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Assessment of bone metabolism in premenopausal females with hyperthyroidism and hypothyroidism

Ocena metabolizmu tkanki kostnej u kobiet przed menopauzą chorujących na nadczynność i niedoczynność tarczycy

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Abstract

Introduction: Osteoporosis is one of the commonest metabolic diseases of bone. Its possible causes may include thyroid hormonal dysfunction. The objective of this study was to evaluate the effects of hyperthyroidism and hypothyroidism on osseous tissue metabolism in premenopausal women.
Material and methods: 38 women with hyperthyroidism, 40 with hypothyroidism and 41 healthy women participated in this study. Initially after 6 and 12 months, each patient underwent selected hormonal, immunological and biochemical tests, measurement of concentrations of bone turnover markers and densitometry were also performed.
Results: On initial evaluation, lower cortical bone density was found in patients with hyperthyroidism (femoral neck). After 12 months, an increase in BMD was seen, but it was still lower than in the control group. Statistically significantly higher concentrations of bone turnover markers, decreasing from the sixth month of treatment, were noted only in the group with hyperthyroidism. Statistically significant differences were not noted in the femoral neck nor in the lumbar spine BMD in patients with hypothyroidism.
Conclusions: Hyperthyroidism poses a negative effect on bone metabolism. Hypothyroidism in premenopausal females does not have any influence on bone density. **(Endokrynol Pol 2013; 64 (1): 40–44)**

Key words: *hyperthyroidism, hypothyroidism, bone mineral density (BMD), osteocalcin (OC), collagen type 1 crosslinked C-telopeptides (CTx)*

Streszczenie

Wstęp: Osteoporoza należy do najczęstszych chorób metabolicznych kości. Jej przyczynami mogą być między innymi choroby gruczołu tarczowego. Celem pracy była ocena wpływu nadczynności i niedoczynności tarczycy na metabolizm tkanki kostnej u kobiet w okresie przedmenopauzalnym.
Materiał i metody: Badaniem objęto 38 kobiet z nadczynnością tarczycy, 40 — z niedoczynnością tarczycy i 41 zdrowych kobiet. Oceniano wyjściowo, po 6 i 12 miesiącach wybrane parametry hormonalne, immunologiczne i biochemiczne, stężenie markerów obrotu kostnego oraz wykonano badanie densytometryczne kości.
Wyniki: W grupie z nadczynnością tarczycy stwierdzono obniżenie BMD w zakresie kości korowej (szyjka kości udowej). Po rocznym leczeniu tyreostatykiem obserwowano wzrost BMD, ale była ona nadal mniejsza niż w grupie kontrolnej. Tylko w grupie z nadczynnością tarczycy wykazano statystycznie istotnie większe stężenie markerów obrotu kostnego, które w sposób istotny zmniejszało się od 6 miesiąca leczenia. W grupie z niedoczynnością tarczycy nie wykazano wpływu na BMD zarówno w zakresie szyjki kości udowej, jak i kręgosłupa lędźwiowego.
Wnioski: Niekorzystny wpływ na metabolizm kostny wywiera nadczynność tarczycy. Niedoczynność tarczycy u kobiet przed menopauzą nie wpływa na gęstość kości. **(Endokrynol Pol 2013; 64 (1): 40–44)**

Słowa kluczowe: *nadczynność tarczycy, niedoczynność tarczycy, gęstość mineralna kości (BMD), osteokalcyna (OC), C-końcowe telopeptydy prokolagenu typu 1 (CTx)*

Introduction

Bone is a very metabolically active tissue: the processes of bone resorption and formation last throughout life. Osteoporosis is a systemic disease of the skeleton in which reduced bone mineral density and deterioration of microarchitecture lead to an increased risk of fractures [1, 2]. Osteoporosis is one of the commonest metabolic bone diseases, and it can be classified as primary or secondary. Primary osteoporosis is most common in women after the menopause, whereas secondary osteoporosis may arise at any age and can be caused by for example endocrinopathies, including hormonal thyroid dysfunction [3–5].

