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Late Recovery of Parathyroid Function after Total Thyroidectomy in Children and Adults: Is There a Difference?

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Keywords
Hypoparathyroidism · Parathyroid · Recovery · Total thyroidectomy

Abstract
Background: Parathyroid failure after total thyroidectomy is the commonest adverse event amongst both children and adults. The phenomenon of late recovery of parathyroid function, especially in young patients with persistent hypoparathyroidism, is not well understood. This study investigated differences in rates of parathyroid recovery in children and adults and factors influencing this. ***Methods:*** A joint dual-centre database of patients who underwent a total thyroidectomy between 1998 and 2018 was searched for patients with persistent hypoparathyroidism, defined as dependence on oral calcium and vitamin D supplementation at 6 months. Demographic, surgical, pathological, and biochemical data were collected and analysed. Parathyroid Glands Remaining in Situ (PGRIS) score was calculated. ***Results:*** Out of 960 patients who had total thyroidectomy, 94 (9.8%) had persistent hypoparathyroidism at 6 months, 23 (24.5%) children with a median [range] age 10 [0–17], and 71 (75.5%) adults aged 55 [25–82] years, respectively. Both groups were comparable regarding sex, indication, extent of surgery, and PGRIS score. After a median follow-up of 20 months, the parathyroid recovery rate was identical for children and adults (11 [47.8%] vs. 34 [47.9%]; $p = 0.92$). Sex, extent, and indication for surgery had no effect on recovery (all $p > 0.05$). PGRIS score = 4 (HR = 0.48) and serum calcium >2.25 mmol/L (HR = 0.24) at 1 month were associated with a decreased risk of persistent hypoparathyroidism on multivariate analysis ($p < 0.05$). ***Conclusion:*** Almost half of patients recovered from persistent hypoparathyroidism after 6 months; therefore, the term persistent instead of permanent hypoparathyroidism should be used. Recovery rates of parathyroid function in children and adults were similar. Regardless of age, predictive factors for recovery were PGRIS score = 4 and a serum calcium >2.25 mmol/L at 1 month.

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Introduction

Hypoparathyroidism is the commonest adverse event after total thyroidectomy for any indication. It is defined by low post-operative calcium and parathyroid hormone levels (PTH), which require supplementation with oral calcium and active metabolites of vitamin D. Transient hypoparathyroidism affects 20–25% of adult patients who undergo a total thyroidectomy. Hypoparathyroidism which continues beyond 6 months after surgery is often called long term or even persistent and is diagnosed in up to 10% of adult patients [1–4]. Published evidence suggests that this complication might even be more common among children who undergo a total thyroidectomy (~10–20%) [5–11].

Approximately 90% of adult patients who develop parathyroid failure immediately after total thyroidectomy recover; most within 1–3 months, but in 4–27%, recovery occurs after a period of 6 months [12–15]. The return of the ability to produce an adequate amount of PTH, and thus being capable of maintaining stable calcium levels without supplementation, is thought to be the effect of regeneration of parathyroid tissue, which had either been damaged or deprived of adequate blood supply at the time of surgery.

There is, however, very little evidence on the rate of parathyroid function recovery in children who underwent a total thyroidectomy complicated by hypoparathyroidism persisting beyond 6 months. It is commonly thought that children have an increased capacity to heal and regenerate tissue in comparison with adults [16–18]. We have explored the hypothesis that a younger biological age might be a factor influencing late parathyroid function recovery and that children could therefore have a better rate of late recovery than adults.

The primary aim of our study was therefore to investigate whether the rate of late parathyroid function recovery is different in children and adults who underwent a total thyroidectomy, resulting in hypoparathyroidism persisting beyond 6 months. Our secondary aim was to identify factors influencing the capacity for the late recovery of parathyroid function in both groups.

