Universitat Autònoma de Barcelona

POSTOPERATIVE HYPOPARATHYROIDISM: IMPORTANCE OF TIME AND GENDER

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Tesi Doctoral realitzada per Inés Villarroya-Marquina

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POSTOPERATIVE HYPOPARATHYROIDISM:

IMPORTANCE OF TIME AND GENDER

Memòria presentada per Inés Villarroya Marquina

per a optar al grau de Doctora en Medicina codirigida pel

Professor Titular Juan José Sancho Insenser i Dra Leyre Lorente Poch

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INFORME DELS DIRECTORS

Aquesta Tesi Doctoral presenta un resum de la investigació clínica original duta a terme per Inés Villarroya Marquina sobre la insuficiència paratiroidal post-tiroïdectomia total, la complicació més freqüent després d'un procediment que és àmpliament emprat per al tractament quirúrgic de moltes patologies tiroidals, tant benignes com malignes. Aquesta Tesi Doctoral representa la continuació d'una de les línies de recerca més antigues i productives de la Unitat de Cirurgia Endocrina del Servei de Cirurgia General i Digestiva de l'Hospital del Mar.

Els resultats d'aquesta recerca, que s'han publicat en dos articles originals, aprofundeixen en aspectes crucials de la fisiopatologia i enriqueixen amb aportacions originals el coneixement sobre aquesta malaltia.

En primer lloc, aprofundeixen en l'anàlisi de la major prevalença de hipocalcèmia després de tiroïdectomia en dones, principalment en les joves, en comparació amb els homes. A diferència d'altres estudis, es demostra que les dones pre-menopàusiques presenten una prevalença més elevada d'hipoparatiroïdisme tant a curt com a llarg termini amb similar nombre de paratiroides *in situ* que les dones de major edat, suggerint la presència d'un factor hormonal femení involucrat en la disfunció paratiroidal postoperatòria.

En segon lloc, demostren que en una proporció no menyspreable de pacients, la recuperació de la funció paratiroidal pot tenir lloc més tard d'un any després de tiroïdectomia. Aquesta demostració contrasta fortament amb les definicions actuals de vàries societats científiques que estableixen el límit en sis mesos, i alterarà de ben segur les tasses d'hipoparatiroïdisme permanent. Tanmateix, l'anàlisi detallat dels factors implicats, dóna llum a la poc explorada recuperació tardana de l'hipoparatiroïdisme.

Per tals motius creiem que la present Tesi Doctoral és apta per a ser presentada per obtenir el grau de Doctor en Medicina.

Barcelona, 15 d'Abril de 2021

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ABBREVIATIONS USED IN THIS DOCUMENT

Ca	Calcium
cm	Centimeters
CND	Central node dissection
CI	Confidence interval
mm^3	Cubic milimeters
ECG	Electrocardiogram
e.g.	Exempli gratia (for example)
eGFR	Estimated glomerular filtration rate
F:M	Female-to-male ratio
FSH	Follicular stimulating hormone
g, mg	Grams, miligrams
h	Hours
HT	Hemithyroidectomy
hypoPT	Hypoparathyroidism
ie	*Id est* (that is)
IL	Inferior limit
iPTH	Intact parathyroid hormone
µg	Micrograms
mg/dL, mg^2/dL^2	Miligrams per decilitre, squared miligrams per decilitre
mg/kg/h	Miligrams per kilogram per hour
mmol/L, $mmol^2/L^2$	Milimols per litre, squared milimols per litre
mCi	Millicurie
mo	Months
MLR	Multivariate Logistic Regression
N	Number of patients
OR	Odds ratio
P	P-value of significance
PGRIS	Parathyroid glands remaining *in situ*
PTH	Parathyroid hormone
pg/mL	Picograms por mililitre
pmol/L	Picomol per litre
postop	postoperatory
pH	Potential of hydrogen

preop	Preoperatory
QoL	Quality of life
RPF	Recovery of parathyroid function
RR	Risk ratio
s-Ca	Serum calcium
S.D.	Standard deviation
S.E.M.	Standard error of the mean
ST	Subtotal thyroidectomy
SL	Superior limit
TSH	Thyroid stimulating hormone
TT	Total thyroidectomy
y	Years

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1 INTRODUCTION

1.1 Parathyroid insufficiency after total thyroidectomy

Total thyroidectomy implies a significant traumatic aggression to the parathyroid glands. With the increased use of this surgical technique for a variety of benign and malignant disorders, postoperative parathyroid insufficiency has become the most common short-term complication following total thyroidectomy. Permanent hypoparathyroidism represents the last stage of postoperative parathyroid failure. Even though hypoparathyroidism was designated as an orphan disease by the European Commission in 2014 [1], it is currently considered to be the most common permanent complication after total thyroidectomy [2,3,4].

1.1.1 Definitions: heterogenicity and lack of standardization

Despite been considered as the most frequent complication after total thyroidectomy, there is still a lot of variability and lack of standardization regarding the definition of postoperative parathyroid insufficiency.

In 2015, our group [5] highlighted such ambiguity of definitions and showed the wide variety of thresholds and parameters used in the scientific literature to define both postoperative hypocalcemia and permanent hypoparathyroidism. Approximately half of the authors defined postoperative hypocalcemia as the need for calcium or vitamin D supplements whereas the rest defined it according to s-Ca concentrations. In addition, some of these analyses include conservative bilateral procedures and not only total thyroidectomies [6,7,8,9,10]. Other authors have also highlighted the lack of standardised definitions for postoperative hypocalcemia and hypoparathyroidism after total thyroidectomy [11,12,13]. A review of 19 publications showed that 26% of the studies failed to provide appropriate definitions for hypocalcemia, transient and permanent hypoparathyroidism [11]. When provided, there was inconsistency in the biochemical definition of hypocalcemia (cut-off points ranging from 1.8 to 2.12 mmol/L). In a revealing exercise, Mehanna *et al.* applied different definitions from the literature to their cohort of thyroidectomy patients and demonstrated how the rate of hypocalcemia ranged from 0% to 46% depending on the definition used [13]. Later, in 2019, Harsløf *et al.* conducted a systematic review and identified 89 articles published from 2010-2017 that used twenty different definitions for hypoparathyroidism [14].

Oftentimes, the biochemical parameters used to define postoperative hypocalcemia differed among studies as well as the timming of blood sampling in the postoperative period and the cut-off value. Some authors chose calcium and iPTH at 24 hours after the thyroidectomy, whereas others consider 4 hours [15] or 48 hours [9] to be more accurate. A similar disparity is seen when establishing the diagnosis of permanent hypoparathyroidism. Some authors define permanent hypoparathyroidism as the need for calcium and or vitamin D supplements at 6 months after surgery [6,9,16,17] whereas others extend this definition to a year [2,18,19].

1.1.2 Definitions of postoperative parathyroid failure syndromes

Given the lack of standardized definitions, our group proposed precise definitions which may facilitate the approach to post-thyroidectomy hypoparathyroidism by the understanding of the three different metabolic syndromes of parathyroid failure [5].

To define postoperative hypocalcemia, a cut-off value of 8 mg/dL (2 mmol/L) of adjusted serum calcium at one-day from the surgery was chosen. It is the most extended and accepted value, corrects surgical hemodilution and hypocalcemic symptoms are rarely seen above that serum calcium concentration. Measuring adjusted serum calcium is cheaper, easier-to-interpret and less prone to be altered by the quality of the sampling, transportation, and pH than ionized calcium.

A reliable parameter to predict postoperative hypoparathyroidism is the serum concentration of iPTH at 4 hours after the thyroidectomy. Values lower than 10 pg/mL have been shown to have the highest accuracy in predicting post-surgical hypocalcemia in a study by Barczynski *et al.* [15]. Prescribing prophylactic calcium and vitamin D to patients with iPTH < 10 pg/mL effectively prevents the postoperative hypocalcemia and therefore early iPTH must be included as part of the definition of postoperative hypocalcemia.

Hypoparathyroidism one month after total thyroidectomy (or protracted hypoparathyroidism) has clinical relevance as a predicting tool, and it becomes very useful when informing patients. If the patient is hypoparathyroid 1 month after surgery, according to previous studies the probability of recovering the parathyroid function during the next 12 months is 75% [18]. Our group devised a nomogram to predict the likelihood to recover from a protracted postoperative hypoparathyroidism (https://www.evidencio.com/models/show/1066) [20].

Regarding the moment in time when to label a hypoparathyroidism as permanent, our group joined those authors that propose to use the 1-year deadline. As much as 20% of patients who recover from protracted hypoparathyroidism do so after 6 months. This definition has the potential to greatly impact both the reported prevalence of postoperative hypoparathyroidism and the attitude of the treating team.

One of the sources of confusion among postoperative parathyroid insufficiency lies in the fact that many Surgeons and Endocrinologists consider hypoparathyroidism as an on-off phenomenon, whereas the discerning clinical observation identifies a gradation of parathyroid insufficiency situations.

Our group proposed the following definitions for each of the parathyroid failure syndromes:

- **Postoperative hypocalcemia/ Postoperative parathyroid insufficiency** was defined as serum calcium levels < 8 mg/dL (< 2 mmol/L) within 24 hours after thyroidectomy and/or an iPTH concentration ≤ 10 pg/mL 4 hours after thyroidectomy.
- **Protracted hypoparathyroidism** (previously known as transient hypoparathyroidism) was defined as iPTH levels lower than 13 pg/mL (< 1.4 pmol/L) and/or need for calcium ± vitamin D supplements 4-6 weeks after surgery.
- **Permanent hypoparathyroidism** was defined when iPTH levels are lower than 13 pg/mL (< 1.4 pmol/L) and/or calcium ± vitamin D supplements were still required one year after thyroidectomy. It represents the last stage of postoperative parathyroid failure.

Furthermore, a closer look at permanent hypoparathyroidism allows for a subclassification of this syndrome into three severity degrees:

a) **Aparathyroidism**: undetectable iPTH, with high phosphate levels. Vitamin D supplementation is necessary in addition to calcium supplements. Recovery probability is remote.
b) **Hypoparathyroidism**: detectable-low iPTH, with normal phosphate levels. Calcium supplementation is necessary.
c) **Relative parathyroid insufficiency**: detectable-normal iPTH, but insufficient to keep calcium concentration within its normal range in serum; phosphate levels are normal. Often seen in patients with comorbidities such as malabsorption disorders, gastric bypass, or previous intestinal resection.

1.1.3 Prevalence of postoperative hypoparathyroidism

In the last decades, the use of total thyroidectomy as the preferred technique for a variety of benign and malignant thyroid disorders has increased, thus the frequency of postoperative parathyroid failure disorders as the main complications of such surgery has increased accordingly [21].

Postoperative hypocalcemia is the first stage of parathyroid failure and its prevalence varies widely. A review assessing 115 articles found a range of postsurgical hypocalcemia from 19-38% [21], whereas other authors established such prevalence to be as high as 50.2% [18].

The prevalence of protracted hypoparathyroidism has been reported to range from 1.6 [2,7] to 9.1% [8]. Bergenfelz *et al.* [7] found the prevalence of protacted hypoparathyroidism to be 7.8%, 2.6% and 7.3% depending on the need to receive calcium, vitamin D, or a combination of both drugs respectively at six weeks postoperatively. Previous studies from our group found the prevalence of protracted hypoparathyroidism to be around 18% [18,22].

Regarding permanent hypoparathyroidism, its prevalence varies widely ranging from 0-3% [21] when reporting single center results to 6-12% [23] when data is obtained from national registries and large multicenter studies. Our group reported the prevalence of permanent hypoparathyroidism to be around 4% [18,22].

1.1.4 Etiology and pathophysiology of postoperative parathyroid failure

Postoperative parathyroid failure is nothing more than the impairment of the endocrine function of four very small ovoid glands located on the posterior lobar borders of the thyroid gland. There are two superior and two inferior glands, embryologically originated from the fourth and third pharyngeal pouch, respectively. Interindividual variation in number is possible, ranging from two to six glands. Their arterial supply is provided from branches of the inferior thyroid arteries in 80% of the cases and from both inferior and superior thyroid arteries in the remaining 20%. The venous blood drains into the superior, middle, and inferior thyroid veins, and their lymphatics drain into the paratracheal and deep cervical nodes. Innervation is supplied by extensive vasomotor thyroid branches of the cervical ganglia (sympathetic nervous system).
Their anatomical situation is important due to their frequent ectopic location and their tight proximity to the inferior thyroid artery (regularly less than 1 cm apart from the superior glands), which places them at high risk of iatrogenic damage.

The general consensus is that the main cause of post-thyroidectomy hypocalcemia is an acute parathyroid insufficiency due to a reduction of the functioning parathyroid parenchyma. In the event of parathyroid damage, in addition to the reduction of PTH-secreting parenchima, a lesser number of calcium receptors expressed on the chief cells can detect calcemia oscillations and consequently, the secretion of PTH becomes deficient. Impaired PTH secretion leads to postoperative hypocalcemia due to a diminished effect of this hormone over its target organs (bone resorption, renal 1,25-dihydroxyvitamin-D synthesis, and intestinal calcium absorption). The effect of deficient PTH affects the homeostasis of phosphate and magnesium as well, which increase and decrease their serum levels respectively [24,25,26].

The reduction of the functioning parathyroid tissue is secondary to an intraoperative damage to the parathyroid glands caused by a combination of factors such as mechanical or thermal trauma, gland devascularization, obstruction of venous outflow, inadvertent parathyroid excision, and parathyroid autotransplantation.

Other factors that have been cited as marginally participating in the development of post-thyroidectomy hypocalcemia include hemodilution, surgical stress induced urinary calcium excretion, calcitonin release due to thyroid manipulation, pre-existing vitamin D deficiency and hungry bone syndrome [11].

1.2 Risk factors for parathyroid insufficiency

1.2.1 Surgical risk factors for postoperative parathyroid insufficiency

It is commonly accepted that trauma to the parathyroid glands (whether through devascularization, direct injury or inadvertent removal of parathyroid glands) because of inadequate visualization during thyroidectomy accounts for the main risk factor during anterior neck surgeries [11,22,27,28,29,30,31]. As previously reported by our group, the number of parathyroid glands remaining *in situ* –not autotransplanted nor inadvertently excised– (PGRIS) is a key factor for the development of parathyroid insufficiency after total thyroidectomy [22]. Autotransplantation has been defined by some authors [4,32,33] as the best strategy to prevent permanent hypoparathyroidism, despite increasing hypocalcemia in the short-term; however, our group found that this technique leads to more parathyroid function failure, increasing the rates of all three parathyroid insufficiency syndromes.

Other surgical variables may increase the risk of developing postoperative hypoparathyroidism. For instance, an operative time longer than 2 hours has been shown to increase the risk for transient hypocalcemia ($p < 0.05$) [34]. Low surgical expertise and low volume load are two other factors which increase complications rate, including post-surgical hypocalcemia [35,36,37,38,39].

Lastly, reoperation for bleeding, redo surgery for recurrence of benign goiter or completion lobectomy [21] are also risk factors for postoperative hypoparathyroidism. Thomusch *et al.* [16]

described a risk ratio of 1.8-1.9 for both protracted and permanent hypoparathyroidism in patients that had undergone reoperation. The hypothesis is that after a previous neck surgery, the scar density may be extensive, increasing the traction of adjoining tissues which at the same time can alter the integrity of the parathyroid glands.

1.2.2 Non-surgical risk factors for postoperative parathyroid insufficiency

Among non-surgical risk factors for postoperative parathyroid failure, autoimmune thyroid diseases (Graves disease or Hashimoto thyroiditis) account for the second most common cause of hypoparathyroidism [21,30,31]. Thomusch *et al.* [6] reported a relative risk of 2.8 for postoperative hypoparathyroidism when Graves' disease was present, which has been supported by other studies [40]. Pesce *et al.* [29] suggested that there was an association between inflammatory thyroid diseases and the presence of both profuse bleeding and adhesions between the thyroid capsule and the parathyroid glands, which may deter the proper visualization of the parathyroid glands.

Other non-surgical risk factors such as hyperthyroidism [16], retrosternal goiter [31] and radioactive iodine thyroid ablation [41,42] have been also reported to be associated to postoperative hypoparathyroidism.

Whether age is a risk factor for postoperative parathyroid insufficiency, remains unclear. While some studies suggest that patients of younger age are at higher risk for postoperative hypocalcemia and more prone to develop symptoms [3,29,40,43], others found no influence of age on hypoparathyroidism or its recovery [18,44]. On the other hand, some authors found a positive association with increased patient's age and development of post-surgical hypoparathyroidism [16,34,45,46,47].

Regarding biochemical markers preoperative low serum calcium levels have been reported to be a risk factor for protracted hypoparathyroidism, but not for permanent hypoparathyroidism [21,48,49].

The role of preoperative vitamin D status on postoperative parathyroid function is far from clear with few studies suggesting an influence of low circulating vitamin D [50,51] and several others not reproducing these findings [52,53,54].

Low serum magnesium levels, both preoperative [21] and postoperative [55] have been reported to be a risk factor for transient postoperative hypocalcemia.

1.2.3 Female gender as risk factor for parathyroid insufficiency

A gender mismatch regarding the ratio of transient postoperative hypocalcemia has been repeatedly described in literature. Approximately 25~31% of female patients are diagnosed with postoperative hypocalcemia, compared to 12~16% of male patients [56,57].

The meta-analysis carried out by Edafe *et al.* showed women had a significantly higher prevalence of postoperative parathyroid failure (OR = 2.8). The authors hypothesized that this could be related to female patients having lower circulating levels of vitamin D [21]. Some other authors have justified the increased rate of postsurgical hypoparathyroidism due to a higher proportion of female patients who undergo thyroid surgery in population (4 female:1 male) [58] whereas others hypothesize that the cause may be the increased consumption of aspirin-type drugs and/or a more delicate anatomy in females [16].

