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OSTEOPOROSIS IN THYROID GLAND DISEASE

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SUMMARY: Osteoporosis presents the most frequent metabolic bone disease, especially in postmenopausal women. What characterizes hyperthyroidism as a disease is the domination of catabolic process over anabolic ones which causes the reduction of remodelling process, and thus the reduction of bone mass and the occurence of osteoporosis. Subclinical hyperthyroidism is the most frequent in older persons with multinodular goitre or less frequent in those with Graves disease. Symptomatic bone disease is not characteristic for subclinical hyperthyreoidism, however this disorder has a negative effect on bone density and it is a risk factor for osteoporosis. Subclinical hyperthyroidism, as a result of therapy with thyroid hormones also causes the reduction of bone density, but there is no evidence of more frequent bone fractures. The use of L-thyroxine as a suppressive therapy of malignant tumours of the thyroid gland causes the reduction of bone density and the occurrence of osteoporosis. On the other hand, primary hypothyroidism causes the prolongation of bone remodeling and the increase of bone mineral mass. Considering that hyperthyroidism causes the reduction of bone density it is required to achieve euthyroidism as early as possible, and to avoid the occurrence of iatrogenesis hyperthyroidism in hypothyroid patients. Preventive measures and eventual medical prevention of osteoporosis should be taken in patients treated for malignant tumors of the thyroid gland that are receiving L-thyroxine suppressive therapy.

Key words: osteoporosis, hyperthyroidism.

Osteoporosis is a systematic skeleton disease characterised by the decrease of bone mass and lower bone quality caused by the changes in microarchitectonics of bone tissue. (1) Consequently, it is a disorder of quantity and quality of bone tissue resulting in fracture aptitude.

Considering thyroid gland diseases, osteoporosis is related to its increased function.

Hyperthyroidism is one of most frequent endocrinopathies and as a disease is characterised by the increased metabolic rate in which catabolism dominates over anabolic processes. For that reason it belongs to those endocrinopathies where there is an increased inclination toward osteoporosis as one of the clinical manifestations.

Undesired effects of hyperthyroidism to skeleton have been known since the time before the discovery of its successful treatment. One of the first reports of hyperthyroidic bone disease dates back to 1891. when von Recklinghausen described “worm eaten” long bones in young women who died of hyperthyroidism.

By introducing anti-thyroid therapy and radioactive iodine therapy in 1940, clinically manifested bone disease with hyperthyroidism became less frequent.

Due to the introduction of densitometry as a sensitive and precise method in the last thirty years reduction of bone mass with hyperthyroidism has been determined.

Thyroid hormones directly stimulates bone resorption in tissue culture. This effect is probably enabled by triiodothyronine (T3) receptors found in cell lines of mouse osteoblasts and human (2) and in osteoclasts derived from an osteoclastoma. In this way thyroid hormones may effect bone metabolism and calcium by either direct impact on osteoclasts or osteoblasts which are mediators of osteoclastic bone resorption. (3) Increased concentracion of iterleucine-6 (IL-6) in hyperthyroid patients may as well have a part in the beginning of bone mass reduction. (4) IL-6 stimulates osteoclast production and may be the effector of parathormone (PTH) activity on bone.

Hyperthyroidism is associated with bone remodelling rate, reduced density, osteoporosis and increased fracture incidence. Changes in bone density may or may not be reversible with the treatment of basic disease. These changes are associated with negative calcium balance, hypercalciuria and rarely with hypercalcemia.

