

Bone manifestations of thyroid disorders

Kostné prejavy porúch štítnej žľazy

Bence Bakos¹, István Takács¹, Paula H. Stern², Péter Lakatos¹

- ¹1st Department of Medicine, Semmelweis University, Budapest, Hungary
- ²Department of Pharmacology, Northwestern University, Chicago, IL, USA

☑ prof. Péter Lakatos, MD, PhD, DSc | lakatos.peter@med.semmelweis-univ.hu | www.semmelweis.hu

Received | Doručeno do redakce | Doručené do redakcie 12. 10. 2018 Accepted | Přijato po recenzi | Prijaté po recenzii 1. 11. 2018

Abstract

Thyroid hormones affect the metabolism, proliferation, and differentiation of every cell in the body, skeletal tissue being no exception. Thyroxine influences all types of bone cells from osteoblasts and osteocytes to chondrocytes and osteoclasts. It is thus no wonder that disruptions in thyroid function can have a multitude of consequences on both the juvenile and the mature skeleton. Some of these thyroid conditions like resistance to thyroid hormones (RTH) are quite rare, while others are among the most common endocrinopathies both in children and in adults. Hyperthyroidism for example is among the most common causes of secondary osteoporosis, and in recent years, even variations in normal thyroid function have been linked to fracture risk. Therefore, it is vital for the practicing osteologist to familiarize himself or herself with the relationship between different thyroid diseases and the bone. In our paper, we summarize the basics of the cellular actions of thyroid hormones, their role in the regulation of bone metabolism, and the clinical significance of the most common thyroid conditions for everyday practice.

Key words: bone metabolism – endocrinopathies – hyperthyroidism – secondary osteoporosis – thyroid disorders – thyroid hormones – thyroxine

Abstrakt

Hormóny štítnej žľazy ovplyvňujú metabolizmus, proliferáciu a diferenciáciu každej bunky v tele a kostné tkanivo nie z tohto pravidla žiadnou výnimkou. Tyroxín ovplyvňuje všetky typy kostných buniek, od osteoblastov a osteocytov až po chondrocyty a osteoklasty. Neprekvapuje preto, že rôzne narušenia funkcie štítnej žľazy môžu mať pre kostru mladistvého i zrelého človeka celý rad následkov. Niektoré z týchto porúch funkcie štítnej žľazy, ako je rezistencia na tyreoidálne hormóny (RTH), sú pomerne vzácne, zatiaľ čo iné patria medzi najzvyčajnejšie endokrinopatie ako aj u detí, tak aj u dospelých. Napríklad hypertyreóza je jednou z najčastejších príčin sekundárnej osteoporózy, pričom v posledných rokoch je aj kolísanie v normálnej funkcii štítnej žľazy spojované s rizikom zlomeniny. Pre praktikujúceho osteológa je teda nevyhnutné sa dôkladne zoznámiť so vzťahom, ktorý jestvuje medzi rôznymi ochoreniami štítnej žľazy a stavom kostí. V našom príspevku zhŕňame základne poznatky o bunkovom pôsobení tyreoidálnych hormónov, o ich úlohe pri regulácii kostného metabolizmu aj klinický význam najčastejších porúch funkcie štítnej žľazy pre každodennú prax.

Kľúčové slová: endokrinopatie – hormóny štítnej žlazy – hypertyreóza – kostný metaboizmus – sekundárna osteoporóza – tyreopatire – tyroxín

Cellular effects of thyroid hormones

In all types of human cells most, though not all effects of thyroid hormones are mediated through nuclear receptors belonging to either the TR α or TR β class. These receptors are part of the nuclear receptor (NR) superfam-

ily and exert their action by interacting with the thyroid hormone response elements in the target genes' promoter region following the binding of their ligands [1]. In the absence of thyroid hormones TRs can act as repressors of the same target genes as part of a co-repressor complex. Various other complex interactions have also been documented between different types of nuclear receptors, such as thyroid receptors, retinoid receptors, vitamin D receptors, through heterodimerization and the formation of co-activator and co-repressor complexes. TRB (encoded on chromosome 3) is the dominant thyroid receptor isoform in hypothalamus, pituitary and thyroid, playing a crucial role in the negative feedback of the hypothalamic-pituitary-thyroid (HPT) axis. TRB also seems to be the primary isoform in certain peripheral tissues, such as liver and kidneys. TRa1, a splice variant of the TRa gene (located on chromosome 17) seems to be the primary isoform in the heart and the brain and also in both the developing and the adult skeleton [2]. Fast acting non-genomic effects of thyroid hormones have also been recognized for decades. Receptors for T3 have been identified both on the plasma membrane, cytoplasm and in the mitochondria. Non-genomic response to thyroid hormones in osteoblasts has been verified [3]. Though several advances have been made in this area in recognizing the downstream signaling cascade of these receptor types, their clinical significance in bone and other tissues still remains controversial.

