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Thyroid hormones, TSH, thyroid cancer and bones in pre- and postmenopausal women

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Summary
In recent years, progress has been made in regulating skeletal development and maintenance of bone mass of the adult by the hypothalamus-pituitary-thyroid axis. Studies have been carried out into the effect of thyroid hormones on the osteoblasts, osteoclast and the chondrocyte. This research has led to better genetic knowledge into the physiology of the cellular action of these hormones. Recently, possible D2 deodinase interventions in osteoporosis have been proposed. The link between bone mineral dignity, bone quality and the risk of fractures with thyroid hormones in normal postmenopausal women suggest a role for these hormones, even within the range of normal thyroid, in these diseases.

On the other hand, the incidence of differentiated thyroid cancer, experimental in vivo thyroid hormone suppression by therapy, recurrent disease, has increased significantly. There are management guides, but it is clear that the secondary derivatives require a precise balance-adjusted indication, risk-benefit ratio of thyroid hormone dosage, prescribed long term, especially in cases of low tumor aggressiveness, advanced age and even in fragile patients. High risk patients should be referred for a bone densitometry, to consider treating future fractures. Prevention of osteoporosis, particularly in postmenopausal women, is highly desirable and should include adequate diet in calcium and vitamin D supplementation if necessary. There is still no consensus on osteoporosis treatment in the patient with thyroid cancer and suppressive treatment, but the indicated criteria for postmenopausal osteoporosis seem to be applicable in general.

Key words: thyroid cancer, dual-photon densitometry, bone mineral density, trabecular bone score, hyperthyroidism and subclinical hypothyroidism, thyrotrophic hormone.
**Introduction**

Thyroid hormones (HT) are involved in skeletal development, peak bone mass acquisition, and maintenance of bone remodeling. Clinical-epidemiological studies indicate that both deficiency and excess of HT are associated with risk of fractures, with euthyroidism being considered as fundamental for the normal functioning of bone remodeling.

This "homeostatic" response to HT is regulated at different levels, but in particular by the conversion of thyroxine (T4) to triiodothyronine (T3) by iodothyronine deiodinases, responsible for the latter acting on its peripheral receptors.

In this paper, we will review the cellular actions of HT on bone, and especially the *in vivo* experimental model of thyroid stimulating hormone (TSH) in patients with differentiated thyroid carcinoma (CDT) in women pre and postmenopausal. In men with CDT there are no longitudinal quality studies for analysis.

**Thyroid hormones and bone**

HT and bone are closely related, since HT are key regulators of bone remodeling. HT plays a key role in the growth and development of vertebrates. HT are iodothyronines synthesized in the thyroid gland, whose constant secretion is ensured by two mechanisms: 1) secretion of HT controlled by a retroactive mechanism, hypothalamic-pituitary-thyroid gland axis (Figure 1), and 2) by regulated intracellular activation by iodothyronine-deiodinases.

Thyroid stimulating hormone (TSH) produced by the thyrotrophic cells of the pituitary gland, promotes the synthesis and secretion of HT, mainly T3, 5,3',5'-tetraiodothyronine (T4), or thyroxine. It is considered that T4 behaves as a prohormone that needs to be converted to the 3,3',5 triiodothyronine (T3), which is more potent and is considered biologically active, which is carried out through a 5'-monodeiodination present in tissues. If iodine cleavage is position 5, this molecule results in the inactive metabolite 3,3',5'-triiodothyronine, or reverse T3 (rT3), with weak agonist activity on the same receptors as T3.

The thyroid gland secretes T4 and also small amounts of T3, the active hormone. The majority of circulating T3 originates from the deiodination of T4 in peripheral tissues. To perform genomic action, T4 must be converted to T3 (Figure 2). Of the three deiodinases involved in the metabolism of HT, deiodinase type 1 (D1), which is expressed mainly in the thyroid gland, is the main responsible for the transformation of T4 to T3. It is estimated that D2 intervenes in the control of its concentrations, contributing to limit the access of the HT to the tissues, during the processes of tissue development and repair. The joint action of D2 and D3 would be responsible for the intracellular control of the availability of T2.

