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Hypoparathyroidism after thyroid surgery- rates, risks, prevention and consequences

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ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2023

ISSN 1651-6206
ISBN 978-91-513-1722-9
URN urn:nbn:se:uu:diva-497031

Dissertation presented at Uppsala University to be publicly examined in H:son Holmdahlsalen, Ingång 100, Akademiska sjukhuset, Uppsala, Friday, 14 April 2023 at 09:00 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish. Faculty examiner: Associate Professor Erik Nordenström.

Abstract

Annebäck, M. 2023. Hypoparathyroidism after thyroid surgery- rates, risks, prevention and consequences. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1905. 72 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-1722-9.

Hypoparathyroidism is the most common complication after thyroid surgery and associated with short- and long-term consequences. The lack of a consensus on the definition of hypoparathyroidism has led to a broad range in the rates reported in the literature. The overall aim of this thesis was to study different aspects of hypoparathyroidism, in terms rates, risks and long-term impact. **Paper I** is a case control study, investigating prophylactic, preoperative treatment with active vitamin D and early hypocalcemia after total thyroidectomy. The study showed that patients with preoperative treatment had a lower risk of early hypocalcemia and a reduced length of stay in hospital, compared to patients without treatment. No adverse outcomes were found. **Paper II** is a population-based retrospective cohort study on the rate and risks for permanent hypoparathyroidism after total thyroidectomy for benign thyroid disease. Data was retrieved from The Swedish National Patient Register, The Swedish Quality Register for Thyroid, Parathyroid and Adrenal Surgery and The Swedish Prescribed Drug Registry. Permanent hypoparathyroidism was defined as dispensation of calcium and/or active vitamin D >12 months after surgery. Among 7852 patients, 12.5% developed permanent hypoparathyroidism. Surgery at low volume centers, parathyroid autotransplantation, female gender and high age were independent risk factors. In **Paper III** the aim was to validate the high rate of permanent hypoparathyroidism found in Paper II. A regional cohort was extrapolated from the national cohort. A retrospective chart review, of 1636 patients, was performed. Using a strict definition, 6.2 % were found to have definitive permanent hypoparathyroidism. Additionally, 2.5 % were found to have possible permanent hypoparathyroidism. Of these, at least 1.7 % might have been overtreated due to lacking attempts to unwind the treatment. The study also proposed that the rate of low early PTH in a cohort might be useful to predict the rate of permanent hypoparathyroidism. **Paper IV** investigated health related quality of life (HRQoL) in patients with and without permanent hypoparathyroidism using the same cohort as in Paper III and SF-36 v.2. No impact of definitive hypoparathyroidism on HRQoL could be found. **In conclusion**, the use of preoperative active vitamin D may be useful as a tool to lower the risk of early hypocalcemia. The risk of permanent hypoparathyroidism after total thyroidectomy is high and there is a need for improved follow up. Permanent hypoparathyroidism may not have a negative effect on HRQoL in most patients.

Keywords: thyroidectomy, hypoparathyroidism, hypocalcemia, parathyroid hormone, vitamin D, health-related quality of life

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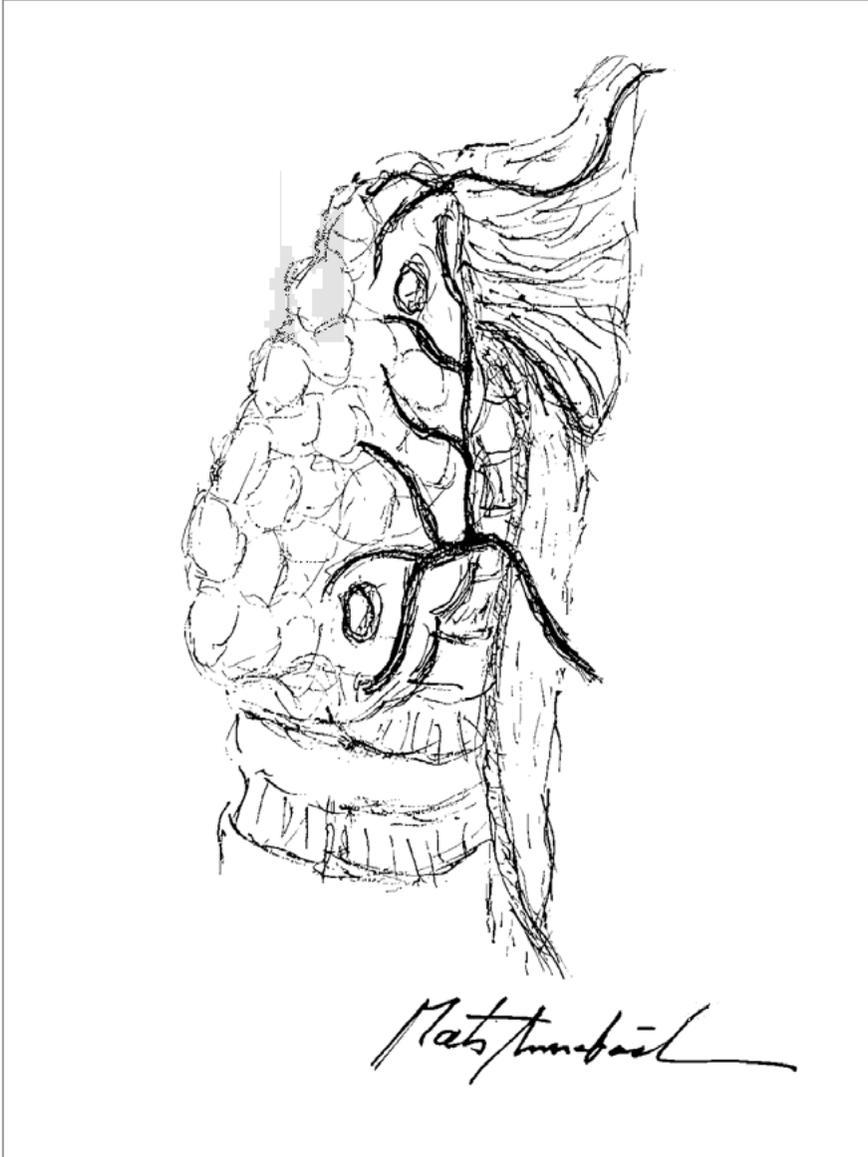
ISSN 1651-6206

ISBN 978-91-513-1722-9

URN urn:nbn:se:uu:diva-497031 (<http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-497031>)

There will be days like this
Van Morrison

To my family
Greta and Henrik



Published with permission of my father

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I. Annebäck M., McHale Sjödin E., Hellman P., Stålberg P., Norlén O. (2022) Preoperative prophylactic active vitamin D to streamline total thyroidectomy. *BJS Open*, May 2;6(3).
- II. Annebäck M., Hedberg J., Almquist M., Stålberg P., Norlén O. (2021) Risk of permanent hypoparathyroidism after total thyroidectomy for benign disease: A nationwide population-based cohort study from Sweden. *Ann Surg*, Dec 1;274(6): e1202-e1208.
- III. Annebäck, M., Osterman C., Arlebrink J., Mellerstedt S., Papatheanasakis N., Wallin G., Hessman O., Annerbo M., Norlén O., Validating the risk of hypoparathyroidism after total thyroidectomy in a population-based cohort- a plea for improved follow-up. *Manuscript*.
- IV. Annebäck M., Wachtmeister S., Stålberg P., Norlén O. Quality of life in patients with permanent hypoparathyroidism after thyroidectomy: a population-based study with long-term follow up. *Manuscript*.

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Contents

Introduction	11
Brief history of thyroid surgery	11
Background	13
Anatomy and function of the thyroid gland.....	13
The parathyroid glands	13
Parathyroid function and calcium homeostasis	14
Indication of thyroid surgery	15
Complication to thyroid surgery.....	16
Hypoparathyroidism	16
Definitions and rates.....	16
Clinical manifestations of hypocalcemia.....	20
Long-term consequences	21
Renal	21
Skeletal.....	21
Mortality and morbidity	21
Health-related quality of life.....	22
Risk factors for hypoparathyroidism	23
Patient related risk factors.....	23
Surgical risk factors	23
Strategies to prevent hypoparathyroidism	25
Surgical technique.....	25
Technical aids	25
Prophylactic supplementation.....	26
Treatment of hypoparathyroidism	26
Conventional treatment.....	26
PTH treatment.....	27
Swedish registers	27
NPR.....	28
SPDR.....	28
The Swedish Cause of Death Register.....	28
SQRTPA	28
Aims of the thesis.....	30

Material and methods	31
Paper I	31
Paper II	31
Paper III	32
Paper IV	33
Statistics	35
Basic statistics.....	35
Propensity score matching.....	35
Survival analysis.....	35
Ethical considerations	36
Paper I.....	36
Paper II	36
Paper III	36
Paper IV.....	36
Results	37
Paper I.....	37
Paper II	39
Paper III	41
Paper IV.....	43
Discussion	46
A strategy to reduce postoperative hypocalcemia	46
Rates and risk factors.....	48
Quality of life.....	51
Conclusions	54
Further perspectives	55
Summary of the thesis in Swedish	57
Populärvetenskaplig sammanfattning på svenska	57
Delarbete I.....	58
Delarbete II	58
Delarbete III	59
Delarbete IV.....	59
Acknowledgements	61
References	64

Abbreviations

CI	Confidence Interval
CVD	Cardiovascular disease
HR	Hazard ratio
HRQoL	Health related quality of life
iCa ²⁺	Ionized calcium
ICD	International Classification of Disease, Injuries, and Death
ICG	Indocyanine green fluorescence
IQR	Interquartile range
NPR	Swedish National Patient Register
NTT	Near total thyroidectomy
OR	Odds Ratio
PTH	Parathyroid hormone
RLN	Recurrent laryngeal nerve
S-Ca	Serum calcium
SMD	Standardized mean difference
SD	Standard deviation
SPDR	Swedish Prescribed Drug Register
SSI	Surgical Site Infection
SQRTPA	Scandinavian Quality Register of Thyroid Parathyroid and Adrenal Surgery
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid stimulating hormone
TRH	Thyrotropin releasing hormone
TT	Total thyroidectomy
UKRETS	The UK Registry of Endocrine and Thyroid Surgery

Introduction

Brief history of thyroid surgery

Thyroidectomy is a common procedure and the indication for it may be malignancy, compression symptoms or thyrotoxicosis. The delicate anatomy of the anterior neck and rich vascularity of the thyroid gland can make thyroidectomy a challenging procedure to perform safely.

In the early history of thyroid surgery, the procedure was associated with high mortality and morbidity. The knowledge about the function of the thyroid gland was limited and many patients undergoing thyroidectomy, unfortunately, died from haemorrhage, sepsis or tetany. In 1846, Robert Liston, a British surgeon, called thyroid surgery “a proceeding by no means to be thought of” after performing five thyroidectomies. Some years later, an American surgeon, Samuel Gross stated: “Can the thyroid in the state of enlargement be removed? Emphatically, experience answers no. Should the surgeon be so foolhardy to undertake it...every stroke of the knife will be followed by a torrent of blood and lucky it would be for him if his victim lived long enough for him to finish his horrid butchery. No honest and sensible surgeon would ever engage in it.”¹

The advancement in thyroid surgery begun in the late-nineteenth century with an increased understanding of thyroid endocrinology and development of new surgical and anaesthetic techniques.² Several surgeons contributed to the tremendous development of thyroid surgery in the late 19th and early 20th century. The story of the modern thyroidectomy starts with Theodor Billroth. He was among the first to use the new available techniques in theatre and thereby reduced his mortality rate from 40% to around 8%.^{2,3} Theodor Kocher started as a pupil of Billroth, and is often called the father of thyroid surgery. He was a surgical pioneer and his principles of thyroid surgery are still valid and the foundation for the classical thyroidectomy. His major contribution to thyroid surgery and research earned him the Nobel Prize in Medicine and Physiology in 1909⁴.

The human parathyroid glands are often called the last major organ to be discovered. They were first recognized in 1880 by Ivar Sandström, a young Swedish medical student at Uppsala University.⁵ At the time of Sandström's discovery the function of the parathyroid glands was still unknown, but in 1909 Berjeley and Beebe were the first to show that removal of these glands could result in hypocalcemia and tetany in humans.⁶

Currently, thyroid surgery is a common operation worldwide. This development can be explained by the advancement in knowledge about the function and diseases of the thyroid, improved surgical techniques, standardized surgical procedures and continuous research. Nevertheless, despite all advancement, thyroidectomy is still not free from complications. Therefore, we owe to our patients, precursors and our-selves to continue to strive for an increased knowledge about the complications of thyroid surgery.

Background

Anatomy and function of the thyroid gland

The thyroid gland is located in the anterior neck and consists of two lobes connected with the central isthmus with or without a pyramidal lobe. The thyroid gland lies posterior to the sternohyoid and sternothyroid muscles and is wrapped around the larynx and trachea at the level of the second and third tracheal rings. The gland is well vascularized and has a rich blood supply from the superior and inferior thyroid arteries⁷.

