Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 61; Numer/Number 1/2010
ISSN 0423–104X

Bone mineral density and metabolism in levothyroxine--treated adolescent girls with euthyroid diffuse goiter

Gęstość mineralna i metabolizm tkanki kostnej u dziewcząt z wolem rozlanym nietoksycznym, leczonych lewotyroksyną

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Abstract
Introduction: Bone and mineral metabolism is influenced by thyroid hormones, and levothyroxine (LT_4) therapy may be associated with reduced bone mass in postmenopausal women.
Material and methods: The aim of the study was to assess the influence of one year of LT_4 treatment in a group of 21 adolescent girls with euthyroid diffuse goiter. Lumbar (L_2–L_4) and total body bone mineral density (TOBMD) (Lunar — DXA), serum PTH, osteocalcin, bone alkaline phosphate, vitamin D_3, calcium, and phosphorus levels and urinary excretion of Ca, P, and hydroxyproline were measured before and after one year of combined LT_4 and iodine treatment.
Results: Patients were matched for age, sex, BMI, and maturation status, with controls treated with iodine only. Markers of bone turnover changed in a similar manner in both groups. There was no significant difference in TOBMD value after one year of therapy between LT_4 treated group and controls. Densitometric lumbar spine parameters increased significantly after 12 months in both groups, with no significant differences between them.
Conclusion: It can be concluded that one year of LT_4 treatment of adolescent girls with euthyroid diffuse goiter does not have a negative impact on their bone remodelling and metabolism. **(Pol J Endocrinol 2010; 61 (1): 14–19)**

Key words: *euthyroid diffuse goiter, children, levothyroxine, bone mineral density, bone turnover markers*

Streszczenie
Wstęp: Metabolizm tkanki kostnej pozostaje pod wpływem hormonów tarczycy, a leczenie lewotyroksyną (LT_4, *levothyroxine*) może być związane z redukcją masy kostnej u kobiet po menopauzie. Celem pracy była ocena wpływu rocznej terapii łączonej lewotyroksyną z preparatem jodu (grupa badana 21 dziewcząt z wolem rozlanym nietoksycznym), w porównaniu z grupą kontrolną leczoną tylko preparatem jodu (22 dziewczęta z wolem nierozlanym nietoksycznym).
Materiał i metody: Gęstość mineralna tkanki kostnej całego ciała (TOBMD, *total body bone mineral density*) oraz w odcinku lędźwiowym (L_2–L_4) została oceniona za pomocą badania densytometrycznego (DXA), w surowicy krwi oznaczono stężenia PTH, osteokalcyny, frakcji kostnej fosfatazy alkalicznej, $25OHD_3$, wapnia i fosforanów, natomiast w dobowej zbiórce moczu oceniono wydalanie Ca, P i hydroxyproliny. Wszystkie parametry były ocenione na początku i po roku leczenia w obu grupach.
Wyniki: Nie wykazano różnic pomiędzy grupą badaną i grupą kontrolną w zakresie wieku oraz stopnia dojrzewania płciowego. Stężenia markerów obrotu kostnego zmieniły się w podobny sposób w obu grupach. Gęstość mineralna tkanki kostnej całego ciała nie różniła się znamiennie przed i po roku leczenie między grupą badaną i grupą kontrolną. Gęstość mineralna kości (BMD, *bone mineral density*) w odcinku lędźwiowym wzrosła znamiennie w obu grupach po 12 miesiącach terapii, ale nie było znamiennej różnicy pomiędzy nimi.
Wniosek: Roczna terapia preparatem LT_4 u dziewcząt z wolem rozlanym nietoksycznym nie wywiera negatywnego wpływu na remodeling i metabolizm tkanki kostnej. **(Endokrynol Pol 2010; 61 (1): 14–19)**

Słowa kluczowe: *wole rozlane nietoksyczne, dzieci, lewotyroksyna, gęstość mineralna kości, markery obrotu kostnego*

Introduction

Bones are a metabolically active tissue. Many hormones, most notably thyroid hormones, influence their growth, maturity, and metabolism. They accelerate remodelling of bone tissue by inducing bone resorption and formation [1]. Decreased growth and skeletal abnormalities in children with congenital hypothyroidism are one of the spectacular examples of thyroid hormone importance in bone mineral metabolism. In patients with hyperthyroidism, bone loss and increased levels of bone specific markers may occur [2]. Several reports have recognized that levothyroxine (LT_4) therapy, particularly in suppressive doses, may be associated with reduced bone mass and increased levels of bone metabolism in adults, especially in postmenopausal women

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[3–5]. Some authors found similar results in subjects receiving lower doses of LT_4 [6, 7].

