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Postmenopausal osteoporosis: therapeutic options

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The aim of this meeting was to suggest state-of-the-art guidelines for research and practice on these themes. This paper was prepared following the presentations and the discussion during the Workshop. Thereafter, the manuscript draft was circulated and was edited by the presenters and Chairmen of the sessions. The final version has been extensively discussed and finally approved, but does not necessarily express or replicate the exact opinion of each individual presenter.

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INTRODUCTION

Osteoporosis is one of the major health problems of modern society. Current estimates indicate that up to 40% of women aged 50 years or older will suffer an osteoporosis-related fracture within their lifetime. Osteoporosis was described at a 1993 consensus conference as 'A systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue with a resultant increase in fragility and risk of fracture'. More recently, a United States National Institutes of Health consensus conference modified this definition as follows: 'A skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength reflects the integration of three main features: bone density, bone structure and bone quality'. Osteoporosis is operationally defined as low bone mineral density (BMD) below the normal range for young adults (a *T*-score of –2.5 or below). Among postmenopausal women, low bone mass is associated with an increased risk of fragility fractures. The World Health Organization (WHO) defines a fragility fracture as 'a fracture caused by injury that would be insufficient to fracture normal bone: the result of reduced compressive and/or torsional strength of bone'. Clinically, a fragility fracture may be defined as one that occurs as a result of modest trauma, such as a fall from a standing height or less, or occurs without identifiable trauma.

Studies have shown that fracture risk increases as bone density decreases. As clinical risk factors increase in number, fracture risk increases. Using a combination of bone density and clinical risk factor information is the preferred method for calculating fracture risk and making clinical management decisions. The pathophysiology of fracture is multifactorial, so that there is no absolute level of BMD that determines whether a fracture will occur. Rather, the fracture risk approximately doubles for each standard deviation decrease in BMD. Obviously, subjects with osteoporosis by BMD have several-fold higher risk of fracture than those with normal BMD. However, many fractures occur in women whose BMD is within the osteopenic range (*T*-score –1 to –2.4), and the risk increases in those with additional clinical risk factors.

Osteoporosis is a serious chronic disease with immense economic costs. Using the WHO definition of osteoporosis, it has been estimated that 30% of American women aged more than 50 years, corresponding to approximately 7 million women, have osteoporosis. The lifetime fracture risk for a 50-year-old woman is about 40% in the USA and in Northern Europe. Osteoporosis-related fractures are an important cause of morbidity, disability and mortality. Both health-related quality of life and global quality of life are negatively affected by fractures. The impact of fractures on quality of life is dependent on the skeletal site and severity of fracture. Hip fractures are the most serious of osteoporosis-related fractures, resulting in excess mortality, in long-term morbidity, and considerable use of resources for long-term care. However, spinal fracture has also been shown to be associated with increased mortality.

Today, osteoporosis is under-diagnosed and under-treated notwithstanding the fact that effective prevention and treatment options are available. Osteoporosis is a global problem with further increases in fracture numbers predicted over the next 50 years, particularly in Asia. Measures are urgently required to avert this trend. Although many organizations and agencies such as WHO are issuing guidelines and recommendations, increased awareness of the burden of the disease is required. Other critical problems are the access to diagnostic technologies, which is limited by both availability and funding, and the availability of reimbursement for appropriate treatments.

PRECLINICAL STUDIES

Various animal models exist for osteoporosis, though none is entirely satisfactory. The differentiation and function of bone cells are regulated by a complex interplay of actions of peptide and steroid hormones. Sex hormones have long been recognized as important factors influencing bone physiology. Regarding estrogen deficiency, it has been shown in different animal models that estrogen deprivation results in an increase in bone turnover, which is mostly an increase in bone resorption, leading to bone loss and to decreased bone density and strength. Among other actions, estrogens and androgens affect both osteoclast and osteoblast functions and reduce bone resorption. Thus, sex steroids affect bone cell function and bone turnover through both direct and indirect mechanisms. By analysis of the bone phenotype in mice deficient of either the estrogen receptor α (ERα) or the ERβ receptor, the ERα receptor was shown to mediate effects in both sexes, whereas the effects of the ERβ receptor were more restricted to female mice. While sex steroids have direct inhibitory effects on osteoclast function and osteoclastogenesis, they also affect