The thyroid gland is composed histologically of two parenchymal cell types: thyroid follicular and C-cells. The follicular cells form follicles, which are the functional units of the thyroid. The follicles are responsible for the synthesis and secretion of the two main hormones- triiodothyronine (T3) and thyroxine (T4) which regulate metabolism, growth as well as development in children. Additionally, the C-cells produce calcitonin which contributes to regulating calcium homeostasis. The thyroid gland is dependent on iodine to produce T3 and T4.⁸

Thyroid activity is regulated through a feedback mechanism involving the pituitary gland and hypothalamus and their hormones- thyroid stimulating hormone (TSH) and thyrotropin-releasing hormone (TRH). The hypothalamus secretes TRH which stimulates the anterior pituitary gland to release TSH, which stimulates the synthesis of thyroid hormones. The release of TRH and TSH are regulated through negative feedback by T3 and T4.^{8 9}

The parathyroid glands

The parathyroid glands are typically comprised of four small glands located posterior to the thyroid, although supernumerary glands are found in 5-13% of autopsy series.^{7, 10, 11} Their colour ranges from reddish-brown to yellow-tan and the average size ranges from 3 to 8 mm in length and to 2 to 4 mm in width. The location of the parathyroid glands is derived from their embryologic development. The paired superior and inferior parathyroid glands develop from the third and fourth brachial pouches. The inferior parathyroid glands derive from the third brachial pouch and descend caudally in close association to the thymus. The relatively long migration and the variable timing in separation from the thymus is the reason for the variability in the final

location of the inferior parathyroid glands. The superior parathyroid glands derivates from the fourth brachial pouch and due to their shorter embryological descent, compared to the inferior glands, their location is less variable.⁷ The superior parathyroid glands are usually located posterior to the recurrent laryngeal nerve and are in over 80% of the cases found within 1 cm above the crossing between the recurrent laryngeal nerve and the inferior parathyroid artery.¹² The inferior parathyroid glands are normally located anterior to the recurrent laryngeal nerve and found on the posterolateral aspect of the inferior thyroid pole, close to the thyrothymic ligament or in the upper part of the thymus. The vascular supply of the parathyroid glands is in most cases derived from the inferior thyroid artery, however the superior parathyroid glands are sometimes supplied by the superior thyroid artery.^{8, 13}

Parathyroid function and calcium homeostasis

The function of the parathyroid glands is to firmly regulate the calcium homeostasis in the blood by the synthesis and secretion of parathyroid hormone (PTH)⁸. PTH is an 84-amino acid polypeptide with a short half-life of approximately 3-5 minutes. The production and release of PTH to the blood stream is stimulated through low serum calcium concentrations. The major target end organs for PTH action are the kidneys and bones, in which the hormone stimulates reabsorption of calcium, promotes phosphate excretion and bone resorption. PTH also stimulates the conversion of 25-hydroxyvitamin D to its active form, 1,25-dihydroxyvitamin D in the kidneys. The active vitamin D facilitates calcium absorption in the intestines as well as bone turnover¹². Low circulating PTH leads to hypocalcemia, hyperphosphatemia and inability to convert vitamin D to its active form in the kidneys.

Of the circulating calcium, approximately 40 % is bound to proteins (predominantly albumin), 10 % bound to anions and the remaining half free, ionized calcium (iCa^{2+}). Only the iCa^{2+} is physiologically active. Calcium concentrations in bloods are measured by either determining total calcium (bound and unbound) or iCa^{2+} . Since a large portion of the circulation calcium is bound to albumin, total calcium levels may not accurately reflect the iCa^{2+} concentration in patients with hypo- or hyperalbuminemia. Therefore, an albumin-corrected calcium concentration can be calculated instead. A commonly used formula is: corrected calcium = total calcium + $0.02 \times (40 - \text{albumin})$, where calcium is stated in mmol/l and albumin in g/l.

Some authors have reported limitations in the use of this formula for certain subgroups, for example in patients with chronic kidney disease.¹⁴ While measuring iCa^{2+} is preferred, the availability and cost for iCa^{2+} assays vary. Moreover, as iCa^{2+} levels are pH-dependent, a delay in processing the blood sample can lead to incorrect results.¹⁵

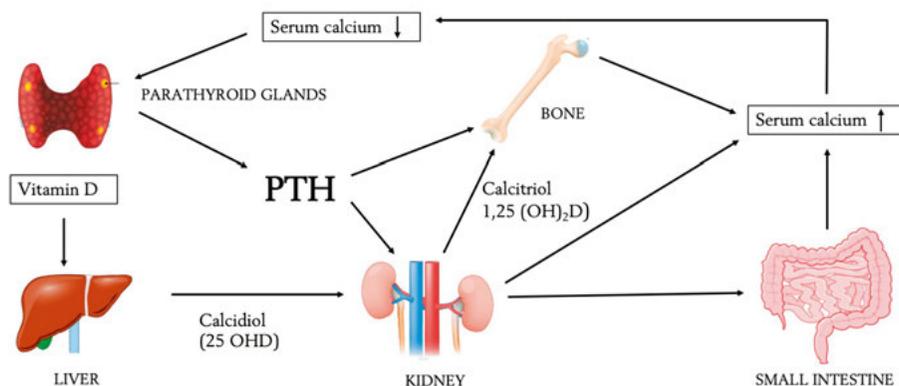


Figure 2. PTH and calcium homeostasis

Indication of thyroid surgery

Thyroidectomy is a common procedure used to treat benign and malignant thyroid disease. Common indications for total thyroidectomy are symptomatic bilateral goiter, Graves thyrotoxicosis and cancer, whereas hemithyroidectomy typically is done in patients with symptomatic unilateral goiter and suspicious cancer.¹⁶

Multinodular goiter is the most common disease in the thyroid gland. Surgery is usually performed in patients with compression symptoms. There are several different surgical options, such as total thyroidectomy, near-total thyroidectomy and subtotal thyroidectomy. The difference between these procedure is the extent of the thyroidectomy with total thyroidectomy and near-total thyroidectomy leaving no or just a shiver of thyroid tissue in the neck. Subtotal thyroidectomy on the other hand, may leave thyroid tissue on both or one side. Subtotal thyroidectomy was the preferred choice for many a couple of decades ago. Nowadays, total or hemi thyroidectomy is the standard treatment for multinodular goiter in most institutions¹⁶.

Graves thyrotoxicosis is an autoimmune disease, causing an overproduction of thyroid hormones. Graves' disease can be treated with antithyroid medication, radioactive iodine or surgery. The first line of treatment is usually antithyroid drugs. In patients non-responsive to medical treatment and unsuitable to radioiodine, Graves' disease is treated with surgery. In those undergoing surgery the gold standard is total thyroidectomy, since all other surgical options increase the risk of recurrence¹⁶.

Complication to thyroid surgery

Thyroid surgery has with time become a routine operation with a significant decline in overall morbidity and mortality. Nowadays most patients will fully recover without any adverse events. However, the delicate anatomy of the anterior neck and the rich vascularity of the thyroid gland can make thyroidectomy a challenging procedure to perform safely. Complications specific to thyroid surgery include neck hematoma, recurrent laryngeal nerve injury and hypoparathyroidism⁸.

Hypoparathyroidism

Hypoparathyroidism is the most frequent complication after total thyroidectomy and a common cause of delayed discharge^{17, 18}. It is caused by intraoperative injury of the parathyroid vascular supply, mechanical or thermal trauma, or unintentional excision, resulting in impaired or absent secretion of PTH. One to two parathyroid glands with intact function are enough for a sufficient parathyroid function, therefore hypoparathyroidism is only seen after total thyroidectomy and not hemithyroidectomy. The complication is in most cases transient; however, some will develop permanent hypoparathyroidism with a life-long need of treatment and follow-up.

Definitions and rates

The biochemical hallmark of hypoparathyroidism is hypocalcemia in combination with undetectable or inappropriate low PTH. It is worth noting that a PTH within normal range do not exclude hypoparathyroidism, as a low calcium accompanied by the absence of an appropriate elevation of PTH also indicates parathyroid insufficiency.

There is a lack of international consensus regarding the definition and criteria of post-surgical hypoparathyroidism, resulting in a broad variety of definitions mentioned in the literature. Hypoparathyroidism can be defined by biochemical findings, hypocalcemic symptoms or the need of treatment with supplementation. A systematic review article by Harsløf *et al.* in 2019, which included 89 articles published between 2010 and 2017, revealed 20 different definitions of hypoparathyroidism.¹⁹ A meta-analysis by Nagel *et al.* also highlighted this issue. Out of 188 articles eligible for inclusion, 31(16.4%) studies were excluded due to a lack of a clear definition of hypoparathyroidism.²⁰

Postoperative hypoparathyroidism and hypocalcemia are often used synonymously. Different cut-off values are used to define postoperative hypocalcemia. Common definitions are s-Ca <2.10mmol/L²¹ and s-Ca <2.0 mmol/L^{22, 23}

postoperative day one. Another frequently used definition is a total s-Ca below the lower limit of the institutional-specific reference range.^{20,24} Traditionally, repeated testing of s-Ca has been used to identify patients at risk of symptomatic hypocalcemia and determine the need of treatment with calcium and/or active vitamin D supplementation. A declining S-Ca, especially in combination with a rising S-phosphate implicates parathyroid failure.²⁵ The short half-life of PTH makes it a useful tool in predicting the development of hypoparathyroidism and hypocalcemia. Since the introduction of PTH assays, early postoperative PTH measurement (within 24 h after surgery) has become routine in most centres. Numerous studies have investigated the relationship between low early PTH and the risk of postoperative hypocalcemia. A PTH level <1.6 pmol/L within 24 h has been shown to be associated with an increased risk of postoperative hypocalcemia²⁶⁻²⁸. The use of early PTH allows for the initiation of replacement therapy with calcium and active vitamin D in patients at risk of hypocalcemia.

Postoperative hypocalcemia has been reported to occur in 14-50% of cases.^{17, 23, 29, 30} In the vast majority of patients, the parathyroid function will recover within a month.^{22, 29, 31} For patients with parathyroid failure lasting longer than 4 weeks, approximately 75% will fully recover within 12 months.²³ Mehanna *et al.* demonstrated the impact of different definitions of hypoparathyroidism on the reported incidence rates. By applying various definitions of hypoparathyroidism described in the literature on the same cohort, they found that the rate of hypoparathyroidism ranged from 0.9 % to 46%.³²

Most guidelines and registers define permanent hypoparathyroidism as parathyroid failure at 6 or 12 months after surgery. The European Guidelines and The American Thyroid Association uses the 6 months cut-off, whereas the American Association of Clinical Endocrinologist extends the time frame to 12 months.^{24, 33, 34} There are studies to support the latter cut-off, showing that some patients will regain full parathyroid function between 6 and 12 months.^{31, 35} Quality register as The Scandinavian Quality Register of Thyroid Parathyroid and Adrenal Surgery (SQRTPA) and The UK Registry of Endocrine and Thyroid Surgery (UKRETS) uses the need of supplementation with calcium and/or vitamin D as a surrogate for hypoparathyroidism, whereas others defines permanent hypoparathyroidism through biochemical findings. The wide flora of definitions contributes to the large span in the reported rates of permanent hypoparathyroidism in the literature. Other factors that contribute to the variation in hypoparathyroidism rates are listed in Box 1

Box 1**Reasons for variation in rate of permanent hypoparathyroidism**

Lack of consensus of the definition
Different case mix
Varying experience among surgeons
Small series
Inclusion of primary unilateral resections
Different department policies to unwind supplementation
Loss in follow up
Missing data in quality register

A large systemic review conducted by Edafe *et al.* in 2014 found the median (i.q.r) incidence of permanent hypoparathyroidism to be 1 (0-3) per cent. This is in contrast to findings in multicenter studies and national databases, which have reported rates of up to 15 %.^{36, 37} Single-center studies are often done by high-volume centers with an expertise in thyroid surgery, therefore their rate of permanent hypoparathyroidism may not be representative of those with less experience and lower operative volume. A previously published study in 2008 by Bergenfelz *et al.* using data from SQRTPA reported that 4.4 % of patients undergoing total thyroidectomy still required vitamin D 6 months after surgery.³⁸ One potential problem with national databases is missing follow-up data, as shown by UKRETS, where almost 22 % had missing data at 6 months follow up.²¹ An adequate evaluation of the rate of permanent hypoparathyroidism requires a complete follow up of all patients with postoperative hypoparathyroidism until they either regain normal parathyroid function, or have been followed for at least 12 months. To avoid overtreatment, attempts to unwind the treatment with calcium and/or vitamin D are also required before confirming the diagnosis of permanent hypoparathyroidism. Any attempt to unwind the treatment should be followed up and evaluated in terms of the development of hypocalcemic symptoms and blood tests with S-Ca and PTH levels. Attempts to unwind the supplementation is seldom mentioned in studies on permanent hypoparathyroidism.

Table 1. National registers and multicenter studies on permanent hypoparathyroidism

Authors	Type of study	Country	No. of procedures and case mix	Rate ^a	Definition ^b	Limitations
Chadwick <i>et al.</i> ³⁹ 2012	National registry based (retrospective)	UK	3,788 TT for benign and malignant thyroid disease	12.1%	Calcium and/or active vit D supplementation 6 months after surgery	Data on Ca and PTH lacking. Missing registration in the registry. Missing follow up data. .
Bergentfelz <i>et al.</i> ⁴⁰ 2019	National registry based (retrospective)	Sweden	4,828 TT for benign thyroid disease	5.0%	Active vit D supplementation 6 months after surgery	Data on Ca and PTH lacking. Missing follow up data. Other reasons for treatment with active vit D possible
Puzziello <i>et al.</i> ⁴¹ 2014	Multicenter (prospective)	Italy	2,631 TT, NTT and completion thyroidectomy for benign and malignant disease.	0.9% ^c	Not clearly stated	Definition of permanent hypoparathyroidism uncertain. Graves excluded. No data on supplementation at 6 months.
Lončar <i>et al.</i> ³⁶ 2021	Multicenter (retrospective)	Netherlands	200 TT or completion thyroidectomy for benign and malignant thyroid disease	15%	Active vit D with or without calcium supplementation 12 months after surgery.	Data on Ca and PTH lacking. No information about withdrawal attempts.
Díez <i>et al.</i> ³⁷ 2019	Multicenter (retrospective)	Spain	1792 TT or completion thyroidectomy for benign and malignant thyroid disease	14.5%	Need of calcium and/or active vit D at last visit of follow up (>12 months after surgery)	No information about withdrawal attempts. Ca and PTH not included in the definition.
Thomusch <i>et al.</i> ⁴² 2003	Multicenter (prospective)	Germany	5846 bilateral thyroid surgery (including subtotal and total) for benign and malignant thyroid disease	9% (among TT)	Undetectable PTH or need of calcium and/or vit D supplementation >6 months after surgery	No information about withdrawal attempts.

^aRate of permanent hypoparathyroidism, ^bDefinition of permanent hypoparathyroidism. TT indicated total thyroidectomy; NTT, near-total thyroidectomy; PTH, parathyroid hormone.

