical activity early in life contributes to higher peak bone mass, with resistance and impact exercise showing the most benefit. (24-26) In postmenopausal women, BMD at the spine can be positively affected by aerobics, resistance, and weight-bearing exercise.

Walking also appears to benefit the hip BMD. Walking may be the most cost-effective exercise accessible to the population (27). Women should be encouraged to perform fast walking in a safe environment as a means of improving bone health.

Exercise interventions that increase strength and improve balance can reduce falls, but there is not yet evidence of fracture reduction in exercise trials.

Benefit accrued from exercise wanes off if exercise is discontinued. Therefore habit should be consistent, optimally at least three times per week (24).

THERAPEUTIC AGENTS

(A) Anti-resorptives

(i) *Hormone therapy (HRT/ERT):* Estrogen decreases bone resorption and may increase osteoblast activity. (9) HRT has been shown to increase BMD. Oral and, transdermal estrogen therapy (ET), decrease bone loss. Lower doses of estrogen taken in combination with calcium may prevent BMD loss. BMD rises in women who begin ET within five years after menopause. Progestins appear to have no independent effect on bone, but at lower doses norethindrone acetate might have additive effect to estrogen.

Since the publication of results from the two hormone randomized controlled clinical trials of the Women's Health Initiative (WHI), (28-30) guidelines

from the Society of Obstetric and Gynaecologists of Canada (SOGC), and a position statement from the North American Menopause Society (NAMS), recommended the use of HRT in postmenopausal women for moderate to severe symptoms of menopause. The risks incurred in WHI made long term use of HRT for bone protection unacceptable. The estrogen and progestin component of WHI randomized controlled trials is the first trial with definitive data supporting the ability of conjugated equine estrogen (0.625 mg/d) and progestins (medroxyprogesterone acetate 2.5 mg) to prevent clinical fractures at the hip, vertebrae, and other sites, in a population of postmenopausal women not selected for osteoporosis based on BMD testing (31). Similar results for prevention of fractures were demonstrated in the estrogen component trial of WHI.

For symptomatic menopausal women choosing HRT as a therapeutic option, osteoporosis prevention can still be considered as a secondary benefit due to the positive effect ovarian hormones have on BMD.

HRT should be prescribed to symptomatic postmenopausal women as the most effective therapy for symptomatic relief and a reasonable choice for prevention of bone loss and fracture. The risks should be weighted against the benefits if estrogen therapy is being used solely for fracture prevention (32). US Food and Drug Administration indicates HRT/ET for prevention (not treatment) of postmenopausal osteoporosis. Patients are now advised to use HRT for the shortest time possible, at as low a dose as possible in order to stop the menopausal symptoms, and only when benefits outweigh the risk (e.g. symptomatic menopausal women).

(ii) *Bisphosphonates:* Bisphosphonates are stable analogues of naturally occurring pyrophosphonate compounds. They bind avidly to hydroxyapatite crystals in bone, and are slowly removed over the years during bone remodeling. Bisphosphonates inhibit bone resorption, decrease recruitment and activity of osteoclasts, and increase their apoptosis (33).

Nitrogen containing bisphosphonates (alendronate, risedronate, pamidronate, ibandronate, and zoledronic acid) increase apoptosis of osteoclasts by interfering with the mevalonate pathway and

protein phenylation. Non-nitrogen containing bisphosphonates (etidronate) are metabolised intracellularly by osteoclasts to nonhydrolysable analogues of ATP, which accumulate to high concentrations and inhibit ATP-dependent enzyme, thereby inhibiting bone resorption and causing osteoclast apoptosis (34).

All decrease markers of bone turnover and increase BMD in the first few years. The largest increase in bone mass occurs during the first 6 months of therapy and in bone with the highest rate of remodeling. Some bisphosphonates continue to increase bone mass for up to three years. Alendronate and risedronate have been shown to continue to increase BMD for up to seven years. The plasma half-life of bisphosphonates is very short, but once deposited in bone; their half-life is probably up to loyears and could be longer (33).

