The Effect of Subclinical Thyroid Dysfunction and L-Thyroxine Treatment on Spinal Bone Mineral Density in Clinically Euthyroid Goitrous Children

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The aim s of this study were to determine the prevalence of subclinical thyroid dysfunction and to evaluate the relationship between hormonal status and spinal bone mineral density (BMD) in clinically euthyroid goitrous children and also to evaluate the impact of long term levothyroxine (L-T4) treatment on spinal BMD.

A total of 142 patients (mean age: 11.3±3.2 years) with clinically euthyroid goiter whose baseline thyroid hormones and sensitive TSH values and TSH response to TRH stimulation on admission had revealed subclinical thyroid dysfunction were enrolled in this study. The patients were divided into two groups: Group I consisted of 66 newly-diagnosed patients who had not received L-T4 whereas Group II consisted of 76 cases who had been taking L-T4 for a mean period of 3.4±2.5 years. These two groups were also subdivided according to their TRH test results: Group Ia and IIa were euthyroid, Group Ib and IIb were subclinical hypothyroid. Lumbar spine (L_{2-4}) BMD was measured by DEXA. The results were compared within each group using unidimensional variance analyses according to the subclinical dysfunction and whether treatment had been implemented or not.

The TRH stimulation test showed that out of 142 cases 95 (66.90%) had euthyroidism, 42 (29.57%) had subclinical hypothyroidism and 5 (3.53%) had subclinical hyperthyroidism. Spinal BMD results on admission were significantly low in the subclinical hypothyroid patients compared to that of euthyroid patients. There was also no adverse effect of L-T4 treatment on the spinal BMD in the 76 treated patients when compared to the 66 non-treated cases.

A TRH stimulation test should be done in all clinically euthyroid goitrous patients to detect subclinical thyroid dysf unction. We suggest that long-term L-T4 therapy in subclinical hypothyroid goitrous children has no adverse effect on BMD.

Key words: **Clinically euthyroid goiter, subclinical thyroid dysfunction, levothyroxine therapy, bon e mineral density**

Introduction

Osteoporosis is a major health problem and future risk is determined at an early age. Bone mineral density in later life largely depends on the peak bone mass achieved in adolescence and young adulthood (1-4) making optimization of bone mass early in life vital. Thyroid hormones exert an important action on bone remodeling and their excess in patients with thyrotoxicosis has long been recognized as being associated with increased bone turnover, affecting bone resorption more than bone formation (5-12). This effect has also been reported in subclinical hyperthyroid patients (13,14). Studies have suggested that adult patients receiving

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chronic levothyroxine (L-T4) treatment, particularly those receiving doses that can suppress TSH, may have a relatively reduced bone mass (15-21). Other authors have reported that long-term L-T4 therapy has no adverse effect on bone mineral density (22-24).

Goiter is a common endocrine disorder in childhood. L-T4 administration is controversial in clinically euthyroid goitrous patients. The thyroid size may decrease in time or remain the same, and L-T4 therapy may not be essential. Euthyroid goitrous patients do not always present with a homogenous thyroid hormone status and may be clinically and biochemically euthyroid, subclinical hypothyroid or subclinical hyperthyroid. The effect of L-T4 therapy on BMD may vary according to the degree of subclinical thyroid dysfunction.

The study objective was to determine the prevalence of subclinical thyroid dysfunction and the relationship between hormonal status and spinal bone mass in 142 clinically euthyroid goitrous children, and to evaluate the impact of long term L-T4 treatment on spinal bone mass according to their thyroidal status.

