



## Mini Review

# Impact of subclinical hyperthyroidism on bone

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## Abstract

Normal balance of thyroid hormones plays a key role on skeletal growth and integrity. Overt hyperthyroidism is an established risk factor for osteoporosis and fractures. However, recent studies report that even subclinical hyperthyroidism has a negative impact on bone health. Screening of subjects at risk and consequent treatment to prevent or recover secondary bone loss depends on age, gender, menopausal status, severity and duration of thyroid dysfunction.

**Keywords:** Thyroid, Subclinical Hyperthyroidism, Bone Mineral Density, Osteoporosis, Fractures

## Introduction

It is well accepted for more than a century, that thyroid hormones are crucial for linear growth and skeletal maintenance. However, the empiric use of sponge and seaweed in the treatment of congenital hypothyroidism dates back to 1600 BC<sup>1</sup>. In the middle of 18<sup>th</sup> century the first cases of hyperthyroidism have been reported and in 1840 Carl Adolf von Basedow contributed with a more complete description of the syndrome. However, it was Paul Möbius in 1886 who linked the symptomatology to a hyperactive thyroid. In 1891, Friedrich Von Recklinghausen was the first to establish a connection between osteoporotic fractures and thyrotoxicosis<sup>2,3</sup>. During the last 25 years, this topic has attracted substantial attention, guiding to important progress in comprehending the impact of thyroid disease on the growing and adult skeleton.

This review aims to present the current knowledge of the consequences of both endogenous and exogenous subclinical hyperthyroidism (SH) on bone mineral density (BMD) and risk of fracture separately in men, pre-menopausal and post-menopausal women. At last, treatment management in accordance to recent international guidelines is also reported.

## Thyroid hormones physiology

Synthesis and secretion of the prohormone 3,5,3',5'-L-tetraiodothyronine (T4) and the active thyroid hormone 3,5,3'-L-triiodothyronine (T3) are regulated by a negative feedback loop driven by the Hypothalamic-Pituitary-Thyroid (HPT) axis<sup>4</sup>. Thyrotropin-releasing hormone (TRH) released from the hypothalamic paraventricular nucleus stimulates pituitary thyrotrophs to secrete thyroid-

stimulating hormone (TSH). TSH subsequently interacts with its receptor (TSHR) on thyroid follicular cells resulting in cell proliferation, synthesis and secretion of T4 and T3<sup>5</sup>. T3 derived from local metabolism in the hypothalamus and pituitary, binds to thyroid hormone receptors (TRs) blocking synthesis and release of TRH and TSH, respectively<sup>6,7</sup>. The aforementioned negative feedback loop maintain euthyroidism<sup>8,9</sup>.

T4 comes from thyroid gland secretion, whereas most circulating T3 is produced by peripheral deiodination of T4. Three iodothyronine deiodinases metabolize thyroid hormones to active or inactive metabolites<sup>4,10</sup>. The Type 2 deiodinase (DIO2) is the principal generator of T3 and thus regulates the intracellular T3 concentration and saturation of the nuclear TRs in target organs<sup>11</sup>. The type 1 deiodinase (DIO1) generates T3, rT3, or 3,3'-diiodothyronine, depending on the substrate. By contrast, the type 3 deiodinase (DIO3) irreversibly inactivates T3 or blocks activation of T4 generating 3,3'-diiodothyronine or rT3, respectively. Both DIO2 and DIO3 alongside with TRs isoforms are expressed in a temporo-spatial and tissue-specific manner<sup>12,13</sup>.

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In the nucleus, T3 interacts with TRs that form heterodimers with retinoid X receptors (RXRs) and bind T3 response elements (TREs) in target gene promoters to control transcription. The two receptor isoforms TR $\alpha$  and TR $\beta$  with their subtypes TR $\alpha$ 1, TR $\alpha$ 2, and TR $\beta$ 1 mediate T3 action and are widely distributed<sup>13,14</sup>. TR $\alpha$ 1 in bone has a 10-fold higher expression than TR $\beta$ 1 as seen by mutant mouse models with absence of TR $\alpha$ 1 (-/-)<sup>15,16</sup>. Classically, bone loss in hyperthyroidism has been attributed to high levels of thyroid hormones. However, recent publications have also implicated low TSH levels alone in accelerated bone turnover<sup>17,18</sup>. This is clinically relevant, since SH is defined by normal T3 and T4 levels with an isolated suppression of TSH and has been related to bone loss over time<sup>19,20</sup>.

