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Review



# IMPACT OF GRAVES' DISEASE AND ANTITHYROID DRUG THERAPY ON BONE MINERAL DENSITY – PATHOPHYSIOLOGICAL MECHANISMS AND CLINICAL RELEVANCE

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SUMMARY – Graves' disease is an autoimmune disease characterized by excessive thyroid hormone production. One of the consequences of that state can be a decrease in bone mineral density (BMD). Graves' disease is often treated with antithyroid drugs (ATD) as first line therapy, which can lead to disease remission. Moreover, recent data show that improvement in BMD can be expected. However, vitamin D deficiency can coexist along with Graves' disease, which is also involved in the process of bone remodeling. It is still not known whether lower values of vitamin D can contribute to onset of Graves' disease and if its supplementation might be helpful in therapy for hyperthyroidism. In the past couple of decades, osteopenia and osteoporosis have become a major health burden not only in post-menopausal women but also as a result of other diseases, leading to extensive research into various pathophysiological mechanisms responsible for bone remodeling. The Wnt (wingless integrated) signaling pathway is a very important factor in bone homeostasis, especially the canonical pathway. Present data indicate that stimulation of the Wnt pathway leads to bone mass increase and, in contrast, its inhibition leads to bone mass decrease. Hence, inhibitors of the canonical Wnt pathway became the focus of interest, in particular sclerostin and dickkopf 1 (DKK1). Hyperthyroidism and osteopenia/osteoporosis are quite common today and can coexist together or as separate entities. In this article, we aimed to give an overview of possible associations and potential mutual pathophysiological mechanisms.

Key words: *Graves' disease; bone mineral density; Wnt signaling pathway; sclerostin; dickkopf 1*

## Introduction

Hyperthyroidism is a state of excessive production of thyroid hormones which causes symptoms and signs of hypermetabolism. Hyperthyroidism can be caused by toxic adenoma (TA), multinodular toxic goiter (MNTG) and Graves' disease. TA and MNTG are usually treated by radioiodine therapy or surgery. Graves' disease is an autoimmune disease caused by elevated TSH receptor autoantibodies (antiTSH-R). First-line treatments are antithyroid drugs (ATD). According to incidence data, which do differ, the frequency is approximately 20-50 cases in 100.000 people, mostly occurring in people from 30 to 60 years of

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age. It is more common in women, in which risk of hyperthyroidism is 3%, compared to 0.5% in men.

Hyperthyroidism, i.e. Graves' disease, can affect the skeletal system by shortening the remodeling cycle of the bone[1]. Phases of bone formation and bone resorption are disrupted in a way that bone resorption overcomes bone formation. The whole process may ultimately cause reduction in bone mineral density (BMD), leading to osteopenia or osteoporosis. Loss of BMD in adults is 10-20%, mostly in the cortical bone[1]. Osteopenia is not a disease, but it can lead to higher fracture risk, and can lead to osteoporosis by exacerbating bone mass loss. Osteoporosis is a disease which is characterized by microarchitecture changes which may lead to fracture and disability. According to the International Osteoporosis Foundation (IOF), more than 200 million people around the world have osteoporosis. It also occurs more commonly in women, and also more frequently with aging. The "Golden standard" for measuring BMD and establishing osteopenia/osteoporosis is dual-energy X-ray absorptiometry, osteoporosis being defined as T-score more than -2.5 standard deviations below the young adult female reference value[2].

Graves' disease is a disease curable with ATD therapy, leading to an euthyroid state. BMD can increase with the achievement of euthyroidism. But the time period necessary to accomplish improvement in bone density can be of variable length. Present data show only a 4% improvement of BMD after a treatment period of one year[3], while in other studies only partial improvement occurred[4,5]. Restoring BMD is important to prevent negative skeletal consequences, the most important of which are bone fractures.

In addition to thyroid hormones, vitamin D is also important in the metabolism of the skeletal system. Its main functions are regulation of bone metabolism and phosphorus and calcium homeostasis. Recent data suggest that vitamin D has an important role in different autoimmune diseases, including autoimmune thyroid disease (AITD)[6,7]. However, vitamin D deficit is becoming a global health problem. Over a billion people around the world have vitamin D deficit or insufficiency[8,9]. The effect of vitamin D is mediated through the intracellular vitamin D receptor (VDR), which belongs to the steroid/thyroid nuclear receptor family. These receptors, as well as 1α – hydroxylase, are present in various organs and cells other than the kidneys. In humans they are also present in immune cells such as macrophages, dendritic cells and T and B lymphocytes[10]. 1α – hydroxylase is an enzyme which converts 25-hydroxy vitamin (25(OH) D) to 1,25-dihydroxy vitamin D (1,25(OH)2D), the biologically active form of the molecule. Vitamin D has an important role in both the innate and humoral immune system, inhibiting inflammatory cytokine production and stimulating anti-inflammatory cytokine production. It also inhibits dendritic cells (DC) maturation and differentiation, indirectly by suppressing T cell proliferation leading to the phenotype Th1 in Th2 change. The result is a reduction of antigen presenting cells, which otherwise stimulate T cells, thus benefiting immune system tolerance[6].

