

# High incidence of chronic hypoparathyroidism secondary to total thyroidectomy

Camilla Uhre Jørgensen<sup>1</sup>, Preben Homøe<sup>2</sup>, Morten Dahl<sup>3</sup> & Mette Friberg Hitz<sup>4</sup>

## ABSTRACT

**INTRODUCTION:** Hypoparathyroidism (HypoPT) is the most common complication after total thyroidectomy (TT). Recent literature report incidences of HypoPT that are higher than previously anticipated. This study aimed to assess the incidence of transient and chronic HypoPT in patients undergoing TT and to specify risk factors and recovery time.

**METHODS:** This was a retrospective review of patients undergoing TT in the period from 2013 to 2018 due to benign thyroid disease in a Danish university hospital. In total, 187 patients were eligible for inclusion. Data were collected from internal medical files, the Thykir database sheets and patient records. HypoPT was defined as SE-ionised-Ca<sup>2+</sup> levels (< 1.16 mmol/l) and inappropriately low parathyroid hormone levels.

**RESULTS:** The incidence of transient and chronic HypoPT was 81 (43.3%) and 25 (13.4%), respectively. Younger ages and toxic indication for surgery were independent risk factors for transient and chronic HypoPT. Incidences in Graves' disease population were 70.5% and 27.3%, respectively. Resolution within the first months was seen in 48.2% of the patients with acute transient HypoPT.

**CONCLUSIONS:** The incidence of chronic HypoPT after TT is higher than previously reported. This is primarily due to a lack of consistency in the definition and follow-up time between studies. Younger patients and those with a toxic indication for surgery are at higher risk of HypoPT after TT than other patients.

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**TRIAL REGISTRATION:** The study was approved by the Danish Data Protection Agency (REG-015-2019) and The Ethical Committee of Central Denmark (No. 66792).

Hypoparathyroidism (HypoPT) is a rare endocrine disorder characterised by absent or inappropriately low levels of circulating parathyroid hormone (PTH) [1-3]. The most common aetiology of HypoPT is iatrogenic injury to the parathyroid glands (PTG) during thyroid surgery, which accounts for approximately 75% of all cases [3-6]. Post-operative HypoPT results in hypocalcaemia, often within the first 24 hours, which can cause acute symptoms such as paraesthesia, muscle cramps and seizures [2, 3]. The risk that acute transient HypoPT becomes chronic is one of the main concerns when performing thyroid surgery. If patients with transient HypoPT return to normal parathyroid function, this

normally occurs within a few weeks to six months [2, 4, 7, 8]. A recent meta-analysis by Edefe et al [6] reported the incidence of transient and chronic HypoPT to fall in the 19-38% and 0-3% range, respectively. Other authors have claimed that the true incidence of chronic HypoPT is underestimated [2], as it is reported to be much higher in more recent studies (2-17.4%), including in Danish reviews [5, 8-12]. No standardised definition of HypoPT is used among the studies.

Treatment of HypoPT involves supplementation with calcium and/or active vitamin D [1], and does not include replacement of the actual missing PTH. This is associated with long-term complications, including renal diseases and impairment of quality of life. To be able to predict and prevent this complication, it is important to continually examine associations between the patient, the surgical technique, relevant biochemical factors and post-operative HypoPT.

This study aimed to assess the incidence of transient and chronic HypoPT secondary to total thyroidectomy (TT) during a five-year period in a single institution and to identify potential risk factors and estimate recovery time.

## METHODS

### Study details

This study was a retrospective review of all consecutive patients undergoing TT during a five-year period in the Department of Otorhinolaryngology and Maxillofacial Surgery, Ear, Nose and Throat (ENT), Zealand University Hospital (ZUH), Køge, Denmark.

Patients were identified and year and type of surgery were collected from the national Thykir database sheets, which contain information about all thyroid procedures performed in the ENT field in Denmark since 2001. The identification was supplemented with procedure codes (KBAA60 and KBAA60A). In our department, this also included completion thyroidectomy. All study subjects were recruited from the same department. Initially, patients were divided into two groups (non-HypoPT versus transient HypoPT) based on post-operative SE-ionised-Ca<sup>2+</sup> levels within the first 24 hours. Transient HypoPT patients were followed retrospectively for a minimum of six months.

All patients met the same inclusion and exclusion criteria.

## ORIGINAL ARTICLE

- 1) Zealand University Hospital Køge
- 2) Department of Otorhinolaryngology and Maxillofacial Surgery, Zealand University Hospital Køge
- 3) Department of Clinical Biochemistry, Zealand University Hospital Køge
- 4) Department of Medical Endocrinology, Zealand University Hospital Køge, Denmark

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*Inclusion criteria*

1) Patients undergoing TT or completion thyroidectomy for a benign disorder performed at the ENT, ZUH Køge, in the period from 01 June 2013 to 30 September 2018.