The uptake of thyroid hormones by tissues is carried out by specific transporter proteins. Both T4 and T3 enter the target cells through membrane-specific transporters, including monocarboxy-
loss, is detected. T3 also stimulates the differentiation of osteoblasts, the synthesis and mineralization of the bone matrix; These effects are carried out through the regulation of procollagen enzymes, including bone alkaline phosphatase, and metalloproteinases 9 and 13. It is not yet clear whether these effects are mediated via the activator receptor ligand pathway for nuclear factor B (RANKL), although studies with cell cultures of osteoblasts or precursors, demonstrate that T3 increases the expression of RANKL and interleukins 6 and 8.

It is possible that the action of T3 on osteoblasts is mediated by the expression of osteoprotegerin, which would act by inhibiting RANKL, which in turn stimulates osteoclastogenesis. What has been demonstrated is that T3 induces the transcription of IGF1, while stimulating its IGFBP-2 and IGFBP-4 transport proteins, which, together with the increased activity of alkaline phosphatase (and, therefore, better quality of mineralization) and the other effects already described, behaves as a stimulator of osteoblastic activity at different levels. The TSH-thyroid axis is necessary for this normal skeletal development; TSH has a direct effect on bone, as demonstrated by in vitro studies in which it behaves as a direct inhibitor of bone remodeling, through acting on TSHR expressed in osteoblasts and osteoclasts. In relation to the skeletal development phase, TSH alterations are implicated in three diseases: 1) in congenital and acquired hypothyroidism that can cause decreased bone remodeling and increased risk of fractures; 2) in hyperthyroidism, with actions contrary to the previous one, greater remodeling, but also greater risk of fractures; and 3) in craniosynostosis with premature closure of cranial sutures, osteoporosis and fractures. However, since there are circulating levels of HT in these diseases, their effects can not be separated from the action of TSH on bone; The description that isolated TSH deficiency with a mutation affecting the beta-subunit TSH is characterized by a shortened metacarpal and metatarsal phenotype but with normal bone mineral density (BMD) response after treatment with HT in the absence of TSH has led to suggest that the predominant role on bone development corresponds to T3.

Recently a heterozygous mutation in the THRt gene has been described in a 6-year-old girl, who had HT at the low or normal limit and normal TSH, had growth retardation and histological bone involvement similar to hypothyroidism, which implies an important role for these TR receptors in human bone development.

In adults, hypothyroidism is characterized by decreased bone remodeling with less osteoclastic resorption and less bone formation. This implies a longer duration of the bone remodeling cycle, with an increase in the secondary period of mineralization. This could lead to an increased risk of fractures in these individuals. In contrast, in adult hyperthyroidism, there is a high bone remodeling with osteoporosis characterized by an increase in net bone resorption. There are also more fractures and lower bone mineral density.

**Figure 1.** Circulating thyroid hormones are under the control of the hypothalamic-pituitary-thyroid axis. TRH stimulates TSH release from the anterior pituitary, which in turn stimulates the synthesis and secretion of T4 and T3, which bind and activate TR, resulting in a retroactive inhibition of TRH production and TSH secretion. D2 converts T4 into T3 in the peripheral organs, contributing significantly to the circulating deposition of T3.

**HT and TSH in relation to bone mineral density and fractures in normal population**

There are prospective studies in premenopausal and postmenopausal women assessing the effect of TSH and HT levels on BMD in the normal population. Kim et al. studied the relationship between circulating T3 and TSH and its effect on bone mass in healthy subjects. In a population of 37,431 adults performed BMD measurement and thyroid function test, excluding diseases that may affect these parameters. Low levels of TSH and elevated T3 were associated with lower BMD values at all skeletal sites, and confirmed a protective effect of TSH on bone loss independent of the effect of T3. The negative impact of T3 on BMD could be offset by an increase in TSH only in those with T3 levels in the normal-high range.

Studies in relation to fracture risk and bone loss and TSH levels have been conflicting. TSH levels in the low-normal range were associated with hip frac-
While, in the same vein, a study of younger postmenopausal women showed that levels above the normal range were associated with a 35% reduction in the risk of non-vertebral fractures. Finally, a meta-analysis performed with 70,298 participants described a risk of hip fractures of 1.61 (95% CI: 1.21-1.15) and for other fractures of 1.98 (95% CI: 1.41 -2.78) in patients with subclinical hyperthyroidism with TSH levels <0.10 mIU/L.