Methods

A joint database of children and adult patients who underwent a total thyroidectomy between 1998 and 2018 either at Centre for Endocrine Surgery (London, UK) or Endocrine Surgery Unit of the Hospital del Mar (Barcelona, Spain) was created. All children (<18 years of age) who were operated at University College or Great Ormond Street Hospitals and adults (≥18 years of age) who underwent an extracapsular total thyroidectomy were included. Exclusion criteria were a near-total thyroidectomy, Dunhill procedure, reoperation, and a coexisting parathyroid adenoma. Among adults, patients operated for Graves' disease were excluded, as these patients in general did not undergo an extracapsular total thyroidectomy. None of the included patients had an intrathoracic goitre which required more than an incision in the neck. While there was no vessel sealing device used for any of the operations on children, an ultrasonic scalpel (i.e., Harmonic®; Ethicon Endo-Surgery, Inc.) was used for vessel sealing and haemostasis for all adult cases. All data were prospectively collected at either location and retrospectively analysed as part of an ongoing audit on outcomes after thyroid surgery.

Patients with persistent hypoparathyroidism defined as dependency on oral supplementation of calcium and vitamin D active metabolites (alfacalcidol/calcitriol) at 6 months after surgery, were identified from the joint database and formed the scope of the study analysis. The term "late recovery of parathyroid function" was used when patients were able to stop supplements after 6 months while maintaining normal calcium and PTH levels and remaining asymptomatic.

Collected data included standard demographic information (age and sex), indication for surgery (benign or malignant thyroid disease), relevant biochemical variables (serum calcium [mmol/L] and PTH levels [classified as undetectable, low, or normal according to local laboratory ranges]), type of surgery (total thyroidectomy with or without lymph node dissection), and information on intraoperative management of parathyroid glands (number identified during surgery, autotransplanted, or found in specimen on histology). Specifically, the Parathyroid Glands Remaining in situ (PGRIS) score was calculated using the formula: 4 – (glands autografted + glands in the specimen) [19]. Moreover, the technique described by Wells et al. [20] was utilized for autotransplantation for parathyroid glands which were accidentally removed. In short, the glands were split into small 1-mm^3 fragments and autotransplanted in the ipsilateral sternocleidomastoid muscle [20]. No pathology confirmation prior to autotransplantation was sought.

Statistical Analyses

Summary statistics were obtained and presented as percentages or median values. Upon comparing categorical data, the χ^2 test, or if deemed appropriate Fisher's exact test, was used, while the Mann-Whitney U test was used to compare continuous data. Overall time to recovery was calculated from date of surgery to date of recovery or of last follow-up. Factors associated with recovery of long-term hypoparathyroidism were examined using cross-tabs and the non-parametric product limit method. The log-rank test was applied to determine the influence of variables on time to recovery of parathyroid function. Cox proportional hazards models were developed using relevant clinicopathologic variables to determine the association of each with delayed recovery of long-term hypoparathyroidism. Relative risks were expressed as hazard ratios (HRs) with 95% CIs. Overall, a $p < 0.05$ was considered significant. All statistical analyses were performed using IBM SPSS Statistics for Macintosh, version 23.0 (IBM Corp. IMB SPSS statistics, Armonk, NY, USA).

Table 1. Demographic, operative, biochemical, and intraoperative management data of 94 patients with hypoparathyroidism at 6 months

Variable, *n* (%)	*N* (%); total *n* = 94		*p* value
	children (*n* = 23)	adults (*n* = 71)	
Patient and disease characteristics			
Sex (male)	4 (17.4)	11 (15.5)	0.83
Age, (median [range]), years	10 [0–17]	55 [25–82]	<0.001
Indication for surgery			
Benign thyroid disease	15 (65.2)	48 (67.6)	0.83
Malignant thyroid disease	8 (34.8)	23 (32.4)	
Perioperative variables			
Type of surgery			
Total thyroidectomy only	15 (65.2)	52 (73.2)	0.55
Total thyroidectomy + central neck dissection +/– lateral neck dissection	8 (34.8)	19 (26.8)	
Number of parathyroid glands identified (median [range])	3 [2–4]	3 [1–4]	0.67
Autotransplantation performed	3 (13.0)	19 (26.8)	0.17
PGRIS score			
1 or 2	7 (30.4)	11 (15.5)	0.075
3	7 (30.4)	31 (43.7)	
4	9 (39.2)	29 (40.8)	
Post-operative variables			
Length of stay (median [range]), days	4 [2–15]	2 [2–23]	<0.001
Levels of calcium <24 h of surgery, (median [range]), mmol/L	1.88 [1.60–2.62]	1.89 [1.55–2.22]	0.10
Levels of PTH <24 h of surgery			
Undetectable	20 (87.0)	26 (36.6)	0.72
Low	3 (13.0)	6 (8.5)	
Unknown	0	39 (54.9)	
Levels of calcium 1 month after surgery, (median [range]), mmol/L	2.27 [1.51–2.53]	2.27 [1.47–2.87]	0.30
Levels of PTH 1 month after surgery			
Undetectable	14 (60.9)	38 (53.5)	0.73
Low	9 (39.1)	29 (40.8)	
Unknown	0	4 (5.6)	

