

The Effect of L-thyroxine Treatment for the Benign Thyroid Nodule on Bone Mineral Density in Premenopausal Women

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In this study, we evaluated the effect of thyroxine treatment on bone mineral density in premenopausal women with thyroid nodules. Twenty women were accepted for this study. L-thyroxine was started at a dose of 100 µg/day by oral route for a 6-month period. Before and after the treatment bone mineral densities of the femur neck and AP spine were measured. Paired-t test and ANOVA were used in statistical analysis. Serum TSH levels of the patients were found to be within the normal range at the 1st, 2nd, 3rd, 4th, 5th and 6th months. But serum TSH levels at these months decreased with the treatment when compared to basal levels (Basal 1.96 ± 0.77 , 6th month 0.23 ± 0.05 and $p=0.0001$). On the contrary, bone mineral density (BMD) and Z-scores of the femur neck and vertebra of the patients did not show any significant change (basal BMD is 1.02 ± 0.10 in femur neck and 1.11 ± 0.11 in vertebra. Bone mineral density was 1.10 ± 0.08 in femur neck and 1.14 ± 0.12 in vertebra at 6th month). Conclusions; treatment of benign thyroid nodules with L-thyroxine leads to hyperthyroidism. L-thyroxine treatment affected neither BMD nor Z-score.

KEY WORDS Bone mineral density, thyroxine, TSH and benign thyroid nodule

Introduction

Hyperthyroidism is associated with increased bone turnover and bone resorption, but the effects of suppressive doses of thyroxine on bone, in treatment of non-toxic goitre remain unclear. De Rose G et al. (1) demonstrated that TSH-suppressive therapy with L-thyroxine for non-toxic goitre did not cause a significant difference in bone mineral density. On the other hand, it is said that osteoporosis occurs in long-standing hyperthyroidism. Patients with hyperthyroidism show an increase in the rate of bone remodelling and biochemical indices of bone turnover (2). The effects, probably due to direct

actions of thyroid hormones on bone turnover, lead to a tendency for plasma calcium to rise, which in turn decreases the secretion of PTH and synthesis of calcitriol to offset this calcium challenge. Both thyrotoxicosis and treatment of hypothyroidism may be associated with osteoporosis (3). Patients in whom thyroid-stimulating hormone (TSH) is suppressed using sensitive assays show accelerated bone losses but normal rates of loss occur when thyroid function tests are kept within the normal range. Treatment of hypothyroid patients results in a decrease in bone mineral density (BMD) consistent with an increase in the activation frequency of bone. Thus, losses are more marked in the first 6 months of treatment and largely completed after 1 year. It is likely that the excessive use of thyroid hormone replacement treatment contributes to additional bone loss (4). In this study, we aimed to

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evaluate the effect of L-thyroxine treatment on bone density in premenopausal women with nodular goitre.

Subjects and Methods

Subjects: In this study we evaluated 20 adult premenopausal women (aged 21-41 yr; mean, 30.95 ± 6.84 years). All of the patients had single or multiple thyroid nodules in varying diameters. The number of patients was limited to 20, because we wanted to evaluate the effect of thyroid hormone in a homogeneous population. The serum T4, TSH and FT4 levels of the patients were determined before the L-thyroxine treatment. All patients were euthyroid. In all patients fine needle aspiration biopsy of the thyroid was carried out. All of the thyroid specimens were evaluated in the Histology and Pathology Departments and found clearly benign. We measured BMD of patients before and after the treatment. In all patients, L-thyroxine treatment was started at a dose of $100 \mu\text{g/day}$ by oral route. Serum T4 and TSH levels of patients were determined every month during the treatment period.

Hormonal measurements: All of the blood specimens were obtained between 08:00 and 09:00 o'clock after a fasting period of 8 hours. All serum samples were stored at -20°C in deep freeze and all of the hormones were measured in the same session. Serum total T4 (T4), freeT4 (FT4) and TSH levels were measured by using Elecsys FT4 immunoassay, T4 immunoassay and TSH immunoassay kits in the electrochemiluminescence immunoassay "ECLIA" Boehringer Mannheim Elecsys 2010 system.

