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Decreased Levels of Ionized Calcium One Year after Hemithyroidectomy: Importance of Reduced Thyroid Hormones

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Key Words

Hemithyroidectomy · Unilateral thyroidectomy · Ionized calcium · Reduced thyroid hormones · Calcium homeostasis · Bone density

Abstract

Background: Previously we have found reduced levels of total serum calcium and $1,25(OH)_2D_3$ despite an unaltered stimulated parathyroid hormone (PTH) secretion 1 year after hemithyroidectomy. The present study was undertaken to elucidate the possible relationship between calcium homeostasis, thyroid hormones and bone resorption in a group of 45 consecutive patients subjected to hemithyroidectomy because of a solitary nodule. All patients had free T_4 and T_3 levels within normal range preoperatively. ***Methods:*** Thyroid hormones, bone mineral and biochemical variables known to reflect calcium homeostasis were studied. Patients were divided into three separate groups depending on their pre- and postoperative thyroid hormone status. ***Results:*** One year postoperatively, serum levels of free T_4 were decreased and that of thyrotropin (TSH) increased in the entire group of patients. The concentration of ionized calcium was reduced from 1.25 ± 0.05 to 1.22 ± 0.04 ($p < 0.001$) despite an unaltered PTH value (2.8 ± 1.0 vs. 3.1 ± 1.5, $p = 0.50$). A significant reduction in C-terminal telopeptide type 1 collagen (1CTP) indicated decreased bone resorption 1 year after surgery ($p < 0.05$). Subgroup analysis showed that a reduction in ionized calcium was seen only among patients with a postoperative decrease in free T_4. Patients with subclinical hyperthyroidism preoperatively presented the lowest postoperative levels of ionized calcium, significantly reduced levels of 1CTP and increased levels of phosphate and creatinine. Multiple linear regression analysis showed that age ($p < 0.05$) and postoperatively changed serum levels of TSH ($p < 0.05$), creatinine ($p < 0.05$), phosphate ($p < 0.001$) and FT_4 ($p < 0.01$) were independently associated with altered levels of ionized calcium. ***Conclusion:*** We conclude that the reduction in ionized calcium 1 year after hemithyroidectomy was not due to PTH deficiency. Instead our results suggest that the reduced effects of thyroid hormones on bone and kidney function is essential.

Introduction

Inadvertent removal of ischemic necrosis of the parathyroid glands is the most widely accepted cause of hypocalcemia after bilateral thyroid surgery. However, also unilateral thyroid surgery, i.e. lobectomy, is followed by a transient decrease in serum calcium. The postoperative

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Table 1. Patient characteristics in the three groups subjected to hemithyroidectomy

	Group I (n = 29) Euthyroid pre- and postoperatively	Group II (n = 8) Low preoperative TSH concentration, euthyroid postoperatively	Group III (n = 8) Euthyroid preoperatively, postoperative *L*-thyroxine substitution
Age, years	43 ± 12*	53 ± 13	58 ± 18*
Female/male	26:3	5:3	8:0
Weight, kg	66 ± 12	70 ± 22	70 ± 13
Pre-/postmenopausal	20/6	3/2	3/5

Results are presented as mean ± SD. A difference between the groups regarding continuous data was evaluated with the Kruskal-Wallis test and when p was < 0.1, Mann-Whitney-U was used for two-groups analysis. For categorical data the χ^2 test was used.

* Significant differences with a p value of < 0.05 between euthyroid and postoperative thyroxine-substituted group.

reduction in serum calcium has therefore been explained by a release of calcitonin, a dilution phenomenon, a temporary decrease in parathyroid hormone (PTH) secretion, and in thyreotoxic patients, by an avidity of the skeleton for calcium [1–4].

Data regarding long-term consequences on calcium homeostasis after thyroid surgery are scarce. According to these previous reports, total serum calcium can remain reduced several years after bilateral as well as after unilateral thyroidectomy [5–7]. In agreement with these studies, we have found a reduction in total serum calcium 1 year after hemithyroidectomy in a small series of euthyroid patients [8]. We assumed that this could not be due to PTH deficiency since at least two parathyroid glands should be intact after a unilateral procedure. Furthermore, in dynamic PTH secretion tests, basal, maximal and total PTH secretion were unchanged [8]. Based on these results we find it reasonable to postulate that other mechanisms than PTH deficiency are involved in the development of hypocalcemia after hemithyroidectomy.

