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Evaluation of Bone Health in Postmenopausal Women Using Long-Term Levothyroxine Treatment Due to Post-Procedural Hypothyroidism

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Purpose: The connection between thyroid disorders and the health of bone is an endocrinological dilemma for physicians. Several studies have been conducted to examine the correlation between levothyroxine use and the risk of fracture. Different results have been obtained in these studies. The objective of the present study is to evaluate the impact of prolonged thyroid hormone replacement therapy on bone health in postmenopausal women.

Patients and Methods: We obtained demographic data, laboratory results, and anthropometric measurements of patients from the hospital database. After the exclusion of patients, 59 patients with post-procedural hypothyroidism (n = 59) and a control group (n = 45) were evaluated. The patient group consisted of individuals who had undergone thyroid surgery for a benign condition and had been on levothyroxine treatment for a minimum of 5 years. Densitometric measurements of bone mass in the hip and spine were performed by bone mineral densitometry.

Results: Groups were similar in age, PTH, vitamin D, bone-specific ALP, and BMI ($p>0.05$). The control group had a significantly lower total T score-F than the hypothyroidism group (−0.77±1.3 to −0.29±1.02, $p= 0.041$). However, total T score-LV, total gr/cm2-LV, and total gr/cm2-F were similar in both groups.

Conclusion: This study showed that long-term levothyroxine therapy, which aims to maintain TSH levels within the normal reference range, is associated with increased bone mineral density (BMD) in postmenopausal women compared with the control group. Thus, to maintain bone health and prevent osteoporosis, it is important that postmenopausal women on long-term levothyroxine replacement undergo medical follow-up to prevent TSH suppression.

Keywords: osteoporosis, hypothyroidism, levothyroxine, bone health, thyroid stimulating hormone, TSH

Introduction

Thyroid dysfunction and hypothyroidism are common endocrine disorders with a global prevalence. The causes of hypothyroidism can be classified as primary hypothyroidism (autoimmune thyroiditis, iodine deficiency, lithium or amiodarone use, surgery, radioiodine, radiation, etc.) and secondary hypothyroidism (pathologies of the pituitary gland or hypothalamus). Postoperative or postprocedural hypothyroidism is expected after the removal of the entire thyroid gland (a total thyroidectomy). Conversely, the incidence of hypothyroidism ranges from 10% to 42.6% in the case series following after hemithyroidectomy.[1] The recommended treatment for overt hypothyroidism is the use of levothyroxine sodium.

Low bone mass and microarchitectural alterations to the bone structure define osteoporosis. Decreased bone strength leads to an increased risk of fracture. Osteoporosis is defined by densitometric measurements of bone mass in the hip or spine rather than by clinical standards. The World Health Organisation defines osteoporosis as having a bone mineral density (BMD) at any location that is 2.5 SD or more below the T score of a young adult, while osteopenia is defined as having a BMD >1 SD and >2 SD below the T score of a young adult.[2,3]

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The correlation between thyroid disorders and skeletal health poses a significant endocrinological dilemma for medical practitioners. Research studies have demonstrated that both overt and subclinical hyperthyroidism can lead to an elevated risk of bone fractures, particularly among postmenopausal women.[4–7] Inconsistencies have been observed in the results of the studies related to the correlation between the use of levothyroxine replacement therapy and the risk of fractures. It has been observed that among older individuals with hypothyroidism, using a large dose of levothyroxine raises the risk of fracture compared to small doses.[8,9] However, it has been demonstrated that patients receiving levothyroxine treatment are safe when serum TSH levels are not suppressed.[10]

This study aims to evaluate the effect of long-term thyroid hormone replacement therapy on bone health in postmenopausal women who have been receiving levothyroxine for at least 5 years due to primary hypothyroidism following thyroid surgery.