LT_4 is commonly used in the therapy of children and adolescents with euthyroid diffuse goiter. It is applied with or without iodine supplementation, and in iodine deficient areas therapy is usually started with iodine only. There are scarce data on the bone metabolism of children and adolescents receiving LT_4 treatment [8–12]. Puberty is the most important period for bone acquisition. In this age, peak bone mass (PBM) develops and a potential LT_4 negative influence may be associated with higher osteoporosis risk at a later age.

The aim of this study was to assess whether 12 months of LT_4 therapy in adolescent girls with euthyroid diffuse goiter (EDG) might have a negative impact on their bone mineral density and metabolism.

Material and methods

The study was performed on a group of 43 girls with euthyroid diffuse goiter (EDG), who were included according to the following criteria: no other diseases and medications known to interfere with bone metabolism, bone age ± 1 SD from chronological age, and puberty stage 2 ≥ according to Tanner. Patients with osteopenia and nodular goiter were also excluded. All girls included to the study had normocalcaemic diet (based on 3-day dietary diary). Informed consent was obtained from each patient and her parents or guardians. The study was approved by the institutional Ethics Committee.

In all subjects, ultrasonography (USG) of the thyroid gland and measurements of TSH and fT_4 serum levels were performed at study entry. All the girls were randomly assigned to one of two groups.

The Study Group (SG) comprised 21 girls aged 10.3–17.3 years (mean 14.2 ± 1.8 SD). Their body mass index (BMI) was 15.8–22.2 kg/m^2 (mean 19 ± 1.8 SD). The girls were treated for 12 months with LT_4 (Eltroxin® — GlaxoWellcome) in the initial dose 1.2–1.5 mg/kg b.w./day and iodine 100 mg/day (Jodid® — Merck). The therapeutic LT_4 dose was adjusted to keep TSH in normal-low and fT_4 in normal-high levels.

The Control Group (CG) comprised 22 girls aged 10.3–16.9 years (mean 14.6 ± 1.4 SD). Their body mass index (BMI) was 14.9–24.8 kg/m^2 (mean 19.9 ± 2.5 SD). The girls were treated for 12 months with only iodine in the dose of 100 mg/day. In this group, TSH and fT_4 levels remained within normal limits during the whole study.

There were no significant differences between SG and CG with respect to age, stage of puberty, BMI, and daily calcium consumption.

Every three months, a USG of the thyroid gland was performed and TSH and fT_4 serum levels were measured in both groups. At study entry and after one year of therapy, in both groups, serum was obtained for markers of bone formation (osteocalcin and bone specific alkaline phosphatase), calcium, phosphorus, 25-hydroxyvitamin D, and intact parathyroid hormone. Samples were frozen immediately and stored at –20°C until the tests were run. A 24-hour urine sample was collected from each individual for measurement of the markers of bone resorption (hydroxyproline and calcium). Serum calcium (Ca) levels, urinary excretion, and inorganic phosphate (P) were measured using standard laboratory methods. Serum parathyroid hormone levels (PTH) were measured by immunoradiometric assay (Cis bio international, France). Osteocalcin (OC) and bone alkaline phosphatase (BALP) were measured in the serum using two-site immunoradiometric assays (Inc Star Corp. Stillwater, USA). Plasma 25-hydroxyvitamin D (25OHD) levels were assessed by radioimmunocompetitive method. Colorimetric method was used for assessment of urinary concentration of hydroxyproline (HP).

Bone mineral density of lumbar spine (L_2–L_4 BMD) and total body (TOBMD) were measured at study entry and after one year of treatment in both groups by dual energy X-ray absorptiometry (DXA) with a Lunar DPXL analyzer. The values were expressed as bone mineral content (BMC [g]) and bone mineral density (BMD [g/cm^2]). For L_2–L_4, the BMD value was corrected by the volume and expressed as volumetric bone mineral density (vBMD [g/cm^3]) according to Kroger at al. [13].