PGRIS, Parathyroid Glands Remaining in Situ; PTH, parathyroid hormone levels.

Results

Data on 960 patients who underwent a total thyroidectomy were entered into the clinical database; 854 of these were adults and 106 children. Overall, 205 patients (21.4%) had disruption in their calcium homeostasis in the immediate post-operative period, more than half of them recovered within 6 months after surgery. Ninety-four (9.8%) patients, who had persistent hypoparathyroidism at 6 months after surgery and were still dependent on oral calcium and active vitamin D supplementation to maintain their normal calcium concentration, were the subjects of this analysis.

Demographics and Perioperative Data

Out of the 94 patients with persistent hypoparathyroidism at 6 months, 23 were children and 71 were adults. The majority of children (17/23; 73.9%) were prepubertal. The eldest child was 17, and the youngest adult was 25 years old. The difference between the median ages of children and adults was 45 years, while sex, indications for surgery, and type of operation were comparable for children and adults. Overall, the majority of patients were female ($n = 79$; 84.0%) and underwent a total thyroidectomy without lymph node dissection ($n = 67$; 71.3%). The median length of stay was 3 days (range: 2–23); children and adolescents stayed longer in hospital than adult patients ($p < 0.001$) (Table 1).

Intraoperative Management of Parathyroid Glands

There were no differences between the intraoperative management of parathyroid glands in children and adults. The number of parathyroid glands visually identified during surgery in both groups was the same (median 3

Table 2. Differences in characteristics between patients who had late recovery and those who remained dependent on oral supplementation of calcium and active metabolites of vitamin D

Variable, *n* (%)	*N* (%); *n* = 94		*p* value
	recovery after 6 months (*n* = 45)	persistent hypoparathyroidism (*n* = 49)	
Sex (male)	9 (20.0)	6 (12.2)	0.31
Age, (median [range]), years	51 [1–75]	51 [0–82]	0.39
Indication for surgery (benign, malignant)	27 (60.0)	36 (73.5)	0.17
Total thyroidectomy only	30 (66.7)	37 (75.5)	0.47
Autotransplantation performed	11 (24.4)	11 (22.4)	0.86
PGRIS score = 4	21 (46.7)	34 (69.4)	0.02
Serum calcium at 1 month >2.25 mmol/L	34 (75.6)	14 (28.6)	<0.001
Undetectable PTH at 1 month	24 (53.3)	28 (57.1)	0.39

PGRIS, Parathyroid Glands Remaining in Situ; PTH, parathyroid hormone levels.

[range: 1–4]; $p = 0.67$). Autotransplantation of one or more glands was performed in 22 (23.4%) patients and although not statistically different between groups, it was performed twice as often in the adult group ($n = 3$, 13.0% in children vs. $n = 19$, 26.8% in adults). The overall median number of glands autotransplanted was 1 (range: 1–2) (Table 1).

A total of 37 patients (39.4%) had one or more parathyroid glands identified in their specimen. The rate of incidental parathyroid removal was similar for children and adults (47.8% vs. 37.1%; $p = 0.36$). Overall, more than half of patients ($n = 56$; 59.6%) had <4 parathyroid glands in situ.

