

# Short and long-term impact of parathyroid autotransplantation on parathyroid function after total thyroidectomy

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**Abstract:** The most common complication of total thyroidectomy is parathyroid insufficiency. Acute, transient, post-operative hypoparathyroidism increases length of hospitalization, morbidity and cost associated with total thyroidectomy. While permanent hypoparathyroidism poses a significant medical burden with lifetime medication, regular follow up and considerable disease burden related to chronic renal failure and other sequelae. Parathyroid autotransplantation has been demonstrated to result in biochemically functional grafts, leading to the procedures' common use during total thyroidectomy. The clearest indications for parathyroid auto transplantation are inadvertently removed or devascularized parathyroid glands. Some centers utilize routine autotransplantation to reduce the risk of permanent hypoparathyroidism. Novel fluorescence techniques to aid in parathyroid detection during thyroid surgery are under evaluation. This review aims to define the role and impact of parathyroid autotransplantation undertaken during total thyroidectomy.

**Keywords:** Parathyroid autotransplantation; total thyroidectomy; hypoparathyroidism; hypocalcaemia

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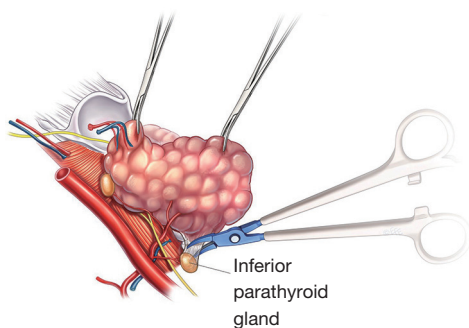
## Introduction

Postsurgical hypocalcaemia due to hypoparathyroidism is the most frequent and occasionally the most serious complication of total thyroidectomy (1). Inadvertent compromise of parathyroid blood supply or unintentional excision of parathyroid glands is the usual etiology of hypoparathyroidism (2). Parathyroid autotransplantation provides a solution to intraoperative parathyroid compromise, despite common utilization, the impact of autotransplantation on parathyroid function remains incompletely understood.

The symptoms of hypocalcaemia due to post-operative hypoparathyroidism usually present in the first 24–72 hours after surgery (3). Features of hypocalcaemia include circumoral or peripheral paraesthesia, tetany, carpopedal spasm,

laryngospasm and ECG changes progressing from long QT interval to VT arrest (4). In addition to patient morbidity and mortality, post-thyroidectomy hypocalcaemia leads to greater healthcare costs due to the need for extra biochemical testing, electrolyte supplementation and increased length of hospital stays (5).

In the longer term, undiagnosed hypoparathyroidism can lead to multiple systemic sequelae such as chronic renal impairment, reduced bone remodeling, increased psychiatric complaints and basal ganglia calcification (6). This is associated with significant morbidity and reduced quality of life. A recent population study by Hadker *et al.* demonstrated that 75% of sufferers of chronic hypoparathyroidism experienced symptoms despite treatment, 79% had required emergency department or hospital admissions and 85% reported inability to perform



**Figure 1** Preservation of the right inferior parathyroid gland.

household tasks (7).

The recognition of the disease burden associated with permanent hypoparathyroidism has led to the emergence of parathyroid autotransplantation as a means to reduce the prevalence of this complication in at risk patients. Parathyroid autotransplantation was first described and performed in humans during a thyroidectomy by Lahey (8) in 1926. The procedure was largely forgotten for 50 years until Wells *et al.* (9) reported the first patient series that confirmed functional autografts clinically, physiologically and histologically.

### Burden of disease and defining parathyroid failure

Part of the difficulty in defining the role of parathyroid autotransplantation relates to the variability in incidence and presentation of hypoparathyroid disease. Reported incidences of transient and permanent hypocalcaemia are highly variable, ranging from 10–61% (10,11) and 1–32% (12–15), respectively. In a more recent meta-analysis the estimated incidence of transient and permanent hypocalcaemia was 19–38% and 0–3%, respectively (16). National registries and large multicenter studies however, consistently demonstrate higher rates of permanent hypocalcaemia ranging from 6.4–9% (1,17) with the Fifth National Audit Report from the British Association of Endocrine and Thyroid Surgeons demonstrating a rate of 6.5% (18), having dropped from 12.1% in 2012 (19). The variable rates of hypoparathyroidism and concomitant hypocalcaemia in the literature partly relates to inconsistent definitions of hypoparathyroidism, hypocalcaemia and the division between transient and permanent conditions (20). A recent paper by Mehanna *et al.* described the reported rate of postoperative hypocalcaemia for the same cohort of patients varied 46-fold depending on

the definitions used (21).