The history of hyperthyroidism appears to be a risk factor. In the SOF (Study of Osteoporotic Fractures) study of 192 elderly women with a follow-up of 4.1 years, the highest incidence of osteoporotic fracture was recorded in patients with a history of fractures and/or hyperthyroidism. In this study, no evidence was found to correlate low TSH levels with low BMD. The authors concluded that hyperthyroidism may or may not reduce bone mass, but that in their study the decline in BMD was not responsible for the strong association between prior hyperthyroidism and the risk of hip fracture.

**HT and TSH: relationship with bone mineral density and fractures in women with thyroid dysfunction**

Clinical hyperthyroidism is recognized as a risk factor for bone loss, promoting bone turnover and trabecular perforation. In relation to endogenous hyperthyroidism (Graves' disease, multinodular toxic goiter), the data indicate that it may also increase the risk of fractures in general and/or vertebral fractures in postmenopausal women. The prospective study by Bauer et al. showed that hyperthyroid women with TSH levels <0.1 mU/L, compared to euthyroid controls, had a three-fold increased risk of hip fracture (OR: 3.6, CI 95%: 1.0-12.9) and four times of vertebral fracture (OR: 4.5; 95% CI: 1.3-15.6).

In a study by Baqi et al. In premenopausal women receiving oral levothyroxine (LT4), there was a significant correlation between BMD at the lumbar spine (CL) level and hip and TSH levels, as well as a negative correlation between TSH levels and markers Osteocalcin and N-terminal telopeptide of type I collagen (NTX). The results were more favorable for BMD and levels of bone remodeling markers (MRO) in patients with TSH >0.3 mU/L than those with values <0.3 mU/L.

However, at the level of subclinical hyperthyroidism (TSH suppressed with thyroid hormones in normal range), the effects of HT on bone are more controversial. A prospective study of 2,004 patients with subclinical hyperthyroidism reported a 1.25-fold increase in fracture in these, similar to
the 1.9-fold increase in fracture risk found in patients treated with $T_4^{0.19}$. However, a recent study by Garin et al., Conducted in 4,936 subjects over 65 years of age for 12 years, found no relation between the risk of hip fracture and subclinical hyperthyroidism$^{20}$.

Two meta-analyses of postmenopausal studies with subclinical hyperthyroidism due to exogenous substitution have found a decrease in BMD with an annual loss of 0.91% of bone mass$^{21,22}$. The meta-analysis of Wirth et al., Which includes only 5 published studies with a high quality index, concludes that subclinical hyperthyroidism may be associated with a risk of 2.16 (95% CI: 0.87-5.37) For hip fractures and 1.43 (95% CI: 0.73-2.78) for non-vertebral fractures$^{23}$.

Most studies in postmenopausal women show an association between high-normal levels of HT and lower BMD values, with an increased risk of non-vertebral fracture. Kim et al.$^{24}$ studied the results of BMD in a group of 959 women with subclinical hyperthyroidism (TSH <0.5 mU/L) vs A group with TSH >0.5 mU/L. Women with TSH values in the normal-low limit maintained lower BMD values in the spine and femoral neck than those with TSH in the normal-high limit. The former also had a 2.2-fold increased risk of osteoporosis. Similarly, Morris et al.$^{25}$, in a sample of 581 healthy American women, describe a higher risk of osteoporosis in women with TSH values at the low-normal limit (0.39-1.8 mU/L) with (OR: 3.4 [95% CI: 1.3-9.2]) and 2.2 [95% CI: 1.2-3.8], respectively.

In summary, published data indicate that to demonstrate clear causality, randomized and controlled trials with a large number of patients are necessary, and to assess whether normalization of TSH levels in subclinical hyperthyroidism is associated with fracture risk. The data suggest that subclinical hyperthyroidism is associated with an increased risk of hip and non-vertebral fractures, but other factors should be analyzed and studies of higher quality should be performed.

In clinical hypothyroidism there is a decrease in bone formation that usually exceeds the decrease in resorption, as confirmed by histomorphometry data. In general, the existence of a normal BMD has been described, contrasting with an increase of 2 to 3 times the frequency of fractures, particularly of forearm in some series. In postmenopausal women with subclinical hypothyroidism, a similar risk of fractures has also been reported, especially those with autoimmune origin$^{26}$.

**HT and bone trabecular microarchitecture**

It has been commented on the possibility that the bone quality, determined by the trabecular microstructure, could also be influenced by the thyroid state. In this sense, Basset et al. have shown thinning and decreased trabecular connectivity in a mouse model with thyrotoxicosis$^{27}$.

