

Incidence, prevalence and risk factors for post-surgical hypocalcaemia and hypoparathyroidism

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Abstract: Hypocalcaemia following thyroid surgery is common and is associated with significant short and long term morbidity. Damage to or devascularisation of parathyroid glands is the predominant underlying mechanism; although other factors such as hungry bone syndrome may occasionally contribute to it in the immediate post-operative period. The reported incidence of post-surgical hypocalcaemia and/or hypoparathyroidism (PoSH) varies significantly in the literature; the variation thought to be at least partly due to differences in the definitions used. Figures on the prevalence of chronic or long term post-surgical hypocalcaemia in the population are unclear. Risk factors for PoSH have been extensively studied in recent years and may be classified into patient, disease and surgery related factors. Some risk factors are modifiable; but both modifiable and non-modifiable factors help in generating a risk profile that may be used to select patients for preventative measures and/or changes in surgical strategy. This narrative review discusses recent literature on the incidence, prevalence and risk factors for PoSH.

Keywords: Post-surgical; hypocalcaemia; hypoparathyroidism

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Introduction

Post-surgical hypoparathyroidism (PoSH) manifests as hypocalcaemia and may be due to damage to parathyroid blood supply and/or inadvertent excision of the gland (1). Another mechanism for temporary post-surgical hypocalcaemia includes hungry bone syndrome where there is rapid and acute shift of calcium into the bones following surgical treatment of patients with preoperative thyrotoxicosis (2). Other postulated reasons include dilutional hypocalcaemia (3) and calcitonin release (4) following surgery; but empiric evidence of these phenomena as significant causes of post-surgical hypocalcaemia are lacking.

Acute hypocalcaemia may present with paraesthesia and

neuromuscular instability. Long term hypocalcaemia is associated with abnormal renal function, cataracts, ectopic calcifications, seizures, abnormal teeth and psychiatric illnesses (5,6).

There is currently no international consensus on the definition of PoSH, resulting in many different definitions mentioned in the literature (7). The British Association of Endocrine and Thyroid Surgeons (BAETS) defines postoperative hypocalcaemia as day one postoperative calcium of less than 2.1 mmol/L (8). Late hypocalcaemia is defined as the need of calcium and/or vitamin D supplement to maintain normocalcaemia at 6 months or more following surgery (8). The European Society of Endocrinology considers chronic PoSH in patients with a low calcium and inappropriately low intact parathyroid hormone (iPTH)

at more than 6 months (9). No specific serum levels of calcium or iPTH levels were given. A recent review by the American Association of Clinical Endocrinologist (AACE) and American College of Endocrinology (ACE) discussed definitions and management of PoSH (10). Hypoparathyroidism was categorised as biochemical and clinical; temporary and permanent. The distinction between temporary and permanent PoSH was made at 12 months. Relative hypoparathyroidism was also recognised as an entity where biochemical parameters were normal but medication was required for symptomatic relief. In terms of postsurgical hypocalcaemia, the same duration was applied to distinguish between temporary and permanent conditions and a total serum calcium of less than 8.5 mg/dL (2.125 mmol/L) or ionised calcium less than 1.15 mmol/L were considered as cut-off levels. In recent literature, 'protracted hypoparathyroidism' has been used to identify patients with persisting hypoparathyroidism at 4–6 weeks of surgery (1,11). This duration is in between those used for immediate or temporary and the long term definitions and is used in studies evaluating relatively short term outcomes.

The lack of inclusion of patients that need calcium and/or vitamin D supplements despite their PTH levels being in the normal range in some of the definitions above risk underestimating the true incidence and prevalence of this problem in the community.

Although PoSH may occasionally be a result of other operative procedures such as parathyroid surgery (12) and laryngeal surgery with concomitant thyroidectomy (13), the focus of this review is primarily on post-thyroidectomy hypocalcaemia and/or hypoparathyroidism. The terms hypocalcaemia and hypoparathyroidism are both used in this paper—this is to accurately reflect the definitions used in the original articles and reviews cited in this article. Although there is controversy over whether the words 'long term' or 'permanent' is most appropriate; both are used interchangeably in the article to reflect the descriptions used in the cited references. This highlights the need for a consensus statement on the definitions of PoSH.