Hyper- and hypothyroidism are the commonest pathologies encountered in everyday endocrinological practice. Thyroid hormones exhibit pleiotropic effects in the human body which are also observed in osseous

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tissue. Thus, any excess or deficiency of thyroxin (fT_4) and triiodothyronine (fT_3) potentially poses a risk to bones [6–8].

The objective of our study was to evaluate the effects of hyper- and hypothyroidism on osseous tissue metabolism (bone mineral density and selected bone turnover markers) at the time of diagnosis of thyroid dysfunction as well as after six and 12 months of treatment (evaluation of potential for reversibility of metabolic bone dysfunction after reaching euthyroidism) in premenopausal women.

Material and methods

A total of 119 women aged 18 to 52 years participated in this study. They were divided into three groups. The first group comprised 38 women aged 22 to 52 years (average age 34.73 ± 7.77) with newly diagnosed hyperthyroidism; the second group was composed of 40 women aged 18 to 51 years (average age 33.37 ± 10.83) with newly diagnosed hypothyroidism; and the third group (the control group) was made up of 41 healthy women aged 18 to 50 (average age 34.43 ± 10.12).

For the purposes of this study, only female patients without previous thyroid disease history were qualified, prior to initiating pharmacological treatment. The study was approved by the Bioethics Committee in Wroclaw. All patients enrolled in the study were provided with written information on the purpose and design of the study.

Patients were followed-up for a period of 12 months. Diagnostics studies were started during the winter (November to April). Subsequently, two control visits were conducted: on average after six months (i.e. between June and September) as well as 12 months after reaching euthyroidism (i.e. between the following November and April).

After initial qualification to the study (written survey, medical history and physical examination), each patient underwent a panel of diagnostic tests: hormonal (concentration of thyroid-stimulating hormone — TSH, free triiodothyronine — fT_3, free thyroxine — fT_4, parathyroid hormone — PTH, follicle-stimulating hormone — FSH, luteinising hormone — LH, oestradiol — E_2, and testosterone), biochemical (concentration of total calcium, inorganic phosphates, magnesium, alkaline phosphatase activity), immunological (levels of antithyroglobulin — ATG, anti-thyroid peroxidase — ATPO, anti-TSH receptor antibodies — TRAB), concentration of markers of bone resorption (collagen type 1 crosslinked C-telopeptides — CTx) as well as osteogenesis (osteocalcin — OC); visual studies: ultrasonographic thyroid study, femoral neck and lumbar spine densitometry (to evaluate BMD among premenopausal women, the Z-score index was chosen).

Six and 12 months after reaching euthyroidism, the above mentioned hormonal, biochemical, and immunological studies and the measurement of markers of bone turnover concentration were repeated on every patient from the group under investigation. In the control group, the measurement of bone turnover markers concentration was performed.

All patients with hyperthyroidism were treated with an oral thyrostatic — methimazole (dose from 60 to 5 mg per day) for the whole 12 months of the study; women from the group with hypothyroidism were treated with levothyroxine (dose from 25 to 150 ug per day).

The results were presented in an average form in sample and standard deviation in sample using the Tukey and Welch tests; to assess for correlation, a Spearman test was employed. Calculations and tests were conducted using the SAS version 9.1 statistical pack.

Results

On initial evaluation, a statistically significant lower femoral neck bone density expressed by the Z-score was found in female patients with hyperthyroidism compared to those with hypothyroidism. Statistically significant differences were not noted in the femoral neck BMD expressed in g/cm^2 nor in the lumbar spine BMD between the studied groups. Statistically significant higher serum concentrations of OC and CTx were noted in the group of females with hyperthyroidism than in the control group and in the group with hypothyroidism.

After 6 months of treatment, in the female patients treated due to hyperthyroidism, a statistically significant higher concentration of OC (versus hypothyroidism and control groups) and of CTx (versus control group) was demonstrated. In this group a statistically significant decrease in concentration of CTx was also seen.