Materials and Methods

Patients

This retrospective study included a total of 463 patients who were diagnosed with post-procedure hypothyroidism and treated at Yozgat City Hospital. We obtained demographic and radiological data, laboratory results, and anthropometric measurements of patients and healthy volunteers from the hospital database. The permission given by Yozgat City Hospital to use the database. Patients with acute or chronic bone diseases, acute or chronic metabolic diseases, a history of anti-resorption or anabolic treatment for osteoporosis and radiation therapy for bone lesions, long-term steroid use, or having suppressed or higher TSH levels than the normal reference range at any time in the last five years were excluded from the study.

Measurements

We used thyroid ultrasonography to evaluate thyroid pathologies and examined them with the help of a single operator. Blood samples were taken for measurements of thyroid stimulating hormone (TSH) and free T4 (fT4), calcium, phosphorus, and parathyroid hormone (PTH). Thyroid function tests were measured with an automated direct chemiluminescent immunoassay (Beckman Coulter, CA, USA). Reference ranges were defined as TSH: 0.38–5.33 mIU/L, fT4: 0.60–1.25 ng/dl, BMD was performed to determine bone health. The mean values of thyroid-stimulating hormone (TSH) and free thyroxine (fT4) were calculated from the annual follow-up of the patients. The BMD was reported as a T-score and gr/cm^2 to measure the severity of osteoporosis. The T-scores and gr/cm^2 of the lumbar vertebra (L1–L4) and femoral neck were measured with dual-energy X-ray absorptiometry and were compared between the two groups. BMD was evaluated using DXA scan images (Lunar Prodigy; GE Medical Systems) and analyzed (Encore Software version 16.0).

Statistical Analysis

Data were analyzed by the SPSS 26.0 package program. Continuous variables were checked with the Shapiro–Wilk test for normal distribution. The Mann–Whitney *U*-test or the independent samples *t*-test was used to compare hypothyroidism and control groups in terms of clinical and laboratory measurements. The Kruskal Wallis test or the ANOVA test was used to compare LT4 dose groups in terms of DEXA results. All p values are bidirectional and $p<0.05$ is statistically significant.

Results

A total of 463 patients with post-procedure hypothyroidism were included in the study. Exclusions were made (Figure 1) and the study was conducted with a post-procedural hypothyroidism or patient group (n=59) and control group (n=45). The mean age of all participants was 59.8±6.3 years. Groups were similar in age, PTH, vitamin D, bone-specific ALP, BMI, total T score-LV, total gr/cm^2-LV, and total gr/cm^2 -F ($p>0.05$). The control group had a significantly lower total T score-F than the hypothyroidism group (−0.77±1.3 to −0.29±1.02, p= 0.041). Table 1 shows a comparison of the groups in terms of demographics and laboratory findings.