Incidence

The incidence of PoSH varies significantly, partly as a result of difference in definitions used. Mehanna *et al.* found that the incidence rate ranges from 0% to 46% for the same cohort of patients depending on the definition used (7). Parameters used in the literature to define temporary postsurgical hypocalcaemia includes calcium level alone;

calcium level and symptoms; calcium level and the need for treatment; calcium level, symptoms and need of treatment; symptoms alone; symptoms; and need for treatment and PTH level (14). To define long term or permanent postsurgical hypocalcaemia and/or hypoparathyroidism, studies have used calcium level alone; calcium level and duration; need for treatment and duration; symptoms and duration; calcium level, symptoms and duration; calcium level, PTH, need for treatment and duration; PTH level and duration; and PTH level, need for treatment and duration (14). Most studies used a duration of six month or more to define long term hypocalcaemia (14).

In a systematic review and meta-analysis of 115 studies, the median (IQR) incidence of temporary and long term post-surgical hypocalcaemia was 27% (19–38%) and 1% (0–3%) respectively (15). However, the studies used different definitions and are therefore not comparable. The fifth BAETS audit reported temporary and late hypocalcaemia rate of 23.6% (95% CI, 22.7–24.5%) and 6.5% (95% CI, 5.8–7.2%) respectively in patients who had total thyroidectomy (8). However, 10.1% and 21.5% of patients had data missing for temporary and long term outcomes respectively. A large multicentre Scandinavian audit reported 6 month hypocalcaemia rate of 4.4% following bilateral thyroid surgery. However, missing data occurred in 4.5% of patients (16).

In the United Kingdom (UK) and elsewhere, some centres routinely give prophylactic calcium and vitamin supplements to patients undergoing bilateral thyroid surgery (8). This can distort the incidence rates of post-surgical hypocalcaemia; especially when the definitions are based on serum calcium level. In a meta-analysis, the use of routine prophylactic calcium and vitamin D supplements (compared to oral calcium only or no supplements) reduced the incidence of temporary hypocalcaemia (14). In a randomised control trial (RCT) of 120 patients, use of calcium and vitamin D supplements reduced symptomatic hypocalcaemia when compared to oral calcium alone (17). However, routine use of supplementations did not impact on the rates of long term hypocalcaemia (14).

Prevalence

Few population studies have examined the prevalence of PoSH.

A Danish population based study (between 1988 and 2012) estimated the prevalence of PoSH using historic data from the Danish National Patient Registry. Patients were identified through the Danish National Patient Registry and

Table 1 List of potential risk factors in the development of post-surgical hypoparathyroidism (PoSH)

Category of risk factor	Individual variables
Perioperative biochemistry	Serum calcium
	Parathyroid hormone
	Vitamin D
	Magnesium
	Alkaline phosphatase
Surgery related	Parathyroid identification
	<i>In situ</i> preservation of parathyroid glands
	Parathyroid auto-transplantation
	Central neck dissection
	Inadvertent parathyroidectomy
	Surgical volume and duration
	Re-operative surgery
Patient factors	Age at surgery
	Gender
Disease related	Graves' disease
	Weight of excised specimen
	Retrosternal extension

Prescription database (18). Long term PoSH was defined as hypocalcaemia with inappropriately low PTH following neck surgery that required treatment with calcium and/or vitamin D supplements for more than 6 months. They identified a total of 980 patients with PoSH; 688 (70%) due to surgery for malignant disease and 292 (30%) for non-malignant disease. The estimated prevalence of long term PoSH in patients who had surgery for non-malignant disease was 22 per 100,000 (18).

Another study from the United States of America estimated the 'diagnosis-based' prevalence of hypoparathyroidism using a large insurance claims database (19). They identified all cases of hypoparathyroidism over a 12-month period (October 2007 and September 2008) and then extrapolated it to the insured US population. The prevalence of chronic hypoparathyroidism (not resolving within 6 months) in the insured US population in the surgical database was 58,793. Assuming that the US population in 2008 was 308.7 million and 82% are insured (20), this translates to a long term prevalence of PoSH of 23 per 100,000.

