

Long-Term Treatment with Calcitriol in Postsurgical Hypoparathyroidism Leads to Renal Function Decline

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ABSTRACT

Hypoparathyroidism is a rare endocrine disease with insufficient parathyroid hormone levels. Replacing the missing hormone is not yet a standard therapy. The objective of this retrospective cohort study was to evaluate if the usual therapy regimens of postsurgical hypoparathyroidism with calcitriol have a negative effect on renal function. We performed a chart analysis of patients who were seen in a tertiary care hospital in Brussels, Belgium. A total of 101 subjects were identified as patients with permanent post-surgical hypoparathyroidism, based on the hospital records of patients who underwent a total thyroidectomy between 1996 and 2016, while still being treated with calcitriol. Patients with pre-existing renal insufficiency and/or active malignancy were excluded. The cohort was predominantly female of Caucasian origin. Renal function was evaluated before and after surgery (with a maximum follow-up of 12 years), using the CKD-EPI equation. A multivariate linear regression model was used to correlate renal function decline with the duration of calcitriol therapy, while correcting for the mean calcium phosphate product and age. We found a statistically significant ($p = 0.027$) relationship between the duration of calcitriol treatment and renal function decline at a rate of 1.06 ml/min/1.73 m² per year of calcitriol therapy. Our study, although being retrospective, is the first one to demonstrate a relationship between the cumulative use of calcitriol therapy and renal function decline.

Introduction

Hypoparathyroidism (hypoPT) is an endocrine disease characterized by inappropriately low circulating parathyroid hormone (PTH) levels. The most common cause is surgery of thyroid gland and/or parathyroid glands. Patients can present with a broad array of symptoms and have a lower quality of life [1, 2]. Standard treatment consists of a lifelong regimen of calcium and vitamin D supplements (ergocalciferol or cholecalciferol), usually combined with active vitamin D analogues (alpha-calcidol or calcitriol) [3–6].

PTH raises serum calcium and lowers phosphate, whereas calcitriol raises both calcium and phosphate, which can lead to a high

calcium phosphate product. This is an important contributor to the higher incidence of arterial calcifications, cardiovascular events, and basal ganglia calcification, well-known complications of hypoPT [7, 8]. Patients with hypoPT may be at an ever greater risk for renal complications, because they lack the stimulatory effect of PTH on the reabsorption of calcium in the renal tubules [9, 10].

There are no large cohort studies looking into long term complications of calcitriol therapy, therefore we performed a retrospective cohort study to observe, if long-term treatment with calcitriol (1,25-dihydroxycholecalciferol = Rocaltrol®), has a negative effect on renal function.

Patients and Methods

Patients

We analyzed the records of all patients who underwent a total thyroidectomy at the University Hospital of Brussels (UZ Brussel) between January 1st 1996 and December 31st 2016 ($n = 2664$) (see ► Fig. 1). We included all patients with hypocalcemia and inappropriate low PTH-levels post-thyroidectomy who were followed in our own academic center and were on continuous therapy with calcitriol ($n = 359$). We used the following exclusion criteria: patients without active calcitriol treatment ($n = 165$), patients who had insufficient data related to their illness and renal function ($n = 63$), patients who died during the course of follow-up ($n = 16$), patients who had an active malignant disease ($n = 9$) and who had pre-existing renal insufficiency, defined as $eGFR < 60$ ml/min at the moment of operation ($n = 5$). The 101 remaining patients were identified as having post-surgical hypoparathyroidism and were includ-

ed in the study, which was approved by the Ethics Committee of the UZ Brussel.

