



Hypoparathyroidism after thyroidectomy: a matter of definition, experience and new adjuncts

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Postoperative hypoparathyroidism is the most common and most important surgical complication following thyroidectomy, associated with significant morbidity, reduced quality of life, and a considerable socioeconomic burden on healthcare systems. It has become clear in recent years that permanent hypoparathyroidism is more prevalent than previously assumed. In particular, nationwide quality registers on relatively large cohorts of patients showed alarmingly high numbers: 12.1% in a British register, 12.5% in a Scandinavian register, and 9% in a German multicentre study (1-3). A Spanish nationwide study found an even higher rate of 14.5% (4). A study focusing on children showed a rate of 7.3% permanent hypoparathyroidism post thyroidectomy, which is particularly concerning (5). In contrast, expert high-volume single centres consistently report rates around or even below 1% (6,7). These discrepancies can be attributed to a variety of factors such as publication bias (we are less likely to report suboptimal results), incomplete follow-up, varying follow-up practitioners (general practitioners, endocrinologists, surgeons, oncologists), differences in surgical expertise, and differences in the definitions of permanent hypoparathyroidism.

The definition of postoperative hypoparathyroidism involves various elements: the duration of hypoparathyroidism

after surgery (greater than 6 or 12 months), biochemical values [low parathyroid hormone (PTH) with or without hypocalcemia, PTH levels not adapted to calcium levels], and the need for calcium and/or active vitamin D supplementation. The American Thyroid Association (ATA) defines permanent hypoparathyroidism as low PTH values with hypocalcemia lasting beyond six months post-surgery (8). However, a systematic review of 89 articles revealed 20 different definitions of permanent hypoparathyroidism used across the literature, none of which adhered to the ATA guidelines (9). This highlights the need to raise awareness and standardize the definition of this complication.

In light of these challenges, a new study by Annebäck *et al.*, featured in *British Journal of Surgery*, provides valuable insight on this topic. Annebäck and colleagues present a population-based retrospective cohort study on 1,636 patients that investigates the rate of permanent hypoparathyroidism after total thyroidectomy for benign thyroid disease in Sweden between 2005 and 2015 (10). The patients for this study were identified through the Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery (SQRTPA) and the Swedish National Patient Register (NPR).

The primary outcome of this study was the rate of permanent hypoparathyroidism, defined by the need

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for calcium and/or active vitamin D supplementation more than 12 months after surgery. This study provides a precise definition of this condition, categorizing it into definitive and possible cases based on specific biochemical criteria and attempts to stop supplementation. Notably, their use of a 12-month cutoff acknowledges that some patients may recover later than initially assumed. They also introduce a new criterion: a (failed) test of stopping all supplementation. This is a significant step forward because some patients with temporary hypoparathyroidism may be misdiagnosed with a permanent condition if no attempt to wean off supplements is made. Correct, structured, and prolonged follow-up by experienced practitioners, such as endocrinologists or endocrine surgeons, is paramount and has been shown to significantly reduce the rate of permanent hypoparathyroidism (11). Unfortunately, it is difficult to assess how many surgeons follow their patients with hypoparathyroidism until recovery. One study, for instance, revealed a deplorably low rate of only 0.5% patients with postoperative hypoparathyroidism being followed up by their surgeons (12). Furthermore, the existence of late recoveries, beyond 12 months, must be taken into consideration. Even if only a minority of patients with permanent hypoparathyroidism recover after this period, this information indicates a trend towards at least partial recovery with prolonged follow-up, which might help reduce the use of supplements.

Their secondary aims were to evaluate the relationship between the rate of low PTH levels within 24 hours post-surgery and the incidence of permanent hypoparathyroidism in the total cohort. No significant differences were found in patient or operation variables between those with and without permanent hypoparathyroidism. Additionally, an interesting new surrogate marker for permanent hypoparathyroidism was introduced: early post-operative PTH that serves as a risk predictor for permanent hypoparathyroidism.