Astor *et al.* examined the prevalence of PoSH in Norway using an electronic hospital registry. They captured around 80% of the Norwegian population. Long term PoSH was defined as low serum calcium and inappropriately low PTH, necessitating treatment for more than one year. The reported prevalence of long term PoSH was 64 per million (21).

The incidence and prevalence of PoSH is likely to increase given the rising numbers of thyroid surgery being performed (22). This is in keeping with the sustained and global increase in diagnosis of thyroid cancer over the past few decades (23-25).

A number of biochemical, surgical related and patient/disease related factors have been identified as predictors of postoperative hypocalcaemia. These are listed in *Table 1*.

Biochemical predictors of hypoparathyroidism

Serum calcium

A low preoperative serum calcium level could potentially increase the likelihood and severity of postoperative hypocalcaemia. The association between preoperative serum calcium levels and post-operative hypocalcaemia is unclear. A large multicentre Scandinavian study of 3,660 patients found that a lower level of preoperative serum calcium was associated with postoperative hypocalcaemia (16). However, no cut off was specified to aid decision-making. In contrast, a recent meta-analysis including 2,493 patients from six studies found no association between preoperative serum calcium levels and postoperative hypocalcaemia (15). However, it would appear reasonable to check calcium levels preoperatively and in those with hypocalcaemia, evaluate and treat accordingly.

Some centres measure changes in calcium levels after surgery ('calcium slope') to predict PoSH and direct management of patients. A positive calcium slope within 24 hours of surgery (i.e., a rise in calcium between two consecutive measurements) has a positive predictive value (PPV) of 86–100% for excluding temporary postoperative hypocalcaemia (15). Pattou *et al.* examined predictors of permanent hypocalcaemia (at 12 months post-thyroidectomy) in 1,071 consecutive patients who underwent total or subtotal thyroidectomy (26). In patients receiving calcium supplementations at 1 to 3 weeks postoperative, they found that serum calcium of 2 mmol/L or lower significantly increased the risk of permanent hypocalcaemia in univariate analysis. Another study of 453 compared serum calcium levels between patient who had temporary and permanent

hypocalcaemia. At one week post-operatively, 2 out of 44 patients in the temporary group had calcium lower than 2 mmol/L compared to 2 out of 3 in permanent group ($P=0.001$) (27). Both these studies were limited by the small numbers of patients who developed permanent hypocalcaemia.

In addition to their role in predicting the likelihood of long term hypocalcaemia and/or hypoparathyroidism, postoperative calcium levels are mainstay for the detection and appropriate treatment of hypocalcaemia.

PTH

Perioperative PTH measurements are used in many centres to predict post-operative hypocalcaemia. Studies have shown patients with low intraoperative PTH (any time from resection of the gland up to 10 minutes after resection), low postoperative PTH levels (30 minutes to 5 days after surgery), and decline of PTH between preoperative and postoperative measurements can be used to predict temporary post-thyroidectomy hypocalcaemia (15).

The utility of 4-hour iPTH and perioperative iPTH decline was studied in a prospective study of 137 patients who underwent total thyroidectomy (28). Decline in iPTH levels (preoperative to 4 hours postoperatively) of 68.5% or more from preoperative levels was more accurate (PPV: 90.5%) compared to 4-hour iPTH (PPV: 82.5%) in predicting postoperative hypocalcaemia. In another prospective study of 106 patients, iPTH decline of 80% or more at 3 hours after surgery was found to have a PPV of 100% for postoperative hypocalcaemia (29).

In the subgroup of patients who had postsurgical PoSH, undetectable serum iPTH (compared to low but detectable) at 4 weeks after surgery was an independent predictor of permanent PoSH. In the group with undetectable PTH ($n=34$), 13/34 (38.2%) had permanent PoSH (1).

A prospective study of 70 patients examined the utility of iPTH at 24 hours after surgery in predicting long term parathyroid function (30). iPTH of 5.8 pg/mL or lower had a poor PPV of 30% in predicting permanent hypoparathyroidism; however, a good negative predictive value (NPV) of 100%.