After 12 months of treatment, a continuing statistically significant lower femoral neck bone density expressed through Z-score index was observed in women from the group with hyperthyroidism compared to the control group ($p = 0.0379$), but a statistically significant increase in the femoral neck ($p = 0.0021$) and lumbar spine ($p = 0.0001$) BMD expressed in g/cm^2 was seen. However, no statistically significant difference was noted in the bone density expressed through the Z-score in the mentioned location of the skeleton ($p = 0.0021$ and $p = 0.0001$), compared to the initial value and after 12 months of anti-thyroid therapy.

In the group with hypothyroidism, no statistically significant difference was found between the femoral

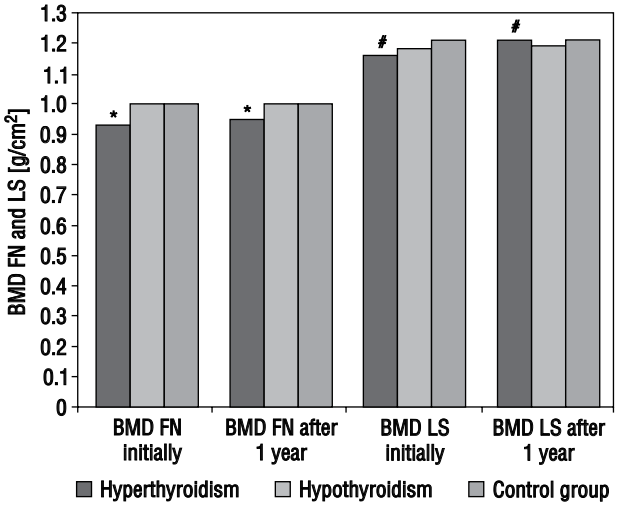

Figure 1. *Changes of femoral neck (FN) and lumbar spine (LS) BMD (g/cm²) among the studied groups in the one year observation period. *p = 0.0021 within group with hyperthyroidism; #p = 0.0001 within group with hyperthyroidism*

Rycina 1. *Zmiany w gęstości kości wyrażonej w g/cm² w zakresie szyjki kości udowej (FN) oraz lędźwiowego odcinka kręgosłupa (LS) w badanych grupach w obserwacji rocznej*

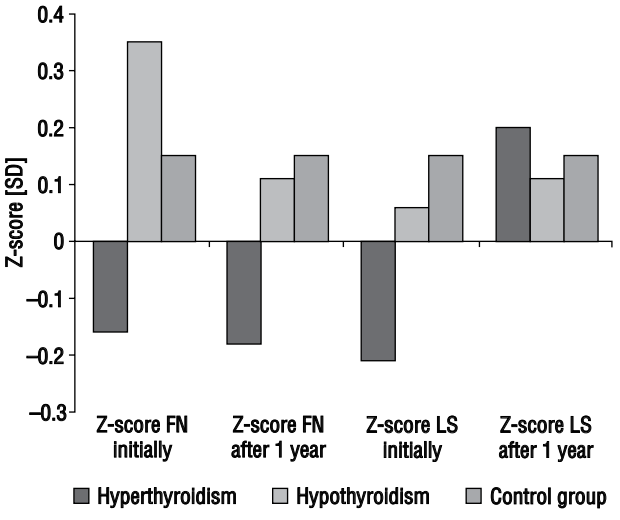

Figure 2. *Changes of femoral neck (FN) and lumbar spine (LS) Z-score among the studied groups in the one year observation period*

Rycina 2. *Zmiany w gęstości kości wyrażonej jako wskaźnik Z-score w zakresie szyjki kości udowej (FN) oraz lędźwiowego odcinka kręgosłupa (LS) w badanych grupach w obserwacji rocznej*

