STRUCTURAL BONE CHANGES IN THYROID DISORDERS PATHOLOGY

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Abstract: *Thyroid hormones represented by triiodothyronine (T3), reverse triiodothyronine (T3) and tetraiodothyronine (thyroxine - T4) are important homeostatic regulators of bone metabolism. They are converted into active and inactive products by the 3 iodothyronin deiodinase D1, D2, D3, providing control tissue and cellular activity accomplished by the thyroid hormones and allow the body to adapt to various pathological changes. Thyroid hormone action on target cells is achieved through their receptors - TRα (α1, α2, α3) and TRβ (β1 and β2). Thyroid disorders affect bone remodelling cycle, either by variations of the circulating serum thyroid hormone levels, or because of the replacement or suppressive therapy with levothyroxine.*

Cuvinte cheie: *hormone tiroidieni, disfuncţie tiroidiană, os*

Rezumat: *Hormonii tiroidieni reprezentaţi de triiodotironina (T3), revers triiodotironina (T3) şi tetraiodotironina (tiroxina – T4) sunt reglatori homeostatici importanţi ai metabolismului osos. Sunt transformaţi în produşi activi şi inactivi de către cele 3 iodotironin deiodinaze D1, D2, D3, care asigură controlul activităţii tisulare şi celulare realizată de hormonii tiroidieni şi permit adaptarea organismului la diferitele modificări patologice. Acţiunea hormonilor tiroidieni asupra celulelor ţintă se realizează prin receptorii lor - TRα (α1, α2, α3) şi TRβ (β1 şi β2). Disfuncţiile tiroidiene influenţează ciclul de remodelare osoasă, fie prin variaţiile nivelelor serice circulante ale hormonilor tiroidieni, fie ca urmare a tratamentului de substituţie sau de supresie cu levotiroxină.*

Influence of thyroid hormone on bone

Thyroid hormones, represented by triiodothyronine (T3), reverse triiodothyronine (RT3) and tetraiodothyronine (thyroxin - T4) are important homeostatic regulators of bone metabolism; they are iodinated hormones and act through their nuclear receptors on all tissues. In blood circulation, they are linked to the transport proteins in a percentage more than 90%: thyroglobulin, transtiretin and other lipoproteins. Biosynthesis and secretion of thyroid hormones, as well as their action at tissue level, regulating the thyroid function, represent the physiological basis on which different pathological processes occur.

Regulating the intracellular formation of T3 triiodothyronine

Iodothyronine deiodinases enzymes containing selenocysteins metabolize the thyroid hormones into active and inactive products. The three iodothyronine deiodinases - D1, D2, D3, provide the control tissue and cellular activity accomplished by the thyroid hormones and allow the body to adapt to various pathological changes (iodine deficiency and chronic thyroid disorders). Deiodinase D1 generates most of circulating triiodothyronine (T3) through the 5 '- T4 hormone deiodation in liver and kidney; also, depending on the substrate, it can generate reverse triiodothyronine (r T3) and 3, 3' - diiodothyronine (T2). Numerous recent studies conducted on transgenic mice showed that D1 is not expressed in bone and cartilage, so it does not directly affects T3 action on bone.(1)

Deiodinase type II (D2) enzyme present in skeletal muscles, heart muscle, central nervous system and pituitary gland, considered more effective than D1, converts T4 to its active metabolite, T3, catalyzing the removal of an iodine atom from position 5'; its major part is to control the intracellular concentration of T3, its availability to the nucleus and that of the nuclear receptor of T3 in the target tissues.(2)

Current research with mutants mice without D2, have issued the conclusion that this enzyme acts specifically on the differentiated osteoblasts without acting on chondrocytes and osteoclasts; at the same time, bone turn-over change has been observed in the sense of reducing osteoblastic bone formation without affecting the osteoclastic resorption, but with a decrease rate of bone mineralization. D2 activity in osteoblast is increased in hypothyroidism and decreased in hyperthyroidism in order to compensate the changes in thyroid hormones and to counterbalance their effects on the skeleton.(1) The absence of the local feedback mechanism, in mice with mutation of D2, brings about cell hypothyroidism contrary to the systemic euthyroidism, which leads to a isolated reduction of osteoblasts activity; this way, bone formation is reduced and mineralization is increased, without assigning a functional deficiency of osteoclasts.(3)