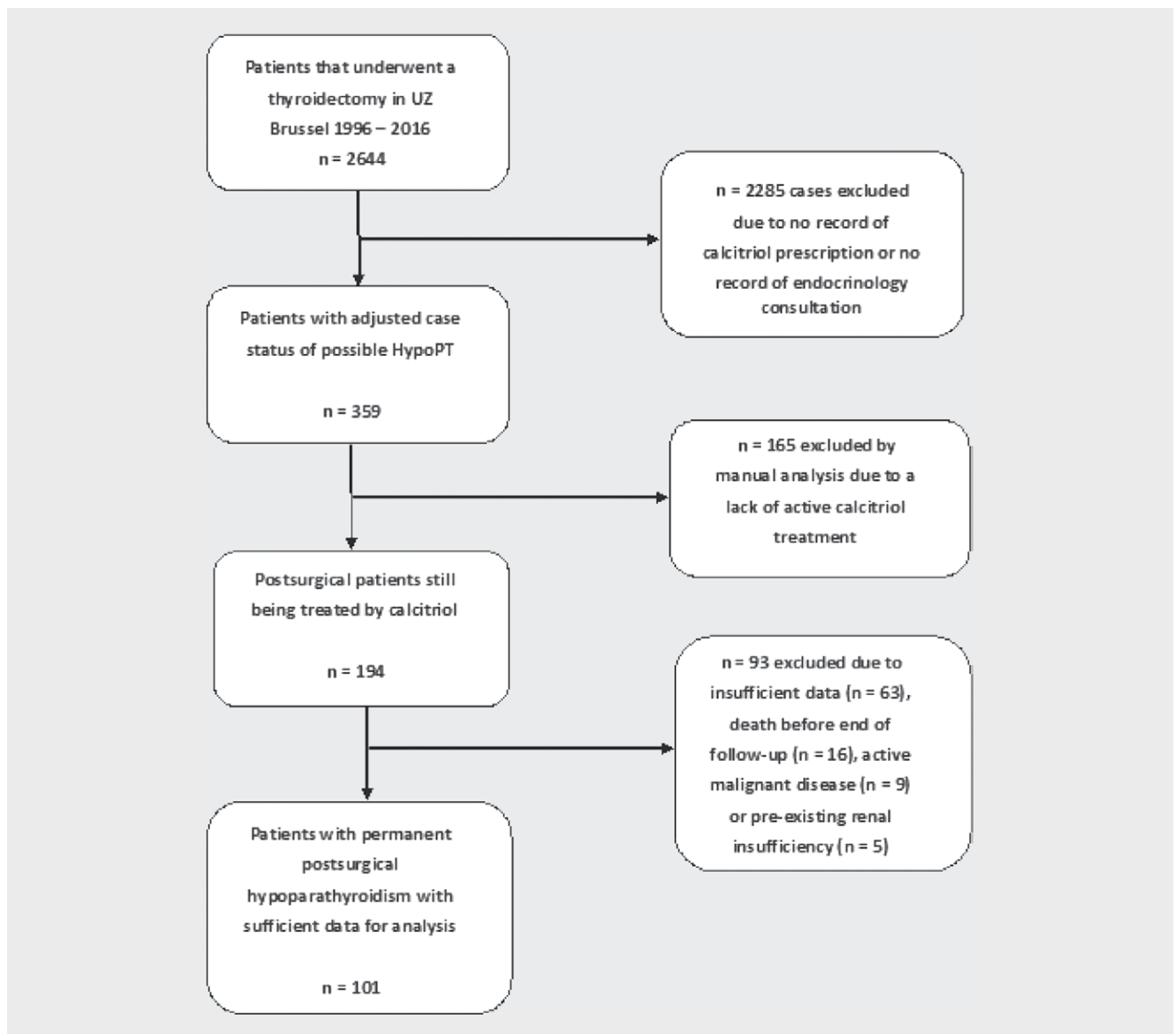
Outcomes

The primary outcome measure was renal function at the beginning and at the end of the study. Secondary outcome measures included mean calcium phosphate product, calcitriol dosage, urinary calcium excretion, serum intact PTH (iPTH), and vitamin D.

Analytical approach

All 101 patients were retrospectively analyzed comparing the present renal function with renal function at the time of diagnosis of hypoPT. The onset of hypoPT was defined as the date of surgery.

Renal function was assessed using the CKD-EPI equation at the onset of hypoPT and compared to the renal function at the maximum duration of follow up [11–14]. This difference in renal function was calculated and used in a multivariate model. The mean



► Fig. 1 Flowchart describing the patient selection method for our study.

calcium phosphate product was calculated using the last measurement available in the year of diagnosis of hypoPT and the last measurement at the maximum duration of follow-up.