Table 1 compiles a summarized literature review of the studies which have discussed the hypothesis of female gender as a risk factor for postoperative parathyroid insufficiency.

To our knowledge, there are only two studies assessing menopausal status as a variable associated with the higher prevalence of postoperative parathyroid failure in females. In a retrospective review of 270 consecutive patients undergoing total thyroidectomy, Sands *et al.* showed that female patients had two-fold prevalence of hypocalcemia in comparison to men (24.7% *vs*. 11.8%, $p < 0.05$). Additionally, they compared youger to older female patients setting the cut-off at 50 years old, assuming equivalence to premenopausal and postmenopausal status and the prevalence of hypocalcemia was similar (22.7% *vs.* 26.6%, $p > 0.05$). The authors concluded that the mechanism underlying the gender disparities could only be inferred by them [56]. On the other hand, a study conducted by Lee *et al*, whose aim was to assess whether routine high-dose calcium supplementation significantly reduced the risk of postoperative symptomatic hypocalcemia, found an association between low PTH (< 13 pg/mL) and age – menopause status. After age-adjusted multivariate regression model menopause status was not significantly associated with postoperative symptomatic hypocalcemia [62].

Significant association between female gender and post-surgical parathyroid insufficiency is not always proved [3,18,44,50,63,64]. **Table 2** summarizes the results found in these studies.

Table 1. Studies assessing female gender as a risk factor for postoperative hypoparathyroidism

Author, year	N	F:M	Study design	Results
Thomusch *et al.*, 2000 [16]	7,266	3.4:1	Prospective. Multicentric Surgery (all types) for benign goiter	Female gender was a significant risk factor for transient and permanent hypoparathyroidism (RR 2.1 and 2.3, p < 0.002, respectively)
Docimo *et al.*, 2017 [34]	328	3.3:1	Prospective. Unicentric TT for benign and malignant conditions	Female gender increased significantly the risk of post-surgical hypocalcemia. Reported F:M ratios for asymptomatic hypocalcemia (6.7:1), symptomatic hypocalcemia (7.7:1), and transient hypocalcemia (8.6:1) (p < 0.05).
Al Qubaisi & Haigh, 2019 [40]	2,143	4.3:1	Retrospective TT for benign conditions	MLR analysis: female gender as an independent risk factor to develop postoperative hypocalcemia (OR = 1.79, p = 0.009). Female gender was a risk factor for clinically severe hypocalcemia (OR = 2.10; p = 0.017).
Yamashita *et al.*, 1997 [43]	1,742	3.5:1	Retrospective. Unicentric ST for Graves' disease	Increased incidence of tetany in females (OR 7.31, p < 0.0001). MLR (excluding males due to low incidence of tetany) isolated female gender as a predicting factor.
Erbil *et al.*, 2009 [45]	200	5.2:1	Prospective. Unicentric Near-total or TT for benign goiter	Higher rate of postoperative hypocalcemia in female patients (27.9% vs. 6.25%; p < 0.01). Lower preoperative serum 25-hydroxy-vitamin D levels within women (p < 0.001). Inverse correlation between female gender and calcemia
Wang *et al.*, 2017 [47]	278	3.6:1	Retrospective. Unicentric TT or HT for benign and malignant conditions	Female gender was associated with both postoperative hypocalcemia (p = 0.015) and hypoparathyroidism (p = 0.014). MLR analysis isolated female gender as one of the independent risk factors for the development of hypoparathyroidism (1/OR = 4.88; p=0.026), but not for postoperative hypocalcemia.
Sands *et al.* [56]	270	4.3:1	Retrospective. Unicentric TT for for benign and malignant conditions	Higher rate of transient postoperative hypocalcemia in female patients (24.7% vs. 11.8%; p < 0.05). Over two-fold risk ratio among women to develop postoperative transient hypocalcemia. No statistically significant differences in rates of hypocalcemia between premenopausal and postmenopausal women.
Cho *et al.*, 2016 [57]	1,030	5.3:1	Prospective. Unicentric TT for benign and malignant conditions	Two-fold risk of transient hypocalcemia in female patients (p = 0.001). Female-to-male ratios for transient and permanent hypocalcemia were 9.8:1 and 2.9:1, respectively.
Luo *et al.*, 2018 [59]	599	2.5:1	Retrospective. Unicentric TT for benign and malignant conditions.	Postoperative hypocalcemia more prevalent among women (F:M ratio 4.8:1; p = 0.001). MLR: female gender was a predicting factor for both postoperative hypocalcemia and transient hypoparathyroidism (1/OR = 2.12 and 1.72, respectively; p < 0.05).
Eismontas *et al.*, 2018 [60]	400	6.8:1	Prospective TT for benign and malignant conditions.	Univariate analysis: female gender did not show a significant impact on developing hypocalcemia (p = 0.351), whereas on binary logistic regression the female gender showed a statistically significant association with the disorder (OR = 5.94; p = 0.035). Probable methodological problem.
Mo *et al.*, 2020 [61]	176	3.5:1	Prospective TT + CND for malignant conditions.	Female gender, PTH level reduction > 71%, and tumor diameter were independent risk factors for transient postoperative hypocalcemia (p < 0.05)

N: number of patients; F:M: female-to-male ratio; OR: odds ratio; RR: risk ratio; p: p-value of significance; MLR: Multivariate Logistic Regression; TT: Total Thyroidectomy; HT: Hemithyroidectomy; ST: Subtotal Thyroidectomy; CND: Central Node Dissection

Table 2. Articles reporting female gender not as a risk factor

Author, year	N	F:M	Study design	Results
Sitges-Serra et al., 2010 18	442	5.4:1	Retrospective TT for benign and malignant conditions	No statistically significant association between female gender and development of protracted hypoparathyroidism, despite finding a larger proportion of females that develop the disease compared to males (19.3% vs. 12%, respectively; p = 0.126)
Moriyama *et al*., 2005 [44]	111	5.5:1	Prospective ST for Graves' disease	No statistically significant differences in gender nor age between the group that presented post-surgical tetany and the asymptomatic group (F:M = 8:1 for both groups, p = 0.70).
Erbil *et al*., 2007 [50]	130	4.9:1	Prospective TT for benign condition	No statistically significant differences between genders when comparing the hypocalcemic group to the normocalcemic one (F:M = 7:1 *vs* 4.4:1, p = 0.44).
Pfleiderer *et al*., 2009 [63]	162	5:1	Prospective Near-total or TT for benign and malignant conditions	No statistically significant differences regarding female-to-male ratios when comparing the groups with temporary hypocalcemia (8.9:1), permanent hypocalcemia (3.5:1), and normocalcemia (3.7:1) (p = 0.158).
Lang *et al*., 2012 [64]	117	8.8:1	Prospective Near-total or TT for benign and malignant conditions	No statistically significant differences found for age or gender of patients with hypocalcemia vs. normocalcemia (age 51.2 vs. 45.0, p = 0.124) (F:M = 8.1:1 *vs* 16:1, p = 1).

N: number of patients; F:M: female-to-male ratio; p: p-value of significance; TT: Total Thyroidectomy; ST: Subtotal Thyroidectomy

1.3 Methods to prevent post-thyroidectomy parathyroid failure

All preventable factors involved in the development of postsurgical hypoparathyroidism depend on the surgeon.

Autotransplantation of parathyroid glands has been considered by some groups as a method to prevent permanent hypoparathyroidsm after a period of transient hypocalcemia, to the point that routine autotransplantation of one gland was once proposed to ensure parathyroid function [65]. The majority of authors agree that autotransplantation should be restrictive and only performed if the gland is completely avascular [30] or partially devascularized [4,66]. Our group provided evidence that implementing such technique does not prevent permanent hypoparathyroidism. On the contrary, it increases the risk of protracted and permanent hypoparathyroidism [22].

Meticulous observation and identification of the parathyroid glands *in situ,* avoiding any injury and preserving their vascular network is generaly accepted as of paramount importance [67,68]. When thyroid surgery is performed by experienced surgerons at a tertiary referral center with appropriate case load, the surgery is followed by lower prevalence of both short and long-term hypoparathyroidism (5.4-9.6% for protracted hypoparathyroidism and 0.5-1.7% for permanent hypoparathyroidism) when comparing with low volume centers [69].

1.4 Clinical syndromes and impact on patients' quality of life

Clinical manifestations of postoperative parathyroid insufficiency result from calcium oscillations and are strongly correlated with the severity of the biochemical imbalance, its duration and onset of presentation [30]. Most patients experience clinical manifestations when the adjusted calcemia is below 7.5-8 mg/dL [42].

If complete parathyroid function is not recovered, lifelong medical treatment, chronic clinical manifestations, and the personal emotional burden impact significantly on the patients' quality of life.

1.4.1 Clinical syndromes of parathyroid failure

The time of onset and severity at presentation determines whether an acute clinical manifestation is an emergency (e.g.: life-threatening conditions like laryngospasm, tetanic attacks, seizures, cardiac arrithmia) or not. Most patients feel their first symptoms as perioral and hand paresthesias, due to hypocalcemia causing a neuronal electrical imbalance on the membrane that ultimately triggers despolarization at a higher pace than normally. Such increase in depolarization frequency is responsible for the neuromuscular irritability and other neuronal manifestations, as well as worsens the already impaired striated muscle contraction (both in skeletal and cardiac muscles), ultimately causing muscular stiffness, spasms, fatigue, and electrocardiac abnormalities.

In the long term, bone turnover becomes abnormal, where the bone resorption is initially reduced (causing an increased bone mass), followed by a reduction in bone formation (which decreases bone quality). Because these modify the bone microarchitecture, there is plenty of controversy regarding hypoparathyroidism modifying the risk for bone fractures and osteoporosis that has not yet been consensed.

During the course of permanent hyporparathyroidism, patients can present with clinical manifestations in a variety of organs. The worst long-term consequences are oftentimes related to treatment, since the rate of calcium-phosphate increases, creating an insoluble product that deposits in ectopic soft tissues, such as the kidneys, vessels, and even the basal ganglia, contributing to a faster deterioration of these organs and their respective functions [70]. Thus, a throughout long-term follow up of these patients is mandatory to guarantee a good control of their biochemical profiles and treatment dosages, to minimize the development of medication-derived clinical manifestations and the chances of being over- or undertreated [30,70].

Table 3 summarizes the clinical manifestations that patients with hypoparathyroidism may experience at some point, sorted by body system.

Table 3. Clinical manifestations of patients diagnosed with parathyroid insufficiency

System	Clinical manifestation
Cardiovascular	Common: QTc interval prolongation, abnormally large U or T wave Rare: treatment-resistant heart failure and dilated cardiomyopathy
Muscular	Common: Neuromuscular irritability (spasms), tonic-clonic seizures, stiffness, pain, weakness, fatigue, increased creatine phosphokinase
Skeletal	Reduced bone remodelling Controversy about modified incidence of bone fractures
Integumentary	Common: dry and scaly skin, weak brittle nails, deformed nails, alopecia, or coarse and thin hair Rare: pustular psoriasis
Nervous	- Peripheral: increased depolarizing frequency, tingling, paresthesias, numbness - Central: basal ganglia calcifications and seizures - Ophtalmological: cortical cataracts, papilledema, blepharospasm, calcifications
Psychiatric	Depression, bipolar affective disorders, somatization disorders, anxiety, impaired neurocognitive functions (decreased concentration, memory, altered mood)
Excretory	Without conventional treatment: rare manifestations With conventional treatment: increased calcium filtered load, nephrocalcinosis, nephrolithiasis, renal colic, renal failure
Digestive	Constipation, abdominal cramps

1.4.2 Impact of permanent hypoparathyroidism on quality of life

There are plenty of studies associating post-surgical hypoparathyroidism with impaired QoL [41,71,72,73]. Patients not only complain about physical signs and symptoms, but also psychological, cognitive, and emotional impairment that affect their daily life [72,73,74,75,76].

Diverging somewhat from the general consensus, our group [23] found a consistent non-significant decrease of the scoring for the perceived QoL for most (75%) patients with permanent hypoparathyroidism followed up in our clinic except for a significant decrease in the emotional dimension.

Regrettably, even if calcium levels are maintained within a normal range with conventional supplementation treatment, the quality of life does not seem to improve considerably [77]. Even with the introduction of new treatment modalities (PTH analogues), QoL has not shown a dramatic improvement. Some authours have found well-being only improved for some patients with post-surgical hypoparathyroidism (specially in those with a low baseline QoL score and those whose need for conventional therapy decreased) [78] whereas others showed inconsistent benefits regarding QoL [76,79].

1.5 Treatment of parathyroid failure

1.5.1 Treatment of postoperative hypocalcemia

In the acute setting of hypocalcemia or acute hypoparathyroidism, the main goal is to quickly raise the calcium levels with supplements of calcium and vitamin D to prevent the appearance of clinical manifestations. In case of serious hypocalcaemia or tetany, intravenous calcium salts should be administered in two steps: first, as a rapid 10-20 minutes solution of 10% calcium gluconate (90-180mg elemental calcium / 50mL of 5% dextrose), with ECG monitoring; then, as a continuous 8-12 hour infusion of calcium gluconate (0.5 – 1.5 mg/kg/h) [17,80].

1.5.2 Parathyroid splinting

Our group [18,20,22] has consistenly found that patients with normal-high calcium levels at one month after surgery showed significant better recovery form protracted hypoparathyroidism.

Opposing to previous publications that suggested low-normal calcemia as the best management to stimulate the parathyroid function [81], Sitges-Serra *et al.* suggested a "parathyroid splinting" effect when high doses of calcium and vitamin D were prescribed, letting the parathyroid glands rest and therefore, increasing their chances of recovering. According to these results, patients receiving a higher dose of calcium and vitamin D at hospital discharge, would have a better biochemical profile at one-month after the thyroidectomy, and recover the parathyroid function in greater proportion than those discharged with lower doses of supplemental treatment.

1.5.3 Treatment of permanent hypoparathyroidism

1.5.3.1 Conventional treatment

The conventional therapy for long-term hypoparathyroidism mainly includes calcium oral supplements.

Oral calcium supplements are prescribed when serum calcium concentration is < 8 mg/dL and/or PTH levels are < 13 pg/mL postoperatively. Several formulations of supplements are available: the cheapest and most used is calcium carbonate salts, which have a 40% of elemental calcium. Other alternatives exist as calcium citrate salts (which contain 20% of elemental calcium), calcium gluconate, and calcium lactate. Compared to calcium carbonate, these three alternatives require a greater number of tablets to get the same therapeutical effect due to the lower proportion of elemental calcium per tablet [82].

When supplements are taken as oral calcium carbonate, it is required an acidic gastric environment to be correctly digested and absorbed, therefore it is recommended to be taken with meals (unlike calcium citrate, which does not require a low pH to be absorbed). Of notice, if other medications are taken simultaneously, calcium absorption could be altered [42].

Despite its lower proportion of available calcium per dose, there are some cases where prescribing calcium citrate is more beneficial for the patient: if the gastric secretion is impaired (because of old age [42], concomitant proton pump inhibitor therapy [83,84], or hypo- or achlorhydria is present [85]), and if the patient complaints of constipation as a side effect of the calcium carbonate treatment [17].

Vitamin D analogues (1,25-$(OH)_2$-D_3 – calcitriol or 1α-hydroxy-vitamin D_3 – alfacalcidol and 25-OH-D_3 –calcifediol) are usually prescribed in combination to help maintain normal calcium levels [17].

Complementarily, thiazide diuretics can be added in those patients with hypercalciuria since they decrease the urinary calcium excretion, reduce the need of vitamin D supplements and decrease the risk of nephrolithiasis [86]. Magnesium supplements are recommended if serum levels are low [55,82].

1.5.3.2 PTH replacement therapy

In 2015 the US Food and Drug Administration approved the use of a synthetic PTH molecule (rhPTH 1-84) as a replacement hormonal treatment for hypoparathyroidism. Potential advantages over the conventional therapy include lower dosage requirements of calcium and vitamin D, reduced calciuria and ectopic calcifications, improved bone turnover, and improved quality of life [87]. Concern about potential carcinogenic effects raised after its approval; however, no associations were reported in a post-marketing surveillance study [88].

1.5.3.2.1 hPTH (1-34)

Teriparatide is the truncated version of a synthetic PTH molecule. It has not been approved yet to treat post-surgical hypoparathyroidism, but the results obtained in several experimental studies in both adults and children seem promising [89,90,91], showing reduced rates of side effects when compared with the conventional treatment [92].

1.5.3.2.2 rhPTH (1-84)

Natpara is the full-length synthetic version of PTH. Its advantages include a once-a-day use (thanks to a long half-life [93]), a reduction of supplements by ≥ 50% in both short- and long-term [75,94], ability to maintain normal ranged calcemia, decreased phosphatemia, an unchanged mean urinary calcium levels, and to increase bone turnover [95]. It is controversial whether it improves the patients' quality of life [75,76].

1.5.3.2.3 PTH analog AZP-3601

AZP-3601 is a peptide analog of PTH that targets a specific configuration of the PTH-1 receptor. It has shown to sustain calcemia and control the symptoms of hypoparathyroidism in a safely manner [96]. The drug prevents chronic kidney disease by limiting the calciuria and preserving bone integrity. After successfully completing several preclinical studies, AZP-3601 was included into a world-wide phase 2 clinical study that started in September 2020 [97,98].

