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The Role of Hormone Replacement Therapy (HRT) and Tibolone in the Prevention and Treatment of Postmenopausal Osteoporosis

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1. Introduction

Life expectancy has increased considerably in recent decades thanks to the improvement of measures for health protection and disease prevention as well as improvements in the quality of health systems. While in the middle of last century the average life expectancy of a woman was about 50 years, today there are over 350 million women older than 60. Furthermore, from the perspective of developed countries, postmenopause is a stage that spans more than one third of the life of a woman. That is why the research on the pathophysiology and treatment of menopause has become necessary and important.

The decrease in sex steroid production by the ovary that occurs in perimenopause and menopause is associated with a rapid loss of bone mass due to increased resorption. In the past two decades, multiple observational studies have noted the beneficial effect of hormone replacement therapy (HRT) in postmenopausal women's health, based mainly on the relief of symptoms associated with estrogen deprivation such as vasomotor and genitourinary symptoms. These studies also indicated a preventive effect on aging-related diseases such as osteoporosis. Estrogens have been shown to be effective in increasing bone mineral density (BMD) and prevent fractures, but information on side effects from long use has reduced their use for the treatment of osteoporosis (Tamborini & Ruiz, 2004).

Tibolone is a synthetic steroid used in the treatment of postmenopausal symptoms and decreased libido that has an estrogen agonist effect on bone.

Although the intimate mechanisms of control of bone remodelling are not still completely known, we do have enough information to say that estrogens have a role in the homeostasis of the skeleton, which is why their decline is associated with reduced bone mass, impaired in the microarchitecture and increased risk of fracture.

The following chapter discusses the role of estrogen therapy and tibolone in the prevention and treatment of postmenopausal osteoporosis.

2. Literature search

Studies with English language abstracts identified in MEDLINE, HealthSTAR, and Cochrane Library databases from 1990 to 2010 are reviewed. Reference lists of key articles

and meta-analyses have also been reviewed. We used all published studies of HRT and tibolone if they contained a comparison group of HRT nonusers and reported data relating to HRT use and clinical outcomes of interest. Studies have been excluded if the population was selected according to prior events or presence of conditions associated with higher risks for targeted outcomes.

3. Hormone replacement therapy (HRT)

3.1 Effect of sex steroids on bone

The possible adverse effects of estrogen deficiency on the bone metabolism are known since the 40 decade (Albright, 1940, 1947). The first studies confirmed a higher rate of oophorectomies among osteoporotic women than in general population, and that the surgical treatment had place earlier than the age for natural menopause. These studies also showed that the negative balance of osteoporosis was normalized with the administration of estrogen. Thus it was postulated that estrogen somehow stimulated the action of osteoblasts, which is now accepted as one of the potential mechanisms of action of estrogen on bone mass (Lindsay, 1995).

Oophorectomized and postmenopausal women have decreased circulating levels of other steroids in addition to estrogens (Lindsay, 1995). In women, circulating androgen concentrations are in the order of nanomoles or micromoles while estrogens do so at concentrations on the order of picomoles. The concept of androgen deficiency syndrome is relatively old, but in recent years there has been a renewed interest in the subject.

The premenopausal ovary produces significant amounts of progesterone during the luteal phase of each cycle. Progesterone appears to act directly on bone turnover and may play a role in the relationship between bone resorption and new bone formation (Prior, 1990).

Although we do not yet fully understand the bone turnover process or control, there is sufficient information to conclude that sex steroids play an important role in skeletal homeostasis. The lack of secretion of ovarian sex steroids results in a net loss of bone tissue. When given to women with deficiency of sex steroids, these hormones reverse many of the effects related to loss of ovarian function. Therefore, it has been suggested that postmenopausal women should take HRT long term to prevent these negative effects, including osteoporosis and fractures.

3.1.1 Estrogens and bone

With the decrease in estrogen levels that occurs at menopause, there is an increase of bone remodelling with a loss of balance between formation/resorption, predominantly the latter. HRT decreases the elevated levels of resorption to those before menopause. Bone cells have estrogen receptors (Vidal et al., 1999). The most important action of estrogen on bone is to inhibit bone resorption. This action indirectly regulates the production of cytokines and growth factors in osteoblasts. Since there are estrogen receptors in osteoclasts, may also be logical to think that there is a direct action. Inhibition of bone resorption by estrogen is probably the conclusion of inducing apoptosis in osteoclasts (Kameda et al., 1997), this action being probably due to increased TGF- β . Estrogens have shown to increase the proliferation of osteoblasts and the expression of different genes that encode enzymes, bone matrix proteins, transcription factors, hormone receptors, growth factors and cytokines. However, these results have varied depending on crop models (Manolagas, 2000). Estrogens

have also shown the ability to inhibit TRAP expression or inhibit certain steps in the RANK-JNK signal (Srivastava et al., 2001).