The results were expressed as mean ± SD. The significance of changes was analysed using Student's paired t-test (within-group comparisons) and unpaired t-test (between group comparisons). In all statistical analyses, $p < 0.05$ was considered significant.

Results

Markers of bone turnover

Serum TSH levels after 12 months of therapy decreased significantly in the SG ($p < 0.05$). In the CG there was no significant difference in TSH levels before and after treatment with iodine. fT_4 values increased significantly in both groups (SG-$p < 0.01$; CG — $p < 0.05$). There were no significant differences between the SG and CG with respect to TSH and fT_4 in all points of the study. Serum Ca values did not differ significantly during therapy and between the groups. Serum P values increased significantly after therapy (SG — $p < 0.001$; CG — $p < 0.01$) without significant differences between the groups. PTH levels increased significantly in both groups ($p < 0.05$) but remained within normal range during the whole study. They did not differ in children from the study group in comparison to the controls. A significant decrease in $25OHD_3$ value was observed after one-year therapy in both the SG and CG groups

Table I. *Bone metabolism parameters in both groups before and after one year of therapy (Mean ± SD)*

Tabela I. *Parametry metabolizmu tkanki kostnej w obu grupach, przed i po rocznej terapii (średnia ± SD)*

	SG		p Value	CG		p Value
	Before	After 1 year		Before	After 1 year	
Ca [mmol/L]	2.45 ± 0.11	2.43 ± 0.10	NS	2.46 ± 0.10	2.45 ± 0.07	NS
P [mmol/L]	1.66 ± 0.23	1.33 ± 0.32	< 0.001	1.65 ± 0.19	1.35 ± 0.25	< 0.01
PTH [pg/ml]	10.87 ± 6.39	28.07 ± 13.98	< 0.01	12.29 ± 8.56	26.33 ± 14.03	< 0.05
$25OHD_3$ [ng/ml]	22.39 ± 10.09	13.07 ± 5.3	< 0.05	23.97 ± 13.32	13.63 ± 5.5	< 0.05
OC [ng/ml]	77.85 ± 34.08	45.73 ± 16.86	< 0.01	65.00 ± 47.69	29.36 ± 12.76	< 0.05
BALP [nmol/L/s]	642 ± 337	626 ± 534	NS	557 ± 491	606 ± 491	NS
HP [mmol/kg/day]	256.74 ± 131.42	276.28 ± 94.55	NS	237.43 ± 89.32	252.11 ± 131.8	NS

SG — study group; CG — control group; Ca — calcium; P — phosphorus; PTH – parathyroid hormone; $25OHD_3$ — 25-hydroxycholecalcipherol; OC — osteocalcin; BALP — bone alkaline phosphatase; HP — hydroxyproline

($p < 0.05$), but there were no significant differences between the SG and CG groups. Serum OC levels were also significantly lower after one year in both groups (SG — $p < 0.01$; CG — $p < 0.05$), without significant differences between groups. BALP values were not significantly different before and after treatment and between study groups. There was no significant difference with respect to urinary excretion of Ca, P, and HP at the beginning or at the end of treatment. There was also no difference between the groups at these two points of the study (Table I).

Densitometric parameters

The TOBMD value did not change significantly after one year of therapy in any of the groups (Fig. 1). Densitometric lumbar spine parameters increased significantly after 12 months in both groups, without any significant difference between SG and CG. BMC L_2–L_4 in SG was 39.8 ± 10.83 g at baseline and 42.9 ± 9.18 g after therapy ($p < 0.01$), and in CG 40.3 ± 9.84 g and 42.4 ± ± 8.54 g ($p < 0.05$), respectively (Fig. 2). BMD L_2–L_4 increased significantly in both groups after 12 months from 1.01 ± 0.2 g/cm^2 to 1.06 ± 0.16 g/cm^2 ($p < 0.001$) in SG and from 1.05 ± 0.15 g/cm^2 to 1.1 ± 0.13 g/cm^2 ($p < 0.01$) in CG (Fig. 3). Calculated vBMD L_2–L_4 values increased insignificantly in the CG group and significantly in the SG group ($p < 0.01$) after one year of treatment. vBMD L_2–L_4 was not significantly different at the beginning and the end of the study or between the groups (0.323 ± ± 0.055 g/cm^3 and 0.336 ± 0.043 g/cm^3 in SG versus 0.352 ± ± 0.046 g/cm^3 and 0.355 ± 0.033 g/cm^3 in CG) (Fig. 4).

