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Main Article

Impact of total versus subtotal thyroidectomy on calcium metabolism and bone mineral density in premenopausal women

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Abstract

Objective: This study aimed to compare the impact of total versus subtotal thyroidectomy on calcium metabolism and bone mineral density in euthyroid, premenopausal women.

Subjects: The study included 24 premenopausal women who had undergone total ($n = 10$) or subtotal ($n = 14$) thyroidectomy and who were receiving nonsuppressive doses of thyroxine. The median post-operative period was four years. We determined, in all patients, the following parameters associated with calcium metabolism: total serum calcium, inorganic phosphate, intact parathormone, calcitonin and alkaline phosphatase. The bone mineral density of the spine and hip were measured using a Hologic QDR 4500C bone densitometer and were compared with controls matched for age and peak bone mineral density (using the *t*-test).

Results: The measured calcium metabolism parameters were normal in all patients, and none had osteoporosis. There was no significant difference in the bone mineral density measurements for the spine and hip, comparing patients who had undergone total versus subtotal thyroidectomy (using the *t*-test).

Conclusion: The impact of total thyroidectomy on bone mineral metabolism is not significantly different from that of subtotal thyroidectomy, in premenopausal women with normal thyroid-stimulating hormone values.

Key words: Thyroidectomy; Bone Density; Thyroxine

Introduction

The use of total or near-total thyroidectomy instead of subtotal thyroidectomy to treat patients with large, euthyroid, multinodular goitre has been advocated, in order to decrease the long term risk of recurrence.[1]

Although the morbidity rate for total thyroidectomy was not found to be significantly higher than that for subtotal resections within experienced referral centres, the detrimental effects of total thyroidectomy on bone mineral content are still controversial.[2–4] Calcitonin deficiency and post-operative thyroxine treatment with suppressive doses were suggested to be the major factors contributing to bone loss following total thyroidectomy.[5–16] Although chronic lack of calcitonin resulting from total thyroidectomy might play an important role in bone degradation, bone mass was found to be preserved in calcitonin-deficient patients in other studies.[5–7,17–19] Thyroxine treatment can be commenced after total thyroidectomy, using substitutional doses in patients operated upon for benign thyroid disorders or suppressive doses in those operated upon for thyroid carcinoma. Following total thyroidectomy, the maintenance of thyroid-stimulating hormone (TSH) values within normal ranges, using substitutional thyroxine treatment, was shown to have no significant effect on bone mineral density in premenopausal women.[20–22] However, suppressive thyroxine doses resulted in decreased bone mineral density, especially in postmenopausal women.[11,12,15,16,23]

No previous clinical study has compared the effects of total versus subtotal thyroidectomy on the bone mineral density of premenopausal women receiving substitutional thyroxine treatment to maintain TSH values within normal limits. In our study, we aimed to evaluate and compare the impact of total versus subtotal thyroidectomy on calcium metabolism and bone mineral density, in premenopausal women who had been operated upon for benign, non-toxic, multinodular goitre and who were receiving nonsuppressive doses of post-operative thyroxine.

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Materials and methods

Twenty-four premenopausal women who had previously been operated upon for benign, non-toxic, multinodular goitre within the general surgery department of the Istanbul Medical Faculty were recalled. The median period of time elapsed since the operation was four years (range, three to six years). All patients received thyroxine at individual replacement doses, not suppressive doses. The operative notes and post-operative data were reviewed for all patients. All patients were premenopausal and were not taking oral contraceptive preparations or any other hormone replacement therapy, other than thyroxine.

Patients were classified into two groups according to the extent of their previous operation. Group one comprised 10 patients who had undergone total thyroidectomy. The mean measurements ± standard deviation (SD) for these women's age, height and weight were 36.4 ± 4.2 years, 165.7 ± 3.3 cm and 62.4 ± 8.5 kg, respectively. The mean ± SD for time elapsed since the operation was 4.2 ± 1 years. Group two comprised 14 patients who had undergone subtotal thyroidectomy (leaving at least 4 g of remnant thyroid tissue). The mean ± SD for the age, height and weight of these patients were 33.5 ± 6.5 years, 166.1 ± 2.7 cm and 61.6 ± 7.9 kg, respectively. The mean ± SD for time elapsed since the operation was 4.8 ± 1.5 years. The mean age, height, weight and time since operation did not differ significantly between the two groups ($p > 0.05$).

Biochemical analysis

Patients' TSH values during the first post-operative month were evaluated retrospectively. Current values for the following parameters were established for all patients: total serum calcium, total serum inorganic phosphate, serum intact parathormone, calcitonin, serum alkaline phosphatase and TSH.

Bone mineral density measurements

Bone mineral density was measured in all patients at the spine and hip, using a Hologic QDR 4500C bone densitometer (Waltham, MA, USA). Bone mineral density measurements were expressed as grams of mineral per cm^2, and were compared with controls matched for age and peak bone mineral density (using the *t*-test), for both patient groups.