## Skeletal physiology

Chondrocytes, osteoblasts, osteocytes and osteoclasts are the four major bone cell types. Chondrocytes appear initially during skeletal development<sup>21</sup>. Bone-forming osteoblasts comprise 5% of bone cells and come from multipotent mesenchymal stem cells. After bone formation, osteoblasts can be destined to bone-lining cells or osteocytes or may undergo apoptosis<sup>22</sup>. Osteocytes that constitute 90-95% of bone cells function as mechanosensors<sup>23</sup>. Osteoclasts that comprise 1-2% of bone cells, are polarized multinucleated cells, derive from myeloid precursors and are responsible for bone resorption<sup>24</sup>. Chondrocytes and osteoblasts are directly responsive to thyroid hormone. If osteoclasts and osteocytes are direct target cells of thyroid hormones remains uncertain<sup>25</sup>.

Bone formation occurs either via the intramembranous ossification from which derive the flat bones or via the endochondral ossification, typical of long bones<sup>26</sup>. Epiphyseal growth plates are responsible for linear growth until puberty when they fuse. However, bone mineral accrual is maintained until peak bone mass is concluded during the third decade<sup>27,28</sup>.

In adults, the skeletal integrity is maintained due to the bone remodeling cycle<sup>29,30</sup>. Conditions of mechanical stress and micro-damage activate the osteocytes which in turn promote the osteoclastogenesis. After bone resorption follows bone formation where osteoblasts are recruited in scene to fill the resorption cavity and mineralize new bone matrix. The entire remodeling cycle is kept in balance thanks to physiological negative regulators secreted by bone cells as soluble factors<sup>30-33</sup>.

## Hyperthyroidism

Overt hyperthyroidism is defined as an undetectable serum TSH with elevated levels of T3 and/or free T4<sup>34</sup>. SH is defined by a subnormal serum TSH, with normal levels of FT4, T3<sup>35-38</sup>. Current assays detect TSH levels as low as 0.01-0.02 mIU/l. According to its severity SH is classified

as grade 1 with low but detectable serum TSH levels (e.g. TSH 0.1-0.39 mIU/l), and grade 2 with undetectable serum TSH levels (<0.1 mIU/l)<sup>35-38</sup>.

Endogenous hyperthyroidism either clinical or subclinical is most commonly due to Graves' disease (GD), toxic adenoma (TA) and toxic multinodular goiter (MNG)<sup>37,38</sup>. While GD is the most common cause in younger individuals in iodine-sufficient areas, TA and toxic MNG are encountered mostly in iodine-deplete areas and in older persons<sup>39</sup>. Suppression of TSH may also be exogenous due to thyroid hormone over-replacement, either intentionally (in patients with Differentiated Thyroid Cancer-DTC), unintentionally (in patients with hypothyroidism) or surreptitiously<sup>36,37</sup>.

The prevalence of endogenous SH varies considerably, between 0.6 and 16% depending on diagnostic criteria, age and sex of the population studied, and iodine intake<sup>39-41</sup>. Conversely, an estimated 3% of women >60 yrs are taking exogenous T4 for medically indicated purposes and recently in the United Kingdom 16% of those on thyroid hormone, excluding DTC, were found to have at least one low TSH by five years of therapy, about a third of these suppressed <0.1 mIU/L<sup>42,43</sup>.

Overt hyperthyroidism in adults is an established cause of osteoporosis and increased fracture susceptibility, although its early diagnosis and treatment has rendered severe secondary osteoporosis now days rare<sup>44</sup>. In children is relatively rare causing increased linear growth rate with persistent short stature<sup>25,45</sup>. At very young age, if severe, can cause craniosynostosis with neurological consequences<sup>46</sup>.

Evaluation of the association between SH and the risk of osteoporosis has produced conflicting results due to heterogeneity among studies. Therefore, BMD and fracture risk in this population are better examined by a subdivision dependent on gender, age, menopausal status, cause of hyperthyroidism, the degree and the duration of TSH suppression<sup>35</sup>.