A recent population study issues the hypothesis that D2 and D3 can influence susceptibility to osteoarthritis and that the availability of T3 in chondrocytes dependent of deiodinases, plays an important part in cartilage homeostasis, also, it has been hypothesized that deiodinase D2 could be included as a target for the treatment of skeletal diseases, such as osteoporosis and osteoarthritis.(1)

Type 3 deiodinase enzyme D3 present in the placenta, central nervous system, liver and fetal skin, inactivates irreversibly T3 or prevents the activation of T4, by removing an iodine atom from position 5' to generate 3, 3', 5 '- L-

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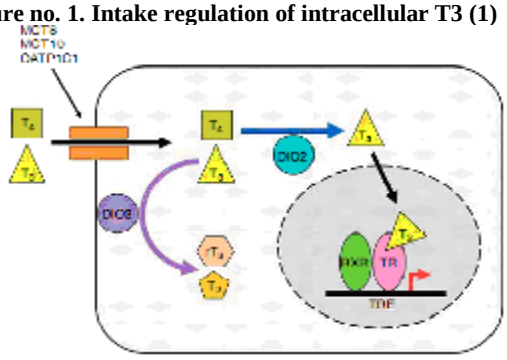
triiodothyronine (reverse T3) and 3, 3' Diiodothyronine (T2); it can be inferred that it prevents thyroid hormones access to the specific tissues in imbalance situations and reduces thyroid hormone receptor saturation. Therefore, we can say that D2 and D3 deiodinases control the intracellular availability of T3 and its action on target cells through a mechanism independent of serum thyroid hormone, so thyroid hormone target tissues are protected from the effects of these variations, either by adopting an efficient local conversion of T4 to T3, or by reducing hormone receptor saturation.

Intracellular availability of T3 and T4 is achieved by a transportation mechanism, energy dependent, that requires ATP, saturable, that is mediated by monocarboxylic-8 (MCT8) transporter, monocarboxylic transporter-10 (MCT 10) and other transporters including the organic acid 1C protein 1 (OATP 1C1). It is estimated that transportation by MCT 8 increases the intracellular uptake of T4 and T3 by 10 times.

In a recent study, Williams and his colleagues, suggested that hormone T3 availability especially during skeletal development may be limited rather by the catabolisation mediated by D3, than by cellular uptake mediated by MCT 8 or by T3 production dependent of D2.

Figure no. 1. Intake regulation of intracellular T3 (1)



Clinical studies indicate that euthyroid status is essential for a normal bone turn-over, for a normal mineralization, for an optimum maintenance of bone strength. An important role in maintaining the euthyroid status is played by the hypothalamic – pituitary - adrenal axis, representing an important factor of skeletal integrity throughout life.

Thyroid hormone receptors

Thyroid hormones action on the hypothalamus and pituitary is accomplished through their receptors (TRS), thus inhibiting the synthesis and secretion of TRH and TSH. On the other hand, thyroid hormone action on target cells is also determined by the availability of T3 to its nuclear receptors.(1) Thyroid hormone receptors are part of many nuclear hormone receptors and function as transcription factors, along with the co-regulating proteins, triiodothyronine receptor complex (T3) - receptor inducing gene transcription.(4.5) In their turn, these receptors represented by TRα (α1, α2, α3) and TRβ (β1 and β2) have been identified in chondrocytes, bone marrow stromal cells and osteoblasts and at hypothalamic and pituitary level; it is unclear if they present in osteoclasts.

New research found the two genes that encode the thyroid hormone receptor - THRA and THRB - of which multiple TRα and TRβ isoformes are transcribed. Other studies have shown that THRA gene encodes three variants C (carbon) – terminals of TR α (α1, α2, α3), and the THRB gene encodes two variants N terminals of TR β (β1 and β2).