The current idea of the action of estrogen is that it is through different pathways. There is, first, an antiapoptotic effect of estradiol on osteoblasts and osteocytes due to rapid non-genomic action (Kousteni et al., 2001). It has succeeded in synthesizing a ligand called ESTREN that act exclusively through this channel, and theoretically could have the same effect as estrogens on bone without the genomic consequences of these. This model has been named to a new class of pharmacological agents called ANGELS (Activators of NonGenotropics Estrogens Like Signalins), and there would be another apoptotic action on osteoclasts (Manolagas et al., 1995). The actions of estrogen on bone cells, are inhibition of bone resorption by decreasing the synthesis or response to interleukins such as IL-6, IL-1 and TNF- α with less differentiation of precursor cells into osteoclasts by increasing IL-4. Among other effects, estrogens decrease lytic enzyme activity of osteoclasts and produce changes in growth factors insulin-like IGF-I, IGF-II and interferon types α , β and γ . The effect of estrogen is mediated in part by growth factors and interleukins such as IL-6, which is a potent stimulator of bone resorption by blocking estrogen synthesis by osteoblasts. Estrogen may also antagonize the interleukin receptors. The apoptosis of osteoclasts is also regulated by estrogens. Faced with reduced levels of estrogen, osteoclasts live longer and have greater capacity of absorption. Estrogens regulate tumor growth factor system associated with the RANK/RANK-L resulting in a decrease in the activity of osteoclasts. They also stimulate the production of osteoprotegerin (OPG) by osteoblasts. Thus, the presence of estrogen prevents binding of RANK-L to RANK resulting in inhibition of the formation, differentiation and survival of osteoclasts (Eghbali-Fatourehchi et al., 2003). In response to increased bone resorption, it exists an increase in bone formation, creating a high turnover that leads to bone loss and deterioration in the microarchitecture. In the first 5 years since menopause, a substantial disruption of the trabecular architecture can be observed, demonstrated by the analysis of iliac crest biopsies using computed microtomography techniques (Issever et al., 2002). Once broken the continuity of a trabecula, we can increase thickness, but will not get a new connectivity.

We could conclude that steroid hormones are involved with a complex action system clearly influencing the bone marrow regulation. They are part of the mechanism regulating RANK-RANKL-osteoprotegerin, whose predominant action is bone resorption, and it is performed through genomic and nongenomic actions. In addition, estrogens also act through indirect mechanisms of action such as reducing the sensitivity of the bone to resorptive effects of parathyroid hormone (PTH), acting as antiresorptive agents. They produce an initial decrease in serum calcium and, therefore, a transient increase in PTH and calcitonin secondary modifications. Due to the increase in α 1-hydroxylase activity and phosphorus decreased, they produce an increase in hydroxyvitamin D3. Estrogens also increase the intestinal absorption and decrease renal excretion of calcium, and have direct effects on the secretion of PTH and calcitonin.

3.1.2 Androgens and bone

Androgens have a profound effect on bone and muscle physiology in women. Both for their intrinsic activity as for their conversion to estrogens, androgens have a modulatory effect on bone remodelling cycle. The androgen deficiency, like estrogen, may facilitate the development of osteoporosis. Androgenic anabolic steroids are sometimes used in the

treatment of osteoporosis but their use is limited by side effects of virilizing type. Evidence of the effects of androgens on bone mass comes from women with polycystic ovary syndrome or steroid-secreting ovarian tumors in which there is an increase in bone mineral density (Gregoriou et al., 2000). On the other hand, we know that the combination of androgens and estrogens for hormone replacement therapy in menopausal women is associated with increased bone mass above that observed with estrogen alone (Castelo-Branco et al., 2000). A cohort study developed to assess BMD in postmenopausal women using estradiol and testosterone hormonal implants comparing to that of patients without hormonal therapy, confirmed that BMD variance between the groups in the period of 1 year was significantly different, and concluded that the combination of estradiol and testosterone promoted bone protection in postmenopausal women (Britto et al., 2011).