Material and Methods

Patients: A total of 142 patients (91 female, 51 male; mean age: 11.3±3.2 years) with clinically euthyroid goiter were studied. The exclusion criteria were nodular goiter, clinical findings consistent with hypo- or hyperthyroidism, chronic systemic disease, malnutrition and growth retardation. The patients were healthy and not taking any other medication known to interfere with bone metabolism. None of the patients had any systemic disease known to influence bone mineralization. Clinically euthyroid goiter was diagnosed by physical examination, thyroid ultrasonography and a normal serum sensitive TSH level with normal serum total and free thyroxine levels. The patients were divided into two groups: Group I consisted of 66 newly-diagnosed patients who had not received L-T4 therapy. Group II consisted of 76 cases who had received L-T4 (100 μg/m^2/day) for a mean period of 3.4±2.5 years to shrink goitrous thyroid tissue. These two groups were also subdivided according to their TRH test resuts at admission: Group Ia and IIa patients were clinically and biochemically euthyroid, Group Ib and IIb patients were subclinical hypothyroid.

Hormonal Measur ement: Serum samples for total triiodothyronine (TT3), free T3 (FT3), total thyroxine (TT4), free T4 (FT4) and baseline thyroid stimulating hormone (bTSH) were obtained. Serum levels of thyroid hormones and sensitive TSH were determined by radioimmunoassay with commercially avaible kits (Amerlax MT4, Amerlax MA8 FT4 and TSH- IRMA MEDGENIX). Intra- and interassay coefficient of variation were 1.6-3.7 and 3.2-4.9 for TT3; 3.5-5.8 and 6.4-9.8 for FT3; 2.6-3.3 and 3.6-4.7 for TT4; 3.7-6.5 and 5-7.5 for FT4; 3.46-4.6 and 5.1-5.8 for TSH.

Subclinical hypothyroidism was diagnosed by mildly elevated serum sensitive TSH or an exaggerated response of TSH to the TRH stimulation test and normal serum thyroxine levels (25,26). Subclinical hyperthyroidism was defined as suppressed serum sensitive TSH (<0.1 mIU/L) and normal serum thyroxine and triiodothyronine levels (25). TRH at a dose of 7 mg/kg (max 200 mg) was injected intravenously and blood samples for TSH were collected at 0, 20, 40, 60 minutes (27). Our unpublished thyroid hormone levels and TSH response to TRH stimulation values determined in 44 age-matched healthy euthyroid children with no goiter served as our control (17 girls and 27 boys with a mean age of 9.91±3.45 years). These reference values were as follows: TT3: 1.53±0.38 ng/ml, FT3: 6.37±1.6 pmol/L, TT4: 9.10±1.77 μg/dl, FT4: 17.18±4.95 pmol/L, baseline TSH: 2.49±0.92 mIU/ml, peak TSH response to TRH (pTSH): 16.12±3.93 mIU/ml and delta TSH (peak TSH- bTSH): 13.75±3.6 mIU/ml. The thyroid hormone and the baseline and TRH-stimulated TSH levels were considered pathological when they were 2SD above or below the control values.

Bone Mineral Measurement: Bone mineral density was measured in Group I on admission and in Group II during L-T4 therapy over one year. The spine is composed primarily of trabecular bone, which is metabolically more active than cortical bone because of its greater surface area. We therefore preferred the measurement of bone mass at the vertebral area. Spinal bone mineral mass BMD and BMC determinations were made at the L2-L4 levels of the spine with a commercially available dual energy X-ray absorbtiometer (DEXA) unit (Hologenic QDR-1000). The subjects were

scanned in the supine position, and no child required sedation to complete the examination. Optimal separation of the lumbar vertebrae and reduction of lumbar lordosis was achieved by propping the patient's legs on foam blocks. The results were expressed as BMD in grams per cm^2 as BMC in grams.

Statistical analysis: The results were expressed as mean ± standard error. Values of $p<0.05$ were considered significant. Differences between the groups were assessed by unidimensional variance analyses for vertebral BMD in accordance with the subclinical dysfunction and whether treatment was administered or not.

Results

Figure 1 shows the distribution of thyroid dysfunction in 142 clinically euthyroid goitrous patients. We found that ninety-five cases (66.90%) were clinically and biochemically euthyroid, forty-two cases (29.57%) were subc linical hypothyroid and five cases (3.53%) were subclinical hyperthyroid.

Hormonal characteristics and vertebral BMD and BMC values of Group I, which did not receive L-T4, are shown in Table 1. Spinal bone mass criteria were significantly low in subclinical hypothyroid patients in comparison with clinically euthyroid patients (Figure 2, upper panel).