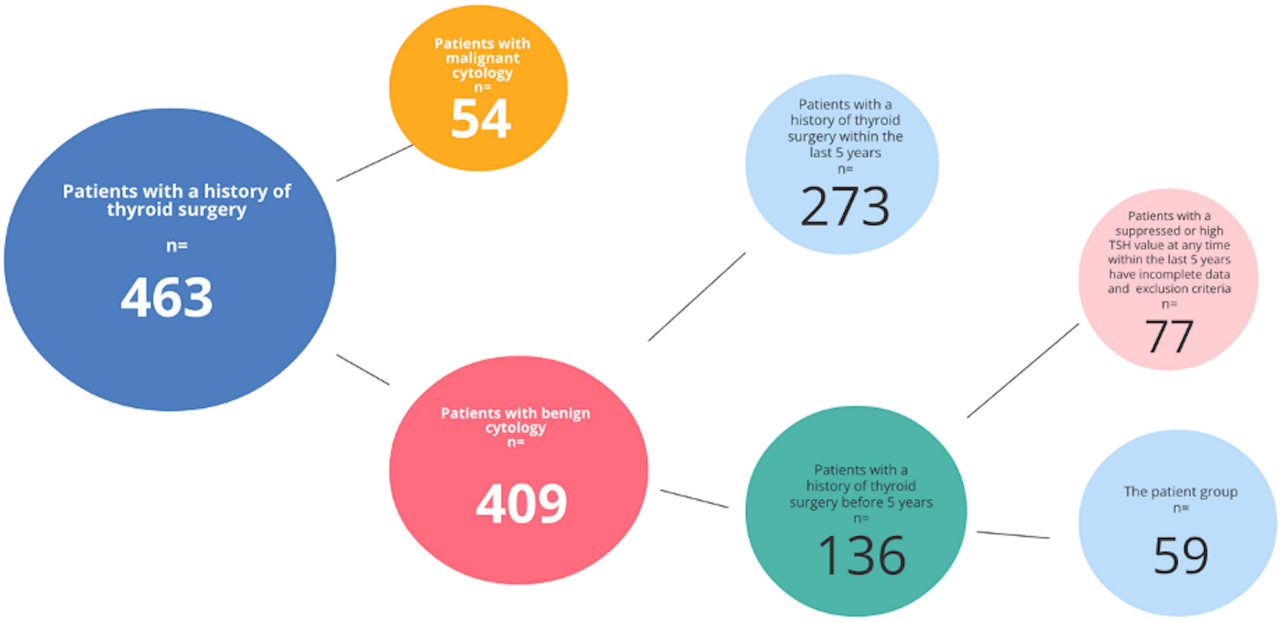

Figure 1 Patient selection protocol.

While mean fT4 levels were similar between the groups (p= 0.800), mean TSH was significantly higher in the patient group (p= 0.001). Figure 2 shows the comparison of mean TSH and mean fT4 of the groups.

Dose-per-body surface area quartiles then regrouped patients. Q1 group had a dose of 1.77 mcg/m^2±0.3, Q2 had a dose of 2.63±0.2 mcg/m^2, Q3 had a dose of 3.16±0.15 mcg/m^2, and Q4 had a dose of 3.89±0.4 mcg/m^2. Groups were similar in terms of total T score-LV, total gr/cm^2-LV, total T score-F, and total gr/cm^2 -F. Dose quartile groups were similar in terms of LV and F measurements (p>0.05). Figure 3 shows the comparison of the T scores of dose quartile groups of the patients.

Table 1 Comparison of the Groups in Terms of Demographics and Laboratory Parameters

Characteristics	Total (n=104)	Hypothyroidism (n=59)	Control (n=45)	p
Age (yr)	59.8±6.3	58.5±5.2	61.5±7.2	0.059
PTH (pg/mL)	66.2±30.1	65.6±32.2	66.9±27.4	0.545
VitaminD (ng/mL)	18.5±12.1	19.2±14.3	17.7±8.5	0.924
ALP (U/L)	92.3±37.1	89.2±21.4	95.4±48.2	0.631
BMI (kg/m^2)	32.9±4.1	33.5±4.4	32.1±3.6	0.105
T score-LV	−1.04±1.3	−0.86±1.34	−1.28±1.25	0.182
gr/cm^2-LV	1.01±0.18	1.04±0.17	0.98±0.19	0.179
T score-F	−0.49±1.17	−0.29±1.02	−0.77±1.3	**0.041**
gr/cm^2 -F	0.92±0.14	0.94±0.12	0.89±0.15	0.085

Abbreviations: PTH, parathyroid hormone; ALP, alkaline phosphatase; BMI, body mass index: LV, lumbar vertebrae; F, femoral neck.