1.6 Management and follow-up of permanent hypoparathyroidism

1.6.1 Lack of consensus diagnosing and monitoring permanent hypoparathyroidism

The European Guidelines [80] define permanent hypoparathyroidism as a low-serum iPTH concentration and/or need for replacement therapy after six postoperative months, whereas the American Association of Clinical Endocrinologists [36] extends the follow-up period to one year.

A direct consequence of such division is a clear lack of consensus regarding the follow-up period necessary to make a firm diagnosis of permanent hypoparathyroidism with consequent clinical relevance since a diagnosis of permanent hypoparathyroidism implies lifelong medical treatment, imposes an economical burden and may impact on the quality of life [30,72].

There is little empirical evidence to establish the follow-up time required to confirm the definitive loss of the parathyroid function after thyroidectomy. Most studies on the recovery of the parathyroid function (RPF) after thyroidectomy are limited in sample size and/or report a short observation time after surgery [99,100,101]. Some anecdotal reports [102] have shown that RPF may take place more than one year after thyroidectomy; however, this prospective study had a follow-up of only three years and patients diagnosed with benign thyroid conditions were excluded.

1.6.2 Recommended follow up and treatment monitoring

The only official recommendations are those held by the European Society of Endocrinology [80] that recommends routine biochemical monitoring of serum levels ionized calcium or albumin adjusted total calcium, phosphate, magnesium and creatinine (eGFR), as well as assessment of symptoms of hypocalcemia and hypercalcemia at regular time intervals (e.g., every 3-6 months). If a change in therapy is applied, the monitoring frequency should change to once a week or every two weeks. It is advisable to check 24-hour calciuria at regular longer time intervals (e.g., once every 1-2 years). Monitoring renal status through imaging studies is recommended if the patient shows symptoms of nephrolithiasis or if the serum creatinine rises. Other comorbidities should be monitored on a yearly basis. Finally, the monitoring of bone mineral density is counter-advised.

In the chronic setting of hypoparathyroidism, the European Society of Endocrinology set these goals [80]:

1) Preventing the appearance of clinical manifestations related to hypocalcemia
2) Maintaining the calcemia in the low to low-normal range (*ie*, ≤ 0.5 mg/dL below normal), which differs from the concept of "parathyroid splinting"
3) Maintaining the calcium-phosphate product < 55 mg^2/dL^2 (< 4.4 $mmol^2/L^2$) to avoid ectopic soft tissue calcifications
4) Preventing the appearance of hypercalciuria, hypercalcemia, hypomagnesemia, and extraskeletal calcifications
5) Monitoring creatinine and keeping glomerular filtration rate within reference range

1.7 Late recovery of parathyroid function

1.7.1 Factors involved in the recovery of parathyroid function

There is scarce data assessing the factors involved in recovery of parathyroid function in a long-term basis. Some authors have suggested factors that predict the speed of recovery (such as the preoperative PTH level, perioperative percent drop in PTH level, diabetes mellitus, and gender [100]); other authors [102] prefer to follow an indirect approach, describing the absence of factors that would prevent the recovery of the parathyroid function (e.g. autotransplantation, node dissection, unnecessary therapeutic supplementation). Besides the fact that information about this topic is scarce, there is also controversy. Our group proposed intensive medical treatment to maintain corrected calcemia above 9.0 mg/dL at one-month after thyroidectomy as it emerged as the prominent factor easing the recovery of the parathyroid function [18].

Nonetheless, detecting recovery relies also on the physician monitoring the patient's progression, and identifying when and if such recovery happens. The difficulty appears in patients who underwent total thyroidectomy but did not present symptoms nor a risky biochemical profile. These patients also benefit from a close-monitor, since they could develop delayed hypoparathyroidism [103]. Some data point to the fact that this is not always executed; an example, the PARADOX study [73], where 374 American patients with post-surgical hypoparathyroidism were studied $\geq$ 6 months, showed that only 0.5% of them were followed up by the surgeons.

2 HYPOTHESES

1) Female gender, especially younger aged, is a risk factor for hypocalcemia after total thyroidectomy. Different menstrual status may play a role in the development of parathyroid insufficiency.

2) Once post-surgical hypoparathyroidism has been diagnosed, late recovery of the parathyroid function occurs beyond one year after the thyroidectomy.

3 AIMS

3.1 General

Assess the influence of gender and menstrual status on postoperative hypoparathyroidism, and the prevalence and variables involved in late recovery of parathyroid function.

3.2 Specific

1) Assess the influence of women's age and menstrual status on postoperative parathyroid function.

2) Analyze the impact of age, PGRIS score and pathology on parathyroid insufficiency after total thyroidectomy in female patients.

3) Determine the prevalence and timing of recovery of the parathyroid function in patients with protracted (> 1 month) post-surgical hypoparathyroidism.

4) Identify variables associated with delayed (> 6 months) recovery of the parathyroid function in patients that have undergone total thyroidectomy.

4 PATIENTS AND METHODS

4.1 Study design and setting

4.1.1 Design

Review of a prospectively maintained clinical database of a cohort of consecutive adult (≥ 18 years old) patients who underwent first-time total thyroidectomy.

For the study assessing the influence of female gender on postoperative hypoparathyroidism, 811 patients who underwent total thyroidectomy for benign multinodular goiter between 2000 and 2017.

For the study evaluating the late recovery of parathyroid function, 854 patients undergoing total thyroidectomy for either multinodular goiter or thyroid cancer between 2000 and 2014.

4.1.2 Setting

The same team of experienced surgeons performed each thyroid surgery in a single tertiary referral center for Endocrine Surgery (Endocrine Surgery Unit of the Hospital del Mar, in Barcelona, Spain).

4.2 Patients

4.2.1 Inclusion criteria

Elegibility criteria were adult patients (≥ 18 years old) undergoing first-time total thyroidectomy for benign multinodular goiter in both studies, and also for thyroid cancer in the study assessing late recovery of parathyroid function.

4.2.2 Exclusion criteria

Exclusion criteria were reoperations, associated parathyroidectomy for primary or secondary hyperparathyroidism, Dunhill or subtotal thyroidectomies (performed for asymmetrical goiter or Graves' disease), completion thyroidectomies and thyroidectomies for recurrent benign or malignant disease. In the study assessing the influence of female gender, patients with thyroid carcinoma were also excluded.

4.3 Instrumentation

4.3.1 Surgical technique

All patients underwent total extracapsular thyroidectomy. Central compartment node dissection was added in patients diagnosed with papillary or medullary thyroid cancer and selective modified radical lateral neck dissection was performed as clinically indicated. Parathyroid glands were sought in their usual position and no effort was made to identify them when located in non-orthotopic places. The identification of parathyroid glands was based solely on visual macroscopic features. Ligation of the inferior thyroid artery was carried out at the level of distal branches and close to the thyroid gland to minimize the devascularization of the parathyroid glands. When parathyroid glands could not be preserved *in situ* (either completely devascularized or accidentally excised), autotransplantation was performed using the technique described by Olson *et al.* [4]: the glands were cut into 1 mm^3 fragments and inserted in several pockets within the ipsilateral sternocleidomastoid muscle, before sending the specimen to the Pathology laboratory.

4.3.2 Parathyroid glands accounting. PGRIS score (Parathyroid Glands Remaining *In Situ)*

The number of parathyroid glands remaining in situ (PGRIS, not transplanted nor resected inadvertently) was calculated as previously reported [22] using the formula PGRIS = 4 – (glands autotransplanted + inadvertently resected), and patients were classified accordingly (PGRIS score 1 to 4). Thyroidectomy specimens were processed by the same dedicated pathologist who actively looked for and consistently reported on the parathyroid glands inadvertently excised.

4.3.3 Postoperative management

In both studies, serum calcium and iPTH concentrations were determined 24 hours after thyroidectomy. Additionally, since 2014, iPTH concentrations are also checked at 4 hours after the end of the thyroidectomy, which applies to the study assessing gender influence. iPTH concentrations were determined using either an immunoradiometric second-generation assay using a Total Intact PTH IRMA assay (Scantibodies Laboratory, Santee, CA, United States) or a solid-phase, two-site chemiluminescent enzyme-labelled assay, IMMULITE® 2000 Intact PTH assay (Siemens Healthcare Diagnostics Spain, Madrid, Spain). The normal range was established at 13-65 pg/mL (1.4-7 pmol/L) and the detection limit was set at 3 pg/mL (0.32 pmol/L). Until 2014, replacement therapy was prescribed only to patients with hypocalcemia (s-Ca < 2 mmol/L or < 8 mg/dL at 24 hours). From 2014 onwards, earlier supplementation was started in patients with low iPTH (≤ 10 pg/mL) at 4 hours after surgery. Suplements were prescribed in the form of 1.5–3 g/day of calcium carbonate and 0.5–1.5 µg/day of calcitriol at the time of hospital discharge according to body weight and severity of hypocalcemia.

4.3.4 Postoperative follow-up

Tipically, patients were discharged on the first or second postoperative day and they were followed thereafter in the outpatient clinic. Thyroid-stimulating hormone, free thyroxine, serum calcium, serum phosphate and iPTH levels were determined within 4–6 weeks of total thyroidectomy. Doses of calcium salts and calcitriol, if supplementation required, were not altered between hospital discharge and the second follow-up visit. Thereafter, patients with benign disease and normal parathyroid function were sent to the referring physicians whereas all patients with thyroid cancer and/or hypocalcaemia (calcium level below 8mg/dL) or protracted hypoparathyroidism at one postoperative month (iPTH concentration lower than 13 pg/mL) were followed by the surgical team with regular interval measurements of calcium and iPTH until recovery of the parathyroid function (RPF) or permanent hypoparathyroidism was diagnosed.

Weaning off replacement therapy was initiated when serum calcium concentration was ≥ 8 mg/dL and iPTH showed a sustained increase up to normal serum concentrations.

4.3.5 Definitions

Parathyroid failure syndromes were defined in line with prior reports [5]:

- Postoperative hypocalcemia / Postoperative parathyroid insufficiency was defined as serum calcium levels < 8 mg/dL (< 2 mmol/L) within 24 hours after thyroidectomy and/or an iPTH concentration ≤ 10 pg/mL 4 hours after thyroidectomy.
- Protracted hypoparathyroidism (previously known as transient hypoparathyroidism) was defined as iPTH levels lower than 13 pg/mL (< 1.4 pmol/L) and/or need for calcium ± vitamin D supplements 4-6 weeks after surgery.

- Permanent hypoparathyroidism was considered when iPTH levels were lower than 13 pg/mL (< 1.4 pmol/L) and/or calcium ± vitamin D supplements were still required one year after surgery.

RPF was defined as a normal value for iPTH in asymptomatic patients not requiring replacement therapy. Permanent hypoparathyroidism was diagnosed if serum iPTH was low (< 13 pg/mL) or undetectable at the last follow-up visit and replacement therapy was still required.

4.4 Data acquisition and processing of data

4.4.1 Variables and database

Data was collected using a database created with FileMaker® Pro-Advance v.13.0 software (File-Maker Inc., Santa Clara, CA, USA) and extracted from the electronic clinical records from the hospital's general database. The prevalence of postoperative, protracted, and permanent hypoparathyroidism was investigated. Demographic, clinical, surgical, pathological, and biochemical variables relevant to the diagnosis and management of postoperative hypocalcemia were included. The following preoperative data were recorded: gender, age, clinical diagnosis, serum calcium and thyroid function tests. For the study assessing gender influence on parathyroid insufficiency, a cut-off at 45 years was chosen to assess differences between pre- and post-menopausal women since the precise age at menopause was not recorded before 2017. After histopathologic analysis, specimen weight, number of resected lymph nodes (if central or lateral neck compartment dissection was performed) and presence of parathyroid glands in the specimen were recorded. The following postoperative variables were also detailed: serum calcium and iPTH concentration at 4 hours and 24 hours, calcium and calcitriol dosage at discharge and iPTH, serum calcium, serum phosphate and thyroid function tests at 4–6 weeks after surgery and regularly thereafter in patients with protracted hypoparathyroidism.

4.4.2 Statistical analysis

Statistical analyses were carried out with SPSS® version 22.0 and 23.0 (IBM, Armonk, NY, USA). Descriptive statistics were used to document the prevalence and characteristics of patients developing parathyroid failure. The Kolmogorov–Smirnov test was used to verify the normal distribution of quantitative variables. Quantitative continuous and normally distributed variables are expressed as mean ± standard deviation and their means compared using Student's t-test for unpaired samples or the ANOVA test. Non-normally distributed variables are expressed as mean ± standard error of the mean and compared using the Mann–Whitney U test or Kruskal-Wallis test. Dichotomous variables were compared using the chi-square or Fisher's exact test as appropriate. Binomial logistic regression analysis with predictors selected by a forward stepwise procedure was used to assess the risk factors for permanent hypoparathyroidism and for postoperative parathyroid failure among women. Time to RPF was analysed using Kaplan–Meier survival curves and groups compared with the Log Rank (Mantel– Cox) test. Statistical significance (two-tailed) was set at $p < 0.05$.

4.5 Ethical and legal considerations

Patients' consent to use anonymized data for this observational clinical research was obtained together with the informed consent for thyroidectomy.

5 RESULTS

5.1 Study population

For the study assessing the influence of female gender on parathyroid insufficiency a sample of 811 total thyroidectomy patients diagnosed with benign multinodular goiter were included in the analysis (**Figure 1**). There were 114 men (14 percent) and 697 women (86 percent) with a mean age of 53.2 years old. Four patients were lost during the follow-up period.

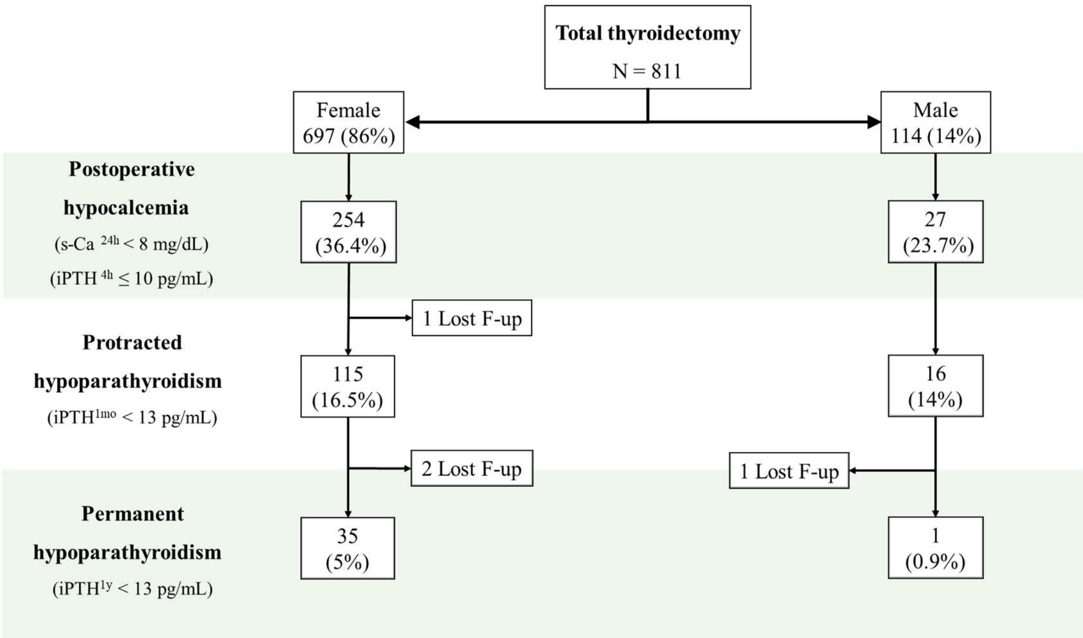

Figure 1. Patient flowchart describing the calcemic and parathyroid post-operative evolution of the 811 total thyroidectomy patients included in the analysis, classified by gender. Patients lost in follow up are shown as well.

s-Ca ^{24h}, serum calcium 24 hours after surgery; iPTH ^{1mo}, intact parathyroid hormone one month after surgery; iPTH ^{1y}, intact parathyroid hormone one year after surgery.

The study analyzing recovery of parathyroid function included an initial sample of 868 patients, as shown in **Figure 2**. After 14 patients did not meet the inclusion criteria, a cohort of 854 patients was studied. Some 666 patients had a benign diagnosis and 188 had thyroid cancer; of the latter group, 115 (61%) received ablative radioiodine therapy between three and six months after thyroidectomy. From the initial cohort, 375 patients (44%) developed postoperative hypocalcemia, of which 39 were excluded (due to exitus, incomplete data, lost to follow-up, or unavailable PTH).

Some 184 patients did not present low iPTH values at one-month postoperatively, thus leaving 152 patients diagnosed with protracted hypoparathyroidism. After excluding 10 patients, 142 patients with protracted hypoparathyroidism were investigated (female-to-male ratio 121:21; mean age 53.5 years old, age range 39-69 years old). Of these, 106 patients (75%) recovered the parathyroid function during follow-up and 36 (25%) were diagnosed with permanent hypoparathyroidism. Recovery of the parathyroid function took place within six months in 73/106 patients (69%), between six and twelve months in 21/106 (20%), and beyond this period in 12/106 (11%) patients.