Androgen receptors have been identified in osteoblasts, osteoclasts and osteocytes. Androgens stimulate the proliferation and differentiation of osteoblasts, stimulate the synthesis of extracellular matrix proteins, and stimulate mineralization. These steroids affect the functionality of bone cells through their effects on local factors that control bone cell microenvironment, have proapoptotic effects on osteoblasts and osteocytes, and increase strength and muscle. This ultimately leads to increased physical activity and this in turn to activation of bone formation by stimulation of the osteocytes (Notelovitz, 2002).

3.1.3 Progestins and bone

The role of progestins in preventing bone loss is less studied. However, there is general consensus that 19-norderived progestins with androgenic properties, such as norethindrone and norethindrone acetate, at higher doses than necessary for hormone replacement therapy, have beneficial effects on bone density.

Thus, for example, progestins can increase bone density in women with postmenopausal osteoporosis and alleviate the effects of estrogen deficiency in young women treated with GnRH agonists. However, data on the effects of progestins C21 derivatives such as medroxyprogesterone acetate are mixed. It has been reported that, in premenopausal women with luteal defects, medroxyprogesterone acetate (10mg/day, 10 days/cycle) can significantly increase vertebral bone density (Prior et al., 1994). In contrast, administration of 20 mg/day of this progestin could not stop the loss of vertebral bone density in postmenopausal women (Gallagher et al., 1991). In addition, premenopausal women using depot medroxyprogesterone acetate as a contraceptive or taking oral doses (50mg/day) of this progestin on gynecologic pathology have varying significantly decreased bone density (Cundy et al., 1996). The different findings in these studies clearly indicate that the effects of medroxyprogesterone acetate on bone may vary according to the dose administered and the estrogen status of the user. When administered in doses sufficient to induce hypogonadism, medroxyprogesterone acetate is associated with a rapid and significant loss of bone mineral density at the lumbar level. This bone loss is the result of estrogen deficiency and occurs despite an increase in body weight, although it seems partially reversible.

Clinical trials have shown that postmenopausal women receiving norethindrone acetate associated with estrogen show a significant increase in bone mineral density compared with patients treated only with estrogen (Speroff et al., 1996). In contrast, neither the micronized progesterone nor medroxyprogesterone acetate contributed significantly to the positive effects of estrogen on bone (PEPI Trial, 1996).

Progestins influence the bone formation within the bone remodelling process (Sootweg et al., 1992). Receptors for progesterone have been identified in human osteoblasts and

osteoclasts. However, the effects of progestagens on bone are not clear. A study about the activity of a "pure progestogen" on human osteogenic osteosarcoma cells did not observe any effect on cell proliferation when progestins were added alone to culture, but after the combined administration with 17β -estradiol, a strong action synergistically was confirmed on the proliferation of osteosarcoma cells. Moreover, other studies show that some synthetic progestins produce their effects through the activation of the estrogen receptor (Jordan et al., 1993).

3.2 HRT - Type, dose

Almost all information about the effects of estrogens on the bone come from the use of estradiol and conjugated equine estrogens (CEE). Isolated estrone also has a beneficial effect on bone, and it seems that estriol does not have an obvious role in skeletal production in postmenopausal women.

The route of administration, oral or transdermal, does not imply differences in the beneficial effect on bone (Hillard et al., 1994). The estrogenic pulsotherapy has also shown a normalization of the markers of resorption and formation to premenopausal values after 3 months of treatment at doses of 300 mcg/day. The increase in BMD at this dose is similar to that found with 50 mcg/day of transdermal 17-beta-estradiol, providing significant differences in the measurement of BMD over baseline in spine and hip in the evaluation performed after 56 weeks treatment (Palacios et al., 2002). In women with uterus is necessary to administer a progestin to counteract endometrial proliferation induced by estrogen. The dosing regimen of progestin does not influence the beneficial effect of estrogen on the bone so the choice is given by the characteristics of women.

Significant BMD improvements have also been noted with systemic estrogen doses delivered via a vaginal ring. In an randomized controlled trial of 174 postmenopausal women younger than age 65, daily doses of 0.05 and 0.1 mg of estradiol acetate delivered via the ring significantly increased hip BMD (1.7% and 1.8%, respectively) and lumbar spine BMD (2.7% and 3.3%) compared with baseline (Al-Azzawi et al., 2005).