Measurement of postoperative PTH levels is becoming the standard in the early detection and treatment of PoSH. Early postoperative PTH and calcium based protocols are used to guide management with calcium and/or vitamin D supplementation and subsequent weaning in many centres.

Vitamin D

Given the importance of vitamin D in calcium metabolism and in particular, calcium absorption, vitamin D status has been investigated for its influence on PoSH. The role of vitamin D deficiency in postoperative hypocalcaemia is controversial, a number of studies have found that low preoperative 25-vitamin D (particularly levels lower than 25–62 nmol/L) was an independent predictor of post-thyroidectomy hypocalcaemia (15). A retrospective study evaluated the role of vitamin D deficiency in post-thyroidectomy hypocalcaemia in 213 consecutive patients who underwent total and completion thyroidectomies (31). Patients were stratified into the following vitamin D status categories: severely deficient (<25 nmol/L); deficient (<50 nmol/L); insufficient (<75 nmol/L) and sufficient (≥ 75 nmol/L). They found that 54% of patients in the severe deficiency group developed hypocalcaemia compared to 3.1% of those with sufficient levels.

Seasonal difference in the rates of post-thyroidectomy was studied in Montreal (32). Mascarella *et al.* found significant differences in the rates of hypocalcaemia between the following months: winter (8.3%); spring (7.3%); summer (1.3%); autumn (3.5%). Thyroidectomy performed in winter was significantly associated with temporary hypocalcaemia in multivariable analysis (32).

In contrast to the above studies, another retrospective study of 150 patients found no significant difference in the rates of postoperative hypocalcaemia in patients with vitamin D <50 nmol/L and those with levels ≥ 50 nmol/L (33). Other recent studies have also found no correlation with preoperative vitamin D levels and postoperative hypocalcaemia (34–36).

Despite this, it appears reasonable to screen for vitamin D deficiency in patients undergoing thyroid surgery as part of preoperative workup and treat them appropriately. This is not only to reduce the incidence but also severity of hypocalcaemia in addition to other long term benefits of treating vitamin D deficiency.

Magnesium

Magnesium plays an important role for secretion of PTH and release of PTH is impaired in magnesium deficiency (37).

Wilson *et al.* prospectively examined the association between postoperative magnesium levels and temporary hypocalcaemia in 50 patients undergoing total thyroidectomy. They found that low magnesium was an

independent predictor of postoperative hypocalcaemia after adjusting variables including postoperative serum calcium. In a retrospective study of 201 patients, Garrahy *et al.* found that low postoperative magnesium was an independent predictor of biochemical hypocalcaemia (38). Both studies did not adjust for PTH levels. Hammerstad *et al.* found that patients with Graves' who had permanent hypocalcaemia following total thyroidectomy (n=40) had a greater decline in serum magnesium (preoperatively to 48 hours post-op) (39). This finding was limited by the relatively small sample size as only four patients developed permanent hypocalcaemia in their cohort.

Cherian *et al.* found no association between low postoperative magnesium (<1.8 mg/dL) and postoperative hypocalcaemia in a prospective analysis of 50 patients who underwent total thyroidectomy (40). Others have also found no association between postoperative serum magnesium and post-thyroidectomy hypocalcaemia (41,42).

On this basis, routine magnesium measurements cannot be recommended, but it would be reasonable to check and treat for hypomagnesemia in patients with severe or protracted hypocalcaemia.

Alkaline phosphatase (ALP)

Sources of ALP include the bone, liver and kidney (43). Patients with primary hyperparathyroidism or hyperthyroidism may have elevated preoperative alkaline phosphate due to increase high bone turnover (44,45). These patients with high bone turnover may be at risk of postoperative hypocalcaemia due to hungry bone syndrome and this elevation could persist for up to 9 months postoperatively (44,45).

Some studies have found that patients with preoperative elevated ALP are at risk of postoperative hypocalcaemia (15). Miah *et al.* retrospectively studied the association between preoperative alkaline phosphate levels and postoperative hypocalcaemia in 225 patients (46). They found that preoperative ALP was significantly higher in patients who developed postoperative hypocalcaemia in univariable analysis, particularly in patients with Graves' disease. They did not adjust for parathyroid or thyroid hormone levels.