Clinical manifestations of hypocalcemia

The clinical features of acute hypocalcemia are primarily caused by an increased neuromuscular irritability and cardiac electrical instability due to a reduced depolarization threshold for nerve and muscle cells. Patients with mild hypocalcemia may be asymptomatic, while severe hypocalcemia can cause life-threatening conditions. The first symptom of hypocalcemia is often tingling, numbness or twitching in hands, feet and/or face. Severe manifestations of postoperative hypocalcemia are rare, since S-Ca and PTH are usually monitored closely after surgery. Although, if unrecognized and left untreated severe hypocalcemia may cause seizures, laryngospasm, tetany and cardiac arrhythmias.^{43, 44}

Clinical signs of hypocalcemia are Trousseau's and Chvostek's sign. Chvostek's sign is elicited through tapping over the facial nerve just anterior to the earlobe. In a positive response twitching or contraction of the facial muscles occurs. A positive sign can be seen in 10% of normocalcemic persons and negative in almost one third of patients with hypocalcemia.⁴⁵ Trousseau's sign is more specific for hypocalcemia and have been found to be present in 94% of patients with confirmed hypocalcemia, as opposed to in only 1% of normocalcemic persons-⁴⁵ Trousseau's sign manifests as limb spasm and is elicited by placing a blood pressure cuff over the upper arm and inflating it to 20 mmHg above the patient's systolic blood pressure. A positive response will render a carpal spasm after 3-5 minutes.

Box 2

Clinical manifestations of hypocalcemia

Neuromuscular

- Tingling/paraesthesia in extremity and perioral
- Muscle cramps
- Fatigue
- Tetany
- Laryngospasm

Neurological

- Altered mental status
- Seizures

Cardiac

- Prolonged QTc interval
- T-wave inversion
- Ventricular tachycardia
- Torsade de pointes

Long-term consequences

Renal

Several long-term consequences in the kidneys have been described in patients treated for permanent hypoparathyroidism, such as renal calcifications, impaired renal function and renal stones. A study by Mitchell *et al.* found that the rates of chronic kidney disease were 2 to 17 times higher in patients with hypoparathyroidism compared to age-appropriate healthy individuals. The majority of cases in the study had postsurgical hypoparathyroidism, although patients with non-surgical hypoparathyroidism were also included.⁴⁶ A large Danish study investigating renal complications in patients with postsurgical hypoparathyroidism confirmed the result by Mitchell *et al.* In this study patients with hypoparathyroidism had an almost five-fold higher risk of renal insufficiency (HR, 4.95; 95% CI, 2.88-8.50) and renal stones (HR 4.82; 95% CI, 2.00-11.64), compared to age- and gender-matched controls, even after adjusting for diabetes and preoperative renal disease.⁴⁷ Renal calcification is also commonly observed in patients with permanent hypoparathyroidism.^{46, 48}

Skeletal

Reduced bone remodelling is characteristic to permanent hypoparathyroidism and leads to low bone turnover and higher bone mass.⁴⁹ Data on the risk of fractures is inconsistent. A systemic review in 2021 found that the risk of vertebral fractures is increased in patients with non-surgical hypoparathyroidism but not in those with hypoparathyroidism as a consequence of neck surgery.⁵⁰ This is contradictory to a small study that showed an increased risk of vertebral fractures in patients with surgical hypoparathyroidism.⁵¹ Moreover, fractures of the upper extremities have been found to be less common in patients with hypoparathyroidism, when comparing to matched controls (HR 0.69, 95% CI 0.49-0.97).⁵²

Mortality and morbidity

In addition to renal and skeletal effects, permanent hypoparathyroidism has also been shown to increase the risk of cataract, basal ganglia calcifications, infection and psychiatric morbidity.^{46, 52, 53} Soft tissue calcifications in basal ganglia are thought to be caused by an elevated calcium-phosphate product.⁵⁴ Moreover, patients with permanent hypoparathyroidism have been shown to have an increased risk of malignancy and mortality.^{40, 55} Almquist *et al.* investigated the mortality among 4899 patients who underwent total thyroidectomy for benign thyroid disease in Sweden and reported a twofold increased risk of death in patients with permanent hypoparathyroidism (defined as the need of active vitamin D six months after surgery). The study was based on data

retrieved from SQRTPA and SPDR, and the rate of permanent hypoparathyroidism was 5.2 %, with a mean follow-up of 4.4 years. The findings of the Swedish study conflict with those of a Danish case-control study by Underbjerg *et al.*, which demonstrated no effect of hypoparathyroidism on mortality.⁴⁷ In this study, 2064 patients with a mean follow-up of 8 years were included, and patients with hypoparathyroidism due to surgery for non-malignant causes were matched in a 1:3 ratio with age- and gender-matched controls from the general population. Permanent hypocalcemia was defined as hypocalcemic with inappropriate PTH levels necessitating treatment with treatment with calcium and/or active vitamin D six months postoperatively. These results are consistent with a smaller Scottish study by Vadiveloo *et al.*, which also reporting no increased risk of death in patients with surgical hypoparathyroidism.⁵⁶

Bergenfelz *et al.* investigated the risk of malignancy and cardiovascular events in patients with permanent hypoparathyroidism in a cohort similar to the cohort used in the study on mortality by Almquist *et al.*⁴⁰ In their population-based study on patients undergoing thyroidectomy for benign disease permanent hypoparathyroidism was associated with a doubled risk of a diagnosis of any malignancy (HR 2.15, 95% CI 1.08-4.27). Furthermore, patients with known cardiovascular disease (CVD) at the time of surgery and permanent hypoparathyroidism had almost twofold increased risk of a new cardiovascular event (HR 1.88 (1.02-3.47)). An increased risk of malignancy has been investigated in previous studies. There are contradictory findings regarding the risk of CVD, although a meta-analysis found a pooled increased risk for CVD.⁵⁷

Health-related quality of life

In the recent years, several studies have investigated the impact of permanent hypoparathyroidism on health-related quality of life (HRQoL). Permanent hypoparathyroidism has repeatedly been reported to have a negative effect on HRQoL. This is illustrated in a systemic review article by Buttner *et al.* on HRQoL in patients with hypoparathyroidism receiving conventional treatment.⁵⁸ To note, this review included only five studies, one of which lacked a clear definition and criteria for permanent hypoparathyroidism. In general, most studies evaluating the link between hypoparathyroidism and HRQoL may be influenced by biases and confounding factors. For instance, some studies compare HRQoL in patients with hypoparathyroidism to a healthy norm population, which could overstate the impact of hypoparathyroidism. Additionally, there may be selection biases in the recruitment of patients. This could be the case in a study by Arlt. *et al.*, where all patients were recruited from a tertiary unit, and in a recent multi-country study by Siggelkow *et al.*, where nearly one-third of the patients were recruited through patient associations.^{59, 60} It is likely that patients who are managed in tertiary centres and

those who are involved in patient's associations have more problematic disease.

Most previous studies on HRQoL in patients with hypoparathyroidism have employed the SF-36 questionnaire to evaluate quality of life. SF-36 is a well-established and validated survey and is frequently used in HRQoL studies.^{61, 62} However, one criticism of SF-36 is that it may not capture all the aspects and symptoms specific to hypoparathyroidism. In recent years, Wilde *et al.* have presented a questionnaire specifically for patients with hypoparathyroidism, called HPQ (Hypoparathyroid Patient Questionnaire).⁶³ Although, HPQ has not yet been validated in Sweden and there is currently no available version in Swedish.

Risk factors for hypoparathyroidism

Patient related risk factors

Among risk patient related risk factors for postoperative hypoparathyroidism, larger and retrosternal goiter, advanced thyroid cancer and female sex has been shown to be associated with postoperative parathyroid failure.^{21, 64-66} In addition, several studies have found low preoperative vitamin D to be an independent risk factor for hypocalcemia following thyroid surgery⁶⁷⁻⁶⁹, while others have not found the same association.⁷⁰ A systemic review showed that vitamin D deficiency was linked to postoperative hypocalcemia, and severe vitamin D deficiency was associated with permanent hypoparathyroidism, although a high degree of variability in the definitions of permanent hypoparathyroidism was noted among the included studies, making the result less reliable.⁷¹ Graves' disease has been shown to increase the risk of postoperative hypoparathyroidism, however there are conflicting results regarding the association between Graves' disease and the risk of permanent hypoparathyroidism.^{21, 64}

Surgical risk factors

Surgical risk factors associated with hypoparathyroidism are bilateral ligation of the inferior thyroid artery, central lymph node dissection, re-operative surgery and re-operation for re-bleeding.^{29, 39, 41, 42, 72}

The extent of surgery also contributes to the risk of hypoparathyroidism. Total thyroidectomy and near total thyroidectomy have been found to have a higher risk of complications, such as hypoparathyroidism and recurrent laryngeal nerve injury, compared to the less extensive procedure such as subtotal thyroidectomy.⁴² However, this must be balanced to the increased risk of complications in reoperations for recurrence, compared with primary surgery.⁷³ Most experts recommend total thyroidectomy or near total thyroidectomy

as treatment of choice for bilateral multinodular goiter, to reduce risk of recurrence.^{74, 75}

In situ preservation of all four parathyroid glands lower the risk of both postoperative hypoparathyroidism and permanent hypoparathyroidism.⁷⁶ According to a study by Thomusch *et al.*, the risk of hypoparathyroidism decreased if at least two parathyroid glands were identified during surgery.⁴² However, a smaller study by Sheahan *et al.* including 126 patients found the opposite result, with a significant lower incidence of clinical hypoparathyroidism in patients in whom the surgeon had identified 0-2 parathyroid glands, compared to in patients with 3-4 identified parathyroid glands (3.2 % vs 17.1%, $p=0.02$).⁷⁷

Autotransplantation of parathyroid glands can be done on a routine basis or selectively when one or more parathyroid glands accidentally have been removed or devascularized during thyroidectomy. Inadvertent parathyroidectomy has been shown to occur in 9-20% of patients undergoing TT and up to 28% in patients undergoing central neck dissection.^{23, 78} Therefore, prompt inspection of the resected thyroid gland should be done and autotransplantation is recommended in cases of accidental parathyroidectomy. Parathyroid autotransplantation has repeatedly been shown to be associated to transient hypoparathyroidism^{23, 78}. There are conflicting results regarding the effectiveness of routine autotransplantation on the risk of permanent hypoparathyroidism.^{22, 79-81}

Surgical volume has been shown to lower the risk of complications after total thyroidectomy, but most studies do not investigate the specific relationship between hypoparathyroidism and surgical volume⁸²⁻⁸⁴. Only a few studies have addressed the threshold number to define a high-volume thyroid surgeon. Adam *et al.* investigated the rate of complications in 16,954 patients undergoing total thyroidectomy in the United States and demonstrated that a surgeon volume > 25 thyroidectomies a year was associated with better outcomes. They also found that approximately 50 % of the surgeons performed only one case per year.⁸⁵ A recent study by Gray *et al.* analysed data on nearly 23,000 total thyroidectomies from UK and found higher surgeon volume was associated with reduced levels of complications, including permanent hypoparathyroidism. However, a low-volume threshold could not be defined.⁸⁴ The impact of surgical volume on the risk of complications can likely be attributed to refined surgical technique, ability to identify and safely protect the delicate structures in the neck and experience in handling more challenging cases.

Both the American Association of Endocrine Surgeons (AAES) and the European Society of Endocrine Surgeons (ESES) have concluded that there is a volume-outcome relationship, and that thyroid surgery preferably should be done by a high-volume thyroid surgeon, if possible.^{16, 86} ESES has stated that a case load of >50 thyroidectomies a year appears to be reasonable for a high-volume surgeon, whereas <25 thyroidectomies a year seems to be an appropriate threshold for low volume. There is no strong evidence for this statement,

although the association between better outcome and high-volume surgeons is plausible.

Strategies to prevent hypoparathyroidism

Surgical technique

In situ preservation of the parathyroid glands and their blood supply is critical to decrease the rate of hypoparathyroidism after thyroid surgery^{18, 87}. However, finding and preserving healthy parathyroid glands can be challenging due to their small size, variable colour and delicate blood supply. The parathyroid glands are often located in close association with the thyroid capsule, and therefore, capsular dissection of the thyroid gland is advocated by most endocrine surgeons. By commencing the dissection high on the surface of the thyroid, only smaller branches from the inferior thyroid artery will be divided, and the vascular supply to the parathyroid gland is therefore more likely to be kept intact.^{88, 89}

Furthermore, the localization of RLN and the starting point for the nerve dissection may also impact the risk of postoperative parathyroid failure. Veysseller *et al.* compared the risk of postoperative parathyroid failure depending on the level of RLN identification during thyroidectomy and found that finding the nerve high close to the entry of larynx was associated with a lower risk of postoperative hypoparathyroidism, as compared to finding the nerve low⁹⁰. The result can be explained by the extent of the nerve dissection and the potential risk of injuring the parathyroid blood supply. Finding the RLN low in the tracheoesophageal groove and following it superiorly to the entry of the larynx requires more dissection, as compared to finding the nerve high, closer to Barry's ligament. However, finding the nerve high can be challenging and since the entry of larynx is the most common place to injure to nerve, dissection here must be done with care.^{91, 92}

There is no evidence that the use of energy devices, like LigasureTM or Harmonic[®], influences the risk of postoperative hypoparathyroidism, compared to the older standard technique using clamp and tie or clips to obtain hemostasis.⁹³⁻⁹⁵

Technical aids

Indocyanine green fluorescence (ICG) and autofluorescence are two relatively new techniques, used to identify and assess the parathyroid glands during surgery. These techniques are used in some centers to facilitate the identification of the parathyroid glands and their viability during surgery.^{96, 97} Autofluorescence is considered to be superior to ICG for localizing the parathyroid glands, whereas ICG is more helpful in assessing parathyroid perfusion.⁹⁸ ICG

angiography has been proven to be helpful in predicting postoperative hypoparathyroidism and the need of supplementation.⁹⁶ However, a study by Di-Marco *et al.* showed no reduction in the incidence of missed inadvertent parathyroidectomy using autofluorescence compared to visual inspection by an experienced thyroid surgeon.⁹⁹ Additionally, a systematic review by Barbieri *et al.* revealed no reduction in long term outcomes with the use of ICG or autofluorescence.¹⁰⁰

Prophylactic supplementation

Previous studies have demonstrated that prophylactic postoperative treatment with calcium and/or active vitamin D is effective in preventing hypocalcemia in patients undergoing total thyroidectomy¹⁰¹. However, only two previous studies have investigated the use of preoperative active vitamin D. In an American study by Maxwell *et al.* preoperative treatment with calcitriol and calcium was found to be associated with reduced incidence of symptomatic hypocalcemia and length of stay.¹⁰² This is in disagreement with a study by Donahue *et al.* which showed no advantages with preoperative calcitriol and calcium.¹⁰³

Preoperative treatment with regular vitamin D (vitamin D₂ and vitamin D₃) has been shown to reduce the risk of hypoparathyroidism and is therefore recommended by some.^{24, 104} Moreover, the use of vitamin D in vitamin D deficient patients are routine and the treatment course usually lasts eight weeks to allow for the vitamin D levels to normalize.¹⁰⁵

Treatment of hypoparathyroidism

Conventional treatment

The conventional management of hypoparathyroidism involves supplemental active vitamin D and/or calcium. The goal is to keep the serum calcium within the low normal reference range, with the patient asymptomatic^{33, 106}. A further aim of the treatment is to minimize hypercalciuria.¹⁰⁷ However, although conventional therapy effectively raises serum calcium, some patient experience gastrointestinal side-effects of high doses of calcium, and the treatment can also lead to hypercalciuria with an increased risk of kidney stones and renal insufficiency³³. Furthermore, it fails to normalize bone turnover. It is unclear whether the other risks associated with permanent hypoparathyroidism are caused by the state itself, or if the treatment with high doses of calcium and/or active vitamin D also contributes.

