

The long term effect of levothyroxine on bone mineral density in patients with well differentiated thyroid carcinoma after treatment

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Abstract

To date a few studies have focused on the possible effects of subclinical hyperthyroidism on bone metabolism, showing conflicting results. This study was designed to evaluate this possibility. *Sixty-six patients*, 22 pre-menopausal women, 33 post-menopausal women and 11 men, who had received iodine-131 (¹³¹I) ablation postoperatively for well differentiated thyroid carcinoma (WDTC) and were treated for a long term with levothyroxine (T₄), entered the study and were compared with sixty-six healthy controls individually matched to the patients for age, gender and menopausal status. The bone mineral density (BMD) of lumbar and hip regions of the patients was measured, while on the T₄ suppressive treatment, with average duration of 14.93±2.17 months after initiation of the T₄ suppressive treatment and was compared with the BMD of healthy controls. All patients were in the subclinical hyperthyroid state, while all controls were serologically and clinically euthyroid. *Our results* show that there was no significant difference in BMD measured at the lumbar spine of patients and controls in any subgroup (P>0.05). Analysis of the data of BMD from the hips in men, pre-menopausal women and controls, also revealed no difference. It was noted that the mean BMD of the femur in the postmenopausal women were at the statistical limit of significance as compared to the control group (P =0.05). *In conclusion*, our findings indicate that the replacement dose of T₄ in WDTC patients after ¹³¹I ablation, does not have a significant effect on BMD in men, in pre and post-menopausal women and hence on the risk of osteoporosis. In post-menopausal women, the mean femoral BMD was at the limit of statistical significance.

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Introduction

Carcinoma of the thyroid gland is an uncommon cancer, but the most common malignancy of the endocrine system [1]. Well differentiated thyroid cancers (WDTC), either papillary or follicular types, are treatable and highly curable, if treated surgically followed by iodine-131 (¹³¹I) ablative treatment and suppression of serum thyroid stimulating hormone (TSH) by the administration of exogenous thyroid hormones [2]. Some investigators have reported that long-term treatment with levothyroxine (T₄) given at suppressive doses inducing subclinical hyperthyroidism has a negative effect on bone metabolism [3-5], while other studies have not confirmed any effect of T₄ on bone mineral density (BMD) in patients with WDTC [6-10].

Since T₄ replacement treatment is mandatory for these patients, any association between subclinical hyperthyroidism secondary to long-term high doses of T₄ treatment and reduction of BMD can be considered as a remarkable side effect. We have examined the effect of long-term high-dose T₄ treatment in a group of patients who had undergone subtotal thyroidectomy followed by ¹³¹I treatment for papillary or follicular WDTC and had no history of thyrotoxicosis. The study was designed in order to establish whether the T₄ treatment schedule we administered can be safely prescribed with no significant side effects on BMD.

Patients and methods

As a cross-sectional study from September 2003 to January 2005, 66 WDTC patients, including 22 pre-menopausal women, 33 post-menopausal women and 11 men, aged 51.72±7.28 years, who were referred to the Research Institute for Nuclear Medicine (affiliated by Tehran University of Medical Sciences) for the evaluation of thyroid function, were ran-

domly selected to be included in the study. All patients had received ¹³¹I ablation postoperatively, and were under TSH suppressive treatment with a mean T4 dose of 168.33±24.3 µg/day. All patients had serum TSH level of less than 0.3 mU/L (normal values: 0.3-4.0 mU/L) and normal free triiodothyronine (FT3) and FT4 values. The commercial kits were prepared from RADIM S.P.A. Roma, Italy. All measurements were performed using the manufacture’s instructions. None of the patients had any clinical evidence of hyperthyroidism during the course of TSH suppression using T4 and in fact, all patients suffered from subclinical hyperthyroidism.

Sixty-six healthy controls were selected from those individuals with no history of any thyroid diseases, referred to the department for a BMD study. The controls were aged 51.15±7.77 years, and matched to the patients’ group for age, sex and the menopausal status. All controls had normal serum levels of FT4, FT3, and TSH (before and at the end of the study).

None of the patients or the controls was taking any drugs affecting bone metabolism (such as glucocorticoids, anticonvulsants, heparin, estrogens, thiazide diuretics, biphosphonates, calcium, vitamin D, or tamoxifen). Subjects younger than 45 years of age with a history of osteoporotic fracture, diabetes mellitus, alcohol abuse, rheumatoid arthritis, chronic amenorrhea of more than 3 months, late menarche, early menopause, oophorectomy or any serious medical disorder, were not enrolled in our study.

The BMD of the total hip and lumbar spine bones were measured by dual-energy X-ray absorptiometry with a dual-photon X-ray system (LEXXOS, Digital 2D Densitometer, Diagnostic Medical System, France). The BMD of the patients were measured 14.93±2.17 months after initiation of the T4 treatment and was compared with the BMD of healthy controls.

The study protocol was approved by the Ethical Committee of Tehran University of Medical Sciences and all patients gave their written informed consent to participate in the study.

Statistical analysis

Data are presented as the mean ± standard deviation (M±SD). Student’s t test was used for comparing M in paired groups. P-values of less than 0.05 were considered significant. For the

analysis of data, commercially available statistical product and service solutions (SPSS ver.13) and SPSS Co., LTD, Tokyo, Japan, were used.