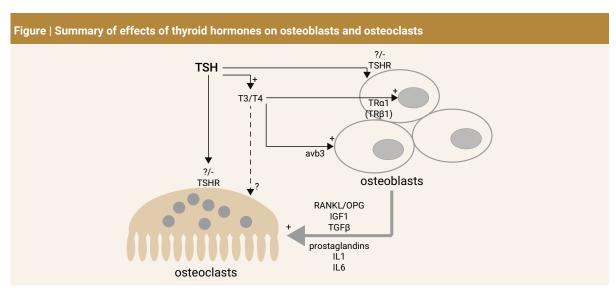
Triiodothyronine (T3) is necessary for chondrocyte differentiation, growth plate development and the preservation of the structure of the epiphyseal cartilage. Thyroid receptors are present on both reserve zone and proliferating chondrocytes while they disappear from differentiated chondrocytes [4]. TRs are also abundant in osteoblast, and osteoblastic bone marrow stromal cells, where T3 promotes differentiation, proliferation and bone formation. Levels of both osteogenic serum markers and secondary mediators of osteoblast differentiation, such as IL6, IL8, IGF1, and FGFR1 increases in response to T3 treatment (Figure), both in vitro and in vivo [5]. Knock-out or knock-in

animal models with functional hypothyroidism show impaired bone formation, growth, and mineralization. Thyroid hormones also stimulate bone resorption, though whether this is a result of a direct stimulatory effect of T3 on osteoclasts or an action mediated by osteoblast derived secondary mediators such as prostaglandins, the RANKL/OPG pathway, IGF1, or TGF β , is still debated. Animal models with signs of hyperthyroid skeletal changes such as the TR β PV knock-in mouse that has dominant-negative antagonistic TR β receptors, show signs of impaired growth, early closure of the epiphyseal plates, decreased trabecular bone mass, and advanced endochondral and intramembranous ossification [6].

In recent years a complex and quasi-independent effect of TSH on bone cells has been hypothesized. TSH-receptors (TSHR) are present in many extrathyroidal organs including the kidneys, the brain, the heart, retroorbital connective tissues, bone marrow and bone cells. TSHR are present on both osteoblasts, osteoclasts and chondrocytes, and a role for potential local ligands besides TSH has also been implied. The physiologic role of TSH and TSHR in the bone is still contradictory [7]. Studies of cell cultures and animals show a potential inhibitory role in remodeling with the inhibition of both osteoblast and osteoclast function, though certain authors report increased bone formation with TSH treatment.

Congenital thyroid disorders

With an incidence of approximately 1:3000, congenital hypothyroidism is the most common inborn endocrine disease. Most cases are caused by thyroid dysgenesis resulting in primary hypothyroidism. Genetic defects of thyroid biosynthesis, congenital central hypothyroidism and syndromic hypothyroidism are also potential causes though extremely rare. Symptoms are min-



imal at birth and manifest later following the first few month of life [8]. Skeletal manifestations are among the first signs of this condition. These include decreased growth or in extreme cases complete growth arrest, delayed bone age and maturation and a typical hypothyroid phenotype with a broad face, flat nasal bridge, patent sutures, hypertelorism, hip dislocation and scoliosis. The high prevalence of the disease, the availability of inexpensive and simple screening, and the dreaded sequela of Intellectual disability resulted in widespread screening beginning in the 1970s. This makes untreated congenital hypothyroidism a rarity in the western world. Skeletal manifestations can be completely ameliorated with timely L-thyroxine substitution.

Compared to congenital hypothyroidism, cases of neonatal hyperthyroidism are rare. Most cases are reported in children with mothers suffering from Graves' disease. In these instances symptoms are usually transient as maternal thyroid-stimulating immunoglobulins passing the placental barrier that are the pathogenic cause get cleared eventually [9]. The genetic background of extremely rare cases of persistent congenital hyperthyroidism has also been elucidated with the description of activating mutations in the thyrotropin-receptor genes [10]. In infants, children and adolescents hyperthyroidism leads to accelerated chondrocyte differentiation and bone formation, increased growth speed followed by an early closure of the epiphyseal plates resulting in a short stature. In extreme cases of congenital hyperthyroidism cranyosynostosis might occur.