Lorente-Poch *et al.* (22) attempted to address the diagnostic confusion by defining three distinct syndromes of parathyroid failure post total thyroidectomy. This consisted of (I) “postoperative hypocalcemia”: a serum calcium of  $<2$  mmol/L or  $<8$  mg/dL within 24 hours after surgery requiring calcium/vitamin D replacement therapy at the time of hospital discharge; (II) “protracted hypoparathyroidism”: a subnormal iPTH concentration  $<13$  pg/mL and/or need for calcium/vitamin D replacement at 4–6 weeks; (III) “permanent hypoparathyroidism”: subnormal iPTH concentration  $<13$  pg/mL and/or need for calcium/vitamin D replacement one year after total thyroidectomy.

The implementation of standardized definitions for hypocalcaemia would greatly improve the quality of literature and improve our understanding of the role of parathyroid autotransplantation in preventing hypoparathyroidism after thyroid surgery.

### Risk factors for hypoparathyroidism and prevention of hypoparathyroidism

The earliest thyroid operations were performed in the mid-1800s. However, at this early juncture, procedures had such a poor outcome that Samuel Gross wrote in 1866 ‘if a surgeon should be so adventurous or foolhardy as to undertake thyroidectomy, every step he takes will be environed with difficulties’ (23). Nevertheless, by the end of the 1800s Professor Theodore Kocher had reported 900 thyroid procedures with a mortality of merely 1% and minimal morbidity. However, Kocher’s case mix included only 18 total thyroidectomies, as he had found that his post-thyroidectomy patients did poorly, developing a condition he termed ‘cachexia strumipriva’, in actuality, hypoparathyroidism. This led Professor Kocher to abandon total thyroidectomy in favor of subtotal procedures (24).

Since then and particularly the last 30 years, improvements in surgical technique such as the advent of capsular dissection (23), careful handling of the parathyroid blood supply, loupe magnification (25) and truncal ligation of the inferior thyroid artery have rendered total thyroidectomy safer (*Figure 1*), allowing modern surgeons to harness the benefits of total thyroidectomy over subtotal approaches such as reduced recurrence for benign disease and increased survival for malignancy. Consequently, total thyroidectomy has become a preferred operation (23,26–28) for many benign and malignant thyroid pathologies. In 2015, Antakia

**Table 1** Risk factors for hypocalcaemia post total thyroidectomy

Transient hypocalcaemia	
Low preoperative calcium, PTH	
Low 25-hydroxyvitamin D	
Graves' disease	
Reoperation for bleeding	
Surgery for recurrent goitre	
Inadvertent parathyroid gland excision	
Parathyroid autotransplantation	
Female sex	
identification <2 parathyroid glands	
Lymph node dissection	
Permanent hypocalcaemia	
Calcium level <1.88 mmol/L 24 h post op	
Identification <2 parathyroid glands	
Graves' disease	
Reoperation for bleeding	
Heavier thyroid specimens	
Lymph node dissection	

*et al.* (29) underwent an extensive systematic review and meta-analysis to evaluate the effectiveness of surgical measures on post-operative hypocalcaemia. This found that less extensive surgery, such as subtotal thyroidectomy, is associated with less risk of transient hypocalcaemia but felt that this did not influence the argument regarding extent of thyroidectomy as there was no impact regarding permanent hypocalcaemia.

Recently Edefe *et al.* (16) undertook a systematic review of predictors for post thyroidectomy hypocalcaemia and found female gender, preoperative calcium, perioperative PTH levels, surgery for recurrent goiter or Grave's disease, reoperation for bleeding, inadvertent parathyroid gland excision, and parathyroid autotransplantation to be predictors for transient hypocalcaemia. Predictors for permanent hypocalcaemia included a calcium level lower than 1.88 mmol/L 7.54 mg/dL at 24 h after surgery, identification of fewer than two parathyroid glands at surgery, reoperation for bleeding, Graves' disease and heavier thyroid specimens. They noted that no study included in the review found parathyroid autotransplantation to be a predictor for permanent