More recently, Hwangbo et al. Have studied 1,376 euthyroid subjects (648 postmenopausal) in which they determine HT, free $T_4$ and trabecular bone score (TBS)$^{28}$. TBS is the technique by which, based on lumbar DXA scanning, it establishes textural gray levels as indirect indices of microarchitecture. They conclude that elevated levels of free $T_4$ were associated with impairment of trabecular microarchitecture, whereas TSH levels were not associated with lumbar TBS. This would support the results described in mice resistant to HT, in which it has been shown that elevated HT rather than TSH predominate in the regulation of bone state.

**Criteria for thyroid suppression in differentiated thyroid cancer**

Differentiated thyroid carcinoma (CDT) is the most common endocrine neoplasia (accounting for 1% of all cancers). 85-90% of thyroid cancers are CDT, which includes two variants, the papillary carcinoma (the most frequent) and the follicular carcinoma. Its incidence has increased in the last 10 years, but its mortality rate remains the same$^{29}$. This increase is due in large part to the increase and improvement of resolution of the diagnostic tests, with greater detection of incidental microcarcinoma.

Treatment indicated in the CDT includes total thyroidectomy completed with ablative dose of radioactive iodine. Subsequently, based on the risk of relapse, a dose of oral replacement (very low risk) or suppressive levothyroxine is given. The suppressive dose aims to induce hyperthyroxinemia with pituitary suppression of TSH that could be a potential stimulus for tumor remnants. The initial suppressive dose of levothyroxine is calculated at 1.8-2.2 µg/kg/day, which is modified according to successive controls. Based on the suppression obtained during hormone therapy, the American Thyroid Association (ATA) has established the following risk groups for treatment with levothyroxine: 1) Low-risk group >0.5 mIU/L; 2) Intermediate risk group: 0.1-0.5 mIU/L and; 3) High risk group: <0.1 mIU/L. Patients with exogenous treatment (by CDT) as well as those with endogenous hyperthyroidism are subjected to prolonged periods of the effect of thyroid hormones on the bone. Many of the aspects related to the bone loss that this therapy can cause, either directly or by suppression of the pituitary-thyroid axis, are now known.

**Suppression of TSH in thyroid carcinoma. Bone loss and relation to the risk of relapse**

Treatment with levothyroxine in CDT is based on doses that suppress serum TSH levels below the normal range, resulting in a condition similar to that of subclinical hyperthyroidism. We have already pointed out how TSH behaves as a stimulus for the proliferation of thyroid cells, in addition to the uptake of radioiodine and the production of thyroglobulin, so suppression seeks to remove this effect and prevent a recurrence. TSH receptors have been described in the membranes of CDT tumor cells whose concentrations are affected by the reduction of TSH by levothyroxine therapy$^{30}$. There are also observational epidemiological studies in which a positive correlation has been
found between elevated serum TSH levels and risk of malignancy in nodules or more advanced stages of CDT (Table 1). Finally, McGriff et al., in a meta-analysis involving 4,174 patients with CDT, demonstrated a decreased risk of tumor progression in patients receiving levothyroxine suppressive therapy (RR=0.73; 95% CI: 0.6-0.88, p<0.05)41.

Although there is no general consensus about optimal TSH levels to decrease relapses and minimize the adverse effects of subclinical hyperthyroidism, the American Thyroid Association (ATA) recently defined the impact of TSH suppression in patients with CDT Characterized by low, intermediate and high risk of relapses taking into account several clinical factors38.

It should be noted that previously Biondi and Cooper, in a review, concluded that aggressive suppression of TSH is important in patients with CDT and high risk, and is much less critical in the other groups39. Based on these criteria, Wang et al. Recently studied 306 non-suppressed patients and 465 suppressed patients with CDT classified as low or intermediate risk, and who presented similar recurrence rates after 6 years of follow-up40. However, patients with TSH suppression <0.4 mIU/L had a higher incidence of osteoporosis and atrial fibrillation compared with non-suppressed patients (HR 2.1; p=0.05), meaning that prolonged treatment with levothyroxine with Suppressive effect increases the risk of postoperative osteoporosis in patients with low and moderate risk of CDT; according to the ATA classification.