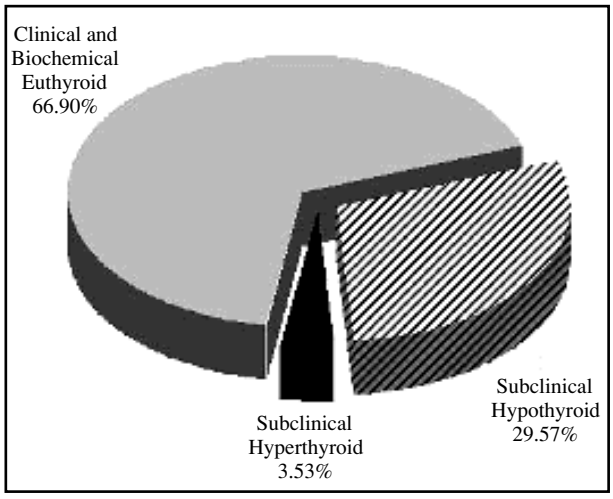

Figure 1. Distribution of thyroid dysfunction in 142 clinically euthyroid goitrous patients according to TRH testing.

Table 1. Goitrous Patients Without L-T4 Treatment (Group I, n=66).

		Clinically Euthyroid n: 51	Subclinical hypothyroid n: 10
On admission	Age (years)	10.48 ± 0.14	11.42 ± 2.58
	$Height_{SDS}$	-0.24 ± 0.88	0.20 ± 0.81
	Free T3 (pmol/l)	5.50 ± 2.06	5.85 ± 1.97
	Free T4 (pmol/l)	19.26 ± 4.43	17.49 ± 5.59
	Baseline sensitive TSH (mlU/ml)	2.24 ± 1.26	3.42 ± 2.06
	D TSH on TRH testing	13.49 ± 9.06	28.35 ± 9.06
	Spinal L2-4 BMD (gr/cm^2)	0.62 ± 0.14	0.59 ± 0.15
	Spinal L2-4 BMC (g)	20.9 ± 8.2	20.2 ± 7.93

Table 2. Goitrous Patients Receiving L-T4 Treatment Over One Year (Group II, n=76).

		Clinically Euthyroid n: 44	Subclinical hypothyroid n: 32
On admission	Age (years)	13.7 ± 0.16	12.07 ± 4.08
	$Height_{SDS}$	0.19 ± 0.99	0.03 ± 1.08
	Free T3 (pmol/l)	5.82 ± 1.86	5.64 ± 1.85
	Free T4 (pmol/l)	15.15 ± 4.75	13.56 ± 4.84
	Basal TSH (mlU/ml)	2.18 ± 1.23	4.54 ± 3.17
	D TSH	13.47 ± 2.95	34.14 ± 16.63
L-T4 treatment duration (3.4 ± 2.5 years)	Spinal L_{2-4} BMD (gr/cm^2)	0.79 ± 0.17	0.76 ± 0.17
	Spinal L_{2-4} BMC (g)	31.5 ± 10.8	29.6 ± 11.2

