

The effects of L-thyroxin replacement therapy on bone minerals and body composition in hypothyroid children

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Abstract

Introduction: Prolonged treatment with levothyroxine 4 (L-T4) is a well known risk factor for osteoporosis. Patients on L-T4 replacement occasionally have a subnormal TSH, which carries a risk of development of bone loss. Thyroid hormones directly affect bone cells, stimulating osteoclastic and osteoblastic activity with a predominance of bone resorption and decrease of bone mineral density (BMD).

Material and methods: The study included 35 hypothyroid patients with mean age 11.57 ± 5.06, while 26 age- and sex-matched children served as controls. Dual energy X-ray absorptiometry (DXA) was done to detect the bone mineral density (BMD), bone mineral content (BMC) and Z score in lumbar and femur neck regions. Body composition was also studied by DXA. Calcium, phosphorus, osteocalcin as a bone formation marker, osteoprotegerin as an indicator of osteoclast activity and urinary deoxypyridinoline as a bone collagen breakdown marker were assessed.

Results: No significant differences were detected in lumbar Z score (-0.12 ± 0.66) and femur Z score (-0.17 ± 0.58) compared to controls (-0.33 ± 0.74 and -0.21 ± 0.53 respectively). Bone mineral density and BMC were not significantly different from controls. No significant difference was detected between cases and controls in body composition. A positive correlation was detected between BMD and age ($r = 0.857, p < 0.01$), and with the period of treatment ($r = 0.766, p < 0.01$). A positive correlation was found between BMD and total body fat ($r = 0.693, p < 0.01$), and with abdominal fat ($r = 0.667, p < 0.01$).

Conclusions: Levothyroxine 4 treatment in hypothyroid children does not alter bone metabolism and body composition.

Key words: bone density, bone mineral, dual energy X-ray absorptiometry, hypothyroid, levothyroxine 4, children.

Introduction

Hypothyroidism is mostly a permanent disease and should be treated lifelong. Synthetic thyroxin is the preferred form of thyroid hormone replacement therapy [1]. Hyperthyroidism causes severe osteoporosis in children [2] but the long-term risk of osteopenia and fracture in patients on replacement therapy for hypothyroidism is less understood [3].

Prolonged treatment with levothyroxine (L-T4) is well known as a risk factor for osteoporosis [4, 5]. Patients on L-T4 replacement occasionally have a subnormal TSH which carries a risk of development of bone loss [6]. Thyroid hormones directly affect bone cells, stimulating osteoclastic and osteoblastic activity with a predominance of bone resorption and decrease of bone mineral density (BMD) [7, 8].

Bone mass increases through childhood, with maximal bone mass accrual occurring in early to mid puberty and continuing, at a lower rate, in late puberty [9, 10].

Effects of treatment with L-T4 on bone metabolism in children have previously been investigated and conflicting results have been published. Demartini *et al.* in 2007 demonstrated that BMD was significantly lower in children with congenital hypothyroidism [11]. Significant reduction in BMD was also reported during a short period of treatment with L-T4 [12]. Other researchers have found no significant change in BMD in congenital hypothyroidism treated with L-T4 [13, 14].

In this study we aim to detect the effects of L-T4 treatment on bone mineral and body composition in paediatric cases with hypothyroidism.

Material and methods

Thirty-five patients suffering from hypothyroidism (25 females and 10 males) were included in this study. Their mean age was 11.57 ± 5.06 years. They are all under L-T4 replacement therapy in a dose ranging from $75 \mu\text{g}$ to $200 \mu\text{g}$ per day ($1-8 \mu\text{g}/\text{kg}/\text{day}$). Mean follow-up thyroid stimulating hormone (TSH) was $4.48 \pm 3.37 \mu\text{U}/\text{ml}$ where minimum TSH level was $0.2 \mu\text{U}/\text{ml}$. Mean serum free T4 ranged from $1.1 \text{ pg}/\text{ml}$ to $9.9 \text{ pg}/\text{ml}$. All patients in their regular follow-up are doing well and their growth parameters are completely satisfactory under their L-T4 dose of replacement therapy. They are all free from diseases other than hypothyroidism. Twenty-six age- and sex-matched healthy children served as controls.