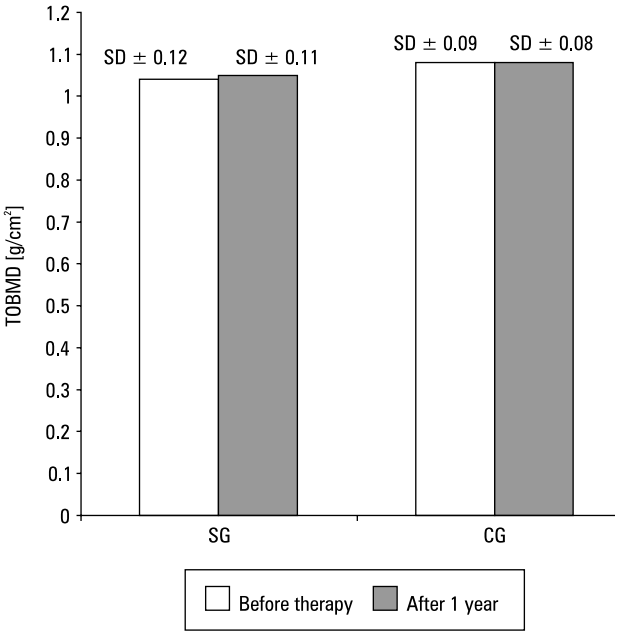

Figure 1. *Change in total bone mineral density (TOBMD) before and after one year of treatment in the study group (SG) and in the control group (CG). Values are mean ± SD*

Rycina 1. *Zmiany całkowitej gęstości mineralnej kości (TOBMD) przed i po rocznym leczeniu w grupie badanej (SG) i grupie kontrolnej (CG). Wartości wyrażono jako średnią ± SD*

Discussion

The accrual of bone mass during childhood and adolescence determines the peak bone mass, and a deficit in bone mass gain may increase the risk of osteoporotic fractures occurring at advanced age. It is well known that women are more prone to osteoporosis. At the same time, levothyroxine is more commonly prescribed for girls as they suffer from enlarged thyroid more often than boys do. The unfavourable effect of levothyroxine therapy on bone mineralization may be associated with excessive suppression of TSH, leading to subclinical hyperthyroidism [14–16].

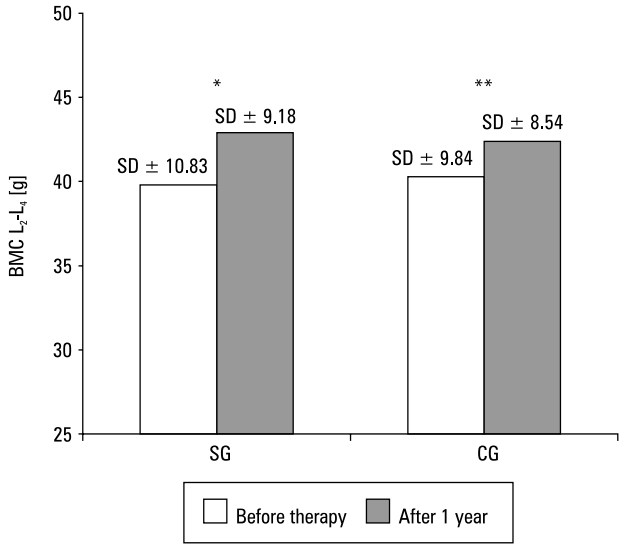

Figure 2. *Bone Mineral Content in lumbar spine (BMC L_2-L_4) before and after one year of treatment in the study group (SG) and in the control group (CG). Values are mean ± SD. * p < 0.01; ** p < 0.05* (v. *before therapy)*

Rycina 2. *Zawartość minerału tkanki kostnej w odcinku lędźwiowym kręgosłupa (BMC L_2-L_4) przed i po roku leczenia w grupie badanej (SG) i grupie kontrolnej (CG). Wartości wyrażono jako średnią ± SD. * p < 0.01; ** p < 0.05* (v. *przed terapią)*