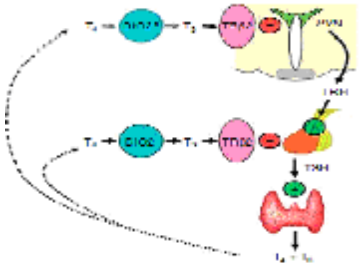
Studies have confirmed that TR α1, β1 and TR TR β 2 are functional receptors that bind DNA and contain the hormone binding sites, while TR TR α 2 and α 3 do not have hormone binding activity and act as weak antagonists. It has been observed that TR α 1 and TR β1 are mainly expressed in bone cells, TR α1 10 times more than in TR β1. TR β 2 is also present in the hypothalamus and pituitary, thus affecting the hypothalamic - pituitary - thyroid axis action by mediating the thyroid hormones action on TRH expression and TSH.(1)

Research made in the last two decades have shown that thyroid hormones through receptors influence the bone remodelling process through the direct effect on osteoblasts, the increase of osteoclasts activity being most likely the consequence of coupling the bone turn-over.(5)

Figure no. 2. D2 deiodinase role on the negative feedback made by the hypothalamic-pituitary-thyroid axis (1)

Hypothalamus

Pituitary



Thyroid

Experimental studies conducted on mice with mutations or with deletions of THRA and THRB genes show that TRα 1 is an important mediator of the action of T3 on bone, particularly on osteoblasts; the absence of TR α1 in transgenic mice, under euthyroid conditions, resulted in delayed skeletal development, increased bone mass with impaired bone remodelling in adulthood. The syndrome of resistance to thyroid hormone action (SRTH), in transgenic mice with a mutation inactivator of TRβ, demonstrated that the latter, interrupt the control conducted by the hypothalamic – pituitary - thyroid axis and thereby, increase the circulating levels of T3, T4 and TSH; therefore, the consequence is the excessive stimulation of TR α1 from the bone with the increase of bone turn-over along with increased osteoclastic resorption; the resulted osteoporosis is characterized by reduced bone mass and low bone density.(6) Triiodothyronine (T3), the active hormone, stimulates osteoblastic differentiation and activity, and the result is increased synthesis and mineralization of osteoid matrix; in cultures of T3 osteoblasts, type I collagen expression increases, as well as of the osteoblastic differentiation markers, including osteocalcin and bone alkaline phosphatase.(4) Also, it regulates the signalling pathways of IGF and receptor 1 of the fibroblast growing factor.(6.7) Recently, it was demonstrated the presence of TSH receptor (RTSH) at the level of osteoblasts and osteoclasts cell precursors, those of mature osteoblasts, indicating the TSH role in regulating bone remodeling. TSH receptor has been shown to be a transmembrane protein that transmits the signal through the secondary messengers, such as cyclic adenosine monophosphate (c AMP).(5) His presence is predominant in thyroid follicular cells where it regulates cell proliferation, the synthesis and secretion of the thyroid hormones, but in other tissues, as well, including brain, heart, kidney, fat, testis, pituitary, immune and hematopoietic cells.

Research with mice without TSH receptor showed the presence of osteoporosis due to increased bone remodelling, even if the compensation is made by the thyroid hormones; this suggests that TSH has an inhibitory effect on bone resorption and stimulates bone formation.

There are studies that try to argue that there is an association between TSH receptor deficiency and increased production of cytokine TNF, osteopenia and increased osteoblastogeneseis.(8) In another provocative study, Abe and

colleagues have attempted to demonstrate that TSH inhibits osteoclast formation and survival by attenuating c-Jun N-terminal kinase (JNK) and NFkB signaling in response to RANK-L; also, it has been suggested that HRT inhibits the differentiation of osteoblasts and the expression of type 1 collagen by decreasing the different signalling pathways: Wnt (LRP - 5) and vascular endothelial growth factor (VEGF).