A possible association of Graves' disease and decreased 1,25(OH)2D raises questions about the molecular mechanisms involved. In an experiment involving mice with induced hyperthyroidism by triiodothyronine (T3), significantly reduced mRNA expression of gene encoding 1α – hydroxylase (CYP27B1 gene) was observed. T3 also reduced transcriptional activity of that gene through both types of thyroid receptors, TRα and TRβ1[10].

Still, it remains unclear whether vitamin D supplementation should be implemented as a modification of inflammatory disease. It is unclear whether vitamin D status is causally connected to the disease pathogenesis or if it is just a disease marker[11].

**Pathophysiological mechanisms of thyroid hormone on bone metabolism**

Thyroid hormone production is regulated by the hypothalamus – pituitary gland – thyroid axis. The hypothalamus produces thyrotropin-releasing hormone (TRH) which stimulates production of thyroid stimulating hormone (TSH) from the pituitary gland. Finally, TSH affects the thyroid and influences hormone production. Thyroid hormones, T3, tetraiodothyronine or thyroxine (T4), are synthetized in thyroid follicular cells under the TSH stimulation, which is secreted by the pituitary gland. Following secretion from the thyroid, hormones circulate in the blood where they are 99% bounded with plasma proteins. The most likely reason for this is to secure thyroid hormone reserve for cells and tissues so that they will not be secreted in urine[12]. Before entering target cells, thyroid hormones can rapidly unbind plasma proteins. The main hormone which thyroid secretes is T4[13]. It acts as a prohormone and is converted to T3[14]. Eighty per-

cent of T3 is converted from T4 and is much more biologically active than T4. Conversion of T4 to T3 is mediated by the deiodinases enzyme[13]. There are three types of deiodinases: 1, 2 and 3 (D1, D2 and D3). D1 is inefficient or it inactivates T4, D2 mediates conversion from T4 to T3 by deiodination of T4, and D3 inactivates T3, and in a minor part prevents activation of T4[15]. Thyroid hormones enter target cells through transmembrane transporters. They are proteins which can be divided in two groups. The first group comprises anionic transporters, (Na(+) taurocholate cotransporting polypeptide – NTCP – and organic anion transporting polypeptide – OATP. The second group includes amino acid transporters type L (LAT 1 and LAT 2) and type T (monocarboxylate transporters MTC 8 and MTC 10)[16]. MTC 8 is one of the most efficient and specific transporters for thyroid hormones, but also the most important transporter in the brain[17,18]. After entering target cells, T3 bounds to thyroid hormone receptors (TR) in the nucleus. There are more than one receptor form and isoform: TRα1, TRα2, TRβ1 and TRβ2[19].

TRβ is predominantly located in the hypothalamus and pituitary gland, liver and kidneys. TR is predominantly located in the heart, central nervous system (CNS), intestine, skeletal muscles and bones. Both TRα1 and TRβ1 are present in bone cells, but TRα1 is expressed about 10 times more than TRβ1 and it is a crucial mediator for T3 in the bones[20].

T3 regulates chondrocyte proliferation, promotes terminal differentiation, and induces mineralization and angiogenesis. It also stimulates production of type II and X collagen and alkaline phosphatase, which are markers of bone mineralization[21].

## Clinical relevance of thyrotoxicosis for BMD and fracture risk

Hyperthyroidism can affect skeletal turnover since bone cells have TR. Thyroid hormones affect all cells and processes in the bone, but mainly bone turnover, which may consequently decrease BMD. It can be hypothesized that BMD will be increased by restoring euthyroidism, implying that the process is reversible[22,23]. The time to restore normal BMD can be different in individuals, which is already known[24].

Numerous studies have shown that hyperthyroidism causes BMD reduction[25-29]. Additionally, fracture risk is increased and can stay increased for the next five years[30]. The therapeutic effect of ATD diminishes that risk, regardless of the drug dose[31]. Achieving BMD increase or restoration can take as much as 1-4 years after hyperthyroidism is diagnosed[32]. Increase in BMD may also be partial[33]. In some studies, alendronate was used along with ATD to improve osteoporosis caused by hyperthyroidism, and the results were favorable for that group of patients compared with those treated only with ATD[34]. Other bisphosphonates can also be used in addition to alendronate, especially in postmenopausal women, since hyperthyroidism alone is a risk factor for development of osteoporosis[35,36]. Osteoporosis could be a reversible process in younger patients, but not in postmenopausal women. However, in this group of patients, bisphosphonates can prevent development of osteoporosis and incidence of fractures at older ages[37].

Results regarding antiTSH-R and the association with bone are ambiguous. According to some studies, antiTSH-R may have negative impact on bone metabolism[38,39]. Other studies have shown that antiTSH-R could have a protective effect on bone[40]. Possible explanations involve thyroid status, i.e. whether overt or subclinical hyperthyroidism or euthyroidism are present, as well as the type of the existing antibodies (blocking or stimulating). In overt hyperthyroidism, antiTSH-R could have a protective role, while in subclinical hyperthyroidism or an euthyroid state they could accelerate bone loss[41]. Some researchers did not find a direct causal association or the underlying mechanism.

In conclusion, since hyperthyroidism is a secondary risk factor for osteoporosis, BMD measurement as a standard protocol in Graves' disease should be considered in order to identify patients who require further management[42].

## Impact of vitamin D deficiency associated with hyperthyroidism on bone health

Vitamin D has an important role in maintaining bone health. Its main source is dermal synthesis stimulated by ultraviolet B radiation (UVB), which comprises 90% of all vitamin D in the human body[43].