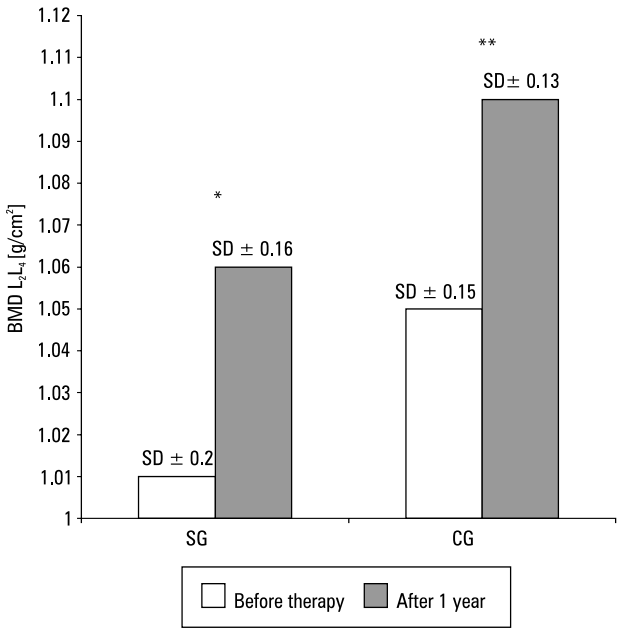

Figure 3. *Bone Mineral Density in lumbar spine (BMD L_2-L_4) before and after one year of treatment in the study group (SG) and in the control group (CG). Values are mean ± SD. * p < 0.001; ** p < 0.01* (v. *before therapy)*

Rycina 3. *Gęstość mineralna tkanki kostnej w odcinku lędźwiowym kręgosłupa (BMD L_2-L_4) przed i po roku leczenia w grupie badanej (SG) i grupie kontrolnej (CG). Wartości wyrażono jako średnią ± SD. * p < 0.001; ** p < 0.01* (v. *przed terapią)*

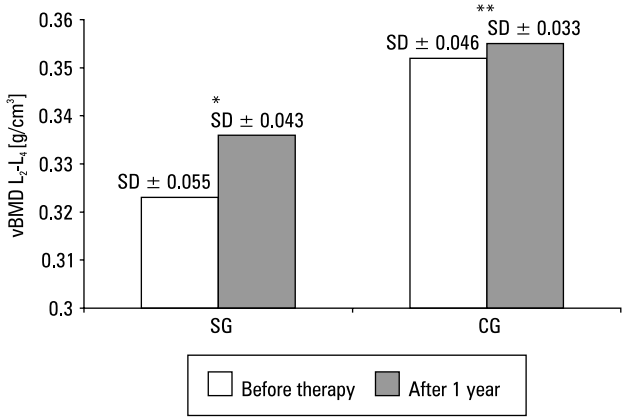

Figure 4. *Volumetric Bone Mineral Density in lumbar spine (vBMD L_2-L_4) before and after one year of treatment in the study group (SG) and in the control group (CG). Values are mean ± SD. * p < 0.01* (v. *before)*

Rycina 4. *Objętościowa gęstość mineralna tkanki kostnej w odcinku lędźwiowym kręgosłupa (vBMD L_2-L_4) przed i po roku leczenia w grupie badanej (SG) i grupie kontrolnej (CG). Wartości wyrażono jako średnią ± SD. * p < 0.01;* (v. *przed terapią)*