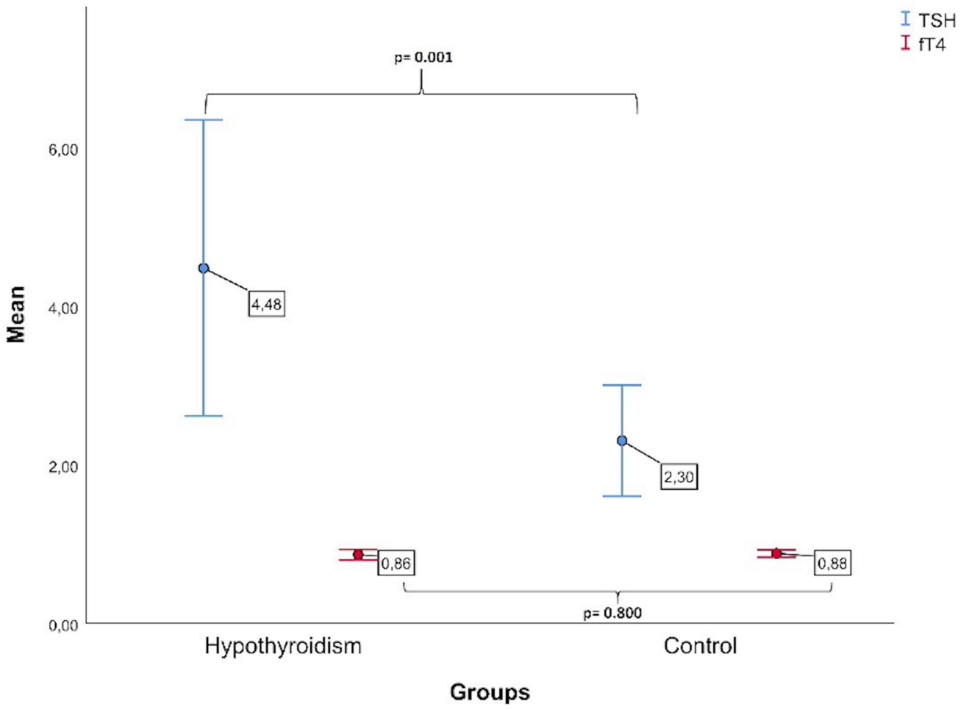

Figure 2 Comparison of the groups in terms of TSH and fT4.

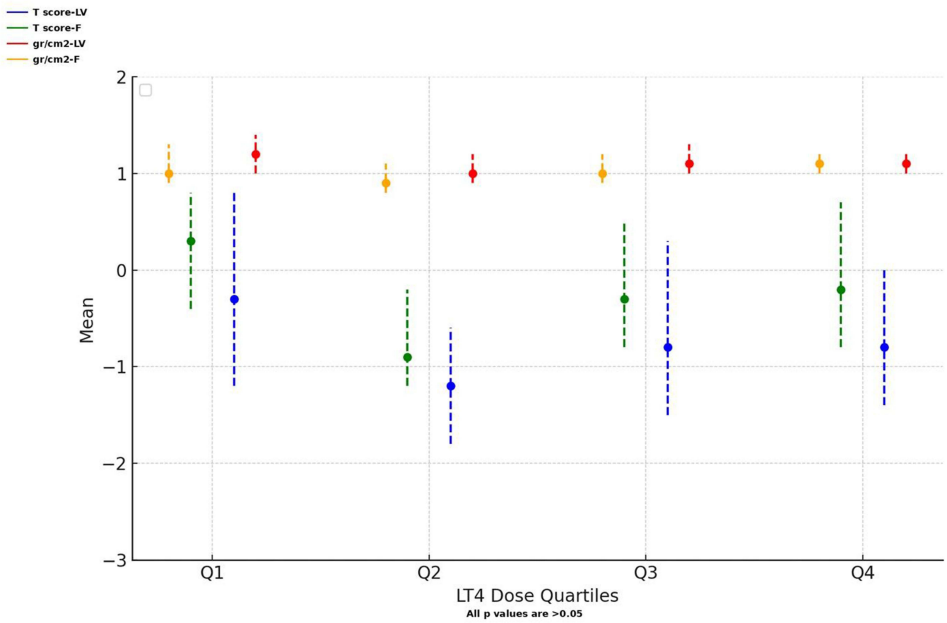

Figure 3 The comparison of the T scores and gr/cm^2 of dose quartile groups of the patients.

Discussion

The present study was a retrospective case-control study that examined the correlation between bone health and the usage of levothyroxine in postmenopausal women. The results of our study showed that the measurements of BMD (total gr/cm^2-LV, total g/cm^2-F, and total T score-LV) were similar between the groups, however, the total T score-F was significantly lower in the control group. Varied outcomes have also been observed in patients undergoing levothyroxine replacement for hypothyroidism, where the suppression of TSH is not the primary goal. In a retrospective study conducted by *Alotañbe* et al, the

administration of levothyroxine to elderly women for the treatment of hypothyroidism was found to be associated with an increased risk of osteoporosis in BMD outcomes.[11] On the contrary, *Gonzalez* et al demonstrated that no adverse effect on bone health was observed from the use of levothyroxine for over one year in older adults with subclinical hypothyroidism.[12] A similar result has been achieved in the current study, even though the patient group comprised individuals who had been using LT4 medication for 5 years or more.