Results

The detailed data of the M±SD of the BMD values and their significance for the lumbar and the femoral area as measured for men, pre-menopausal women, post-menopausal women, are shown in Table 1. There was no significant difference between the mean values of BMD of patients and controls. Only the statistical significance of the difference between the femoral BMD of post-menopausal women and controls was at a borderline level: (P=0.05).

Discussion

Our findings suggest that long-term induced subclinical hyperthyroidism as the treatment option for WDTC patients after surgery and ¹³¹I ablation, does not have any significant effect on BMD in men or in pre- and post-menopausal women and hence on the risk of osteoporosis. A number of studies reported that subclinical hyperthyroidism of variable etiologies accelerates bone loss at a rate of about 2% per year [7, 8], while others showed no significant change of bone metabolism parameters in these patients as compared to healthy controls [9, 10]. However, it should be emphasized that there are some major considerations and contributing factors, the most important of which are reviewed and discussed hereunder: *The etiology of subclinical hyperthyroidism*. Patients with subclinical hyperthyroidism can be categorized as those from endogenous or exogenous (such WDTC patients with subsequent T4-suppressive treatment) etiologies. Based on our findings and also those of others [11], exogenous induced subclinical hyperthyroidism has no significant effect on BMD. Others suggest that post-menopausal WDTC women with exogenous subclinical hyperthyroidism are the most at risk group of treated patients, whereas no increased risk is present in pre-menopausal women and men [12]. The same authors believe that assessment of BMD should be recommended in post-menopausal WDTC women starting TSH suppressive treatment at the end of the second year and this should be reg-

Table 1. BMD values of lumbar and femoral regions, as compared between the three different groups of patients with controls (Mean ± SD)*.

Region	Groups					
	First pair		Second pair		Third pair	
	Pre-menopausal women	Controls	Post-menopausal women	Controls	Men	Controls
Lumbar BMD (gr/cm ²)	1.08±0.18	1.05±0.09	0.98±0.21	0.95±0.17	1.11±0.21	1.04±0.09
	P=0.520		P=0.579		P=0.359	

* Based on a previous study**, normal values are: In male healthy Iranian population, peak lumbar bone mass is considered to be 1.22±0.16 gr/cm² and for the femur to be 1.08±0.15 gr/cm², while in female population is considered to be 1.19±0.12 gr/cm² for the lumbar region and 1.02±0.12 gr/cm² for the femur.

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ularly repeated to enable timely interventions with bone protective agents. As in our study the only borderline significant difference between BMD values were found between postmenopausal women and controls, our findings seem to support these conclusions.

On the contrary, others showed that in all WDTC patients, bone loss is observed after a period of 24 months of T4-suppressive treatment [13, 14]. In concordance with our study, in WDTC patients, others, after a mean treatment period of at least 11 years, found completely different results than the above [13,15,16]. These conflicting conclusions emphasize the need for further studies on increased numbers of WDTC patients and for different time schedules.

Our study and those of others suggest that regardless of the etiology of subclinical hyperthyroidism, the most important contributor in the risk of osteoporosis is the menopausal status of the patient [17]. A number of studies report a reduction of 5%-15% of BMD, especially at the cortical level of the femoral neck and radius in post-menopausal women with subclinical hyperthyroidism for a mean duration of 5 years or more [18-21].

Others emphasized the fact that menopause is not characterized by altered skeletal responsiveness to thyroid hormones [22] and in WDTC patients who require life-long T4 suppressive treatment, bone loss may be observed regardless the menopausal status of the women treated [13].

About the serum level of serum thyroxine values. Another contributing factor is the serum level of T4. Similar to others [23, 24], we found that as long as the serum T4 level is maintained in the normal range (all our subclinically hyperthyroid patients had normal T4 level), there is no decrease in BMD in these patients. It was emphasized that the serum level of circulating thyroid hormones is of paramount importance [13] and also that patients receiving T4 should be carefully evaluated and maintained at the lowest dose required to achieve TSH suppression, as controlled biochemically and by a supersensitive TSH radioactive assay. However, it has been stated that in patients receiving T4 suppression treatment for WDTC, the degree of TSH suppression required is still controversial [13].

Regarding these discrepancies, it seems that bone loss in the context of subclinical hyperthyroidism is a multi-factorial phenomenon and factors, such as sex, age, menopausal status, underlying thyroid disease, treatment schedule, and length of treatment are its major contributors. There are major drawbacks in various studies, which make it difficult to achieve a reliable conclusion [24]. For example, most of these studies are retrospective, no data are provided on the hormonal status during the follow-up period [18-20, 25, 26] and in the majority of them a fixed dose of T4, not adjusted for each individual patient, was prescribed [20, 25]. Also the reported doses of T4 used in some of these studies are higher than those currently recommended, which means that many patients may have been thyrotoxic during treatment [27, 28]. Our study is not free of drawbacks, too. For example, we did not address the influence of physical activity or familial occurrence of os-

teoporosis or the body mass index. Also the rather small number of patients studied is a major limitation.

In conclusion, our findings indicate that suppressive doses of T4 inducing subclinical hyperthyroidism in WDTC patients after surgery and ¹³¹I ablation administered for about 15 months, did not have any significant effect on BMD in men or in pre-menopausal females and hence on the risk of osteoporosis. However, in post-menopausal women, the mean femoral BMD was on the limit of statistical significance. Further studies are needed in order to reach safer conclusions on this issue.

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