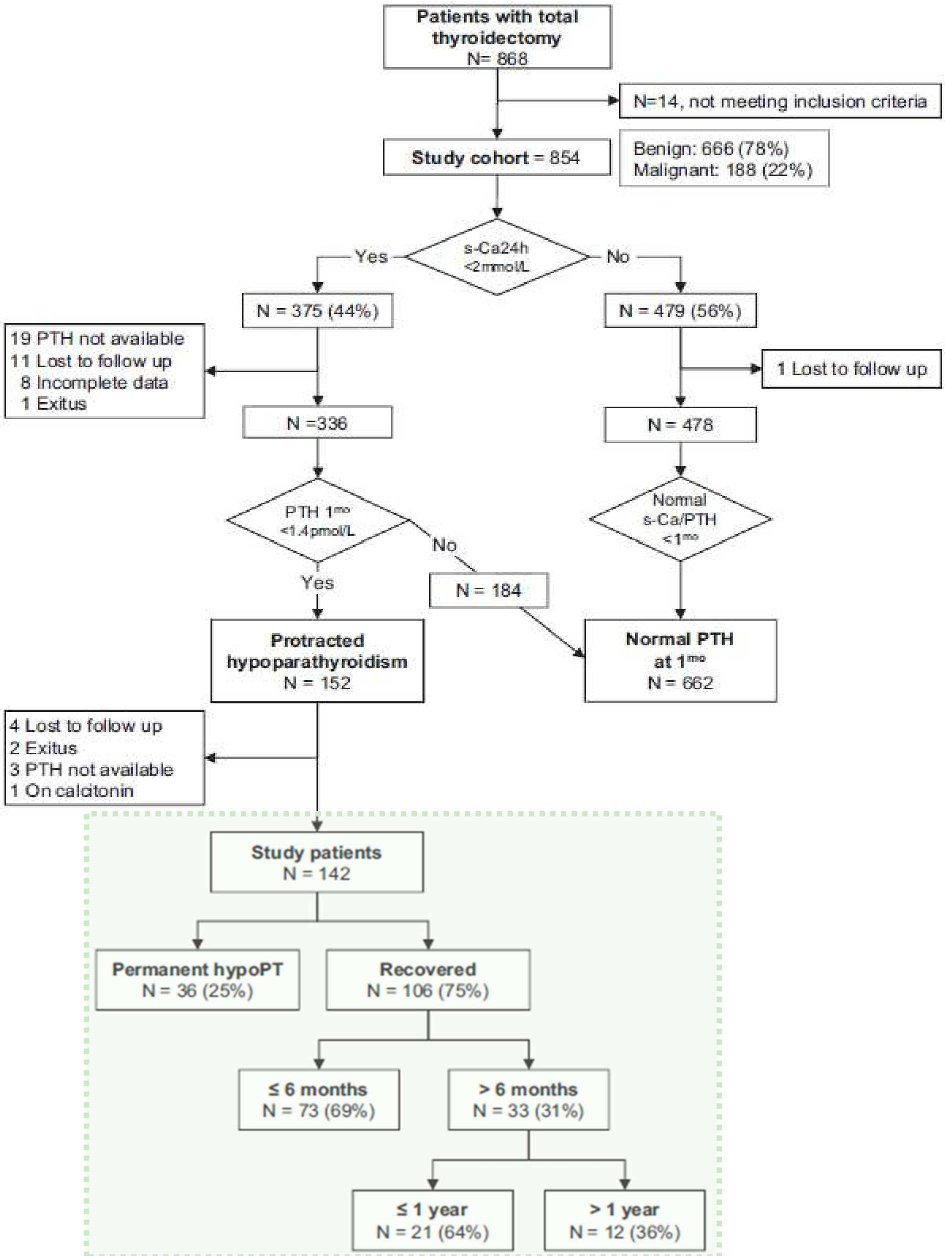

Figure 2. Patient flow diagram of 868 patients included in the study of RPF. Highlighted area encloses the studied patients. Percentages are over the immediately preceding group.

HypoPT: hypoparathyroidism; PTH: parathormone; s-Ca: serum calcium.

5.2 Influence of female gender and menstrual status on parathyroid insufficiency after total thyroidectomy

5.2.1 Influence of female gender on parathyroid insufficiency

The prevalence of postoperative hypocalcemia was 23.7% in men and 36.4% in women ($p = 0.008$). Protracted hypoparathyroidism did not show a statistically significant difference between genders (prevalence of 14% for males *vs*. 16.5% for females; $p = 0.055$). Permanent hypoparathyroidism was more common in women (5% *vs*. 0.9%; $p = 0.047$).

The gender differences in clinical and biochemical parameters are shown in **Table 4**.
Preoperative serum calcium and calcemia 24 hours after surgery were lower in the female group when compared to men. Women presented higher rates of postoperative hypocalcemia than men (female-to-male ratio: 9.4:1; $p < 0.001$). iPTH values at one-month after the thyroidectomy were also higher among the male group ($p = 0.001$). The prevalence of protracted and permanent hypoparathyroidism was higher among females (7.2-fold and 35-fold, respectively), although gender differences for these two outcomes did not show statistical significance.

Table 4. Parathyroid failure syndromes, biochemical and clinical variables after total thyroidectomy in male and female patients

	Male (N = 114)	**Female< 45-yo (N = 140)**	**Female≥ 45-yo (N = 557)**	**p-value**
Age, mean (SD), (years)	56.28 (13.9)	33.60 (5.3)	60.18 (11.1)	< 0.001**
Preoperative s-Ca, mean (SD), (mg/dL)	9.56 (0.5)	9.34 (0.5)	9.45 (0.5)	< 0.001**
s-Ca ^{24h}, mean (SD), (mg/dL)	8.46 (0.7)	8.01 (0.7)	8.19 (0.8)	< 0.001**
Postoperative hypocalcemia, No. (%)	27 (23.7)	71 (50.7)	183 (32.9)	< 0.001*
iPTH ^{24h}, mean (SD), (pg/mL)	24.2 (23.8)	17.0 (15.8)	20.24 (19.2)	0.525***
s-Ca $^{1\ month}$, mean (SD), (mg/dL)	9.26 (0.6)	9.23 (0.8)	9.32 (0.7)	0.003**
iPTH $^{1\ month}$, mean (SD), (pg/mL)	46.1 (47.3)	26.6 (28.6)	32.82 (26.7)	0.001***
Protracted hypoparathyroidism, No. (%)	16 (14.0)	31 (22.1)	84 (15.1)	0.055*
Permanent hypoparathyroidism [a], No. (%)	1 (0.9)	11 (7.9)	24 (4.3)	0.070*
PGRIS score [b], No. (%)				0.416*
1 or 2	2 (1.8)	4 (2.9)	26 (4.7)	
3	19 (16.7)	30 (21.4)	133 (23.9)	
4	92 (80.7)	105 (75.0)	396 (71.1)	

*, Chi-squared test; **, One-way ANOVA test; ***, Kruskal-Wallis test; [a], Data not available for one male patient and one female patient; [b], Data not available for two female patients. PGRIS: Parathyroid Glands Remaining *In Situ*.

The mean of PGRIS scores were similar in males and females [3.7 (0.6) *vs.* 3.6 (0.6); p = 0.484]. Thus, different rates of postoperative hypocalcemia between men and women cannot be attributed to variations in the intraoperative management of the parathyroid gland.

5.2.2 Influence of menstrual status on parathyroid insufficiency

Regarding the group of female patients, age cut-off was set at 45 years old. Hypocalcemia was developed in half of those aged < 45 years whereas it was documented in only one-third of those aged ≥ 45 years (p < 0.001). Accordingly, young women showed a higher prevalence of protracted and permanent hypoparathyroidism. Although PTH concentration at 24 hours after surgery was not different, serum calcium levels were significantly lower in young patients.

To adjust for the intraoperative management of the parathyroid glands, a final analysis was performed in cases where the four glands were left in situ (PGRIS 4). Women < 45 years exhibited a worse biochemical and clinical profile than those aged 45 years or more with over a two-fold prevalence of permanent hypoparathyroidism (**Table 5**).

Table 5. Parathyroid failure syndromes after total thyroidectomy in women with four parathyroid glands remaining in situ (PGRIS 4)

	< 45 years old (N = 105)	**≥ 45 years old (N = 396)**	**p-value**
Age, mean (SD), (years)	36.3 (5.8)	61.4 (10.3)	< 0.001**
Preoperative s-Ca, mean (SD), (mg/dL)	9.29 (0.4)	9.49 (0.4)	< 0.001**
s-Ca 24h, mean (SD), (mg/dL)	8.03 (0.7)	8.34 (0.7)	< 0.001**
Postoperative hypocalcemia, No. (%)	49 (46.7)	102 (25.8)	< 0.001*
iPTH 24h, mean (SD), (pg/mL)	21.3 (17.3)	23.42 (20.1)	0.469***
s-Ca 1 month, mean (SD), (mg/dL)	9.11 (0.7)	9.36 (0.6)	0.004**
iPTH 1 month, mean (SD), (pg/mL)	30.44 (26.5)	37.58 (27.4)	0.051***
Protracted hypoparathyroidism, No. (%)	20 (19.0)	38 (9.6)	0.007*
Permanent hypoparathyroidism, No. (%)	7 (6.7)	9 (2.3)	0.022*

*, Chi-squared test; **, Students t-test; ***, U de Mann-Whitney. SD, Standard Deviation; s-Ca, serum calcium; iPTH, intact parathyroid hormone.

5.2.3 Predicting factors of postoperative parathryoid function in female patients

A binomial logistic regression analysis of variables protecting from postoperative hypocalcemia in females, showed that the independent factors were preoperative serum calcium OR: 0.5 (95% CI: 0.35–0.82), age > 45 years with OR: 0.6 (95% CI: 0.39–0.96) and high PGRIS (PGRIS 3–4) scores with OR: 0.6 (95% CI: 0.45–0.76) (**Table 6**).

Table 6. Binomial logistic regression of independent predictor variables of postoperative hypocalcemia in females

Predicted variables	Wald statistic*	Odds ratio (95% CI)	p-value
Preoperative s-Ca	9.018	0.5 (0.35 – 0.82)	< 0.003
Age > 45 years old	4.614	0.6 (0.39 – 0.96)	< 0.032
PGRIS 3-4	14.138	0.6 (0.45 – 0.76)	< 0.001

5.3 Recovery of parathyroid function after postoperative parathyroid insufficiency

5.3.1 Outcome of parathyroid function after protracted hypoparathyroidism

Differences between the 142 patients who recovered and did not recover from protracted hypoparathyroidism are shown in **Table 7**. There was no difference in RPF between patients operated for benign or malignant disease. The PGRIS score was significantly better in patients recovering the parathyroid function. No early biochemical parameter was predictive of the long-term parathyroid function. At one postoperative month, however, both normal–high serum calcium and detectable iPTH serum concentrations were associated with a higher proportion of RPF. Calcium and calcitriol dosages at the time of hospital discharge were higher (and significant for calcium) in patients with RPF. Serum calcium concentration at one month, however, did not correlate with the amount of replacement therapy. The multivariate analysis (**Table 8**) identified that the relevant independent variables predicting RPF were PGRIS score, serum calcium level at 1 month and a detectable iPTH (0.4–1.4 pmol/L) at 1 month.

Table 7. Demographic and disease-related variables of 142 patients with protracted hypoparathyroidism who did or did not recover the parathyroid function

	Recovered (N = 106)	**Permanent hypoparathyroidism (N = 36)**	**p-value**
Age (years) **	53 ± 14	54 ± 15	0.626
Gender, *n* (%)			0.370
Male	18 (86)	3 (14)	
Female	88 (73)	33 (27)	
Indication for surgery, *n* (%)			0.298
Goiter	72 (72)	28 (28)	
Malignancy	34 (81)	8 (19)	
Associated procedure, *n* (%)			
Central neck dissection			0.267
Yes	28 (82)	6 (18)	
No	78 (66)	30 (34)	
Lateral neck dissection			0.978
Yes	8 (80)	2 (20)	
No	98 (74)	34 (26)	
Number of lymph nodes resected	5 ± 1	3 ± 1	0.835
Specimen weight (g)	79 ± 7	77 ± 11	0.847
PGRIS score*** *n* (%)			0.014
1 or 2	12 (63)	7 (37)	
3	36 (66)	19 (34)	
4	57 (86)	9 (14)	
s-Ca preop (mmol/L) **	2.34 ± 0.1	2.30 ± 0.2	0.123
s-Ca ^{24h} postop (mmol/L)	1.87 ± 0.02	1.85 ± 0.03	0.326
s-Ca $^{1\ month}$ (mmol/L)	2.38 ± 0.02	2.14 ± 0.05	0.001
< 2.25 mmol/L, n (%) ****	20 (51)	19 (49)	0.001
≥ 2.25 mmol/L, n (%) ****	82 (86)	13 (14)	
PTH ^{24h} postop (pmol/L)	0.10 ± 0.04	0.04 ± 0.03	0.603
PTH $^{1\ month}$ (pmol/L)	0.58 ± 0.04	0.39 ± 0.06	0.009
Detectable (> 0.4 pmol/L) ****	66 (87)	11 (13)	0.001
Undetectable (≤ 0.4 pmol/L)	40 (63)	25 (37)	
Last PTH (pmol/L)	2.97 ± 0.17	0.57 ± 0.07	0.001
Follow-up (days)	828 ± 113	2216 ± 270	0.001
Days until recovery	192 ± 20	--	--
Calcium dosage at discharge (g/day)	2.8 ± 0.08	2.5 ± 0.2	0.033
Calcitriol dosage at discharge (μg/day)	0.76 ± 0.04	0.65 ± 0.08	0.213

*Quantitative variables given as mean ± S.E.M. except where noted; **mean ± S.D.; ***PGRIS, parathyroid glands remaining *in situ*; ****Fisher's test

Table 8. Multivariate analysis for permanent *vs*. recovery from protracted hypoparathyroidism

Predicted variables	OR	IL (95%)	SL (95%)	p-value
Permanent hypoparathyroidism				
PGRIS (1-4)	0.331	0.170	0.646	0.001
Serum calcium $^{1\ month}$ (mg/dL)	0.205	0.100	0.419	0.001
Detectable iPTH $^{1\ month}$ (1 if Yes)	0.105	0.031	0.350	0.001

*Stepwise forward conditional binomial logistic regression. Values within parenthesys correspond to the 95% confidence interval. Parameters included in the binomial logistic regression: age, gender, autotransplant, surgical extension, and PGRIS. OR: odds ratio; IL: inferior limit; SL: superior limit

5.3.2 Factors predicting early *versus* late recovery of parathyroid function

Thyroidectomy for cancer was the only significant clinical variable associated with RPF after six months (**Table 9**). This was independent of the PGRIS score and serum calcium and iPTH concentrations at 1 month. Patients recovering early had a better biochemical profile at one month suggesting a less severe parathyroid injury in this subgroup.

In agreement with this, final iPTH concentrations were higher in patients recovering within six months. Time to RPF or to diagnosis of permanent hypoparathyroidism is shown in **Figure 3**. About two-thirds of the patients showed an early RPF (< 6 months) but one-third recovered after six months. Factors significantly favoring an early RPF were a detectable iPTH and a serum calcium concentration > 2.25mmol/L at 1 month. The different PGRIS groups had a rather parallel RPF rates during the first six months. Only the PGRIS 3 and 4 groups, however, had some chances of late RPF. No patient in the PGRIS 1–2 group recovered beyond one year (**Figure 3D**).

The relationship between serum calcium and iPTH concentrations at one month in 142 patients with protracted hypoparathyroidism is shown in **Figure 4**. No correlation was found between these two variables for any of the three groups of patients. Sixteen patients had a serum calcium concentration ≥ 2.62 mmol/L associated with low or undetectable iPTH concentration. Of these, 10 recovered within six months (mean: 108 ± 52 days, range 49–140 days), 4 after six months and 2 developed permanent hypoparathyroidism. In these 10 patients with an early RPF, an inverse correlation was found between serum calcium and days to RPF ($r^2 = 0.55$; $p < 0.001$).

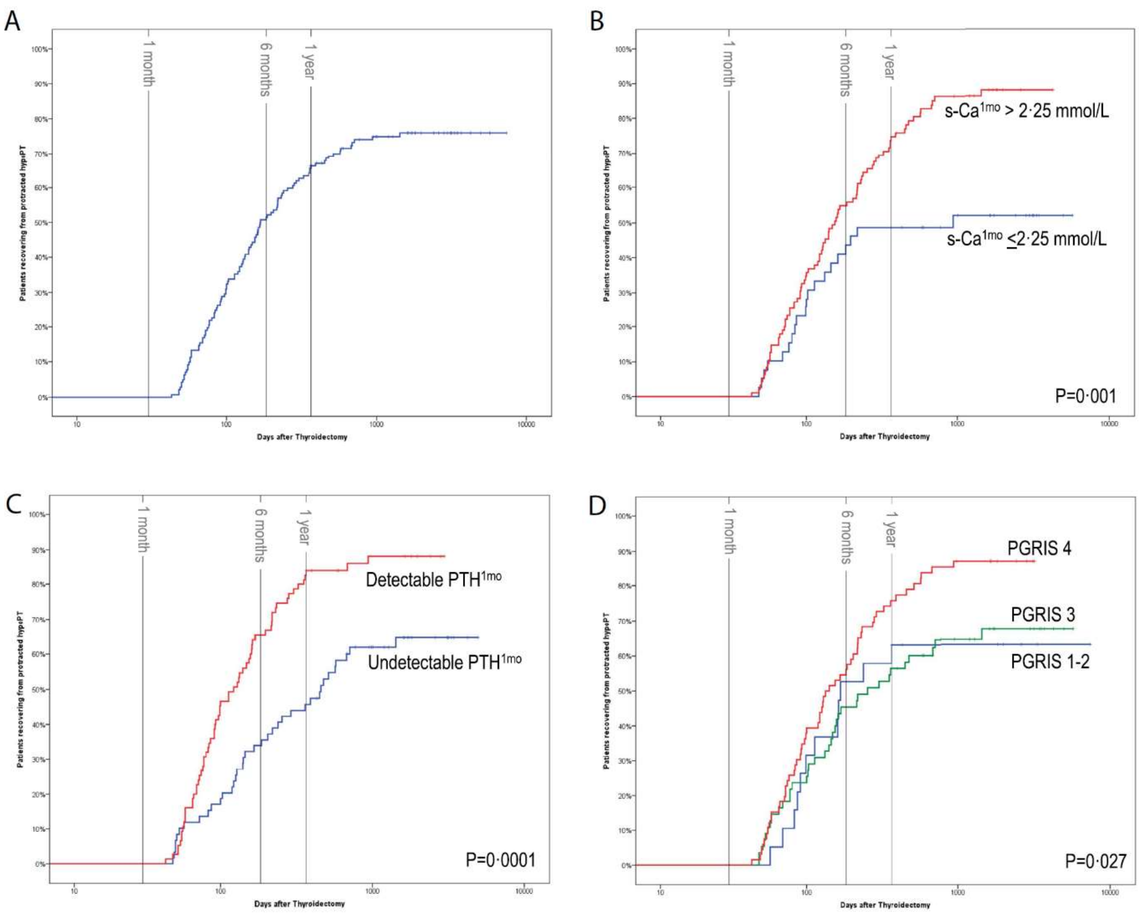

Figure 3. Time to recovery of the parathyroid function (RPF) in patients with protracted hypoparathyroidism.