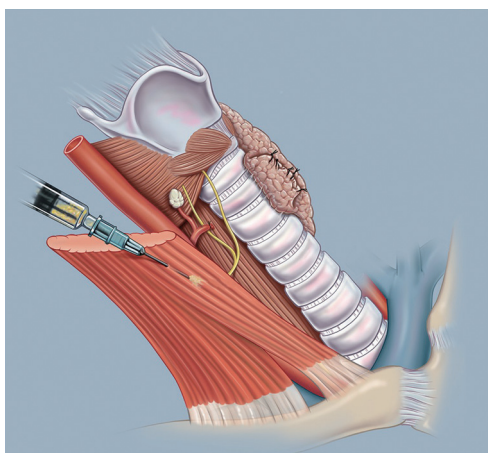
hypocalcaemia.

Any factor that compromises parathyroid gland function is a potential risk factor for post-operative hypoparathyroidism (2,4,11,30). Hence, the extent of surgery, inadvertent excision of parathyroid glands and identification of viable glands are repeatedly demonstrated to be factors in post-operative hypoparathyroidism (16,17,31,32). The incidence of incidental parathyroidectomy during thyroidectomy can be as high as 17.7% (32). Selective parathyroid autotransplantation with functional grafted parathyroid tissue theoretically should negate other factors causing dysfunction. However, it has also been demonstrated that the number of parathyroid glands remaining *in situ* is a critical factor in prevention of permanent hypoparathyroidism (33). Therefore, the success of parathyroid autotransplantation relies on the recognition of compromised parathyroid glands while maintaining the function of parathyroid glands left in place (*Table 1*).

#### **Identifying devascularized glands**

Parathyroid glands are usually identified by experienced surgeons through subjective visual assessment and detailed knowledge of anatomy (34). With appropriate training, Endocrine surgeons have been shown to develop satisfactory skills for the visual identification of viable parathyroid glands (35). Sung *et al.* (36) found that if at least one parathyroid gland was deemed to have a normal appearance at the time of closure then the development of hypocalcaemia requiring treatment is uncommon. However, it has also been demonstrated that even with meticulous dissection, anatomically intact glands may not be physiologically viable due to thrombosis of the delicate parathyroid vascular pedicle, or parathyroid capsule oedema (37). This is reinforced by Lang *et al.* (38) who found that parathyroid gland dusky discoloration was associated with transient hypoparathyroidism but also found that apparently normal glands with seemingly intact vascularity does not always imply that the gland is functional.

The most straightforward indication for parathyroid autotransplantation is when parathyroid glands are inadvertently removed with the thyroid specimen or when glands are obviously devascularized. Novel fluorescence techniques are currently under evaluation to improve parathyroid identification during thyroidectomy. The parathyroid glands exhibit significantly higher fluorescence intensity than surrounding tissues and this has been suggested as a tool for identification of parathyroid tissue



**Figure 2** Injection of parathyroid tissue into the sternocleidomastoid muscle.

(39,40). However, fluorescence only has the benefit of improving gland localization, it does not indicate that the gland remains viable after dissection. For this reason, some studies advocate for a 'knife test' of questionable glands checking for capillary bleeding (41), this has the added benefit of avoiding venous congestion in the gland, yet there is some concern that this may compromise viable glands. Routine frozen section of potential parathyroid tissue is used in some centers to confirm parathyroid tissue prior to transplantation (42). However Lo and Lam (43) determined that this was unnecessary for experienced surgeons as they felt unquestionable macroscopic appearance negated the need for frozen sections which risked reducing the amount of parathyroid tissue available for transplantation. There has also been an initial report regarding use of doppler ultrasound however clinically this is not easily feasible intraoperatively (44).

Perhaps the most useful assessment of parathyroid function intraoperatively is use of parathyroid hormone immunoassay. Barczyński *et al.* (45) demonstrated that taking a PTH level 10–20 minutes after total thyroidectomy prior to closure and utilizing a level <10 ng/L as an indicator for parathyroid autotransplantation resulted in a lower incidence of transient hypocalcaemia and reduced the risk of permanent hypothyroidism. This was also cost effective, being calculated to cost \$35 USD and time effective with results available within 8–10 minutes. Utilizing parathyroid level biochemistry and visual assessment of incidentally removed or discolored compromised glands as a guide to parathyroid auto transplant may reduce the incidence of

transient hypoparathyroidism while mitigating the risk of permanent hypothyroidism.