Bone mineral density: Evaluation of bone mineral density of the patients was carried out by the Lunar DPX densitometry (Lunar DPX, Lunar Corp., Madison, WI). In this instrument bone mineral density is measured by Dual Energy x-ray absorptiometry (DEXA). In this method, the source of radiation is X-ray, dose $<3 \text{ mR}$, duration of measurement is 5 minutes for the vertebra, accurate ratio is $> 99\%$. Bone mineral density of the femur was measured in femur neck, whereas the lowest value that was found between L1 and L4 in the vertebra area (AP spine) was accepted

for the vertebral bone mineral density. All values which were found in bone mineral density measurement were calibrated with % young adult and % age matched automatically. There were no actual data of bone mineral density and Z-scores related to Turkish people. A multicentric study whose aim is to determine the BMD and Z-score of Turkish people is continuing at present. Therefore, we had to use data obtained from a NIH study realised in USA in the comparison of BMD and Z-score. This study is a prospective study. Therefore, we did not compare BMD and Z-scores of the patients and control subjects. Results received by the Lunar DPX computer software were explained as Z-Score for the evaluation of bone fracture risk.

Statistical analysis: Results were presented as mean \pm standard deviation. In the comparison of results of values before and after the treatment paired-t test was used, whereas in the evaluation of repeated measurements ANOVA (analysis of variance) was used. $p < 0.05$ and further values were accepted as having statistical significance.

Results

a. Serum T4 and TSH levels of patients and changes in them with the treatment: Serum T4, FT4 and TSH values of all patients were within normal ranges and none of them had clinical signs of hyperthyroidism. The mean age of the patients was 30.95 ± 6.84 years. Serum TSH levels of the patients changed between 0.67 and $2.04 \mu\text{IU/ml}$ at the first month of treatment. Serum TSH levels of the patients were found between 0.236 and $0.814 \mu\text{IU/ml}$ at the second month. TSH levels of the patients at the 3rd, 4th, 5th and 6th months remained within the normal ranges. Time related serum T4 and TSH levels of the patients are shown in Table 1. Serum T4 levels showed significant differences before and after the treatment ($F=12.32$, $p=0.0001$), whereas in the comparison of serum T4 levels among the 2nd, 3rd, 4th, 5th and 6th months a significant difference was not seen. Serum TSH level of patients were decreased by the treatment at the first month of treatment and this decrement continued during the other months significantly ($F=86.77$, $p=0.0001$). These results revealed that L-thyroxine treatment caused suppression of serum

TSH levels of patients with euthyroid nodular goitre.

b- Bone mineral density and Z score of the patients and changes in them with the thyroxine treatment: Bone mineral density and Z-score results of patients are shown in Table 2. Bone mineral density of both femur neck and vertebra did not show any significant difference related to the L-thyroxine treatment at either lumbar spine or femur neck. In addition to this result, Z-scores of femur neck and vertebra also did not show a significant decrement related to thyroxine administration.

Table 1. Serum basal and treatment time related T4 and TSH levels of the patients.

	T4 (5.13-13.52 µg/dl)	TSH (0.210-4.20 µIU/ml)
Basal	8.00±1.36	1.96±0.77
1 st month	8.67±1.13*	1.06±0.33*
2 nd month	9.05±0.78	0.52±0.18*
3 rd month	9.28±1.17	0.29±0.09*
4 th month	9.47±1.00	0.31±0.007*
5 th month	9.16±0.93*	0.27±0.06*
6 th month	9.52±0.92*	0.23±0.05*

* p=0.0001

Discussion

Thyroid hormone preparations have been used for the treatment of nodular goitre. Although the effectiveness of this treatment is still debated, this preparation is used extensively. In our study, administration of L-thyroxine treatment in euthyroid patients with thyroid nodules caused an increase in serum T4 level at the first month, but this incre-

ment remained at the same level and did not change in the following months. On the other hand serum TSH levels of patients were clearly decreased by the treatment. L-thyroxine suppresses the release of TSH from the pituitary gland. This result indicated that L-thyroxine treatment is effective in suppression of the release of TSH from the pituitary gland.

Hyperthyroidism is associated with increased bone turnover and bone resorption, but the effects of suppressive doses of thyroxine in treating non-toxic goitre remain unclear. Some authors claimed that bone density decreased with suppressive doses of L-T4 treatment (12). Whereas, other authors such as Ribot C et al. (4) claimed minimal or no impact of L-T4 therapy on skeletal integrity. Therefore this issue is still debated. Patients with hyperthyroidism show an increase in the rate of bone remodelling and biochemical markers of bone turnover (2). Hyperthyroid patients may have hypercalcemia, and postmenopausal patients on chronic thyroid suppression treatment may be prone to develop osteopenia (5,6). In our study, patients did not show any clinical or hormonal sign of hyperthyroidism related to L-thyroxine treatment. Therefore, lack of change in bone mineral density may be due to euthyroidism. Our data suggested that L-T4 suppressive therapy, if carefully carried out and monitored, using the lowest dose necessary to suppress TSH secretion, had no significant effect on bone mass. Marcocci C et al. (7) also found similar results. But Marcocci C et al studied a non-homogeneous patient population. On the contrary, our study patients were selected homogeneously among euthyroid people. We determined the BMD and Z-score of the same patients as related with

Table 2. Bone mineral density and Z-score of both femur neck and vertebra body (before and after the L-thyroxine treatment).