the osteoblast lineage. Recent data suggest that the increased osteoclast number and activity following estrogen deprivation in the mouse is, for the most part, dependent on estrogen effects on bone marrow stromal/osteoblastic cells. In this model, estrogen provides an inhibitory effect on proliferation and activity of early osteoblast precursors (transit-amplifying osteogenic cells), which in turn control osteoclastogenesis. An increased number of osteoclast supporting cells, the consequence of a release from an inhibitory action of estrogen, is the pathogenic mechanism of estrogen-dependent increased bone turnover and bone loss. This effect is not specific for estrogens, as the same mechanism occurs after orchidectomy in male mice. Androgens can stimulate the growth of osteoprogenitor cells, stimulating differentiation of osteoblasts and mineralization. In addition, androgens have been reported to suppress osteoclast formation and differentiation. Estrogen action on bone cells is almost exclusively mediated by the ERα. Similarly, other steroid hormones modulate cell activity via the 'classical' steroid receptor mechanism, which involves homodimerization and transactivation via estrogen response elements. Recent data show that some of the actions of estrogen (and androgen) are also mediated by 'non-genomic' activation of intracellular signaling pathways, such as the ERK/MAPK pathway, which are usually linked to peptide hormone signaling. In fact, the anti-apoptotic action of sex hormones, an action that plays a role in estrogen modulation of bone cells, appears to be mediated by modulation of these non-genomic signaling systems.

GENES AND OSTEOPOROSIS

Bone mineral density, bone turnover and geometry are highly inheritable. However, genetic predisposition to fracture is still uncertain, although hip fracture is familial, and it is not entirely explained by reduced BMD. Linkage analyses have identified several chromosome regions associated with high or low BMD in humans. Mutations of genes have been associated with high or low bone mass in humans. Gene polymorphisms have been shown to be associated with variation in bone mineral densities and impaired bone strength. Gene polymorphisms may also affect the response to treatment, and will likely allow novel therapeutic targets to be identified. However, most predictors of BMD remain to be discovered. In the future, genetic markers will likely enter clinical practice to assist in fracture risk assessment and in targeting anti-osteoporosis therapy to specific patients.

BONE MINERAL ACQUISITION IN INFANCY AND ADOLESCENCE

Bone mass acquisition occurs during childhood and adolescence and early adult life. The attainment of an optimal peak bone mass may be important in the prevention of osteoporosis. Maximization of peak bone mass may be aided by obtaining adequate dietary intake of nutrients such as calcium and vitamin D, by increasing physical activity, limiting certain lifestyle activities such as smoking, and by having a normal pubertal transition. Additionally, the maintenance of regular menstrual function after menarche is of utmost importance.

POSTMENOPAUSAL OSTEOPOROSIS AND DENTAL HEALTH

Osteoporosis and periodontal disease have many similar risk factors. Several studies indicate a correlation between lower BMD and/or postmenopausal osteoporosis and parameters of periodontal disease, such as alveolar crestal bone height, tooth loss and, to a lesser degree, gum recession. Hormone replacement therapy has been associated with reduced tooth loss in several observational studies. One recent, randomized, clinical trial found that hormone replacement therapy is associated with increased oral and systemic BMD and with increased alveolar crestal height. The potential mechanisms linking osteoporosis to tooth loss include decreased BMD leading to enhanced alveolar bone resorption or enhanced sensitivity to periodontal infections. Genetic and other factors that predispose generalized bone loss may also contribute to tooth loss. Studies have shown improved tooth retention in women using HRT, calcium supplements, or bisphosphonate therapy.

VERTEBRAL FRACTURE ASSESSMENT

The assessment of vertebral fractures in osteoporosis management has proven difficult to standardize and universally implement but is important for clinical research and patient care. The presence of a vertebral fracture is the most powerful independent predictor of future vertebral fracture risk, and also predicts the risk of fractures at other body sites. Vertebral fractures

are currently under-diagnosed, by both radiologists and clinicians. The result is that osteoporosis is under-treated. Assessment of vertebral fractures can be made with conventional radiographs, although new techniques such as computed tomography and magnetic resonance imaging are also available for more refined assessment. There is currently an international initiative striving to enhance and expand the diagnostic assessment of vertebral fractures.