Factors Predicting Late Recovery of Parathyroid Function

The overall median follow-up for all patients was 20 months. At the time of the last follow-up (Table 2), parathyroid function had recovered in 45 patients (47.5%) and these patients were no longer dependent on oral calcium and vitamin D supplements and maintained normal serum calcium levels (Fig. 1a). The rate of recovery was similar in children and adults ($p = 0.92$) (Fig. 1b).

Moreover, there were no differences in the parathyroid function recovery after 6 months between males or females ($p = 0.39$), patients operated on for benign or malignant disease ($p = 0.17$), extent of surgery performed ($p = 0.47$), or whether autotransplantation was performed ($p = 0.86$) (Table 2). No difference in the rate of accidental parathyroid removal was found when looking at the extent of surgery. Specifically, one or more parathyroid glands were found in the pathology specimen in 29 patients (43.9%) who underwent a total thyroidectomy only compared with 8 (28.6%) who also underwent a lymph node dissection ($p = 0.15$). Moreover, there was no difference in the number of patients in whom autotransplantation was undertaken between those who did and did not undergo a lymph node dissection ($n = 16$ [24.2%] vs. $n = 6$ [21.4%]; $p = 0.74$). Specifically, no association between parathyroid autotransplantation and recovery of function was found (HR = 1.02 [95% CI: 0.52–2.00]; $p = 0.35$).

The only clinical factor associated with late parathyroid function recovery was PGRIS score, which was significantly higher in patients who recovered from hypoparathyroidism after 6 months (Fig. 2a). Specifically, a PGRIS score of 4 was associated with a significantly lower risk of ongoing hypoparathyroidism (HR = 0.47 [95% CI: 0.26–0.85]; $p = 0.01$) on univariate analysis.

No early biochemical parameter (<24 h after surgery), such as the median levels of calcium (1.89 mmol/L [range: 1.62–2.27] vs. 1.89 mmol/L [range: 1.55–2.61]; $p = 0.10$) or the PTH being detectable (46.7 vs. 42.9%; $p = 0.72$), was predictive of late parathyroid function recovery. However, when looking at the biochemistry data at 1 month after surgery, patients who had calcium levels within the normal-high range seemed to have a higher rate of late recovery (Fig. 2b). Specifically, a calcium level of >2.25 mmol/L at that time point was associated with a significantly lower risk of persistent hypoparathyroidism on univariate analysis (HR = 0.24 [95% CI: 0.12–0.48]; $p < 0.001$). There was no such difference with regard to the PTH levels at 1 month ($p = 0.39$).

Table 3. Univariate and multivariate analyses of factors proposed to be associated with late recovery of parathyroid function

Prognostic factor	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Children	1.03	0.52–2.04	0.93	0.72	0.35–1.47	0.36
Male sex	1.49	0.72–3.89	0.29			
Benign indication for surgery	0.68	0.37–1.23	0.20	0.73	0.40–1.36	0.32
Performance of neck dissection	1.27	0.68–4.17	0.45			
Autotransplantation performed	1.02	0.52–2.00	0.96			
PGRIS score = 4	0.47	0.26–0.85	0.012	0.48	0.26–0.88	0.018
Detectable PTH at <24 h	1.45	0.59–3.54	0.42			
Serum calcium at 1 month >2.25 mmol/L	0.24	0.12–0.48	<0.001	0.24	0.12–0.49	<0.001
Detectable PTH at 1 month	0.72	0.40–1.30	0.27			

HR, hazard ratio; PGRIS, Parathyroid Glands Remaining in Situ; PTH, parathyroid hormone levels.