Our prospective study was designed to examine whether 12 months of treatment with levothyroxine has a negative impact on bone mass metabolism and accrual in adolescent girls. The simplest method to assess bone metabolism is determination of calcium concentration in serum and its urine excretion. Since this parameter has a low specificity it is usually assessed together with other parameters of calcium-phosphate metabolism, such as inorganic phosphates, parathyroid hormone, and 25-hydroxycholecalciferol ($25OHD_3$). Calcium concentrations in hyperthyroidism are usually normal or slightly elevated. In the examined population of girls, calcium concentrations in serum and in 24-hour urine collection did not differ significantly after one-year therapy compared to baseline. However, inorganic phosphate concentrations decreased significantly both in the group treated with LT_4 and in the controls. No significant change was found in urinary excretion of phosphates in any of the groups. Serum PTH concentrations increased significantly after one-year therapy in both groups but remained within the normal range. Such a change in PTH concentration mainly exerts an anabolic effect on the bone tissue, activating synthesis of an active form of D_3 vitamin which leads to intensification of bone mineralization and maintenance of normocalcaemia. It may also be responsible for a decrease in inorganic phosphate concentration. Concentration of hydroxyproline in urine is another marker of bone resorption, as well as calcium urine excretion. Its renal clearance is increased in hyperthyroidism and is nor-

malised during therapy. In our study, concentrations of HP in the excreted urine did not differ significantly at the baseline and after one-year therapy in both groups. An explanation of the significant decrease of $25OHD_3$ concentrations in the group of girls treated with LT_4 and in the control group is difficult. One of the possible mechanisms may be increased synthesis of the active form of D_3 vitamin.

The effect of LT_4 therapy of non-toxic diffuse goitre on bone formation markers was assessed mainly in postmenopausal women, and the results were often divergent [4, 7]. In this study, concentrations of osteocalcin (OC) decreased significantly during one year of LT_4 therapy in both groups, which might be due to the fact that osteocalcin concentrations decrease gradually until the age of menarche, even by 1/3 of the value per year [17, 18]. Bone alkaline phosphatase (BALP) did not differ significantly at the baseline and after one-year therapy. These results are consistent with a similar study performed on children with non-toxic diffuse goitre, in which no significant changes of OC and BALP concentrations were found during one and a half years of therapy with 100 $\mu g/m^2$/day of LT_4 [10]. Thus, although other investigators found increased concentrations of bone formation markers during levothyroxine therapy in older patients [19–22], it seems that levothyroxine therapy in peripubertal girls does not interfere with physiological changes of bone formation markers.

Studies concerning the effect of LT_4 therapy on bone mineralization also refer mainly to postmenopausal women, and most investigators showed significant BMD decrease [4, 7, 23]. This was confirmed by meta-analyses of data performed by Faber et al. [24] and Uzzan et al. [25]. Data published by Mohammadi showed that in this age group the first 6 month of LT_4 therapy seem to be the most important [5]. Conversely, data presented by Appetecchia in both pre- and postmenopausal women with benign nodular goiter showed that there were no adverse effects on BMD with an LT_4 dose which slightly suppressed TSH levels [26]. In the study of Radetti at al. [8], adolescent girls receiving high doses of LT_4 for non-toxic goiter, Hashimoto«s thyroiditis, or thyroid cancer for 6 to 96 months had a significant reduction of bone mineral content as compared to the controls. Tumer et al. [10] showed that treatment of non-toxic diffuse goitre with lower LT_4 does not does not have a negative impact on bone remodelling and metabolism. A similar observation was made by Poomthavorn et al., who compared a group of young adults treated from early adolescence with suppressive doses of LT_4 (Hashimoto thyroiditis or euthyroid goiter) with healthy controls and showed no detrimental effect on peak bone mass attainment in the LT_4-treated group [12]. Recent data concerning long-term LT_4 therapy in children with congenital hypothyroidism showed no negative impact on BMD in young adulthood, even for prolonged treatment starting from the neonatal period [11].

The TOBMD, assessed in this study, did not differ significantly after one-year therapy in any of the groups, and no statistically significant difference was shown between the groups. The lack of significant change of this parameter is associated with the fact that during puberty certain regions of the skeleton mainly increase their area whereas in others there is intensified mineralization and an increase of BMC expressed in grams.

Densitometric data indicate that LT_4 treatment with maintenance of TSH and fT_4 concentrations within the normal range did not influence bone mineral density in our group of patients. The positive changes in BMC and BMD in lumbar spine noted in both groups of girls are due to the physiological process of bone mass accrual in this age.

Conclusions

The results of the study show that correctly monitored levothyroxine therapy in girls with non-toxic diffuse goitre does not negatively influence their bone metabolism and BMD accrual.

Acknowledgements

We would like to thank Professor Christopher H.J. Kelnar for his kind assistance in reviewing the manuscript.

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