Measurements of iPTH, vitamin D and HbA1c were the most recent ones available in the hospital electronic system. The 24-hour urine collection measuring calcium, phosphate, and creatinine was used at the year of diagnosis of hypoPT and at the maximum duration of follow-up.

Statistical analysis

Data are presented as (n) with percentages within group (%) for discrete variable, and median with range (minimum-maximum) for continuous variables. A multiple linear regression analysis was used to predict renal function evolution (eGFR Δ) values with duration of disease, calcium phosphate product and age as independent variables. A two sided $p < 0.05$ was considered significant. All calculations were performed using the IBM Statistical Package for Social Sciences (SPSS 23.0) (IBM, New York, USA) for Windows.

Results

Cohort description

► **Table 1** describes the full demographic data of our cohort, which was predominantly female of Caucasian origin. The median age was 50 years at the beginning and 55 years at the end of follow-up. Thyroidectomy for thyroid cancer was identified in 44 (43.6%) patients, while 57 (56.4%) patients had a benign etiology. Mean duration of follow-up was 6.6 years calculated as the time between the operation and the end of the study. The iPTH median value of the cohort was 1.41 pmol/l (normal value: 1.06–6.90 pmol/l) with an interquartile range (IQR) of 0.88–2.23 pmol/l. The median value of 25(OH) vitamin D was 60 nmol/l (IQR 44–85 nmol/l) (n = 94).

Calcium phosphate product

The median calcium phosphate product was 2.56 mmol²/l² (IQR 2.27–2.89 mmol²/l²) at the start and 2.81 mmol²/l² (IQR 2.54–2.97 mmol²/l²) at the end of follow-up. The mean calcium phosphate product was 2.75 mmol²/l² (IQR 2.54–2.97 mmol²/l²).

Urinary calcium excretion

Fifty-three patients (52.3%) had an at least one 24-hour urinary collection, but only 34 patients (33.7%) had a recorded 24-hour urinary calcium measurement. Median urinary calcium was 6.54 mmol/24 h (IQR 4.76–8.65 mmol/24 h). Only 10 patients (29.4% of measured) had a measurement of urinary calcium exceeding 7.5 mmol/24 h and were thus hypercalciuric.

Co-morbidities

Co-morbidities with possible effect on renal function (diabetes mellitus, arterial hypertension, and renal stones) were recorded and are described in ► **Table 2**. Both arterial hypertension and diabetes mellitus were well controlled in all of the patients.

► **Table 1** Demographic of patient cohort.

Age (at operation, median, years)	50 (18–75)
Age (at end of study, median, years)	55 (28–85)
Follow-up (mean, years)	6.6
Sex	
Male	21 (20.8%)
Female	80 (79.2%)
Race	
Caucasian	85 (84.2%)
Black	2 (1.9%)
Mediterranean	14 (13.9%)
Surgical etiology	
Benign	57 (56.4%)
Malignant	44 (43.6%)

Data are presented as (n) with percentages within group (%), median with range (minimum-maximum) or mean.

► **Table 2** Co-morbidities.

Diabetes Mellitus	20 (19.8%)
HbA1c (mmol/mol)	44 (31–86)
Arterial hypertension	30 (29.7%)
Renal stones (total)	7 (6.9%)
Male	6 (28.6%)
Female	1 (1.3%)

Data are presented as (n) with percentages within group (%) or median with range (minimum-maximum).

► **Table 3** Calcitriol dosage.

0.25 µg/day	31 (30.7%)
0.50 µg/day	46 (45.5%)
0.75 µg/day	13 (12.9%)
1.00 µg/day	9 (8.9%)
1.25 µg/day	1 (1.0%)
2.00 µg/day	1 (1.0%)

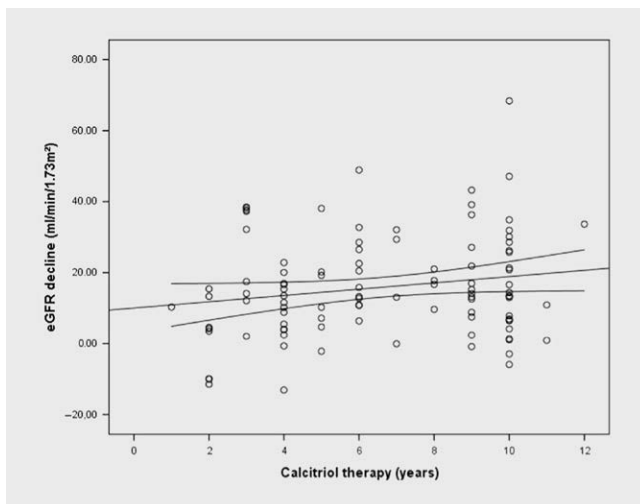
Data are presented as (n) with percentages within group (%).