It has been established that a dose range of estradiol between 40 and 50 pg/ml is enough to increase BMD, although a safe level is 60 pg/ml. A dose-response study indicated that daily doses would have more generalizable effect: 0.625 mg of conjugated equine estrogens (CEE), or their equivalents: 0.05 mg of transdermal 17-beta-estradiol or 15 mcg of oral ethinyl estradiol (EE). The standard dose preserves bone mass in at least 80% of postmenopausal women (Table 1). These doses of estrogen and progestogen can induce side effects in both regimes (continuous and sequential), being the most frequent irregular bleeding and breast tenderness. To minimize these undesirable effects, the use of low doses has shown to be also effective in improving menopausal symptoms and quality of life and prevent or reverse bone loss in postmenopausal women (Delmas et al., 2000).

The loss of bone mass and the incidence of vertebral and hip fractures are inversely related to circulating estrogen levels. It has been confirmed that in elderly women estrogen circulating levels of 10 pg/ml improves both BMD and fracture rate. Any increase in estrogen levels has a beneficial effect especially in older women, even when the ultra-low dose is given (25% of the standard dose) (Simon & Snabe, 2007). Neither age nor initial BMD do seem to affect the effectiveness of patterns of low-dose. The effect of low doses of estrogen in women with low BMD has been analyzed in a randomized, double-blind, placebo-controlled trial, using CEE 0.3 mg/day and 2.5 mg/day of progesterone in women over 65 years and low BMD, in which after 3.5 years of follow up, an increase in vertebral

BMD of 5% and 1.6% in hip has been confirmed, with significant increase in total skeletal and forearm (Recker et al., 1999).

	Low dose	Standard dose	High dose
Estradiol valerate	1 mg	2 mg	3 mg
Transdermal Estradiol	25-37,5 mcg	50 mcg	75-100 mcg
CEE	0,3 mg	0,625 mg	1,25 mg
Estrogen pulsotherapy		300 mcg	
Tibolone	1,25 mg	2,5 mg	

Table 1. Estrogen dose used in HRT

The HOPE study (Women's Health Osteoporosis Progestin Estrogen) (Lindsay et al., 2005), evaluates the effectiveness of low and moderate doses, 0.45 mg/day and 0.30 mg/day alone or combined CEE on vasomotor symptoms, genital atrophy, metabolism, endometrial response and bone density in 2805 women aged 40-65 years treated for 2 years. The results confirmed an improvement in vasomotor symptoms and genital atrophy with low doses comparable to improvement obtained with standard doses, with less bleeding and the beneficial effect on lipid profile. Bone turnover markers such as osteocalcin and N-telopeptide of type I collagen were significantly reduced compared to baseline in the treatment group while no changes were found in the placebo group. BMD increased in both vertebral and hip evaluation. Another study showed similar results (Gambacciani et al., 2001), suggesting that low doses of HRT were able to reduce climacteric symptoms resulting in a decrease in bone turnover and protect against bone loss. The same study showed significant increases in BMD of $2.72 \pm 0.3\%$ in women treated while not receiving estrogen therapy had a loss in BMD of $7.9 \pm 0.8\%$.

In an open trial healthy postmenopausal women received for 2 years a low-dose continuous combined HRT containing 1mg estradiol plus 0.5 mg norethisterone acetate, or 0.5 mg of 17-estradiol and 0.25 mg of norethisterone acetate (ultra low dose) along with 1000 mg of calcium per day. The study confirmed that low-dose-HRT and Ultra-low-dose-HRT can alleviate subjective symptoms providing an effective protection against the postmenopausal decrease of BMD (Gambacciani et al., 2008).

Despite the large amount of literature about the beneficial effect of low doses in the bone, there are no studies linking low doses of HRT to the prevention of fractures.

3.3 HRT limitations

Women who may benefit from HRT are those showing climacteric symptoms and also osteoporosis risk. There is general consensus with regard to women with premature menopause should be treated until at least the theoretical age of menopause.

At present there are few absolute contraindications to HRT, being as such pregnancy, vaginal bleeding not studied, active hepatitis, active venous thromboembolism and hormone-specific cancer history.

However, there are circumstances that require careful consideration and consensus with the patient and the presence of pathological conditions such as lupus or endometriosis. Women treated with thyroid hormones or coumarin may need a dose adjustment.