Given the presence of other indicators of hypocalcaemia and the lack of utility of ALP levels in guiding treatment, routine measurements are not currently indicated.

Surgery related factors

Several surgical factors may help in predicting the risk of

PoSH. These have been recently detailed in a systematic review (15). Factors such as surgical approach, operating technique, use of specific hemostatic techniques and parathyroid imaging are considered as preventative measures and are therefore outside the scope of this review.

Intraoperative identification

This issue is also discussed in more detail elsewhere in this journal. Large retrospective studies have shown that identification of fewer parathyroid glands at surgery may independently predict transient (16) and permanent (47) hypocalcaemia. This supports routine identification and meticulous dissection to avoid inadvertent damage and preserve long term function. In contrast, another retrospective study found higher rates of transient and permanent hypocalcaemia in patients where more parathyroid glands were identified (48). The authors used capsular dissection and avoided excessive/prolonged dissection to identify the parathyroid glands. A potential explanation for this finding could be that the glands identified represent those at or within the capsule, thus at greater risk of devascularisation. In addition, in the absence of routine search for the glands, identified glands may represent those that have been devascularised; as these are more obvious during dissection.

In a prospective study of 126 patients (49), patients who had 0–2 glands identified intraoperatively had a lower incidence of clinical hypocalcaemia compared to patients who had 3–4 glands identified (3.2% *vs.* 17.1%).

Puzziello *et al.* also evaluated the association between intraoperative identification and postoperative hypocalcaemia in a prospective multicentre study of 2,631 patients (50). Information on the surgical technique was not presented. They found that intraoperative identification of parathyroid gland is associated with increased risk of temporary hypocalcaemia, but, it significantly reduced the rates of permanent hypocalcaemia. This finding suggests that identification was associated with partial devascularisation but preservation of the gland in the long term.

In summary, the authors of this review do not advise an extensive dissection and search for parathyroid glands during surgery, but recommend that surgeons 'look out' for parathyroid glands and keep to capsular dissection to avoid damage to unidentified glands.

Preservation of parathyroid gland in situ

Preservation of parathyroid glands is expected to reduce

the risk of PoSH. Lorente-Poch *et al.* proposed that this be quantified using the following formula: 4 – (number of gland autotransplanted + gland in the excised specimen). The underlying assumption here is that any parathyroid gland left behind has an intact blood supply.

They examined the association between *in situ* preservation of parathyroid gland and postoperative hypocalcaemia in 657 patients who underwent total thyroidectomy (51). They found that fewer parathyroid glands preserved *in situ* significantly increased the rates of temporary and permanent post-thyroidectomy hypocalcaemia. The authors therefore argue against parathyroid autotransplantation. However, this was not a controlled study and it could be that the technique of autotransplantation was suboptimal.

Selective parathyroid gland autotransplantation

In meta-analysis of 823 patients included in four studies who underwent bilateral thyroid surgery, selective autotransplantation of one or more parathyroid glands was evaluated as a risk factor for PoSH (15). Studies included in the review used fairly similar techniques for autotransplantation. However, Lang *et al.* immediately autotransplants any devascularised gland, while Asari *et al.* sent a specimen for frozen section and performed the autotransplantation at the end of the procedure, during which the gland was kept in cold saline.

The meta-analysis showed an increase in the risk of temporary hypocalcaemia with autotransplantation (OR, 2.03; 95% CI, 1.44–2.86) (15). However, no association was found between autotransplantation and permanent hypocalcaemia in individual studies (15).

On this basis, it would be reasonable to advise selective autotransplantation of glands that are clearly ischaemic or have been devascularised, but assessment of this is currently subjective and may not be accurate. In the future, technologies such as fluorescent imaging of parathyroid glands may help in accurately determining tissue viability and guide selective autotransplantation.