Uses

- First line for treatment of postmenopausal osteoporosis.
- Drugs of choice for treatment of glucocorticoid-induced osteoporosis (GIOP).
- Prevention of postmenopausal osteoporosis (estrogen is superior in this regard).
- Prevention of glucocorticoid-induced osteoporosis (GIOP).
- Treatment with alendronate or risedronate should be considered to decrease vertebral, non-vertebral, and hip fractures. Treatment with etidronate can be considered to decrease vertebral fractures (32).

Tolerability and safety: Adverse effects from bisphosphonates are rare, and in a meta-analysis of cyclical etidronate, alendronate, and risedronate, there was no difference in withdrawals, compared with placebo for adverse events.

The most frequent concerns associated with cyclical etidronate are diarrhea, nausea, and, rarely, osteomalacia if cyclical therapy is not used, Nitrogen containing bisphosphonates (alendronate and risedronate) may be associated with gastrointestinal side effects in patients with prior upper gastrointestinal disease, concomitant NSAID use, and those on already using antireflux medications. To minimize the risk for esophagitis, patients must take bisphosphonates on an empty stomach with a full glass of water, then remain

upright and avoid food, beverage, and other medications for 30 minutes (5). Patients who have mechanical problems of the oesophagus, renal dysfunction (creatinine clearance <30 ml/ml), hypersensitivity to the drug, or suffer from hypocalcemia should avoid bisphosphonates (35). Preclinical studies using doses five times higher than the dose used in humans have shown that the marked suppression of bone turnover is associated with microcracks, raising issues about the optimal duration of treatment (36).

Specific bisphosphonates

Etidronate: First to be approved for Paget's disease and, hypocalcaemia. It is approved for treatment of postmenopausal osteoporosis (in UK but not by FDA). Etidronate is also used for male osteoporosis.

Cyclical etidronate is currently prescribed as 400 mg daily for 14 days followed by 76 days of calcium (90 day cycle). A meta-analysis (37) of 13 RTCs (of which 6 were placebo controlled) of cyclical etidronate found;

- BMD increased by 4.06% ($P < 0.01$) at the lumbar spine
- BMD increased by 2.35% ($P < 0.01$) at the femoral neck
- Significant reduction of vertebral fractures (37% reduction; $P = 0.02$)
- No significant reduction for non-vertebral fractures ($P = 0.97$).

Alendronate: This is a second generation nitrogen-containing bisphosphonate, indicated for treatment of postmenopausal osteoporosis (PMO), GIOP, osteoporosis in men, and prevention of PMO. It has been shown to reduce fractures both in high-risk women with fractures and those with osteopenia. The most commonly prescribed alendronate doses are currently 70mg once weekly or 10mg daily, (5mg daily for prevention).

A meta-analysis (38) included 11 RPECTs of 12,855 postmenopausal women. Three years of therapy with alendronate resulted in BMD increases of 7.48% ($P < 0.01$) in the lumbar spine and 5.6% ($P < 0.01$) in the total hip. The pooled relative risk reduction for vertebral and non-vertebral was 48% and 49% respectively ($p < 0.01$). The daily doses ranged from 5 to 40 mg.

In the Fracture Intervention Trial (FIT) (39) in which postmenopausal women with a prevalent vertebral fracture were studied, treatment with alendronate reduced the incidence of hip fracture by 51% (P 0.047) over three years. BMD was increased at all skeletal sites (6.2% at lumbar spine, 4.7% at total hip). In post hoc pooled analysis alendronate reduced the relative risk of hip fracture by 53% (p = 0.005) over three to four years in women with established osteoporosis. Furthermore, clinical vertebral fracture rate reduction (59%; P<0.001) was demonstrated as early as one year into the study. In a more recent post hoc analysis of a subgroup of women who had T-scores of -1.6 to -2.5; there was a significant relative risk reduction in clinical and radiographic fractures of 60 and 43% respectively, compared with placebo with three years of therapy. Fractures appear to remain significantly reduced up to seven years on therapy, with BMD increases 11.4% at the lumbar spine (40). Incidence of gastrointestinal side effects was similar to placebo arm.