It is well documented that thyroid hormones have a stimulatory effect on bone resorption [9, 10]. Consequently, methimazole and radioiodine therapy has been used to prevent excessive loss of bone in postmenopausal women with multinodular goiter and subclinical hyperthyroidism [11, 12].

Since there is a long-lasting reduction in thyroid hormone concentrations following both bilateral and unilateral thyroid surgery [13], we have questioned whether a postoperative reduction in thyroid hormones may account for the decrease in serum calcium after thyroid surgery.

Material and Methods

Patients

Forty-five consecutive patients operated upon with a unilateral thyroidectomy entered the study. Their median age was 44 (range 19–81) years (table 1). The indication for surgery was a solitary cold nodule in 33 cases, an autonomous solitary nodule in 5 cases and atoxic goiter with symptoms of compression in 7 cases. All patients had free T_4 and T_3 levels within normal range preoperatively. However, in 8 patients the preoperative thyrotropin (TSH) concentration was below normal reference, indicating subclinical hyperthyroidism.

Surgery

Operations were performed as standardized hemithyroidectomies, including resection of the isthmus, as described previously [14]. In each case the recurrent laryngeal nerve was freely exposed and the branches of the inferior thyroid artery were divided close to the thyroid capsule.

The parathyroid glands were meticulously dissected from the thyroid gland and an effort was made to identify both parathyroid glands. However, if the lower parathyroid gland was not found at the lower thyroid pole, it was presumed to be in the thymus or in the thyro-thymic ligament. This area was not dissected. Two parathyroid glands were identified in 16 cases, one parathyroid gland was visualized in 21 and in 8 patients no parathyroid gland was visualized in the operating field. Histopathologic examination verified 27 resections as nodular goiter and 18 as follicular adenomas. One parathyroid gland was accidentally excised.

Study Design

Thyroid hormones, bone density and biochemical variables known to reflect calcium homeostasis, bone resorption and formation were analyzed. Pre- and 1 year postoperative data were compared. To assess the influence of thyroid hormones on postoperative serum calcium levels, the patients were divided into three separate groups depending on their pre- and postoperative thyroid hormone status. Patients with normal levels of free T_4, T_3 and TSH pre- and 1 year postoperatively, were assigned to group 1 (n = 29). Patients with

Table 2. Comparison between pre- and 1 year postoperative values in 45 patients subjected to hemithyroidectomy

	Preoperative	Postoperative	Reference	p value
Ca^{2+}, mmol/l	1.25 ± 0.05	1.22 ± 0.04	1.15–1.35	<0.001
PTH, pmol/l	2.8 ± 1.0	3.1 ± 1.5	1.0–5.0	0.50
Ca^{2+}/PTH, mmol/pmol	0.50 ± 0.18	0.47 ± 0.25		0.39
Creatinine, µmol/l	67 ± 10	69 ± 8	45–116	0.05
Phosphate, mmol/l	1.04 ± 0.15	1.10 ± 0.14	0.70–1.60	0.06
25(OH)D_3, nmol/l	63 ± 19	67 ± 17	20–100	0.28
1,25$(OH)_2D_3$, pmol/l	73 ± 20	67 ± 15	24–120	0.08
P1CP, µg/l	104 ± 29	102 ± 25	38–202	0.33
1CTP, µg/l	3.5 ± 0.8	3.2 ± 0.9	1.8–5.0	<0.05
BMD L2–L4, g/cm^2	1.18 ± 0.18	1.18 ± 0.19		0.69
BMD neck, g/cm^2	0.97 ± 0.16	0.99 ± 0.16		0.71
BMD Ward's, g/cm^2	0.81 ± 0.16	0.80 ± 0.16		<0.01
BMD troch, g/cm^2	0.79 ± 0.16	0.80 ± 0.16		0.64
BMC forearm, g/cm	3.19 ± 0.79	3.26 ± 0.92		0.50
TSH, mU/l	1.04 ± 0.71	1.97 ± 1.3	0.4–4.0	<0.001
FT_4 pmol/l	14 ± 2	12 ± 2	9–22	<0.01
FT_3, pmol/l	4.9 ± 0.6	4.7 ± 0.8	3.4–7.2	0.24
Calcitonin, pmol/l	13 ± 4	13 ± 6	<27	0.06

a preoperative TSH value below, and postoperatively within normal reference range, were allocated to group II (n = 8). Patients that preoperatively had normal levels of T_4, T_3 and TSH, but postoperatively were in demand of *L*-thyroxine substitution, were allocated to group III (n = 8).