Process of bone remodelling begins with “activation”. It can be initiated by either local changes such as mechanical force or microfracture, or by system hormones or local factors effecting the overall bone reorganization. (5) Activation is initiated by effects on osteoblastic cells, although these responsory cells are probably not totally differentiated osteroblasts but rather precursor cells in bone marrow or cells lining surface of cells. These cells have receptors for factors which are said to effect bone resorption. Factors stimulating bone resorption may change the appearance of cell surface, therefore, their names of osteoclast differentiation factor (ODF), osteoprotegerin ligand (OPGL), TRANCE or RANK ligand. (6) Not only that osteoblast forms this ligand but it produces osteoprotegerin (OPG) which can be attached to OPGL and block interaction between responsory cells and osteoclast precursor. Molecule receptor on osteoclast precursors which responsory cells have an interaction with is probably a form of RANK. These molecules have mutual action with RANK on the surface of osteoclast precursor and activate osteoclasts. PTH, PGE2, IL-1 and 1. 25-D have positive effect on OPGL and result in increased osteoclast activation , i.e. bone resorption. Osteoblasts produce osteoprotegerin which may be attached to OPGL and block interaction of osteoblast precursor and osteoclast. PTH, PGE2, IL-1 and 1,25-D show negative effect on the production of OPG and the result is increased bone resorption.

Osteoblasts precursors produce histiocyte stimulating factor (M-CSF) which acts in a different way to activate osteroclasts. It seems that both types of osteoblast-osteoclast interaction are necessary for the activation of bone remodelling cycle. Interaction between RANK and OPGL is necessary but not enough for the information on active functional osteoclasts. At least one of other factors, hystiocyte stimulating factor (M-CSF or SSF 1) which may be produced by osteoblast is also important in osteoclastogenesis. M-CSF has a part in the initial replication and activation of osteoclast precursors, as well as in later differentiation phases and fusion leading to total osteoclast activation. (7) After osteoclastic resorption, there is

a so called " reversed" remodelling phase in which mononuclear cells are present on bone surface. The function of these cells is not clear, however, mononuclear cells may be included in further matrix degradation , in forming the so called "cement coating" present between old and new bone, or signalling osteoblasts to migrate and differentiate so that new bone formation may begin at the resorption place.

In normal sequence of remodeling osteoclastic resorption is disproportionately stimulated more than osteoblastic remineralisation. There is biochemical evidence of significant excess of bone resorption (free pyridinoline) comparing to formation (osteocalcine) in patients with hyperthyroidism. (8) As a result, normal cycle duration of 200 days is broken in two and each cycle has 9.6% of mineralised bone loss. Contrary, in hypothyroidism, cycle duration is 700 days with 17% of increased mineralised bone mass by each cycle. Most studies with hyperthyroid patients show the intensity of bone mass reduction of 10-20%.

Histomorphometry of iliac crest shows significant differences in thyroid hormones effects on trabecular and cortical bone. (9) Reduction of trabecular bone is only 2.7%. The surface of osteoclastic resorption of cortical bone is increased for 40% and the porosity of cortical bone is increased for 32%.

Biochemical markers

During the new bone formation and degradation or resorption of the old one components of non-collagenic bone matrix are also released from cells into circulatory system, so their measurement may provide "window" for clinical evaluation of resorption process and bone formation. Biochemical markers may be divided into two groups: bone resorption markers (acidic phosphatase resistant to tartarate, free pyridinoline and deoxypyridinoline, N or C telopeptide type I collagen crossed links in blood, relation of calcium and creatinine, hydroxyproline, glycosides of hydroxylisine, pyridinoline and deoxypyridinoline and N and C telopeptide collagen type I in urine) and markers of bone formation (total or bone specific alkaline phosphatase, osteocalcine and procollagen I C and N terminal extension peptides).

Biochemical markers of bone and mineral metabolism are changed in hyperthyroidism. Serum concentration of alkaline phosphatase and osteocalcine is increased in hyperthyroidism. It may remain increased for months after therapy, mostly as a result of increased osteoblast activity. (10) Urinary excretion of pyridinium cross-links originating from bone collagen is increased and falls to normal shortly after therapy. (11)

Influence of hyperthyroidism on mineral metabolism

The increased release of calcium in circulation as a result of increased bone resorption, influences mineral metabolism leading to the negative calcium balance in hyperthyroid patients. Hypercalcemia suppresses parathormone secretion (PTH) leading to hypercalciuria. It prevents hypercalcemia but leads to negative calcium balance. Decreased concentration of serum PTH reduces conversion 25OHD (calcidiol) to 1.25 OH2D (calcitriol). (12) Reduced calcitriol production is supplemented by the increased calcitriol metabolism caused by hyperthyroidism. Reduced calcitriol concentration decreases intestinal calcium absorption (and

phosphorous) leading to stool calcium loss. Calcium malabsorpion may be additionally deteriorated because of steatorea and increased intestine motility.