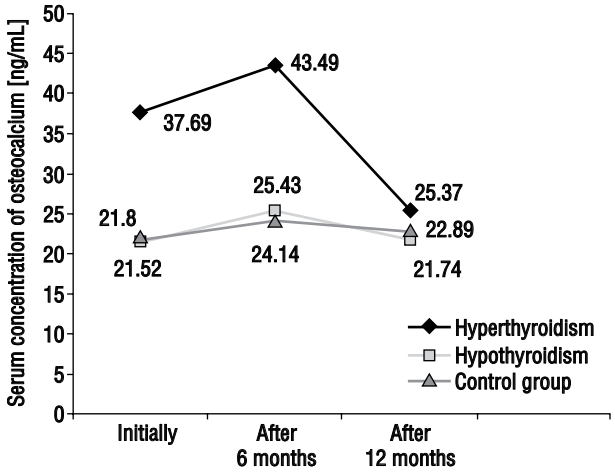

Figure 3. *Changes in serum concentrations of osteocalcin (OC) among the studied groups in the one year observation period*

Rycina 3. *Zmienność stężenia osteokalcyny (OC) w surowicy w badanych grupach w obserwacji rocznej*

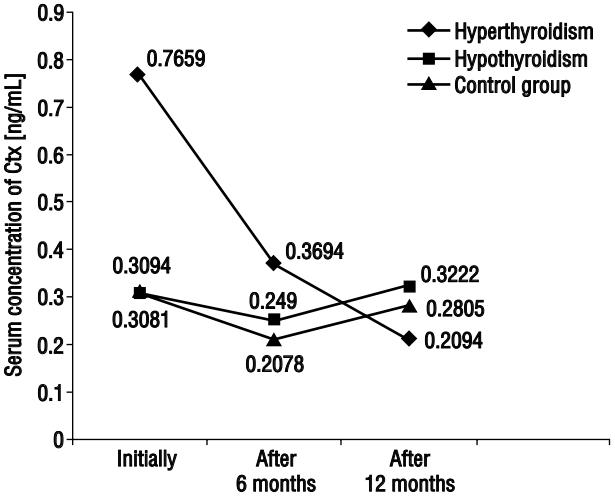

Figure 4. *Changes in serum concentrations of collagen type 1 crosslinked C-telopeptides (CTx) among the studied groups in the one year observation period*

Rycina 4. *Zmienność stężenia C-końcowych telopeptydów prokolagenu typu 1 (CTx) w surowicy w badanych grupach w obserwacji rocznej*

neck and lumbar spine BMD as expressed through g/cm² (p = 0.9903 and p = 0.5638) and Z-score (p = 0.4303 and p = 0.4787) (Fig. 1, 2).

In the group with hyperthyroidism, a statistically significant decrease in OC and CTx concentration was observed. In the group of females treated due to hypothyroidism, no statistically significant difference in the concentration of markers of bone turnover before initiating the treatment and after 12 months of therapy with levothyroxine was seen (Fig. 3, 4).

Discussion

In this study, we assessed BMD changes among patients with hyperthyroidism and hypothyroidism before and

after reaching normal thyroid function compared to a control group. We estimated Z-score index as a point of reference to assess bone mineral density. A decrease in the BMD occurred in cortical bone (femoral neck) in the group with hyperthyroidism. No trabecular bone (lumbar spine) loss was seen in this group and this agrees with previously published data [9–11]. Overt hyperthyroidism in adults leads to shortening of the cycle of bone remodelling by as much as 50% and to disturbance of the proportions of bone formation and resorption processes [12], which can cause the loss of more than 10% of mineral bone for one cycle [4], and increase the risk of fractures [9, 10, 12]. After one year of anti-thyroid treatment, a continuing statistically significant lower femoral neck BMD expressed through Z-score index was observed in the group with hyperthyroidism compared to the control group. But a statistically significant increase in the femoral neck and lumbar spine BMD expressed in g/cm^2 was noted in this group. There was no statistically significant difference in BMD expressed through Z-score comparing initial parameters and after 12 months of treatment.

These results showed that after one year of antithyroid treatment an increase in BMD was seen, but BMD was still lower than in the control group. This means that reaching euthyroidism does not fully normalise bone density, at least in a one year observation period.