It can be concluded that the optimal dose of maintenance of TSH in patients with CDT of low or intermediate risk of relapse has not yet been well established. Studies suggest that a level of 0.9-1.0 mIU/L could be the optimal suppression value for low- and intermediate-risk CDTs, in order to further reduce the development of osteoporosis and long cardiological complications Term, without increasing the risk of relapse. It is possible, therefore, that TSH suppression is an independent predictor of bone damage that, moreover, does not seem to diminish relapses in these low and intermediate-risk patients.

Impact of TSH suppression: adverse effects and quality of life
The prescription of thyroid hormones is ample, reaching almost 5.1% of the adult population. It is generally a well tolerated medication and few immediate side effects. In the last years, publications are being made regarding whether levothyroxine therapy increases the incidence of fracture in the long term. Current evidence is not definitive, although Turner et al. Showed an increase in fractures in elderly patients (>70 years) treated for long periods with thyroxine38. The mechanisms by which thyroxine would induce these fractures are unknown, but it has been suggested that bone mineral density would be decreased through induction of subclinical hyperthyroidism, or that normal-high levels cause it. The greater frequency of falls due to arrhythmias favored by this increa-
nosis of these patients, which could lead to the appearance of fractures in prolonged periods of suppressive therapy. In general, the studies describe more aggressive treatments for suppression of TSH in patients at high risk of disease or tumor recurrence, while a less aggressive suppression seems advisable in patients with low risk. In addition, it should be noted that, in recent years, the increase in the prevalence of papillary microcarcinomas with good survival requires modification of these suppression criteria. The maintenance of TSH numbers in the normal range may be advisable for long-term treatment in patients with advanced CDT and relapse-free.

Suppressive treatment with HT in cancer differentiated from thyroid and bone. Longitudinal studies vs transverse

To date, a large number of cross-sectional studies have been published on the effect of suppressive therapy with HT on CDT in both premenopausal and postmenopausal women. In premenopausal studies, there are three studies that find a decrease in BMD in some of the studied areas\textsuperscript{44-46}. In front of them, there are three times more studies that do not find any deleterious effect of TSH suppression on the bone in these patients\textsuperscript{47}. In postmenopausal patients with CDT, there is a greater disparity of results: some report a decrease in lumbar and neck BMD, and in some, there is also bone loss in radio\textsuperscript{46,48,49}, in contrast to a large majority who register changes in BMD with suppressive treatment\textsuperscript{50-53}. It is possible that the heterogeneity of the thyroid cancer patients selected for the studies, the different levels of TSH suppression and the different techniques used for hormonal determinations and bone mineral density may influence the significant differences of these results.

For the above reasons, we believe that the study of bone mass follow-up in these patients with CDT is of more value, disregarding cross-sectional studies that reflect a specific situation. Compared with longitudinal studies, cross-sectional analyzes are more susceptible to sample error and other bias\textsuperscript{54}. The objective was to review the publications with prospective criteria, the possible bone losses in the different areas studied with bone densitometry, with time of treatment and detailed follow-up, as well as the criteria and times of TSH suppression of these patients. Following these objectives we found in PubMed 11 publications, with longitudinal follow-up, including one from our group\textsuperscript{55}, which we will analyze next (Table 2).

The first longitudinal study was Pioli et al.\textsuperscript{56}, who studied 14 premenopausal patients (age 43±6.8 years) with CDT, with densitometries every six months and during follow-up with levothyroxine reaching 3 years. Although ten of these patients underwent almost total thyroidectomy and 5 to subtotal, the HT and suppression patterns were similar, reaching suppression at 4 months, which was maintained during the study. The authors reported bone loss at the spine level of 2.6±1.9% per year, vs the 0.2±1% found in the control group of 15 normal. Paradoxically, if this loss were continued for ten years, it would be 26% in excess of the controls, a fact that has not been repeated in any other study. The radial bone density was normal. It is possible that in these results the large inter-individual variety of the bone para-

Table 1. TSH targets for prolonged treatment with thyroid hormone in differentiated thyroid carcinoma. According to Haugen BR et al.\textsuperscript{32}

<table>
<thead>
<tr>
<th>Risk of suppression of TSH</th>
<th>Excellent</th>
<th>Undetermined</th>
<th>Incomplete biochemistry\textsuperscript{**}</th>
<th>Structural incomplete</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopause</td>
<td>Moderate</td>
<td></td>
<td></td>
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<tr>
<td>Tachycardia</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Osteopenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td></td>
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<td></td>
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<tr>
<td>Atrial fibrillation</td>
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</tbody>
</table>

\textsuperscript{*}0.5 mIU/L represents the lowest reference limit of the TSH determination method which may vary between 0.3-0.5 mIU/L depending on the method.