### *Technique of autotransplantation*

There are various techniques for autotransplantation, these include thin section slicing, mincing and injection of a suspension of parathyroid tissue (9,42,46,47). The most widely utilized technique for parathyroid autotransplantation is described by Wells *et al.* (9) In this approach, parathyroid tissue is placed in saline at 4 °C or in tissue culture medium as soon as possible after excision. After cooling for 30 min, the glands are sufficiently firm to be sliced into 1 mm slices or 1 mm cubes. Generally, 10–20 pieces are inserted into individual muscle pockets of muscle. The incision is closed with a non-absorbable suture or clip to assist subsequent identification.

Another common technique involves injection of a suspension of parathyroid tissue in buffered saline into the sternocleidomastoid muscle as demonstrated in *Figure 2*. This is our preferred technique and one which we have found to be reliable and easy to perform. We use 1–2 mL of sterile physiological salt solution such as BSS and carefully mince the de-vascularized parathyroid gland using fine scissors. The small fragments of tissue are drawn into a syringe and the suspension is injected into the right sternomastoid muscle at its midpoint. This produces comparable return of parathyroid outcome when compared to thin sectioning or mincing (46). This technique should be avoided when there may be a need for subsequent excision of part of the graft, as injected parathyroid tissue is diffuse and difficult to localize for re-excision. When surgery is undertaken for Multiple Endocrine Neoplasia Types 1 and 2, or renal failure patients with secondary and tertiary hyperparathyroidism this approach should be avoided. On the other hand, the relative ease of this technique makes it the procedure of choice for parathyroid autotransplantation during thyroidectomy in general cases.

### *Site for auto transplant*

There are many different potential sites for re-implantation of parathyroid tissue including the sternocleidomastoid, brachio-radialis, pectoralis major muscles (48) and, more recently, into the subcutaneous tissue of the forearm (49). Most common in total thyroidectomy is the sternocleidomastoid muscle which usually already lies exposed in the operative field (44,50,51). As the parathyroid

glands are expected to be functionally normal in the vast majority of cases of thyroid surgery this is a safe and easily accessible area. However, it is not possible to biochemically prove graft hyper-function when implanted into the neck. If there was a future need for removal of the graft, then re-operative surgery requires repeat cervical exploration.

Hence, if parathyroid autotransplantation is indicated for abnormal or hyperplastic parathyroid tissue, then the preferred graft location is usually in the brachio-radialis muscle of the non-dominant forearm (52). Sampling of venous return in the forearm containing the graft allows checking of graft function or dysfunction. A gradient of 1.5 or greater in PTH measurement between grafted and non-grafted arms has been generally accepted as proof of graft hyper-function (53). Additionally, if removal of the graft is indicated, the potential difficulties and risks associated with redo cervical surgery are alleviated. Although rare, auto transplanted parathyroid tissue has been demonstrated to result in primary hyperparathyroidism even after grafting of normal parathyroid tissue in total thyroidectomy (54). Utilizing, the brachio-radialis muscle has been successfully used by Lo and Tam to demonstrate parathyroid graft function after autotransplantation for total thyroidectomy (53).

More recently, Cavallaro *et al.* (49) have demonstrated parathyroid autotransplantation into forearm subcutaneous tissue to be a safe and effective procedure when used for normal functioning parathyroid glands inadvertently removed during total thyroidectomy. This had previously been documented to be effective in parathyroid hyperplasia (55). In a small study of 25 cases, they demonstrated recovery of reimplanted glands in 96% of cases at three months. This technique is faster and less invasive than intramuscular techniques, requiring only 2 mm skin excisions.

Forearm implantation provides an effective alternative to the traditional technique of reimplantation into the sternocleidomastoid muscle, and has the added benefit of easier monitoring of graft function and subsequent removal if graft dysfunction ensues. However, it is more time consuming due to the need for secondary incisions at a distant site. For this reason, the sternomastoid muscle with its ease and proximity, is the preferred site for autotransplantation of parathyroid tissue during thyroidectomy.