## Endogenous subclinical hyperthyroidism and bone disease

### *The impact of endogenous subclinical hyperthyroidism on bone mineral density of postmenopausal women*

Endogenous SH has consistently been correlated with an increased risk of reduced BMD in postmenopausal women<sup>19,47-50</sup>. In a cross-sectional study of pre- and postmenopausal women, BMD of postmenopausal women at sites of predominantly cortical bone was significantly affected<sup>20</sup>. Conversely, in another study amongst 88 postmenopausal women both lumbar spine (LS) and femoral neck (FN) BMD were found significantly decreased in those with endogenous but not exogenous SH<sup>51,52</sup>. In a retrospective cross-sectional study of older women, SH was related to low BMD at FN but not at LS after adjustment for age and BMI. TSH in the lower two quartiles were independently related to osteoporosis and osteopenia<sup>53</sup>. The effects of endogenous

SH especially on sites of cortical bone, the duration and the degree of TSH suppression were also confirmed by other recent studies<sup>54-56</sup>.

### ***The impact of endogenous subclinical hyperthyroidism on bone mineral density of premenopausal women***

Multiple studies of premenopausal women with SH have consistently reported not pathologically decreased BMD levels<sup>20,36,49,50,57,58</sup>. Seems that reserved ovary function plays a major protective role<sup>59</sup>. Only two small studies have reported statistically significant reduction of BMD at FN, but not at LS compared to significantly low values at both sites in postmenopausal subjects<sup>58,60</sup>. Normal values of bone turnover markers was also the finding of the majority of studies, except in the two aforementioned, where a significant increase was reported in both pre- and postmenopausal women<sup>20,57,61</sup>.

### ***The impact of endogenous subclinical hyperthyroidism on bone mineral density of men***

Nearly 50% of the cases of male osteoporosis are due to an underlying cause. Most of the studies in men have been focused on fracture risk. A retrospective study revealed a hazard ratio (HR) of 4.91 for hip fracture risk in men compared to a HR of 2.42 in postmenopausal females<sup>62</sup>. Similarly, in other studies where BMD was examined by dual energy x-ray absorptiometry and calcaneal quantitative ultrasound proportional changes between TSH and BMD and inverse associations between FT4 and BMD were reported<sup>63-65</sup>. The first prospective study that assessed fracture incidence has found no increase in hip fracture risk, although there was an association with TSH as a continuous variable (relative HR 1.31 per SD decrease in TSH, 95% CI 1.01-1.71)<sup>66</sup>. A more recent prospective study demonstrated that neither SH nor FT4 or TSH within the euthyroid range are related to altered bone turnover markers and/or incident hip fracture in older men. Based on their findings they do not support a role for subclinical thyroid dysfunction as a biomarker for bone-related outcomes in older men<sup>67</sup>.

### **Endogenous subclinical hyperthyroidism and risk of fracture**

Conflicting results have also been reported regarding the risk of fractures in endogenous SH<sup>55,62,68,69</sup>. In a large prospective cohort study elderly men with SH had a higher incidence of hip fracture than normal controls (HR=4.91; 95% CI: 1.13-21.27) but no clear association was found in women<sup>62</sup>. In TEARS study was reported a HR of 1.25 for osteoporotic fracture in patients with SH compared to matched controls which was then lost during follow up<sup>68</sup>. Conversely, in a population-based cohort study, a single first measurement but also persistence of low TSH was associated with an increased long-term risk of

hip fractures in older women<sup>70</sup>. In a subsequent study, the same group has found that the excess risk of major osteoporotic fractures in postmenopausal women with SH depended on cumulative hyperthyroid time<sup>71</sup>. A meta-analysis of seven prospective cohort studies that examined the association between SH and risk for hip and non-spine fractures found that particularly patients with SH grade 2 had greater risk for fractures at both sites compared to those with mild SH<sup>72</sup>. Similarly, a recent meta-analysis, including data from 13 prospective cohorts, confirmed that SH is associated with an increased risk of fractures with an HR of 1.52 (95% CI: 1.19-1.93) for hip fracture, 1.42 (95% CI: 1.16-1.74) for any fracture and 1.74 (95% CI: 1.01-2.99) for spine fracture, with even higher fracture rates in SH grade 2<sup>73</sup>.