*Exclusion criteria*

Patients with 1) a diagnosis of thyroid cancer, 2) prior parathyroid disease, 3) prior disturbances in calcium homeostasis, e.g., hypo-/hypercalcaemia, estimated glomerular filtration rate < 30 ml/min. or plasma creatinine > 200 µmol/l.

**Outcome measures and data collection**

*Primary outcome*

*The incidence of post-operative transient and chronic HypoPT*

In accordance with the European Society of Endocrinology Clinical Guideline [1], HypoPT is defined as hypocalcaemia and an inappropriately low SE-PTH due to insufficient production of PTH. It is considered chronic if the condition persists ≥ 6 months and/or if the patient needs continuous treatment with active vitamin D to stay normocalcaemic. Hypocalcaemia is defined as SE-ionised-Ca<sup>2+</sup> < 1.16 mmol/l in two consecutive measurements, in accordance with the lower limit of the local laboratory. SE-ionised-Ca<sup>2+</sup> was measured systematically on the first day post-operatively and then three times daily until stabilisation or normal values with or without treatment, whereupon discharge occurred.

*Secondary outcomes*

*Risk factors for HypoPT and recovery time*

After identification, we retrieved data on age, sex, surgical indication, former thyroid surgeries, bleeding during surgery, total number of identified PTG and PTG auto-transplantation from the patient record. Furthermore, we registered relevant treatment by post-operative days and follow-up. Patients in continuous need of treatment with active vitamin D were followed up by endocrinologists. Systematic attempts to reduce doses or stop treatment are standard procedure. Finally, data on all available biochemistry on SE-PTH, SE-ionised-Ca<sup>2+</sup>, TSH, renal function, pre- and post-operatively and after six months were extracted in the period from 01 January 2013 to 31 March 2019 for the entire Region Zealand via the Biochemical Clinical Laboratory Information System. Renal function was assessed because of the exclusion criteria.

The surgical indications were most often pressure and dysphagia. Some patients with preoperative hyperthyroidism had surgery due to multiple relapses of toxicity and few were non-tolerant to medicine. Additionally, the condition of each patient was defined as either toxic or non-toxic thyroid disease. A patient was considered toxic if diagnosed with Graves' disease or hyperfunctioning thyroid nodules (including multinodular goitre and toxic adenoma). Remission of transient HypoPT was defined as normalisation of SE-ionised-Ca<sup>2+</sup> ≥ 1.16 mmol/l in ≥ 2 consecutive measurements and simultaneous cessation of active vitamin D supplementation.

**TABLE 1** / Characteristics of patients with transient and chronic hypoparathyroidism secondary to total thyroidectomy.

	All TT patients (N = 187)	Non-HypoPT (n = 106)	Transient HypoPT (n = 81) <sup>b</sup>	p-value	Chronic HypoPT (n = 25) <sup>c</sup>	p-value
Female, n (%)	164 (87.7)	94 (88.7)	70 (86.4)	0.64	19 (76)	0.056
Age, mean ± SD, yrs	53.6 ± 13.8	56.3 ± 13.1	50.0 ± 13.9	< 0.01	43.3 ± 11.2	< 0.001
Indication for surgery, n (%)				< 0.001		< 0.001
Non-toxic	127 (68)	86 (81.1)	41 (50.6)		9 (36)	
Toxic: Graves' disease/HTN	60 (32)	20 (18.9)	40 (49.4)		16 (64)	
Type of surgery, n (%)				0.026		0.60
TT	150 (80.2)	79 (74.5)	71 (87.7)		21 (84)	
Completion thyroidectomy	37 (19.8)	27 (25.5)	10 (12.3)		4 (16)	
Parathyroid glands						
Identification, mean (range) (n = 185) <sup>a</sup>	2.1 (0-4)	2.0 (0-4)	2.3 (0-4)	0.017	2.5 (1-4)	0.029
Autotransplantation, n (%)	24 (12.8)	13 (12.3)	11 (13.6)	0.79	3 (12)	0.90
Bleeding, mean (range), ml (n = 182) <sup>a</sup>	192.4 (5-1,550)	164.5 (5-1,300)	228.1 (10-1,550)	0.11	208.6 (20-1,550)	0.77

HTN = hyperfunctioning thyroid nodules; HypoPT = hypoparathyroidism; SD = standard deviation; TT = total thyroidectomy.

a) Missing data.

b) Vs non-HypoPT patients.

c) Vs non-chronic HypoPT patients.