Resistance to thyroid hormones (RTH) has been first described in the 1960s. The first of these conditions to be recognized was RTHB, caused by a dominant negative mutation of the TRB gene. To this date approximately 3000 cases with over 120 causative mutations have been described with an autosomal dominant heritability. Animal models like the above mentioned TRBPV mice have also been generated. With the disruption of the HPT axis, patients suffering from RTHβ have unsupressable TSH and elevated T3 and T4 levels. Symptoms present with different expressivity and include goiter, cognitive impairment, tachycardia, hypacusis, and decreased weight. Skeletal manifestations can be characterized as hyperthyroid with accelerated bone age and chondrocyte maturation resulting in early closure of the growth plates and short stature. In certain patients growth delay is accompanied with hypothyroid-like bone changes are dominant with retarded bone age and stippled epiphyses. Treatment when necessary consists of additional L-thyroxine supplementation [11].

While animal models have existed in the past, the human condition of RTHa, with a dominant negative mutation in the TRa gene has just been recently demon-

strated. With the HPT axis intact, laboratory changes are usually minimal in these patients, though the low number of reported cases makes it harder to generalize. TSH is mostly reported to be within normal limits, accompanied with only slight changes in free thyroid hormone levels of which an increase FT3/FT4 and FT3/rT3 ratio seem to be the most consistent. Skeletal manifestations of this probably underdiagnosed disease seem to be the most dominant, though other signs of hypothyroidism can also be present. Delayed growth and decreased bone age resulting in patent sutures macrocephaly and epiphyseal dysgenesis are most commonly reported [12]. No consensus exists regarding treatment, and thyroxine substitution seems to have limited effect.

Thyroid disorders in adults

Hyperthyroidism is one of the most common causes of secondary osteoporosis. Skeletal abnormalities in untreated Graves' patients have been described in the 19th century. Though thyroid hormones exert a stimulatory effect on both osteoblasts and osteoclasts, the net result of this is an increased turnover, a shortened remodeling cycle and a net bone loss that is most pronounced at the cortical-rich sites of the skeleton. This high turnover state is evident by the increased levels of both formation and resorption markers reported in human, animal and in vitro studies. The formers include alkaline phosphatase, osteocalcin, carboxyterminal propeptide of type I procollagen (PICP), while the latters: pyridinoline and hydroxypyridinoline crosslinks, urinary N-terminal telopeptide of type I collagen (NTX), and carboxyterminal-1-telopeptide (ICTP) [13]. Bone density is accordingly decreased at all sites of measurement, especially at the distal radius, and fracture risk is substantially increased in all patients, especially in the elderly and in postmenopausal women [14-15]. The increment in the risk of fractures seems to be associated with the severity and duration of the thyrotoxic state and it also seems to exceed the degree of which the bone density is affected. This discrepancy seems to be partly explained by the decreased muscle strength and increased fall risk in untreated hyperthyroidism. Bone quality may also be compromised in hyperthyroidism as shown by Kuzma et al [16]. Serum fractalkine, an important chemokine linking thyroid status to bone metabolism, was positively correlated with fT4 and negatively with trabecular bone score values.

Severe osteoporosis resulting from untreated thyrotoxicosis is now rare because of early diagnosis and treatment. Antiporotic agents seem to be equally effective in hyperthyroidism-related bone disease, though in these patients treatment of the underlying thyroid disease is paramount [17]. Use of antithyroid drugs is

associated with a significantly reduced fracture risk which might be caused by the reduction in thyroid hormone levels [18]. There seems to be no difference between different treatment modalities e.g. thyrostatic drugs, radioactive iodine and surgery in their ability to ameliorate hyperthyroidism-related osteoporosis secondary osteoporosis.

Bone loss and increased fracture risk also characterize subclinical hyperthyroidism. Whether this is a consequence of the slight changes in thyroid hormone levels and ratios or the direct effect of decreased thyrotropin levels is still debated. Subclinical hyperthyroidism is even more common than overt hyperthyroidism, and apart from Graves' disease and toxic adenomas it is often a result of deliberate thyroxine "overdosing" as part of the follow up of the treatment of differentiated thyroid cancers. Data regarding the magnitude of the effect of subclinical hyperthyroidism on BMD and fracture risk is still controversial [19-22]. Age, sex, menopausal status and the etiology of hyperthyroidism seem to be key factors. Based on the findings of large meta-analyses on the topics, current guidelines advocate for the treatment of otherwise symptom-free individuals with subclinical hyperthyroidism who present with severe osteoporosis or low-energy fractures irrespective of the degree of TSH suppression. In patients receiving large doses of L-thyroxine as part of their treatment for reducing risk of thyroid cancer recurrence, risk of fractures must be weighted by the clinician on an individual basis.