Risedronate: A third generation bisphosphonate, indicated for treatment and prevention of PMO and GIOP. It is prescribed either as 35mg once weekly or 5 mg daily.

A meta-analysis (41) of 8 RPCTs (dose 2.5 to 5 mg, duration of at least one year) of 14,832 postmenopausal women with osteoporosis reported a BMD increase of 4.54% at the lumbar spine (p<0.01) and, 2.75% (p<0.01) at the femoral neck, 38% relative risk reduction in vertebral fractures and 32% in non-vertebral fractures.

A significant reduction in new vertebral fractures (61% to 65%) in high-risk women with osteoporosis and vertebral fractures has been observed within the first year of therapy with risedronate. (VERT trials) These risk reductions have subsequently been demonstrated in individuals with and without vertebral fractures. Non-vertebral fractures were reduced by 71% within the one year of therapy.

BMD continues to increase with long-term use. The mean increase from baseline in lumbar spine BMD over five and seven years was 9.3% (P = 0.001) and 11.3% (P<0.05) respectively.

In a large RTC designed to determine hip fracture efficacy, risedronate was shown to reduce hip fracture rates in those with low femoral neck BMD by 40% (P = 0.009) and prior vertebral fractures by 60% (P = 0.003). (42)

Ibandronate: Indicated for treatment and prevention of PMO (150mg p.o. once a month), treatment of hypercalcaemia of malignancy (2-4 mg single infusion), bone metastasis in cancer of breast (50 mg/d p.o or 6 mg infusion every 3-4 weeks).

It is efficacious in preventing vertebral fractures as reported in BONE study (43). Ibandronate has been specifically approved for the prevention of vertebral fractures (21).

Pamidronate: No study to show that it is indicated for osteoporosis. Used for:

- (i) hypercalcaemia of malignancy (15-60 mg infusion, dose divided over 2 to 7 days. Max dose per course is 90 mg)
- (ii) osteolytic lesions and bone pain in bone metastasis associated with Ca breast and multiple myeloma (90 mg single infusion every 4 weeks)
- (iii) paget's disease of bone (30 mg once per week for 6 weeks)

Zoledronic acid: FDA approved in 2002. For advanced malignancies involving bone, to decrease bone damage (4 mg infusion every three to four weeks). It is given as 4 mg single infusion for hypercalcaemia of malignancy.

Clodronate: Clodronate is given as 1.6 g per day either OD or BID for osteolytic lesions and bone pain associated with skeletal metastasis (Ca breast, multiple myeloma). It is also used to treat hypercalcaemia of malignancy (300 mg infusion for seven to ten days, or single infusion of 1.5 g).

NEWER ANTIRESORPTIVES

(i) Selective estrogen receptor modulators (serms)

SERMs consist of a group of structurally diverse compounds that are distinguished from estrogen by their ability to interact with estrogen receptors, and act either as an estrogen agonist or antagonist depending on the particular environment. A receptor changes its shape when a SERM binds to it, and its particular shape determines which gene it will activate. Subsequently, the activated genes will produce proteins that regulate different processes in the body. Presently, raloxifene is the only SERM approved for management of osteoporosis.

Raloxifene exhibits agonist effects on bone and cardiovascular system and antagonist effects on the breast and uterus.

The Multiple Outcomes of Raloxifene Evaluation (MORE) Trial (44) was a large RCT of postmenopausal women with or without prevalent vertebral fractures with a BMD of -2.5 in either the lumbar spine or the hip. The study showed that raloxifene is efficacious (vertebral fracture reduction of 30% in women with and 55% in women without prevalent fractures in three years), sustainable (50% in fourth year versus 55% in years 0-3), and fast acting (68%, $P = 0.01$, in a one year post hoc analysis).

The risk reduction for non-vertebral fractures in the overall MORE population is not significant, but was in patients with severe prevalent vertebral fractures (post hoc analysis).