Biochemical Analysis

All blood samples were drawn after an overnight fast. Preoperative blood samples were obtained the day before surgery. Serum ionized calcium concentrations were analyzed from blood samples normalized to a pH of 7.4 with the ion-selective electrode ABL 505 (Radiometer, Copenhagen, Denmark). The method has a total intra- and interassay imprecision (CV) of 1.2% at an assigned value of 1.14 mmol/l. Serum levels of PTH were measured with the intact PTH assay (Incstar, Stillwater, Minn., USA). The method has a CV of 9% at a value of 5 pmol/l. The phosphate concentration was measured on a routine autoanalyzer (Hitachi 917). The method for phosphate analysis has a CV of 2.2% at a level of 1.0 mol/l. Serum creatinine was assayed on a routine autoanalyzer (Kodak Ektachem 700xR-C). The method has a CV of 2.3% at a value of 90 µmol/l.

High-performance liquid chromatography was used for assessment of 25-hydroxyvitamin D_3 (25(OH)D_3). 1,25-Dihydroxyvitamin D_3 (1,25$(OH)_2D_3$) was measured with a radioreceptor assay (Incstar). The analytical methods of 25(OH)D_3 and of 1,25$(OH)_2D_3$ have a CV of 15% at 50 nmol/l and 12% at a level of 70 pmol/l respectively. The serum concentrations of procollagen type 1 C-terminal propeptide (P1CP) and of C-terminal telopeptide type 1 collagen (1CTP) were determined with the commercially available radioimmunoassay kits (Orion Diagnostica, Espoo, Finland). The method for P1CP analysis has a CV of 5.5% at 108 µg/l. The CV for 1CTP is 3% at 8 µg/l.

TSH and free T_4 concentrations were assessed with the fluoroimmunoassay kits AutoDELFIA hTSH Ultra and AutoDELFIA Free Thyroxine from Wallace Oy (Turku, Finland). The analytical methods for TSH and T_4 have a CV of 2.2% at a level of 0.18 mU/l and 3.6% at a level of 11 pmol/l respectively. The serum concentrations of free T_3 were analyzed with the radioimmunoassay Amerlex-MAB FT_3 kit (Johnson & Johnson Clinical Diagnostics, Amersham, UK). This method has a CV of 4.7% at a level of 4.7 pmol/l. Calcitonin concentration was measured with a radioimmunoassay from Diasorin, USA. This method has a CV of 16% at a level of 30 pmol/l. For reference ranges, see table 2.

Bone Mineral

Assessment of bone mineral density (BMD) in lumbar spine (L2–L4), femoral neck, Ward's triangle, and in trochanter major was done by dual-energy x-ray absorptiometry (DEXA) with the Lunar Expert-XL equipment, software version 1.72 (Lunar Corp., Madison, Wisc., USA). This technique has a CV of 1%. Bone mineral content (BMC) was evaluated by single-energy photon absorptiometry (SPA) in both forearms at one fourth of the distance from the styloid process to the olecranon. The photon source used was ^{241}Am and the detector a modified Gambro bone mineral detector (Gambro, Lund, Sweden). This technique has a CV of 1–2% [15].

Statistics

The results are presented as mean ± SD. Comparison between pre- and postoperative values were made using the Wilcoxon signed rank test. Statistical significance between the three groups was analyzed with the Kruskal-Wallis test. When $p < 0.1$, a two-groups analysis was done with the χ^2 test for categorical data, and for numeric results the Mann-Whitney U-test was used. A p value < 0.05 was considered significant. In the multivariate analysis, a stepwise multiple linear regression was used. The final model included independent variables with a p value < 0.20.