### **Treatment management of bone loss induced by endogenous subclinical hyperthyroidism**

There is a proved association between SH and low BMD in postmenopausal women, leading physicians to test the efficacy of antithyroid therapy on bone recovery in these patients. An improvement in BMD within as little as 6 months after establishment of euthyroidism has emerged from studies in this subgroup of patients<sup>74-76</sup>. Mudde et al. studied postmenopausal women with SH for a 2-year period after antithyroid treatment and found that mean BMD, but not bone turnover markers, in treated women was significantly higher compared to untreated controls<sup>49</sup>. In a prospective study radioiodine treatment in postmenopausal women increased BMD at LS of 1.9% after 1-year and remained increased by 1.5% at 2 years follow up<sup>77</sup>. Similarly, FN BMD increased by 2.3% after 1 year of treatment and remained increased by 1.7% at 2 years follow up. By contrast, in untreated controls BMD declined by about 2% per year at the hip and the spine<sup>77</sup>. Similar results emerged from a recent prospective study where BMD at 1 year after achievement of euthyroidism had increased by 1.9% at the FN and by 1.6% at the LS<sup>78</sup>. Conversely, in the four patients with persistent SH, the average BMD had declined by 2% at the FN and by 1.8% at the LS<sup>78</sup>. Since SH in premenopausal women seems not to influence negatively bone integrity the clinical benefit of active treatment in this group has been questioned.

In 2015 the European Thyroid Association released guidelines on the diagnosis and treatment of endogenous SH. In older patients with SH grade 2 treatment is highly recommended whereas in those with SH grade 1 may be considered mainly in order to avoid the risk of cardiovascular events. In younger patients with SH grade 2 treatment is suggested mainly to those with cardiovascular risk factors and other co-morbidities<sup>35</sup>. On the contrary there is no evidence for treating young patients with SH grade 1 where monitoring alone is more than sufficient<sup>35</sup>.

## Exogenous subclinical hyperthyroidism and bone disease

### *The impact of exogenous subclinical hyperthyroidism on bone mineral density of postmenopausal women*

Postmenopausal women over treated with thyroid hormones have been found to be at risk for hyperthyroid-induced skeletal changes<sup>47,79,80</sup>. Faber et al found a significant decline of BMD by 9% after 10 years of thyroxine treatment in postmenopausal women compared to controls, which means that exists an additional annual bone loss of nearly 1% besides the already estimated 1-2.5% annual bone loss<sup>81</sup>. Similar results emerged from another study with BMD losses of 7% at LS, 5% at FN, 9% at the trochanter and Ward's triangle, and 7% at the distal radius, implying a 12-44% lifetime risk of hip fracture due to a bone loss of 6-10% over a 10- year period<sup>82</sup>. A large longitudinal study in DTC patients showed low BMD only in older women on suppression therapy compared to those with normal TSH levels postoperatively at 1 and 5 years of follow-up<sup>83</sup>. On the other hand, two recent cross-sectional studies failed to demonstrate differences on BMD between postmenopausal women on long term suppressive levothyroxine therapy for DTC and age matched controls<sup>84,85</sup>. However, in one of these Tournis et al reported a decrease of volumetric BMD by QCT at the radius and tibia<sup>85</sup> confirmed later by J.H. Moon et al concluding that TSH suppression in postmenopausal DTC patients was associated with decreased bone strength by altering bone geometry rather than BMD in hip area, especially in the FN<sup>86</sup>.

### *The impact of exogenous subclinical hyperthyroidism on bone mineral density of premenopausal women*

Premenopausal women due to preserved estrogen production exhibit less or no impact of thyroxine over-replacement on bone mass as proved by large population analyses and reviews<sup>47,79,81,82,87</sup>. On the contrary, a recent longitudinal study with a mean follow-up of 6.5 years showed that the risk of secondary osteoporosis in premenopausal women with low- or intermediate-risk thyroid cancer, adjusted for age, increased 4-fold when their TSH was suppressed long term, without decreasing cancer recurrence<sup>88</sup>.