Alfacalcidol (1 α -Hydroxyvitamin D) and Calcitriol (1 α ,25-Hydroxyvitamin D), are frequently used vitamin D metabolites. Calcitriol is the most active form of vitamin D, whereas Alfacalcidol requires 25-hydroxylation to

become active. In Europe, up to 96 % of hypoparathyroid patients are treated with Alfacalcidol.⁴⁸ The bioavailability is almost twice as high for Calcitriol than Alfacalcidol, why Alfacalcidol typically requires a higher dose.¹⁰⁸ The average dose of Alfacalcidol in hypoparathyroidism is 1 to 2 micrograms per day.¹⁰⁹ The time of onset is 1-3 days, with a duration of up to 5-7 days.¹⁰⁷ This needs to be accounted for when planning follow-up blood tests to assess withdrawal attempts of the treatment.

PTH treatment

For a long time, hypoparathyroidism was the only classic endocrine disease without an available hormone replacement. However, PTH is now available as a pharmaceutical treatment, as recombinant human PTH (1-84) and fragmented recombinant human PTH (1-34). Both drugs have been evaluated as treatment for hypoparathyroidism and been found to be effective. Patient treated with PTH (1-84) and PTH (1-34) are able to reduce the calcium and active vitamin D dose.^{110,111} These drugs are given as subcutaneous injections, with PTH (1-84) administered once daily and PTH (1-34) requiring at least twice-daily injections. While PTH (1-34) is not approved for hypoparathyroidism, it has been used in osteoporosis for several years. It is important to wean off the treatment slowly, as an abrupt stop may cause severe hypocalcemia.¹¹²

A recent randomized, double-blind, placebo-controlled phase 2 study assessing long-acting PTH (1-34) in patients with hypoparathyroidism have shown promising results. Most patients treated with PTH (1-34) were able to stop active vitamin D treatment, reduce calcium supplement, achieving normal calcium homeostasis and improved HRQoL.¹¹³ PTH (1-84) has been approved as a treatment for patients with hypoparathyroidism by both the European Medicines Agency (EMA) and the American Food and Drug Administration (FDA). This treatment is currently only available for a small number of patients with hypoparathyroidism who are not controlled on the standard therapy with active vitamin D and calcium¹⁰⁶. The high cost of this treatment, as well as lack of data on possible long-term risks, makes strict patient selection necessary.

Swedish registers

Sweden has a system of unique personal identification numbers. This in combination with a long history of national registers offers great opportunities for registry-based research.¹¹⁴ The personal identification numbers allow for cross-linking of personal data between registers. The Swedish National Board of Health and Welfare maintains several national registers related to healthcare, which are often used for research purposes. These include, among

others, the Swedish National Patient Register, the Swedish Prescribed Drug Register, and the Swedish Cause of Death Register.

In addition, Sweden also has a tradition of national quality registers. These registers are typically used both for quality improvements and for research purposes. They are recognized by the National Board of Health and Welfare and receive financial support from the Swedish State and Sweden's municipalities and regions (SKR). Data suggests that patients registered in quality registers have improved outcomes.¹¹⁵

NPR

The Swedish National Patient Register has existed since 1987 and includes all in-patient care in Sweden. From 1987 the Swedish NPR includes all in-patient care in Sweden. For over twenty years, since 2001, the register also covers out-patient care, although not primary care. The register holds data that can be divided into 4 different groups: patient information (such as personal identification number, age, gender), geographical information (such as hospital/clinic, department), administrative information (such as date of admission and discharge and length of stay) and diagnosis information (such as diagnosis and procedures). The register has been shown to have a high validity.¹¹⁶

SPDR

The Swedish Prescribed Drug Register (SPDR) was established in 2005. The register contains information on all prescribed drugs dispensed in pharmacies in Sweden. Data on ATC codes, dosages, date of prescription, as well as data on the patient and prescriber. Drugs administered in hospitals is not registered in the register. SPDR is frequently used for research.^{117, 118}

The Swedish Cause of Death Register

The Swedish Cause of Death Register comprise data on all deaths of people in Sweden since the beginning of the 1950s. It collects data on cause of death based on ICD codes, as well as the date and place of death, and information on any surgeries within four weeks before death, among other information.¹¹⁹

SQRTPA

The Swedish Quality Register for Thyroid, Parathyroid and Adrenal Surgery (SQRTPA) was started in 2004. The register contains data on patients undergoing endocrine neck- and adrenal surgery. Enrolment in the register is voluntary, however recommended by the Swedish Society for Endocrine Surgery. Data on reporting clinic, diagnosis, inpatient care, pathology and follow up are collected in the register. Follow up data are registered on day 1, week 6

and 6 months after surgery. Audits are carried out each year, at 4-6 units at the time. During the audit, 25 cases are selected randomly. Register data and data from medical records are reviewed by an assigned auditor. ¹²⁰

Aims of the thesis

The overall aim of this thesis was to study hypoparathyroidism after total thyroidectomy.

Specific aims:

- I. To examine the potential benefit of prophylactic pre-operative active vitamin D on early hypocalcemia and its symptoms after total thyroidectomy
- II. To investigate the rate and risk factors for permanent hypoparathyroidism after total thyroidectomy for benign thyroid disease in a nation-wide population-based setting.
- III. To validate the rate of permanent hypoparathyroidism found in paper II in a population-based regional cohort, using a strict definition of permanent hypoparathyroidism. Secondary aims were to investigate the relationship between the rate of early low PTH levels and the rate of permanent hypoparathyroidism, and moreover to validate the reported data on complications in SQRTPA.
- IV. To investigate health-related quality of life in patients with and without permanent hypoparathyroidism. A secondary aim was to evaluate the risk of death in patients with and without permanent hypoparathyroidism after total thyroidectomy for benign thyroid disease.

Material and methods

Paper I

This study includes all patients subjected to total thyroidectomy at Uppsala University Hospital between 2013 and 2017. Data was collected prospectively and saved in the local hospital electronic records and then extracted for analysis. Preoperative alfacalcidol was introduced as routine praxis on 1 January 2017 and based on surgery date two groups were formed. The group that received preoperative alfacalcidol was given one microgram twice daily for three days before surgery. The study aimed to compare the two groups to determine if preoperative treatment with active vitamin D reduced the risk of hypocalcemia after surgery. The primary outcome in the study was early postoperative hypocalcemia, defined as S-Ca <2.1 mmol/L day one after surgery. Secondary outcomes included any difference in S-Ca day one after surgery between groups, symptoms of hypocalcemia after surgery and length of hospital stay. Corrected calcium was used and calculated. Baseline characteristics, indication of surgery, perioperative findings and biochemical data including S-Ca, albumin and PTH were collected. Patients with concurrent parathyroid surgery, previous thyroid surgery or other major surgery were excluded, as well as those under 18 years of age.

Paper II

Paper II is a nationwide population-based retrospective study, including all patients who underwent total thyroidectomy for benign thyroid disease in Sweden from 2005 to 2015. Data was retrieved from the Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery (SQRTPA), the Swedish National Patient Register (NPR) and the Swedish National Register for Prescribed Drugs (SPDR). Permanent hypoparathyroidism was defined as treatment with calcium and/or active vitamin D more than 12 months after surgery. Data on dispensation of calcium and active vitamin D was obtained from SPDR. Treatment with Levothyroxine was used as a negative control. Patients with preoperative treatment with calcium and/or active vitamin D, thyroid malignancy, concurrent parathyroid surgery, concurrent or previous lymph node dissection, previous thyroid or parathyroid surgery or sternotomy were excluded. Center volume was calculated from total thyroidectomies

(ICD BAA60) and thyroid lobectomies (BAA40) per center in NRP and SQRTPA. Annual center volume was calculated using the total operation volume (total thyroidectomies and lobectomies) The rate and risk factors of permanent hypoparathyroidism in the cohort was investigated.

Paper III

The cohort in Paper III is based on the cohort from Paper II. A regional cohort was defined from the nationwide cohort, including all patients who underwent surgery at two University hospitals (Uppsala, Örebro) and four surrounding regional hospitals (Falun, Gävle, Karlstad, Västerås). Patients who met any of the exclusion criteria mentioned in Paper II were excluded, as well as those with missing health records at the local hospitals. Local hospital records were reviewed at the participation hospitals. Data was collected using a structured form for pre-, peri-, and postoperative information. Patients were divided into three groups; no hypoparathyroidism (group A: no hypo), definitive permanent hypoparathyroidism (group B: definitive hypo) or possible hypoparathyroidism. A strict definition was used, and patients were considered to have definitive hypoparathyroidism if they met the following criteria 12 to 24 months after surgery:

1. Low intact PTH level (below the lower limit of the local hospital's standard) accompanied by hypocalcemia (albumin corrected or ionized calcium below the lower limit of the local hospital's standard)
2. Hypocalcemia without an appropriate physiological elevation of PTH
3. At least one unsuccessful attempt to unwind calcium and/or active vitamin D supplementation

Patients were considered to have possible permanent hypoparathyroidism if they remained on supplementation and had no documented attempt to unwind the supplementation between 12 and 24 months after surgery, or if they remained on supplementation at the time of loss in follow-up.

Data on postoperative bleeding and surgical site infection (SSI) was retrieved from the local hospital records. Postoperative bleeding was defined as the need of re-operative surgery due to bleeding, and the diagnosis of SSI was left to the discretion of the attending surgeon or physician. Patients were considered to have an SSI if this was noted in the charts within 30 days after surgery. Permanent recurrent laryngeal injury was defined as vocal cord paresis or palsy on laryngoscopy more than 12 months after operation. Patients

without a documented laryngoscopy in the local health records were registered as missing data

Comparisons between group A (no hypo) and group B (definitive hypo) were made to analyse patient characteristics, the relation between immediate low postoperative PTH (defined as a S-PTH 1-24h post-surgery) and permanent hypoparathyroidism. The agreement between the reported rate of complications in SQRTPA and local hospital records were investigated.

Paper IV

This study is based on the cohort from Paper III and aims to evaluate the impact of permanent hypoparathyroidism on HRQoL. All patients from the regional cohort in Paper III were assessed for eligibility to participate in this study, and all eligible patients were invited to participate. An invitation letter containing study information, a consent form and a HRQoL questionnaire was sent out on 26 August 2021. An identical letter was sent out to all non-responders after 4 weeks. The participating patients could either fill-out the paper questionnaire received with the invitational letter, or chose to complete the questionnaire at a platform, U-CARE, a web portal provided by Uppsala University. Data on deaths and date of death was collected from the Swedish Cause of Death Register. HRQoL was evaluated with the Swedish version of SF-36 v.2, using the 4-week recall questionnaire.

SF-36 v2. is a survey designed to capture patients' perception on their own health and well-being. The questionnaire consists of 36 questions and measures eight domains; physical functioning (PF), role physical functioning (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH). Out of the domains two component scores are created, physical component score (PCS) and mental component score (MCS).

SF-36 data were scored and recoded according to SF-36v2 user's manual.¹²¹ Using the scoring algorithm, scales raw scores were transformed to a scale score range from 0-100. The transformed scale scores were standardized to a mean score of 50 and a standard deviation of 10, to allow comparisons between studies. The average norm range for group-level results is a mean T-score between 47 and 53. A higher score signifies a better health related quality of life. Missing data, i.e., incomplete responses within the items of the domain, entailed exclusion from the said domain. For the summary scores, PCS and MCS, only patients with complete responses within all domains were included.

Differences in HRQoL were compared between patients with definitive permanent hypoparathyroidism and those with no permanent hypoparathyroidism. Mortality was assessed in all patients eligible for participation, again comparing patients with definitive permanent hypoparathyroidism and those

without hypoparathyroidism. Data on deaths and date of death was collected from the Swedish Cause of Death Register.

Statistics

Basic statistics

Continuous variables were presented as mean (\pm SD), median (range) or interquartile range (i.q.r). For unmatched data, differences between groups were analysed with Chi Square Test and Fischer's exact test to compare proportions and Student's t-test and Mann-Whitney U test to compare continuous data, as appropriate. For matched data, differences between groups were analysed with McNemar-Bowker test to compare proportions and Paired-samples t-test and Wilcoxon sign test to compare continuous data, as appropriate. Univariate and multivariate logistic regression was used to identify categorical variables associated with permanent hypoparathyroidism, presented as odds ratio (OR) with 95% confidence interval (CI). Statistical significance was defined as $p < 0.05$. Statistical analysis was carried out with SPSS version 22 and 28 (IBM, Armonk, New York, USA).

Propensity score matching

In paper I, propensity score matching was used to minimize the effect of possible confounding variables and create two comparable groups.^{122, 123} The propensity score was calculated based on the following characteristics: age, sex, S-Ca before surgery, indication for surgery, type of operation, number of parathyroid glands identified, parathyroid autotransplantation, operating time, and thyroid weight. A caliper width of 0.05 was used to match the groups in a 1:1 ratio. Standardized mean difference (SMD) was calculated to indicate differences between the groups.

Survival analysis

Kaplan Meier curves were constructed for visual demonstration of survival in patients with and without permanent hypoparathyroidism and compared using log rank test. Time was calculated from date of surgery until 19 April 2019 or date of death. Risk of death in patients with permanent hypoparathyroidism was evaluated by Cox regression, yielding hazard ratios (HR) with 95 % CI.¹²⁴

Ethical considerations

Paper I

Approved by the Swedish Ethical Review Authority on 24 February 2021. (Diary no. 2021-00402).

Paper II

Approved by the Regional Ethical Committee in Uppsala on 30 November 2016 (Diary no. 2016/479).