### Results of parathyroid autotransplantation

Parathyroid autotransplantation has been demonstrated to be effective, clinically and biochemically, with a functional

graft survival rate of 93% (9). However, the clinical utility of parathyroid autotransplantation following thyroid surgery is more difficult to evaluate, because it is a rare event for all four parathyroid glands to be removed or devascularized during thyroidectomy. Indeed, Song *et al.* found that even one remaining functional gland *in situ* provides a safe guard against permanent hypoparathyroidism; although the incidence of transient hypocalcaemia correlates with the number of parathyroid glands damaged or removed.

The question which arises is whether parathyroid autotransplantation should be performed when only one or two parathyroid glands have been removed accidentally or suspected to be devascularized. In other words, is there any additional benefit of parathyroid gland re-implantation in the likely presence of at least one functional *in situ* parathyroid gland? Delbridge (23) suggested that “the viability of *in situ* vascularized parathyroid remains unpredictable with late ischemia always a possibility. The routine autotransplantation of at least one parathyroid gland during every total thyroidectomy, while unnecessary in most cases, provides insurance in cases where late ischemia of the remaining glands actually occurs.” (23) Zedenius *et al.* (41) demonstrated this, showing that routine autotransplantation of one parathyroid gland during total thyroidectomy eliminated permanent hypoparathyroidism in a study of 100 consecutive total thyroidectomies.

Conversely, Lo and Lam (12) examined a policy of routine parathyroid autotransplantation compared to selective autotransplantation and found no significant difference in the rates of permanent hypoparathyroidism, 0% compared to 1.8% respectively but a significantly higher rate of transient hypocalcaemia, 23% versus 13%. This is reinforced by Barczynski *et al.* (45) who utilized PTH assay intraoperatively to guide parathyroid autotransplantation and found that selective autotransplantation yielded a lower incidence of transient hypocalcaemia when compared to routine autotransplantation, 11.2% versus 22.4% respectively. Both approaches yielded a 100% success rate in preventing permanent hypoparathyroidism. Thus, routine autotransplantation although still highly effective in preventing permanent hypoparathyroidism likely increases transient parathyroid dysfunction which extends hospital stays, causing discomfort and potentially life-threatening complications and could be avoided if a normal well vascularized gland had remained *in situ*.

Although some studies appear to demonstrate lower rates of permanent hypoparathyroidism after parathyroid autotransplantation compared to controls, most of these

were underpowered and failed to demonstrate statistically significant differences. On the other hand, some scholars have argued that parathyroid autotransplantation places potentially viable parathyroid glands at risk, and have cautioned against routine autotransplantation. Lorente-Poch *et al.* (33) measured the parathyroid glands remaining in situ score (PGRIS), and found this inversely related to the rate of permanent hypoparathyroidism. However, this score included both auto transplanted and removed glands, thereby not directly testing function of the grafted parathyroid gland. A further study by the same authors found that the rates of permanent hypoparathyroidism were similar whether the glands are incidentally resected or auto transplanted. In a larger population study (56), parathyroid autotransplantation significantly increased the risk of transient hypoparathyroidism, OR 5.19, P value <0.0001, whilst it showed a non-statistically significant trend toward minimizing the risk of permanent hyperparathyroidism.

Parathyroid autotransplantation has repeatedly been found to be a risk factor for transient hypocalcaemia (11,12,16,56-58). Edefe *et al.* (16) conducted a systematic review and meta-analyses of predictors of post-operative hypocalcaemia and found that patients undergoing parathyroid autotransplantation had double the risk of transient hypocalcaemia. However, these studies instituted selective autotransplantation only in cases when the blood supply to a gland was deemed to be questionable, which in turn were compared against controls in which autotransplantation had not been indicated. Therefore, on the basis of this evidence, it cannot be answered if parathyroid gland autotransplantation is an independent risk factor. Additionally, Testini *et al.* (51) found that parathyroid autotransplantation reduced the incidence of transient hypocalcaemia when they compared age, sex and surgical indication matched controls with one devascularized gland, to patients undergoing parathyroid autotransplantation due to having one devascularized gland. Therefore, despite the strong correlation between autotransplantation and transient hypocalcaemia, these results may be partially confounded by the indication for autotransplantation being parathyroid devascularization.

