# Tibolone

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Contributor: Martha A. Sanchez-Rodriguez

Low bone mineral density (osteoporosis) is associated with vertebral and nonvertebral fractures in postmenopausal women. Tibolone is a low-risk hormone replacement therapy alternative to estrogen therapy, effective in the treatment of menopausal symptoms and prevention of bone loss, but the evidence is controversial. This study with meta-analysis summarizes the clinical trials of the tibolone effect on percentage change of bone mineral density in the lumbar spine, femoral neck, and total hip in postmenopausal women.

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## 1. Introduction

Osteoporosis is characterized by a reduction in bone mass and micro-architectural deterioration of bone tissue, that cause an increase in bone fragility and susceptibility to fracture risk. In postmenopausal women, osteoporosis is the most frequent primary form of the pathology observed after the fifth decade due to bone loss caused by estrogen deficiency that increases bone turnover with an imbalance between bone formation and resorption [1][2].

Different treatment options are recommended in postmenopausal women with osteoporosis, such as selective estrogen receptor modulators (SERMs), bisphosphonates, peptides of the parathyroid hormone family, denosumab, romozumab and other pharmacological intervention to prevent bone loss, like hormone therapy (HT) [1].

HT prevents the accelerated bone turnover and bone loss at all skeletal sites and is considered effective to prevent postmenopausal osteoporosis and reduce the risk of vertebral and non-vertebral fractures regardless of baseline bone mineral density (BMD) [1]. Furthermore, HT alleviates bothersome vasomotor symptoms, menopausal genitourinary syndrome and related issues including impaired sleep, irritability and reduced quality of life [3]. However, HT has some contraindications as estrogen is sensitive to breast, endometrial cancer and adverse effects like weight gain, bloating [3] and unwanted bleeding [4].

Otherwise, tibolone, a synthetic steroid with a structure different from estrogens and SERMs [5], acts differently in distinct tissues and organs and has been classified as a selective tissue estrogenic activity regulator (STEAR) [6]. After absorption, tibolone is metabolized in different tissues, producing estrogenically active metabolites that stimulate estrogen, progesterone, and androgen receptors, with an effect on bone preserving or increasing BMD [5]

[6]. In addition, tibolone's clinical efficacy is similar to conventional HT, without stimulating breast and endometrium [7], and unscheduled bleeding is lower than that induced by HT [8].

Tibolone is a treatment for climacteric complaints; moreover, it could be a therapeutic option to prevent BMD loss and consequently reduce the risk of fractures in postmenopausal women. Therefore, this systematic review with meta-analysis was performed to (1) summarize the effect of tibolone on BMD change in lumbar spine, femoral neck, and total hip in postmenopausal women; (2) assess the quality of identified trials with current available tools; and (3) evaluate the safety of tibolone therapy.

## 2. Effect of Tibolone on Bone Mineral Density in Postmenopausal Women

The present systematic review and meta-analysis synthesizes the evidence of the effect of tibolone in BMD in the lumbar spine, femoral neck, and total hip in postmenopausal women. Concerning that a Cochrane systematic review evaluates the effectiveness and safety of tibolone treatment in postmenopausal and perimenopausal women, most of the included studies reported the effect on vasomotor symptoms (VMS), and five of them had different objectives such as bone loss or fracture prevention, without describing the effect on BMD [8]. Besides, there are two systematic reviews with meta-analysis in the literature regarding the effect of tibolone on bone at 24 months. The first one, published in 2001, analyzed two trials using a Hologic scanner in early postmenopausal women, and showed that a tibolone 2.5 mg dose, compared with placebo, is capable of increasing spinal and femoral BMD [9]. The second, published in 2003, showed that tibolone appears to be as effective at BMD changes as regimens containing any estrogen, using different densitometers [10]. This meta-analysis' strengths include information with accurate data on the effect size of tibolone over BMD, evaluation at 12, 24 months and when possible at 36 months. In addition, this study explored the risk of bias, a sensitivity analysis, heterogeneity and summarized the evidence for adverse effects published in the trials.

