Journal of Research and Practice on the Musculoskeletal System JRPMS

Mini Review

# Impact of subclinical hyperthyroidism on bone

**Stavroula Koutroumpi[1], Theodora Stratigou[2], Varvara Vlassopoulou[2]**

*[1]Endocrinologist, Greece; [2]Department of Endocrinology, Diabetes and Metabolism, Evangelismos Hospital, Athens, Greece*

**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[1]. In the middle of 18th 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 in1886 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[2,3]. 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[4]. 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[5]. 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[6,7]. The aforementioned negative feedback loop maintain euthyroidism[8,9].

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[4,10]. 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[11]. The type 1 deiodinase (DIO1) generatesT3, 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[12,13].

*The authors have no conflict of interest.*

***Corresponding author:*** *Stavroula Koutroumpi, Harilaou Trikoupi 168 Kifisia, Greece*

***E-mail:*** *Koutroumpi.lina@gmail.com*

***Edited by:*** *Konstantinos Stathopoulos*

***Accepted*** *25 February 2019*

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*a* and TR*β* with their subtypes TR*a*1, TR*a*2, and TR*β*1 mediate T3 action and are widely distributed[13,14]. TR*a*1 in bone has a 10- fold higher expression than TR*β*1 as seen by mutant mouse models with absence of TR*a*1 (-/-)[15,16]. 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[17,18]. 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[19,20].

## Skeletal physiology

Chondrocytes, osteoblasts, osteocytes and osteoclasts are the four major bone cell types. Chondrocytes appear initially during skeletal development[21]. 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[22]. Osteocytes that constitute 90-95% of bone cells function as mechanosensors[23]. Osteoclasts that comprise 1-2% of bone cells, are polarized multinucleated cells, derive from myeloid precursors and are responsible for bone resorption[24]. Chondrocytes and osteoblasts are directly responsive to thyroid hormone. If osteoclasts and osteocytes are direct target cells of thyroid hormones remains uncertain[25].

Bone formation occurs either via the intramembranous ossification from which derive the flat bones or via the endochondral ossification, typical of long bones[26]. 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[27,28].

In adults, the skeletal integrity is maintained due to the bone remodeling cycle[29,30]. 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[30-33].

## Hyperthyroidism

Overt hyperthyroidism is defined as an undetectable serum TSH with elevated levels of T3 and/or free T4[34]. SH is defined by a subnormal serum TSH, with normal levels of FT4, T3[35-38]. 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 mU/l), and grade 2 with undetectable serum TSH levels (<0.1 mIU/l)[35-38].

Endogenous hyperthyroidism either clinical or subclinical is most commonly due to Graves' disease (GD), toxic adenoma (TA) and toxic multinodular goiter (MNG)[37,38]. 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[39]. 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[36,37].

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[39-41]. 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[42,43].

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[44]. In children is relatively rare causing increased linear growth rate with persistent short stature[25,45]. At very young age, if severe, can cause craniosynostosis with neurological consequences[46].

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[35].

## 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[19,47-50]. In a cross-sectional study of pre- and postmenopausal women, BMD of postmenopausal women at sites of predominantly cortical bone was significantly affected[20]. 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[51,52]. 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[53]. 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[54-56].

### *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[20,36,49,50,57,58]. Seems that reserved ovary function plays a major protective role[59]. 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[58,60]. 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[20,57,61].

### *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[62]. 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[63-65]. 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)[66]. 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[67].

## Endogenous subclinical hyperthyroidism and risk of fracture

Conflicting results have also been reported regarding the risk of fractures in endogenous SH[55,62,68,69]. 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[62]. 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[68]. 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[70]. 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[71]. 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[72]. 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[73].

## 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[74-76]. 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[49]. 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[77]. 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[77]. 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[78]. 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[78]. 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[35]. On the contrary there is no evidence for treating young patients with SH grade 1 where monitoring alone is more than sufficient[35].

## 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[47,79,80]. 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[81]. 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[82]. 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[83]. 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[84,85]. However, in one of these Tournis et al reported a decrease of volumetric BMD by QCT at the radius and tibia[85] 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[86].

### *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[47,79,81,82,87]. 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[88].

### *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[79,87,89,90]. 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[91].

## 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)[69]. 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 (≤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)[92]. 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[93]. 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[94].