Other authors have found that serum TSH activates type 2 deiodinase in osteoblasts, thus creating a link between HRT and increased cellular availability of thyroid hormones.(9) New research conducted in vivo on stem cells differentiated into osteoblasts, reported that TSH, through the receptors in the osteoblasts, could stimulate bone formation; it was noted that it may inhibit osteoclast activity. These findings have allowed the identification of the relationship between TSH levels, bone mineral density and bone turnover indicators in the thyroidectomied patients for differentiated thyroid carcinoma. The results are in accordance with TSH effects on bone metabolism in animals: there is an inverse relationship between TSH serum levels, indicators of bone formation, bone alkaline phosphatase (FAO), osteocalcin, amino-terminal propeptide of type I procollagen (PINP) and those of bone resorption - C terminal telopeptide cross – linked to collagen type 1 (CT x), N telopeptide cross – liked to type I collagen (NT x), independent relationship of serum levels of the thyroid hormones.(6,9)

By correlating the results of the studies, it has been developed the idea that HRT is an important negative regulator of bone turn-over, its direct effect on bone mineral density, on bone resorption and formation indicators being independent of thyroid hormone concentration. Other studies have concluded that thyroid status independently influences the serum concentration of osteoprotegerin (OPG). Osteoprotegerin, traditionally considered a soluble receptor secreted by different tissues and cells, acts as an inhibitor of osteoclastogenesis. This function is mediated by binding and subsequently neutralizing the receptor activator of nuclear factor κB ligand.(10)

Alteration of the euthyroid status influences the serum concentration of OPG cytokine system/RANKL.(5) There is research on animals showing the presence of increased amounts of mRNA that encodes OPG in the thyroid follicular cells; it has been also found that mRNA encoding RANKL is better expressed in the lymphocytes that populate the thyroid parenchyma.

Recent studies suggest that thyroid dysfunctions may influence the serum concentrations of osteoprotegerin.(10) There is a hypothesis according to which TSH would act as a negative regulator of bone metabolism, OPG mediated effect, resulting in inhibition of osteoclastogenesis; excessive levels of thyroid hormone determine the acceleration of osteoclast and osteoblasts activity. There is also research on culture samples according to which thyroid hormones stimulate the osteoclast activity, mainly by inducing RANKL gene expression in osteoblasts, this effect being amplified by the presence of 1,25-dihydroxyvitamin D3.(11)

Studies on transgenic mice with deletion of the gene encoding OPG, have demonstrated that these ones have developed severe osteoporosis, while gene suppression determines the occurrence of osteosclerosis.(10) We can say that OPG/RANKL cytokine system changes may play a role in changes in bone metabolism in the patients with thyroid dysfunction.(5)

Thyroid pathology and the bone

Thyroid disorders have a negative impact on bone metabolism and influences bone remodelling cycle, either by changes in circulating serum thyroid hormone levels, or as a result of the replacement or suppressive therapy with levothyroxine.

Hyperthyroidism and the bone

Thyroid hyperfunction, generically called hyperthyroidism, in most cases is due to the emergence of antibodies with stimulating role of the thyroid function, called immunoglobulins (TSI) which activate the specific receptors of THS at thyroid level, leading to the overproduction of thyroid hormones.

The effects of hyperthyroidism on bone are known well before the discovery of the beneficial action of the treatment specific to this disease. In 1891, von Recklinghausen describes for the first time, the appearance of “bone eating worms” in a young patient died due to complications of hyperthyroidism. Under normal bone remodeling, there is a balance between osteoclastic resorption and osteoblastic bone formation. The results of the studies made on animals and of population studies concluded that hyperthyroidism is associated with increased bone remodeling cycle and the reduction of its duration by almost 50%, reduced DMO and increased fracture risk.(12)

The existence of changes in bone metabolism is associated with a negative balance of calcium, hypercalciuria and rarely hypercalcemia (it may occur in up to 20% of cases). Also, increased mobilization of bone calcium inhibits the secretion of parathyroid hormone (PTH) and reduces renal hydroxylation in position 1 - α of 25 (OH) vitamin D; as a result, circulating levels of 1,25 (OH) 2 - vitamin D decrease, as well as the intestinal absorption of calcium and phosphorus.(6) The alterations in calcium metabolism in thyrotoxicosis may be due to the direct effect of thyroid hormones in stimulating bone resorption; they are reversible if the euthyroid status is drug restored. Some studies have shown that bone loss in thyrotoxicosis is independent of the circulating TSH levels and is determined by the catabolic effect of the excess of the thyroid hormones mediated by the TR α receptor. Other studies have raised the possibility that suppressed levels of TSH, independent of thyroid hormone levels, can contribute to bone loss in thyrotoxicosis as evidenced by DXA measurements, knowing the role of negative regulator of bone over-turn tof TSH.(2)

It was found that regardless of the exact mechanism of bone loss, in clinically manifested hyperthyroidism, but also in the subclinical one, the serum and urinary markers of bone remodeling are raised: serum bone alkaline phosphatase (enzyme produced by osteoblasts), osteocalcin (synthesized by osteoblasts), urinary hydroxyproline and hydroxy derivatives 3 pirinidinei. Despite the long-term treatment of hyperthyroidism, the mortality rate may increase to 2.9% due to the risk of femoral neck fracture.