In this study, most of the available data were derived from a comparison with non-active controls. For both densitometers, the increase in BMD is observed for 12 months, with the percent change being greater at 24 months in the lumbar spine and femoral neck, especially with a 2.5 mg tibolone dose. At menopause, both trabecular (cancellous) and cortical bone may be affected, but loss of trabecular bone is more clearly associated with the abrupt decline of the ovarian function at menopause. Trabecular bone consists of 20% of the total bone, which is in the flat bones and in the ends of long bones, and it has ten times the surface/volume ratio of cortical bone. Sex steroids contribute to maintain bone mass mainly by decreasing osteoclastic bone resorption in the trabecular bone, and in this way it suppresses the rate of bone remodeling [11]. In this meta-analysis, the antiresorptive effect of tibolone is observed, and the sensitivity analysis showed a decreased in the heterogeneity of the femoral neck studies; the differences between the results can be explained by the non-randomized study [12] excluded from this analysis. The published meta-analysis, with the Hologic scanner, reports in early-postmenopausal women that 2.5 mg dose of Tibolone at 24 months increases the BMD lumbar spine (MD 5.5%, 95%CI: 4.4 to 6.7, 147 subjects) in data superior to our analysis, and in the femoral neck (MD 4.6%, 95%CI: 3.0 to 6.2, 147 subjects) [9], gaining similar results to this study. On the other hand, bone density measurements from

different devices cannot be directly compared with the meta-analysis. In this study, measurements with the Lunar densitometer are greater than those with the Hologic densitometer, in line with this, the reported evidence shows that Hologic spine BMD is typically 11.7% lower than the GE-Lunar BMD [13][14].

According to the comparison between tibolone and estrogens, the information about the 1.25 mg tibolone dose compared with estrogen therapy is scarce [15]. The most frequently used dose in the included studies is 2.5 mg with the Hologic scanner. In our research, at 12, 24 and 36 moths, tibolone 2.5 mg and different estrogen doses in the lumbar spine and femoral neck showed no difference between treatments, in total hip at 24 months, suggesting that tibolone is as effective as estrogen therapy. Similarly, findings of a previous meta-analysis concluded that regarding BMD changes after 2 years of treatment, there is no difference between any estrogen and tibolone [10]. Our results demonstrate that the tibolone effect appears to have a greater effect at the lumbar spine compared with femoral neck and total hip. In addition, BMD increase is observed through time, being greater at 36 months, this trend is observed in the three sites. Heterogeneity in the three measurement sites is probably because of the different estrogen doses.

Consistently, tibolone is an antiresorptive drug, a synthetic steroid analogue of the progestin, norethynodrel, and structurally different from estradiol and SERMs, with unique tissue-specific effects. Tibolone influences the synthesis and metabolism of estrogens, progesterone and endogenous androgens; for example, in the breast it regulates enzymes, in the endometrium the metabolism is tissue-selective, and in bones it acts via activation of estrogen receptors [5][16]. The unique structure of this drug determines its pharmacokinetics, allowing its oral administration once daily. Tibolone is metabolized in the gastrointestinal tract and liver, and its molecular products have different properties: estrogenic (3alpha and 3beta hydroxytibolone) and progestogenic/androgenic (delta$^4$ tibolone). About 80% of the total oral dose of tibolone circulates as an inactive sulfated form (3alpha and 3beta sulfated tibolone), then in locally tissues, the sulfatase enzymes desulfated the metabolites into active estrogenic molecules [16]. These metabolites avoid estrogenic stimulation of the breast, inhibiting the sulfatase enzyme and provoking apoptosis; likewise, metabolized progestin prevents the stimulation of the endometrium [7].