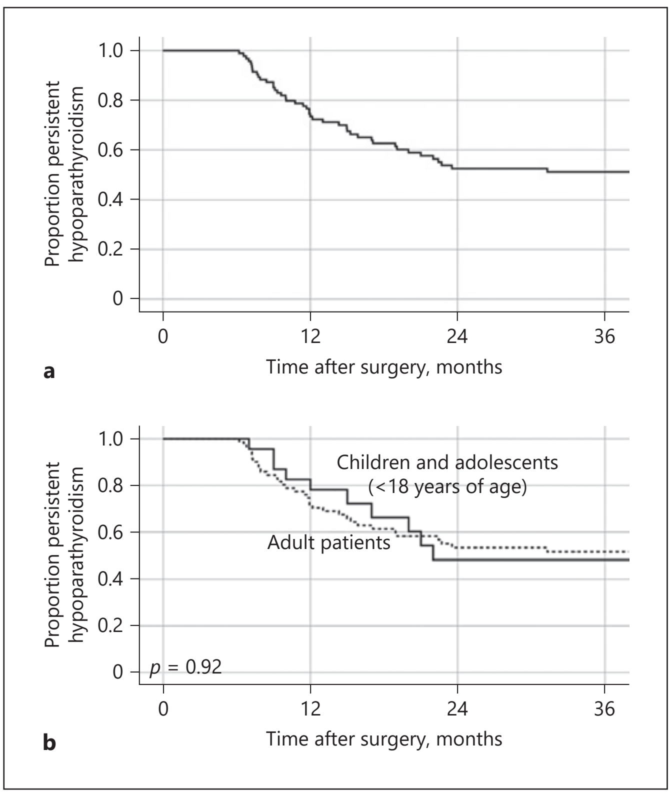

Fig. 1. a Kaplan-Meier curve displaying time to late recovery of parathyroid function for all patients. **b** Kaplan-Meier curve comparing the time to recovery of persistent hypoparathyroidism, stratified by age group ($p = 0.92$).

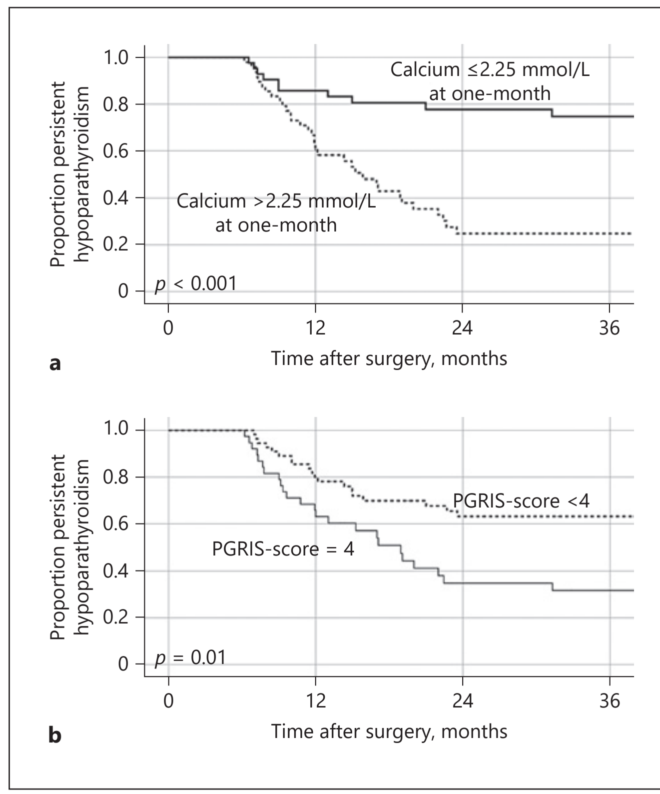

Fig. 2. a Kaplan-Meier curve comparing the time to recovery of persistent hypoparathyroidism, stratified by PGRIS score ($p = 0.01$). **b** Kaplan-Meier curve comparing the time to recovery of persistent hypoparathyroidism, stratified by calcium levels ($p < 0.001$). PGRIS, Parathyroid Glands Remaining in Situ.

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To control for competing factors, specifically the age group of the patient, a multivariate analysis (Table 3) was performed. This analysis confirmed that the relevant independent variables predicting the rate of late recovery of hypoparathyroidism were the PGRIS score and the serum calcium level at 1-month post-surgery.