In recent years a number of studies found an increased fracture risk in association with lower TSH and higher FT3 and FT4 values even among individuals with normal thyroid function [23-25]. Similarly to studies addressing subclinical hyperthyroidism, results seem to be most consistent in case of postmenopausal women. It is hypothesized that turnover and bone loss in response to thyroid hormones (or a decrease in TSH) increases in a linear fashion with no clear line separating physiologic from pathologic remodeling. Thus, in patient populations with an already high risk for osteoporosis, minimal variations in thyroid function could lead to an increase in osteoporosis and fracture risk. Due to the ambiguity that characterize this field of inquiry, no treatment recommendations exist currently for patients with severe osteoporosis and thyroid function at the upper ranges of the normal spectrum.

Hypothyroidism in infants and adolescents, as mentioned previously can lead to potentially severe skeletal consequences like growth impairment and a persistent short stature. In adults the situation is much more benign. Most cases of thyroid hypofunction is caused by Hashimoto's thyroiditis with a prevalence of 0,1–2%. Based on experimental models and the histomorpho-

metric analysis of patients, both osteoblast and osteoclast function decrease in hypothyroidism. Biochemical markers of bone formation and resorption also follow this pattern of reduction. Nevertheless, patients with long-standing untreated hypothyroidism are scarce, and the decreased remodeling rarely leads to significant changes in bone mineral content. Somewhat more surprisingly fracture risk also remains unchanged although certain studies show an increased risk of fracture in hypothyroid patients following the initiation of hormone replacement [26]. The most plausible explanation of the increased fracture risk is a possible sudden increase in remodeling related to treatment, and/or a certain risk of overtreatment in this patient population. Although more recent studies failed to reproduce an increased fracture risk [27], careful initiation and dose changes in thyroxine treatment of elderly osteoporotic patients is still warranted. Like overt thyroid hypofunction, subclinical hypothyroidism seems to have no deleterious effect on the adult skeleton.

References

- 1. Germain P, Staels B, Dacquet C et al. Overview of nomenclature of nuc1. Germain P, Staels B, Dacquet C et al. Overview of nomenclature of nuclear receptors. Pharmacol Rev 2006; 58(4): 685–704. Available on DOI: https://doi:10.1124/pr.58.4.2.
- 2. Abu EO, Bord S, Horner A et al. The expression of thyroid hormone receptors in human bone. Bone 1997; 21(2): 137–142.
- **3.** Lakatos P, Stern PH. Evidence for direct non-genomic effects of triiodothyronine on bone rudiments in rats: stimulation of the inositol phosphate second messenger system. Acta Endocrinol (Copenh) 1991; 125(5): 603–608.
- **4.** Gouveia CHA, Miranda-Rodrigues M, Martins GM et al. Thyroid Hormone and Skeletal Development. Vitam Horm 2018; 106: 383–472. Available on DOI: http://doi:10.1016/bs.vh.2017.06.002.
- **5.** Varga F, Rumpler M, Zoehrer R et al. T3 affects expression of collagen I and collagen cross-linking in bone cell cultures. Biochem Biophys Res Commun 2010; 402(2): 180–185. Available on DOI: http://doi:10.1016/j.bbrc.2010.08.022.
- **6.** O'Shea PJ, Bassett JH, Cheng SY et al. Characterization of skeletal phenotypes of TRalpha1 and TRbeta mutant mice: implications for tissue thyroid status and T3 target gene expression. Nucl Recept Signal 2006; 4: e011. Available on DOI: https://doi:10.1621/nrs.04011.
- 7. Ma R, Morshed S, Latif R et al. The influence of thyroid-stimulating hormone and thyroid-stimulating hormone receptor antibodies on osteoclastogenesis. Thyroid 2011; 21(8): 897–906. Available on DOI: http://doi:10.1089/thy.2010.0457.
- **8.** Ford G, LaFranchi SH. Screening for congenital hypothyroidism: a worldwide view of strategies. Best Pract Res Clin Endocrinol Metab 2014; 28(2):175–187. Available on DOI: http://doi:10.1016/j.beem.2013.05.008>.
- **9.** Polak M, Legac I, Vuillard E et al. Congenital hyperthyroidism: the fetus as a patient. Horm Res 2006; 65(5): 235–242. Available on DOI: http://doi:10.1159/000092454>.
- **10.** Chester J, Rotenstein D, Ringkananont U et al. Congenital neonatal hyperthyroidism caused by germline mutations in the TSH receptor gene. J Pediatr Endocrinol Metab 2008; 21(5): 479–486.
- **11.** Refetoff S1, Weiss RE, Usala SJ. The syndromes of resistance to thyroid hormone. Endocr Rev 1999; 14(3): 348–399. Available on DOI: http://doi:10.1210/edrv-14-3-348.
- **12.** Demir K, van Gucht AL, Büyükinan M, et al. Diverse Genotypes and Phenotypes of Three Novel Thyroid Hormone Receptor-α Mutations. J Clin Endocrinol Metab 2016; 101(8): 2945–2954. Available on DOI: http://doi.org/10.1210/jc.2016-1404.