The values of the biochemical parameters and the bone mineral density measurements for groups one and two were compared. All data were expressed as mean ± standard error of the mean. The Wilcoxon signed ranks test was used for statistical analysis, and $p < 0.05$ was accepted as significant.

Results and analysis

Biochemical analysis

The mean TSH value during the first post-operative month was significantly higher in group one (41 ± 26.6 mIU/L) compared with group two (3.04 ± 1.5 mIU/L) ($p = 0.005$). The current TSH values of patients in both groups were within the normal range, being 2.2 ± 1 mIU/L for group one *vs* 2.9 ± 1.9 mIU/L for group two ($p = 0.7$). The total serum calcium, total serum inorganic phosphate, serum alkaline phosphatase, serum intact parathormone and calcitonin levels were within the normal range in both groups, with no significant differences between the groups (Table I).

Bone mineral density measurements

None of the patients in either group had osteoporosis. Osteopenia was detected in four patients from group one and in two from group two, compared with controls matched for peak bone mineral density and age ($p = 0.4$; *t*-test). Bone mineral density measurements at the spine and hip did not differ significantly between groups one and two ($p = 0.2$ for spine density comparisons and $p = 0.65$ for hip density comparisons) (Table II). Comparison of spine and hip densities in group one and group two versus controls matched for age and peak bone mineral density indicated no significant differences ($p = 0.88$ for spine density comparisons and $p = 0.84$ for hip density comparisons; *t*-test) (Table III).

Discussion

In this study, we compared the impact of subtotal versus total thyroidectomy on calcium metabolism and bone mineral density in premenopausal, euthyroid women who had previously undergone surgery for benign, non-toxic, multinodular goitre. Bone mineral density and biochemical parameters associated with calcium metabolism were within the normal range for all patients. Total thyroidectomy had no additional detrimental effect on bone mineral density in premenopausal women who were confirmed to have normal TSH values.

Thyroidectomy was suggested to render the patients prone to bone loss, due to calcitonin deficiency and post-operative thyroxine treatment.[5–16] Increased serum levels of thyroid

TABLE I

BIOCHEMICAL PARAMETERS ASSOCIATED WITH CALCIUM METABOLISM, FOR GROUPS I AND II

Group	Ca (mg/dl)	P (mg/dl)	ALP (U/L)	iPTH (pg/ml)	CT (pg/ml)
I	9.3 ± 0.3	3.7 ± 0.38	152.6 ± 67.3	44.9 ± 17.7	7.54 ± 8.4
II	9.26 ± 0.4	3.7 ± 0.43	135.3 ± 32.7	44.8 ± 16.8	7.38 ± 5.3
p	0.75	0.83	0.96	0.24	0.85

Data are expressed as mean ± standard error of the mean. Ca = total serum calcium; P = total serum inorganic phosphate; ALP = serum alkaline phosphatase; iPTH = serum intact parathormone; CT = calcitonin

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TABLE II

BONE MINERAL DENSITY MEASUREMENTS AT SPINE AND HIP, FOR GROUPS I AND II

Group	Spine (g/cm^2)	Hip (g/cm^2)
I	1.095 ± 0.14	0.93 ± 0.12
II	1.055 ± 0.18	0.936 ± 0.16
p	0.2	0.65

Data are expressed as mean ± standard error of the mean.

hormones promote both osteoblastic and osteoclastic activity, but osteoclastic activity is more prominent.[24] The results of studies on the effect of post-thyroidectomy thyroxine treatment on bone mineral density are inconsistent. Suppressive thyroxine doses were reported to have no significant effect on bone mineral density in premenopausal women; however, postmenopausal women may be at considerable risk of osteoporosis due to such treatment.[12,15,16,20,23,25–27] All our patients were premenopausal women receiving thyroxine at non-suppressive doses. Therefore, we were able to assess only the effect of the extent of thyroidectomy on bone mineral density.