Paper III

Approved by the Regional Ethical Review Board of Uppsala on 30 November 2016 (Diary no. 2016/479) and from the Swedish Ethical Review Authority on 23 November 2020 (Diary no. 2020-05744).

Paper IV

The study was approved by the Swedish Ethical Review Authority on 23 April 2021 (Diary no. 2021-01997).

Results

Paper I

A total of 401 patients were included. A 1:1 propensity score matched resulted in 108 patients in each group. Preoperative treatment with active vitamin D reduced the risk of hypocalcemia (S-Ca <2.1 mmol/L) postoperative day one ($p < 0.001$). The treated group also had a higher mean serum calcium day one after surgery (2.32 vs 2.27, $p = 0.022$) and a shorter length of stay in hospital ($p < 0.001$). There was a trend with fewer cases experiencing symptoms of hypocalcemia after surgery in the treated group, however this did not achieve statistical significance ($p = 0.099$). Nil in the treated group and four in the non-treated group had serum calcium below 2.00 mmol/L, however there was no significant difference between the groups.

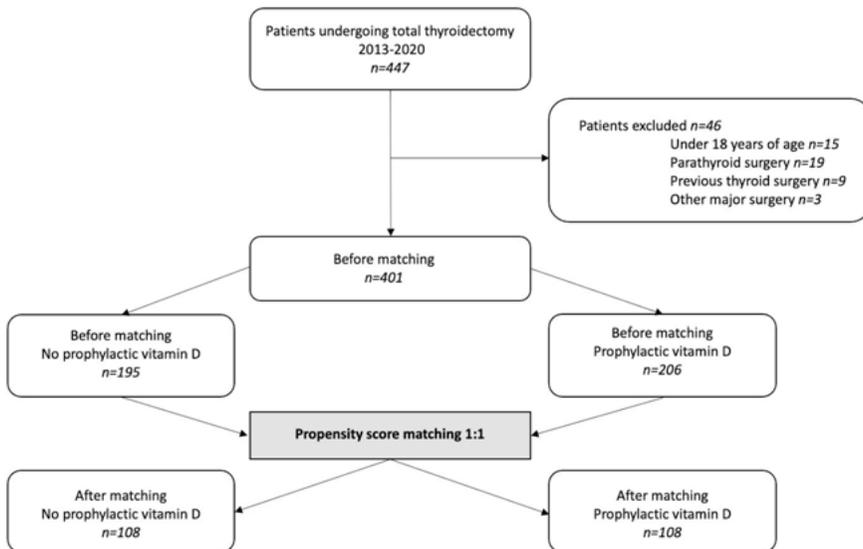


Figure 3. Study population diagram

Table 2 Results before and after matching

Patient variables	Before matching			After matching		
	Preop vitamin D n=206	No preop vitamin D n=195	P-value	Preop vitamin D n=108	No preop vitamin D n=108	P-value
PTH one hour postop, ^{‡‡} mean (SD) pmol/L	2.0 (1.4)	2.6 (2.3)	0.002*	1.8 (1.2)	2.5 (2.2)	0.011**
PTH one hour postop, pmol/L ^{‡‡}						
<1.6	94 (46.8)	79 (41.4)	0.283 [†]	51 (51.0)	45 (45.0)	0.480 [¶]
≥1.6	107 (53.2)	112 (58.6)		49 (49.0)	55 (55.0)	
S-Ca day one postop, mean (SD), mmol/L ^{††}	2.33 (0.14)	2.27 (0.14)	<0.001*	2.32 (0.15)	2.27 (0.15)	0.022**
S-Ca day one postop, mmol/L ^{††}						
<2.00	0 (0.0)	5 (2.6)	0.061 [‡]	0 (0.0)	4 (3.8)	0.083 [¶]
≥2.00	188(100)	184 (97.4)		97 (100.0)	102 (96.2)	
S-Ca day one postop, mmol/L ^{††}						
<2.10	5 (2.6)	16 (8.2)	0.023 [†]	2 (2.1)	10 (9.4)	<0.001 [¶]
≥2.10	183 (88.8)	173 (88.7)		95 (97.9)	96 (90.6)	
Hospital stay, days, median (i.q.r)	1 (1-1)	1 (1-2)	<0.001 [§]	1 (1-1)	1 (1-2)	<0.001 [#]
S-Ca at 4-6-week follow-up, mean (SD) mmol/L ^{††}	2.38 (0.13)	2.38 (0.16)	0.950*	2.37 (0.13)	2.37 (0.12)	0.514**
Symptoms of hypocalcemia from surgery to follow-up						
Yes	34 (17.8)	51 (27.7)	0.022 [†]	18 (18.9)	29 (30.5)	0.099 [¶]
No	157 (82.2)	133 (72.3)		77 (81.1)	66 (69.5)	
Permanent hypoparathyroidism						
Yes	12 (6.2)	15 (8.2)	0.450 [†]	6	6	1 [¶]
No	183 (93.8)	169 (91.8)		92	92	
Reoperation for bleeding						
Yes	3 (1.5)	5 (2.6)	0.428 [‡]	2 (1.9)	3 (2.8)	1 [¶]
No	203 (98.5)	190 (97.4)		106 (98.1)	105 (97.2)	
Surgical site infection						
Yes	15 (7.3)	9 (4.7)	0.303 [†]	6	4	0.754 [¶]
No	190 (92.7)	183 (95.3)		100	102	

SD indicated standard deviation; PTH, parathyroid hormone; S-Ca, corrected serum calcium; i.q.r, interquartile range. *Student's t test. †Chi-squared test. ‡Fishers exact test. §Mann-Whitney U test. ¶McNemar-Bowker test, two-sided. #Wilcoxon signed rank test. **Paired samples t test. ††Reference range 2.15-2.50 mmol/l. ‡‡Reference range 1.6-6.9 pmol/l.

Paper II

A total of 7852 patients were included, as seen in Fig. 6. In total, 938 (12.5%) developed permanent hypoparathyroidism.

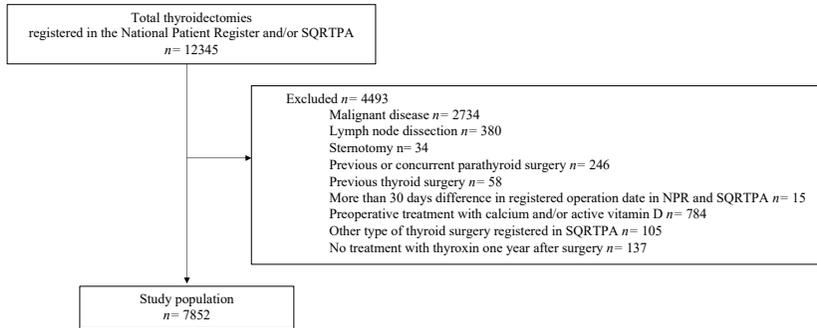


Figure 4. Study flow chart

The risk of permanent hypoparathyroidism was lower in patients registered in SQRTPA (11.0 % vs 16%, $p < 0.001$). Independent risk factors for permanent hypoparathyroidism were: surgery at units with a center-volume < 100 thyroidectomies per year (OR 1.22; 1.03-1.44), parathyroid autotransplantation (OR 1.72; 95% CI 1.47-2.01), age above 60 year (OR 1.64; 1.36-1.98) and female sex (OR 1.27; 1.05-1.54). Reported data from SQRTPA only identified 178 of all 938 patients with permanent hypoparathyroidism. Dispensing data of prescribed calcium and active vitamin D from SPDR showed no sign of recovery from year 1 after surgery and onwards (Fig 7).

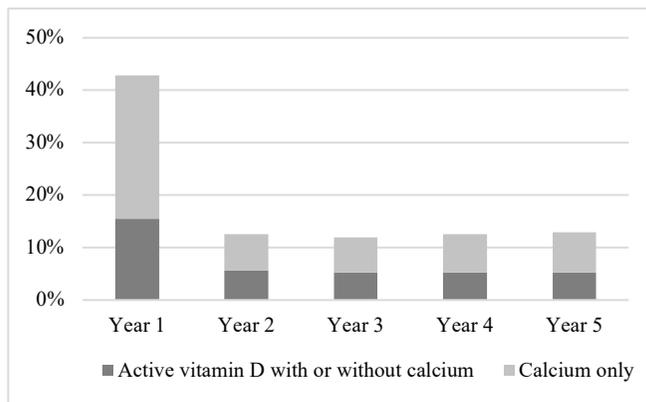


Figure 5. Treatment with active vitamin D and calcium after total thyroidectomy. Dispensing data from the Swedish Prescribed Drug Register.

Table 3. Multivariable analysis of risk factors for permanent hypoparathyroidism

Baseline variables	Permanent hypoparathyroidism OR (95% CI)	p-value
Age		
<40 years	ref.	
40–60 years	1.10 (0.93-1.29)	.26
>60 years	1.64 (1.36-1.97)	<.001
Sex		
Female	1.27 (1.05-1.54)	.02
Male	ref.	
Registration in SQRTPA		
Yes	ref.	
No	3.84 (0.52-28.6)	.19
Center volume per year		
>100	ref.	
≤ 100	1.21 (1.03-1.43)	.02
Parathyroid autotransplantation		
Yes	1.71 (1.46-2.01)	<.001
No	ref.	
Indication of surgery		
Thyrotoxicosis	ref.	
Compression symptoms	1.01 (0.88-1.38)	.41
Excluding malignancy	1.09 (0.73-1.64)	.67
Recurrent cyst	1.41 (0.31-6.38)	.66
Other indication	0.39 (0.05-2.96)	.37
No data ^a	0.28 (0.04-2.08)	.21
Duration of surgery		
<90 min	ref.	
90-150 min	0.87 (0.66-1.14)	.32
>150 min	1.15 (0.86-1.55)	.36
No data ^a	1.18 (0.85-1.63)	.33
Thyroid weight		
<25 g	ref.	
25-70 g	1.22 (0.94-1.58)	.14
>70 g	1.20 (0.88-1.63)	.24
No data [^]	1.49 (1.12-1.98)	.01

^aPatients not registered at all, or missing data in SQRTPA. OR indicates odds ratio; CI, confidence interval; SQRTPA, Scandinavian quality register for thyroid, parathyroid and adrenal surgery.

Paper III

A total of 1636 patients were included in the study. Altogether, 143 (8.7%) patients developed definitive or possible permanent hypoparathyroidism. Out of these, 102 (6.2%) patients had definitive permanent hypoparathyroidism, while 41 (2.5%) patients had possible permanent hypoparathyroidism, as a result of lacking attempts to unwind the treatment (n=28) or loss of follow-up (n=13).

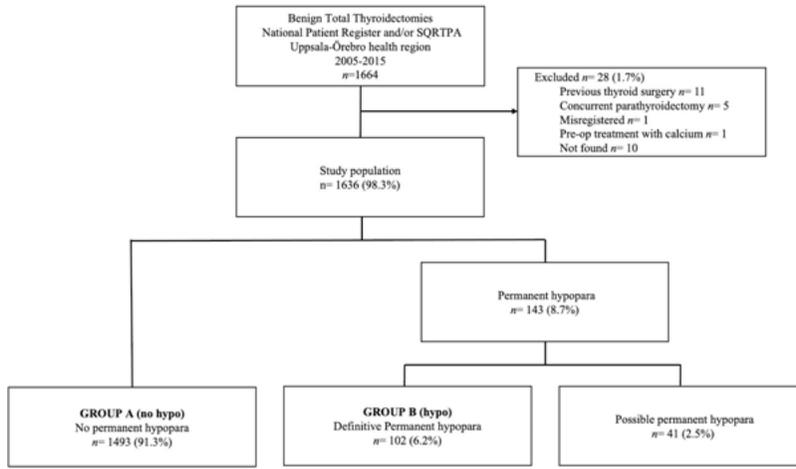


Figure 6. Study flow chart

A proportion of 23.2 % with a low early PTH below the reference corresponded to a 6.7% rate of permanent hypoparathyroidism, among patients with a documented PTH within 24 h after surgery.

Table 4. PTH values 1-24 hours after surgery

PTH 1-24 hours after surgery	Definitive permanent hypoparathyroidism n=42 (6.7%) [^]	No permanent hypoparathyroidism. n=528 (93.3%) ^{^^}	p-value
Below lower ref limit	39 (26.9)	106 (73.1)	<0.01
Within or above ref. interval	3 (0.6)	476 (99.4)	

Values are number (percent). [^]Missing data on PTH n=61, ^{^^}Missing data on PTH n=911. PTH indicates Parathyroid hormone; Ref, reference

During the study period, 1306 (79,8%) patients were registered in SQRTPA. Among these, 85 (6.5%) patients were found to have definitive permanent hypoparathyroidism according to the study definition, compared to 62 (4.7%)

patients with registered permanent hypoparathyroidism in SQRTPA and 124 (9.5%) patients using the definition of permanent hypoparathyroidism applied in Paper II. SQRTPA identified 45.9% (n=39) of the patients with definitive hypoparathyroidism and the agreement in total between the study definition of definitive hypoparathyroidism and the reported data in SQRTPA was 29.3%. The agreement between the reported data in SQRTPA and the data collected in the chart review was 91.3 % for reoperation due to rebleeding, 14.3 % for surgical site infection and 60.0% for permanent RLN injury.