The rest is ingested by food and absorbed in the intestines. It is estimated that short-term and occasional arm and face sun exposure equals ingestion of 200 (international units) per day[44]. However, it is not clearly defined how long the exposure should last. After ingestion or skin synthesis, vitamin D is hydroxylised in the liver, resulting in 25(OH)D2 or 25(OH)

D3 synthesis. The next step is conversion of 25(OH) D to to 1,25(OH)2D or calcitriol, which happens in the kidneys mediated by 1α – hydroxylase[45]. The modern life style, encouraging spending less time outdoors and using sun cream with high protection factor, could diminish vitamin D skin synthesis[46]. Additionally, seasonal and race differences also exist[47].

Vitamin D mostly circulates as 25(OH)D, calcidiol. Its half-life in circulation is 2-3 weeks. It is active in the bones and intestines, but significantly less potent than calcitriol. Calcitriol is the most active form of vitamin D, and its half-life in circulation is 4-6 hours[10]. In hyperthyroidism, levels of vitamin D can be decreased, caused by increase in calcium levels as a result of faster bone turnover. Hypercalcemia leads to a decrease in parathyroid hormone (PTH) excretion, which causes diminished conversion of 25(OH)D to 1,25(OH)2D and/or intestine absorption[48-50].

However, it has been noted that vitamin D has a role in the pathogenesis of autoimmune diseases. Therefore, investigating the possible association between vitamin D and Graves' disease is of great interest. However, the results remain variable and inconclusive.

Xu conducted a meta-analysis[51] which included 13 studies. Vitamin D status was determined in patients with Graves' disease and in the control group of healthy patients. It was concluded that patients with Graves' disease were more likely to have a vitamin D deficit. In some of these studies, the results were compatible with the general conclusion[52, 53], but in others there was no greater risk for vitamin D deficit in patients with Graves' disease[5].

In another meta-analysis conducted by Wang, 20 studies were analyzed, and in the majority vitamin D deficit or lower vitamin D status was present in patients with autoimmune thyroid diseases (AITD) compared with the control group., both patients with Graves' disease and with Hashimoto thyroiditis (HT) were included in this meta-analysis[54].

In another study, vitamin D was not significantly lower in patients with Graves' disease[55]. Those results were explained by the variability of the patients included in the study, which was conducted in different centers. Newly-diagnosed patients had different levels of antithyroid peroxidase antibodies, which could be associated with variable levels of serum calcium and ultimately have an effect on vitamin D. No change in vitamin levels was found when comparing patients with hyperthyroidism to those with hypothyroidism. However, comparing hyperthyroid and hypothyroid patients found that hyperthyroidism was not associated with lower vitamin D levels when compared with hypothyroidism[53]. However, the prevalence of the vitamin D deficiency in the same study was significantly higher in patients with AITD than those with non-AITD. Such results could be the outcome of positive antithyroid peroxidase antibodies and abnormal thyroid function tests, and ultimately the role of vitamin D in AITD pathogenesis. In other studies, lower serum vitamin D levels were found in patients with AITD, regardless whether it was Graves' disease or HT. Based on these findings, the authors concluded that vitamin D levels were not associated with thyroid function[56].

In a group of female patients treated for Graves' disease with ATD, vitamin D levels were lower in women without disease remission compared with the group with Graves' disease in remission[57]. In addition, according to some authors, vitamin D deficit could cause and/or aggravate Graves' disease[58].

A good therapeutic effect was achieved by implementing vitamin D as a therapeutic agent in Graves' orbitopathy[59], possibly due to modulation of immune response involved in pathogenesis of Graves' orbitopathy.

Lower concentrations of vitamin D were present in patients with Graves' disease with positive anti TSH – R compared with controls[52], suggesting that vitamin D could have a role in physiological mechanisms involved in Graves' disease. AITD incidence was more frequent in subjects with lower vitamin D concentrations[56]. However, no association between Graves' disease and antiTSH–R was found in another study, only in patients with HT[55].

**Possible pathophysiological mechanism involved in the reversibility of bone loss with antithyroid therapy**

The bone system is very active. It is constantly remodeling throughout a person's life in order to maintain its main functions: body support, protection of internal organs and maintaining mineral homeostasis in the body[60].

The main bone cells included in bone remodeling are osteoblasts, osteocytes and osteoclasts. Osteoblasts comprise 5% of the above and have a role in bone formation. Osteocytes comprise 90-95% of the above and regulate osteoblast and osteoclast activity. Osteoclasts comprise 1-2% and have role in bone resorption[61]. Bone remodeling is an active process through the life-

time. A signal that points which part of bone should be remodeled could be structural damage or systemic paracrine factor that regulates mineral homeostasis of the body[20].

Bone remodeling is a process that has four phases. Osteocytes are activated in the first phase. They regulate osteoblast and osteoclast activity. A specific structure on the bone surface that needs to be remodeled is called the bone remodeling compartment, where osteocyte apoptosis and the release of growth factor takes place. The second phase is resorption. During that phase, osteoclasts are activated by cytokines and growth factors released during osteocyte apoptosis. Osteoclasts resorb the damaged area, and different growth factors and degraded matrix proteins are released during that process, attracting osteoblasts. In the third phase, reversal, the resorption phase ends and matrix formation begins. Mononuclear cells remove the remnants of the resorbed matrix and prepare the resorbed area for the next phase where preosteoblasts proliferate and differentiate to osteoblasts. Osteoblasts synthetize matrix compounds and regulate mineralization of the new matrix by excretion of calcium and phosphates as well as degradation of mineral inhibitors. The results of the bone remodeling cycle is reparation of damaged bone to maintain strength, mineralization and structure[60,61].