Again we divided cases depending on age and period of treatment into three groups: group 1, of which the period of treatment with L-T4 is less than 10 years and patients showed no signs of puberty; group 2 where the period of treatment with L-T4 is more than 10 years and patients showed no signs of puberty; and group 3 where the period of treatment with L-T4 is more than 10 years and patients showed pubertal changes either completed or started.

For all patients and controls BMD in g/cm^2 and bone mineral content (BMC) in g of the lumbar spine and the left proximal femur (if unaffected by disease, otherwise the right proximal femur) were measured by dual energy X-ray absorptiometry (DXA) using the Norland XR 46. The mean BMD values of the second, third and fourth lumbar vertebrae (lumbar spine BMD) and of the femoral neck of the proximal femur (femoral neck BMD) were used in the present analysis. Z score > -1 was considered normal, Z score between -1 and -2.5 was considered osteopenia and Z score $= -2.5$ was considered osteoporosis. Body composition was also studied for all by DXA.

Serum levels of calcium, phosphorus, osteocalcin as a bone formation marker [15], osteoprotegerin (OPG) as an indicator of osteoclast activity [16] and urinary deoxypyridinoline (DPD) as a bone collagen breakdown marker [17] were assessed for all patients and controls.

The study was approved by the ethical committee of the National Research Centre as part of a project concerning early detection of osteopenia and osteoporosis in Egyptian children. All patients or their parents gave written informed consent after full discussion about the whole procedures.

Laboratory methods

A 10 ml fasting venous blood sample was taken from each subject in the study. The serum was separated by centrifugation and stored at -20°C for the determination of: serum calcium, phosphorus, osteocalcin, calcitonin, OPG, free T4 and TSH. Random urine samples were also taken from each subject in the study and stored at -20°C for determination of DPD.

Serum calcium and phosphorus were assayed using an Olympus autoanalyser (AU 400). Quantitative measurements of FT4 and TSH in serum were made using an Immulite analyser. Kits were supplied from Siemens Medical Diagnostics, cat. no. LKF41 and LKRT1 respectively.

Quantitative assays by enzyme-linked immunosorbent assay (ELISA) using solid phase amplified sensitivity immunoassays were used to determine the following parameters: osteocalcin (kit supplied from Bio Source Europe S.A., cat. no. KAP1381); OPG (kit supplied from Bio Vendor Laboratory Medicine, Inc., cat. no. RD 194003200); calcitonin (kit supplied from Diagnostic Systems Laboratories, Inc., cat. no. DSL-10-7700); and DPD (kit supplied from METRA, Quidel Corporation worldwide headquarters, 10165 McKellar Court, San Diego, CA 92121 USA).

To detect the possible effects of the different periods of treatment on bone tissue and body composition cases were divided into 3 groups: group 1 where the period of treatment with L-T4 was less than 10 years and no signs of puberty had appeared in any of the patients; group 2 where the period of treatment was more than 10 years and patients did not show any signs of puberty either; and group 3 for patients treated for more than 10 years and showing pubertal changes either completed or started. Each group was compared with age-, sex- and pubertal stage-matched controls.

Statistical analysis

The statistical package SPSS version 15 was used for statistical analysis. Data were presented as means \pm standard deviation. Independent sample

t-test was used to compare between cases and controls and between the different groups. Pearson correlation was used to correlate multiple variants. A *p*-value of less than 0.05 was considered statistically significant.

Results

No significant differences were detected between cases and controls in weight, height and BMI. Table I shows the results of the bone study by DXA where no significant results were detected between cases and controls in different Z scores, total BMD in g and BMC in g/cm². Table II shows the laboratory results where no significant differences were found between cases and controls. The calcitonin hormonal study for all the patients gave results within the normal ranges for patients under L-T4 replacement therapy.