Table 3. Comparison between pre- and postoperative values in three groups with different thyroid hormone status subjected to hemithyroidectomy

	Group I (n = 29) Euthyroid pre- and postoperatively			Group II (n = 8) Low preoperative TSH concentration, euthyroid postoperatively			Group III (n = 8) Euthyroid, preoperatively postoperative *L*-thyroxine substitution		
	preoperative	postoperative	p value	preoperative	postoperative	p value	preoperative	postoperative	p value
Ca^{2+}, mmol/l	1.25±0.06	1.22±0.04	<0.01	1.25±0.04	1.21±0.02	<0.05	1.25±0.03	1.24±0.03	0.17
PTH, pmol/l	2.8±0.9	3.0±1.8	0.60	2.5±1.3	3.3±0.7	0.18	3.5±1.0	3.2±1.3	0.32
Ca^{2+}/PTH, mmol/pmol	0.50±0.17	0.50±0.25	0.72	0.60±0.26	0.37±0.07	0.18	0.38±0.12	0.49±0.39	0.46
Creatinine, µmol/l	67±10	69±8	0.17	67±10	72±10	<0.05	70±9	70±9	0.75
Phosphate, mmol/l	1.01±0.15	1.01±0.14	0.10	1.06±0.15	1.16±0.14	<0.05	1.10±0.15	1.07±0.11	0.62
25(OH)D_3, nmol/l	66±20	69±16	0.92	57±19	64±23	0.09	60±15	64±14	0.93
1,25$(OH)_2D_3$, pmol/l	72±16	64±15	<0.05	75±31	73±14	1.00	75±20	69±15	0.40
P1CP, µg/l	103±34	103±21	0.57	111±25	93±11	0.09	99±20	110±43	0.45
1CTP, µg/l	3.5±0.9	3.2±0.9	0.48	3.5±0.6	2.8±0.7	<0.05	3.6±0.8	3.7±1.2	0.55
BMD L2–L4, g/cm^2	1.21±0.14	1.22±0.14	0.94	1.15±0.17	1.16±0.17	0.92	1.08±0.29	1.10±0.30	0.48
BMD neck, g/cm^2	1.00±0.14	1.03±0.12	0.99	0.94±0.16	0.94±0.13	0.60	0.90±0.22	0.89±0.24	0.48
BMD Ward's, g/cm^2	0.85±0.14	0.86±0.12	0.20	0.78±0.11	0.73±0.13	<0.05	0.72±0.23	0.67±0.22	<0.05
BMD troch, g/cm^2	0.81±0.13	0.82±0.13	0.85	0.80±0.15	0.82±0.11	0.53	0.73±0.24	0.73±0.24	0.89
BMC forearm, g/cm	3.27±0.69	3.39±0.93	0.76	3.60±0.78	3.62±0.76	0.15	2.55±0.81	2.57±0.76	0.57
TSH, mU/l	1.11±0.48	2.06±0.85	<0.001	0.20±0.15	1.65±1.16	<0.01	1.67±0.98	1.92±2.5	0.29
FT_4, pmol/l	14±2	12±2	<0.001	14±1	11±2	<0.01	13±2	16±3	0.05
FT_3, pmol/l	4.8±0.7	4.7±0.8	0.60	5.1±0.4	4.6±0.7	<0.05	4.8±0.6	4.6±0.7	0.73
Calcitonin, pmol/l	14±4	14±7	0.38	11±2	10±1	0.18	12±3	11±2	0.18

Results

Entire Group of 45 Patients Subjected to Hemithyroidectomy (table 2)

As expected, the concentration of free T_4 decreased and TSH increased 1 year after hemithyroidectomy. Ionized calcium decreased significantly. The serum levels of PTH did not change (2.8 ± 1.0 vs. 3.1 ± 1.5 pmol/l) nor did the ratio of ionized calcium/PTH. Furthermore, there was a tendency towards an increase in phosphate and a reduction in the level of 1.25$(OH)_2D_3$. The biochemical marker of bone resorption, 1CTP, decreased 1 year postoperatively. Most sites of bone density assessment did not change. In Ward's triangle however, a minor decrease was noticed. Hemithyroidectomy had no significant influence on the level of calcitonin.