Discussion

Patients with persistent hypoparathyroidism after total thyroidectomy are at risk of developing health problems associated with insufficient secretion of PTH and under- or overtreatment with calcium and active vitamin D metabolites. Suboptimal treatment can lead to either too low serum calcium levels or to hypercalcaemia with hypercalciuria and is associated with neuromuscular and psychiatric symptoms, cataract, nephrocalcinosis, and bone demineralization (adynamic bone disease) [21–23]. It is therefore important to understand what the risks for developing this condition are and to identify factors predicting late parathyroid function recovery and the resolution of hypoparathyroidism, allowing patients to stop treatment with supplements and avoiding complications related to this. Combining high-quality clinical information from 2 endocrine surgery centres allowed us to analyse data from almost a 1,000 children and adults who underwent a total thyroidectomy for both benign and malignant thyroid diseases.

The primary objective of our study was to assess the rate of late parathyroid function recovery among patients who are still suffering from hypoparathyroidism at 6 months after their total thyroidectomy and whether the rate of recovery is different in children and adults. Firstly, we have found that the overall rate of immediate postoperative parathyroid failure in our cohort was 21.4%, comparable to other published data [1, 24]. More than half of these patients recovered early, but 94 patients (9.8%) remained hypoparathyroid and thus still required treatment to maintain normal calcium levels 6 months after surgery. In almost half of them (47.9%), late recovery of parathyroid function took place between 6 and 20 months after surgery. This is an important observation as the European guidelines define the presence of hypoparathyroidism at 6 months as permanent [25]. Our data indicate that such a definition may be debatable since the timing of parathyroid function recovery seems to be more variable and dynamic than originally assumed [19, 26, 27]. We therefore propose to use the term "persistent hypoparathyroidism" instead. Consequently, long-term follow-up, review of medications and regular blood tests are necessary not only to maintain normal calcium levels but also to periodically reconsider the diagnosis of "permanent" hypoparathyroidism. Confirming the recovery of parathyroid function will have important implications for patient management and should prevent complications related to treatment with calcium and vitamin D supplements.

Secondly, our study showed that there are no differences between both the rates and times to late recovery of parathyroid function between children and adults. This is a somewhat unexpected finding, as healing in children is thought to be better than in adults. It is generally understood that a gradual loss of capacity for tissue regeneration and repair is one of the hallmarks of ageing, as a possible result of specific genes, which are active during the foetal stages of development, and their gradual switch off with age. For example, it is known that cardiac regeneration is very limited in adults, while the hearts of young children have an impressive cardiac regeneration capacity [28]. Moreover, the clinical characteristics of cranial nerve palsies in childhood are influenced by the child's remarkable ability to repair and regenerate after injury [29]. Furthermore, complete pancreatic regeneration resulting in a normal size and function has been observed in half of the children after near-total pancreatic resection for nesidioblastosis [30].

Several authors have reported an increased risk of short-term post-operative hypoparathyroidism in children when compared to adults [31, 32] although the incidence of this complication seems to be lower when the operation is performed in a high-volume centre [32–35]. Most of these studies, however, did not examine the rate of late recovery in children, as most have a relatively short observation time after surgery. Zobel et al. [36] reported on a cohort of 68 patients of whom 8 (11.8%) were dependent on oral supplementation to maintain their normal calcium concentration at 6 months post-surgery. Their rate of persistent hypoparathyroidism at 12 months following surgery was <3%. However, conversely in the current study, the maximum age of inclusion was higher (patients younger than 21 years). Our study is unique because it includes a large number of patients with a long-term follow-up and provides detailed clinical and biochemical data. Importantly, the groups of children and adults are comparable in terms of sex, type of surgery, and indications. The only significant difference between these groups is their age, with most children being prepubertal and the youngest adult being 25 years old. Therefore, this substantial age gap between the 2 groups suggests that our study was well poised to answer the question about a potential different ability of children and adults to recover from hypoparathyroidism. However, no such difference was found, and at the time of the last follow-up, the proportion of persistent hypoparathyroidism among children and adults with postoperative hypoparathyroidism was similar. These findings indicate that although children are at an increased risk of developing long-term hypoparathyroidism, their ability to recover from it is not different to adults.