In addition to its skeletal effects, the MORE trial demonstrated that raloxifene reduces breast cancer by 76% in postmenopausal women with osteoporosis. The recent results of Continuing Outcomes of Raloxifene Evaluation (CORE), the extension arm of the MORE trial, confirms that the breast cancer reduction effect in osteoporotic women lasts up to 8 years, with a reduction rate of 66%.

Unlike the HERS trials, which indicated an increased risk of cardiovascular events, the MORE trial did not demonstrate harmful effects of raloxifene on the cardiovascular system. In fact, in a subset of women at high risk of CVS disease, it may have a beneficial effect. However, more data on its safety is awaited in the ongoing STAR and RUTH trials.

A meta-analysis (45) of 7 RPCT of raloxifene found BMD increased by 2.51% ($P < 0.01$) at the lumbar spine and 2.11% at the total hip ($P < 0.01$). There was evidence for reduction of vertebral fractures (40% reduction; $P = 0.01$) but not for non-vertebral fractures ($P = 0.24$).

The side effects of raloxifene are minimal. It increases the incidence of hot flashes and leg clamps. The incidence of DVT doubles, but the absolute incidence is small. Venous thromboembolism is reported infrequently. The magnitude of relative risk is similar to that observed with both HRT or 1-IT, and tamoxifen.

Raloxifene decreases total cholesterol, LDL, Lipoprotein a, and fibrinogen level (31).

Recommendation: Because of its vertebral fracture efficacy and its additional extraskeletal benefit,

raloxifene 60 mg daily is recommended to prevent and treat osteoporosis in young, asymptomatic postmenopausal women. It is an alternative to estrogen for PMO. Treatment with raloxifene should be considered to decrease vertebral fractures (32).

(ii) Calcitonin

A polypeptide hormone produced in the thyroid gland. Its physiological role is unclear as no disease has been associated with its deficiency or excess. It inhibits osteoclastic bone resorption. Poor oral absorption necessitates either subcutaneous, IM or intranasal administration. Nasal spray calcitonin 200 IU is approved for the treatment of PMO, and has a possible analgesic effect (via release of endogenous opioids) that may be useful in managing the pain of acute vertebral compression fractures (32,33).

It produces a small increase in bone mass and a small decrease in new vertebral fractures. There is no significant reduction in rates of non-vertebral or hip fracture. A meta-analysis of 30 RCTs (of which 15 were placebo controlled) of calcitonin found a significant relative risk reduction of 21% ($P = 0.05$) in vertebral fractures but not in non-vertebral fractures ($P = 0.12$).

In the PROOF study, nasal salmon calcitonin significantly reduced vertebral fractures by 33% to 36% using a daily 200 IU in postmenopausal women with and without prior vertebral fractures (32).

Nasal spray is better tolerated than SC/IM. Side effects include rhinitis, nasal ulceration and GI upset.

Uses:

- FDA approved for osteoporosis in women less than 5 years postmenopausal (not potent enough to prevent bone loss in early postmenopausal period)
- Used where bisphosphonates and estrogen are contraindicated or not tolerated.
- Treatment with calcitonin can be considered to decrease vertebral fractures and to reduce pain associated with acute vertebral fractures.

POTENTIAL ANTIRESORPTIVE AGENTS

Osteoprotegerin: This is a glycoprotein member of the TNF receptor family. It prevents osteoclast formation and then bone resorption. Dietary sources of phytoestrogen may increase osteoprotegerin

production, thereby preventing bone loss and resorption. Rigorous data is needed before clinical recommendation can be made (33).

Antibodies to RANKL: AMG 162 is a fully human monoclonal antibody that specifically binds with high affinity to RANKL and prevents it from binding to its receptor, so inhibiting osteoclast differentiation, activation, and survival. This effect is quite long lasting and, in a phase II dose-ranging trial, twice yearly injections significantly increased bone mineral density at the total hip to a similar or greater extent than that seen with alendronate. A phase III fracture trial is now in progress (21,33).