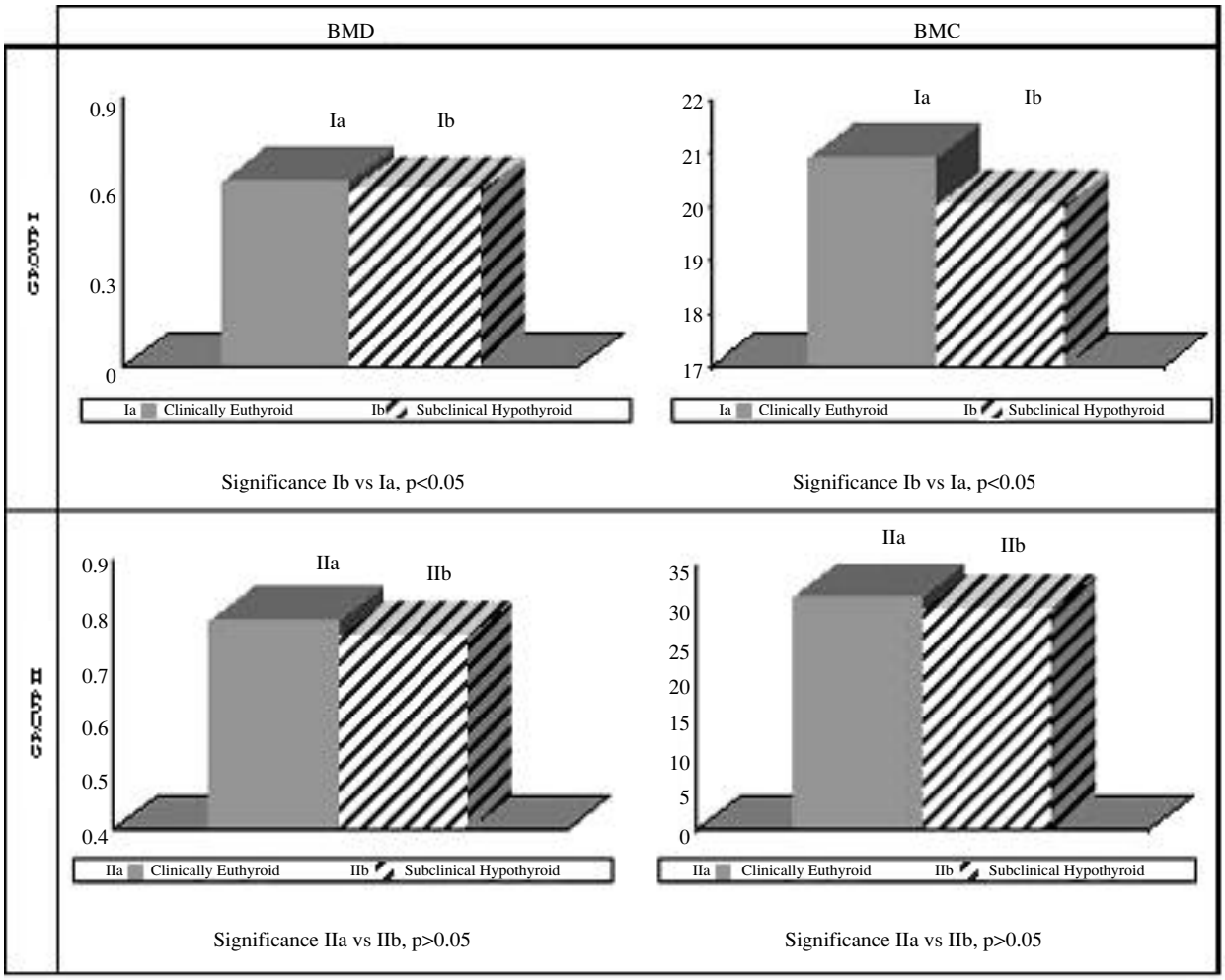

Figure 2. Vertebral BMD and BMC values of goitrous children according to their thyroid dysfunction. Upper panel shows vertebral bone mass criteria of Group I which did not receive L-T4 treatment. Lower panel shows vertebral bone mass criteria of Group II receiving L-T4 treatment for over one year (3.4±2.5 yrs)

Table 3. Vertebral BMD and BMC values in L-T4 untreated (Group I) and treated (Group II) groups without taking subclinical thyroidal dysfunction into account.

	Number of pts (n)	BMD L_{2-4} (g/cm^2)	BMC L_{2-4} (g)
Group I (ages 11.3 ± 3.2)	66	0.64 ± 0.16	21.6 ± 8.8
Group II (ages 13.1 ± 3.1)	76	0.75 ± 0.18	28.7 ± 11.5
Significance		p>0.05	p>0.05

In Group II, receiving L-T4 treatment for over one year (mean 3.4±2.5 years), 44 of the patients (57.89%) were clinically euthyroid while 32 (42.11%) were subclinical hypothyroid. Their hormonal characteristics on admission and spinal bone mass criteria on L-T4 therapy are shown in Table 2. There was no significant difference in spinal BMD and BMC values between treated clinically euthyroid and subclinical hypothyroid patients (Figure 2, lower panel).