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[95].

Schneider et al. examined the effects of concomitant estrogen therapy in a large cohort of postmenopausal women under levothyroxine treatment[96]. 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 hormone96. 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[97].

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[93,98,99].

## 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[100].

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.

## *References*


1. Medvei VC. A history of endocrinology. Lancaster, UK: MTP Press; 1982.
2. Delling G, Kummerfeldt K, Von Recklinghausen F.D. A reminiscence on the occasion of the centenary of his publication Osteitis fibrosa or deformans, osteomalacia and osteoplastic carcinosis in their interrelationships [in German]. Dtsch Med Wochenschr 1991; 116:1976-1979.
3. Von Recklinghausen FD. Die Fibrose oder deformierende Ostitis, die Osteomalacie und die osteoplastische Carcinose in ihren gegenseitigen Beziehungen. In: Festschrift Rudolf Virchow zum 13. Berlin: Georg Reimer Verlag;1891.
4. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev 2002;23:38-89.
5. Kopp P. The TSH receptor and its role in thyroid disease. Cell Mol Life Sci 2001;58:1301-1322.
6. Abel ED, Ahima RS, Boers ME, Elmquist JK, Wondisford FE. Critical role for thyroid hormone receptor $\beta 2$ in the regulation of paraventricular thyrotropin-releasing hormone neurons. J Clin Invest 2001;107:1017-1023.
7. Nikrodhanond AA, Ortiga-Carvalho TM, Shibusawa N, et al. Dominant role of thyrotropin-releasing hormone in the hypothalamic-pituitary-thyroid axis. J Biol Chem 2006;281:5000-5007.
8. Andersen S, Bruun NH, Pedersen KM, Laurberg P. Biologic variation is important for interpretation of thyroid function tests. Thyroid 2003;13:1069-1078.
9. Bassett JH, WilliamsGR. Critical role of the hypothalamic-pituitary-thyroid axis in bone. Bone 2008;43:418-426.
10. St Germain DL, Galton VA, Hernandez A. Minireview: defining the roles of the iodothyronine deiodinases: current concepts and challenges. Endocrinology 2009;150:1097-1107.
11. Luongo C, Martin C, Vella K, et al. The selective loss of the type 2 iodothyronine deiodinase in mouse thyrotrophs increases basal TSH but blunts the thyrotropin response to hypothyroidism. Endocrinology 2015;156:745-754.
12. Bates JM, St Germain DL, Galton VA. Expression profiles of the three iodothyronine deiodinases, D1, D2, and D3, in the developing rat. Endocrinology 1999;140:844-851.
13. Forrest D, Sjöberg M, Vennström B. Contrasting developmental and tissue-specific expression of $\alpha$ and $\beta$ thyroid hormone receptor genes. EMBO J 1990;9:1519-1528.
14. Wexler JA, Sharretts J, Thyroid and bone. Endocrinology and Metabolism Clinics of North America 2007;36(3):673-705.
15. Bassett JHD, Williams GR. The skeletal phenotypes of TR$\alpha$ and TB$\beta$ mutant mice. Journal of Molecular Endocrinology 2009; 42(4):269-282.
16. Gauthier K, Plateroti M, Harvey CB et al., Genetic analysis reveals different functions for the products of the thyroid hormone receptor $\alpha$ locus. Molecular and Cellular Biology 2001;21(14):4748-4760.
17. Abe E, Marians RC,Yu W et al.TSH is a negative regulator of skeletal remodeling. Cell 2003;115(2):151-162.
18. Sun L, Davies TF, Blair HC, Abe E, Zaidi M. TSH and bone loss. Annals of the New York Academy of Sciences 2006;1068(1):309-318.
19. Grimnes G, Emaus N, Joakimsen RM, Figenschau Y, Jorde R. The relationship between serum TSH and bone mineral density in men and postmenopausal women: the Tromsø study. Thyroid 2008;18(11):1147-1155.
20. Foldes J, Tarjan G, Szathmari M, Varga F, Krasznai I, Horvath C. Bone mineral density in patients with endogenous subclinical hyperthyroidism: is this thyroid status a risk factor for osteoporosis? Clinical Endocrinology 1993;39(5):521-527.
21. Craft AM, Ahmed N, Rockel JS, et al. Specification of chondrocytes and cartilage tissues from embryonic stem cells. Development 2013;140:2597-2610.
22. Long F. Building strong bones: molecular regulation of the osteoblast lineage. Nat Rev Mol Cell Biol 2012;13:27-38.
23. Bonewald LF, Johnson ML. Osteocytes, mechanosensing and Wnt signaling. Bone 2008;42:606-615.
24. Väänänen HK, Zhao H, Mulari M, Halleen JM. The cell biology of osteoclast function. J Cell Sci 2000;113:377-381.
25. Bassett JH, Williams GR. Role of thyroid hormones in skeletal development and bone maintenance. Endocr Rev 2016;37(2):135-187.
26. Karsenty G, Kronenberg HM, Settembre C. Genetic control of bone formation. Ann Rev Cell Dev Biol 2009;25:629-648.
27. Kronenberg HM. Developmental regulation of the growth plate. Nature 2003;423(6937):332-336
28. Bonjour JP, Chevalley T. Pubertal timing, bone acquisition, and risk of fracture throughout life. Endocr Rev 2014;35(5):820-847.
29. Raggatt LJ, Partridge NC. Cellular and molecular mechanisms of bone remodeling. J Biol Chem 2010;285(33):25103-25108.
30. Dallas SL, Prideaux M, Bonewald LF. The osteocyte: an endocrine cell . . . and more. Endocr Rev 2013;34:658-690.
31. Lacey DL, Timms E, Tan HL, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell. 1998;93:165-176.
32. Baron R, Rawadi G. Wnt signaling and the regulation of bone mass. Curr Osteoporos Rep 2007;5:73-80.
33. Tolar J, Teitelbaum SL, Orchard PJ. Osteopetrosis. N Engl J Med 2004;351:2839-2849.

34. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P et al. American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis Thyroid 2016;26:1343-1421.
35. Biondi B, Bartalena L, Cooper DS, Hegedós L, Laurberg P, Kahaly GJ. The 2015 European Thyroid Association Guidelines on Diagnosis and Treatment of Endogenous Subclinical Hyperthyroidism Eur Thyroid J 2015;4:149-163.
36. Biondi B, Palmieri EA, Klain M, Schlumberger M, Filetti S, Lombardi G. Subclinical hyperthyroidism: clinical features and treatment options. Eur J Endocrinol 2005;152:1-9.
37. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocr Rev 2008; 29: 76-131.
38. Cooper DS, Biondi B. Subclinical thyroid disease. Lancet. 2012; 379: 1142-1154.
39. Bulow Pedersen I, Knudsen N, Jorgensen T, Perrild H, Ovesen L, Laurberg P. Large differences in incidences of overt hyper- and hypothyroidism associated with a small difference in iodine intake: a prospective comparative register-based population survey. J Clin Endocrinol Metab 2002;87:4462-4469.
40. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160:526-534.
41. Hollowell JG, Staehling NW, Flanders WD et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988-1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002;87:489-499.
42. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotropin (TSH) concentrations in the elderly in the United Kingdom. Clinical Endocrinology 1991;34(1):77-83.
43. Taylor PN, Iqbal A, Minassian C, Sayers A, Draman MS, Greenwood R et al. Falling threshold for treatment of borderline elevated thyrotropin levels-balancing benefits and risks: evidence from a large community-based study. JAMA Intern Med 2014;174:32-39.
44. Bours SP, van Geel TA, Geusens PP, Janssen MJ, Janzing HM, Hoffland GA et al. Contributors to secondary osteoporosis and metabolic bone diseases in patients presenting with a clinical fracture. J Clin EndocrinolMetab 2011;96(5):1360-1367.
45. Segni M, Gorman CA. The aftermath of childhood hyperthyroidism. J Pediatr Endocrinol Metab 2001;14(5):1277-1282.
46. Rasmussen SA, Yazdy MM, Carmichael SL, Jamieson DJ, Canfield MA, Honein MA. Maternal thyroid disease as a risk factor for craniosynostosis. Obstet Gynecol 2007;110(2):369-377.
47. Gorka J, Taylor-Gjevre RM, Arnason T. Metabolic and Clinical Consequences of Hyperthyroidism on Bone Density. Volume 2013, Article ID 638727, 11 pages.
48. Cummings SR, Nevitt MC, Browner WS et al. Risk factors for hip fracture in white women. New England Journal of Medicine 1995;332(12);767-773.
49. Mudde AH, Houben AJHM, Nieuwenhuijzen Kruseman AC. Bone metabolism during anti-thyroid drug treatment of endogenous subclinical hyperthyroidism. Clinical Endocrinology 1994; 41(4):421-424.
50. Ugur-Altun B, Altun A, Arikan E, Guldiken S, Tugrul A. Relationships existing between the serum cytokine levels and bone mineral density in women in the premenopausal period affected by Graves' disease with subclinical hyperthyroidism. Endocrine Research 2003;29(4):389-398.
51. Belaya ZE, Melnichenko GA, Rozhinskaya LY, Fadeev VV, Alekseeva TM, Dorofeeva OK et al. Subclinical hyperthyroidism of variable etiology and its influence on bone in postmenopausal women. HORMONES 2007;6(1):62-70.
52. Biondi B. Natural history, diagnosis and management of subclinical thyroid dysfunction. Best Pract Res Clin Endocrinol Metab 2012; 26: 431-46.