Bone resorption lasts 50 days, and bone formation lasts 150 days [62], i.e. a little less than 7 months.

To maintain bone integrity, the processes of resorption and formation must be coordinated in time and space[20]. In hyperthyroidism, the bone remodeling cycles are more frequent, and the cycle is shortened so it lasts 3-4 months, which is shorter by about 50%[63]. The formation phase is more reduced than resorption, consequently leading to bone loss of 10% per cycle[41]. Thyroid hormones have direct effects on osteoblasts and chondrocytes. T3 directly stimulates osteoblasts activity and differentiation, as well as indirectly through cytokines and growth factors[41]. Thyroid hormones have a catabolic effect on the adult skeleton[64].

Apart from investigating whether thyroid hormones influence the skeleton, studies investigating whether TSH acts on bone remodeling and whether there is an association between TSH receptors (TSHr) and changes in BMD have also been conducted. A role of TSH in those processes was suggested in 2003[65,66]. Such a link was demonstrated, as well as the direct action of TSH on the bone by inhibiting osteoclastogenesis and osteoblastogenesis[66]. It was postulated that TSH inhibits formation and survival of osteoclasts and inhibits osteoblast differentiation and the expression of type 1 collagen through TSHr in osteoblasts and osteoclast cells. Another effect of TSH is increased expression of D2 in human osteoblasts[67]. However, suppressed TSH levels in Graves' disease lead to decreased expression of D2 enzyme, culminating in high levels of triiodothyronine and thus stimulating bone resorption[68]. Additionally, research on hyperthyroid Tshr–/–(TSH receptor knockout) mice completely devoid of TSH signaling showed higher levels of bone resorption and bone loss compared with hyperthyroid wild type mice in which TSH levels were undetectable[69].

Different results were reported regarding the impact of antiTSH-R on bone metabolism, ranging from having a protective role on bone tissue to stimulation of bone loss[25,40,70]. This effect could depend on the status of thyroid hormones and whether euthyroidism, subclinical or over hyperthyroidism is present. In addition, it could also depend on the dominating type of the antiTSH-R, namely stimulating or blocking[41].

In the past decade, research on diseases caused by rare gene mutations has expanded. These gene mutations lead to BMD disorders[71], and it became obvious that the Wnt (wingless integrated) signaling pathway is a very important factor for bone homeostasis. It is divided into (1) Wnt/β-catenin (also called the canonical Wnt path) and (2) non canonical Wnt. This second path can be further divided into (A) planar cell polarity (PCP) and (B) the Wnt calcium path, Wnt – Ca2+ [72]. The canonical pathway is the most important for all three bone cell types of the adult skeleton. Present data indicate that stimulation of the Wnt pathway leads to bone mass increase, while in contrast its inhibition leads to bone mass decrease. Hence, inhibitors of the canonical Wnt pathway have become the focus of interest, in particular sclerostin and dickkopf 1 (DKK1). Sclerostin is almost exclusively produced by osteocytes[73]. It is therefore dependent on bone mass and osteocyte presence. Sclerostin inhibits osteoblasts activation and induces their apoptosis, consequently inhibiting bone formation and promoting bone resorption[74]. The Dickkopf group consists of four members in vertebras (DKK 1,2,3,4). Evidence shows that DKK1 has a role in the Wnt canonical pathway. It acts in the bone by inhibiting osteoblast development and

activation. Thus, increased levels or activity of DKK1 can damage osteoblast activation and lead to bone loss[74].

Although both thyroid hormones and the Wnt signaling pathway are important for bone homeostasis, the possible influence of thyroid hormones on the regulation of the Wnt signaling pathway has only recently been investigated in vivo[75]. In the abovementioned study, the data suggest that regulation of sclerostin and DKK1 by thyroid hormones is distinctive and could have different roles in the pathogenesis of thyroid hormone-induced bone loss. Data on the association of thyroid hormones and Wnt inhibitors are scarce and varied. It has been shown that serum sclerostin concentrations were increased in hyperthyroid patients, and sclerostin concentrations decreased after the restoration of euthyroidism[76]. However, the pathophysiological mechanism responsible for that change is still unclear[77]. It has been speculated that the decrease in sclerostin concentrations may be due to the normalization of the bone metabolism[76]. However, one recently conducted study showed no differences regarding sclerostin levels in the hyperthyroidism group in comparison with the control group. It is possible that the change of sclerostin levels depended on the duration of exposure of the bone tissue to elevated thyroid hormones[78]. Additionally, the effect of thyroid hormones and sclerostin on the Wnt signaling pathway could be independent from each other, with regard to numerous cofactors and antagonists that influence them.