(A)Time to RPF for the whole cohort (N = 142).

(B) RPF according to serum calcium concentration at one month.

(C) RPF according to detectable *vs* undetectable parathormone at one month.

(D) RPF according to PGRIS (parathyroid glands remaining in situ).

Horizontal axis uses logarithmic scale (days).

hypoPT, hypoparathyroidism. **P-**values from the Log Rank (Mantel–Cox) test.

Table 9. Demographic and disease-related variables of 106 patients recovering from protracted hypoparathyroidism within or beyond six months after total thyroidectomy.*

	≤ 6 months (N = 73)	**> 6 months (N = 33)**	**p-value**
Age (years) **	53 ± 15	53 ± 13	0.855
Gender, *n* (%)			0.337
Male	10 (56)	8 (44)	
Female	63 (71)	25 (29)	
Indication for surgery, *n* (%)			0.014
Goiter	55 (76)	17 (24)	
Malignancy	18 (53)	16 (47)	
Associated procedure, *n* (%)			
Central neck dissection			0.425
Yes	16 (60)	11 (40)	
No	57 (72)	22 (28)	
Lateral neck dissection ****			0.251
Yes	4 (50)	4 (50)	
No	69 (70)	29 (30)	
Number of lymph nodes resected	3.8 ± 1	6.6 ± 2	0.351
Specimen weight (g)	88 ± 9	61 ± 10	0.059
PGRIS score, *n* (%) ****			0.453
1 or 2	10 (83)	2 (17)	
3	25 (70)	11 (30)	
4	37 (65)	20 (35)	
s-Ca preop (mmol/L) **	2.34 ± 0.4	2.37 ± 0.2	0.165
s-Ca ^{24h} postop (mmol/L)	1.87 ± 0.02	1.87 ± 0.03	0.865
s-Ca $^{1\ month}$ (mmol/L)	2.39 ± 0.03	2.39 ± 0.03	0.474
< 2.25 mmol/L, n (%) ****	17 (85)	3 (15)	0.052
≥ 2.25 mmol/L, n (%) ****	52 (63)	30 (37)	
PTH ^{24h} postop (pmol/L)	0.09 ± 0.05	0.10 ± 0.05	0.403
PTH $^{1\ month}$ (pmol/L)	0.63 ± 0.04	0.47 ± 0.06	0.033
Detectable (> 0.4 pmol/L) ****	50 (76)	16 (24)	0.049
Undetectable (≤ 0.4 pmol/L)	23 (47)	17 (53)	
Last PTH (pmol/L)	3.21 ± 0.22	2.49 ± 0.22	0.046
Follow-up (days)	622 ± 124	1258 ± 220	0.001
Days until recovery	96 ± 38	405 ± 45	0.001
Calcium dosage at discharge (g/day)	2.8 ± 0.1	2.8 ± 0.1	0.456
Calcitriol dosage at discharge (μg/day)	0.73 ± 0.04	0.83 ± 0.07	0.182

*Quantitative variables given as mean ± S.E.M. except where noted; **mean ± S.D.; ***PGRIS, parathyroid glands remaining *in situ*; ****Fisher's test

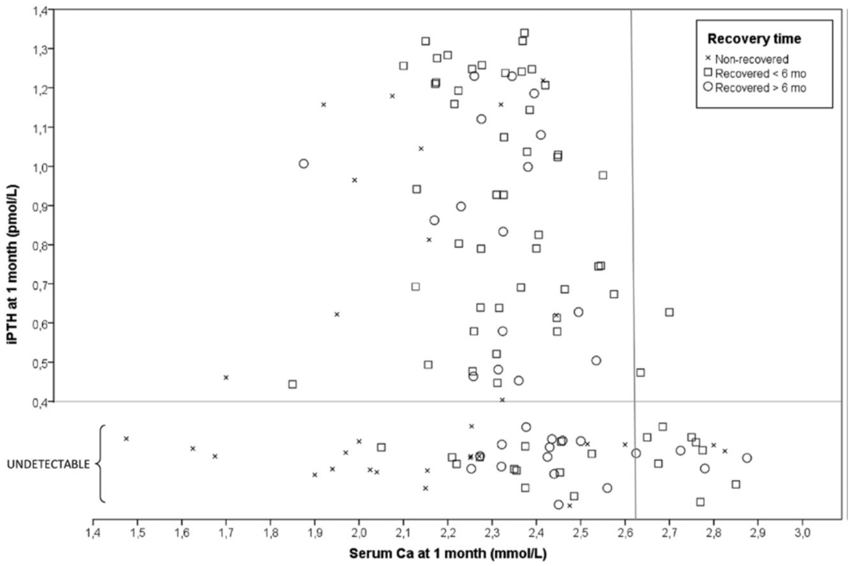

Figure 4. Serum calcium (mmol/L) vs iPTH (pmol/L) in patients with protracted hypoparathyroidism at one month after total thyroidectomy. The vertical line at 2.62 mmol/L marks the upper limit of normal serum calcium concentration. Values of iPTH concentrations below 0.40 pmol/L are labelled as ‘UNDETECTABLE’ and plotted with randomly assigned iPTH values between 0 and 0.39 pmol/L.

6 DISCUSSION

6.1 Gender influence on postoperative parathyroid failure

Traditionally, patients'gender has been considered to be among the main clinical variables associated with hypocalcemia after total thyroidectomy [22,50,52,53,54,104]. Some authors have even suggested that replacement therapy should be given to all female patients undergoing total thyroidectomy, even if three parathyroid glands were correctly preserved [105]. On the other hand, several reports have not identified an increased risk for hypocalcemia in women. Most of these, however, are flawed by the inclusion of conservative surgical procedures, different definitions of postoperative hypocalcemia and lack of long-term follow-up [6,55,106].

The present study was carried out in a homogeneous series of total thyroidectomies for multinodular goiter, and it confirms the higher prevalence of postoperative parathyroid failure in women. Moreover, it further deepens into the issue by adding to the analysis the presumed menopausal status and the number of PGRIS, a key variable influencing the postoperative parathyroid function [22,107].

Sands *et al.* [56] were the first to address in some detail the issue of female gender as a risk factor for post-thyroidectomy hypocalcemia and reported that women showed a 2.14 relative risk for this complication. However, they did not find a significant difference in rates of transient hypocalcemia between premenopausal and postmenopausal women using a cut-off age of 50 years. In this retrospective study of a small female cohort, the authors did not take into account the indication for surgery nor PGRIS. A high rate of inadvertent parathyroidectomy (one gland every two thyroidectomies in women) could have also influenced the results.

The present study found that female patients developed postoperative hypocalcemia more often than men and had a prevalence of permanent hypoparathyroidism five times higher. Gender differences were particularly noticed in young women in whom all parathyroid failure syndromes were more prevalent. Mean PGRIS scores were similar in males and females, thus, different rates of postoperative hypocalcemia between men and women cannot be attributed to variations in the intraoperative management of the parathyroid glands.

Furthermore, the present work reveals that half of the females under 45 years of age developed postoperative hypocalcemia compared to just one-third of those > 45 years, regardless of similar concentration of iPTH at 24 hours after surgery and similar PGRIS scores. A final analysis in female patients adjusting for PGRIS 4, showed that age is a key variable for the development of postoperative parathyroid failure: despite proper preservation of the four parathyroid glands, women under 45 years old had a significantly worse biochemical and clinical profiles than older women.

Similarly to the study performed by Sands *et al.* [56], we studied female patients setting an age cut-off assuming it would be a surrogate variable for the menopausal stage.

We set the cut-off to 45 years for two reasons: fisrtly, this is the average age women become perimenopausal in Spain where the mean age for post-menopause is 51 years; and secondly, a five to six-year prior interval is a sound assumption based on FSH dynamics [108]. Using this age cut-off, substantial and statistically significant differences were observed in all clinical and biochemical parameters of parathyroid function between both age groups. This assumption, however, limits the precision of our analysis and calls for further investigations in which the exact age at menopause should be recorded prospectively.

6.2 Suggested mechanisms to explain female gender as risk factors for post-surgical hypoparathyroidism

Several authors have tried to provide an explanation as to why women are more prone to develop post-surgical parathyroid insufficiency.

The article published in 2011 by Sands *et al.* [56] provides two hypotheses for this phenomenon: a genetic difference between genders that may put women at higher risk for developing the hypocalcemic disorder; and anatomic differences between males and females. This would be related to the smaller size of the female parathyroid glands, their parenchymal and stromal fat composition variance from those of men, and a more delicate anatomy of the surrounding structures, which may complicate the surgical procedure and increase the frequency of inadvertent parathyroidectomies and other damage to the glands. This theory can not be supported by our findings since the mean of PGRIS scores were similar in males and females.

Some other authors have hypothesized the reason of such increased incidence may not be due to the features of the parathyroid failure *per se*, but because of women having a higher prevalence of thyroid disorders that require total thyroidectomy; the increased frequency of these surgeries accompanies the increased rate of parathyroid complications in this group of population. This theory would be supported by the fact that when analyzing the epidemiology of non-surgical hypoparathyroid syndromes, such female > male ratio is not seen [71].

Yamashita *et al.* [109] described female gender as the most important risk factor for tetany. The authors suggested that women may be more susceptible to calcium and vitamin D deficiency than men, thus presenting symptoms at a lower metabolic imbalance threshold. Erbil *et al.* [106] suggested also a higher risk of vitamin D deficiency among the female population. In alignment with this, Vitamin D levels have been shown to decline at older age in osteoporotic female population. Insufficient intake of calcium and vitamin D, the decreasing accumulation of 7-dehydrocholesterol in the skin leading to less pre-vitamin D3 levels [110]; disminished activity of renal 1-α-hydroxylase [111] and decreased intestinal calcium [112] have all been postulated as possible mechanisms. In a healthy subject, this process would result in decreased calcium levels that would trigger an increase in the secretion of PTH. In the case of our patients whose parathyroid glands are damaged, the compensatory PTH response is weak or absent, which most probably would lead them to develop hypocalcemia.

Nonetheless, unanimity about vitamin D deficiency as a risk factor for postoperative parathyroid insufficiency has not been reached, since there are other studies that did not find a significant association between preoperative vitamin D deficiency and post-thyroidectomy hypocalcemia [113].

Furthermore, in the current study, precisely the group of younger female patients had the highest prevalence of parathyroid insufficiency. This finding does not support vitamin D deficiency –purportedly more prevalent at older age–, as a determining factor of postoperative hypocalcemia.

Female hormones levels related to menstrual status in pre-menopausal women, may constitute a risk factor explaining why all parathyroid failure syndromes were more prevalent in this group in our study. We can only speculate about the possible influence of circulating estrogens on the parathyroid function after thyroidectomy. Recently, Haglund *et al.* [114] have identified estrogens receptors (ERB1 and ERB2) in normal parathyroid cells. They also found that the ERB1-negative parathyroid adenomas had significantly higher adenoma weight, serum calcium, and iPTH serum concentration. This suggests a potential downregulating effect of estrogens on PTH synthesis and secretion, a pathophysiological event which would be supported also by animal studies pointing in this same direction [115]. In addition, estrogens *per se* inhibit osteoclast activity and bone resorption and may render the bone more resistant to the effects of PTH.

6.3 Follow-up and time to recover the parathyroid function

The definition of permanent hypoparathyroidism after total thyroidectomy is still under debate since the timing of RPF and the variables that influence it are poorly understood. Data are accumulating to indicate that RPF is a dynamic process which may occur long after thyroidectomy [36,100,116]. Evidence presented here confirms that a prolonged follow-up is essential before a diagnosis of permanent hypoparathyroidism can be made with certainty. A follow-up postoperative period of just six months may lead to overdiagnosis and overtreatment of this condition in as much as one-third of the patients with protracted hypoparathyroidism [72].

Two previous reports have presented evidence for long-term (> 6 months) RPF. Kim *et al.* [102] studied a cohort of 1,467 total thyroidectomy patients for thyroid cancer; 22 patients (1.8%) developed 'permanent' hypoparathyroidism, but five of these showed long-term RPF after a mean of 30 months. Factors associated with these late RPFs were not investigated. Ritter *et al.* [99] followed 1,054 patients after total thyroidectomy, of whom 18% had transient hypoparathyroidism; 70% of the patients recovered within 2 months, 5% recovered between 6 and 12 months and 1.9% showed permanent hypoparathyroidism. This study, however, had a short follow-up (≤ 1 year); transient hypocalcaemia and protracted hypoparathyroidism patients were studied as a single group, and used a vague hypoparathyroidism definition (PTH < 10 pg/mL after surgery).

From our initial cohort of 142 patients with protracted hypoparathyroidism, 25% were diagnosed with permanent hypoparathyroidism. Among the 106 patients who recovered the parathyroid function, about two-thirds showed an early recovery within six months and one-third recovered after: between six and twelve months in 20% and beyond this time period in 11% of patients.

Correctly monitoring the recovery of the parathyroid function not only has clinical relevance for the patient, but also lifts an economical burden on the health system that would otherwise manage these patients for longer time than actually needed to be.

6.4 Factors influencing timing to RPF

The fact that RPF is a lengthy and dynamic process is further emphasized by the inability of early biochemical variables to predict permanent hypoparathyroidism. Immediate postoperative low/undetectable iPTH serum concentration is a good marker for the development of postoperative hypocalcemia; its ability to predict protracted or permanent hypoparathyroidism, however, is very limited [116,117,118,119].

A study assessing factors that positively influence the RPF in patients with postoperative hypocalcaemia identified preoperative iPTH concentration of > 5 pmol/L and a < 88% drop after thyroidectomy as variables favoring early RPF [100]. The authors suggested that these findings reflect both a better preoperative baseline parathyroid function and lesser degree of intraoperative parathyroid gland injury. They did not report, however, the technical issues that influence the prevalence of postoperative hypocalcaemia and the RPF, such as the extension of surgery, inadvertent parathyroidectomy [120] or autotransplantation rates.

In the current study, patients with low but detectable iPTH serum concentration at one month recovered in greater proportion and faster than those with undetectable iPTH. RPF in patients with undetectable iPTH concentration depended more heavily on other variables such as PGRIS and a serum calcium concentration at one month ≥ 2.25 mmol/L. The latter positively influenced RPF after protracted hypoparathyroidism and allowed some hope for patients with hypoparathyroidism lasting for one year.

As we have hypothesized according to previous findings, this study confirms the favorable prognostic value of high–normal calcium concentration during the first weeks of postoperative parathyroid failure may be due to a *parathyroid splinting* effect [18]. Data from the present study suggest that serum calcium concentrations at one month in patients with RPF were influenced by higher doses of calcium and calcitriol being prescribed at the time of hospital discharge. An alternate or complementary explanation of the beneficial effects of a normal–high serum calcium concentration could be that some patients might have been erroneously diagnosed with protracted hypoparathyroidism because low or undetectable iPTH at one month resulted from iatrogenic hypercalcemia. No correlation was found, however, between serum calcium and iPTH. Moreover, in the group of hypercalcemic protracted hypoparathyroidism patients that recovered, an inverse correlation was found between serum calcium and days to RPF: patients with more elevated serum calcium concentrations recovered earlier than those with mild hypercalcemia.

The third variable modulating RPF was the PGRIS score, which indirectly translates the amount of potentially viable remaining parathyroid tissue: a PGRIS 4 score predicted a significantly higher proportion of RPF. Although PGRIS did not positively influence an early recovery, patients with three or four parathyroid glands remaining *in situ* still had some chances of recovery after one year of replacement therapy. This means that surgeons should make all possible efforts to preserve the parathyroid glands *in situ* avoiding autotransplantation, inadvertent parathyroidectomy and thymectomy [22,120,121,122,123,124].

A limitation of the study is that 10% of the patients with postoperative hypocalcaemia were lost to follow-up before the final parathyroid status could be assessed. Our unit serves a geographical area that hosts a considerable proportion of mobile migrant population. We cautiously infer that most of the patients not coming back after the first postoperative visit at one week did not develop long-term calcium metabolism disturbances.

6.5 Directions for future research

We can only speculate about the possible influence of circulating estrogens on the parathyroid function after thyroidectomy in female patients at reproductive age. Additional prospective studies are needed to further elucidate the complex interaction between female sex hormones and postoperative parathyroid cell function, since the mechanism underlying the gender disparities can only be inferred for now.