53. Ding B, Zhang Y, Li Q, Hu Y, Tao XJ, Liu BL et al. Low Thyroid Stimulating Hormone Levels Are Associated with Low Bone Mineral Density in Femoral Neck in Elderly Women Archives of Medical Research 2016;47;310-314.
54. Segna D, Bauer DC, Feller M, Schneider C, Fink HA, Aubert CE et al. Association between subclinical thyroid dysfunction and change in bone mineral density in prospective cohorts. Journal of Internal Medicine 2018;283:56-65
55. Yang R, Yao L, Fang Y, Sun J, Guo TK, Yang K et al. The relationship between subclinical thyroid dysfunction and the risk of fracture or low bone mineral density: a systematic review and meta-analysis of cohort studies. J Bone Miner Metab 2018;36(2):209-220.
56. Rosario PW, Carvalho M, Calsolari MR. Symptoms of thyrotoxicosis, bone metabolism and occult atrial fibrillation in older women with mild endogenous subclinical hyperthyroidism. Clinical Endocrinology 2016;85:132-136.
57. Gurlek A, Gedik O. Effect of endogenous subclinical hyperthyroidism on bone metabolism and bone mineral density in premenopausal women. Thyroid 1999;9(6):539-543.
58. Tauchmanova L, Nuzzo V, Del Puente A et al. Reduced bone mass detected by bone quantitative ultrasonometry and DEXA in pre- and postmenopausal women with endogenous subclinical hyperthyroidism. Maturitas 2004;48(3):299- 306.
59. Saler T, Ahbab S, Sağlam ZA, Keşkek ŞÖ, Kurnaz S. Endogenous subclinical hyperthyroidism may not lead to bone loss in premenopausal women. HIPPOKRATIA 2014;18(3):240-244.
60. PW Rosario. Bone and heart abnormalities of subclinical hyperthyroidism in women below the age of 65 years. Arquivos Brasileiros de Endocrinologia e Metabologia 2008;52(9):1448-1451.
61. De Menis E, Da Rin G, Roiter I, Legovini P, Foscolo G, and Conte N. Bone turnover in overt and subclinical hyperthyroidism due to autonomous thyroid adenoma. Hormone Research 1992;37(6):217-220.
62. Lee JS, Buzkova P, Fink HA et al. Subclinical thyroid dysfunction and incident hip fracture in older adults. Archives of Internal Medicine 2010;170(21):1876-1883.
63. Chin KY, Soelaiman IN, Mohamed IN, Aminuddin A, Johari MH, Ngah WZW. Thyroid-stimulating hormone is significantly associated with bone health status in men. Int J Med Sci 2013;10:857-863.
64. Roef G, Lapauw B, Goemaere S, et al. Thyroid hormone status within the physiological range affects bone mass and density in healthy men at the age of peak bone mass. Eur J Endocrinol 2011;164:1027-1034.
65. Shi Y, Sun M, Wang Z, et al. Association between calcaneus quantitative ultrasound (QUS) parameters and thyroid status in middle-aged and elderly Chinese men with euthyroidism: a population-based cross-sectional study. Endocrine 2014;47:227-233.
66. Waring AC, Harrison S, Fink HA, et al. A prospective study of thyroid function, bone loss, and fractures in older men: The MrOS study. J Bone Miner Res 2013;28:472-479.
67. Siru R, Alfonso H, Chubb SAP, Golledge J, Flicker L, Yeap BB. Subclinical thyroid dysfunction and circulating thyroid hormones are not associated with bone turnover markers or incident hip fracture in older men doi: 10.1111/cen.13615
68. Vadiveloo T, Donnan PT, Cochrane L, Leese GP. The Thyroid Epidemiology, Audit, and Research Study (TEARS): morbidity in patients with endogenous subclinical hyperthyroidism. J Clin Endocrinol Metab 2011;96:1344-1351.
69. Bauer DC, Ettinger B, Nevitt MC, Stone KL. Study of Osteoporotic