Two recent long-term studies have shown that long-term TSH suppressive therapy which is the primary goal of thyroid cancer management, did not significantly increase the risk of bone loss in postmenopausal women during a 5- to 10-year follow-up period.[13,14] The results of these studies showed that the use of long-term levothyroxine has no adverse effect on bone health, even at high doses. Nevertheless, in a study by *Dominguez* et al, long-term TSH suppressive treatment hurt trabecular bone scores only in women transitioning from premenopausal to postmenopausal.[13] The longitudinal study conducted by *Sugitani* et al is one of the most patient-recorded studies in the literature. At the end of 5 years of TSH suppression therapy after PTC surgery, there are adverse effects on BMD in women aged 50 years and older.[15]

In the present study, patient groups were categorized into quartiles (Q1- Q4) based on their dose-per-body surface area. Dose quartile groups were similar in terms of LV and F measurements. Similar to our findings, the study conducted by *Ko* et al found that the administration of levothyroxine at a dosage of 150 µg/d or less did not demonstrate any correlation with an increased risk of fractures. However, doses of levothyroxine higher than 150 µg/day have been associated with an increased incidence of bone fractures in elderly women.[9]

Studies investigating the effects of TSH levels on bone health in a healthy population have shown that individuals with low normal TSH levels are associated with low BMD.[16–18] *Grimnes* et al found that postmenopausal women with high normal TSH levels had increased femoral neck bone density compared to women with normal TSH levels.[19] Similarly, in the study by *Zaidi* et al has shown that whereas TSH inhibits bone resorption, it actively promotes osteogenesis.[20] On the contrary, the study conducted by *A. Kopiczko* et al demonstrated that elevated thyroid-stimulating hormone (TSH) levels in postmenopausal women with subclinical hypothyroidism (SCH) are associated with an increased risk of osteoporosis.[21] The effects of TSH on bone health can be both protective and detrimental, depending on various factors. Therefore, it is crucial to evaluate the potential impacts of TSH on immune balance and the structural integrity of bone microarchitecture. On the basis of our findings, we suggest that the significantly lower T-score-F value observed in the control group may be due to lower TSH levels. In this context, high-normal TSH levels may independently exert a protective effect by regulating bone resorption and promoting osteogenesis, particularly in individuals whose thyroid function remains within the normal range.

The present study had the following strengths. One of the potential strengths of this study was that it has an age-matched case-control design. Another important strength is the inclusion of patients who have been on levothyroxine treatment for at least 5 years but whose annual laboratory tests did not reveal abnormal TSH values, whether high or low. However, this study had some limitations. Firstly, this is a retrospective cross-sectional study and has a relatively small sample size. Significant factors that could influence the association between osteoporosis and bone health, such as family history, lifestyle, daily calcium intake, and duration of sun exposure, were not available in the patient files. Additionally, some laboratory results, such as free T3 levels, were also missing.

In conclusion, this study demonstrated that maintaining TSH levels within the normal reference range through levothyroxine treatment for post-procedure hypothyroidism for at least five years in postmenopausal women was associated with a higher BMD score when compared to a control group. It is crucial to prevent suppressed TSH levels in these patients to preserve bone health and prevent the development of osteoporosis. Further studies are needed to establish evidence for the adverse effect of levothyroxine treatment on bone health.

Ethics Approval

We conducted the study based on the principles of the Declaration of Helsinki and obtained the Ethics Committee Approval (Decision No:2011-KAEK-2: 2020/511) from Afyonkarahisar Health Sciences University. We obtained informed consent from all individual participants included in the study.

Disclosure

Mahmut Apaydin, Ferda Surel and Sinan Kazan declare that they have no conflict of interest.

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