### *The impact of exogenous subclinical hyperthyroidism on bone mineral density of men*

Few studies have included male cohorts examining the consequences of thyroid hormone therapy on BMD. Meta analyses and literature reviews have concluded that no significant effect on BMD has been observed in men receiving suppressive thyroxine therapy<sup>79,87,89,90</sup>. Conversely a small longitudinal study by Karner et al showed a statistically significant difference at the distal radius in men on long term suppressive levothyroxine therapy for DTC<sup>91</sup>.

## Exogenous subclinical hyperthyroidism and risk of fracture

Postmenopausal women with suppressed TSH levels (<0.1 mU/L) due to T4 over replacement are further exposed to a 4-fold increase of vertebral and hip fractures after 4 years of follow up than subjects with normal TSH values (>0.5 mU/L)<sup>69</sup>. A recent large observational study that evaluated fracture risk in patients >18 yrs old on long-term T4 therapy found a 2-fold increase in fracture risk in patients who had undetectable TSH levels ( $\leq 0.03$  mU/L) compared to those with low TSH concentrations (0.04-0.4 mU/L) and normal range TSH levels (0.4-4.0 mU/L)<sup>92</sup>. Therefore, the greatest risk exists with postmenopausal status, greater and longer TSH suppression.

### **Treatment management of bone loss induced by exogenous subclinical hyperthyroidism**

Harmful skeletal effects of exogenous SH can be avoided by appropriate titration of thyroxine therapy<sup>93</sup>. Indeed current American Thyroid Association guidelines for DTC patients recommend suppressed levels of TSH (<0.1 mU/L) only in patients at high risk with incomplete response to therapy, whereas a lesser degree of suppression (TSH 0.1-0.5 mU/L) is acceptable for those at intermediate risk. No suppression (TSH 0.5-2 mU/L) is recommended in those at low risk and/or without post-thyroidectomy remnant ablation<sup>94</sup>.

Kung and Yeung et al studied the implication of calcium supplementation (1000 mg daily for 2 years) in a small cohort of postmenopausal women with exogenous SH. The results, at 6-month intervals and at the end of study, revealed stable BMD in calcium supplemented patients, whereas the placebo group had significant bone loss of 5% at LS, 6.7% at FN, 4.7% at the trochanter, and 8.8% at Ward's triangle, with significantly lower BMD compared to the supplemented cohort<sup>95</sup>.

Schneider et al. examined the effects of concomitant estrogen therapy in a large cohort of postmenopausal women under levothyroxine treatment<sup>96</sup>. BMD in the estrogen replacement group was significantly higher at all sites compared to the group taking only thyroid hormones. After adjustment for multiple factors the BMD in women on both levothyroxine and estrogen was comparable to that of women solely taking estrogen, without use of thyroid hormone<sup>96</sup>. Although estrogens were routinely prescribed prior to the Women's Health Initiative, now days it is not recommended solely for the prevention or treatment of osteoporosis<sup>97</sup>.

It is well established that in peri- and postmenopausal women at risk for bone loss, adjunctive therapy with calcium supplements, Vitamin D, and other bone enhancing agents (bisphosphonates, denosumab, etc.) should be considered<sup>93,98,99</sup>.

## Conclusions

Normal balance of thyroid hormones plays a key role on skeletal growth and integrity. Studies in rodents show that not only thyroid hormones but also TSH is involved in the regulation of bone remodeling and perhaps in the increased turnover and subsequent osteoporosis observed in the hyperthyroid state. Overt hyperthyroidism is an established risk factor for osteoporosis and fracture. The fine control of bone health by thyroid hormones is documented by the negative effects on BMD and increased fracture risk seen in postmenopausal women with either endogenous or exogenous SH. Postmenopausal women and perhaps older men with endogenous SH should be considered for BMD testing and subsequent anti-thyroid therapy, especially those with SH grade 2. Postmenopausal women with exogenous SH should have BMD evaluation, with appropriate titration of suppressive therapy when indicated. Calcium/vitaminD3 supplementation and bone anti-resorption drugs, may be administered if necessary. Another key area requiring further studying is whether permanent post-operative hypoparathyroidism in DTC patients on long standing exogenous SH could offer a protection against thyroxine-mediated loss of BMD and fractures<sup>100</sup>.

Overall, effects of both endogenous and exogenous SH on bone is a field of ongoing research where larger and better designed studies are needed to answer today's gaps of knowledge.

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