Fractures Research Group: Risk for fracture in women with low serum levels of thyroid-stimulating hormone. Ann Intern Med 2001; 134: 561-568.
70. Abrahamsen B, Jorgensen HL, Laulund AS, Nybo M, Brix TH, Hegedus L. Low serum thyrotropin level and duration of suppression as a predictor of major osteoporotic fractures. The OPENTHYRO Register Cohort. J Bone Miner Res 2014;29:2040-2050.
71. Abrahamsen B, Jorgensen HL, Laulund AS, Nybo M, Bauer D, Brix TH, Hegedus L. The excess risk of major osteoporotic fractures is driven by cumulative hyperthyroid as opposed to hypothyroid time. An observational register-based time resolved cohort analysis. J Bone Miner Res 2015 May;30(5):898-905
72. Wirth CD, Blum MR, da Costa BR, Baumgartner C, Collet TH, Medici M et al. Subclinical thyroid dysfunction and the risk for fractures: a systematic review and meta-analysis. Ann Intern Med 2014;5;161:189-199.
73. Blum MR, Bauer DC, Collet TH, Fink HA, Cappola AR, da Costa BR et al. Thyroid Studies Collaboration: Subclinical thyroid dysfunction and fracture risk: a meta-analysis. JAMA 2015;313:2055-2065.
74. Greenlund LJS, Nair KS, Brennan MD. Changes in body composition in women following treatment of overt and subclinical hyperthyroidism. Endocrine Practice 2008;14(8):973-978,.
75. Vestergaard P, Mosekilde L, Brixen K. Treatment of osteoporosis with antiresorptive drugs (vitamin D, calcium, estrogen and gestagen, raloxifene, bisphosphonates and calcitonin). Ugeskrift for Laeger 2005;167(8):883-887.
76. Buscemi B, Verga S, Cottone S et al. Favorable clinical heart and bone effects of anti-thyroid drug therapy in endogenous subclinical hyperthyroidism. Journal of Endocrinological Investigation 2007;30(3):230-235,.
77. Faber J, Jensen IW, Petersen L, Nygaard B, Hegedus L, Siersbæk-Nielsen K. Normalization of serum thyrotropin by means of radioiodine treatment in subclinical hyperthyroidism: effect on bone loss in postmenopausal women. Clinical Endocrinology 1998;48(3):285-290.
78. Rosario PW. Radioiodine therapy in elderly patients with subclinical hyperthyroidism due to non-voluminous goiter and its effects on bone metabolism. Arquivos Brasileiros deEndocrinologia & Metabologia 2013;57(2):144-147.
79. Heemstra KA, Hamdy NAT, Romijn JA, Smit JWA. The effects of thyrotropin-suppressive therapy on bone metabolism in patients with well-differentiated thyroid carcinoma. Thyroid 2006; 16(6):583-591.
80. Cipriani C, Romagnoli E, Scarpiello A, Angelozzi M, Montesano T, Minisola S. Phalangeal quantitative ultrasound and bone mineral density in evaluating cortical bone loss: a study in postmenopausal women with primary hyperparathyroidism and subclinical Iatrogenic hyperthyroidism. Journal of Clinical Densitometry 2009;12(4):456-460.
81. Faber J, Galloe AM. Changes in bone mass during prolonged subclinical hyperthyroidism due to L-thyroxine treatment: ameta-analysis. European Journal of Endocrinology 1994;130(4):350-356.
82. Uzzan B, Campos J, Cucherat M, Nony P, Boissel JP, Perret GY. Effects on bone mass of long term treatment with thyroid hormones: a meta-analysis. Journal of Clinical Endocrinology and Metabolism 1996;81;(12):4278-4289.
83. Sugitani I, Fujimoto Y. Effect of postoperative thyrotropin suppressive therapy on bone mineral density in patients with papillary thyroid carcinoma: A prospective controlled study. Surgery 2011;150:1250-1257