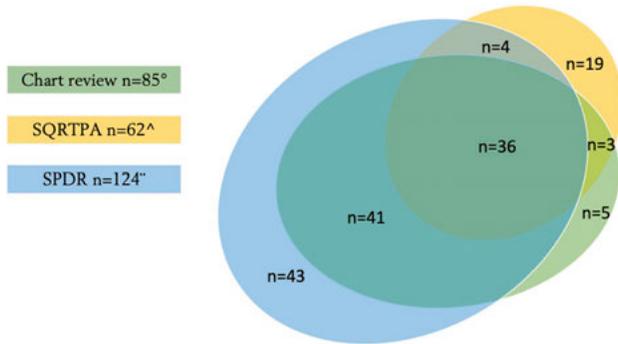


Figure 7. Agreement on diagnosis of permanent hypoparathyroidism- Chart review vs. SQRTPA vs. SPDR. Only including patients registered in SQRTPA (n=1306). Patients with possible hypoparathyroidism excluded (n=41). Missing data on permanent hypoparathyroidism in SQRTPA (n=165). SQRTPA indicates Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal surgery; SPDR, Swedish Prescribed Drug Register. Definitions of permanent hypoparathyroidism: °Chart review: Low PTH and hypocalcemia or low calcium with inappropriate normal PTH or at least one unsuccessful attempt to unwind the supplementation (def in Paper III); ^SQRTPA: Need of calcium and/or active vitamin D 6 months after surgery; **SPDR: Dispensation of calcium and/or active vitamin D > 12 months after surgery (def. in Paper II)

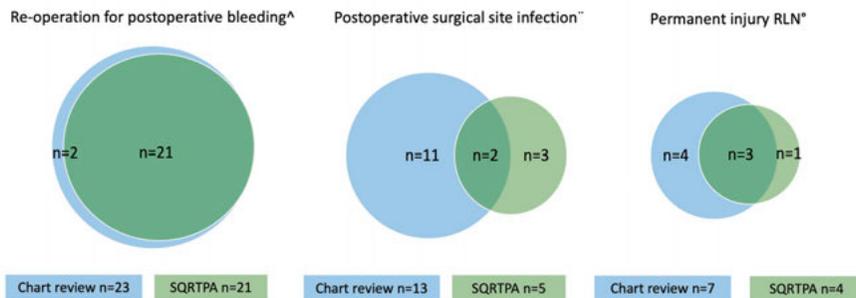


Figure 8. Agreement between chart review and SQRTPA. Only including patients registered in SQRTPA, n=1306. Patients with possible hypoparathyroidism excluded (n=41). ^Missing data on re-operative surgery for postoperative bleeding in SQRTPA, n=10, ™ Missing data on surgical site infection in SQRTPA, n=7, ° No laryngoscopy performed according to SQRTPA, n=826. RLN indicates recurrent laryngeal nerve

Paper IV

Results

All patients from the regional cohort in Paper III were assessed for eligibility. Out of 1636 patients, 1483 patients were eligible and invited to participate in the study. In total 716 (48.3%) patients answered the SF-36 v2 questionnaire and were enrolled in the study. Patient characteristics did not differ between responders and non-responders, with the exception that non-responders were younger (mean age 44.5 (SD±15.1) vs 42.4 (SD±15.7) years, $p=0.008$)

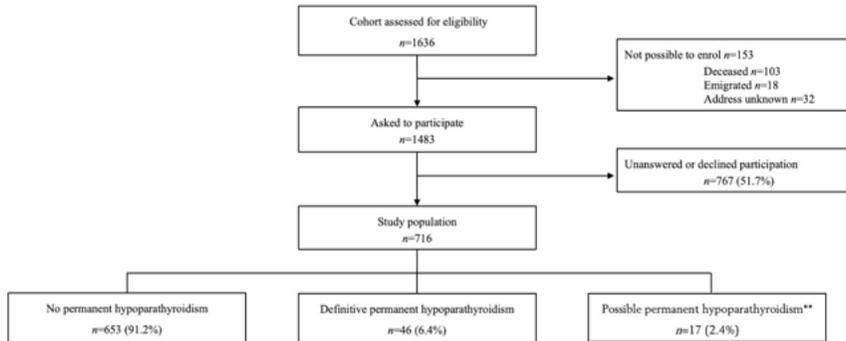


Figure 9. Study flow chart ** This group was excluded from the analysis as the diagnosis of permanent hypoparathyroidism was ambiguous

Among the responders, the mean age at surgery was 44.5 (SD ±15.1) years and 84.5 % were female. Overall, 473 (67.7%) underwent surgery because of thyrotoxicosis and 202 (28.9%) because of compression symptoms. Mean-follow up was 10.9 (SD ±3.2) years. All patients received conventional therapy with calcium and active vitamin D.

Patients with and without permanent hypoparathyroidism did not differ in baseline characteristics, with the exception that patients with permanent hypoparathyroidism were younger (mean age 35.8 (SD ±14.4) vs. 45.7 (SD ±15.0) years, $p<0.001$). The results of the SF 36 v.2 questionnaire revealed no difference between the groups regarding all health domains and the summary component scores

Table 5. SF-36 v2 health domains and summary component scores

Domain	Total cohort Mean (\pmSD)	Permanent hypo- parathyroidism Mean (\pmSD)	No permanent hypo- parathyroidism Mean (\pmSD)	p-value^ˆ	N
PF	48.51 (10.4)	50.17 (10.08)	48.39 (10.3)	0.247	681
RP	47.75 (11.48)	50.10 (10.08)	47.58 (11.56)	0.151	685
BP	48.33 (12.63)	48.46 (12.79)	48.32 (12.63)	0.944	684
GH	44.21 (11.97)	44.96 (12.20)	44.96 (12.20)	0.661	686
VT	45.64 (13.19)	46.06 (12.11)	45.55 (13.27)	0.826	684
SF	45.68 (12.55)	45.58 (11.81)	45.69 (12.61)	0.954	688
RE	45.88 (13.02)	48.27 (11.70)	45.71 (13.10)	0.198	686
MH	46.8 (11.97)	46.75 (11.66)	46.82 (12.00)	0.972	688
PCS	48.17 (11.14)	49.15 (10.96)	48.10 (11.16)	0.540	641
MCS	45.49 (13.42)	45.65 (11.41)	45.47 (13.57)	0.930	641

Means are presented in T scores (Standard Deviation). ^ˆComparing the group with definitive permanent hypoparathyroidism with the group without permanent hypoparathyroidism. PF indicates Physical Functioning; RP, Physical Role Functioning; BP, Bodily Pain; GH, General Health; VT, Vitality; SF, Social Functioning; RF, Role Emotional; MH, Mental Health; PCS, Physical Component Score; MCS, Mental Component Score

Both patients with and without permanent hypoparathyroidism had lower scores in all health domains compared to a healthy Swedish population⁶².

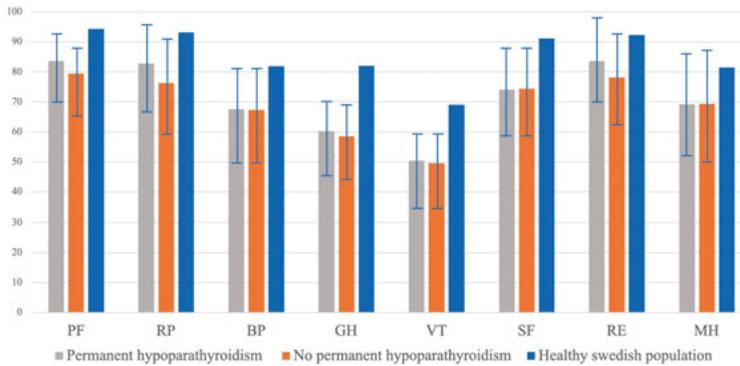


Figure 10. SF 36 v2 health domain sum scores in comparison with a healthy Swedish reference population. Mean values with estimates, with SF-36v2 health domains presented in sum scores. Scores from healthy Swedish reference population included.⁶² PF indicates Physical function; RP, Physical Role functioning; BP, Bodily Pain; GH, General Health; VT, Vitality; SF, Social Functioning; RE, Role Emotional; MH, Mental health.

Mortality was evaluated in the total cohort assessed for eligibility for participation, after excluding the group with possible permanent hypoparathyroidism (n=1596). During follow-up, 58 (3.6%) patients died. There was no significant difference in survival between patients with permanent hypoparathyroidism and patients without. (HR 1.009; 95% CI 0.31.3.24). A sensitivity analysis that included only those treated with active vitamin D (monotherapy or in combination with calcium) was made, yet no difference in overall survival was found between the two groups.

Discussion

This thesis focuses on different aspects of hypoparathyroidism after total thyroidectomy for benign thyroid disease. Total thyroidectomy is a common procedure and is nowadays considered to be associated with low risks of complications. Nonetheless, iatrogenic postoperative hypoparathyroidism and hypocalcemia continues to be a clinical problem, carrying both short- and long-term consequences for the affected patients and health-care system.

A strategy to reduce postoperative hypocalcemia

Hypocalcemia is the most common complication after thyroidectomy and the main reason for protracted stays in hospital after thyroidectomy. In Sweden, as well as other high-income countries, there has been a reduction in hospital bed capacity in the past two decades.^{125, 126} The decreasing number of hospital beds has led to the need of timely discharges to improve bed turnover. While most total thyroidectomies are still performed as inpatient procedures, some centres are adopting ambulatory or 23-hour surgery.¹²⁷

To address these challenges and improve patient care, a new clinical routine was introduced in 2017 at Uppsala University Hospital for all patients undergoing total thyroidectomy. As part of this routine, patients were started on prophylactic, preoperative, high dose of Alfacalcidol three days before surgery in an attempt to prevent postoperative hypocalcemia and delayed discharges. The objective of paper I was to evaluate the effect of this routine on biochemical postoperative hypocalcemia after total thyroidectomy, and to investigate its impact on length of stay and hypocalcemic symptoms.

Paper I demonstrated a significant decrease in hypocalcemia day one after surgery and shorter length of stay in the treated group. This result is in disagreement with a RCT by Donahue *et al.*, which found no significant difference in either length of stay or hypocalcemia. However, it is consistent with the result in a retrospective cohort study by Maxwell *et al.*^{102, 103} Notably, the protocols used in these studies also included calcium and had significantly lower doses of active vitamin D, compared to the dose of active vitamin D used in Paper I.

The rate of hypocalcemia, reported in Paper I was substantially lower compared to findings in other studies. These differences can likely be attributed to

a variety of factors, such as differences in the routines for postoperative supplementation, early PTH measurement, and the rate of parathyroid preservation. Early postoperative PTH measurement allows for the identification of patients at risk of hypocalcemia, thereby enabling an early start of supplementation to avoid this. The routine in our department is to measure PTH one hour after surgery.

Interestingly, PTH was significantly lower in the treated group. There could be at least two explanations for this. First, it could be a consequence of the high dose of Alfacalcidol. As vitamin D deficiency leads to an elevated level of PTH, a boost of active vitamin D could possibly cause a decrease in PTH levels in patients with vitamin D deficiency.¹²⁸ Secondly, it could reflect a higher number of patients with parathyroid failure. Regardless, preoperative treatment with active vitamin D will not decrease the risk of parathyroid injury, but the risk of developing hypocalcemia in patients with hypoparathyroidism.

Prophylactic treatment with active vitamin D in all patients undergoing total thyroidectomy will inevitably lead to overtreatment since most patients do not develop postoperative hypoparathyroidism. However, the treatment is easy to manage and its duration is short. No adverse effects were noted and no patient required re-admission within 30 days due to hypocalcemia. The potential cost-benefit is in favour of prophylactic treatment, as the cost for three days of treatment with Alfacalcidol according to the protocol is around 0.60 Euro per patient in Sweden. This needs to be compared to the cost for a hospital bed in Sweden, which exceeds this cost by at least a thousandfold, making the cost for Alfacalcidol negligible if even a single bed can be spared.

One of the greatest strengths in this study was the relatively high number of patients included and the propensity score matching to reduce bias when comparing the two groups.^{123, 129} However, since matching reduces the sample size, it is possible that a part of the cohort, significant for the outcome, was excluded from the analysis. Additionally, propensity score matching can only adjust for measured confounding variables, and there may be unknown confounders that were missed.^{130, 131}

The fact that the two groups underwent surgery at different time periods is a limitation, as some outcome data, such as length of stay, can be difficult to evaluate. Therefore, further studies are necessary and a randomized controlled trial (RCT) would be ideal to confirm whether preoperative supplementation with active vitamin D reduces postoperative hypocalcemia and length of stay after surgery. Until such data are available, the protocol used at Uppsala University Hospital is still in place.

Rates and risk factors

The lack of a standardised definition of hypoparathyroidism is indeed problematic and makes data interpretation and comparisons difficult. While single-center studies have shown low rates of postoperative parathyroid failure, an emerging number of multicenter and registry-based nationwide studies have demonstrated higher rates of hypoparathyroidism, as presented in Table 1. As previously mentioned, there can be multiple reasons for the wide variation in the reported rates of surgical hypoparathyroidism in the literature.

Sweden's long history of maintaining population-based healthcare registers offers unique possibilities for conducting register-based research. The aim of Paper II was to investigate the rate of permanent hypoparathyroidism in a population-based setting using register-based data. All patients undergoing total thyroidectomy for benign thyroid disease in Sweden during more than a decade were included in the study. We chose to include only benign disease to make the cohort more homogenous. Treatment with calcium and/or active vitamin D more than 12 months after surgery was used as a surrogate for permanent hypoparathyroidism, and information on prescription and dispensation of these drugs was obtained from SPDR.

The high rate of permanent hypoparathyroidism of 12.5% was surprising, although not unique.^{37, 39, 42} Moreover, no signs of recovery were seen, as the dispensation of calcium and active vitamin D in SPDR showed minimal change from the first year after surgery and onwards. In Sweden, all prescribed drugs dispensed at pharmacies are registered in SPDR, making the data from SPDR highly reliable. A drug prescription is valid for one year, making prescriptions and dispensations of calcium and active vitamin D done more than one year after surgery less likely to be attributed to transient hypoparathyroidism. The exclusion of all patients with preoperative treatment with calcium and active vitamin D, reduced the likelihood of patients being treated with these supplementations for other reasons than hypoparathyroidism. Furthermore, a sensitivity analysis, which excluded all patients with a pre- or postoperative diagnosis of osteoporosis and kidney failure, did not substantially alter the rate.

Undergoing surgery at a unit with an annual center-volume <100 thyroidectomies was found to be an independent risk factor for permanent hypoparathyroidism. This finding is concerning, given that only four centers had a total volume of > 100 thyroidectomies per year. The relationship between surgeon-volume and improved outcome has been highlighted in the literature previously, however the association between center-volume and risk of complications is less clear.⁸⁶ The largest study evaluating the impact of volume and outcome in neck surgery was conducted by Loyo *et al.* They retrospectively analysed almost 900,000 patients undergoing neck surgery over a 15-year period in the United States using data from the Nationwide Inpatient Sample (NIS) register. They found that postoperative hypocalcemia was less likely to

occur in patients operated by high-volume surgeons and at high-volume centers. However, after adjusting for surgeon-volume, center volume had no impact on the rate of hypocalcemia.¹³² A systemic review by Melfa *et al.* published in 2018 concluded that high-volume surgeons had the best outcome in terms of complications, while high-volume centers had mainly shorter hospital stays and lower costs.¹³³ The individual surgeon-volume was not possible to examine in our study as this data was not available in the registers. However, it is possible, maybe even likely, that high volume-centers are a surrogate for high volume-surgeons.