The present study also sheds new light on factors influencing timing to RPF. From a clinical standpoint, early RPF was more common if thyroidectomy had been performed for multinodular goiter and this was independent of the PGRIS score and the metabolic parameters, suggesting that RPF may be impaired and/or delayed by treatment with radioiodine. Guven *et al.* [125] investigated the parathyroid function at baseline and at several time intervals after high-dose radioiodine ablation (100–150 mCi) in 19 patients after total thyroidectomy for differentiated thyroid cancer. Their study showed a 25% transient decline in iPTH concentrations around the sixth month after radioiodine treatment. This did not cause symptomatic hypocalcemia, but the authors suggest that radioiodine treatment in patients with a limited parathyroid reserve may well lead to parathyroid insufficiency. The possibility that radioiodine may interfere with the RPF deserves further research.

7 CONCLUSIONS

1) Young females present higher prevalence of post-thyroidectomy parathyroid failure syndromes compared to both men and post-menopausal women.

2) The higher prevalence of postoperative parathyroid failure among young women appears to be independent of PGRIS and could be mediated by higher levels of circulating estrogens.

3) Preoperative calcemia, age older than 45 years, and high PGRIS (3-4) seem to be the only independent factors protecting female patients from developing postoperative hypocalcemia.

4) Up to one-third of the patients with hypoparathyroidism lasting more than six months recovered after this period, and a few ones even after one year. Thus, permanent hypoparathyroidism should not be diagnosed if replacement therapy is still required six months after thyroidectomy.

5) Recovering early (< 6 months) from protracted hypoparathyroidism is conditioned by PGRIS 3-4, normal-high calcemia and detectable iPTH, both at one-month postoperatively. This subgroup presented a better biochemical profile at one month, suggesting a less severe parathyroid injury.

6) Candidates for late RPF (> 1 year) are those patients operated on for thyroid cancer in whom three or four glands are preserved in situ, have undetectable iPTH and serum calcium concentration is in the normal-upper range, both values at one month after total thyroidectomy.

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Original Article

Influence of gender and women's age on the prevalence of parathyroid failure after total thyroidectomy for multinodular goiter

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Background: Female gender, particularly of a young age, has been reported as a risk factor for hypocalcemia after total thyroidectomy. There are no studies, however, addressing specifically the influence of women's age and menstrual status on postoperative parathyroid function.

Methods: Cohort study of consecutive patients undergoing total thyroidectomy for benign goiter between 2000–2017, excluding those with associated hyperparathyroidism, reoperation or conservative procedures. Prevalence of postoperative hypocalcemia (s-Ca <8 mg/dL at 24 hours), protracted (1-month) and permanent hypoparathyroidism (>1 year) were the main variables studied. Complete >1-year follow-up was achieved for all patients developing post-thyroidectomy hypocalcemia. Demographic, disease-related, number of parathyroid glands remaining in situ (PGRIS), biochemical and surgical variables were recorded. The impact of menstrual status on parathyroid function was analyzed by comparing two groups of women using a cut-off age of 45 years.

Results: A total of 811 patients were included: 14 percent were males and 86 percent females with a mean age of 53.2 years. The prevalence of postoperative hypocalcemia was ten points higher in women than in men (23.7% *vs.* 36.4%; P=0.008). Permanent hypoparathyroidism was more common in women than in men (5% *vs.* 0.9%; P=0.048). Compared to females ≥45 years, young women presented higher rates of all three parathyroid failure syndromes despite similar PGRIS scores. Age <45 years and low PGRIS scores were the only independent variables predicting postoperative hypocalcemia in females.

Conclusions: Premenopausal patients presented a higher prevalence of parathyroid failure and permanent hypoparathyroidism with similar PGRIS scores suggesting the presence of a sex-hormone factor influencing post-thyroidectomy parathyroid function.

Keywords: Hypocalcemia; hypoparathyroidism; menopause; parathyroid glands remaining in situ (PGRIS); prevalence; women

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Introduction

Total thyroidectomy implies a significant traumatic aggression to the parathyroid glands. With the increased use of this surgical technique for a variety of benign and malignant disorders, postoperative hypocalcemia has become the most common complication following total thyroidectomy with a prevalence ranging from 19 to 38 percent (1). Acute parathyroid insufficiency due to gland devascularization, autotransplantation or inadvertent gland resection is currently considered the main, if not the only, cause of post-thyroidectomy hypocalcemia. Our group previously reported that the number of parathyroid glands remaining in situ (PGRIS)—not autotransplanted nor inadvertently excised- is a key factor for the development of parathyroid insufficiency after total thyroidectomy (2). Additionally, biochemical and clinical factors such as preoperative calcium levels, perioperative PTH levels, hyperthyroidism, reoperation and female gender have been occasionally associated with postoperative hypocalcemia (3-5).

Several studies have reported that female gender is a risk factor for post-thyroidectomy hypocalcemia (1,2,5,6). Edafe *et al.* (1) carried out a metanalysis with a total of 3,443 patients, examining gender as a predictor of hypocalcemia, and found that women had a significantly higher prevalence of postoperative parathyroid failure (OR 2.8). The authors hypothesized that this could be related to female patients having lower circulating levels of vitamin D. The role of vitamin D status on postoperative parathyroid function, however, is far from clear with a single study suggesting an influence of low circulating vitamin D (7) and several others not reproducing these findings (8-10). In addition, this metanalysis emphasized the role of both accidental parathyroidectomy and autotransplantation as predictors of postoperative hypocalcemia. It did not assess, however, a possible difference in hypocalcemia rates between pre- and postmenopausal women. In fact, studies evaluating the influence of age or menstrual status on postoperative hypocalcemia in female patients are not available.

In the present work, we aimed to further analyze the impact of age, PGRIS score and pathology on parathyroid insufficiency after total thyroidectomy in female patients. In order to analyze a homogenous series of patients and to avoid confounding factors (bone hunger, lymphadenectomies, extended resections), we decided to analyze only total thyroidectomies for multinodular goiter.

Methods

Study design

Review of a prospectively maintained clinical database of a cohort of consecutive adult (>18 years) patients who underwent first-time total thyroidectomy for multinodular goiter between 2000 and 2017 at the Endocrine Surgery Unit of the Hospital del Mar, a tertiary teaching hospital in Barcelona, Spain. The same experienced team of surgeons performed all the thyroidectomies. Exclusion criteria were reoperations, associated parathyroidectomy for primary or secondary hyperparathyroidism, Dunhill procedures for asymmetrical goiter, thyroid carcinoma and Graves' disease (usually treated with less than total surgical techniques). The prevalence of postoperative, protracted and permanent hypoparathyroidism was investigated. Demographic, disease-related, PGRIS score (see below), biochemical and surgical variables were recorded. A cut-off at 45 years was chosen to assess differences between pre- and post-menopausal women since the precise age at menopause was not recorded before 2017.

Surgical technique

Total extracapsular thyroidectomy was performed in all cases. Parathyroid glands were sought in their usual position and no effort was made to identify them when located in non-orthotopic places. The identification of parathyroid glands was based solely on visual macroscopic features. Ligation of the inferior thyroid artery was carried out at the level of distal branches and close to the thyroid gland to minimize the devascularization of the parathyroid glands. Parathyroid autotransplantation was performed when glands were completely devascularized or accidentally excised and spotted before sending the specimen to the pathology lab.

Definitions

Parathyroid failure syndromes were defined in line with prior reports (11). Postoperative hypocalcemia was defined as a serum calcium levels <8 mg/dL (2 mmol/L) 24 hours and/or a PTH concentration <10 pg/mL 4 hours after thyroidectomy; protracted hypoparathyroidism as iPTH levels lower than 13 pg/mL and/or the need for calcium ± vitamin D supplements one month after surgery; and permanent hypoparathyroidism was considered when PTH levels were lower than 13 pg/mL and/or replacement therapy was still required one year after surgery (12). The number of PGRIS was calculated as PGRIS =4– (glands autotransplanted + inadvertently resected) (2). Patients were classified according to the PGRIS score as 1–2 (one or two PGRIS), 3 (three PGRIS) or 4 (all four glands remaining *in situ*). Patients' consent to use anonymized data for this observational clinical research was obtained together with the informed consent for thyroidectomy.

Patient management

Selective replacement therapy with calcium and calcitriol

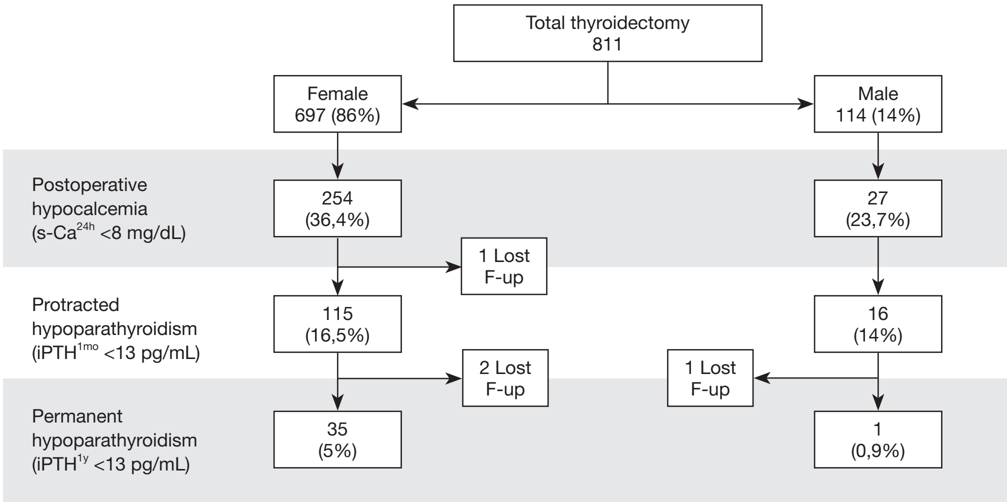

Figure 1 Flowchart describing the calcemic and parathyroid post-surgical evolution of the 811 total thyroidectomy patients included in the analysis classified by gender. Patients lost in follow up are shown as well.

(1.5–3 g/day of calcium carbonate and 0.5–1.5 µg/day of calcitriol) was started in patients with low iPTH (<10 pg/mL) at 4 hours after surgery or s-Ca <8 mg/dL at 24 hours after thyroidectomy.

Patients were discharged on the first or second postoperative day and they were followed in the outpatient clinic. In patients with postoperative hypocalcemia, iPTH and serum calcium were measured at regular intervals until recovery or diagnosis of permanent hypoparathyroidism, after at least one-year follow-up (12). Weaning off replacement therapy was initiated when serum calcium concentration was ≥8 mg/dL and iPTH showed a sustained increase up to normal serum concentrations.

Serum iPTH levels were determined using either an immunoradiometric second-generation assay using an iPTH IRMA assay (Scantibodies Laboratory, Santee, CA, USA) or a solid-phase, two-site chemiluminescent enzyme-labeled assay, IMMULITE 2000 Intact PTH assay (Siemens Healthcare Diagnostics Spain, Madrid, Spain). The normal range was 13–65 pg/mL and the detection limit 3 pg/mL (1.4–7.5 pmol/L, detection limit 0.4 pmol/L). Thyroidectomy specimens were processed by the same dedicated pathologist who consistently reported on the parathyroid glands inadvertently excised.

Statistical analysis

The main outcome variable of the study was the prevalence of postoperative hypocalcemia, protracted and permanent hypoparathyroidism in relation to gender and female age. Data was collected using a database created with FileMaker® Pro-advance 13.0 v4 software (File-Maker, Santa Clara, CA, USA) and extracted from the clinical records from the hospital's general database. Demographic, clinical, surgical, pathological and biochemical variables relevant to the diagnosis and management of postoperative hypocalcemia were included.

Statistical analyses were done using SPSS® version 23.0 (IBM, Armonk, NY, USA). The normal distribution of quantitative variables was assessed with the Kolmogorov-Smirnov test. Quantitative continuous and normally distributed variables are expressed as mean (SD) and compared using Student's *t*-test for unpaired samples or the ANOVA test. Non-parametric tests (Mann-Whitney U test and Kruskal-Wallis test) were used when required. Dichotomous variables were compared using the Chi-square or Fisher's exact test as appropriate. Binomial logistic regression analysis with predictors selected by a forward stepwise procedure was used to assess the risk factors for postoperative parathyroid failure among women. Statistical significance (two-tailed) was set at P<0.05.

Results

Some 811 total thyroidectomy patients were included in the analysis (*Figure 1*). There were 114 men (14 percent) and 697 women (86 percent) with a mean age of 53.2 years. The prevalence of postoperative hypocalcemia was 23.7%

Table 1 Parathyroid failure syndromes, biochemical and clinical variables after total thyroidectomy in male and female patients.

Variables	Male (N=114)	Female <45 years old (N=140)	Female ≥45 years old (N=557)	P
Age, mean (SD), (years)	56.28 (13.9)	33.60 (5.3)	60.18 (11.1)	<0.001**
Preoperative s-Ca, mean (SD), (mg/dL)	9.56 (0.5)	9.34 (0.5)	9.45 (0.5)	<0.001**
s-Ca^{24h}, mean (SD), (mg/dL)	8.46 (0.7)	8.01 (0.7)	8.19 (0.8)	<0.001**
Postoperative hypocalcemia, No. (%)	27 (23.7)	71 (50.7)	183 (32.9)	<0.001*
iPTH^{24h} mean (SD), (pg/mL)	24.2 (23.8)	17.0 (15.8)	20.24 (19.2)	0.525***
s-Ca^{1month} mean (SD), (mg/dL)	9.26 (0.6)	9.23 (0.8)	9.32 (0.7)	0.003**
iPTH^{1month} mean (SD), (pg/mL)	46.1 (47.3)	26.6 (28.6)	32.82 (26.7)	0.001***
Protracted hypoparathyroidism, No. (%)	16 (14.0)	31 (22.1)	84 (15.1)	0.055*
Permanent hypoparathyroidism†, No. (%)	1 (0.9)	11 (7.9)	24 (4.3)	0.070*
PGRIS score‡, No. (%)				0.416*
1 or 2	2 (1.8)	4 (2.9)	26 (4.7)	
3	19 (16.7)	30 (21.4)	133 (23.9)	
4	92 (80.7)	105 (75.0)	396 (71.1)	

*, Chi-squared test; **, one-way ANOVA test; ***, Kruskal-Wallis test; †, data not available for one male patient and one female patient; ‡, data not available for two female patients. PGRIS: parathyroid glands remaining in situ.

in males and 36.4% in women (P=0.008). Permanent hypoparathyroidism was more common in women (5% *vs.* 0.9%; P=0.047).

The gender differences in clinical and biochemical parameters are shown in *Table 1*. The mean of PGRIS scores were similar in males and females [3.7 (0.6) *vs.* 3.6 (0.6); P=0.484]. Thus, different rates of postoperative hypocalcemia between men and women cannot be attributed to variations in the intraoperative management of the parathyroid glands.

Regarding just female patients, hypocalcemia developed in half of those aged <45 years whereas it was documented in only one-third of those aged ≥45 years. Accordingly, young women showed a higher prevalence of protracted and permanent hypoparathyroidism. Although PTH concentration at 24 hours after surgery was not different, serum calcium levels were significantly lower in young patients.

To adjust for the intraoperative management of the parathyroid glands, a final analysis was performed in cases where the four glands were left *in situ* (PGRIS 4). Women <45 years exhibited a worse biochemical and clinical profile than those aged 45 years or more with over a two-fold prevalence of permanent hypoparathyroidism (*Table 2*).

A binomial logistic regression multivariate analysis of variables protecting from postoperative hypocalcemia in females, showed that the only independent factors were preoperative serum calcium OR: 0.5 (95% CI: 0.35–0.82), age >45 years with OR: 0.6 (95% CI: 0.39–0.96) and high PGRIS (PGRIS 3–4) scores with OR: 0.6 (95% CI: 0.45–0.76).

Discussion

Patients' age and gender are among the few clinical variables traditionally associated with hypocalcemia after total thyroidectomy (2,7-10,13). Some authors have even suggested that replacement therapy should be given to all female patients undergoing total thyroidectomy even if three parathyroid glands were correctly preserved (14). On the other hand, several reports have not identified an increased risk for hypocalcemia in women. Most of these, however, are flawed by the inclusion of conservative surgical procedures, different definitions of postoperative hypocalcemia and lack of long-term follow-up (15-17).

The present study focused on a homogeneous series of thyroidectomies for multinodular goiter, confirms the higher prevalence of postoperative parathyroid failure in

Table 2 Parathyroid failure syndromes after total thyroidectomy in women with four parathyroid glands remaining in situ (PGRIS 4)

Variables	<45 years old (n=105)	≥45 years old (n=396)	P
Age, mean (SD), (years)	36.3 (5.8)	61.4 (10.3)	<0.001**
Preoperative s-Ca, mean (SD), (mg/dL)	9.29 (0.4)	9.49 (0.4)	<0.001**
s-Ca^{24h}, mean (SD), (mg/dL)	8.03 (0.7)	8.34 (0.7)	<0.001**
Postoperative hypocalcemia, No. (%)	49 (46.7)	102 (25.8)	<0.001*
iPTH^{24h}, mean (SD), (pg/mL)	21.3 (17.3)	23.42 (20.1)	0.469***
s-Ca^{1month}, mean (SD), (mg/dL)	9.11 (0.7)	9.36 (0.6)	0.004**
iPTH^{1month}, mean (SD), (pg/mL)	30.44 (26.5)	37.58 (27.4)	0.051***
Protracted hypoparathyroidism, No. (%)	20 (19.0)	38 (9.6)	0.007*
Permanent hypoparathyroidism, No. (%)	7 (6.7)	9 (2.3)	0.022*

*, Chi-squared test; **, Students *t*-test; ***, U de Mann-Whitney. iPTH, intact parathyroid hormone.

women and further deepens into the issue by adding to the analysis the presumed menopausal status and the number of PGRIS, a key variable influencing the postoperative parathyroid function (2,18).