Table III shows the comparison between cases and controls in body composition where total fat is slightly lower and lean body mass slightly higher in cases than controls. However, both fail to show this difference at a significant level.

Positive correlations were detected between BMD, BMC and both the age of the patients and

their period of treatment with L-T4. Positive correlations were also detected between BMD, BMC, lean body mass, total fat and abdominal fat. The highest correlations in BMD and BMC were detected with total lean mass.

Further correlations between BMD, BMC, Z scores and dose of L-T4, and levels of TSH and FT4 in serum were insignificant.

In our study we did not observe a significant difference between male and female cases in BMD, BMC and Z scores. Body composition studies showed a significant difference in gender regarding BMI (males = 16.80 ± 2.49 and females = 21.10 ± 5.20, *p* = 0.02) and total body fat (males = 6.34 ± 5.23 and females = 14.61 ± 9.17, *p* = 0.01). Lean body mass showed insignificant differences between them (males = 22.97 ± 11.96 and females = 26.80 ± 10.32, *p* = 0.35).

Data from the different periods of treatment in the three divided groups are shown in Tables IV-VI. Again no significant differences between cases and controls were found. A significant difference was detected only in total body fat, it being significantly lower in L-thyroxin treated hypothyroid pubertal children than their age- and sex-matched controls (Table VI).

Table I. DXA bone study data

	Cases	Controls	Value of <i>p</i>	95% Confidence interval of the difference	
Z-s FEMUR	-0.167 ± 0.579	-0.210 ± 0.530	0.781	-0.263	0.486
Z-s LUMBAR	-0.197 ± 0.656	-0.331 ± 0.751	0.187	-0.241	0.508
BMD [g/cm ²]	0.712 ± 0.152	0.6831 ± 0.0997	0.406	-0.399	0.097
BMC [g]	1532.26 ± 694.54	1364.462 ± 485.935	0.296	-150.74	488.332

Results are shown as means ± standard deviations, Zs – Z score, BMD – bone mineral density in g/cm², BMC – bone mineral content in g

Table II. Laboratory bone study

	Cases	Controls	Value of <i>p</i>	95% Confidence interval of the difference	
Osteocalcin [ng/ml]	38.250 ± 19.317	49.644 ± 34.151	0.186	-2.8509	5.7218
Osteoprotegerin [pmol/l]	2.878 ± 0.925	3.500 ± 1.552	0.161	-1.5051	0.2617
DPD [mmol/mmol creatinine]	47.781 ± 25.454	60.830 ± 33.632	0.706	-31.832	5.7334
Calcium [mg/dl]	9.77 ± 0.80	9.75 ± 0.50	0.922	-0.4840	0.5332
Phosphorous [mg/dl]	4.78 ± 0.74	4.71 ± 0.91	0.803	-0.5139	0.6953

Results are shown as means ± standard deviations

Table III. Body composition

	Cases	Controls	Value of <i>p</i>	95% Confidence interval of the difference	
Total fat [kg]	12.25 ± 8.10	14.45 ± 13.15	0.441	-7.8727	3.4772
Abd. fat [kg]	2.01 ± 1.77	2.11 ± 2.43	0.830	-1.0417	0.8396
Lean mass [kg]	25.71 ± 10.78	21.96 ± 7.83	0.138	-1.2426	8.7424

Results are shown as means ± standard deviations

Table IV. Group 1 (period of treatment with L-T4 is less than 10 years and patients showed no signs of puberty)