## Conclusion

Hyperthyroidism can cause a decrease in BMD leading to osteopenia/osteoporosis. ATD are the first-line therapy for Graves' disease. With treatment, disease remission along with relief of symptoms and signs of hypermetabolism can be achieved. Additionally, lower values of vitamin D and a decrease in BMD can coexist in Graves' disease. It can sometimes be difficult to distinguish whether there is a causal relationship between the two or if they a consequence of life style, age, race or a mixture of all of these. In addition to vitamin D, an important factor for bone homeostasis is the Wnt signaling pathway, especially the canonical pathway. It is significant for all three bone cell types. Since present data indicate that inhibition of the Wnt pathway can lead to bone mass decrease, it is plausible that inhibitors of this pathway are responsible, especially sclerostin and DKK1, for bone mass restoration process in hyperthyroid patients treated with ATD.

In conclusion, the question remains whether densitometry be included in the initial diagnostic procedures in newly-diagnosed patients with Graves' disease. Additionally, should vitamin D levels be determined and does its supplementation provide an additional benefit in treatment, and should it therefore be recommended as a therapeutic agent. We suggest that larger and possibly multicentric studies could provide a better perspective of the state of the targeted population, and the data thus acquired could facilitate patient management, while additional data on sclerostin and DKK1 could contribute to better understanding of bone processes.

## References

1. Tuchendler D, Bolanowski M. The influence of thyroid dysfunction on bone metabolism. Thyroid Res. 2014;7(1):12. doi: 10.1186/s13044-014-0012-0.
2. Punda M, Grazio S. Bone densitometry--the gold standard for diagnosis of osteoporosis. Reumatizam. 2014;61(2):70-4.
3. Udayakumar N, Chandrasekaran M, Rasheed MH, Suresh RV, Sivaprakash S. Evaluation of bone mineral density in thyrotoxicosis. Singapore Med J. 2006;47(11):947-50.
4. Rosen CJ, Adler RA. Longitudinal changes in lumbar bone density among thyrotoxic patients after attainment of euthyroidism. J Clin Endocrinol Metab. 1992;75(6):1531-4. doi: 10.1210/jcem.75.6.1464660.
5. Jyotsna VP, Sahoo A, Ksh SA, Sreenivas V, Gupta N. Bone mineral density in patients of Graves disease pre- & post-treatment in a predominantly vitamin D deficient population. Indian J Med Res. 2012;135:36-41.
6. Altieri B, Muscogiuri G, Barrea L, Mathieu C, Vallone CV, Mascitelli L et al. Does vitamin D play a role in autoimmune endocrine disorders? A proof of concept. Rev Endocr Metab Disord. 2017;18(3):335-46. doi: 10.1007/s11154-016-9405-9.
7. Kim D. The Role of Vitamin D in Thyroid Diseases. Int J Mol Sci. 2017;18(9). doi: 10.3390/ijms18091949.
8. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr. 2008;87(4):1080S-6S. doi: 10.1093/ajcn/87.4.1080S.
9. Mackawy AM, Al-Ayed BM, Al-Rashidi BM. Vitamin d deficiency and its association with thyroid disease. Int J Health Sci (Qassim). 2013;7(3):267-75.
10. Vondra K, Stárka L, Hampl R. Vitamin D and thyroid diseases. Physiol Res. 2015;64 Suppl 2:S95-S100.
11. Yin K, Agrawal DK. Vitamin D and inflammatory diseases. J Inflamm Res. 2014;7:69-87. doi: 10.2147/JIR.S63898.
12. Feldt-Rasmussen U, Krogh Rasmussen Å. Thyroid Hormone Transport and Actions. Basel: Karger; 2007. p. 80-103.
13. Friesema EC, Jansen J, Visser TJ. Thyroid hormone transporters. Biochem Soc Trans. 2005;33(Pt 1):228-32. doi: 10.1042/BST0330228.