Cathepsin inhibitors: Cathepsin K is a tissue-specific cysteine protease that plays a part in the degradation of protein components of the bone matrix in bone resorption. Phase-II studies of cathepsin K inhibitors are underway (21).

Androgens (testosterone): It is presumed to act as an antiresorptive agent. Studies have shown that replacement in men with severe deficiency increases spinal, but not hip BMD.

ANABOLIC AGENTS

(i) Parathyroid hormone

PTH and its analogues present a new class of anabolic agents for treatment of severe osteoporosis. PTH directly stimulates osteoblast activity and markedly increases bone formation to a greater extent than bone resorption.

Teriparatide (recombinant human PTH (1-34): Teriparatide, an analogue of PTH, is the only approved drug in this class. It has shown a significant relative risk reduction in vertebral (65%; $P < 0.001$) and non-vertebral fractures (53%; $P < 0.02$).

Teriparatide is administered as a daily subcutaneous injection of 20 mcg and is approved for therapy of up to 18 months. This regimen increased lumbar spine BMD by 9.7% ($P < 0.001$), total hip BMD by 2.6% ($P < 0.001$) and, femoral neck BMD by 2.8% ($P < 0.001$). It also showed unique improvement of bone microarchitecture. Histomorphometric study of paired bone biopsies reported significant increase in cancellous bone volume and cancellous trabecular number and connectivity density, as well as increase in cortical thickness (46).

Teriparatide is recommended for patients with prior fragility fractures; patients with very low BMD, below -3 to -3.5; or patients who continue to fracture or to lose BMD while taking antiresorptive therapy (32).

Use of teriparatide is not associated with major adverse reactions. There is higher incidence of nausea, dizziness, and leg clamps (compared with placebo). Hypercalcemia is an occasional occurrence but rarely clinically significant. Rats developed osteosarcoma after receiving teriparatide (3-58 times the normal human dose, for their entire lifespan 8 weeks to 2 years). Osteosarcoma has not been reported in humans.

Teriparatide is contraindicated in: metabolic bone diseases other than osteoporosis, patients with cancer or at risk of bone metastasis, patients with prior bone radiation therapy, children and adolescents, pregnancy and while breastfeeding, and in renal impairment (5,32,46).

Other PTH fragments: Include: PTHrP, PTH (1-31), PTH (2-34), PTH (8-84), PTH (2-28), PTH (13-34), PTH (3-34). Some are at preclinical, others at clinical evaluation level (47).

(ii) Strontium ranelate

Anabolic agent, the first anti-osteoporotic treatment to have a dual mode of action; simultaneously increases bone formation and decreases bone resorption. This action rebalances bone turnover in favor of bone formation. It does this by increasing the replication of preosteoblasts into mature osteoblasts, and consequently promotes the synthesis of the bone matrix by mature osteoblasts. It also decreases the differentiation of preosteoclasts into osteoclasts, and decreases their resorbing activity. The new bone formed with strontium ranelate has been shown to be of good quality and increased strength.

It is indicated for treatment of postmenopausal osteoporosis in women to reduce the risk of vertebral and hip fractures, and was recently licensed in Europe for this indication. It should be considered if bisphosphonates are unsuitable.

Studies done on strontium ranelate: Spinal Osteoporosis Therapeutic Intervention (SOTI) study (48) was to demonstrate the vertebral antifracture efficacy of the drug. Seven hundred and nineteen and 723 women

with established osteoporosis (low femoral neck BMD and prevalent vertebral fracture) received 2g strontium ranelate and placebo respectively, for a duration of 3 years. The risk of vertebral fractures was reduced by 41% compared to placebo.

The Treatment Of Peripheral Osteoporosis (TROPOS) study (48) was to demonstrate the peripheral antifracture efficacy of strontium ranelate. Out of 4,932 women with PMO, 2479 received 2g of the study drug while the rest placebo. There was significant increase in femoral neck BMD, and a 33% decrease in risk of nonvertebral fractures, compared with placebo arm.