Distribution	N	Mean	Standard deviation	Value of p	95% Confidence interval of the difference	
Age [years]	Case l	14	6.286	0.190	-3.219	0.679
	Cont l	9	7.556			
BMI [kg/m ²]	Case l	14	17.002	0.295	-1.262	3.962
	Cont l	9	15.651			
Z-score FEMUR	Case l	14	-0.243	0.903	-0.615	0.546
	Cont l	7	-0.209			
Z-score LUMBAR	Case l	14	-0.139	0.897	-0.693	0.786
	Cont l	7	-0.186			
Fat total [kg]	Case l	14	7.354	0.239	-2.275	8.625
	Cont l	9	4.179			
BMD [g/cm ²]	Case l	14	0.581	0.163	-0.094	0.017
	Cont l	9	0.620			
BMC [g]	Case l	14	880.142	0.443	-336.334	152.400
	Cont l	9	972.111			
Lean total [kg]	Case l	14	15.175	0.231	-6.823	1.741
	Cont l	9	17.716			

Case l – cases treated for less than 10 years with no signs of puberty yet, cont l – age- and sex-matched controls, BMI – body mass index, BMD – bone mineral density, BMC – bone mineral content

Table V. Group 2 (period of treatment with L-T4 is more than 10 years and patients showed no signs of puberty)

Distribution	N	Mean	Standard deviation	Value of p	95% Confidence interval of the difference	
Age [years]	Case m	7	12.00	0.71	-0.798	1.131
	Cont m	6	11.83			
BMI [kg/m ²]	Case m	7	20.46	0.47	-12.183	6.074
	Cont m	6	23.52			
Z-score FEMUR	Case m	7	-0.35	0.70	-0.876	0.609
	Cont m	6	-0.22			
Z-score LUMBAR	Case m	7	-0.64	0.34	-0.856	0.323
	Cont m	6	-0.37			
Fat total [kg]	Case m	7	13.22	0.20	-23.843	5.710
	Cont m	6	22.28			
BMD [g/cm ²]	Case m	7	0.67	0.56	-0.134	0.076
	Cont m	6	0.70			
BMC [g]	Case m	7	1495.28	0.59	-656.94	396.84
	Cont m	6	1625.33			
Lean total [kg]	Case m	7	27.62	0.41	-6.019	13.66
	Cont m	6	23.80			

Case m – cases treated for 10 years or more with no signs of puberty yet, cont m – age- and sex-matched controls, BMI – body mass index, BMD – bone mineral density, BMC – bone mineral content

Table VI. Group 3 (Period of treatment with L-T4 is more than 10 years and patients showed pubertal changes either completed or started)

Distribution		N	Mean	Standard deviation	Standard error mean	Value of p	95% Confidence interval of the difference	
Age [years]	Case p	14	16.643	1.336	0.357	0.288	-0.577	1.863
	Cont p	13	16.00	1.732	0.480			
BMI [kg/m ²]	Case p	14	22.462	4.477	1.196	0.113	-10.748	1.248
	Cont p	9	27.211	6.780	3.390			
Z-score FEMUR	Case p	14	0.003	0.587	0.156	0.222	-0.185	0.756
	Cont p	11	-0.281	0.533	0.160			
Z-score LUMBAR	Case p	14	-0.038	0.515	0.137	0.980	-0.378	0.367
	Cont p	10	-0.030	0.282	0.089			
Fat total [kg]	Case p	14	16.668	8.163	2.181	0.005	-17.267	-3.34
	Cont p	12	26.973	9.037	2.608			
BMD [g/cm ²]	Case p	14	0.859	0.105	0.028	0.843	-0.090	0.074
	Cont p	13	0.867	0.102	0.028			
BMC [g]	Case p	14	2202.85	407.110	108.805	0.429	-200.03	455.89
	Cont p	13	2074.92	420.180	116.537			
Lean total [kg]	Case p	14	35.285	6.107	1.632	0.094	-0.958	10.46
	Cont p	13	30.532	8.010	2.221			

Case p – cases treated for 10 years or more with signs of puberty, Cont p – age- and sex-matched controls, BMI – body mass index, BMD – bone mineral density, BMC – bone mineral content

Discussion

Thyroid hormone replacement has been used for more than 100 years in the treatment of hypothyroidism. Effects of L-T4 treatment on bone mineralization of children are of great concern. Our data showed no significant deteriorating effects on BMD and BMC during the course of treatment with L-T4. We also did not find any significant differences in laboratory bone turnover markers such as osteocalcin, calcitonin, OPG, DPD, calcium and phosphorus between cases and controls.