**Surgical procedure**

Surgical procedures included the cold steel technique and LigaSure with an attempt to find and secure the PTG. If a PTG could not be secured, the gland was cut and transplanted into the sternocleidomastoid. We routinely and meticulously examined the PTG and performed dissection as close as possible to the thyroid gland. A total of eight experienced consultant surgeons performed all surgeries, but without specialised parathyroid expertise.

**Ethics**

We conducted the study in accordance with the Declaration of Helsinki II.

**Statistics**

All analyses were conducted using R-studio v. 1.2.1335. The incidence of HypoPT was reported as the number of patients (and %) of all included patients with 95% confidence intervals. The characteristics of transient HypoPT were compared to those of patients with non-HypoPT, whereas chronic HypoPT characteristics were compared to those of patients with non-chronic HypoPT. The two-sample t-test was used for continuous variables and the chi-squared test for categorical variables. Logistic regression was used to identify independent risk factors. Only significant and suspected high-risk variables on univariate analysis were included in the multivariate analysis. The level of significance was set to  $p < 0.05$ .

*Trial registration:* The study was approved by the Danish Data Protection Agency (REG-015-2019) and the Ethical Committee of Central Denmark (No. 66792).

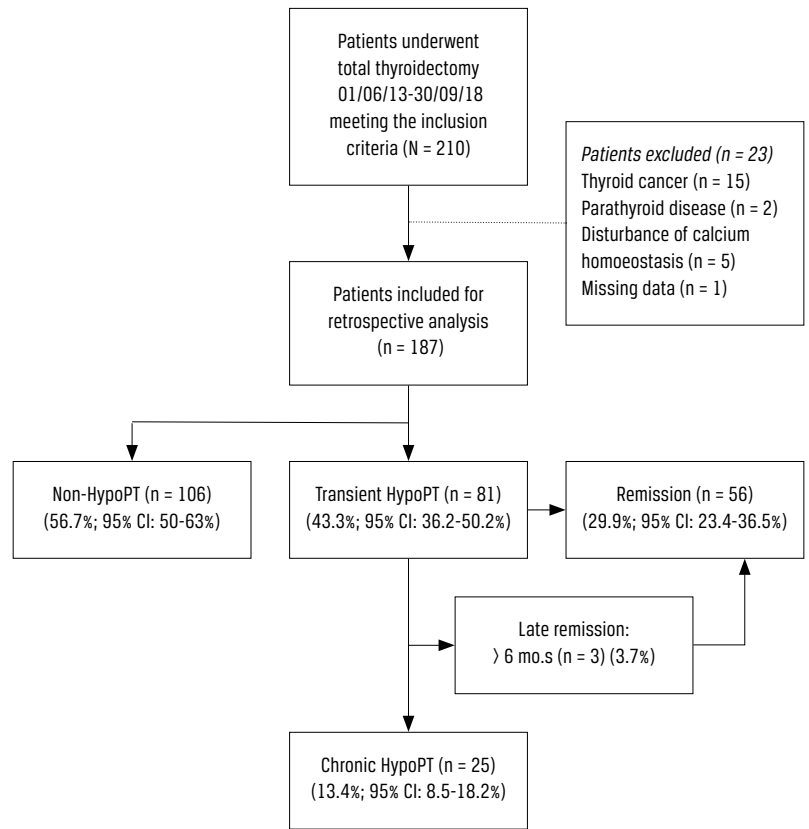
**RESULTS**

Characteristics of all 187 included patients are presented by outcome groups in **Table 1**. In total, the mean age was 53.6 years and 87.7% were females. In the group of patients classified with a toxic thyroid diagnosis ( $n = 60$ ), 44 (73.3%) were diagnosed with Graves' disease. Two-thirds of patients with Graves' disease (66%) were  $\leq 50$  years old.

**Incidence**

In the entire group of 187 patients, 81 (43.3%) had transient HypoPT during the first 24 hours after TT, whereas 25 (13.4%) remained chronic HypoPT  $\geq 6$  months (**Figure 1**). Three patients (3.7%) had a resolution time between six and 13 months which was probably due to late follow-up, and these patients were not included in the chronic HypoPT group. Graves' disease was seen in 31 (38.3%) of the transient cases and 12 (48%) of the chronic cases. This correspond to incidences in the Graves' disease population of 70.5% and 27.3%, respectively.

**FIGURE 1** / Flow chart and distribution of patients undergoing total thyroidectomy in the period from 1 November 2013 to 30 September 2018 at Zealand University Hospital Køge.