BONE STRENGTH

Bone mass, its distribution (geometry and architecture – macro and micro) and the material properties (mineralization, collagen and matrix quality, microdamage) are all thought to contribute to the strength of bone. The term 'bone quality' is often used to define those aspects of bone strength not revealed by BMD measurement, which by itself is estimated to predict about 65% of the strength of bone. In premenopausal women, optimum levels of bone remodeling maintain bone mass and its architecture and repair microdamage. Menopause is associated with a long-standing, sustained increase in bone turnover that is sustained over time, with bone resorption occurring at a faster rate than formation. Fracture risk is associated with increased turnover irrespective of bone mineral density. High remodeling alters trabecular bone structure, with a significant loss in trabecular number and connectivity that leads to a significant decrease in bone strength. Cortical bone deteriorates as well with aging, the cortex becoming thinner and more porous; in women, there is little cortical expansion which, in men, compensates for these structural changes. Increased remodeling is associated with a reduced degree of skeletal mineralization, which may impair bone strength. However, the degree of bone mineralization has a complex relationship with bone strength. The greater the mineralization, the greater the stiffness and the physical load the bone can resist. But hyper-mineralized bone may become brittle and not be able to absorb energy without cracking at impact load. High mineralization and low rates of remodeling are also associated with microdamage accumulation. Techniques to assess bone material properties are still restricted to research settings. In contrast, techniques to assess structural properties (geometry and microarchitecture) may soon be available in the clinical setting. New imaging techniques such as high-resolution micro-computerized tomography or magnetic resonance imaging can provide information on microstructure of the bone. Some of these techniques are being used in clinical trials in research centers.

BONE ULTRASOUND

Quantitative bone ultrasound (QUS) is influenced by bone density, cortical thickness, microstructure and elasticity. QUS can be performed only at peripheral sites. The os calcis and the phalanges of the hand are the most accessible sites, but they exhibit significant differences. QUS does not measure bone mineral content or BMD, and should not be used to diagnose osteoporosis as currently defined by bone mineral density assessment. However, prospective studies have underlined the ability of some QUS to predict osteoporotic wrist, spine and hip fractures as efficiently as dual X ray absorptiometry (DXA). Thus, low QUS is a BMD-independent risk factor for fractures. Since low QUS parameters are predictors of fracture risk, individuals found to have low QUS parameters may either be referred for confirmation of the diagnosis using axial (preferably hip) BMD measurement, or be advised to receive preventive therapy if other clinical risk factors are present.

RISK FACTORS FOR FRACTURE

The most important risk factors for fracture at all sites are old age, previous fracture, maternal history of fractures of the hip, low BMD and low QUS values. Since the majority of fragility fractures occur in women who have yet to develop osteoporosis (by BMD criterion), prevention of bone loss and its related fractures in women is needed. Techniques to identify women with increased fracture risk but with BMD within the normal premenopausal range are urgently required. Falls are significant risk factors for fractures, although only about 5% of falls result in fracture. Biochemical and hormonal testing can be used to exclude secondary causes of osteoporosis. Bone turnover markers (matrix proteins, enzymes, collagen degradation products) are used to estimate bone turnover. However, their value has not yet proven to be useful in the clinical setting. The identification of the rate of bone loss (fast vs. normal loser) around the age of menopause may offer a way to identify the women at high risk for fracture. This could be done combining measurement of bone mass at the age of menopause with a biochemical marker of bone turnover. The use of bone turnover markers for

monitoring of treatment of osteoporosis may help to identify non-responders or to encourage adherence to treatment.