Parathyroid autotransplantation was also found to be an independent risk factor for permanent hypoparathyroidism in Paper II. Parathyroid autotransplantation can be performed either by routine or selectively. Selective use of parathyroid autotransplantation is uncontroversial and should be done whenever parathyroid glands are inadvertently removed during a thyroidectomy. However, a surgical dilemma is when to decide on autotransplantation of *in situ* parathyroid glands with suspected injured vascular supply, as discoloured glands may have a normal or only transient impaired function.¹³⁴

Whether routine parathyroid autotransplantation increases or decreases the risk of permanent hypoparathyroidism is debatable. Much of the literature on parathyroid autotransplantation focuses on autotransplantation in patients with underlying hyperparathyroidism, and the findings in these studies may not be translatable to the success rate of autotransplantation of normal parathyroid glands. Only a few studies have investigated the association between routine parathyroid autotransplantation in patients undergoing total thyroidectomy and preoperative normal parathyroid function, with varying results.^{79, 135}

Paper II has some limitations due to its retrospective study design and the absence of biochemical data, such as S-Ca and PTH. Furthermore, since treatment with calcium and active vitamin D was used as a surrogate for permanent hypoparathyroidism, it cannot be excluded that some patients were prescribed these drugs for other reasons than permanent hypoparathyroidism. Nevertheless, the strength of the study is the population-based cohort, including all patients undergoing total thyroidectomy for benign thyroid disease in Sweden for over 10 years, along with the crosslinking with SPDR, which provides a complete follow-up with reliable data.

The high rate of permanent hypoparathyroidism found in Paper II was striking and surprising, and prompted us to consider several possible explanations. Could the high rate be due to overtreatment resulting from lacking attempts to unwind the supplementation? Did some patients actually have other indications for the treatment with calcium and active vitamin D? Or was the rate of permanent hypoparathyroidism truly this high? The ideal way to answer these questions would be to reassess all patients considered to have permanent hypoparathyroidism in paper II. This would require performing biochemical tests, attempts to unwind the treatment in all patients with questionable diagnosis of permanent hypoparathyroidism and considering other reasons for the

treatment. However, this would be an enormous undertaking that would require significant resources. Furthermore, it could raise some ethical issues. Another possibility to confirm the high rate of permanent hypoparathyroidism would be to conduct a prospective, population-based cohort study. This would be an excellent option to answer our questions. Although, the drawbacks with this approach are the long timeframe needed, inevitable costs and possible challenges in recruiting participating centres.

Therefore, in Paper III, we proceeded with a retrospective chart review study of a regional cohort, based on the nationwide cohort in Paper II. In this population-based study of 1636 patients, we could conclude that 8.7 % had definitive or possible permanent hypoparathyroidism. This should be compared with a rate of 11.0% in the same regional cohort, using the definition of permanent hypoparathyroidism stated in Paper II. In other words, the definition of permanent hypoparathyroidism used in Paper II slightly overestimated the risk of permanent hypoparathyroidism, even though the rate was still found to be remarkably high. Using a strict definition of definitive hypoparathyroidism, including calcium and PTH levels and data on attempts to unwind the treatment, 6.2 % were found to have definitive permanent hypoparathyroidism. Additionally, 2.5 % were found to have possible permanent hypoparathyroidism. Of these, 1.7 % (n=28) remained on treatment with calcium and/or active vitamin D 12 to 24 months after surgery, but had no documented attempts to unwind the treatment. Consequently, these patients with may or may not have permanent hypoparathyroidism. This is problematic since they might be overtreated, generating both costs and use of unnecessary resources, as well as potential side effects and long-term consequences of the treatment.

Moreover, Paper III, proposes that the rate of patients with low early post-operative PTH (PTH below the lower limit of the reference interval within 1-24 hours after surgery) may correspond to the rate of permanent hypoparathyroidism within a cohort. We found that the proportion of 23.2 % (95% CI; 20.0-26.8%) of the patients having a low early PTH, corresponded to 6.7 % (95% CI; 4.9-9.0%) of the patients developing definitive permanent hypoparathyroidism. The relationship between the rate of low early PTH after total thyroidectomy and the rate of definitive permanent hypoparathyroidism should, of course, be validated in other cohorts. If further studies conform the results using equally strict definitions of permanent hypoparathyroidism and rigorous follow-up, the rate of patients with early low PTH after surgery could serve as a surrogate for evaluating the quality and effectiveness of new techniques used to maintain normal parathyroid function during surgery.

PTH measurement was not routinely used in the early years of the study and was introduced during different time periods at the participation hospitals. Moreover, the reference interval for both PTH and calcium measurement differed during the study period and also in between the hospitals. We acknowledge that this might be a limitation. We therefore chose to classify PTH and calcium as below, within or above the reference interval at the

participating hospital. In the setting of this study we believe this information to be sufficient for the diagnosis of permanent hypoparathyroidism and for the analysis comparing the relationship between the rate of low early PTH and the rate of permanent hypoparathyroidism.

The coherence between the reported data in SQRTPA and the collected data from medical records was found to be high for reoperation due to rebleeding, but low for follow up data regarding surgical site infection, permanent RLN injury and permanent hypoparathyroidism. This suggests that follow-up data in SQRTPA on these complications should be interpreted with some caution. However, the mismatch between the rate of permanent hypoparathyroidism found in this study and SQRTPA may be explained by the difference in the definition of permanent hypoparathyroidism. While Paper III defines permanent hypoparathyroidism as parathyroid dysfunction more than 12 months after surgery, the cut off used in SQRTPA is 6 months after surgery. The fact that some patients will recover their parathyroid function after 6 months, could explain the proportion of patients with registered permanent hypoparathyroidism solely in SQRTPA.

Given the fact that this study is a retrospective chart review there are some disadvantages with this methodology that needs to be pointed out.¹³⁶ First, the data relies on the accuracy of the written record. Secondly, important data may not be available. As some of the older charts in Paper III were written in paper and later scanned into electronic records, it is possible that some information has been lost in that transition. Thirdly, bias can be difficult to control as the chart review is not blinded or randomized. Some of these factors are impossible to adjust for, however we tried to minimize misclassification bias with the use of a structured form for the data collection.

The strengths of this study are the population-based study design and the strict definition of definitive permanent hypoparathyroidism, including both biochemical data on PTH and calcium, as well as information about documented attempts to unwind the treatment.

The findings in Paper II and Paper III have shown a high risk of permanent hypoparathyroidism after total thyroidectomy, which is in line with most previous multicenter and register-based studies. Further, the findings also call attention on the need of a strict diagnosis of permanent hypoparathyroidism, including both biochemical data and attempts to unwind the treatment. Without the use of these criteria there is an obvious risk of overtreatment and misdiagnosis.

Quality of life

In recent time, there has been an increased focus on the impact of permanent hypoparathyroidism on HRQoL. However, most previous studies have either compared patients with hypoparathyroidism to the general population or to are

subjected to possible bias and confounders. After having established a population-based cohort with definitive permanent hypoparathyroidism in Paper III, we wanted to proceed with a study on the HRQoL. In Paper IV we use the same cohort and definitions as in Paper III and compare HRQoL in patients with and without hypoparathyroidism. This is the first study to investigate quality of life in patients with permanent hypoparathyroidism in Sweden.

No difference in HRQoL was found when comparing patients with definitive hypoparathyroidism and patients without permanent hypoparathyroidism, in either of the eight health domains or the summary component scores.

This finding is in conflict with previous studies displaying a lower quality of life in patients with hypoparathyroidism.⁵⁸ As mentioned before, there may be several reasons for this. Some studies have found hypoparathyroidism to be associated with an impaired quality of life by comparing the HRQoL outcome to a norm population.^{53, 137, 138} This approach will likely overestimate the impact of permanent hypoparathyroidism. As shown in Paper IV, both patients with definitive permanent hypoparathyroidism and no hypoparathyroidism had lower summary score in all health domains compared to previously established norms in a healthy Swedish population.⁶² This could possibly be attributed to other complications to the surgery, as hypothyroidism, voice impairment, bad scarring, or autoimmune conditions, which sometimes are associated to Graves.¹³⁹ Moreover, the inclusion of patients with thyroid cancer in other studies may also impact the outcome.^{140, 141} Selection bias is another issue. Two previous studies, one by Arlt *et al.* and the second by Siggelkow *et al.*, recruited the patient cohorts through a tertiary unit and partly through patient's associations, respectively, making it likely that they included patients with more severe hypoparathyroidism.^{59, 60}

A recent Danish study by Jørgensen *et al.* evaluated a similar, yet smaller, cohort to ours, also using a strict definition of permanent hypoparathyroidism and found a correlation between impaired HRQoL and permanent hypoparathyroidism.¹⁴² Although, it is possible that their result could have been influenced by the fact that a large proportion of their patients with permanent hypoparathyroidism more frequently underwent surgery for thyrotoxicosis and had a significantly lower TSH postoperatively.

The divergent results in our study compared to previous studies could possibly be credited to the fact that we might have included a wider range of grades of permanent hypoparathyroidism, covering mild to severe disease. Further, the mean follow-up was 11 years after surgery. Perhaps, the impact of permanent hypoparathyroidism is most prominent early on after surgery? On the other hand, other long-term consequences of permanent hypoparathyroidism, like kidney failure, takes time to develop and should therefore more likely have an impact on HRQoL over time.

No increased risk of death could be found in association to definitive permanent hypoparathyroidism. This is in line with the findings in some previously mentioned studies, however opposite to the result in a study by Almquist

et al.^{55, 56 47} An explanation to this might reveal itself in the definition of permanent hypoparathyroidism. Almquist *et al.* defined permanent hypoparathyroidism as a de novo prescription of active vitamin D more than 6 months after surgery. Since patients with more severe hypoparathyroidism always requires active vitamin D and are unlikely to be managed on calcium supplementation alone, Almquist *et a.* might have captured a patient cohort with more complications of their hypoparathyroidism. Another possibility, is that some of the patients might have been prescribed active vitamin D for chronic kidney failure and not hypoparathyroidism. As chronic kidney failure is associated to increased risk of death, this could have affected the result.^{47, 143} On the other hand, it needs to be pointed out that Paper IV might be underpowered to properly assess a clinically significant increased risk of death associated with permanent hypoparathyroidism.

Paper IV has several limitations. Data on socio-economic status and TSH levels are missing, factors which may have an impact on wellbeing and quality of life. Also, the response rate of 48.3 % could cause non-response bias. Although a sensitivity analysis showed no difference in baseline characteristics, except that non-responders were slightly younger, the individual reason for not answering the questionnaire remains unknown. A recent systemic review on global response rates reports a general response rate of 65 % for postal surveys, 46 % for web surveys, and higher for in-person surveys.¹⁴⁴ Given our mean follow-up of 11 years, we consider our response rate to be acceptable. An in-person survey would likely have yielded a higher response rate in Paper IV, however it would have been challenging to perform in real life, as it is both costly and time consuming. Another strategy shown to improve the response rate is telephone follow up, however this approach should be used with care as it may be perceived as violating the patient's privacy.¹⁴⁵ We acknowledge that our result on HRQoL could have been affected by the COVID pandemic and that this might reflect on the differences found when comparing HRQoL in patients with definitive hypoparathyroidism with an older Swedish norm data, stemming from 1998-1999.⁶² However, as far as we are aware no newer norm-based data from Sweden is available.

Another limitation to be mentioned, is the fact that SF36 v2 might not capture all symptoms of hypoparathyroidism. Therefore, our study may underestimate the impact of permanent hypoparathyroidism on patients' wellbeing. A questionnaire specific for hypoparathyroidism has fairly recent been presented, Hypoparathyroid Patient Questionnaire (HPQ).⁶³ It has yet not been validated in Sweden, but could be valuable to include in future studies.

The greatest strength in Paper IV is the strategy to circumvent bias and confounders. Also, the population-based study design with a well-defined cohort, strict definition of permanent hypoparathyroidism and the long follow-up after surgery are also important aspects enhancing the trustworthiness of the data and the result.

Conclusions

- I. Prophylactic preoperative treatment with a short course of Alfacalcidol was associated with reduced hypocalcemia and length of stay after total thyroidectomy.
- II. The risk of permanent hypoparathyroidism after total thyroidectomy for benign thyroid disease in Sweden is high. Independent risk factors for permanent hypoparathyroidism are surgery at low volume-centres, parathyroid autotransplantation, higher age and female sex.
- III. Some patients may be overtreated for permanent hypoparathyroidism, due to lacking attempts to unwind the supplementation. The rate of low early PTH is a promising surrogate for the risk of permanent hypoparathyroidism in a cohort. SQRTPA may underestimate complications to thyroid surgery
- IV. HRQoL was not impaired by permanent hypoparathyroidism, when using a strict definition of permanent hypoparathyroidism. Permanent hypoparathyroidism did not affect mortality; however, this needs to be further investigated with larger studies.

Further perspectives

The findings in this thesis highlight the high risk of permanent hypoparathyroidism after total thyroidectomy and emphasize the need of strategies to lower the rates and improve outcomes.

The use of prophylactic preoperative treatment with active vitamin D and its association with a decreased risk of postoperative hypocalcemia and reduced length of stay after surgery should ideally be further investigated in a RCT. If our results can be confirmed, the use of preoperative treatment with active vitamin D could possibly facilitate ambulatory or 23-hour surgery in selected cases.

Prospective multicenter studies on long-term consequences, such as impaired HRQoL, mortality and morbidity, are warranted and should include a strict definition of permanent hypoparathyroidism.

Preserving the parathyroid glands and their blood supply during surgery is critical for maintaining normal parathyroid function. All surgeons undertaking thyroidectomies know that this can be challenging at times, as this thesis clearly shows. Further research efforts can be directed towards the continued development of technical aids, such as ICG and autofluorescence. Although, these methods are yet to be proven to enhance long-term outcome, the concept of having aids to facilitate the visualisation of the parathyroid glands and their vascularisation is intriguing.

The rate of low PTH within 24 h after surgery may be a promising surrogate for the rate of permanent hypoparathyroidism, however prospective studies confirming the relationship is warranted. If the rate of low early PTH can be established as a surrogate for the rate of permanent parathyroid failure in a cohort, it could simplify quality measurements and evaluation of technical aids.