The comparison of the spinal bone mass of Group I and Group II is given in Table 3. The spinal BMD and BMC mean values of the Group I patients were 0.64±0.16 g/cm ^{2} and 21.60±8.80 g, respectively. The same values for the Group II patients were 0.75±0.18 g/cm ^{2} and 28.70±11.50 g, respectively. There was no significant difference between the two groups.

Discussion

The results of our study revealed that L-T4 therapy in clinical and biochemical euthyroid and subclinical hypothyroid groups has no adverse effect on spinal bone density, if monitored carefully (0.5 > TSH < 0.2 mIU/ml).

Thyroid hormones are important regulators of normal growth and bone metabolism (5,8,10). Although thyroid hormones stimulate both the osteoblastic and the osteoclastic activity, their effects are much stronger on osteoclasts (5,10,12), leading to osteopenia and the risk of repeated bone fractures in hyperthyroid patients (6,11,14,28,29). L-T4 is given either as physiological replacement therapy in children with hypothyroidism or as suppressive treatment in children with goiter or thyroid cancer. The management of euthyroid goiter is still debated. Euthyroid goiter is not a homogenous clinical entity as regards subclinical thyroid dysfunction. Up to 80-90% of goiter patients are considered clinically euthyroid. This incidence reflects only overt thyroid dysfunction, not subclinical forms. Subclinical thyroid dysfunction and the balance between the potential benefits (shrinking the gland) and risk (e.g. L-T4 induced osteopenia) of treating patients has received attention. The present study supports the existence of biochemical subgroups of clinically euthyroid goitrous children. In our series 66.99% of patients were clinically and biochemically euthyroid, 29.57% were subclinical hypothyroid and 3.53% were subclinical hyperthyroid.

The relation between thyroid function and bone mass has been examined in several cross-sectional and prospective studies (15-24). To our knowledge, this is the first study of vertebral bone density in clinically euthyroid goitrous children regarding their subclinical dysfunction with or without L-T4 treatment.

Recent studies have suggested that adult patients receiving chronic L-T4 treatment, particularly those receiving suppressive L-T4 therapy, have relatively reduced bone mass (6,15-20, 30). Other authors have reported that long–term L-T4 therapy has no adverse effect on mineral density (22-24,31). Leger et al reported that congenital hypothyroid children show normal bone mass, confirming the validity of dose replacement therapy applied throughout infancy and childhood (31). Several authors have reported a reduction in bone density following TSH suppressive doses of L-T4 among patients with non-toxic goiter. Nevertheless, others have demonstrated that an average of 8-10 years of L-T4 suppressive therapy has no adverse effect on bone density (23). In a study by Raidetti et al bone mineral content was significantly low compared to controls in adolescents and children taking high doses of L-T4 for endemic goiter, Hashimato's thyroiditis or thyroid cancer (30). Some degree of L-T4 overtreatment leading to mild subclinical hyperthyroidism might be the cause of the decreased bone mass. Duncan et al have demonstrated that thyroid hormone therapy in the absence of TSH suppression is not associated with a significant effect on BMD (32). On the contrary, Tumer et al have found no correlation between BMD and TSH levels, which is the index of tissue hyperthyroidism (22). They suggested that long-term L-T4 therapy in children has no adverse effect on BMD.

We found that treated euthyroid goitrous children show normal bone mass irrespective of their subclinical thyroid dysfunction. Our data do not reveal any consequence on spinal bone mass acquisition when compared with control subjects.

In conclusion TRH-stimulated TSH levels are more useful than basal sensitive TSH levels for determining subclinical thyroid dysfunction. The long-term carefully monitored (0.5>TSH >0.2 mIU/ml) L-T4 therapy (100 μg/m^2/day) in clinically and biochemically euthyroid and subclinical hypothyroid children has no adverse effect on spinal BMD.

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