Total or subtotal thyroidectomy was found to have either no significant effect or an exacerbating effect on the development of osteoporosis due to calcitonin deficiency.[5–7,17–19,28] Calcitonin is mainly secreted by thyroid C-cells, but significant amounts of calcitonin may also be secreted by extrathyroidal tissues.[29] Although the exact role of calcitonin in bone mineral metabolism is not certain, it is known to inhibit bone degradation.[30] Thyroidectomy may either decrease or abolish the secretion of calcitonin, but normal serum levels of calcitonin could be maintained following total or subtotal thyroidectomy.[5,6,8,9,12,17,28,31] The majority of studies suggesting a significant bone loss associated with total thyroidectomy included patients receiving suppressive thyroxine doses as treatment for thyroid carcinoma, and it was not clear whether the bone loss was associated with thyroxine excess or calcitonin deficiency following total thyroidectomy.[5,6,22,26] Following thyroidectomy, the effect of the resultant calcitonin deficiency on bone mineral density is controversial. Endogenous calcitonin was suggested to have no effect on skeletal mass.[18] Although plasma immunocalcitonin levels were found to significantly decrease in patients who underwent subtotal thyroidectomy or radioactive iodine ablation treatment, compared with controls, bone densities were not significantly reduced in calcitonin-deficit patients compared with controls.[9] Preservation of bone mineral content, in spite of low calcitonin levels in euthyroid patients following subtotal thyroidectomy, might be associated with a simultaneous increase in androgen levels.[19] Several studies found that calcitonin deficiency associated with thyroidectomy caused bone loss, particularly in men and postmenopausal women with normal but not reduced parathyroid activity.[6,26] Several factors interfere with bone mineral content in postmenopausal patients, including age, decreased calcium intake, physical activity and parathyroid function; therefore, it is difficult to assess the exact impact of thyroidectomy or calcitonin deficiency on bone loss.[6,9,10,25,26,32]

Some authors suggested that, in premenopausal women, unlike postmenopausal patients, calcitonin deficiency due to total thyroidectomy caused no significant decrease in bone mineral density, even in patients receiving suppressive doses of thyroxine.[6,26] However, others found a significant decrease in bone mineral content in both sexes, associated with calcitonin deficiency, independent of the degree of TSH suppression.[5–7,17] Although men were found to be more susceptible to bone degradation resulting from calcitonin deficiency due to prior thyroidectomy, compared with women, thyroidectomy did not have any significant influence on the risk of age-related fractures in men.[6,7,17,33]

- **The use of total or near-total thyroidectomy, instead of subtotal thyroidectomy, in patients with large, euthyroid, multinodular goitre has been advocated in order to decrease the long term risk of recurrence**
- **Suppressive doses of thyroxine treatment have been reported to have no significant effect on bone mineral density in premenopausal women. However, postmenopausal women may be at considerable risk of osteoporosis due to such treatment**
- **This study found that bone mineral density and biochemical parameters related to bone metabolism, including calcitonin level, did not differ significantly in patients who had undergone a total *vs* subtotal thyroidectomy**

TABLE III

COMPARISON OF BONE MINERAL DENSITY OF PATIENT GROUPS *VS* CONTROLS*

Group	Spine	Hip
I	-0.286 ± 0.94	-0.41 ± 0.83
II	-0.01 ± 1.58	-0.26 ± 1.17
$p^\dagger$	0.88	0.84

Data are expressed as mean ± standard error of the mean. *Matched for peak bone mineral density and age. †Using the *t*-test.

Sugino *et al.*[28] measured the bone mineral content in 38 patients with thyroid carcinoma who had undergone total thyroidectomy or lobectomy (32 female and six male patients). Bone mineral content was measured using a quantitative calcitonin method and compared with age-matched controls. The authors documented no significant difference in the bone mineral content in patients who had undergone total thyroidectomy or lobectomy. No significant correlation was observed between serum calcitonin level and bone mineral content.[28] Our findings were consistent with those of Sugino *et al.*,[28] but the setting of our study was different. Patients' menopausal status is an important determinant of their calcium

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metabolism and bone mineral density, and perimenopausal and postmenopausal states are associated with osteoporosis.[34] Therefore, we only included premenopausal patients in our study, none of whom were receiving suppressive thyroxine doses following thyroidectomy. These patients were selected in order to reduce the influence of other, confounding factors on bone mineral density, such as gender, degree of TSH suppression and menopausal status. In this study, bone mineral density was measured using bone densitometry. We found that bone mineral density and biochemical parameters related to bone metabolism, including calcitonin level, did not significantly differ between patients who had undergone total versus subtotal thyroidectomy, after a mean post-operative period of four years.

Conclusion

The impact of thyroidectomy on calcium metabolism and bone mineral density is controversial. Total and subtotal thyroidectomy were documented to have either no significant effect or to exacerbate the development of osteoporosis due to calcitonin deficiency. The majority of studies suggesting a significant bone loss associated with total thyroidectomy included patients receiving suppressive thyroxine doses, and it was not clear whether the bone loss was associated with thyroxine excess or calcitonin deficiency following total thyroidectomy. Suppressive doses of thyroxine treatment were reported to have no significant effect on bone mineral density in premenopausal women; however, postmenopausal women may be at considerable risk of osteoporosis due to such treatment.

In this study, we included premenopausal women who had undergone either total or subtotal thyroidectomy and who received nonsuppressive thyroxine doses. These patients were selected in order to reduce the influence of other, confounding factors affecting bone mineral density, such as gender, degree of TSH suppression, and menopausal status. We found that bone mineral density and biochemical parameters related to bone metabolism, including calcitonin level, did not differ significantly in patients who had undergone total versus subtotal thyroidectomy, after a mean post-operative period of four years.

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