The results of a recent meta-analysis showed that 8% of the studied patients may have symptoms due to osteoporosis, mostly being postmenopausal women; also, more than half of them had less than a year thyrotoxicosis.(13) Some recent studies support the idea that the increased turn-over was related to the increased levels of cytokines such as TNF-α and of its receptors.(8) In the patients with hyperthyroidism, increased concentration of IL 6 has been noted, which may be involved in bone loss stimulated by thyroid hormones; it has been suggested that IL 6 has a role in coupling formation with bone resorption, the presence of its receptor in osteoclast having been demonstrated. Recent research argues that together with its soluble receptor it also stimulates the osteoblastic synthesis of IGF-1. It was concluded that serum OPG levels in hyperthyroidism are significantly elevated compared to euthyroid subjects; these changes are interpreted as being directly related to the excess of thyroid hormones and to an

increased bone turn-over. The most likely mechanism is a direct one, by stimulating the OPG gene expression in bone cells induced by triiodothyronine.(5)

The excess of thyroid hormones increase osteoclasts activity, in particular by increasing RANKL secretion from the osteoblasts; RANK/RANKL/OPG system is also important for the development of mature osteoclasts.

On the other hand, some studies suggest that serum value of OPG is directly correlated with that of bone resorption markers, suggesting that increased OPG would represent a physiological counter-regulatory mechanism of excessive bone resorption. The treatment of thyrotoxicosis with synthesis antithyroid agents normalizes the serum OPG values in a temporal relation with the normalization of some of the bone metabolism markers.(5) It has been questioned whether impaired bone microarchitecture during hyperthyroidism is reversible after treatment, the conclusion was the need for multiple subsequent follow up studies.

Subclinical hyperthyroidism

Of thyroid disease, subclinical hyperthyroidism characterized by low serum levels of TSH and normal serum levels of free T4 and T3, has been shown to affect predominantly the cortical bone as against the trabecular one. The prevalence of subclinical hyperthyroidism in the general population, according to some recent studies, is between 0.7 to 12.4%.(14)

Regarding the effect of this glandular dysfunction on the bone, the increased risk of osteoporosis and fractures is facilitated in postmenopausal women due to the reduction of the bone mineral density; also the markers of bone resorption and formation are increased - osteocalcin, telopeptide type 1, and urinary hydroxyproline pyridinoline. The results of several prospective studies conducted on postmenopausal patients diagnosed with subclinical hyperthyroidism have shown that the low levels of TSH significantly affect the risk of fracture, study groups had TSH values between 0.1 to 0.4 mU/l and <0.1 mU/l.

The conclusion of these findings was that for the patients with levels of TSH <0.1 mU/l, the risk of fracture is 3 times higher for the hip and 4 times higher than the vertebral as against the patients with normal TSH; a different conclusion taken from these studies was that progression towards clinically manifested hyperthyroidism which still occurs in the patients with TSH <0.1 mU/l.(15) Cross-sectional findings of multiple studies and meta-analyses, conducted both on postmenopausal women and on those in premenopausal, suggested contradictory ideas compared to other results obtained: bone mineral density is not affected in those premenopausal, it can be reduced in those in post menopause, but the effect on bone markers and risk fracture is not certain

It was found that serum levels of osteoprotegerin (OPG) in subclinical hyperthyroidism appear to be unchanged compared with witness euthyroid patients, which is explained by the presence of serum T3 concentrations within the normal range; elevated levels of thyroid hormones determine increases in serum OPG, the increase of the latter representing a physiological counter-regulatory mechanism of excessive bone resorption.(5)

Graves–Basedow disease and the bone

Graves disease is an autoimmune disease, the most common cause of hyperthyroidism; in the development of the disease, the major part is played by the presence of thyroid stimulating immunoglobulins (TSI) acting on the TSH receptor and determining the continued gland stimulation; the result is excessive synthesis and secretion of T4 and T3.(16,17) Disproportionately elevated serum levels of T3 compared to T4 are due on one hand to the thyroid secretion of T3, and on the other hand to the peripheral conversion of T4 in T3 under the action of DI deiodinase.