\textsuperscript{**}The TSH target for patients with incomplete biochemical response may vary depending on the initial ATA risk, Tg levels, Tg trend over time, and risk of suppression.
meters referred to is affected, as well as the use of two different techniques, such as SPA (single photon absorptiometry) and DXA.

The second longitudinal study is Muller et al. They studied 15 premenopausal women and 10 postmenopausal women in TSH suppressive treatment for a variable period of 1.5 years. Of this group, 24 patients with CDT were re-evaluated with DXA with a follow-up interval of 1.5±0.5 years. They selected 15 matched controls in sex, menopausal status, age and BMI. They concluded that suppression of TSH was accompanied by non-significant reductions (2-5%) of lumbar BMD and femoral neck BMD, without any incident fractures. The decrease in BMD found is lower than the classic one described by Mazess, in which the increased risk of vertebral fracture increases 1.5-2 times for each standard deviation (DS) that decreases BMD, which senses no effect to this level.

In the Fujiyama et al. series, 24 postmenopausal patients were described, divided into two groups, with and without TSH suppressor doses, with 12 patients with CDT each. Both groups had a similar bone loss rate: -0.849±0.605 in the suppressed ones, and -0.669±0.659 in the non-suppressed ones. On the other hand, Z-score values for lumbar and total body BMD were similar to those reported for healthy controls.

In 1996, Kung et al. detailed a study in CDT-operated postmenopausal women who distributed in three subgroups with 15 patients in each: the first, in treatment with calcitonin; The second,

<table>
<thead>
<tr>
<th>Authors/year</th>
<th>Pre-m</th>
<th>Post-m</th>
<th>% patients with suppression of TSH</th>
<th>Duration average tracing with DXA</th>
<th>Duration average treatment with HT</th>
<th>Effect on BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioli G and cols. 1992a</td>
<td>14</td>
<td>-</td>
<td>100%</td>
<td>1-3 years</td>
<td>1-3 years</td>
<td>Decrease in BMD-L</td>
</tr>
<tr>
<td>Muller CG and cols. 1995c</td>
<td>15</td>
<td>10</td>
<td>40%</td>
<td>1.5 years</td>
<td>10 years</td>
<td>No decreases in BMD-L, BMD-CF</td>
</tr>
<tr>
<td>Fujiyama K and cols. 1995b</td>
<td>-</td>
<td>24</td>
<td>50%</td>
<td>1 year</td>
<td>11-15 years</td>
<td>No decreases in BMD-L, BMD-RD</td>
</tr>
<tr>
<td>Kung AWC and cols. 1996a</td>
<td>-</td>
<td>15</td>
<td>100%</td>
<td>2 years</td>
<td>11.3±6 years</td>
<td>Decreases BMD-L, BMD-CT, BMD-CF, BMD triangle Ward</td>
</tr>
<tr>
<td>Guo CY and cols. 1997c</td>
<td>-</td>
<td>23</td>
<td>100%</td>
<td>2 years</td>
<td>NE</td>
<td>No decrease in BMD-L, BMD-CF and BMD-CT</td>
</tr>
<tr>
<td>Jódar E and cols. 1998e</td>
<td>14</td>
<td>13</td>
<td>50%</td>
<td>2.3 years</td>
<td>5.7 years</td>
<td>No decrease in BMD-L, BMD-CF and minimal reduction BMD-RD</td>
</tr>
<tr>
<td>Sijanovic S and cols. 2001d</td>
<td>19</td>
<td>-</td>
<td>100%</td>
<td>4 years</td>
<td>9 years</td>
<td>No decrease in BMD-L, BMD-CF and minimal reduction BMD-RD</td>
</tr>
<tr>
<td>Sugitani I and cols. 2001c</td>
<td>-</td>
<td>120</td>
<td>100%</td>
<td>5 years</td>
<td>NE</td>
<td>Decreased BMD-L alone in patients &gt;50 years</td>
</tr>
<tr>
<td>Karner and cols. 2005b</td>
<td>19</td>
<td>-</td>
<td>100%</td>
<td>1 year</td>
<td>9.4±6 years</td>
<td>No decrease in BMD-L, BMD-CF or in BMD-RD Schneider R and cols. 2012c</td>
</tr>
<tr>
<td>Kim MK and cols. 2015e</td>
<td>49</td>
<td>44</td>
<td>NE</td>
<td>1 year</td>
<td>2 months-1 year</td>
<td>Decrease BMD-L, BMD-CF and BMD-CT in postmenopausal</td>
</tr>
<tr>
<td>Kim CW and cols. 2015f</td>
<td>24</td>
<td>100</td>
<td>100%</td>
<td>1-1.5 years</td>
<td>NE</td>
<td>No decreases in BMD-L and CF</td>
</tr>
</tbody>
</table>