- **13.** Garnero P, Vassy V, Bertholin A et al. Markers of bone turnover in hyperthyroidism and the effects of treatment. J Clin Endocrinol Metab 1994; 78(4): 955–959. Available on DOI: http://doi: 10.1210/jcem.78.4.8157727.
- **14.** Vestergaard P, Mosekilde L. Hyperthyroidism, bone mineral, and fracture risk a meta-analysis. Thyroid 2003; 13(6): 585–593. Available on DOI: http://doi:10.1089/105072503322238854.
- **15.** El Hadidy el HM, Ghonaim M, El Gawad SSH et al. Impact of severity, duration, and etiology of hyperthyroidism on bone turnover markers and bone mineral density in men. BMC Endocr Disord 2011; 11:15. Available on DOI: http://doi: 10.1186/1472-6823-11-15.
- **16.** Kužma M, Vaňuga P, Binkley N et al. High serum fractalkine is associated with lower trabecular bone score in premenopausal women with Graves' disease. Horm Metab Res 2018; 50(8): 609–614. Available on DOI: https://doi:10.1055/a-0633-2814.
- 17. Nagasaka S, Sugimoto H, Nakamura T et al. Antithyroid therapy improves bony manifestations and bone metabolic markers in patients with Graves' thyrotoxicosis. Clin Endocrinol (0xf) 1997; 47(2): 215–221.
- **18.** Vestergaard P, Rejnmark L, Mosekilde L. Influence of hyper- and hypothyroidism, and the effects of treatment with antithyroid drugs and levothyroxine on fracture risk. Calcif Tissue Int 2005; 77(3): 139–144. Available on DOI: http://doi:10.1007/s00223-005-0068-x.
- **19.** Segna D, Bauer DC, Feller M et al. Association between subclinical thyroid dysfunction and change in bone mineral density in prospective cohorts. Intern Med 2018; 283(1): 56–72. Available on DOI: http://doi.doi.10.1111/joim.12688.
- **20.** Kim CW, Hong S, Oh SH, Lee JJ et al. Change of Bone Mineral Density and Biochemical Markers of Bone Turnover in Patients on Suppressive Levothyroxine Therapy for Differentiated Thyroid Carcinoma.

- J Bone Metab 2015; 22(3): 135–141. Available on DOI: http://doi:10.11005/jbm.2015.22.3.135.
- **21.** 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(3): 472–479. Available on DOI: http://doi.10.1002/jbmr.1774.
- **22.** Garin MC, Arnold AM, Lee JS et al. Subclinical thyroid dysfunction and hip fracture and bone mineral density in older adults: the cardiovascular health study. J Clin Endocrinol Metab 2014; 99(8): 2657–2664. Available on DOI: http://doi: 10.1210/jc.2014-1051.
- **23.** van Rijn LE, Pop VJ, Williams GR. Low bone mineral density is related to high physiological levels of free thyroxine in peri-menopausal women. Eur J Endocrinol 2014; 170(3): 461–468. Available on DOI: http://doi:10.1530/EJE-13-0769>.
- **24.** Leader A, Ayzenfeld RH, Lishner M et al. Thyrotropin levels within the lower normal range are associated with an increased risk of hip fractures in euthyroid women, but not men, over the age of 65 years. J Clin Endocrinol Metab 2014; 99(8): 2665–2673. Available on DOI: http://doi:10.1210/jc.2013-2474>.
- **25.** Hwangbo Y, Kim JH, Kim SW et al. High-normal free thyroxine levels are associated with low trabecular bone scores in euthyroid postmenopausal women. Osteoporos Int 2016; 27(2): 457–462. Available on DOI: http://doi:10.1007/s00198-015-3270-3.
- **26.** Vestergaard P, Mosekilde L. Fractures in patients with hyperthyroidism and hypothyroidism: a nationwide follow-up study in 16,249 patients. Thyroid 2002; 12(5): 411–419. Available on DOI: http://doi:10.1089/105072502760043503.
- **27.** González-Rodríguez LA, Felici-Giovanini ME, Haddock L. Thyroid dysfunction in an adult female population: A population-based study of Latin American Vertebral Osteoporosis Study (LAVOS) Puerto Rico site. P R Health Sci J 2013; 32(2): 57–62.