The results of the meta-analyses of several studies stress the idea according to which important bone loss, due to excess thyroid hormone, causes changes in bone microarchitecture and increases bone fragility, these changes being undetectable by osteodensitometry.(4)

By correlating the data from other studies, susceptibility of the patients with Graves' disease to osteoporosis and fractures is not consistent with the hypothesis that TSH negatively regulates the bone turn-over, because the presence of antibodies that stimulate the TSH receptor is supposed to protect against osteoporosis.(2) Thyroid hormones in excess in Graves' disease are directly related to the elevated levels of serum osteoprotegerin (OPG), the most likely mechanism is the direct stimulation of OPG gene expression in bone cells. It was also found persistent increased levels of OPG for longer periods of time, within this thyroid dysfunction, even after the establishment of the drug therapy.

Iodine-induced hyperthyroidism

The intake of iodine is considered as the main cause of hyperthyroidism with low thyroid iodocapture, characterized by increased synthesis and release of excess thyroid hormones from the thyroid gland. The most common substances responsible are drugs such as amiodarone, expectorants or iodine containing contrast substances used in cardiological and radiological examinations.(7) Amiodarone, a drug commonly used to combat cardiac arrhythmias, acting on thyroid function, although studies show that most patients (80%) remain euthyroid. It has been proven that structurally, it resembles T4 and contains 37% iodine; it has a half life of 50 -60 days and thus, it remains available long time after the treatment.

In terms of action, it inhibits DI and DII 5' deiodinase, increases the level of T4 and TSH concentrations; it has a direct cytotoxic effect on thyroid cells inducing their apoptosis and acts in competition with T3 hormonal receptors. Thus, iodine administration in the treatment with amiodarone may precipitate the installation of the autoimmune thyroid disease, in the susceptible individuals.

The hyperthyroidism induced by this medication may develop rapidly or after several years of treatment. There are two types: type 1-secondary excess iodine is installed under a changed thyroid function, type 2-secondary destructive thyroiditis drug induced, in this case, increased serum IL-6 are present.(17)

Hypothyroidism and the bone

Hypothyroidism is classically defined as a condition characterized by reduced production of thyroid hormones; it is a condition that can occur at any age.(17) A recent study in England, on a population with a mean age of 58 years, demonstrates a high prevalence in women compared to men (6:1). Following the Framingham study, it has been reported an incidence of hypothyroidism (TSH> 10 mIU/l) in women than in men (5.9% in women and 2.4% in men), aged 60 years old.(18) Internationally, the most common cause of hypothyroidism is considered the iodine deficiency; in terms of prevalence, there are reports between 2-5% depending on the study, increasing up to 75% at the age of 75.(6)

Both in the hypothalamic and pituitary hypothyroidism, upon exogenous TSH administration, a prompt response is registered from the thyroid. TSH response to TRH exogenous intake may be a useful criterion for distinguishing the two forms: for the hypothalamic hypothyroidism, a delayed TSH increase has been noted, while the absence of a significant change of serum TSH after TRH is characteristic for the pituitary hypothyroidism. There are cases of congenital central

hypothyroidism due to some functional defects in the biosynthesis and release of TSH such as mutations in the genes encoding β subunit of TSH (9 dr ol), TRH receptor (8), pituitary transcription factor Pit - 1.(19)

In the case of postoperative hypothyroidism due to surgical extirpation of the thyroid, the risk factors are represented by insufficient thyroid remnants of lymphocytic infiltration and subsequent exposure to radioactive iodine. A recently described congenital anomaly is the decrease of the cell transportation of T4 at the level of brain; this syndrome is the result of certain mutations of the monocarboxylic transporter 8 (MCT 8), located on the X chromosome and occurs in men with severe neurological abnormalities and limited hypothyroidism.(20)