14. Cardoso LF, Maciel LM, Paula FJ. The multiple effects of thyroid disorders on bone and mineral metabolism. Arq Bras Endocrinol Metabol. 2014;58(5):452-63.
15. Bianco AC, Kim BW. Deiodinases: implications of the local control of thyroid hormone action. J Clin Invest. 2006;116(10):2571-9. doi: 10.1172/JCI29812.
16. Williams GR, Bassett JHD. Thyroid diseases and bone health. J Endocrinol Invest. 2018;41(1):99-109. doi: 10.1007/s40618-017-0753-4.
17. Groeneweg S, Visser WE, Visser TJ. Disorder of thyroid hormone transport into the tissues. Best Pract Res Clin Endocrinol Metab. 2017;31(2):241-53. doi: 10.1016/j.beem.2017.05.001.
18. Visser TJ. Thyroid hormone transporters and resistance. Endocr Dev. 2013;24:1-10. doi: 10.1159/000343695.
19. Cheng SY, Leonard JL, Davis PJ. Molecular aspects of thyroid hormone actions. Endocr Rev. 2010;31(2):139-70. doi: 10.1210/er.2009-0007.
20. Nicholls JJ, Brassill MJ, Williams GR, Bassett JH. The skeletal consequences of thyrotoxicosis. J Endocrinol. 2012;213(3):209-21. doi: 10.1530/JOE-12-0059.
21. Amashukeli M, Giorgadze E, Tsagareli M, Nozadze N, Jeiranashvili N. The impact of thyroid diseases on bone metabolism and fracture risk. Georgian Med News. 2010(184-185):34-9.
22. Greenlund LJ, Nair KS, Brennan MD. Changes in body composition in women following treatment of overt and subclinical hyperthyroidism. Endocr Pract. 2008;14(8):973-8. doi: 10.4158/EP.14.8.973.
23. van de Ven AC, Erdtsieck RJ. Changes of bone mineral density, quantitative ultrasound parameters and markers of bone turnover during treatment of hyperthyroidism. Neth J Med. 2008;66(10):428-32.
24. Wakasugi M, Wakao R, Tawata M, Gan N, Koizumi K, Onaya T. Bone mineral density in patients with hyperthyroidism measured by dual energy X-ray absorptiometry. Clin Endocrinol (Oxf). 1993;38(3):283-6.
25. Tuchendler D, Bolanowski M. Assessment of bone metabolism in premenopausal females with hyperthyroidism and hypothyroidism. Endokrynol Pol. 2013;64(1):40-4.
26. Barbosa AP, Rui Mascarenhas M, Silva CF, Tavora I, Bicho M, do Carmo I et al. Prevalence of silent vertebral fractures detected by vertebral fracture assessment in young Portuguese men with hyperthyroidism. Eur J Endocrinol. 2015;172(2):189-94. doi: 10.1530/EJE-14-0602.
27. Jódar E, Muñoz-Torres M, Escobar-Jiménez F, Quesada-Charneco M, Lund del Castillo JD. Bone loss in hyperthyroid patients and in former hyperthyroid patients controlled on medical therapy: influence of aetiology and menopause. Clin Endocrinol (Oxf). 1997;47(3):279-85.
28. Boonya-Ussadorn T, Punkaew B, Sriassawaamorn N. A comparative study of bone mineral density between premenopausal women with hyperthyroidism and healthy premenopausal women. J Med Assoc Thai. 2010;93 Suppl 6:S1-5.
29. Amashukeli M, Korinteli M, Zerekidze T, Jikurauli N, Shanava S, Tsagareli M et al. The negative correlation between thyrotropin receptor-stimulating antibodies and bone mineral density in postmenopausal patients with Graves' disease. J Investig Med. 2013;61(5):842-7. doi: 10.2310/JIM.0b013e31828fcafb.
30. Vestergaard P, Mosekilde L. Fractures in patients with hyperthyroidism and hypothyroidism: a nationwide follow-up study in 16,249 patients. Thyroid. 2002;12(5):411-9. doi: 10.1089/105072502760043503.
31. 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):139-44. doi: 10.1007/s00223-005-0068-x.
32. Vestergaard P, Mosekilde L. Hyperthyroidism, bone mineral, and fracture risk--a meta-analysis. Thyroid. 2003;13(6):585-93. doi: 10.1089/105072503322238854.
33. Dhanwal DK, Gupta N. Bone mineral density trends in Indian patients with hyperthyroidism--effect of antithyroid therapy. J Assoc Physicians India. 2011;59:561-2, 7.
34. Yang LJ, Shen FX, Zheng JC, Zhang HL. Clinical application of alendronate for osteoporosis/osteopenia secondary to hyperthyroidism. Zhongguo Gu Shang. 2012;25(2):133-7.
35. Saito J, Nishikawa T. Osteoporosis treatment in patients with hyperthyroidism. Nihon Rinsho. 2009;67(5):1011-6.
36. Svare A, Nilsen TI, Bjøro T, Forsmo S, Schei B, Langhammer A. Hyperthyroid levels of TSH correlate with low bone mineral density: the HUNT 2 study. Eur J Endocrinol. 2009;161(5):779-86. doi: 10.1530/EJE-09-0139.
37. Sato K. Graves' disease and bone metabolism. Nihon Rinsho. 2006;64(12):2317-22.
38. Kumeda Y, Inaba M, Tahara H, Kurioka Y, Ishikawa T, Morii H et al. Persistent increase in bone turnover in Graves' patients with subclinical hyperthyroidism. J Clin Endocrinol Metab. 2000;85(11):4157-61. doi: 10.1210/jcem.85.11.6979.
39. Ercolano MA, Drnovsek ML, Silva Croome MC, Moos M, Fuentes AM, Viale F et al. Negative correlation between bone mineral density and TSH receptor antibodies in long-term euthyroid postmenopausal women with treated Graves' disease. Thyroid Res. 2013;6(1):11. doi: 10.1186/1756-6614-6-11.
40. Cho SW, Bae JH, Noh GW, Kim YA, Moon MK, Park KU et al. The Presence of Thyroid-Stimulation Blocking Antibody Prevents High Bone Turnover in Untreated Premenopausal Patients with Graves' Disease. PLoS One. 2015;10(12):e0144599. doi: 10.1371/journal.pone.0144599.
41. Siderova M, Hristozov K, Tsukeva A. TSH-receptor antibodies may prevent bone loss in pre- and postmenopausal women with Graves' disease and Graves' orbitopathy. Arch Endocrinol Metab. 2018;62(2):221-6. doi: 10.20945/2359-3997000000027.
42. Majima T, Komatsu Y, Doi K, Takagi C, Shigemoto M, Fukao A et al. Negative correlation between bone mineral density and TSH receptor antibodies in male patients with untreated Graves' disease. Osteoporos Int. 2006;17(7):1103-10. doi: 10.1007/s00198-006-0091-4.
43. Norval M, Wulf HC. Does chronic sunscreen use reduce vitamin D production to insufficient levels? Br J Dermatol. 2009;161(4):732-6. doi: 10.1111/j.1365-2133.2009.09332.x.