Medical therapy

All the patients in the cohort were taking calcitriol therapy with a dosage varying between 0.25 and 2.00 µg per day. The most frequent dosage used was 0.5 µg/day (n = 46; 45.5%) (► **Table 3**). Other medication used consisted of thyroid hormone replacement (n = 99; 98%), calcium supplementation (n = 77; 76.2%), vitamin D

	Coefficient	95% CI	p-value
Calcitriol therapy (years)	1.055	0.123 – 1.987	0.027
Mean $\text{Ca}_3(\text{PO}_4)_2$ product (md^2/dl^2)	0.752	0.107 – 1.398	0.023
Age (years)	-0.164	-0.376 – 0.047	0.126

► **Fig. 2** Multiple linear regression analysis with the renal function decline (eGFR Δ) as dependent variable. Duration of calcitriol therapy, mean calcium phosphate product and age were used as independent variables.



► **Fig. 3** Univariate relation between the eGFR decline (eGFR Δ) and the duration of calcitriol therapy in years. Longer treatment is associated with a greater decline. R^2 linear = 0.034.

supplementation (n = 29; 28.7%), and other treatments consisting of cholesterol-lowering therapy (n = 27; 26.7%) and antihypertensive therapy (n = 30; 29.7%).

Renal function analysis

Using a multivariate regression model correcting for patient age and mean calcium phosphate product (► **Fig. 2**), calcitriol therapy was found to be significantly correlated (p = 0.027) with renal function loss. When corrected for age and average calcium phosphate product, the patients in our cohort lost 1.06 ml/min/1.73 m² per year of calcitriol therapy (► **Fig. 3**). There was also a significant correlation (p = 0.023) between the average calcium phosphate product and renal function loss. Age was not significantly correlated (p = 0.126). The dosage of calcitriol was not significantly correlated with renal function loss or with mean calcium phosphate product or urinary calcium excretion.

Only 7 patients (6.9%) underwent imaging studies of the kidneys, and none of them showed signs of nephrocalcinosis. Out of the 101 patients, 7 (6.9%) developed renal stones during the follow-up period. Six of them were male (28.6% of the male cohort), one was female (1.3% of the female cohort).

Discussion

This is the first study describing a retrospective analysis of renal function evolution in patients with postsurgical hypoPT on calcitriol therapy, demonstrating a statistically significant correlation between long term calcitriol therapy and loss of renal function.

All patients in our cohort had acceptable calcium phosphate products < 4.4 mmol²/l², which is the recommendation of the current guidelines. The values of the mean calcium phosphate product in our cohort were surprisingly low compared to values reported by similar studies [2, 10]. Despite this fact, 10 patients (29.4% of those with data) had hypercalciuria. Data on nephrocalcinosis were not sufficient as only 7 patients (6.9%) underwent imaging studies of the kidneys. Seven (6.9%) patients developed renal stones and our findings of hypercalciuria and increased renal stone risk agree with previous studies [4, 15, 16].

One of the strengths of our study is that we identified a large cohort of 101 post-surgical hypoPT patients with a suitable duration of follow up.

The major limitation of our study is the retrospective nature with some missing data, specifically on magnesium levels. Only one study has prospectively evaluated the effect of calcitriol versus recombinant human parathyroid hormone (rhPTH) on renal function [2]. They found no noticeable worsening of renal insufficiency using a short period of follow up of just 24 weeks.

In conclusion, this study is the first one to show a statistically significant correlation between the cumulative calcitriol therapy and renal function decline at a rate of 1.06 ml/min/1.73 m² per year of calcitriol therapy. This may have an impact on future guidelines and prompt further research into other treatment options of chronic hypoPT, such as rhPTH.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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