3.4 Duration of HRT

The reduction of bone loss will last as long as you keep the estrogen therapy. When you cease treatment, bone loss returns to pretreatment rate, therefore, to obtain maximum benefit, treatment should begin as early after menopause and stay as long as possible. The optimal duration of treatment has not been fully established, but the results from the Women's Health Initiative (WHI) suggest that estrogen therapy should take the lowest dose for the shortest possible time but then we know that short treatment will not positively affect bone mass.

Analyzing the evolution of bone mass in climacteric women, it has been shown that during the 5 years after the time of onset of menopause the bone loss is equivalent to 60% of what is lost along the climacteric stage; it is at this time when occur the disruption of the trabecular architecture. Once the trabeculae are broken, they will not reconnect again, which would lose bone strength despite getting increases in BMD. Thus, estrogen therapy, at least theoretically, should start as early and stay at least that long in women with natural menopause and up to 55 years in women with early menopause. This would ensure that the loss of bone mass will be delayed, and it will have a positive impact on the possibility of developing osteoporosis and hence on the quality of life.

The use of combined HRT has been associated with an increased risk of venous thromboembolism or coronary artery disease (after a year of use), acute stroke (after 3 years of use), breast cancer (after 5 years of use) and gallbladder disease. Long use of estrogen alone was associated with increased stroke and gallbladder disease. According to recent re-analysis, age is a determining factor in establishing the risks, resulting in very young women (50-59 years) a very low absolute risk (Farquhar et al., 2005).

However, even if treatment is started long after menopause, there are substantial gains in bone mass. In the Framingham study, elderly women with a mean age of 76 years and 7 years since menopause had a significant increase in BMD compared to nonusers, although the effect was less marked in women over 75 years (Felson et al., 1993).

3.5 Estrogen and progestogen combined treatment

The association of progestin does not counteract the beneficial effect of estrogen on bone. It has been reported that derivatives of 19-norethisterone are effective in preventing bone loss even when associated with low estrogen dose (Christiansen & Riis, 1990).

Some studies suggest a greater benefit by associating progestin, while others have failed to show this superiority to estrogen alone. It is possible that the effect has to do with the type of progestin used and it seems that this superior effect is limited exclusively to the administration of compounds of the family of 19-norethisterone. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, multicenter randomized controlled trial of 875 postmenopausal women with an average age of 56 years, which after 3 years of follow-up BMD increases are seen in lumbar spine (3-5%) and hip (1.7%) with no differences between groups treated with estrogen alone or combined with progestin (The Writing Group of the PEPI Trial, 1996).

The BMD status before the start of hormonal treatment will not influence the effect of it. It has been shown that estrogen administered with and without progestin increases bone mass in healthy women as well and even in osteopenic women with osteoporosis and fractures (established osteoporosis) (Adachi et al., 1997).

3.6 Estrogen effect on BMD

Estrogen administration, associated or not with progestin, has been shown highly effective in the prevention of bone loss in both natural and surgical menopause. It has been shown how treatment with estrogen and progestin can not only maintain but also increase BMD in postmenopausal women, compared to the decline experienced by the placebo group (Christiansen et al., 1981). More than 50 randomized, placebo-controlled studies have shown that estrogen alone or combined with progestin increases BMD, with values ranging from 4-6% in spine and 2-3% in hip, justifying the difference by the different rate of remodelling of these places (Wells et al., 2002).

Estrogen therapy also appears to be effective in patients with established osteoporosis. Women with low bone mass generally have higher turnover and this turnover increases with age. So the best response to estrogen observed in older women or in women with low BMD might result from the suppression of increased bone turnover associated with improvement in the bioavailability of calcium due to improved intestinal absorption of vitamin D. Using CEE double dose (1.2 mg/day) for one year, a double-blind, placebo-controlled study in 21 osteoporotic women showed an improvement in BMD, more marked in the lumbar spine than in femoral neck and an increase in intestinal absorption of calcium (Citivelli et al., 1988). The authors suggest that the beneficial effect is due to inhibition of bone resorption associated with an increased secretion of calcitonin.

A trial of 50 women aged over 75 years and "physical frailty", of which 90% were osteopenic or osteoporotic, who received 9 months of CEE 0.625 mg/day, showed an increase in lumbar spine BMD of 4, 3% (Villareal et al., 2001). The increase was 1.7% in total hip and 2.3% in trochanter 2.3%, these results being similar to those observed in previous studies.