44. Haddad JG. Vitamin D--solar rays, the Milky Way, or both? N Engl J Med. 1992;326(18):1213-5. doi: 10.1056/NEJM199204303261808.
45. Muscogiuri G, Mitri J, Mathieu C, Badenhoop K, Tamer G, Orio F et al. Mechanisms in endocrinology: vitamin D as a potential contributor in endocrine health and disease. Eur J Endocrinol. 2014;171(3):R101-10. doi: 10.1530/EJE-14-0158.
46. Macdonald HM. Contributions of sunlight and diet to vitamin D status. Calcif Tissue Int. 2013;92(2):163-76. doi: 10.1007/s00223-012-9634-1.
47. Klingberg E, Oleröd G, Konar J, Petzold M, Hammarsten O. Seasonal variations in serum 25-hydroxy vitamin D levels in a Swedish cohort. Endocrine. 2015;49(3):800-8. doi: 10.1007/s12020-015-0548-3.
48. Jastrup B, Mosekilde L, Melsen F, Lund B, Sørensen OH. Serum levels of vitamin D metabolites and bone remodelling in hyperthyroidism. Metabolism. 1982;31(2):126-32.
49. MacFarlane IA, Mawer EB, Berry J, Hann J. Vitamin D metabolism in hyperthyroidism. Clin Endocrinol (Oxf). 1982;17(1):51-9.
50. Bouillon R, Muls E, De Moor P. Influence of thyroid function on the serum concentration of 1,25-dihydroxyvitamin D3. J Clin Endocrinol Metab. 1980;51(4):793-7. doi: 10.1210/jcem-51-4-793.
51. Xu MY, Cao B, Yin J, Wang DF, Chen KL, Lu QB. Vitamin D and Graves' disease: a meta-analysis update. Nutrients. 2015;7(5):3813-27. doi: 10.3390/nu7053813.
52. Zhang H, Liang L, Xie Z. Low Vitamin D Status is Associated with Increased Thyrotropin-Receptor Antibody Titer in Graves Disease. Endocr Pract. 2015;21(3):258-63. doi: 10.4158/EP14191.OR.
53. Kivity S, Agmon-Levin N, Zisappl M, Shapira Y, Nagy EV, Dankó K et al. Vitamin D and autoimmune thyroid diseases. Cell Mol Immunol. 2011;8(3):243-7. doi: 10.1038/cmi.2010.73.
54. Wang J, Lv S, Chen G, Gao C, He J, Zhong H et al. Meta-analysis of the association between vitamin D and autoimmune thyroid disease. Nutrients. 2015;7(4):2485-98. doi: 10.3390/nu7042485.
55. Ke W, Sun T, Zhang Y, He L, Wu Q, Liu J, et al. 25-Hydroxyvitamin D serum level in Hashimoto's thyroiditis, but not Graves' disease is relatively deficient. Endocr J. 2017;64(6):581-7.
56. Ma J, Wu D, Li C, Fan C, Chao N, Liu J et al. Lower Serum 25-Hydroxyvitamin D Level is Associated With 3 Types of Autoimmune Thyroid Diseases. Medicine (Baltimore). 2015;94(39):e1639. doi: 10.1097/MD.0000000000001639.
57. Yasuda T, Okamoto Y, Hamada N, Miyashita K, Takahara M, Sakamoto F, et al. Serum vitamin D levels are decreased and associated with thyroid volume in female patients with newly onset Graves' disease. Endocrine. 2012;42(3):739-41.
58. Alhuzaim ON, Aljohani N. Effect of vitamin d3 on untreated graves' disease with vitamin d deficiency. Clin Med Insights Case Rep. 2014;7:83-5. doi: 10.4137/CCRep.S13157.
59. Sheriba N, Elewa A, Mahdy M, Bahaa El Din A, Ibrahim N, Marawan D et al. Effect of vitamin D<sub>3</sub> in treating hyperthyroidism in patients with graves' disease. The Egyptian Journal of Internal Medicine. 2017;29(2):64-70. doi: 10.4103/ejim.ejim_10_17.
60. Zoričić Cvek Sa, Bobinac D, Đudarić L, Cvijanović O. The remodeling of the skeleton. Medicina Flumensis. 2015;51(4):11.
61. Bassett JH, Williams GR. Role of Thyroid Hormones in Skeletal Development and Bone Maintenance. Endocr Rev. 2016;37(2):135-87. doi: 10.1210/er.2015-1106.
62. Williams GR. Thyroid hormone actions in cartilage and bone. Eur Thyroid J. 2013;2(1):3-13. doi: 10.1159/000345548.
63. Gorka J, Taylor-Gjevre RM, Arnason T. Metabolic and clinical consequences of hyperthyroidism on bone density. Int J Endocrinol. 2013;2013:638727. doi: 10.1155/2013/638727.
64. Bassett JH, O'Shea PJ, Sriskantharajah S, Rabier B, Boyde A, Howell PG et al. Thyroid hormone excess rather than thyrotropin deficiency induces osteoporosis in hyperthyroidism. Mol Endocrinol. 2007;21(5):1095-107. doi: 10.1210/me.2007-0033.
65. Sendak RA, Sampath TK, McPherson JM. Newly reported roles of thyroid-stimulating hormone and follicle-stimulating hormone in bone remodelling. Int Orthop. 2007;31(6):753-7. doi: 10.1007/s00264-007-0417-7.
66. Abe E, Marians RC, Yu W, Wu XB, Ando T, Li Y et al. TSH is a negative regulator of skeletal remodeling. Cell. 2003;115(2):151-62.
67. Morimura T, Tsunekawa K, Kasahara T, Seki K, Ogiwara T, Mori M et al. Expression of type 2 iodothyronine deiodinase in human osteoblast is stimulated by thyrotropin. Endocrinology. 2005;146(4):2077-84. doi: 10.1210/en.2004-1432.
68. Ale AO, Ogbera AO, Ebili HO, Adeyemo OL, Afe TO. Prevalence, Predictive Factors, and Characteristics of Osteoporosis in Hyperthyroid Patients. Int J Endocrinol. 2018;2018:3540256. doi: 10.1155/2018/3540256.
69. Baliram R, Sun L, Cao J, Li J, Latif R, Huber AK et al. Hyperthyroid-associated osteoporosis is exacerbated by the loss of TSH signaling. J Clin Invest. 2012;122(10):3737-41. doi: 10.1172/JCI63948.
70. Ma R, Morshed S, Latif R, Zaidi M, Davies TF. The influence of thyroid-stimulating hormone and thyroid-stimulating hormone receptor antibodies on osteoclastogenesis. Thyroid. 2011;21(8):897-906. doi: 10.1089/thy.2010.0457.
71. Baron R, Kneissel M. WNT signaling in bone homeostasis and disease: from human mutations to treatments. Nat Med. 2013;19(2):179-92. doi: 10.1038/nm.3074.
72. Komiya Y, Habas R. Wnt signal transduction pathways. Organogenesis. 2008;4(2):68-75.
73. Kubota T, Michigami T, Ozono K. Wnt signaling in bone metabolism. J Bone Miner Metab. 2009;27(3):265-71. doi: 10.1007/s00774-009-0064-8.
74. Zhang W, Drake MT. Potential role for therapies targeting DKK1, LRP5, and serotonin in the treatment of osteoporosis. Curr Osteoporos Rep. 2012;10(1):93-100. doi: 10.1007/s11914-011-0086-8.
75. Tsourdi E, Rijntjes E, Köhrle J, Hofbauer LC, Rauner M. Hyperthyroidism and Hypothyroidism in Male Mice and Their Effects on Bone Mass, Bone Turnover, and the Wnt Inhibitors Sclerostin and Dickkopf-1. Endocrinology. 2015;156(10):3517-27.
76. Skowrońska-Jóźwiak E, Krawczyk-Rusiecka K, Lewandowski KC, Adamczewski Z, Lewiński A. Successful