Central neck dissection (CND)

Prophylactic central neck dissection in thyroid cancer remains controversial, particularly due to its associated morbidity. Studies have shown that prophylactic central neck dissections increase risk of temporary PoSH (14). In addition, limiting central neck dissection to ipsilateral side reduces risk of

temporary PoSH compared to routine bilateral central neck dissection (14). In a meta-analysis of five observational studies with a total of 1,132 patients, Chisholm *et al.* compared rates of hypocalcaemia between patients who underwent total thyroidectomy with CND and those had total thyroidectomy alone (52). The CND group included patients who had either therapeutic or prophylactic CND. In addition, there was variability on the definition of temporary and permanent hypocalcaemia between studies. Patients who had total thyroidectomy with CND had an increased risk of temporary hypocalcaemia (risk difference, 7.7; 95% CI, 5.6–14.3). A total of 14 patients developed permanent hypocalcaemia; eight in prophylactic CND group and six in the total thyroidectomy alone group. There were no significant differences between groups in the rates of permanent hypocalcaemia. Another meta-analysis (15 observation studies and one RCT) compared rates of hypocalcaemia between total thyroidectomy with CND (includes prophylactic, therapeutic, bilateral and ipsilateral procedures) and total thyroidectomy alone (53). In 11 studies, total thyroidectomy with CND significantly increased risk of temporary hypocalcaemia (262/845, 31% *vs.* 239/1,478, 16%). No significant difference was seen in the rates of permanent hypocalcaemia between the two groups. In addition, there was no significant difference between total thyroidectomy (TT) alone and TT with CND in locoregional recurrence rates. In another meta-analysis, Lang *et al.* compared surgical morbidity and short-term local regional recurrence between patients who had TT with prophylactic CND and those who had TT alone (54). Pooled results of 11 studies that examined temporary hypocalcaemia found that TT with prophylactic CND had significantly higher rates [336/1,294 (26.0%)] *vs.* TT alone [114/1,330 (10.8%)]. Again, no significant difference was seen in the rates of long term hypocalcaemia (2% *vs.* 1.2%). However, total thyroidectomy with CND significantly reduced the risk of locoregional recurrence compared to total thyroidectomy alone (4.7% *vs.* 8.6%).

Although therapeutic CND is not controversial, the practice of prophylactic CND is variable across centres. Local rates of PoSH following CND should therefore be used to guide surgeons and patients in deciding on whether prophylactic CND should be done.

Inadvertent excision of parathyroid gland

This factor is discussed in more detail elsewhere in this journal. Rates of inadvertent parathyroidectomy range from 3.7% to 21.6% (55). This is higher in patients who had concomitant central neck dissection (56). In most instances,

only one gland is excised, although occasionally two or more parathyroid glands may be removed (55). Of these, the rates of intrathyroidal position ranges from 5.2–68.8% (57). A meta-analysis of 1,482 patients involved in four studies demonstrated that inadvertent excision was significantly associated with transient hypocalcaemia (OR, 1.90; 95% CI, 1.31–2.74) (15).

Although intra-thyroidal parathyroid excision cannot be avoided, the surgeon should take care to preserve extra-thyroidal glands by ensuring that the dissection is at the capsular plane at all times. Inadvertent excision of extra-thyroidal glands could be considered a surrogate marker for lack of capsular dissection and therefore a predictor for PoSH.

Surgical volume

High volume surgeons may represent surgeons with endocrine or thyroid specialisation. In a prospective study, Gonzalez-Sanchez *et al.* examined the association between surgical volume (surgeons performing <5 *vs.* >40 cases per year) and postoperative hypocalcaemia (58). The low volume group had a significantly higher rate of hypocalcaemia compared to high volume surgeons at 6 months (8/16 *vs.* 8/130) and 12 months (3/16 *vs.* 3/130) postoperatively. They concluded that specialised training in endocrine surgery may account for differences seen in complication rates. No recommendation was given on the minimal number of cases required to achieve optimal results or to be considered a high volume surgeon. In another multicentre study however, Thomusch *et al.* found no link between surgical volume (<10 and 10–50 compared to >50 cases per year) and temporary or permanent postsurgical hypocalcaemia (47). However, other clinical outcomes also improve with the volume of thyroid surgery performed and most national and international guidelines now advocate that thyroid surgery be avoided by low or very low volume surgeons.