4. Fracture prevention and HRT

Randomized, case control and cohort studies indicate a potential effect of HRT in the prevention of vertebral, hip and forearm fractures in osteoporotic populations.

A cohort study (Cauley et al., 1995) conducted in 9706 women aged over 65 years, and whose main objective was the evaluation of appendicular bone fractures in women treated with HRT, showed that current users who started treatment within 5 years after menopause decreased the risk of wrist fractures (RR = 0.39, 95% CI = 0.24 to 0.64), hip fractures (RR = 0.60, 95% CI = 0.36 to 1.02) and other nonvertebral fractures (RR = 0.66, 95% CI = 0.54 to 0.80) when compared with nonusers of estrogen. HRT is more effective in reducing fracture risk if you start the five years following menopause, and if their use continues for more than 10 years.

A randomized controlled trial of 4 years of follow up in 464 recently menopausal women (Komulainen et al., 1998), treated with 2 mg estradiol valerate and 1 mg cyproterone acetate daily, demonstrated a reduction in risk with RR 0.29 (0.10 to 0.90 CI).

A meta-analysis (Grady et al., 1992) concluded that there is a 25% reduction in risk of hip fracture in postmenopausal women who used HRT. Subsequently, other published meta-analysis (Torgerson & Bell-Syer, 2001) finds that the use of estrogen alone or combined with progestin for at least one year reduces the risk of nonvertebral fracture (RR 0.73, 95% CI: 0.56-0.94, P = 0.02). In women over 60 years, the effect was less marked (RR 0.88, 95% CI 0.71 to 1.08, p = 0.22).

In women with established osteoporosis (one or more prior vertebral fractures) has also shown a positive effect of HRT in preventing fractures. In a randomized study (Gonnelli et al., 1997), double-blind, placebo-controlled trial conducted in 75 women who were given

treatment with 0.1 mg of 17-beta-estradiol transdermal and oral medroxyprogesterone acetate, 11 days per month, analyzing the BMD, markers of bone turnover and histomorphometric study of iliac crest biopsy, demonstrated a positive effect of estrogen on the parameters analyzed resulting in a reduction given the frequency of vertebral fracture in the treated group versus placebo (RR = 0.39, 95% CI = 0.16-0.95). It can be inferred that the number needed to treat (NNT) is 7 women/year to reduce vertebral fracture.

However, other studies have shown no differences between the treatment groups and placebo. The Heart and Estrogen/Progestin Replacement Study (HERS) included 584 women with coronary disease, with an age range of 44-79 years who were treated with 0.625 mg/day CEE and 2.5 mg/day medroxyprogesterone acetate were compared with a placebo group in a follow-up period of 45 months. In this study, there was no beneficial effect of treatment compared with placebo in hip fracture rates or overall rates of fracture in such women not selected for risk factors for osteoporosis and had a low risk of osteoporosis. After 3 years, they published another analysis of these data, reaching the same results (Cauley et al., 2001).

A review of 57 prospective cohort and retrospective case-control studies noted the limited evidence to confirm the anti-fracture efficacy in women who are on hormone replacement therapy (Reginster et al., 2000). Another review (Beral et al., 2002) of 4 randomized studies that included 20,000 women followed an average of 4.9 years, estimated a reduction of fractured neck of femur in 17/1000 users aged 50-59 years, this reduction rising to 5.5/1000 in older women, 60-69 years.

The highest level of evidence on the effect of HRT on fracture was obtained from the Women's Health Initiative (WHI) (Rossouw et al., 2002). This study was carried out in order to assess the main risks and benefits of the combined hormone preparation most commonly used in the United States, 0.625 mg CEE plus 2.5 mg of medroxyprogesterone acetate to health of postmenopausal women. The study included 8506 women in the treatment group and 8102 in the placebo group, with a follow-up time of 5.2 years. This study (The WHI Steering Committee, 2004) shows unequivocally that estrogen with or without progesterone reduce the risk of hip fracture, vertebral and other fractures, the only treatment that has demonstrated this effect in osteoporotic woman, regardless personal risk for fracture.

The reduction observed was similar to that reported in previous observational studies and meta-analysis. The results in terms of fractures indicated that estrogen alone or in combination with progestin reduces the rate of hip fractures and clinical vertebral fractures by one third compared with placebo. Reductions in other osteoporotic fractures and total fractures were also statistically significant.