Symptomatic bone disease

Some older studies point out to symptomatic bone disease associated with reduced bone density with hyperthyroidism.

Bernandes M et al. (13) got the investigation results wchich have shown that hyperthyroidism significantly reduces bone density of lumbar spine and proximal part of femur while there is an increased bone resorption parameters and falling level of osteocalcine. Women had increased bone turnover in contrast to euthyroid women.

Isasa GC et al. (14) in his study has concluded that hyperthyroidism, based on monitoring formation markers and bone resorption, leads to increased bone turnover and to decreased mineral bone density.

Ben-Shlomo A et al. (15) has examined in his study the effect of hyperthyroidism on bone density in women after menopause. It has been proved that this effect was especially evident at the beginning of post-menopausal period, mostly on cortical bones.

Jana Ilic (16) has shown in her work the effect of hyperthyroidism on bone mass reduction with women in their generative period. Results proved that hyperthyroidism causes bone mass reduction. Bone density parameters with hyperthyroid women were of significantly lower values comparing to control group (sound signal rate BUA 63,25±12,17; 69,73±10,02 dB/MHz, weakening of sound signal SOS: 1523,90± 24,47; 1540,19 ±26,59 m/s, quantitative ultrasonographic index/firmness QUI/STIFF 79,78±13,95; 89,09±13,99%) Bone density parameters were observed in relation to the duration of hyperthyroid condition (up to 1 year, from 1-3 years, 3 years and more). Parameter BUA was 74,35±7,61 in the first group, 60,41±11,41 in the second and 63,36 ±13,12 in the third group. Parameter SOS was 1553±16,20 in the first 1519,77±22,5 in the second and 1518,74 ±23,50 in third group. QUI/STIFF parameter was 96,5±4,55 in the first,76,94±12,55 in the second and 77,64±14,64 in third group. It has been determined that values of bone density of hyperthyroid condition while it is mostly evident when compared disease duration up to 1 year with that of 1-3 years.With the prolongation of hyperthyroidism negative trend of the mentioned factors is alleviated, probably due to possible compensatory mechanisms in the complex bone metabolism regulation.

Hyperthyroidism can be considered one of the causes of secondary osteoporosis and certainly one of the risk factors of involutional osteoporosis occurring in later life period. It can be concluded that fracture aptitude is higher in patients with hyperthyroidism than in healthy ones, waich may be reflected as a disadvantage in the incidence of hip fracture, vertebra and forearm in general population taking into account the frequency of hyperthyroidism.

Nodular goitre with subclinical hyperthyroidism

Patients with subclinical hyperthyroidism have normal concentration of free thyroxine (FT4) and free triiodothyironine (FT3), but they have subnormal concentrations of thyroid stimulating hormone. (TSH) Subclinical hyperthyroidism is most frequent in aged patients with multinodular goitre, and rarely iy occurs with mild Graves disease. Symptomatic bone disease is not characteristic for subclinical hyperthyroidism, but this disorder has negative effect on bone density and presents a risk factor for osteoporosis. Reduced bone density of forearm which has negative correlation with serum FT4 level has been observed in women with nodular goitre and subclinical hyperthyroidism. (17)

Subclinical hyperthyroidism as a consequence of egsogenic therapy with thyroid hormones

Many patients trated with thyroxine have subclinical hyperthyroidism while some of them have increased bone resorption and decreased density. There is no evidence about frequent fractures with these patients.

Stall GM et al (18) have shown in their study with 10 patients having subclinical hyperthyroidism caused by L-thyroxine therapy statistically significant bone loss at lumbar spine.