In contrast, VMS described by women as hot flashes or night sweats represent the most bothersome symptoms of menopause and the most common reason women seek medical care [17]. Besides, women do not perceive bone demineralization as a negative aspect, until it manifests clinically with a fracture. Regarding this, 45% of 50-year-old women with postmenopausal osteoporosis will suffer fractures of spine, hip, proximal humerus or forearm in the next 10 years; however, 96% of these fractures could occur in women without osteoporosis [18]. The decreased bone strength in osteoporosis predisposes an increased risk of fracture; therefore, bone strength = bone mineral density + bone quality [19].

In this way, a meta-regression of published trials concluded that greater improvements in DXA-based BMD is strongly associated with greater reduction in fracture risk, particularly for spine and hip fractures. For example, if tibolone increases the BMD at 2% of the lumbar spine, it could be associated with a 28% reduction in spine fracture or 22% hip fracture, whereas 4% improvement in femoral neck could be associated with a 55% reduction

in spine fracture or 32% hip fracture, according to the meta-regression published [20]. Meanwhile, a network meta-analysis has demonstrated that tibolone is effective for preventing vertebral and non-vertebral fractures [21].

In addition, our analysis supports that tibolone is associated with a lower rate of vaginal bleeding compared to estrogen therapy, and it is suggested that if 47% of women taking combined hormone therapy experience unscheduled bleeding, between 18% and 27% of women taking tibolone will do so [8]. A study has demonstrated that tibolone improved persistent bleeding and breast discomfort after switching from estrogen treatment [22]. Moreover, the evidence suggests that tibolone is more effective than placebo, but less effective than estrogen therapy in reducing VMS [8]. Finally, in this analysis, the relationship between tibolone and anxiety is different to other studies [23][24].

In women with a history of breast cancer, tibolone increase the risk of cancer recurrence and, in women over 60 years of age, it may increase the risk of a stroke. Concerning other long-term adverse events, there is no evidence that tibolone increases the risk or that it differs from estrogen therapy with respect to long-term safety [8]. In relatively healthy postmenopausal women using combined continuous estrogen treatment for one year, the risk of a heart attack and the risk of venous thrombosis increases with longer use. Estrogen therapy also increases the risk of a stroke, breast cancer, gallbladder disease and death from lung cancer [25]; furthermore, common estrogen adverse effects include breast tenderness, bloating, and uterine bleeding [17].

This analysis focused on preventing bone decline with tibolone; however decision-making also incorporates side effects and other measures to improve bone health such as aging, appropriate physical activity, lifestyle, environmental factors, good nutrition, adequate intake of calcium and vitamin D. It is possible to prevent osteoporosis and therefore avoid the intervention of antiresorptive medications or stimulators of bone formation to treat this disease, such as bisphosphonates, demosumab, romosozumab, teriparatide and abaloparatide [21]. Considering the balance between the benefits and risks of tibolone, in addition to using tibolone for postmenopausal symptoms, it is useful for improving BMD.

The findings of this systematic review suggest that tibolone is useful to prevent the decrease in BMD. However, some limitations need to be considered when interpreting the results of this study. First, the evidence from this research cannot be extrapolated to women with osteoporosis or previous fractures, because this population has a greater increase in BMD in response to antiresorptive agents. Second, there are no recent studies, and much of the evidence included was unclear or had a high risk of bias in more than one domain. Third, according to the ISCD, the region of interest in spine BMD measurement is L1–L4. Finally, the comparison and pooling of Hologic and Lunar BMD values is difficult. To solve this problem, raw BMD could be standardized with equations; however, the percentage difference between these two systems could be reduced but not eliminated.

The strengths of this study over meta-analysis is that it is the only one that reports a percentage change in BMD with current available tools and that assesses the quality of identified trials. The specific data of the mean difference in percentage change in BMD could be useful in monitoring bone health, in addition to the possible

prediction of fractures. Moreover, the evidence from this systematic review may be valuable in clinical decision-making to treat bothersome menopausal symptoms, with the benefit of bone loss prevention.

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