Both the SOTI and TROPOS (RPCT phase III trials) demonstrated the uncoupling of bone turnover, with formation (bone ALP) increasing and resorption decreasing (decreased serum C-terminal telopeptide of collagen 1).

(iii) Potential anabolic agents

Fluoride: Despite being available for many years, Fluoride remains an experimental agent. (47) It has been used in multiple osteoporosis studies, with conflicting results, in part due to use of varying doses and preparations. It causes an increment in bone mass of up to 10%, but there is no consistent effects on vertebral or nonvertebral fractures, which might actually increase when high doses are used. Fluoride gets incorporated into bone-mineralized matrix. Fluoroapatite is not as strong as hydroxyapatite. Thus resulting bone is not as strong as normal mineralized bone.

Growth hormone: Recombinant human GH is approved by FDA for use in improving muscle and bone mass in those GH deficient. GH is critical for the development and maintenance of bone mass. It exerts its effects via IGF-I which stimulates osteoblast differentiation. GH deficiency is associated with an increased incidence of fractures in adults. (47) Studies done using GH alone or in combination with HRT are small and have reported no consistent or substantial positive effect on bone mass. In addition, GH may predispose patient to risk of breast, prostate, and colon cancer, and DM.

Statins: Observational studies have suggested that statins may be associated with increased bone mass and a decrease in fractures, but conclusions from clinical trials are mixed. (47) Possible mechanisms

of action (in bone formation) involve stimulation of bone morphogenetic protein (BMP-2) and endothelial nitric oxide synthase.

Women (in WHI) who used statins did not have a significant decrease in fractures after 3 years, but these patients may not have had osteoporosis or risk factors for it. Studies are needed to evaluate the effects on fracture reduction in patients with osteoporosis.

Cytokines: These include IGF-1, TGF- β , VEGF, BMP-2, and BMP-7 (OP-1). Recombinant human bone morphogenetic protein-2 (rhBMP-2). was approved by FDA in 2002 for use in human fractures, and lumbar interbody spinal fusion. (47) It induces mesenchymal differentiation into osteoblasts, via stimulation of *cbfa 1* gene, essential for osteoblast differentiation. BMP-7(OP-1) promotes bone repair, and can be used for established nonunions. It is also directly angiogenic.

Vascular endothelial growth factor (VEGF) promotes osteoblast differentiation, migration, and bone healing. PTH also increases VEGF production. Transforming growth factor (TGF- β) is the most abundant growth factor. In rats, TGF- β increase bone matrix, adipogenesis, increased VEGF expression by osteoblasts.

Fibroblast growth factor (FGF) acts as mitogen for cells involved in bone growth and healing (fibroblasts, osteoblasts, and chondrocytes).

Anabolic steroids: These are derivatives of testosterone. They are primarily antiresorptives but may also be anabolic. The effect of bone mass remains unclear, but appears weak. Use is limited by their masculinising side effects (47).

COMBINATION THERAPY

(i) **Antiresorptives:** Although combination of antiresorptive therapies may be synergistic in increasing BMD, the anti-fracture effectiveness has not been proven; therefore, it is not recommended (32).

(ii) **PTH and Antiresorptives:** Fracture data are lacking and combination therapies are usually not recommended. Giving Bisphosphonates after a course of PTH therapy will enhance and maintain the bone mass (good evidence). Bisphosphonates

may slightly blunt the effect of PTH therapy if they are given concurrently or preceding PTH therapy. Estrogen and Raloxifene do not appear to have the blunting effect on PTH therapy. Sequential therapies preceding or following PTH treatment are useful in maintaining and enhancing bone mass.

When HRT is used for symptomatic treatment of postmenopausal women, addition of bisphosphonate or PTH is indicated in:

- Significant bone loss despite use of HT.
- Glucocorticoid therapy (at least 7.5 mg prednisone/day, or equivalent, for at least three months)
- Osteoporotic fracture in a woman on HT.

CONCLUSION

This paper outlines the underlying bone biology and describes the therapies currently used to treat osteoporosis. It also reviews new approaches to the treatment of this very important condition.

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