Two studies have demonstrated a statistically significant decrease in permanent hypoparathyroidism after parathyroid autotransplantation. Ahmed *et al.* (59) demonstrated a 3.09% incidence of permanent hypocalcaemia in patients with no parathyroid autotransplantation and a 0.34% incidence in patients following autotransplantation with a P value of 0.0417. The patients in this study were initially randomly

assorted but favorable results in the autotransplantation group led to a policy of routine autotransplantation, this demonstrates a bias towards the use of parathyroid grafting. Wei *et al.* (60) examined the role of selective autotransplantation of inferior thyroid glands in patients undergoing total thyroidectomy and central neck dissection. They found that permanent hypoparathyroidism was lower after parathyroid autotransplantation compared with preservation in situ, 0.9% and 3.8% respectively with a P value of 0.003. The authors also note that autotransplantation may allow a more comprehensive central neck dissection. This may illustrate that parathyroid autotransplantation is more effective in cases where central neck dissection is required as these have been demonstrated to have an increased risk of post-operative hypocalcaemia (29). Additionally, a large retrospective cohort study of 1,196 patients demonstrated that using a selective policy of autotransplantation maintains a rate of permanent hypoparathyroidism at less than 1% (11). However, no significant difference was found between patients undergoing parathyroid transplantation or controls.

Overall parathyroid autotransplantation is associated with transient hypoparathyroidism but a reduction in rates of permanent hypoparathyroidism. Although the number of patients benefitted will be low, as only one functioning gland *in situ* may be enough for prevention, the morbidity related to permanent hypocalcaemia is so significant that this small potential benefit is more advantageous than leaving devascularized or jeopardized glands in place where their ongoing function is unpredictable. Despite a lack of clear empirical evidence, parathyroid autotransplantation is an effective procedure that can safeguard against permanent hypoparathyroidism (Table 2).

### *Cryopreservation*

Cryopreservation is another method, again pioneered by Wells (61), to avoid permanent hypoparathyroidism following parathyroid or thyroid surgery (9,62). Cryopreservation involves the freezing and storage of parathyroid tissue in case permanent hypoparathyroidism occurs (63). It has been advocated in patients undergoing surgery for persistent or recurrent hyperparathyroidism and patients requiring subtotal or total parathyroidectomy but also in thyroid and central neck dissection due to the risk of failure of immediately transplanted autografts (64). Although its most obvious indication remains primary multi-glandular hyperparathyroidism when it is unclear if post-operative

**Table 2** Impact of autotransplantation on hypocalcaemia in studies comparing selective autotransplantation to preservation *in situ* with no autotransplantation

Paper	Impact on transient hypocalcaemia			Impact on permanent hypocalcaemia		
	Impact	Autotransplant	No autotransplant	Impact	Autotransplant	No autotransplant
Testini <i>et al.</i>	↓	17.7%	45.7%	-	0%	2.5%
Lo and Lam (59)	↑	21.4%	8.1%	-	0%	2.9%
Kirdak <i>et al.</i> (58)	↑	55.7%	26.2%	-	11.5%	3.3%
Wei <i>et al.</i> (61)	-	26.5%	25.0%	↓	0.9%	3.8%
Ahmed <i>et al.</i> (60)	-	16.8%	23.7%	↓	0.3%	2.9%
Palazzo <i>et al.</i> (11)	↑	13.3%	9.8%	-	0.58%	0.98%

patients will go on to develop further hyperparathyroidism but remain at considerable risk of developing permanent hypoparathyroidism postoperatively (65).

Transplantation of cryopreserved tissue is less effective than immediate autotransplantation with a highly variable reported success rate from 10–100% (64–66). Agarwal *et al.* (66) cryopreserved 630 specimens following parathyroid surgery, and reported a 100% success rate as measured by an increase in circulating parathyroid hormone from 9 delayed parathyroid transplantation procedures utilizing stored parathyroid tissue. However, 2 of the patients remained on high dose calcium at the conclusion of their study. They did not offer parathyroid gland cryopreservation for routine thyroidectomy patients. On the other hand, a large multicenter trial in France cryopreserved 1,376 parathyroid tissue samples. Of these, only 22 were auto grafted into 20 patients, of which only 10%, were fully functional and another 10% retained partial function with patients requiring ongoing calcium and vitamin D supplementation.

Cryopreservation is a useful and potentially beneficial procedure in only a very small number of selected cases of permanent hypocalcaemia. The benefit of retaining parathyroid tissue for cryopreservation following the majority of cases of thyroidectomy remains doubtful, given that rates of permanent hypoparathyroidism are below 1% when selective immediate parathyroid autotransplantation is utilized (11).