INTERVENTION THRESHOLDS FOR OSTEOPOROSIS

There is no consensus on the criteria used to select patients for treatment. Different National and International Societies have released their own guidelines. Divergences in patient selection for testing or treatment are rather narrow, and they are conceptually similar. Patients presenting with fragility fractures should be considered for treatment. For asymptomatic women, a simple measurement of BMD is often used, but does not seem to fulfill the required criteria to be offered as a screening test. In addition, BMD alone may not identify those who may best benefit from treatment. One method of identifying high-risk patients might be to select those with clinical risk factors, and to perform BMD for this subgroup. If BMD is in the osteoporotic range (-2.5 *T*-score), these individuals should also be considered for treatment. This is a conservative approach. An alternative is to offer a BMD screen to all the individuals older than 65 years if they have clinical risk factors. The BMD threshold for treatment might then be different in view of the increased risk associated with the risk factor, for example, a *T* score of -1.5 if clinical risk factors are present vs. a *T*-score of -2.0 without risk factors. There are other independent risk factors for fractures that should be taken into account in parallel with BMD. Age, low QUS results and prior vertebral fracture are the most important. Other relevant risk factors are low body mass index, maternal history of osteoporotic fractures, smoking, long-term glucocorticoids, and high consumption of alcohol and/or coffee. The combined use of different risk factors may allow for a better determination of fracture risk.

VITAMIN D AND CALCIUM

Adequate calcium and vitamin D intake is crucial throughout life for skeletal health. In aging women, there is an increase in the need for calcium and vitamin D. Reduced supplies of calcium may be associated with a reduced bone mass and osteoporosis, whereas a chronic and severe vitamin D deficiency leads to osteomalacia. Vitamin D deficiency is common in the elderly, particularly in institutionalized subjects. The major causes of vitamin D deficiency are a low exposure to sunlight, a decline in the synthesis of vitamin D in the skin, poor nutrition, and a decreased renal hydroxylation of vitamin D. A subclinical vitamin D deficiency, as characterized by a circulating level of 25-hydroxy-vitamin D lower than 20 ng/ml, is also common with aging. In the presence of osteoporosis, vitamin D insufficiency may amplify bone loss and thus enhance fracture risk. It follows that, at any age, but especially in the elderly, an adequate intake of both calcium and vitamin D is important for the preservation of bone mass and prevention of osteoporosis. The recommended dosage in postmenopausal women is at least 1000 mg/day calcium and 400 IU vitamin D. Solid data from randomized, controlled trials on the prevention of osteoporotic fracture with calcium and vitamin D supplementation are very limited in women within the first years of menopause. However, these compounds have been demonstrated to be pharmacologically active, safe and cost-effective for the prevention and treatment of osteoporosis in older women. Their use should therefore be encouraged, particularly in the elderly as well as in other conditions of dietary deficiencies. There is also consistent evidence that calcium and vitamin D supplementation exerts a synergistic effect with antiresorptive agents on bone, and, certainly, most patients will derive further benefit in terms of fracture prevention from the addition of an antiresorptive agent. Further studies will be needed to evaluate the relative impact of different vitamin D formulations (i.e. vitamin D or active vitamin D metabolites) as well as the relative contribution of calcium and vitamin D compounds on fracture prevention.

ORAL CONTRACEPTIVES AND OSTEOPOROSIS

Administration of oral contraceptives in normal eumenorrheic women is thought to have no effect on bone mineral density and bone metabolism. Conversely, long-term depot-medroxyprogesterone acetate (DMPA) is associated with bone loss and blocks the attainment of peak bone mass in adolescents. The prevention of bone loss is one of the recognized non-contraceptive benefits of oral contraceptives in hypoestrogenic women. Women with functional hypothalamic amenorrhea may have lower BMD than age-matched eumenorrheic women, and the administration of an oral contraceptive is effective in increasing BMD. In the menopausal transition, low-dose oral contracep-

tives prevent the increase in bone turnover and subsequent bone loss.