The consequences of permanent hypoparathyroidism have been extensively studied and involve an increased risk of renal insufficiency, basal ganglia calcifications, impaired cognitive function, and increased risk of new cardiovascular events for patients with cardiac comorbidities. It has been suggested that permanent hypoparathyroidism might be associated with a higher risk of malignancy and death (13). Symptoms experienced by patients are complications of both the disease and currently available management regimens, significantly impacting everyday life. The PARADOX study found that nearly 80% of patients

required hospital admission, 85% reported inability to perform household activities, and 20% had a change in employment status due to the illness (12). Consequently, the economic impact is considerable, encompassing sick leave, life-long supplementation, and surveillance.

Treatment for permanent hypoparathyroidism involves lifelong calcium and/or active vitamin D supplementation. But even with proper follow-up, serum calcium fluctuations are common and some patients experience refractory symptomatic hypocalcemic episodes that require repetitive hospitalizations and intravenous calcium administration. Recombinant human PTH can be used if hypoparathyroidism is unmanageable with conventional methods. It is administered subcutaneously and may require repetitive frequent injection, often with suboptimal efficacy (14). Recently, new substances like PTH analogs have been marketed, but their efficacy still needs to be demonstrated in further studies (15). What is more, those treatments are far from being widely available in everyday practice for most clinicians. Thus, faced with a lack of efficient treatment for permanent hypoparathyroidism, emphasis must be placed on its prevention.

Annebäck *et al.* report a rate of 8.7% of permanent hypoparathyroidism that aligns with several other studies and is, in fact, unacceptable when considering that rates less than 1% are routinely achievable in numerous centres.

The patients included in their study had benign thyroid disease, in most cases Graves' disease, followed by multinodular goitre. There were no cases of lymph node dissection [which has been shown to be one of the risk factors for a postoperative hypoparathyroidism (16)], no complex cancer cases, and no cases of redo surgery, as previous thyroid surgery was an exclusion criterion. Their study is thus not only a call for improved follow-up but also a plea for sufficient surgical expertise, in a changing landscape where new adjuncts like fluorescence-based imaging become widely available, potentially helping to reduce these high rates. It underscores that total thyroidectomy, even for a benign condition, is a complex procedure with a high risk of lifelong complications for mostly young patients—the mean age of the patients in the study was 45 years, likely reflecting the average age of those undergoing surgery for benign thyroid disease in a regular endocrine surgery department.

This issue relates to the highly debated issue of minimum case load and the outcome-volume correlation. A recent study found a 31% rate of permanent hypoparathyroidism in a low-volume centre (17), and strong evidence in

the literature indicates that the prevalence of this complication is highly dependent on surgical expertise (18). Restricting total thyroidectomy to high-volume centres has been proposed as an effective but radical solution. Moreover, preserving functional parathyroid glands can be complex, often challenging even for expert surgeons, particularly in complex cancer cases and in redo surgery.

More restrictive surgical indications like performing hemithyroidectomies instead of total thyroidectomies when possible, in line with the current trend of avoiding overtreatment, or abstaining from preforming prophylactic central lymph node dissection if there is insufficient surgical expertise, are efficient means to reduce postoperative hypoparathyroidism rates. In cases where the extent of surgery cannot be reduced, fluorescence-based imaging is a valuable adjunct.

Fluorescence-based imaging in thyroid surgery is a promising tool that can counteract these challenges. Mapping of the parathyroid glands position with near-infrared autofluorescence (NIRAF) imaging leads to earlier and more frequent identification of the glands, lowers the rate of inadvertent resection, and helps to salvage parathyroid glands from the resected specimen (19,20). Additionally, contrast-enhanced fluorescence imaging [indocyanine green (ICG) angiography] can help identify parathyroid glands' vessels at the beginning of surgery. This approach helps evaluate parathyroid vascularisation, and in turn viability, after dissection to determine whether or not autotransplantation is necessary (21,22).

Fluorescence-based imaging may help lower-volume surgeons reduce hypoparathyroidism rates. One of the main challenges for less experienced surgeons is parathyroid gland localisation and identification. NIRAF imaging enables earlier and more frequent visualisation of parathyroid glands. A meta-analysis of nearly 1,200 patients found that NIRAF can identify parathyroid glands with a remarkable sensitivity, specificity, negative predictive value, and positive predictive value of 97%, 92%, 95%, and 95%, respectively (23). Furthermore, NIRAF helps "mapping" of the operating field, scanning its surface and guiding dissection by avoiding accidental injury to the parathyroid glands.