### New techniques and the future of treatment for permanent hypoparathyroidism

Most studies continue to focus on prevention of parathyroid dysfunction by careful preservation *in situ*

and utilizing selective parathyroid autotransplantation when necessary. Yet the disease burden of post-operative hypocalcaemia remains high with many studies reporting a low level of permanent hypocalcaemia despite utilizing autotransplantation. Considering the relative success of parathyroid autotransplantation and the innate characteristic of parathyroid tissue to be transplanted (67) it is worth considering allotransplantation in the treatment of chronic hypoparathyroidism.

Unfortunately, to date, allotransplantation has had variable results usually due to rejection by alloimmunization or inflammatory responses causing fibrosis compromising graft survival (68,69). The risks involved in immunosuppression both from medication side effects and risk of infection are generally not considered to outweigh the benefit in terms of long term treatment for hypoparathyroidism. Yet Agha *et al.* argue in a recent case study that this needs to be considered on an individual basis after demonstrating successful allotransplantation in a 30-year-old with post-operative permanent hypocalcaemia who had failed medical therapy. Alternatively, Nawrot *et al.* (70) demonstrated that it is possible to culture non immunogenic parathyroid cell populations. They found that of 85 allotransplants, 65 cellular allografts retained endocrine function for two months with a mean overall graft survival of 6.3 months. Graft function was considered present when overall PTH level increased compared to pre-operatively, there was an evident PTH gradient between ipsilateral and contralateral arms and patients no longer required vitamin D and only minimal calcium supplementation. Case reports have also demonstrated increased survival through the use of microencapsulated parathyroid tissue. Cabané *et al.* (71) demonstrated a 20-month graft survival in a patient

previously needing continuous intravenous calcium for survival. Therefore, parathyroid allotransplantation is a potential option for long term hypoparathyroidism however it doesn't negate the importance of *in situ* preservation and parathyroid autotransplantation in total thyroidectomy.

Alternatively, new stem cell research has yielded promising results regarding the generation of parathyroid-like cells. Ignotski *et al.* and Bingham *et al.* have demonstrated a method of generating cells producing parathyroid hormone RNA and parathyroid hormone from two different human embryonic stem cell lines (72,73) utilizing activin A and soluble sonic hedgehog. They note that parathyroid cells are optimal for cellular replacement as each cell contains that complete function of the organ, no architectural structure is needed for parathyroid cells to resume function and autotransplantation has been demonstrated to reconstitute normal parathyroid function. *In vitro* studies in rats' post parathyroidectomy have demonstrated survival benefit after implantation of differentiated human tonsil-derived mesenchymal stem cells (TMSC) (74,75). However, these studies are short term and demonstrate limited survival benefit with a 40% increase in mortality at 28 days and 50% at three months. Therefore, more research is required before stem cells differentiated to produce parathyroid hormone are useful in the treatment of post thyroidectomy hypoparathyroidism.

Another potential treatment option is recombinant human PTH which has been accepted for use by the FDA in America in 2015 and in the EU since earlier this year. In a phase III trial, subcutaneous rhPTH 1–84 was effective in maintaining total serum calcium levels while reducing or eliminating the need for oral calcium and active vitamin D (76). However, studies in rats have demonstrated a risk of osteosarcoma (77). As yet, no skeletal malignancies have been described by clinical trials in humans with cumulative numbers of 16,000 subjects treated with up to three years of continuous therapy (78). Currently, recombinant PTH is a promising option in the treatment of permanent hypoparathyroidism however long term studies of ongoing follow up of patients using these medications are needed to further determine their efficacy and safety.

## Conclusions

Minimizing the costs and morbidity associated with hypoparathyroidism following thyroid surgery should begin with the implementation of standardized definitions of hypocalcaemia so that individual surgical units can quantify

their own rates. A strong emphasis on surgical technique to avoid vascular injury to the parathyroid is critical to good long term outcomes as well as an awareness of the high risk cases which include multi-glandular parathyroid disease and lymph node dissection in which increase there is a greater risk of disrupting parathyroid function. Parathyroid function, and its permanence, correlates with the number of functioning parathyroid glands which remain *in situ*. The functional viability of parathyroid glands may best be assessed by visual inspection and the use of intraoperative PTH immunoassays. An approach of selective autotransplantation of de-vascularized glands provides an effective means of restoring parathyroid function and is protective against permanent hypoparathyroidism.

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## Footnote

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

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