Subclinical hypothyroidism

Subclinical hypothyroidism is characterized by increased serum levels of TSH in the presence of normal serum concentrations of free T4 and T3. It is a biochemical abnormality and the incidence is increased in the elderly women, especially in those with Hashimoto thyroiditis background, those with high intake of iodine and in Caucasians, (21) where antibodies ATPO autoimmune etiology is more common than in those who have antitireoglobulin antibodies.(17)

The prevalence of subclinical hypothyroidism is of 4-10% in the general population up to 25% in women over 60 years.(21) Disease evolution can be spontaneous or clinically manifested hypothyroidism especially in the presence of antithyroid antibodies. There is research supporting the idea that 30% of the diagnosed patients develop manifested hypothyroidism in 10 years; on the other hand, only in 4%, TSH values.(13) The risk for developing clinically manifested hypothyroidism, described by a study in England, is high (4.3%/year), particularly in the female patients who present high levels of TSH and antitireoglobulin antibodies.

Hypothyroidism causes low bone turn-over with the reduction of osteoblastic and osteoclastic activity, longer cycle remodelling and increase bone mineralization; however a 2-3 times increased susceptibility to fractures is mentioned.(3,6) Other studies have shown that hypothyroidism decreases recruitment, the development and the activity of the trabecular bone cells resulting in decreased bone remodelling; also, cortical thickness is reduced, fact demonstrated by histomorphometric studies. The results of the recent studies conclude that there is an influence of thyroid dysfunction on serum levels of osteoprotegerin (OPG).

Both clinically manifested hypothyroidism and the subclinical one are associated with the increase of OPG concentration. It has not been yet elucidated the mechanism by which thyroid hormone deficiency increases the serum levels of OPG; it was suggested as a cause, either the reduction of the renal clearance of OPG or the influence of elevated TSH levels that characterize hypothyroidism; persistently elevated levels of TSH would act as a negative regulator bone metabolism and OPG would mediate TSH effect at the level of this metabolism with the final inhibitor effect on osteoclastogenesis; these findings could represent a pathophysiological link between hypothyroidism and decreased bone resorption.

Thyroid cancers and the bone

The thyroid is the most common site of endocrine tumours, and the frequency of thyroid cancer is between 25 and 65, which does not exclude its occurrence in children and elderly. The record in this century, a natural tendency to increased incidence and proper therapy provides a survival rate exceeding 90%. Studies have shown a marked variability in aggressiveness, from an almost benign behaviour of those differentiated papillary to an increased aggressiveness of the anaplastic cancers, non-differentiated occurring particularly in the elderly.(16) There is research conducted on thyroidectomied patients with differentiated carcinoma, in which the identification of the relationship between TSH levels, bone mineral density and bone turn-over indicators were aimed at.

The results are consistent with the reported effects on bone metabolism in experimental animals, ie an inverse relationship between serum TSH levels, indicators of bone formation and resorption independent of serum levels of thyroid hormones.(9) Studies conducted on patients with differentiated thyroid cancers under suppressive therapy with thyroid hormone, upon the interruption of the treatment for cancer evaluation, showed increases in serum levels of osteoprotegerin (OPG), together with the installation of the clinical hypothyroidism. There are studies made by Diamond and his collaborators, trying to demonstrate that in the patients with differentiated thyroid cancer, in pre-menopause, treated with suppressive doses of thyroxin (100-150 mg/day), there is a reduced bone mineral density at the femoral neck; according to these authors, only in postmenopausal women, bone mineral density is lower at the lumbar spine. The results of a recent meta-analysis on 41 studies, concluded that the suppressive treatment with thyroid hormone resulted in an average bone loss seen as more than 1 standard deviation from DXA measurements, mainly in the postmenopausal patients with a predominant involvement of the cortical bone.(13)

There are other authors that consider that in the case of the subclinical excess of thyroid hormones, still within the suppressive treatment, serum levels of OPG do not seem to be changed, as compared with the euthyroid patients; these findings are explained by maintaining serum concentrations of T3 within the normal limits in this particular category of patients.(5)

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