The most straightforward approach to lower the risk of permanent hypoparathyroidism is to reduce the extent of the surgery. Subtotal thyroidectomies have been abandoned due to the risk of recurrence, however sometimes a lobectomy may be sufficient for symptom relief in multinodular goiter¹⁴⁵. Avoiding unnecessary bilateral thyroidectomy is the easiest way to decrease the rate of hypoparathyroidism. Although this thesis evaluates the risk of permanent hypoparathyroidism in patients with benign thyroid disease, the results are applicable to patient with malignant thyroid disease as well. Currently, there is an international trend towards lobectomies rather than total

thyroidectomies in low-risk thyroid cancer. This shift in practice should be evaluated in further studies. The cost-benefit for both the patient and healthcare system regarding the need for further surgery with completion thyroidectomies, revisions for recurrent disease, and perhaps need of prolonged follow-up needs to be weighed against the lower risk for complications and hypothyroidism.

Finally, there is an obvious need for international consensus on the definition of permanent hypoparathyroidism. A uniform definition would simplify interpretations and comparisons of studies and results. National guidelines on the management of patients with hypoparathyroidism, including recommendations on biochemical testing, attempts to unwind the treatment, and long-term follow-up, would be beneficial and likely reduce the number of patients misdiagnosed and overtreated for permanent hypoparathyroidism. Given the fact that high-volume centers⁸ have a lower risk for permanent hypoparathyroidism, a discussion about the implication of these results seems appropriate.

Summary of the thesis in Swedish

Populärvetenskaplig sammanfattning på svenska

Den här avhandlingen belyser olika aspekter av hypoparathyroidism, dvs underfunktion i bisköldkörtelfunktionen, efter operation av sköldkörteln. Hypoparathyroidism är den vanligaste komplikationen efter borttagande av hela sköldkörteln och en vanlig orsak till behov av förlängd vårdtid efter operation. Obehandlat leder tillståndet till låga kalknivåer i blodet och den konventionella behandlingen utgörs av kalk och aktivt vitamin D. Akut lågt kalk kan ge symptom i form av stickningar och domningar i armar, ben och mun, muskeltkramp, tetani, hjärtrytmrubbningar, laryngospasm och koma.

De flesta patienter som drabbas av hypoparathyroidism till följd av sköldkörteloperation återfår normal bisköldkörtelfunktion inom 6-12 månader men en andel av patienterna får en permanent hypoparathyroidism som kräver livslång behandling och uppföljning. Permanent hypoparathyroidism ökar risken för njurstensproblematik, njursvikt, förändringar i benomsättning och kalkinlagringar. Tidigare studier har även visat att tillstånden kan vara kopplat till en ökad risk för cancer, överdödlighet och sänkt livskvalitet.

Förekomsten av permanent hypoparathyroidism varierar kraftigt mellan studier. En orsak till det är avsaknaden av en tydlig definition av tillståndet. Generellt sätt har nationella studier påvisat en högre förekomst av permanent hypoparathyroidism, jämfört med mindre studier från högspecialiserade center. Det finns en osäkerhet kring långtidsdata i kvalitetsregister och tidigare studier har visat ett högt bortfall i uppföljningsdata.

Avhandlingen undersöker förekomsten av permanent hypoparathyroidism både ur ett nationellt perspektiv, baserat på läkemedelsanvändning och registerdata, och ur ett regionalt perspektiv, baserat på journalgranskningsdata med biokemi och upprepad utvärdering av behovet av behandling. Vidare undersöks riskfaktorer för permanent hypoparathyroidism och möjliga långtidskonsekvenser av komplikationen i form av påverkan på livskvalitet och överdödlighet. Utöver det utvärderas om förebyggande läkemedelsbehandling innan operation kan minska risken för lågt kalk under det tidiga förloppet efter operation.

Delarbete I

Delarbete I är en retrospektiv kohortstudie. I arbetet har vi undersökt om förebyggande behandling med aktivt vitamin D innan borttagande av hela sköldkörteln kan minska risken för lågt kalk i det omedelbara förloppet efter operation. 2017 ändrades den kliniska rutinen för patienter som planeras för sköldkörtelkirurgi vid kirurgkliniken i Uppsala, då alla patienter började förbehandlas med aktivt vitamin D i hög dos under tre dagar innan operation, i syfte att försöka minska risken för lågt kalk efter operation. Alla patienter som genomgått borttagande av hela sköldkörteln på Akademiska sjukhuset mellan 2013 till 2020 inkluderades. De patienter som tidigare genomgått sköldkörtelkirurgi eller genomgick samtidig bisköldkörteloperation eller annan stor kirurgi exkluderades. Sammanlagt inkluderades 401 patienter i studien, varav ungefär hälften fått förbehandling med aktivt vitamin D och hälften inte fått det. Data hämtades via journalgranskning och samlades i en strukturerad mall. Propensity score-matchning gjordes för att få fram två jämförbara grupper och minska risken för förväxlingseffekter. Vid jämförelse av de två grupperna, fann vi att gruppen som fått förbehandling med aktivt vitamin D innan operation hade mindre risk för lågt kalk första dagen efter operation, jämfört med den gruppen som inte fått förbehandling.

Delarbete II

Delarbete II är en nationell, retrospektiv kohortstudie som undersöker förekomsten av och riskfaktorer för permanent hypoparathyroidism efter borttagande av hela sköldkörteln pga godartad sköldkörtelsjukdom. Studien bygger på data från patientregistret, läkemedelsregistret och det svenska kvalitetsregistret för endokrinkirurgi. Alla patienter som genomgått borttagande av hela sköldkörteln i Sverige mellan 2005-2015 inkluderades. Patienter med behandling med kalk och eller vitamin D innan operation exkluderades, liksom patienter med tidigare sköldkörtel- och bisköldkörtelkirurgi eller sköldkörtelcancer. Permanent hypoparathyroidism definierades som förskrivning och expediering av kalk och/eller aktivt vitamin mer än 12 månader efter operation. I arbetet fann vi överraskande att 12,5 % av patienterna drabbades av permanent hypoparathyroidism efter operation. Riskfaktorer som påvisades var hög ålder, kvinnligt kön, reimplantation av bisköldkörtel under operation och operation vid enhet med mindre än 100 utförda sköldkörteloperationer per år. Den höga andelen patienter med permanent hypoparathyroidism var förvånande även om ett fåtal tidigare andra nationella registerstudier från Europa visat liknande siffror. I arbetet kunde vi också påvisa en diskrepans mellan den inrapporterade datan i det svenska kvalitetsregistret för endokrinkirurgi och våra fynd. Knappt en femtedel av patienterna som bedömdes ha permanent nedsatt bisköldkörtelfunktion i vårt arbete hade det som registrerad komplikation i kvalitetsregistret.

Delarbete III

Då vi i delarbete II fann en oväntad hög förekomst av permanent nedsatt bisköldkörtelfunktion och en diskrepans mot den inrapporterade datan i kvalitetsregistret, gick vi i delarbete III vidare med en journalgranskning utav en regional kohort från den nationella studiekohorten i delarbete II. Syftet med arbetet var att validera den höga förekomsten av permanent nedsatt bisköldkörtelfunktion via journalgranskning. Alla patienter som opererats i region Uppsala-Örebro inkluderades (Uppsala, Örebro, Falun, Gävle, Västerås och Karlstad). Totalt journalgranskades 1664 patienter, varav 1636 kunde inkluderas i arbetet. En strukturerad mall användes för datainsamlingen. I arbetet använde vi oss av en strikt definition av permanent nedsatt bisköldkörtelfunktion baserat på biokemi med nivåer på kalk och bisköldkörtelhormon samt dokumenterade utsättningsförsök av kalk och aktivt vitamin D ett år efter operation. I arbetet kunde vi visa att vår definition av permanent nedsatt bisköldkörtelfunktion i delarbete II överskattade förekomsten av denna komplikation något, då den faktiska andelen med permanent bisköldkörteldysfunktion var 6,2 % jämfört med 11 % i samma regionala kohort baserad på registerdata. Vidare fann vi ytterligare 2,5% med möjlig permanent bisköldkörteldysfunktion, där det gick att vara sig fastslå eller avskryva det då patienterna antingen saknade dokumenterade utsättningsförsök eller hade tappats bort under uppföljningen. Slutligen kunde vi konkludera att det var en god samstämmighet mellan inrapporterad data i kvalitetsregistret jämfört med fynden vid journalgranskningen avseende akuta komplikationer, medan kvalitetsregistret underrapporterar andelen patienter med permanent nedsatt bisköldkörtelfunktion i långtidsdata.

Delarbete IV

Delarbete IV undersöker om permanent hypoparathyroidism efter operation påverkar patienters livskvalitet. Studiekorten bygger på samma kohort som inkluderades i delarbete III. Samma strikta definition av permanent hypoparathyroidism användes som i delarbete III. Patienter som inte var möjliga att kontakta exkluderades (registrerad som avliden/emigrerad eller utan känd adress). SF-36 version2 är ett välkänt och validerat verktyg för att utvärdera livskvalitet och användes i arbetet. Totalt kontaktades i augusti 2021, 1483 patienter brevledes och inbjöds till deltagande i studien. Patienterna kunde välja att svara brevledes eller via en webbaserad dataportal, U-CARE, som tillhandahålls av Uppsala Universitet. Sammanlagt 716 (48,3%) patienter tackade ja till deltagande i studien och inkluderades. Uppföljningstiden efter operation var i snitt nästan 11 år hos de deltagande patienterna. I arbetet fann vi att patienter som genomgått sköldkörteloperation har en lägre självskattad livskvalitet jämfört svensk normalbefolkning från tidigare publicerade normdata. Vi

fann dock ingen skillnad i livskvalitet vid jämförelse av patienter med och utan permanent hypoparathyroidism efter sköldkörteloperation.

Acknowledgements

I would like to express my sincere gratitude to all that have contributed to make this thesis possible. A special thanks to:

Olov Norlén, my main supervisor, for being an outstanding supervisor and a scientific super-force! Sharp-minded and always involved but with the ability to let me become more independent over time. Little surprise, since you excel in everything you do. Working with and learning from you is a true treat! Your great taste in music, friendship and fantastic skiing skills have enriched my years working on this thesis.

Peter Stålberg, my co-supervisor, for generously sharing your supreme scientific and clinical expertise. For your straightforwardness and ability to see the bigger picture without losing sight of the people in it. For always keeping your door open and making me feel that you believe in me. For creating opportunities, pushing me beyond my limits and letting me grow. Thank you for sending me off to London and for your great and sometimes twisted humour.

Jakob Hedberg, my co-supervisor, for guidance, scientific and clinical advice and continuous encouragement. Your dedication and enthusiasm for research and surgery has been an inspiration. Thank you!

Bengt Isaksson, Peter Stålberg and Claes Julhin, present and former Head of the Department of Surgery, and **Liisa Byberg** and **Per Hellman**, present and former Head of the Department of Surgical Sciences, for providing the time and resources for me to finish this thesis.

All my co-authors for your invaluable contributions to this thesis: **Edward McHale Sjölin, Sofia Wachtmeister, Carolina Österman, Jesper Arlebrink, Simon Mellerstedt, Nicolas Papatanasakis, Göran Wallin, Ola Hessman, Maria Annerbo and Martin Almquist**. I look forward to future collaborations.

Anna- Maria Lundgren and **Sofia Wachtmeister**, for handling over 2000 letters and questionnaires, more than 700 responses and endless of hours

entering data into the database. A HUGE thank you. Paper IV is dedicated to you!

My other colleagues in the endocrine surgery team- with you there is never a dull day at work! To work with you is a luxury. **Per Hellman**, for being one of the humblest experts I know. Brilliant, generous and kind. You are a great inspiration. **Branislav Klimacek**, working with you is nothing less than amazing. You are skilled, hardworking and a great friend. Looking forward to visiting you in London! **Josefine Kjaer**, there are few persons I have shared so many laughter and funny moments with as with you. Being a PhD student alongside with you has made the journey so much easier. We have experienced both challenges and triumphs together, ranging from mastering End-Note and SPSS to supporting and motivating one another. Congratulations on your thesis- you will pass with flying colours!

Professor Fausto Palazzo, Professor Neil Tolley and Miss Aimee DiMarco, for all the generous support and teaching during my fellowship in endocrine surgery at Hammersmith Hospital, London. I will be forever grateful for all that you have taught me and for showing me the importance of good music in theatre!

Anna-Maria Lundgren, Nataliia Sochivets, Gisela Öhman, Emma Strandqvist and Lise-Lotte Lind with colleagues. For managing our quality registers, research assignments, theatre lists and outpatient clinics with a smile. Thank you for all your gentle reminders whenever I have forgotten about something. Everything is a team effort. Without you the rest of us would be lost (at least me!).

All my follow colleagues and friends at the Department of Surgery, Uppsala University Hospital for being such a talented, hardworking and inspirational bunch of people. You make the sometimes many hours at work to feel like an instant. You are the best! A special thank you to: **Åsa Collin**, for being extraordinary in all important aspects and for being the reason why I became a surgeon at this clinic; **Sara Artursson** and **Maria Söderström**, for great friendship since we started out as registrars. For sharing proud moments of progress and offering support whenever it has been needed. **My former registrar colleagues:** *We have come a long, long way together, through the hard times and the good. I have to celebrate you, dearest, I have to praise you like I should.*

All of my **friends**, thank you for listening to all of my struggles throughout the work with this thesis. I am sorry for my frequent reschedules and constant time optimism. I have not always been present and the best of friends, but you

have stayed by my side showing nothing but great friendship. Thank you for all the laughter and happiness you bring into my life. I adore you all.

My parents, **Eva-Lena and Mats**, for being my biggest supporters. For teaching me to work hard and always do my best. For reminding me that the strongest also needs to be the kindest and the value of being compassionate.

My brother, **Jonatan**, for being one of the smartest and most warm-hearted persons I know. For having the ability to cheer me up and always manage to give me a new perspective on things. You make my life better and richer in so many different ways.

Maja, our newest family member, for being brave enough to move to a new country with a family you barely knew. I cannot imagine our family without you now.

Finally, and foremost, thank you to my closest family. My first, my last, my everything. My husband **Henrik** for love and support. Thank you for always believing I can achieve anything and everything. I wish I could ski every mountain with you! **Greta**, our daughter and sunshine. Thank you for keeping me grounded and reminding me about what is really important in life. You will always be my top priority. I love you!

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