ESTROGEN AND HORMONE REPLACEMENT THERAPY FOR OSTEOPOROSIS

In postmenopausal women, standard estrogen or hormone replacement (ERT, HRT) with 0.625 mg conjugated equine estrogen (CEE) or equivalent, reduces bone turnover, increases bone density and reduces the risk of all fractures, including wrist, hip and clinical vertebral fractures. HRT increases bone mineral density at all skeletal sites and the number of non-responders is extremely low. HRT reduces fracture incidence in normal women, not selected for increased fracture risk or osteoporosis. Thus, HRT/ERT relies on the most robust data for fracture prevention in this group, since other bone-specific agents have limited data in this population. Adequate calcium intake is necessary as an adjunct to HRT to achieve best/optimal antifracture efficacy. It is unclear how long the antifracture efficacy of HRT persists after treatment withdrawal. However, some recent data suggest that 3–5 years' use in women in the early menopause may lead to a fracture reduction many years later in life, although this observation remains controversial. The main indication for HRT remains the relief of postmenopausal symptoms, which brings about a major improvement in quality of life. In the aftermath of the publication of the Women's Health Initiative (WHI) trial, today most professional societies do not recommend HRT for chronic menopausal disorders, including osteoporosis. HRT should be used for osteoporosis only after discussing with the patient the relative risks and benefits of the treatment. The best knowledge available today, in line with evidence-based medicine, should be used to balance benefits and risks of HRT for individual patients. The development of a model to balance the different outcomes associated with HRT could help to improve decision-making about individual patient treatment from a therapeutic and health-cost perspective.

LOW-DOSE HRT

Recently, several estrogen or estrogen–progestin preparations with doses lower than standard HRT have been studied and are currently available. The rationale is based on the observations that BMD and fractures in elderly women are inversely associated with endogenous levels of estradiol and directly with sex hormone binding globulin. For example, women with estradiol levels lower than 5 pg/ml have approximately 7–9% lower BMD compared to women who have estradiol levels of 10–25 pg/ml. Furthermore, women with the lowest levels of estradiol have a significantly higher risk of hip and spine fractures compared to those with higher levels. Recent observations in studies of low-dosage (one-half and one-quarter the current standard dosages) estrogen preparations have shown that they have positive effects on BMD and bone turnover, thus suggesting that they could also reduce fracture risk, although this occurrence remains unproven. There are indications, from other agents that a large part of the fracture reduction is linked to the inhibition of bone remodeling, rather than to an improvement in BMD. Data from randomized clinical trials (RCTs) clearly show that low estrogen doses (1 mg of oral estradiol, 0.3 mg/day of CEE), administered alone or in association with a lower-dose progestin are able to reduce markers of bone turnover, and increase BMD at different skeletal sites (lumbar spine, hip, the radius and the total body BMD). Low-dose HRT ensures similar effectiveness on hot flushes as standard-dose HRT, combined, however, with significantly fewer undesirable side-effects. An ultra-low-dose transdermal estradiol product (14 μg 17β-estradiol/day) has recently been approved for the prevention of osteoporosis by the US Food and Drug Administration. Confirmation from fracture studies is, however, required with these lower doses of estrogens. Low-dose estrogen preparations could be an approach to step down from a standard HRT dose, or be used by women who have discontinued HRT. In addition, ultra-low-dose estradiol could be appropriate as a new start for women 60 years and older who might benefit from modest increases in estradiol up to levels sufficient for their age to preserve skeletal integrity, without significant endometrial stimulation, possibly leading to bleeding. Safety data suggest that such doses may not be able to stimulate endometrium and thus could be used without the daily addition of a progestin. In conclusion, the physiological concentration of estradiol around age 60 years and older is 7–10 pg/ml, but many women have lower levels. Restoration of their estradiol level to this postmenopausal physiological level may be indicated.

Side-effects such as deep venous thrombosis and stroke are also dose-dependent. There are observational studies suggesting that the use of a low-dose estrogen would result in preserved

reduction of myocardial infarction without an increase in stroke.

ANDROGENS AND BONE

Androgen therapy is increasingly employed in women, either before or after menopause. However, the androgen effects on bone metabolism and bone mineral maintenence are not fully documented and data on humans are largely anecdotal. The synthetic androgen 17α-methyl testosterone is the most widely used of these androgens. Animal and *in vitro* studies demonstrate that 17α-methyl testosterone is a powerful bone-sparing agent in the ovariectomized mouse model. The mechanism of action appears to be mediated not only by androgenic metabolites, but also via estrogenic metabolites.