All types of therapy, route of application and guidelines-beneficial as indicated in the results of a prospective cohort study with more than one million women (Million Women Study Collaborators, 2003), HRT users had significantly more low risk of fracture than nonusers (RR = 0.62, 95% CI = 0.58-0.66).

A meta-analysis (Wells et al., 2002) indicates that BMD measurements are similar when comparing studies of prevention or treatment, estrogen alone or estrogen plus progestin, transdermal or oral, and different types of progestins. The duration and doses of treatment affect the dose effect on BMD.

HRT has a tendency to reduce the risk of vertebral (RR = 0.66, 95% CI = 0.411 to 0.7) and non-vertebral fracture (RR = 0.87, 95% CI = 0.711 to 0.8). The protection against fractures require longer use of HRT. Cross-sectional studies indicate that for hip fracture prevention. Treatment duration should be between 5 and 10 years (Kiel et al., 1987). Swedish Hip

Fracture In Study, a case-control study (Michaëlsson, 1998) on 1327 women aged 50-81 years who had suffered a hip fracture and 3262 controls, current users of HRT have a substantial decrease in fracture risk compared to older users. The RR of hip fracture was 0.35 (95% CI = 0.24 to 0.53) versus 0.76 (95% CI = 0.57 to 1.01). These data indicate that HRT is effective after menopause to maintain protection against fracture but only recent use was associated with optimal protection, since after 5 years without the protective effect of HRT use drops significantly. The beneficial effect is displayed even when treatment is started long after menopause. Thus, in current users, the initiation of therapy nine or more years after menopause provides a reduced risk of hip fracture are equivalent to those women who started early after menopause but who discontinued treatment.

5. Tibolone

Tibolone is a synthetic steroid derived from 19-nortestosterone, structurally similar to norethisterone and norethindrol, first generation nor-derived progestagens. It is described as a selective tissue estrogenic activity regulator (STEAR) because it has specific effects in different tissues after conversion to three active metabolites following oral ingestion (Kenemans, 2004). It has estrogenic, progestogenic and androgenic effects. Estrogenic metabolites act centrally, on the vagina and other tissues and, together with androgenic metabolites, relieve hot flushes and improve energy and sexual well-being (Nathorst-Booszz, & Hammar, 1997; Nijland et al., 2008). On bone, tibolone has estrogenic effect acting on the estrogenic receptor (Modelska & Cummings, 2002).

5.1 Effects on bone

Preclinical studies indicate that tibolone prevents bone loss (axial and appendicular), caused by oophorectomy or low calcium intake in both young and mature rats and in rats with established osteopenia (Yoshitake et al, 1999). Experimental data conclude that tibolone is as effective as estrogen to prevent bone loss secondary to the decline of ovarian function, observed even in osteopenic rats an increase in BMD and femoral and vertebral bone strength, similar to estrogen (Berning et al., 2001).

In humans, the action of tibolone on the skeletal system is also largely mediated by estrogen receptor binding and stimulation of it by some of its metabolites.

5.2 Tibolone and bone turnover markers

In general, studies show that tibolone decreases bone turnover (decrease in the formation and resorption) similar to that obtained with both estrogen in postmenopausal women with normal BMD and in the osteoporotic patient and, returning the process of turnover the existing levels in premenopausal women (Moore, 1999).

Analyzing the effect of tibolone on BMD, it is shown to be capable of inhibiting the decrease and increase BMD compared with placebo or untreated control in both spontaneous and surgical menopause. Like estrogen, we analyzed the results of the use of low doses of tibolone. Low doses of 1.25 mg/day have an effect on the spine and hip similar to that found with standard doses of 2.5 mg/day, in elderly women and women younger postmenopausal (Gallagher et al., 2001). It has proven effective in maintaining BMD in menopausal women at standard doses.

5.3 Tibolone and prevention of fractures

Tibolone (1.25 and 2.5 mg, respectively) increased lumbar and hip bone mineral density to a significantly greater extent than placebo in women with and without osteoporosis (Kenemans et al., 2009), as it was shown with a dose of 1.25 mg/day compared with raloxifene in a study of older osteopenic women (mean age 66 years) (Delmas et al., 2008). The lower dose also reduced the risk of vertebral and non-vertebral fractures in older osteoporotic women (mean age 68.3 years) in the LIFT study (Cummings et al., 2008).

The data described about tibolone, in both experimental and clinical studies about the turnover markers and BMD, tibolone is similar to estrogen, and considering its relationship to fractures, it is conceivable that tibolone may have a similar effect on them.