Sands *et al.* (6) were the first to address in some detail the issue of female gender as a risk factor for post-thyroidectomy hypocalcemia and reported that women showed a 2.14 relative risk for this complication. However, they did not find a significant difference in rates of transient hypocalcemia between premenopausal and postmenopausal women using a cut-off age of 50 years. In this retrospective study of a small female cohort, the authors did not take into account the indication for surgery nor PGRIS. A high rate of inadvertent parathyroidectomy (one gland every two thyroidectomies in women) could have also influenced the results. We set the age cut-off to 45 years for two reasons: (I) this is the average age women become perimenopausal in Spain where mean age at full menopause in 51 years, and (II) a five to six-year prior interval is a sound assumption based on FSH dynamics (19). Using this age cut-off, substantial and statistically significant differences were observed in all clinical and biochemical parameters of parathyroid function between both age groups. This assumption, however, limits the precision of our analysis and calls for further investigations in which the exact age at menopause should be recorded prospectively.

The present study reveals that half of the females under 45 years of age developed postoperative hypocalcemia compared to just one-third of those >45 years, regardless of similar concentration of iPTH at 24 hours after surgery and similar PGRIS scores. Furthermore, permanent hypoparathyroidism was more common in women than in men operated on for multinodular goiter. Gender differences were particularly noticed in young women in whom all parathyroid failure syndromes were more prevalent.

A final analysis adjusting for PGRIS 4, showed that age is a key variable for the development of postoperative parathyroid failure: despite proper preservation of the four parathyroid glands, women under 45 had a significantly worse biochemical and clinical profiles.

We can only speculate about the possible influence of circulating estrogens on the parathyroid function after thyroidectomy. Recently, Haglund *et al.* (20) have identified estrogens receptors (ERB1 and ERB2) in normal parathyroid cells. They also found that the ERB1 negative parathyroid adenomas had significantly higher adenoma weight, serum calcium, and iPTH serum concentration. This suggests a potential downregulating effect of estrogens on PTH synthesis and secretion, a pathophysiological event which would be supported also by animal studies pointing in this same direction (21). In addition, estrogens inhibit osteoclast activity and bone resorption and may render the bone more resistant to the effects of PTH.

Conclusions

The higher prevalence of post-thyroidectomy parathyroid failure in young females compared to both men and post-menopausal women appears to be independent of PGRIS and could be mediated by higher levels of circulating estrogens. Additional prospective studies, however, are needed to further elucidate the complex interaction between female sex hormones and postoperative parathyroid cell function.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the institutional review board (2017/7557/I). Patients' consent to use anonymized data for this observational clinical research was obtained together with the informed consent for thyroidectomy.

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Time to parathyroid function recovery in patients with protracted hypoparathyroidism after total thyroidectomy

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Abstract

Objective: Hypocalcaemia is the most common adverse effect after total thyroidectomy. It recovers in about two-thirds of the patients within the first postoperative month. Little is known, however, about recovery of the parathyroid function (RPF) after this time period. The aim of the present study was to investigate the time to RPF in patients with protracted (>1 month) hypoparathyroidism after total thyroidectomy.
Design: Cohort prospective observational study.
Methods: Adult patients undergoing total thyroidectomy for goitre or thyroid cancer. Cases with protracted hypoparathyroidism were studied for RPF during the following months. Time to RPF and variables associated with RPF or permanent hypoparathyroidism were recorded.
Results: Out of 854 patients undergoing total thyroidectomy, 142 developed protracted hypoparathyroidism. Of these, 36 (4.2% of the entire cohort) developed permanent hypoparathyroidism and 106 recovered: 73 before 6 months, 21 within 6–12 months and 12 after 1 year follow-up. Variables significantly associated with RPF were the number of parathyroid glands remaining *in situ* (not autografted nor inadvertently resected) and a serum calcium concentration >2.25 mmol/L at one postoperative month. Late RPF (>6 months) was associated with surgery for thyroid cancer. RPF was still possible after one year in patients with four parathyroid glands preserved *in situ* and serum calcium concentration at one month >2.25 mmol/L.
Conclusions: Permanent hypoparathyroidism should not be diagnosed in patients requiring replacement therapy for more than six months, especially if the four parathyroid glands were preserved.

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Introduction

Permanent hypoparathyroidism after thyroidectomy represents the last stage of postoperative parathyroid failure. Even though hypoparathyroidism was designated as an orphan disease by the European Commission in 2014 (1), it is currently considered as the most common permanent complication of total thyroidectomy.

Lorente-Poch *et al.* (2) defined the different syndromes of postoperative parathyroid failure as follows: (a) postoperative hypocalcaemia: serum calcium concentration <2 mmol/L (<8 mg/dL) within 24 h after thyroidectomy; (b) protracted hypoparathyroidism: low-serum iPTH (<1.4 pmol/L or <13 pg/mL) and need for calcium and vitamin D replacement at 4–6 weeks after surgery; (c) permanent hypoparathyroidism: low-serum iPTH and need for calcium and vitamin D replacement 1 year after total thyroidectomy.

There is, however, a lack of consensus regarding the follow-up period necessary to make a firm diagnosis

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of permanent hypoparathyroidism. The European Guidelines (3) define permanent hypoparathyroidism as a low-serum iPTH concentration and/or need for replacement therapy after six postoperative months, whereas the American Association of Clinical Endocrinologists (4) extends the follow-up period to one year. In fact, there is little empirical evidence to establish the follow-up time required to confirm the definitive loss of the parathyroid function after thyroidectomy. The issue has clinical relevance since a diagnosis of permanent hypoparathyroidism implies lifelong medical treatment, imposes an economical burden and may impact on the quality of life (5, 6).

Most studies on the recovery of the parathyroid function (RPF) after thyroidectomy are limited in sample size and/or report a short observation time after surgery (7, 8, 9). Some anecdotal reports (10) have shown that RPF may take place more than one year after thyroidectomy.

The aim of this study was to determine the prevalence and timing of RPF in patients with protracted postsurgical hypoparathyroidism and to identify variables associated with delayed (>6 months) RPF.

Subjects and methods

Study design

This was an observational prospective cohort study of consecutive patients undergoing total thyroidectomy for benign goitre or thyroid malignancy at the Endocrine Surgery Unit of the Hospital del Mar (Barcelona, Spain), a tertiary referral centre for endocrine surgery, between 2000 and 2014 where only a single experienced team performs thyroid surgery. A retrospective chart review of a prospectively maintained database was carried out. Eligibility criteria were adult patients (≥18 year/old) undergoing first-time total thyroidectomy for either multinodular goitre or thyroid cancer. Exclusion criteria were associated parathyroidectomy, Dunhill or subtotal thyroidectomies (performed for asymmetrical goitre or Graves' disease), completion thyroidectomies and surgery for recurrent benign or malignant disease. The main outcome variables of the study were the prevalence of permanent hypoparathyroidism and the time to RPF. The secondary endpoint was to investigate factors influencing early (≤6 months) or late (>6 months) RPF. Consent to use anonymized data for clinical research was obtained together with the informed consent for thyroidectomy.

Surgical technique

All patients underwent total extracapsular thyroidectomy. Central compartment node dissection was performed in patients diagnosed with papillary or medullary thyroid cancer and selective modified radical lateral neck dissection was performed as clinically indicated.

Parathyroid glands were sought in their usual position. No effort was made to identify parathyroid glands located in non-orthotopic places. In all patients, identification of parathyroid glands was based solely on visual macroscopic features. Parathyroid glands that could not be preserved *in situ* were chopped into 1 mm^3 fragments and autotransplanted into several pockets into the ipsilateral sternocleidomastoid muscle. (11) The number of parathyroid glands remaining *in situ* (PGRIS, not transplanted nor resected inadvertently) was calculated as previously reported (12) and patients were classified accordingly (PGRIS score 1–4).

Data acquisition

The following preoperative data were obtained: gender, age, clinical diagnosis, serum calcium and thyroid function tests. After histopathologic analysis, specimen weight, number of resected lymph nodes (if central or lateral neck compartment dissection was performed) and presence of parathyroid glands in the specimen were obtained. The following postoperative variables were recorded: serum calcium and iPTH concentration at 24 h, calcium and calcitriol dosage at discharge and iPTH, serum calcium, serum phosphate and thyroid function tests at 4–6 weeks after surgery and regularly thereafter in patients with protracted hypoparathyroidism.

Serum iPTH levels were determined using either an immunoradiometric second-generation assay using an iPTH IRMA assay (Scantibodies Laboratory, Santee, CA, USA) or a solid-phase, two-site chemiluminescent enzyme-labelled assay, IMMULITE 2000 Intact PTH assay (Siemens Healthcare Diagnostics Spain, Madrid, Spain). The normal range was 1.4–7.5 pmol/L and the detection limit was 0.4 pmol/L.

Patient management and follow-up

Serum calcium and iPTH concentrations were determined 24 h after surgery. Replacement therapy was prescribed only to patients with hypocalcaemia (s-Ca < 2 mmol/L at 24 h) in the form of 1.5–3 g/day of calcium carbonate and 0.5–1.5 µg/day of calcitriol at the time of hospital discharge according to body weight and severity of hypocalcaemia. They were followed thereafter in the outpatient clinic until RPF or permanent hypoparathyroidism was diagnosed. RPF was defined as a normal value for iPTH in asymptomatic patients not requiring replacement therapy. Permanent hypoparathyroidism was diagnosed if serum iPTH was low (<1.4 pmol/L) or undetectable at the last follow-up visit and replacement therapy was still required. Specifically, patients with protracted hypoparathyroidism at one postoperative month were followed indefinitely until RPF or permanent hypoparathyroidism was diagnosed. Weaning off replacement therapy after one month was initiated when serum calcium concentration was ≥2.60 mmol/L and/or iPTH became detectable or showing a sustained increase.

Statistical analysis

Descriptive statistics were used to analyse the prevalence and characteristics of patients developing protracted hypoparathyroidism. A univariate analysis was performed comparing patients who recovered or did not recover from protracted hypoparathyroidism, and those who recovered before or after six months. The Kolmogorov–Smirnov test was used to assess the normal distribution of quantitative variables. Continuous and normally distributed variables are expressed as mean ± s.d. and compared using Student's *t*-test for unpaired samples. Non-normally distributed variables are expressed as mean ± s.e.m. and compared using the Mann–Whitney *U* test. Dichotomous variables were compared using the χ^2 or Fisher's exact test as appropriate. Binomial logistic regression analysis with predictors selected by a forward stepwise procedure was used to assess the risk factors for permanent hypoparathyroidism. Time to RPF was analysed using Kaplan–Meier survival curves and groups compared with the Log Rank (Mantel–Cox) test. The statistical analysis was carried out using SPSS version 22.0 (IBM). Statistical significance was set at $P < 0.05$.

Results

Figure 1 shows the flow chart of patients included in the study. Some 188 patients had thyroid cancer and of those, 115 (61%) received ablative radioiodine therapy between three and six months after thyroidectomy. From the initial cohort, 142 patients with protracted hypoparathyroidism (21M, 121F) were investigated. Of these, 106 patients (75%) recovered the parathyroid function during follow-up and 36 (25%) were diagnosed with permanent hypoparathyroidism. RPF took place within six months in 73/106 patients (69%), between six and twelve months in 21/106 (20%) and beyond this time period in 12/106 (11%) patients.

Outcome of parathyroid function after protracted hypoparathyroidism

Table 1 shows the differences between patients who recovered or did not recover from protracted hypoparathyroidism. There was no difference in RPF between patients operated on for benign or malignant disease. The PGRIS score was significantly better in patients recovering the parathyroid function. No early biochemical parameter was predictive of the long-term parathyroid function. At one postoperative month, however, both normal–high serum calcium and detectable iPTH serum concentrations were associated with a higher proportion of RPF. Calcium and calcitriol dosages at the time of hospital discharge were higher (and significant for calcium) in patients with RPF. Serum calcium concentration at one month, however, did not correlate with the amount of replacement therapy. The multivariate analysis (Table 2) identified that the relevant independent variables predicting RPF were PGRIS score, serum calcium level at 1 month and a detectable iPTH (0.4–1.4 pmol/L) at 1 month.

Early vs late RPF

Thyroidectomy for cancer was the only significant clinical variable associated with RPF after six months (Table 3). This was independent of the PGRIS score and serum calcium and iPTH concentrations at 1 month. Patients recovering early had a better biochemical profile at one month suggesting a less severe parathyroid injury in this subgroup. In agreement with this, final iPTH concentrations were higher in patients recovering within six months.

Time to RPF or to diagnosis of permanent hypoparathyroidism is shown in Fig. 2. About two-thirds of the patients showed an early RPF (<6 months) but one-third recovered after six months. Factors significantly favouring an early RPF were a detectable iPTH and a serum calcium concentration >2.25 mmol/L at 1 month.

The different PGRIS groups had a rather parallel RPF rates during the first six months. Only the PGRIS 3 and 4 groups, however, had some chances of late RPF. No patient in the PGRIS 1–2 group recovered beyond one year (Fig. 2D).

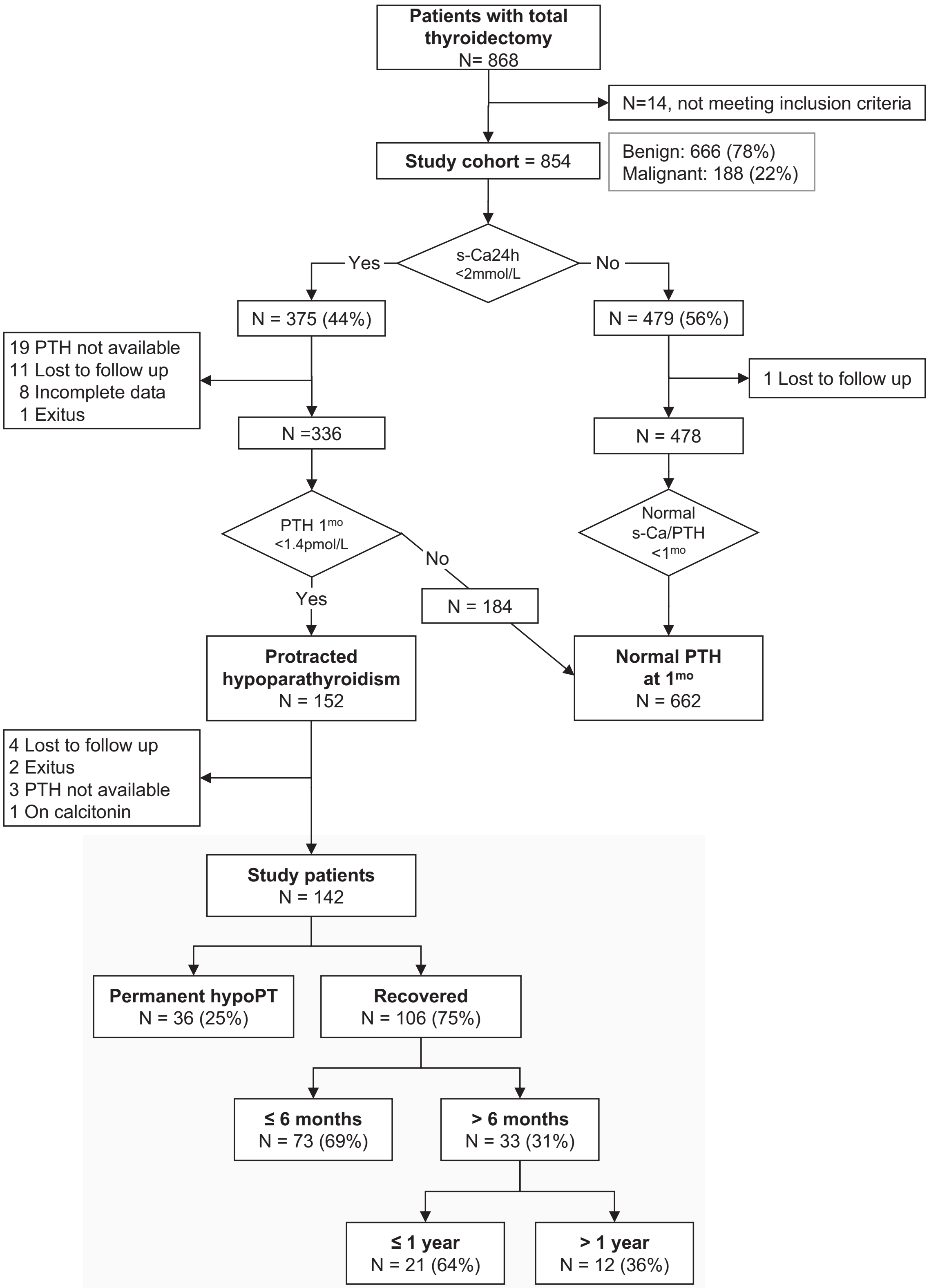

Figure 1 Patient flow diagram. Highlighted area encloses the study patients. Percentages are over the immediately preceding group. HypoPT, hypoparathyroidism; PTH, parathormone; S-Ca, serum calcium.