The application of L-thyroxine as a suppressive therapy with operated and X-ray trated malignant tumor of thyroid gland, in order to achieve subclinical hyperthyroidism, may lead to the reduction of bone mass and occurrence of osteoporosis. Diamond T et al (19) has obtained the same results in his study.

New studies are needed to define the degree of TSH suppression necessary for achieving desired effect with T4 suppressive therapy. Many authors recommend that patients with thyroid carcinoma should have very low TSH concentrations (below 0.01 mU /L) for the reason of better basic disease control. In such conditions an intervention is often necessary in order to prevent bone tissue by using antiresorptive therapy.

Bone density in primary hypothyroidism

Hypothyroidism is related to the increased bone density except if it is related to some degree of hypogonadism (e.g. hyperprolactinemia) when this protective effect may not be present. During early period of hypothyroidism treatment decreased bone density may be expected as the result of increased remodelling and osteoclastic resorption which by the time gets back to “steady state” conditions.

Vestergaard P et al. (20) has shown in his study that usage of T4 in hypothyroid patients which in the first two years of therapy leads to an increased bone resorption surface,increases bone fracture risk as well.

Treatment of subclinical hypothyroidism with T4 has not shown bone density reduction if TSH values are in the scope of referrential values.

Prevention and treatment of reduced bone density in hyperthyroidism

Considering the influence of hyperthyroidism on bone mass, it is necessary for its diagnostics to be well-timed and treated in order to define euthyroid condition

as soon as possible. This should help bringing back the intensity of metabolic bone activity to normal level. Life period of patients should not be neglected i.e. if they are close to menopause. It practically means that if patients are young women far from the menopause, prevention from the negative effect on bone mass may consider only treatment.of hyperthyroidism as the basic disease. However, if women are at the end of their generative period, treatment of hyperthyroidism itself is not enough therefore it is necessary to introduce or include subsidiary means of therapy such as vitamine D or in some cases classical therapy for osteoporosis. For better treatment of possible bone changes in hyperthyroidism, at the beginning and during therapy of basic disease, it is necessary to measure bone density and control metabolic parameters.

There are several measures for preventing bone density loss:

- application of bone resorption inhibitors –biphosphonates or calcitonine

-titration of suppressive therapy for achieving minimal subnormal serum TSH concentration (between 0.1 and 0.5 mU/L)

-calcium and vitamine D application

- hormone replacement therapy in menopause women

Treatment by bone resorption inhibitors may be useful in patients with continual loss of bone mass and those who are relatively resistant to the basic disease therapy. Rosen et al. (21) in his stady has determined that pamidronat reduces the increased bone turnover parameters caused by thyroid hormones.

Cailcium application as a natural bone anti-resorber may be useful. Calcitonine reduces urinary excretion of hydroxyproline and serum calcium in patients with manifested hyperthyroidism. Combination of intranasal calcitonine and calcium has not given better results in relation to bone density.

Adequate calcium intake in diet is very important for reducing the negative effect of thyroid hormones to bone. Kung et. al. (22) has shown in his study including 46 postmenopausal women receiving suppressive T4 therapy that those who were taking placebo had 5-8% of bone density reduction in the period of two years while those receiving 1000 mg of calcium a day had an unmeasurable bone loss.

Hormone replacement therapy proved to be effective applied together with thyroid hormones therapy. While considering possible introduction of hormone replacement therapy to patients with hyperthyroidism should be taken into account.

Summary

Hyperthyroidism leads to the reduction of quantitative bone mass parameters and to the reduced quality of bone tissue as well. Consequences of such effects of hyperthyroidism is a naturally increased aptitude to bone fracture risk. Taking this into account, it is necessary to achieve euthyroid condition as early as possible in hyperthyroid patients, to avoid the occurence of iatrogenesis hyperthyroidism, i.e. to

insist on optimum substitution, and with operated patients and malignant tumors of thyroid gland on suppressive L-thyroxine therapy to introduce protective measures and possible medical prevention of osteoporosis.

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