Femur neck	BMD (g/cm ²)	Basal•	1.02±0.10	t=-1.2	p=0.2 (NS)**
		6 th month••	1.10±0.08		
Vertebra (AP spine)	Z-score	Basal	0.98±0.52	t=0.72	p=0.48 (NS)
		6 th month	0.91±0.26		
	BMD (g/cm ²)	Basal	1.11±0.11	t=-1.26	p=0.22 (NS)
		6 th month	1.14±0.12		
	Z-score	Basal	-0.42±0.43	t=-1.14	p=0.26 (NS)
		6 th month	-0.033±0.44		

*t=t-test

**NS=non-significant

•Before the treatment

••After the treatment

L-T4. The difference of our study is that it is a prospective study. This result is in compliance with data realised in patients in whom thyroid-stimulating hormone (TSH) is suppressed using sensitive assays who have accelerated losses of bone, but in whom normal rates of loss occur when thyroid function tests are kept within the normal range. It is likely that the excessive use of thyroid hormone replacement treatment contributes to additional bone loss in hypothyroid patients (4). It is said that thyroxine treatment does not cause a decrease in bone mineral density unless this treatment causes hyperthyroidism. Ross DS (8) also claimed that there was no short-term reduction in bone density with levothyroxine treatment of subclinical hypothyroidism in post menopausal women. De Rose G et al. (1) demonstrated that TSH-suppressive therapy with L-thyroxine for non-toxic goitre did not cause a significant difference in bone mineral density. Hanna FW et al. (9) also claimed that there was no evidence for a difference in bone mineral density in patients receiving replacement doses of thyroxine irrespective of the etiology of their hypothyroidism. In some studies realised by a few authors no relationship between the duration of L-thyroxine therapy and BMD was shown. Thus, doses of L-T4 sufficient for suppressing plasma TSH, but not high enough to cause biochemical thyrotoxicosis, have no harmful effect on trabecular bone mineral density (10). Consequently it can be claimed that the treatment of benign thyroid nodules with L-thyroxine does not cause a decrement in bone mineral density if serum T4 and TSH levels remain in the normal range. In addition to these data, Rosen HN et al. (11) found also that premenopausal women and men on suppressive therapy with T4 did not lose bone density rapidly, and were not at increased risk of developing osteoporosis.

Z -scoring not only compares age group, but also compares adult values. Consequently any Z-score that is found must be checked with an age matched Z-score first. If the age matched Z-score is greater than +1, it will be said that patient's Z-score value is greater than the normal range. On the contrary, if the Z-score of the patient is lower than -1, it will be said that the Z-score value of the patient is below the normal range. If the Z-score is lower than

2, it will mean a risk of osteoporosis. If the Z-score is lower than 3, it will mean osteoporosis. If the Z-score is lower than 4, it will mean that fracture risk with minimal trauma has been developed. Z-scores of the patients in this study did not show a risk of osteoporosis or fracture from the point of view of Z-score. After the L-thyroxine treatment, the Z-score of patients in both femur neck and vertebra did not show any significant changes. The Z-score of bone mineral density is quite useful in the evaluation of risks of osteoporosis and fracture. Contrary to others (7, 8, 11), our study showed also that L-T4 treatment did not cause a decrease in Z-score or an increasing risk of bone fracture. The formation of new bone at the end of the resorptive sequence may be responsible for this result. These results indicate that L-thyroxine treatment for the thyroid nodule does not cause any important change in the Z-score of bone. In conclusion; treatment of benign thyroid nodules with L-thyroxine does not decrease bone mineral density of either vertebra or femur neck, unless this treatment leads to hyperthyroidism. Therefore carefully monitored levothyroxine suppressive therapy is not associated with bone loss in premenopausal women. L-thyroxine treatment not only causes no decrement in BMD, but also does not lead to a decrease in Z-score.

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