Subgroup Analysis of Patients with Different Thyroid Hormone Status (table 3)

In group I, patients were euthyroid preoperatively and 1 year after hemithyroidectomy. The levels of free T_4 decreased and TSH increased. The concentrations of ionized calcium and 1,25$(OH)_2D_3$ decreased. The serum levels of PTH and the ionized calcium/PTH ratio did not change. Bone density was unaltered 1 year after hemithyroidectomy.

In group II, the preoperative laboratory findings were consistent with subclinical hyperthyroidism and 1 year after hemithyroidectomy these patients were euthyroid. The levels of free T_4 and T_3 decrease and TSH increased. This group had the lowest postoperative level of ionized calcium while the concentration of PTH did not change significantly (2.5 ± 1.3 vs. 3.3 ± 0.7 pmol/l, p = 0.18). The ionized calcium/PTH ratio was unaltered postoperatively. The concentration of 1,25$(OH)_2D_3$ was not changed 1 year after surgery whereas the levels of phosphate and creatinine were increased. Furthermore, the biochemical marker of bone resorption, 1CTP, decreased while most sites of bone density assessment did not change. In Ward's triangle however, a minor decrease was noticed.

In group III, patients were euthyroid preoperatively and postoperatively substituted with *L*-thyroxine. Preoperatively, serum from 3 of these patients showed positive titers of autoantibodies to thyroglobulin and/or microsomal antigens (data not shown). The free T_4 concentration was significantly higher postoperatively in this group compared to the two other groups ($p < 0.01$). Except for a decreased level of bone density in Ward's triangle, no other changes were recorded in this group. Patients in this group were the oldest (table 1).

Table 4. A multiple linear regression analysis showing determinants of ΔCa^{2+} in 45 patients subjected to hemithyroidectomy (the whole model explained 76.7% ($R^2 = 0.767$) of the variability in ΔCa^{2+}; the residual standard deviation was 0.0208)

Variable ΔCa^{2+}	β-Coefficient	SE (± β)	p value
Constant	0.03298	0.01822	
Age, years	–0.00108	0.00036	0.012
Δ-TSH, mU/ml	0.01266	0.00547	0.039
Δ-FT_4, pmol/l	0.00712	0.00218	0.007
Δ-Creatinine, μmol/l	–0.00342	0.00150	0.041
Δ-Phosphate, mmol/l	0.22408	0.03990	<0.001

Influence of Gender and Menopausal Status on Postoperative Calcium Homeostasis

In the entire study group, premenopausal women (n = 26) showed a significant postoperative decrease in ionized calcium from a preoperative value of 1.25 ± 0.05 to 1.22 ± 0.03 mmol/l (p = 0.01), whereas a tendency towards a reduction was seen among men (n = 6) 1.26 ± 0.03 vs. 1.22 ± 0.03 (p = 0.06). The corresponding values for postmenopausal women (n = 13) were 1.24 + 0.04 vs. 1.22 ± 0.04 mmol/l (p = 0.12). In the postmenopausal group, bone density in Ward's triangle decreased from 0.71 ± 0.15 preoperatively to 0.68 ± 0.18 g/cm^2 postoperatively (p = 0.01). Bone density did not change in premenopausal women or in men.

Variables Associated with a Reduction in Ionized Calcium (table 4)

The following clinically important variables, age, sex, serum levels of ionized calcium, creatinine, phosphate, $1,25(OH)_2D_3$, 1CTP, TSH and free T_4 were included in a stepwise multiple logistic regression analysis. The final model showed that age and postoperative changes in serum levels of TSH, free T_4, creatinine and phosphate were independently associated with altered levels of ionized calcium.

Discussion

Data from the present investigation shows that the concentration of ionized calcium was decreased 1 year after hemithyroidectomy. The most pronounced reduction was seen among patients with preoperative thyroid hormone levels consistent with subclinical hyperthyroidism. One year after surgery, these patients had decreased levels of free T_4 and T_3, an increase in phosphate and a decrease in 1CTP, the marker of bone resorption.