CI = confidence interval; HypoPT = hypoparathyroidism.

**Risk factors**

Using univariate logistic analysis, we identified age ( $p < 0.01$ ), toxic thyroid diagnosis ( $p < 0.001$ ), completion thyroidectomy ( $p < 0.05$ ) and identification of several PTGs during surgery ( $p < 0.05$ ) to be significantly associated with transient HypoPT. For chronic HypoPT, this only applied for age ( $p < 0.01$ ) and toxic thyroid diagnosis ( $p < 0.01$ ) (**Table 2**). Multivariate logistic analysis showed that the only independent variables for both transient and chronic HypoPT were younger age and toxic thyroid diagnosis (**Table 2**).

**Parathyroid gland recovery time**

Almost half of the transient HypoPT patients (48.1%) showed recovery within one month after surgery and 19 (23.5%) recovered within the first week. The time needed for a patient with transient HypoPT to recover was associated with the time for cessation of active vitamin D. One third of all patients with transient HypoPT did not show remission and were defined as chronic HypoPT cases. The cumulative recovery time is presented in **Figure 2**.

**TABLE 2 /** Uni- and multivariate analysis examining the independent influence of variables on the development of hypoparathyroidism.

	Transient HypoPT <sup>a</sup>		Chronic HypoPT <sup>b</sup>	
	crude OR (95% CI) <sup>d</sup>	multiadjusted OR (95% CI) <sup>e</sup>	crude OR (95% CI) <sup>d</sup>	multiadjusted OR (95% CI) <sup>e</sup>
Age, 5 yrs <sup>c</sup>	0.84 (0.75-0.94)**	0.89 (0.78-0.99)*	0.70 (0.58-0.84)***	0.75 (0.61-0.90)**
Indication for surgery: toxic	4.20 (2.18-8.06)***	3.45 (1.74-7.03)***	4.77 (1.96-11.57)***	3.96 (1.43-11.81)**
Operation: completion thyroidectomy	0.41 (0.19-0.91)*	0.86 (0.34-2.12)	0.74 (0.24-2.32)	2.88 (0.63-12.21)
Identification of PTG	1.45 (1.06-1.97)*	1.26 (0.89-1.80)	1.59 (0.99-2.53)	1.45 (0.85-2.60)

CI = confidence interval; HypoPT = hypoparathyroidism; OR = odds ratio; PTG = parathyroid glands.

\**p* < 0.05; \*\**p* < 0.01; \*\*\**p* < 0.001.

a) Vs non-HypoPT patients.

b) Vs non-chronic HypoPT patients.

c) OR for age was reported as a 5-yr frequency.

d) Univariate logistic regression.

e) Multivariate logistic regression included all variables shown.

**DISCUSSION**

Despite medical options, TT is gradually becoming a treatment of choice in more cases of benign thyroid diseases, and it accounts for approximately 75% of all cases of HypoPT [3, 5, 6]. If transient HypoPT persists and becomes chronic, patients need lifelong medication and are at risk of severe long-term complications. This condition is known to have a profound impact on the patient’s quality of life.

This study examines the incidence, risk factors and recovery time for HypoPT due to TT in patients with a benign thyroid diagnosis.

**Incidence**

The reported incidence of HypoPT after TT is highly variable, and some authors claim that it is underestimated [2]. We found that 43.3% of the patents suffered from acute transient HypoPT after TT and 13.4% of the patients had chronic HypoPT. The here reported incidence of chronic HypoPT is remarkably higher than the 0-3% previously reported by Edafe et al and Mannstadt et al [3, 6]. However, in contrast, our incidences are in accordance with those of other Danish retrospective studies [5, 9]. This contributes to a concern regarding a tendency towards HypoPT underestimation. One explanation may be international differences between definitions of HypoPT.

Our definition of HypoPT is in line with that of the European Society of Endocrinology Clinical Guideline [1], suggesting a diagnosis dependent on biochemical hypocalcaemia and inappropriately low PTH levels. We have no cut-off limit for PTH levels as hypocalcaemia in a healthy person would trigger a secondary hyperparathyroidism.

**Risk factors**

Multivariate analysis indicates that the incidence of transient and chronic HypoPT is significantly associ-

ated with younger age and a toxic indication for surgery, as the only independent variables (Table 2). These findings have previously been suggested in other studies as potential risk factors [1, 9, 13].

Edafe et al [6] suggest no significant difference in mean age between HypoPT and non-HypoPT, whereas other studies are in line with our findings [1, 9] regarding younger age as a risk factor. In our study, the odds ratio for transient and chronic HypoPT decreased for every five-year increase in age, by 16% and 28%, respectively. Two-thirds (66%) of patients with Graves’ disease formed part of the younger population (≤ 50 years old), why this finding may be due to interaction which we have not tested for in this study due to the relatively small number of patients.