BMD L: lumbar bone mineral density; BMD CT: bone mineral density total hip; BMD T: trochanteric lumbar bone mineral density; BMD RD: bone mineral density ultradistal radio; BMD CT: total body; NE: not specified; -: they do not have patients in that group.
with calcium alone; And the third group, with placebo without any treatment, which is the group we included in this review. Patients in this third group were followed for two years after the administration of levothyroxine and effective suppression of TSH (<0.05 mIU/L) postoperatively for approximately 9 years. They found a significantly superior bone loss at the lumbar, total hip, trochanter and Ward triangles (5.0%, 6%, 4.7%, 8.8%, respectively, p<0.05). However, when no fractures were found, they thought that the clinical importance of this bone decrease should be questioned.

Guo et al.62 performed a prospective study in 23 postmenopausal women with intervened CDT and subsequent TSH suppression, followed by 2 years with bone densitometry and bone markers. Serum TSH levels were measured every 6-12 months to control TSH suppression. TSH levels were correlated with bone markers (osteocalcin, bone alkaline phosphatase and NTX). This group of postmenopausal women was compared with two other control groups (with and without suppressed TSH levels) who had primary hypothyroidism or Hashimoto's thyroiditis (n=41). They found that control patients had an increase in lumbar and femoral neck BMD and a decrease in bone remodeling values found in these patients were correlated with bone mass, except for alkaline phosphatase at Ward's triangle level and ultradistal radius. This is consistent with normal BMD and bone remodeling values found in these patients with prolonged suppressive treatments. The suppressed patients showed a small reduction in BMD in 1/3 distal radius (Z-score = -0.77±0.98, CI 95: -1.11, -0.44), without differences between the pre and postmenopausal.

The study with longer duration of follow-up is that of Sijanovic et al.92. These authors studied 19 premenopausal women with intervened CSD (mean age 59±8 years) who underwent T_{4} suppression treatment for an average of 9.4 years. The prospective study with bone densitometry was performed in 4 years. They noted that after one year there was no significant bone loss in any region of the skeleton, and yet, after performing 3 measurements, at 4 years they recorded significant loss of BMD in the distal radius and not in other areas. They commented, surprisingly, that in their analysis there is a decrease although not significant of bone mass in other areas (data not given), so suppressive TSH therapy with thyroxine in a period of approximately 10 years may induce a risk of osteopenia in premenopausal women who reach menopause.

In a selective, rather large group of postmenopausal patients with papillary CDT, Sugintani et al.63 analyzed the effect of post-operative suppressive TSH therapy on disease-free survival and its effects on BMD. Two groups were analyzed: 140 patients with suppression (mean TSH: 0.07±0.10 mIU/L, and 127 without suppression (mean TSH: 3.14±1.60 mIU/L). In the non-suppressed group, 120 patients Postmenopausal women were followed for 5 years, showing a decrease in lumbar BMD subgroup of postmenopausal women over 50 years of age. TSH suppression had no significant effects on the prevention of relapses in papillary CDT, although most of its In the end, it is recommended that suppression of TSH, especially in patients with low risk and in elderly patients, is not indicated, taking into account that it has not been shown to decrease recurrences even in patients with high risk.

The longitudinal study by Karner et al.64 was carried out in premenopausal women with CDT for one year. The duration of TSH suppression at the start of the study was 9.4±6.4 years, and therefore broad. BMD measurements were performed twice over a period of one year. Using single photon absorptiometry (SPA) for extremities and DXA, they found no decrease in BMD at the distal radius, or in lumbar and/or hip BMD. It is a longitudinal study of short duration, small number of subjects (19 premenopausal). Its main recommendation is to practice the bone densitometry study before initiating the suppressor therapy of TSH to identify the patients with high risk of osteoporosis.