84. De Melo TG, Da Assumpção LV, Santos AO et al. Low BMI and low TSH value as risk factors related to lower bone mineral density in postmenopausal women under levothyroxine therapy for differentiated thyroid carcinoma. Thyroid Res 2015;8:7.
85. Tournis S, Antoniou JD, Liakou CG et al. Volumetric bone mineral density and bone geometry assessed by peripheral quantitative computed tomography in women with differentiated thyroid cancer under TSH suppression. Clin Endocrinol (Oxf) 2015;82:197-204.
86. Moon JH, Jung KY, Kim KM, Choi SH, Lim S, Park YJ et al. The effect of thyroid stimulating hormone suppressive therapy on bone geometry in the hip area of patients with differentiated thyroid carcinoma. Bone 2016;83:104-110.
87. Nicholls JJ, Brassill MJ, Williams GR, Bassett JHD. The skeletal consequences of thyrotoxicosis. The Journal of Endocrinology 2012;213:209-221.
88. Wang LY, Smith AW, Palmer FL et al. Thyrotropin suppression increases the risk of osteoporosis without decreasing recurrence in ATA low- and intermediate-risk patients with differentiated thyroid carcinoma. Thyroid 2015;25:300-307.
89. HeijckmannAC, HuijbertsMSP, Geusens Pet al. Hip bone mineral density, bone turnover and risk of fracture in patients on long-term suppressive L-thyroxine therapy for differentiated thyroid carcinoma. Eur J Endocrinol 2005;153:23-29.
90. Reverter JL, Colome E, Holgado S et al. Bone mineral density and bone fracture in male patients receiving long-term suppressive levothyroxine treatment for differentiated thyroid carcinoma. Endocrine 2010;37:467-472.
91. Karner I, Hrgovic Z, Sijanovic S et al. Bone mineral density changes and bone turnover in thyroid carcinoma patients treated with supraphysiologic doses of thyroxine. Eur J Med Res 2005;10:480-488.
92. Flynn RW, Bonellie SR, Jung RT, MacDonald TM, Morris AD, Leese GP. Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-termthyroxine therapy. Journal of Clinical Endocrinology and Metabolism 2010;95(1):186-193.
93. Appetecchia M. Effects on bone mineral density by treatment of benign nodular goiter with mildly suppressive doses of Lthyroxine in a cohort women study. Hormone Research 2005;64(6):293-298.
94. Haugen BR, Alexander EK, Bible KC, Doherty G.M, Mandel S.J, Nikiforov Y.E, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26(1):1-133
95. Kung AWC, Yeung SS. Prevention of bone loss induced by thyroxine suppressive therapy in postmenopausal women: the effect of calcium and calcitonin. Journal of Clin Endocrinol and Metabol 1996;81(3):1232-1236.
96. Schneider DL, Barrett-Connor EL, Morton DJ. Thyroid hormone use and bone mineral density in elderly women. Effects of estrogen. Journal of the American Medical Association 1994;271(16):1245-1249.
97. Anderson GL, Limacher M. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the women's health initiative randomized controlled trial. Journal of the American Medical Association 2004;291(14):1701-1712.
98. Williams GR. Is prophylactic anti-resorptive therapy required in thyroid cancer patients receiving TSH-suppressive treatment with thyroxine? J Endocrinol Invest 2014;37(8):775-779.
99. Vescini F, Attanasio R, Balestrieri A, Bandeira F, Bonadonna S, Camozzi V et al. Italian association of clinical endocrinologists (AME) position statement: drug therapy of osteoporosis. J Endocrinol Invest 2016;39(7):807-834.
100. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. Postsurgical hypoparathyroidism- risk of fractures, psychiatric diseases, cancer, cataract and infections. J Bone Miner Res 2014;29(11):2504-2510.