To understand the effects of tibolone on the incidence rate of new vertebral fractures in postmenopausal osteoporotic women began the Long-term Intervention on Fractures with Tibolone (LIFT) (Cummings, 2006), a multinational, double-blind trial, including 4000 women with tibolone versus placebo with calcium and a duration of 3-5 years. This study indicates the beneficial effect of tibolone on vertebral fractures (RR = 0.59) but has been discontinued by the increased risk of ischemic and hemorrhagic stroke (RR = 2.3 after 2.75 years).

In a randomized, double-blind, placebo-controlled clinical trial (Cummings et al., 2008), they examined the effect of 1.25 mg of tibolone daily on the risk of vertebral and clinical fractures after 3 years and planned to assess the risks of breast cancer, cardiovascular disease, and endometrial cancer after 5 years. During a median of 34 months of treatment, the tibolone group, as compared with the placebo group, had a decreased risk of vertebral fracture, with 70 cases versus 126 cases per 1000 person-years (relative hazard, 0.55; 95% CI, 0.41 to 0.74; $p < 0.001$), and a decreased risk of nonvertebral fracture, with 122 cases versus 166 cases per 1000 person-years (relative hazard, 0.74; 95% CI, 0.58 to 0.93; $p = 0.01$).

5.4 Adverse effects of tibolone

The results of the LIFT study (Cummings et al., 2008) showed that the tibolone group also had a decreased risk of invasive breast cancer (relative hazard, 0.32; 95% CI, 0.13 to 0.80; $p = 0.02$) and colon cancer (relative hazard, 0.31; 95% CI, 0.10 to 0.96; $p = 0.04$). However, the tibolone group had an increased risk of stroke (relative hazard, 2.19; 95% CI, 1.14 to 4.23; $p = 0.02$), for which the study was stopped in February 2006 at the recommendation of the data and safety monitoring board. There were no significant differences in the risk of either coronary heart disease or venous thromboembolism between the two groups.

6. Conclusions

HRT produce increases in BMD at all skeletal sites. The reduction in fracture risk has been documented by data from a meta-analysis, cohort studies and the WHI study.

Estrogen is a therapeutic option for the prevention and treatment of osteoporosis especially in women with postmenopausal symptoms, with consideration of their long-term use increases the risk.

Therefore, treatment should be individualized by assessing the potential personal risks associated with therapy against the expected benefits. In this way, the patient will maintain continuity in the treatment, and will get the benefit sought in the bone.

Tibolone is as effective as hormone replacement therapy (HRT) in treating symptoms and preventing bone loss, and it improves sexuality. It reduces bone turnover and improves

BMD, specially in trabecular bone. Published studies include few patients and have a short duration. Several large, randomized trials have since yielded additional data on tibolone's efficacy and safety profile.

7. References

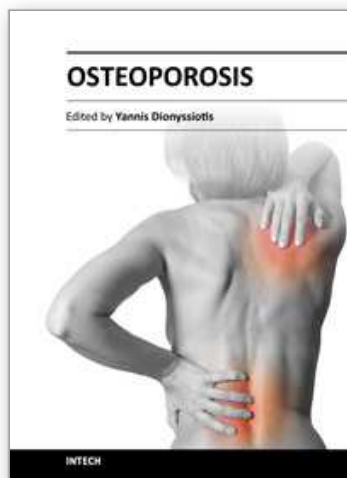
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Osteoporosis is a public health issue worldwide. During the last few years, progress has been made concerning the knowledge of the pathophysiological mechanism of the disease. Sophisticated technologies have added important information in bone mineral density measurements and, additionally, geometrical and mechanical properties of bone. New bone indices have been developed from biochemical and hormonal measurements in order to investigate bone metabolism. Although it is clear that drugs are an essential element of the therapy, beyond medication there are other interventions in the management of the disease. Prevention of osteoporosis starts in young ages and continues during aging in order to prevent fractures associated with impaired quality of life, physical decline, mortality, and high cost for the health system. A number of different specialties are holding the scientific knowledge in osteoporosis. For this reason, we have collected papers from scientific departments all over the world for this book. The book includes up-to-date information about basics of bones, epidemiological data, diagnosis and assessment of osteoporosis, secondary osteoporosis, pediatric issues, prevention and treatment strategies, and research papers from osteoporotic fields.

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