More recently a study was published by Schneider R et al.65 to evaluate the potential effects of LT_{4} suppressive treatment in 46 premenopausal women undergoing CDT on BMD and bone and muscle strength. It is a prospective, cohort-controlled, 1-year follow-up, in which bone mass is measured by dual lumbar and hip photometry, and bone and muscle strength using the polar stress index with dynamometry. They are simultaneously studying 23 premenopausal women undergoing LT_{4} replacement therapy. In both premenopausal populations, with suppressive treatment or with substitutive treatment, they do not find a decrease in axial BMD. The annual loss (g/cm²) in patients with CDT was not significantly different from those receiving LT_{4} replacement therapy (BMD -0.005 vs +0.004; BMD femoral neck: -0.005 vs +0.00; total hip BMD: +0.001 vs +0.003, respectively). The authors concluded that there is little evidence of adverse effects of levothyroxine on bone, and that premenopausal women with CDT may be at risk for lower BMD at the ultradistal radius. In spite of their null data in this sense, they attribute loss of unbalanced cortical BMD by trabecular augmentation, probably indicating a high endocortical trabecularization.
Kim et al. in a one-year prospective study, found a decrease in bone mass that predominantly affects postmenopausal women compared to premenopausal women in their study. The annual postmenopausal loss was -2.1% in the lumbar spine, -2.2% in the femoral neck, -2.1% in the total hip, significantly higher than the premenopausal women (p<0.05 for all). Although the authors report that bone loss was primarily during the early post-thyroidectomy period, a longer study might confirm this.

Finally, Kim et al. conducted a prospective 12-18 month study in 24 premenopausal women with CDT (6 hypoparathyroid glands) and 100 postmenopausal women (50 hypoparathyroid glands), concluding that they found no deleterious effect of suppressive therapy with T₄. Even a protective effect in patients with post-operative hypoparathyroidism.

Risk factors in patients with CDT and TSH suppressor therapy
López Alvarez et al. studied the risk factors involved in possible bone loss in 43 premenopausal and 53 postmenopausal women with TDC treated with suppressive thyroid hormones and followed up for an average of 75 months. Age, as a risk factor, and weight as a protective factor were the variables that most influenced BMD. No significant differences were found when comparing patients with normal concentrations of free thyroxine versus those who had them slightly elevated. In postmenopausal women, there was greater lumbar BMD in the group with adequate calcium intake (957 mg/day) compared to those who did not (855 mg/day) (p<0.05). At the level of the femoral neck and lumbar region, TSH, along with age and weight, were the variables that influenced the most. Gómez de Melo et al. carried out another similar study in 109 postmenopausal women with CDT and suppressive treatment, in which they identified that, in the multivariable logistic regression analysis, the factors significantly related to lower BMD values were: low BMI and TSH; Do not find relation between the BMD and the average values of free T₄. They suggest that TSH can have negative effects on BMD only when levels are suppressed.

In summary, most of what has been reported in relation to premenopausal women with CDT and suppressive therapy of TSH shows no deleterious effects on BMD in any anatomical site. In postmenopausal women with CDT and TSH suppression the studies are more heterogeneous, but, nevertheless, it must be pointed out that there are three studies, commented, with important contribution that refer to bone loss.

Conclusions
In recent years, there have been important contributions to the better understanding of the regulation of the skeleton by HT and the hypothalamic-pituitary axis. The deiodination of the HT during its metabolism is considered an important determinant of the thyroid state at the circulating level and of the peripheric tissues. In bone, the activity of deiodinase D2 is involved in osteoblasts and in maintaining adequate mineralization and bone strength. Deiodinase D3 would intervene very early, at cartilage level favoring skeletal growth and development.

In subjects with subclinical hyperthyroidism other than CDT, controlled trials with a significant number of patients are considered necessary to evaluate the efficacy of normalizing TSH levels associated with fracture risk. The accumulated experience with the suppressive treatment of TSH in the CDT is configuring a therapeutic strategy with greater evidence for the treatment of patients with low risk and intermediate, in whom this approach would not be necessary. In contrast, patients at high risk could benefit; However, it is the elderly patients with high risk who usually have greater comorbidities and, in whom the indication will often have to be evaluated.

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