PROGESTINS AND BONE

When used in the premenopausal woman, DMPA administration is associated with loss of bone, especially in adolescent girls due to suppression of ovarian function. The potential negative effect of DMPA use on bone density raises particular apprehension in adolescents. The long-term consequences of slowing or reversing bone mass acquisition during early adolescence could be greater than in adult women who have reached their peak bone mass. Progestin-only oral contraceptives will prevent bone loss associated with breast feeding. In postmenopausal women, medroxyprogesterone acetate, megestrol, drospirenone, dydrogesterone and trimegestone have not been shown to have significant effects on bone density, although studies are limited. Levonorgestrel and norethisterone/norethindrone may have independent positive effects on bone alone or when combined with estrogen in postmenopausal women. The effects of these compounds are thought to be related to their partial androgenic action. Progesterone by itself has no demonstrable effects on bone.

SERMS

Selective estrogen receptor modulators (SERMs) act by binding to both the α and β estrogen receptors and act as antiresorptive agents in bone, although their mechanism of action is not fully understood. Their tissue-specific selectivity of action is not related to binding to either receptor isotype, but to recruitment of tissue-specific coactivators and binding to non-estrogen-responsive element (ERE) sequences, probably the result of unique conformations of the ligand–ER complex. The activation of gene expression in bone cells through ERα and ERβ differs from that induced by estradiol, as it differs for different SERMs. Raloxifene is the first compound of this class clinically available for the prevention and treatment of osteoporosis. Raloxifene has been shown to increase BMD at the spine and the hip up to 7 years, and significantly decreases the incidence of vertebral fracture both in women with or without previous vertebral fracture. Raloxifene also appears to reduce in postmenopausal women with osteoporosis the risk of invasive breast cancer over 8 years of treatment, although studies are continuing. The risk of deep venous thrombosis induced by SERMs is similar to that linked to oral estrogen products. Raloxifene administration has been associated with an increased risk of leg cramps and hot flushes. Other SERMs currently in clinical development have also been shown to increase BMD at the lumbar spine and hip.

BISPHOSPHONATES

Bisphosphonates exert protective effects in animal models of osteoporosis and in humans. Bisphosphonates decrease bone resorption and bone turnover, increase BMD and decrease the incidence of vertebral and non-vertebral fractures, including those of the hip in postmenopausal women with osteoporosis. The marked suppression of bone turnover with bisphosphonates is evident after 3 months of treatment and is sustained over the treatment period. Available long-term data indicate that bisphosphonates are safe. Reversal of the effects of bisphosphonates on bone turnover and BMD after cessation of treatment is slow and may not be the same for all bisphosphonates. Once-weekly administration of certain bisphosphonates improved adherence to treatment. A new regimen with once-monthly oral bisphosphonate administration has been developed, and another with once-yearly intravenous administration is under development. Potential differences among bisphosphonates need to be further investigated. A possible association between avascular necrosis of the jaws, inflammatory ocular side-effects, and the use of bisphosphonates has been reported. In addition, oral amino derivatives may induce serious dose-related gastrointestinal lesions, with the sporadic appearance of erosive esophagitis. In single cases, the use of bisphosphonates has been correlated

with irritative reactions at the skin, peritoneum and pericardium.

PHYTOESTROGENS

Phytoestrogens are non-steroidal compounds with putative estrogenic and anti-estrogenic properties. Studies investigating the actions of phytoestrogens on BMD or bone turnover have been carried out in populations of small size, are of short duration, and are largely contradictory, making them inconclusive. Studies have not shown fracture efficacy.