To our knowledge, only few studies have investigated the impact of a toxic thyroid diagnosis on the development of HypoPT. The present study indicates that the risk for HypoPT is higher among patients with a toxic thyroid disease as surgical indication than among patients with a non-toxic indication. It is noteworthy that the incidence of transient and chronic HypoPT in patients with Graves’ disease as surgical indication are substantially higher than in the total population (70.5% and 27.3%, respectively). A prospective multicentre study [13], investigating 5,846 patients, previously described Graves’ disease as a risk factor for transient as well as chronic HypoPT with a significant odds ratio of 2.4 for chronic HypoPT.

Among surgeons, it is well known that TT due to Graves’ diseases can be troublesome. This is claimed to be caused by hypervascularisation and inflammation of the gland, which makes it difficult to find the PTGs and to preserve their blood supply [14]. We were unable to establish whether patients with a toxic thyroid diagnosis were at higher risk of HypoPT because of surgical difficulties and/or due to the biochemical influence of toxicity, as data on thyroid gland weight and preoperative

TSH were not systematically accessible. The fact that none of the eight experienced thyroid surgeons performing the surgeries had specialised parathyroid expertise may potentially also constitute a risk factor.

**Recovery time**

Most patients recover from transient HypoPT within a few weeks to six months [2, 4, 7, 8]. In our study, almost half (48.1%) of the patients with transient HypoPT recovered within the first month. Furthermore, late recovery was a result of late follow-up and phasing out of active vitamin D, as recovery within the first months would have been found if we had considered only biochemistry levels of SE-ionised-Ca<sup>2+</sup> to determine recovery. In addition, another Danish study by Jensen et al [5], reported the incidence of chronic HypoPT to be caused, in part, by this phenomenon.[5], reported the incidence of chronic HypoPT to be caused, in part, by this phenomenon.

**Limitations**

This study carries some limitations. Firstly, the study is retrospective, making data collection potentially less accurate than would have been the case for a prospective design. Not all the desired data were recorded, e.g., preoperative SE-PTH and SE-TSH and duration of surgery. Furthermore, physicians might have different definitions to determine, e.g., thyroid toxicity when making the diagnosis. Finally, our sample size may have been too small to identify additional associations and may have overestimated others. Nevertheless, the study is one of few investigating the outcome of HypoPT on patients undergoing TT for benign thyroid disorders including incidences and time to recovery.

**CONCLUSIONS**

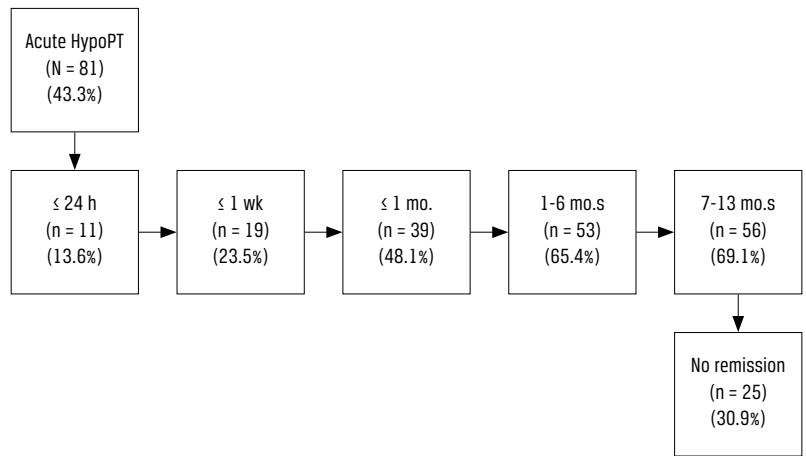
In conclusion, this study reported higher incidences of post-operative transient and chronic HypoPT than previous studies. This finding indicates a need for a common definition of HypoPT in accordance with the European Society of Endocrinology Clinical Guideline across nations. Our study suggests that independent risk factors for transient and chronic HypoPT include younger age and a toxic surgical indication, typically Graves' disease. Future studies on improved surgical methods and the influence of biochemical toxicity in patients with Graves' disease undergoing TT may be useful.

**CORRESPONDENCE:** Camilla Uhre Jørgensen.  
E-mail: cuj@regionsjaelland.dk

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**FIGURE 2 /** Cumulative recovery time of parathyroid glands for patients with acute transient hypoparathyroidism (HypoPT).



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