Other surgical related factors identified as potential predictors of temporary hypocalcaemia in multivariable analysis in various studies are longer duration of surgery (59), reoperation for bleeding (16,59), and re-operative surgery for recurrent goitre (60).

Patient and disease related factors

Age at surgery

Association between advanced age and PoSH could be due to vitamin D deficiency with advance age (61).

There are conflicting reports with regards to age and the developments of postoperative hypocalcaemia. Some studies have identified older age as risk factors while others have found younger aged to be at risk (15). In a meta-analysis of 2,576 patients (from five studies) who underwent bilateral surgery, age at surgery was not significantly associated with postoperative hypocalcaemia (15).

Female gender

Female gender has been identified as an independent risk factor for the development of post-thyroidectomy hypocalcaemia (16,47,62). In addition, a meta-analysis of 3,860 patients (from 10 studies) who underwent bilateral thyroid surgery found that female had a significantly higher rates of temporary hypocalcaemia compared to male patients (OR, 1.7; 95% CI, 1.03–2.8). The mechanism of this phenomenon however remains unclear despite some speculation on the ‘smaller operative field’ in females (61) and the prevalence of vitamin D deficiency, in female patients with Graves’ disease (63).

Graves’ disease

Hungry bone syndrome is an accepted mechanism for the link between Graves’ disease and temporary hypocalcaemia. In addition, parathyroid preservation during surgery for Graves’ disease may be more technical challenging given the increased gland vascularity.

The association between Graves’ disease and postoperative hypocalcaemia has been studied in a meta-analysis. The meta-analysis included six studies with a total number of 6,779 patients who underwent bilateral thyroid surgery (15). Graves’ disease significantly increased the risk of postoperative hypocalcaemia (OR, 1.8; 95% CI, 1.4–2.4). Furthermore, Thomusch *et al.* found that Graves’ disease (when compared to multinodular goitre) was an independent predictor of permanent hypocalcaemia (47).

In patients with Graves’ disease, adequate optimisation of thyroid status, treatment of existing vitamin D deficiency, reduction of vascularity with preoperative Lugol’s iodine and careful capsular dissection should help reduce PoSH rates.

Weight of excised specimen

Heavier specimen may represent more extensive surgery, thus predisposing to PoSH. Heavier weight of resected specimen had been shown to be an independent predictor

of temporary (64) and six month hypocalcaemia (59).

Retrosternal goitre

Surgery for retrosternal goitre could predispose to PoSH due to extent of surgery and longer dissection. In a multicentre study of 19,662, Testini *et al.* examined the morbidity of retrosternal goitres (65). Patients who had surgery (cervical approach or sternotomy) for retrosternal goitre had significantly higher rates of temporary and permanent hypocalcaemia compared to cervical goitre group (temporary, 33.8% *vs.* 21.6%; permanent, 2.2% *vs.* 1.0%).

Care should therefore be taken with large multinodular and retrosternal goitres to help reduce this risk. In patients with predominantly unilateral disease, a hemithyroidectomy should therefore be considered.

Conclusions

This review summarises literature on the epidemiology of PoSH. Given the increasing numbers of thyroid surgery worldwide, PoSH is assuming increasing significance and adding to the burden of disease in the community. The epidemiological data are hindered by the lack of a widely accepted consensus on the definition of both temporary and long term or permanent hypocalcaemia and/or hypoparathyroidism. It is imperative that medical and surgical societies and associations arrive at a consensus on how to define this condition to enable appropriate treatment, comparison of studies in literature and effective assessment of preventative measures.

Risk factors for the occurrence of PoSH may be classified as modifiable or treatable (such as Vitamin D deficiency or hypomagnesemia) or non-modifiable (such as postoperative PTH level or Graves' disease). A more accurate understanding of risk attributable to individual risk factors would help in a better prediction of risk of PoSH and this can be factored into the discussions regarding the risks and benefits of surgery. When the risk is considered high, it may be possible and appropriate to modify approach or extent of surgery in 'high risk' patients or use some of the novel preventative measures such as fluorescent imaging for parathyroid identification or preservation.

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Footnote

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