ANABOLIC AGENTS

Parathyroid hormone (PTH) administered daily increases bone formation. PTH administration determines an increase of both markers of bone resorption and formation peaking after 6–12 months, and declining thereafter, even if treatment is continued. PTH treatment induces a marked thickening of trabeculae, followed by increased trabecular connectivity. PTH increases cortical bone remodelling and increases endocortical bone formation and periosteal bone formation, the latter increasing bone size. This increase in bone size results in increased bone strength. When PTH is discontinued, BMD decreases, but is maintained if bisphosphonate treatment is initiated, thus suggesting that antiresorptive agents are required when PTH is discontinued. HRT does not antagonize the action of PTH, as estimated by DXA. On the contrary, a prospective study showed an additive effect of a combination of HRT and PTH on BMD in postmenopausal women. However, the combined administration of a bisphosphonate (data on alendronate only) seems to blunt the effects of PTH treatment on BMD and turnover. However, there are no data on fracture prevention. There is a need for data on fracture end-point studies with PTH in comparison to other agents, and in combination with the other available antiresorptive agents. Available data coming from RCTs indicate a reduction of vertebral fracture and non-vertebral fracture with 1–34 h PTH (teriparatide), and a decrease in vertebral fracture for 1–84 h PTH.

TIBOLONE

Tibolone is metabolized to at least two active metabolites with tissue-selective effects. This compound has been defined as a selective tissue estrogenic activity regulator (STEAR). Tibolone action on the bone is mainly mediated through the estrogen receptors. Tibolone has generally been shown to induce effects on BMD similar to those induced by standard estrogen–progestin combinations. The effect on BMD at the spine and the hip is dose-dependent, as is the effect on biochemical markers of bone remodeling. There are no data available on the effect on BMD after discontinuation. A study with fracture as a primary end-point is ongoing. Data from the Million Women Study indicate a 32% reduction in fracture risk in women taking tibolone for a mean duration of 4.8 years. Tibolone shifts body mass composition, enhancing lean body mass and decreasing fat tissue. Tibolone increases hand grip strength and knee extension strength. Effects on breast cancer, cardiovascular risk and endometrial safety are currently being evaluated in large, long-term studies.

STRONTIUM RANELATE

Strontium ranelate is a new agent that reduces osteoclast activity in animal models. In addition, preclinical data indicate an increase in the replication of pre-osteoblasts and a stimulation of collagen synthesis. This would possibly rebalance bone turnover in favor of bone formation. However, the mechanism of action of this compound is not yet fully elucidated. Strontium ranelate increases BMD and bone strength in animals. In the SOTI study, strontium ranelate (2 g/day) almost halves the risk of both radiological and clinical vertebral fracture risk in patients with a previous vertebral fracture, over 3 years of treatment. No effect on non-vertebral fractures was demonstrated in this study, which was not powered to assess non-vertebral fracture risk. Data presented in abstract form show antifracture efficacy against non-vertebral and hip fractures in elderly patients as well as in osteopenic patients. Strontium ranelate increases apparent BMD at the lumbar spine and femoral neck linearly throughout the duration of treatment. The compound is generally well tolerated, especially at the upper gastrointestinal level, with the exclusion of an increased incidence of nausea and diarrhea. In addition, the compound can cause an increased incidence of venous thrombosis, in the same manner as HRT and raloxifene.

CONCLUSION

Osteoporosis and fragility fractures show a steep age-related increase and are major causes of morbidity and mortality in elderly populations. The goal of osteoporosis management is the

prevention of fracture. Physicians should consider a range of treatment options for osteoporosis. Women should be encouraged to have adequate intake of calcium and vitamin D, good nutrition and exercise, and avoidance of negative lifestyle habits (smoking, alcohol). Both a normal exposure to estrogen during the woman's reproductive life and exercise contribute to optimal achievement and maintenance of genetically determined peak bone mass. For early postmenopausal women, adequate calcium and vitamin D intake alone is not sufficient to maintain bone mass. Although the main indication for HRT use in postmenopausal women remains the relief of menopausal symptoms, treatment significantly decreases bone loss and risk of osteoporotic fractures. Due to the individual balance between possible risks and benefits, an appropriate HRT should be given only after a complete individual clinical evaluation. Future research is needed to identify new formulations for HRT and to reduce or eliminate its potential risks. Established osteoporosis can better benefit by specific treatments with bisphosphonates (alendronate or risedronate), SERMS (raloxifene), or, in more severe and selected cases, with anabolic agents (PTH and strontium ranelate).

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