Our secondary aim was to evaluate factors influencing the capacity for late recovery of parathyroid function among both groups. This study has identified 2 such risk factors.

Firstly, patients with a less than full PGRIS score are at a >2-fold increased risk of persistent hypoparathyroidism. Previous studies have shown that accidental parathyroidectomy or parathyroid autotransplantation, resulting in fewer than 4 parathyroid glands remaining in situ, is associated with the development of early post-thyroidectomy hypocalcaemia and protracted/permanent hypoparathyroidism in both adults [19, 37] and children [11]. Data from the current study suggest that the PGRIS score is also important in predicting the risk of long-term hypoparathyroidism and that higher PGRIS score is associated with an increased chance of late recovery after the period of 6 months. As the PGRIS score reflects the amount of parathyroid tissue left in situ, this finding highlights the need to preserve the highest number of parathyroid glands, avoiding accidental parathyroidectomy and autotransplantation, in order to prevent hypoparathyroidism.

Secondly, we have observed that a calcium level of <2.25 mmol/L at 1-month post-surgery is also a risk factor for the development of persistent hypoparathyroidism. Patients whose calcium levels were below this threshold had a >4-fold increased risk of not recovering from their long-term hypoparathyroidism. One possible explanation of this finding is that the higher levels of calcium were due to higher dosages of calcium and active metabolites of vitamin D. This in turn provided a period of metabolic rest for the injured parathyroid glands and allowed for a better recovery of the parathyroid parenchyma. Conversely, parathyroid glands of patients with lower calcium levels were exposed to additional "parathyroid stress testing" which could have affected their ability to regenerate and recover [38]. This theory of "parathyroid splinting" [13, 39] is attractive in its ability to explain this phenomenon, but limited data still exist on this subject, and further research is needed to elucidate this probably multifactorial physiological challenge.

The current study has several limitations. Although it is one of the largest studies on the subject of late recovery of long-term hypoparathyroidism in children and adults, the included numbers are still low, reflecting the rarity of thyroid surgery in children. Moreover, the exact treatment regimen with calcium and active metabolites of vitamin D was not known for each individual patient and there might have been small differences in the management of hypoparathyroidism between children and adults in the different centres. However, we did aim to control for these possible confounders by performance of a multivariate analysis. Like in all retrospective studies, selection bias may also have influenced certain variables measured. Furthermore, the fact that adults and children were operated upon by different surgical teams must be considered as potential cofounders when interpreting the results of this study.

In conclusion, late parathyroid function recovery was observed in almost half of our patients who still had hypoparathyroidism at 6 months; therefore, the term persistent rather than permanent hypoparathyroidism should be used if replacement therapy is still required at 6 months after surgery. The ability to achieve late recovery seems to be the same for children and adults. Regardless of age group, predictive factors for possible late recovery are 4 parathyroid glands preserved in situ at time of surgery and a serum calcium concentration exceeding 2.25 mmol/L at 1-month, indicating a need for both careful intraoperative preservation of parathyroid glands and adequate postoperative management with supplements.

Statement of Ethics

All procedures performed in this study were in accordance with the ethical standards of all institutions and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The paper was exempt from Ethics Committee approval by the UCLH/UCL Joint Research Office, as this retrospective study was registered as an ongoing quality assurance/audit of our current practice to assess outcomes after thyroid. Therefore, seeking of informed consent was not applicable; retrospective data analysis was anonymized, and consent requirement was waived.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.C. de Jong: study design/data collection/data analysis/writing/figures. -L. Lorente-Poch: data collection/data analysis/writing. J. Sancho-Insenser: study design/data collection/data analysis/manuscript review. V. Rozalén García: literature search/data collection/manuscript review. C. Brain: literature search/data acquisition/manuscript review. T.E. Abdel-Aziz: data interpretation/figures/manuscript review. R.J. Hewitt: literature search/data acquisition/manuscript review. C.R. Butler: literature search/data acquisition/manuscript review. A. Sitges-Serra: study concepts/data interpretation/manuscript editing. T.R. Kurzawinski: study concepts/data interpretation/manuscript editing.

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