treatment of thyrotoxicosis is accompanied by a decrease in serum sclerostin levels. Thyroid Res. 2012;5(1):14. doi: 10.1186/1756-6614-5-14.

77. Skowrońska-Jóźwiak E, Lewandowski KC, Adamczewski Z, Krawczyk-Rusiecka K, Lewiński A. Mechanisms of Normalisation of Bone Metabolism during Recovery from Hyperthyroidism: Potential Role for Sclerostin and Parathyroid Hormone. Int J Endocrinol. 2015;2015:948384. doi: 10.1155/2015/948384.

78. Sarıtekin İ, Açıkgöz Ş, Bayraktaroğlu T, Kuzu F, Can M, Güven B, Mungan G, Büyükuysal Ç, Sarıkaya S. Sclerostin and bone metabolism markers in hyperthyroidism before treatment and interrelations between them. Acta Biochim Pol. 2017;64(4):597-602. doi: 10.18388/abp.2016_1303.

Sažetak

## UČINAK HIPERTIREOZE I ANTITIROIDNE TERAPIJE NA KOŠTANU GUSTOĆU – PATOFIZIOLOŠKI MEHANIZMI TE KLINIČKO ZNAČENJE

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Gravesova bolest je autoimuna bolest karakterizirana prevelikom proizvodnjom hormona štitnjače. Jedna od posljedica toga stanja može biti sniženje mineralne gustoće kosti. Liječi se antitireoidnim lijekovima kao prvim izborom čime se može postići remisija bolesti. Postizanjem remisije, može se očekivati i poboljšanje mineralne gustoće kosti. No, uz Gravesovu bolest, može postojati i snižena vrijednost vitamina D koji je također važana za procese pregradnje kosti. Još je uvijek otvoreno pitanje mou li snižene vrijednosti vitamina D pridonijeti nastanku Gravesove bolesti i da li bi njegova supstitucija mogla pomoći u liječenju hipertireoze. Kako je smanjena mineralna gustoća kosti danas rasprostranjena širom svijeta, u prošlim desetljećima počeo se istraživati Wnt put. Ovaj put vrlo je važan za homeostazu kosti, osobito njegov dio koji se naziva kanonički put u kojem sudjeluju i sklerostin i dickkopf 1 kao inhibitori. Svi spomenuti čimbenici, odnosno stanja, danas su učestala i mogu postojati zajedno i odvojeno. Ovim člankom pokušali smo dati pregled moguće veze između njih.

Ključne riječi: *Gravesova bolest, koštana gustoća, Wnt signalni put, sklerostin, dickkopf 1*