PTH

The prevailing explanation of hypocalcemia after thyroid surgery is PTH deficiency. In the present study, microscopic examination of the excised thyroid glands showed that one parathyroid gland inadvertently was removed among 45 patients. Even if our pathologist might have missed to recognize more parathyroid glands in the specimens, we were not able to detect a reduction in PTH levels. Instead we found that PTH concentrations increased, and the ratio ionized calcium/PTH decreased 1 year postoperatively, although these changes were not statistically significant. Furthermore, recently we were able to show that stimulated basal, maximal and total PTH secretion were unaltered 1 year after hemithyroidectomy [8]. Although a reduction in $1,25(OH)_2D_3$ and an increase in phosphate imply parathyroid insufficiency, the previous finding of a preserved PTH secretion suggests that other mechanisms than parathyroid gland removal or necrosis are involved in the reduction of calcium after hemithyroidectomy. According to the literature, the calcium-retaining effect of PTH is diminished during overt hypothyroidism [16, 17]. Therefore, it cannot be excluded that the slight reduction in thyroid hormones seen after hemithyroidectomy may have attenuated the peripheral effects of PTH.

Phosphate

In the entire group of patients, there was a tendency towards an increase in phosphate at the 1-year follow-up. Furthermore, a close association between phosphate and ionized calcium changes was found in multiple linear regression analysis. We have observed this late postoperative increase in phosphate concentration after hemithyroidectomy previously [18] and others have reported on increased renal tubular phosphate reabsorption during early postoperative hypocalcemia [19]. Since renal tubular reabsorption is the overriding determinant of serum phosphate concentration [20], it seems unlikely that the increase in phosphate 1 year after hemithyroidectomy could be attributable to an increase in dietary intake. In the present study, the most pronounced increase in phosphate was seen in the group with subclinical hyperthyroidism preoperatively. Furthermore, in multiple linear regression analysis, we found an association between ionized calcium and creatinine. Since the group with preoperative subclinical hyperthyroidism presented a postoperative reduction in both free T_4 and T_3 concentrations and a concomitant increase in creatinine, one may speculate whether the effect of thyroid hormones on kidney function [21–23] may be responsible for the phosphate retention seen in our study.

$1,25(OH)_2D_3$

In previous investigations, we have found the concentration of $1,25(OH)_2D_3$ reduced 1 year after hemithyroidectomy [8, 18]. Whereas a tendency towards a reduction was noticed among the 45 patients presently studied, a significant decrease was found in the group with thyroid hormone levels within normal reference ranges both pre- and postoperatively. This result could not be explained by seasonal variation since sampling was done with a 1-year interval. However, the reduction in $1,25(OH)_2D_3$ concentration may be attributed to the increase in phosphate since this compound has a documented ability to control $1,25(OH)_2D_3$ production [24, 25]. Due to the principal function of $1,25(OH)_2D_3$ to enhance intestinal calcium absorption and to mobilize calcium from bone [26], it might be suggested that the reduction in $1,25(OH)_2D_3$ could contribute to decreased levels of ionized calcium postoperatively.

1CTP and Bone Density

1CTP, the marker of bone resorption, has convincingly been shown to correlate to free T_4 and T_3 concentrations [27, 28]. We found that in the entire group of patients, the serum levels of free T_4 and 1CTP were decreased 1 year after hemithyroidectomy. In the subgroup analysis however, a significant reduction in 1CTP was seen only in the group with preoperative subclinical hyperthyroidism and a postoperative decrease in both free T_4 and T_3 levels. In this group we expected a postoperative increase in bone density, since a negative correlation between free T_3 and BMD has previously been recognized [29, 30]. Even if most locations of bone density assessment did not change, a significant decrease was noticed in Ward's triangle. We suggest that this result might be due to the influence of menopause on bone resorption since the decrease in Ward's triangle only was significant for postmenopausal women.

Thyroid Hormones

The influence of thyroid hormones on calcium homeostasis after hemithyroidectomy is suggested by the more pronounced alterations observed among patients with subclinical hyperthroidism preoperatively. The close association between free T_4 and ionized calcium further supports this interpretation. Even if the preoperative thyroid hormone status is of major importance, it seems as if the decrease in thyroid hormones per se can induce a calcium reduction.

In conclusion, we have shown that the serum level of ionized calcium is decreased 1 year after hemithyroidectomy. Data from the present and previous [8, 18] investigations strongly suggests that the decrease in calcium is not due to low levels of PTH. Instead our results highlight the importance of reduced thyroid hormone levels and their implications on bone resorption and kidney function.

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