Table 1 Demographic and disease-related variables of 142 patients with protracted hypoparathyroidism who did or did not recover the parathyroid function.*

	Recovered (*n* = 106)	Permanent hypoparathyroidism (*n* = 36)	*P*
Age (years)**	53 ± 14	54 ± 15	0.626
Gender, *n* (%)			0.370
Male	18 (86)	3 (14)	
Female	88 (73)	33 (27)	
Indication for surgery, *n* (%)			0.298
Goitre	72 (72)	28 (28)	
Malignancy	34 (81)	8 (19)	
Associated procedure, *n* (%)			
Central neck dissection			0.267
Yes	28 (82)	6 (18)	
No	78 (66)	30 (34)	
Lateral neck dissection			0.978
Yes	8 (80)	2 (20)	
No	98 (74)	34 (26)	
No. of lymph nodes resected	5 ± 1	3 ± 1	0.835
Specimen weight (g)	79 ± 7	77 ± 11	0.847
PGRIS*** score, *n* (%)			0.014
1–2	12 (63)	7 (37)	
3	36 (66)	19 (34)	
4	57 (86)	9 (14)	
s-Ca preop (mmol/L)**	2.34 ± 0.1	2.30 ± 0.2	0.123
s-Ca^{24h} postop (mmol/L)	1.87 ± 0.02	1.85 ± 0.03	0.326
s-Ca^{1month} (mmol/L)	2.38 ± 0.02	2.14 ± 0.05	0.001
<2.25 mmol/L, *n* (%)****	20 (51)	19 (49)	0.001
≥2.25 mmol/L, *n* (%)	82 (86)	13 (14)	
PTH^{24h} postop (pmol/L)	0.10 ± 0.04	0.04 ± 0.03	0.603
PTH^{1month} (pmol/L)	0.58 ± 0.04	0.39 ± 0.06	0.009
Detectable (>0.4 pmol/L)****	66 (87)	11 (13)	0.001
Undetectable (≤0.4 pmol/L)	40 (63)	25 (37)	
Last PTH (pmol/L)	2.97 ± 0.17	0.57 ± 0.07	0.001
Follow-up (days)	828 ± 113	2216 ± 270	0.001
Days until recovery	192 ± 20	–	
Calcium dosage at discharge (g/24 h)	2.8 ± 0.08	2.5 ± 0.2	0.033
Calcitriol dosage at discharge (μg/24 h)	0.76 ± 0.04	0.65 ± 0.08	0.213

*Quantitative variables given as mean ± s.e.m. except where noted; **mean ± s.d.; ***PGRIS, parathyroid glands remaining *in situ*; ****Fisher's test.

The relationship between serum calcium and iPTH concentrations at one month in 142 patients with protracted hypoparathyroidism is shown in Fig. 3. No correlation was found between these two variables for any of the three groups of patients. Sixteen patients had a serum calcium concentration ≥2.62 mmol/L associated with low or undetectable iPTH concentration. Of these, 10 recovered within six months (mean: 108 ± 52 days, range 49–140 days), 4 after six months and 2 developed permanent hypoparathyroidism. In these 10 patients with an early RPF, an inverse correlation was found between serum calcium and days to RPF (R^2 = 0.55; P < 0.001).

Table 2 Multivariate analysis for permanent vs recovery from protracted hypoparathyroidism.*

Predicted variable	OR	IL (95%)	SL (95%)	*P*
Permanent hypoPT				
PGRIS (1–4)	0.331	0.170	0.646	0.001
Serum calcium$^{1\ month}$ (mg/dL)	0.205	0.100	0.419	0.001
Detectable iPTH$^{1\ month}$ (1 if Yes)	0.105	0.031	0.350	0.001

*Stepwise forward conditional binomial logistic regression.OR, odds ratio; IL, inferior limit; SL, superior limit.

Discussion

The definition of permanent hypoparathyroidism after total thyroidectomy is still under scrutiny since the timing of RPF and the variables that influence it are poorly understood. Data are accumulating to indicate that RPF is a dynamic process which may occur long after thyroidectomy. (4, 8, 13) Evidence presented here confirms that a prolonged follow-up is essential before a diagnosis of permanent hypoparathyroidism can be made with certainty. A follow-up postoperative period of just six months may lead to overdiagnosis and overtreatment of this condition in as much as one-third of the patients with protracted hypoparathyroidism (5).

Two previous reports have presented evidence for long-term (>6 months) RPF. Kim *et al.* (10) studied a cohort of 1467 total thyroidectomy patients for thyroid cancer; 22 patients (1.8%) developed 'permanent' hypoparathyroidism, but five of these showed long-term RPF after a mean of 30 months. Factors associated with these late RPFs were not investigated. Ritter *et al.* (7) followed 1054 patients after total thyroidectomy, of whom 18% had transient hypoparathyroidism; 70% of the patients recovered within 2 months, 5% recovered between 6 and 12 months and 1.9% showed permanent hypoparathyroidism. This study, however, had a short follow-up (≤1 year); transient hypocalcaemia and protracted hypoparathyroidism patients were studied as

Table 3 Demographic and disease-related variables of 106 patients recovering from protracted hypoparathyroidism within or beyond six months after total thyroidectomy.*

	≤6 months (n=73)	>6 months (n=33)	*P*
Age (years)**	53±15	53±13	0.855
Gender, *n* (%)			0.337
Male	10 (56)	8 (44)	
Female	63 (71)	25 (29)	
Indication for surgery, *n* (%)			0.014
Goitre	55 (76)	17 (24)	
Malignancy	18 (53)	16 (47)	
Associated procedure, *n* (%)			
Central neck dissection			0.425
Yes	16 (60)	11 (40)	
No	57 (72)	22 (28)	
Lateral neck dissection****			0.251
Yes	4 (50)	4 (50)	
No	69 (70)	29 (30)	
N of lymph nodes resected	3.8±1	6.6±2	0.351
Specimen weight	88±9	61±10	0.059
PGRIS score, *n* (%)****			0.453
1–2	10 (83)	2 (17)	
3	25 (70)	11 (30)	
4	37 (65)	20 (35)	
s-Ca preop (mmol/L)**	2.34±0.4	2.37±0.2	0.165
s-Ca^{24h} postop (mmol/L)	1.87±0.02	1.87±0.03	0.865
s-Ca^{1month} (mmol/L)	2.39±0.03	2.39±0.03	0.474
<2.25 mmol/L, *n* (%)****	17 (85)	3 (15)	0.052
≥2.25 mmol/L, *n* (%)	52 (63)	30 (37)	
PTH^{24h} postop (pmol/L)	0.09±0.05	0.10±0.05	0.403
PTH^{1month} (pmol/L)	0.63±0.04	0.47±0.06	0.033
Detectable (>0.4 pmol/L) ****	50 (76)	16 (24)	0.049
Undetectable (≤0.4 pmol/L)	23 (47)	17 (53)	
Last PTH (pmol/L)	3.21±0.22	2.49±0.22	0.046
Follow-up (days)	622±124	1258±220	0.001
Days until recovery	96±38	405±45	0.001
Calcium dosage at discharge (g/24 h)	2.8±0.1	2.8±0.1	0.456
Calcitriol dosage at discharge (μg/24 h)	0.73±0.04	0.83±0.07	0.182

*Quantitative variables given as mean±S.E.M. except where noted; **mean±S.D.; ***PGRIS, parathyroid glands remaining *in situ*; ****Fisher's test.

a single group, and used a vague hypoparathyroidism definition (PTH <10 pg/mL after surgery).

A recent report (8) on factors that positively influence the RPF in patients with postoperative hypocalcaemia identified preoperative iPTH concentration of >5 pmol/L and a <88% drop after thyroidectomy as variables favouring early RPF. The authors suggest that these findings reflect both a better preoperative baseline parathyroid function and lesser degree of intraoperative parathyroid gland injury. They did not report, however, on the technical issues that influence the prevalence of postoperative hypocalcaemia and the RPF such as the extension of surgery, inadvertent parathyroidectomy (14) or autotransplantation rates.

The fact that RPF is a lengthy and dynamic process is further emphasized by the inability of early biochemical variables to predict permanent hypoparathyroidism. Immediate postoperative low/undetectable iPTH serum concentration is a good marker for the development of postoperative hypocalcaemia; its ability to predict protracted or permanent hypoparathyroidism, however, is very limited (13, 15, 16, 17).

The present study sheds new light on factors influencing timing to RPF. From a clinical standpoint, early RPF was more common if thyroidectomy had been performed for multinodular goitre and this was independent of the PGRIS score and the metabolic parameters, suggesting that RPF may be impaired and/or delayed by treatment with radioiodine. Guven *et al.* (18) investigated the parathyroid function at baseline and at several time intervals after high-dose radioiodine ablation (100–150 mCi) in 19 patients after total thyroidectomy for differentiated thyroid cancer. Their study showed a 25% transient decline in iPTH concentrations around the sixth month after radioiodine treatment. This did not cause symptomatic hypocalcaemia but the authors suggest that radioiodine treatment in patients with a limited parathyroid reserve may well lead to parathyroid insufficiency. The possibility that radioiodine may interfere with the RPF deserves further research.

From the endocrine point of view, patients with low but detectable iPTH serum concentration at one month (0.4 < iPTH < 1.4 pmol/L) recovered in greater proportion and faster than those with undetectable iPTH. RPF in patients with undetectable iPTH concentration depends more heavily on other variables such as PGRIS and a serum calcium concentration at one month ≥2.25 mmol/L. The latter positively influences RPF after protracted hypoparathyroidism and allows some hope for patients with hypoparathyroidism lasting for one year. We have hypothesized that the favourable prognostic value of high–normal calcium concentration during the first weeks of postoperative parathyroid failure may be due to a parathyroid splinting effect (19), which holds that serum calcium concentrations in the upper normal range put at rest the injured/ischaemic parathyroid glands

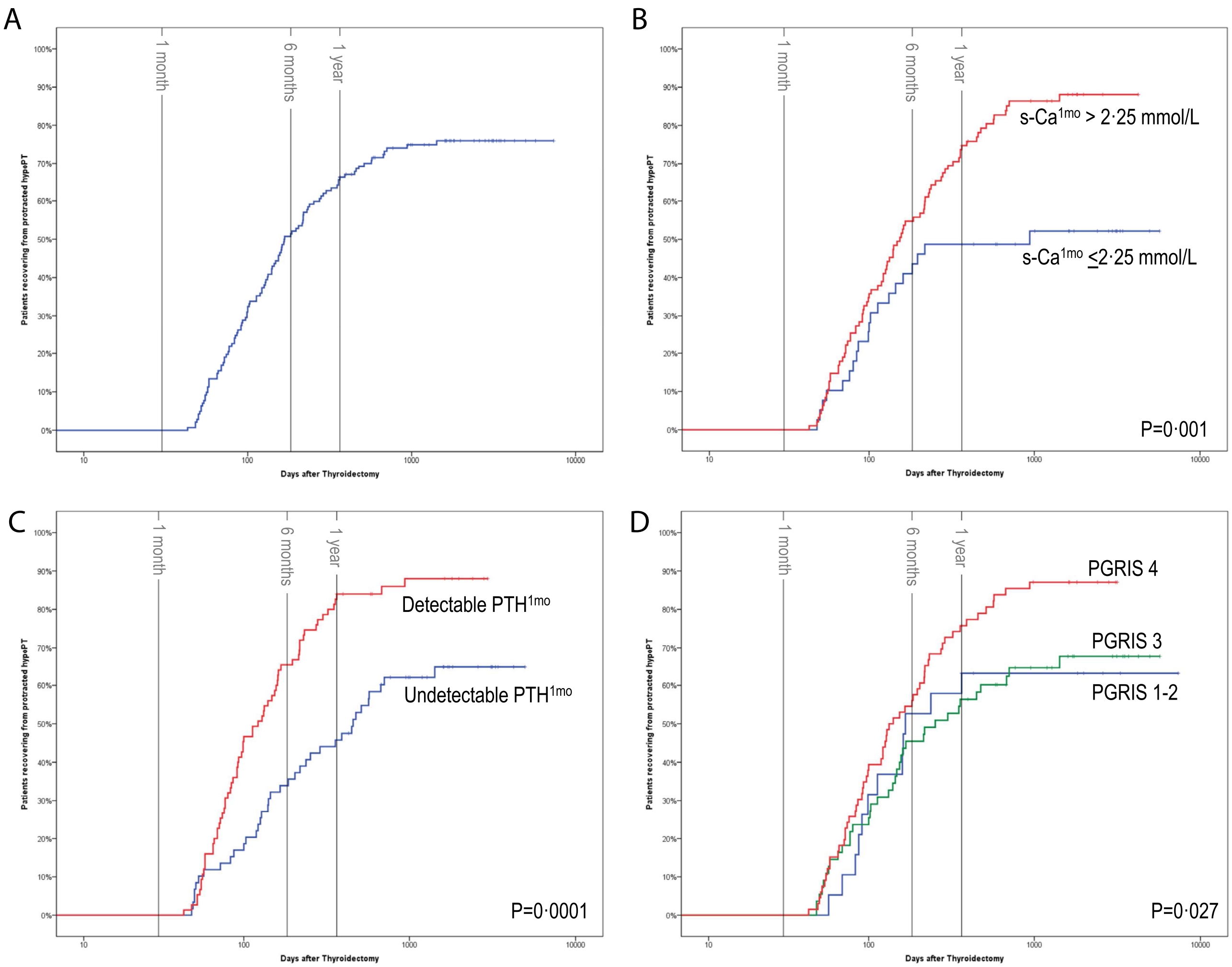

Figure 2

Time to recovery of the parathyroid function (RPF) in patients with protracted hypoparathyroidism. (A) Time to RPF for the whole cohort ($n = 142$). (B) RPF according to serum calcium concentration at one month. (C) RPF according to detectable vs undetectable parathormone at one month. (D) RPF according to PGRIS (parathyroid glands remaining *in situ*). Horizontal axis uses logarithmic scale (days). hypoPT, hypoparathyroidism. *P* values from the Log Rank (Mantel–Cox) test.

and allow for a better recovery of the remaining viable parathyroid parenchyma from intraoperative injury. Data from the present study suggest that serum calcium concentrations at one month in patients with RPF were influenced by higher doses of calcium and calcitriol being prescribed at the time of hospital discharge. An alternate or complementary explanation of the beneficial effects of a normal–high serum calcium concentration could be that some patients might have been erroneously diagnosed with protracted hypoparathyroidism because low or undetectable iPTH at one month resulted from iatrogenic hypercalcaemia. No correlation was found, however, between serum calcium and iPTH. Moreover, in the group of hypercalcaemic protracted hypoparathyroidism patients that recovered the parathyroid function, an inverse correlation was found between serum calcium and days to RPF: patients with more elevated serum calcium concentrations recovered early than those with mild hypercalcaemia. Further studies are needed to clarify this multifaceted physiological riddle.

The third variable modulating RPF is the PGRIS score, which indirectly translates the amount of potentially viable remaining parathyroid tissue: a PGRIS 4 score predicts a significantly higher proportion of RPF. Although PGRIS did not positively influence an early recovery, patients with three or four parathyroid glands remaining *in situ* still have some chances of recovery after one year of replacement therapy. This means that surgeons should make all possible

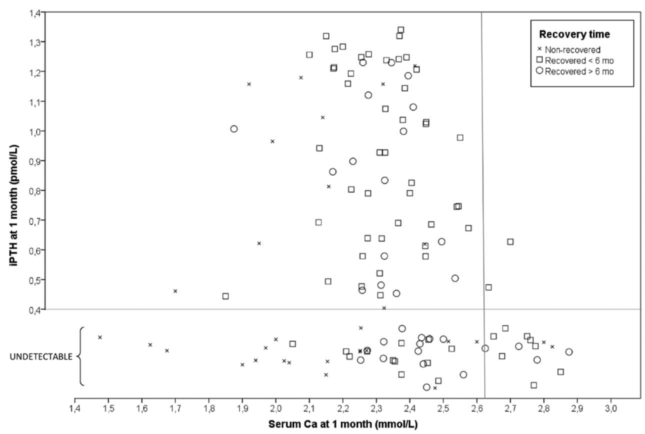

Figure 3
Serum calcium (mmol/L) vs iPTH (pmol/L) in patients with protracted hypoparathyroidism at one month after total thyroidectomy. The vertical line at 2.62 mmol/L marks the upper limit of normal serum calcium concentration. Values of iPTH concentrations below 0.40 pmol/L are labelled as 'UNDETECTABLE' and plotted with randomly assigned iPTHN values between 0 and 0.39 pmol/L.

efforts to preserve the parathyroid glands *in situ* avoiding autotransplantation, inadvertent parathyroidectomy and thymectomy (12, 14, 20, 21, 22, 23).

A limitation of the study is that 10% of the patients with postoperative hypocalcaemia were lost to follow-up before the final parathyroid status could be assessed. Our unit serves a geographical area that hosts a considerable proportion of mobile migrant population. We cautiously infer that most of the patients not coming back after the first postoperative visit at one week did not develop long-term calcium metabolism disturbances.

In conclusion, it is suggested that the average patient with hypocalcaemia after total thyroidectomy should be discharged on calcium and calcitriol to maintain serum calcium concentrations of at least 2.25 mmol/L during the first weeks. If he or she cannot be weaned off within the first month, RPF will mostly depend on the serum calcium concentrations achieved, PGRIS and whether iPTH is detectable or not. Permanent hypoparathyroidism should not be diagnosed if replacement therapy is still required six months after thyroidectomy, since up to one-third of the patients will recover beyond this time period and a few ones even after one year. Candidates for late RPF are those patients operated on for thyroid cancer in whom three or four glands were preserved *in situ*, with undetectable iPTH and serum calcium concentration in the normal upper range one month after total thyroidectomy.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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