A recent study showed that a probe-based device for NIRAF is more accurate than both junior and senior surgeons at identifying parathyroid glands, with a more significant improvement seen in the former (24), suggesting that fluorescence-based imaging could be particularly beneficial for low-volume surgeons, and even more for

junior surgeons.

However, the use of fluorescence techniques itself is associated with a learning curve and requires practice in order to exploit their maximum benefits. Some aspects, such as the optimal timepoints during surgery when fluorescence imaging yields the best results, or the interpretation of the ICG grey scale, remain subjective and thus constitute new exciting fields of research.

Numerous studies, including randomized controlled trials, consistently show that fluorescence imaging in thyroid surgery reduces temporary hypoparathyroidism (7,25). However, no reduction in permanent hypoparathyroidism has been observed, possibly because most research has been conducted in high-volume centres with already low rates of permanent hypoparathyroidism.

Annebäck *et al.* also attempt to assess whether an early post-operative PTH level is an appropriate surrogate marker for predicting permanent hypoparathyroidism. In fact, normal PTH values on the first day post-surgery make permanent hypoparathyroidism unlikely. More research is needed to validate early post-operative low PTH levels as a reliable surrogate marker for predicting the rate of permanent hypoparathyroidism. If further studies confirm this correlation, it would greatly facilitate and simplify the evaluation of the impact of new technologies, such as NIRAF and ICG angiography. Additionally, since not all endocrine surgery centres consistently perform complete follow-ups of 6–12 months and many patients might get lost to follow-up, this surrogate marker would provide a more precise quality control measure.

Adopting fluorescence-based imaging in everyday surgical practice involves a learning curve. Determining the optimal moments to scan the operating field with the NIRAF camera and inject ICG to visualise the vascular pedicles of the parathyroid glands comes with practice. However, fluorescence-based imaging could help teach even experienced surgeons about the unusual vascular anatomy of the parathyroid glands and help them adopt new dissection methods. More research, particularly on the impact of fluorescence-based imaging for low-volume surgeons, is needed to establish the benefits of this technology in settings with high rates of temporary and permanent hypoparathyroidism, as reported by Annebäck *et al.*

The study's limitations include its retrospective nature, varying PTH measurement methods and timepoints, diverse follow-up and medication weaning practices, as well as the incompleteness of the data common to nationwide registers. Regarding the surrogate marker, the authors found that a

rate of 30% of patients with low early post-operative PTH levels would correspond to a rate of 8.0% (6.0% to 10.5%) developing permanent hypoparathyroidism, suggesting that early PTH values can predict later complications and serve as a quality control measure. But it seems that high-volume expert centres report some rates of temporary hypoparathyroidism while maintaining very low rates of permanent hypoparathyroidism (7,25). Thus, the relationship reported by the authors in this study may not be universally applicable and has to be validated in larger series.

Overall, the results reported by Annebäck *et al.* provide valuable evidence that permanent hypoparathyroidism is more frequent than previously assumed. Most published data on very low permanent hypoparathyroidism rates comes from expert centres and university hospitals. Population-based registries like this one provide a comprehensive overview of the true occurrence of this complication. Furthermore, the study introduces an interesting concept of early low PTH levels as a possible surrogate marker for the rate of a permanent hypoparathyroidism. Thus, one of the central messages of the study is the need for all surgical teams to quantify the PTH values in all patients in the early post-operative period. Another one is the necessity for a more structured follow-up by experienced practitioners who will periodically evaluate the possibility to wean off the calcium supplements to avoid overtreatment and to detect the late recovery cases.

The rates reported by this study should not be acceptable in an era of valuable adjuncts developed to counteract this complication. New research focusing on the benefits of fluorescence-based imaging in low-volume surgeons is of particular interest in this context. Expert centres should make efforts to further develop and popularise these adjuncts and establish guidelines for better prevention of this complication.

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