Then in the group with hypothyroidism, no statistically significant changes in femoral neck and lumbar spine BMD (expressed in g/cm^2 nor through Z-score) were seen after one year of levothyroxine replacement. According to the literature, hypothyroidism leads to a distinct drop of the rate of bone turnover: the processes of bone formation become about 50%, and of bone resorption about 40%, slower compared to the bone turnover observed during a state of euthyroidism [12]. The influence of the lack of free thyroid hormones on BMD is a matter of dispute [9, 12–14]. However, hypothyroidism is connected with higher fractures risk, although the mechanism remains unknown [15]. In our study, hypothyroidism had no influence on the BMD of studied women.

The assessment of bone turnover markers concentration is an additional and complementary to densitometry method which enables us to estimate bone tissue metabolism. Bone turnover markers allow us to define the level of intensity of catabolic and anabolic processes in osseous tissue, and enable us to perform a current estimation of the skeleton's state because their concentrations in blood serum change faster than BMD.

In this study, we assessed the concentration of one bone formation marker (osteocalcin) and one bone resorption marker (collagen type 1 crosslinked C-telopeptides). Initially, the concentrations of OC and CTx were significantly higher in women with hyperthyroidism (versus the control group and the group with hypothyroidism), although there was no statistically significant difference in bone turnover markers concentration between the group with hypothyroidism and the control group.

These results are consistent with published data describing enhanced bone metabolism among patients with hyperthyroidism [16–18]. In thyrotoxicosis, we observe high bone turnover, increased concentration of bone formation, and resorption markers and disturbance of mineral homeostasis, which can have a negative influence on bone mineral density.

After six months of anti-thyroid treatment, the concentration of OC was still statistically significantly higher in women treated due to hyperthyroidism (versus the hypothyroidism and control groups). However, there was no statistically significant difference in OC concentrations between women with hypothyroidism and the control group. A statistically significant higher concentration of CTx and statistically significant decrease in its concentration was observed in the group with hyperthyroidism after six months of treatment with a thyrostatic.

After one year of anti-thyroid treatment, a statistically significant decrease in concentrations of OC and CTx was observed and this was seen between the sixth and the 12th month of treatment. There was no statistically significant difference in OC and CTx concentrations initially, or after 12 months of treatment with levothyroxine, in the group with hypothyroidism.

The intensity of bone turnover in the group with hyperthyroidism was high in the first half of the year of anti-thyroid treatment. Despite laboratory-confirmed euthyroidism, high concentrations of bone formation and bone resorption markers were maintained in blood serum in this group, which confirmed persistent enhanced bone turnover. Nevertheless, already in the sixth month of antithyroid treatment, a decrease of bone resorption marker concentration was noted, which showed a gradual drop in the resorption process and the beginning of an improvement of bone formation. A decrease in both bone formation and bone resorption markers concentration were seen from the sixth month of treatment with antithyroid drugs: this confirmed a gradual drop in bone metabolism due to normalised concentrations of free thyroid hormones and was reflected in the results from densitometry after one year of treatment.

The analysis of bone turnover markers concentration in female patients with hypothyroidism showed no statistically significant changes initially, or after 6 and 12 months of treatment. This was consistent with the results from densitometry and confirmed no influence of hypothyroidism on bone tissue metabolism.

Conclusions

1. A negative effect on bone metabolism is observed only in the group of female patients with hyperthyroidism. A decrease in the bone density occurs in cortical bone (femoral neck). After one year of anti-thyroid treatment, an increase in bone density is demonstrated, although it is still lower than in the control group, which indicates that correcting the hormonal dysfunction does not fully normalise bone density.
2. Hypothyroidism in premenopausal females does not have any influence on bone density.
3. The negative impact on bone equilibrium expresses first as an increase in markers of bone turnover. This permits detection of bone loss at an earlier stage, preceding the changes observed in densitometry. After one year of anti-thyroid treatment, concentrations of bone turnover markers decrease in a statistically significant way.

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