The results of Ribot *et al.*, in 1990, suggest that in the case of primary hypothyroidism even appropriate thyroid replacement therapy could lead during the first year of treatment to a significant reduction in vertebral and femoral BMD [12]. Demartini *et al.*, in 2007, challenged the previously published results in the literature showing that hypothyroid children and adolescents with congenital hypothyroidism had a significant decrease in BMD compared to age- and sex-matched controls [11].

Our data are in accordance with Salerno *et al.*, 2004, who concluded that prolonged treatment for congenital hypothyroidism does not affect bone tissue for 17 years of treatment [14]. In 1999 another study in children treated with L-T4 showed that BMD at both the femur neck and lumbar spine

was not significantly different from that of the control group. It also showed that osteocalcin and calcitonin levels were not significantly different [13]. In a study with L-T4 replacement for eight years, in children with congenital hypothyroidism, including BMD, osteocalcin and urinary DPD, similar results to this study were obtained [18]. Kooh *et al.*, in 1997, indicated that even large doses of L-T4 therapy for congenital hypothyroidism do not cause osteopenia in childhood [19].

Saggese *et al.*, in 1996, examined adolescent girls only and concluded that long-term L-T4 therapy in adolescent girls has no adverse effect on BMD or bone turnover and peak bone mass is not impaired [20]. Our results showed no gender differences in bone metabolism during treatment with L-T4 in hypothyroids.

In a recent animal study TSH prevented bone loss and restored bone mass in rats through both anti-resorptive and anabolic effects on bone remodelling [21]. Adverse effects of thyroxin such as osteopenia are considerably more common when serum thyrotrophin has been suppressed. Thus, avoidance of dosages that cause thyrotrophin suppression, when not clinically indicated, is the primary approach to management of these adverse effects [22, 23].

It was revealed that BMC and BMD values intensively increase with age [24]. The positive

correlation detected in our study between period of treatment and both BMC and BMD is probably related to the change of age, as the same positive correlation was detected with age. Period of treatment alone does not affect bone tissue metabolism. Our three groups divided based on the different periods of treatment showed no significant differences in comparison to the age-, sex- and pubertal stage-matched controls.

Longer period of treatment in group 2 and group 3 showed better results in body composition, which appeared as a slight decrease in fat and increase in lean mass. However, body composition does not alter with treatment with L-T4 in our study and no significant changes in BMI, body fat and total lean mass were detected in comparison with controls except in pubertal children in group 3 where a significant decrease in total body fat was detected in treated cases. Similar results were obtained by Brunova *et al.* in 2007, as they concluded that long-term treatment of hypothyroidism did not lead to weight loss or body composition changes [25]. Similar results were also reported by Lomenick *et al.* in 2008 [26]. Normal physiological differences between males and females in body composition did not alter either.

The correlations detected in our study concerning body composition are in accordance with other studies in normal children and adolescents. The correlations between BMI and both BMD and BMC found in this study agree with Lim *et al.*, 2004 [27] and Leonard *et al.*, 2004 [28]. Positive correlations between lean body mass and both BMD and BMC have been documented by many investigators. They all agree that it is the most important related factor determining bone mineralization in males and females [27, 29-31]. Positive correlations of BMD and BMC with total fat and regional fat have also been detected by other researchers [32, 33]. However, many of them concluded that it is a better predictor of bone mass in females [27, 34].

In conclusion, proper controlled replacement therapy with L-T4 in hypothyroid children and adolescents does not affect the BMD, BMC and body composition or alter their normal age- and sex-related physiological changes.

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