Postoperative Hypoparathyroidism

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15.1 Introduction

Hypoparathyroidism is a pathological clinical condition characterized by low serum calcium levels in the presence of absent or inappropriately low parathyroid hormone (PTH) levels. It is usually caused by reduced parathyroid gland (PG) function due to secondary (and often iatrogenic) causes (>75%); less frequently, it occurs as a primary disorder caused by intrinsic genetic defects (Di George syndrome) or an autoimmune disease [1].

The most common cause of secondary/acquired hypoparathyroidism is postoperative hypoparathyroidism (POH), caused by intraoperative injury to the PG through compromising the vascular supply, thermal injury or inadvertent excision [2]. The surgical procedures causing POH include thyroid, parathyroid, laryngeal, or other neck surgeries for both benign and malignant diseases. POH is the most frequent complication after thyroid surgery, and it is influenced by several operative factors, including the underlying thyroid disease and the extent of the surgical procedure; it occurs most often after a bilateral thyroid excisional procedure, followed by extensive bilateral parathyroid surgery (10–15%) [1, 3]. Iatrogenic hypoparathyroidism may be also caused by neck radiotherapy.

POH is usually defined as transient when lasting less than 6 months after surgery, or definitive if low calcemic and/or PTH levels and the need for calcium and/or vitamin D supplementation last more than 6 months from initial operation [4].

After total or completion thyroidectomy, various institutional and individual surgeon protocols have been developed to prevent POH or detect it at the earliest possible time point to be able to manage it promptly. However, as confirmed by a recent metanalysis [5], the definition of POH is vastly heterogeneous in the literature, and the best approach for the early recognition of POH is not uniquely defined. The

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most used definitions of POH are reduced PTH levels only, hypocalcemia only, reduced PTH or hypocalcemia, or a combination of both. Moreover, some studies included the presence or absence of symptoms to define the diagnosis of POH. Thus, considering the various definitions in the determination of postoperative recovery of PG function after thyroid surgery and the different biochemical assays used, also the incidence of POH varies widely in the surgical literature and even within the same center and in the same cohort of patients; it may range from 0% to 46% for transient POH and 0–15% for its definitive variant, depending on the definition used [6].

15.2 Etiology

The identification and preservation of the PG with their blood supply is the greatest technical issue during thyroid surgery. In fact, the main causes of transient and permanent POH are inadvertent resection or devascularization of PG.

In fact, PG identification and preservation during total thyroidectomy are critical to avoid POH and require, in addition to knowledge of their anatomical locations and vascular supply, an experienced surgeon. The PG are indeed difficult to distinguish from other cervical tissues because of their small size and similar color compared to the thyroid, fat, and lymph nodes. Therefore, an anticipatory visual approach using surgical landmarks by a skilled surgeon is crucial. Moreover, the anatomy of the PG is extremely variable and related to their embryologic development. While the area of distribution of the superior PG, which arise from the fourth branchial pouches, is fairly constant due to the short embryonic migration path, the normal distribution of the inferior PG, derived from the third branchial pouches, varies widely owing to the longer migration path [7]. The superior PG are found in over 80% of cases posterior to the thyroid lobe, above the intersection of the recurrent laryngeal nerve and the inferior thyroid artery; the inferior PG are located in half of the cases on the anterior surface of the inferior thyroid lobe, and in a quarter of cases along the thyrothymic ligament or in ectopic position. Moreover, more than four PG may be found in at least 10% of patients [8]. Hence, despite all efforts, inadvertent parathyroidectomy is reported in up to 20% of patients.

In addition to PG identification, the critical point is to preserve PG vitality by maintaining an adequate blood supply. In order to guarantee this, gentle handling of the PG and their vessels is required. The small vessels between the PG and the thyroid capsule should be preserved by careful dissection of the thyroid capsule from the perithyroid fatty tissues, without injuring or cauterizing the PG; if necessary, hemoclips or fine-tip bipolar forceps should be used to divide these vessels near the parathyroid gland.

Recently, near-infrared (NIR) autofluorescence of PG, a technique that uses the unique property of intrinsic autofluorescence of parathyroid tissue, has been proposed; this technique allows the surgeon to recognize and protect the PG since the spontaneous signal they emit is up to 11-times higher than surrounding tissues. Moreover, the intraoperative use of NIR combined with indocyanine green angiography to assess PG perfusion at the end of the operation seems to reliably predict PG

vascularization, potentially POH and the need for calcium-vitamin supplementation in patients with at least one well-perfused PG [9]. However, further studies are needed to obtain a standardized protocol and to replicate these results.

In cases of inadvertently removed or definitively devascularized PG, autotransplantation into a muscle pocket, where they will recover their vascular supply and secretory function, is usually suggested. In the past, systematic autotransplantation of at least one PG was proposed to decrease the risk of permanent POH [10]. However, it has been demonstrated that the autotransplantation of normal PG does not avoid permanent POH, while it increases the rate of transient POH; thus, autotransplantation is recommended only when the gland is completely devascularized or definitively removed, since PG function may be better preserved if the glands are left in situ rather than autotransplanted [11].

The preferred site for autotransplantation is the sternocleidomastoid muscle. Different techniques have been described, including the reimplantation of 10–20 small fragments of the gland, or the intramuscular injection of a suspension of parathyroid tissue in buffered saline [12].

15.3 Patient- and Disease-Related Risk Factors

Beside the surgery-related predictive factors of POH, several other individual and disease-related risk factors have been reported. As reported in some metanalysis [13], women and patients with Graves' disease had a significantly higher incidence of transient hypocalcemia. Other potential risk factors identified in multivariable analysis in individual studies included: heavier thyroid specimens [14] and longer duration of Graves' disease [15]. Permanent POH was found to be associated with more advanced stage of thyroid cancer [16].

15.4 Diagnosis

15.4.1 Clinical Presentation

The clinical manifestations of POH depend on the severity of hypocalcemia because low serum ionized calcium can alter neurological, cognitive, muscular, and cardiac function. The spectrum of symptoms can range from asymptomatic or mild disturbances to bronchospasm, laryngospasm, seizures, tetany, and cardiac rhythm disturbances [17].

Symptoms of neuromuscular irritability are the most common in the setting of acute hypocalcemia. They can range from numbness and tingling in the fingertips, toes and circumoral region in mild hypocalcemia, to paresthesias of the upper and lower extremities in moderate hypocalcemia and tetanic muscle cramps such as carpal spasms or diffuse tetany in the most severe forms. Rarely, bronchospasm and laryngospasm with acute respiratory failure may occur. Neurological symptoms,

including confusion, delirium, seizure, and cardiac abnormalities, such as prolonged QT interval on electrocardiogram and arrhythmias, can also occur [18].

The Chvostek and Trousseau signs are useful to detect a latent tetany. However, the Chvostek sign, consisting of a contraction of ipsilateral facial muscles after tapping the facial nerve, has low sensitivity and specificity; it has been reported to be present in up to 10–15% of normal individuals, while 29% of patients with biochemical confirmation of POH have a negative Chvostek sign. The Trousseau sign consists of a carpal spasm (extension of the wrist, extension of interphalangeal joints, adduction of the thumb) evoked by inflation of a sphygmomanometer above systolic blood pressure for a few minutes. Hyperventilation and the subsequent metabolic alkalosis, increasing the binding of calcium to albumin and decreasing the available ionized calcium, increases the sensitivity of this maneuver by worsening the symptoms.

15.4.2 Biochemical Testing

Several institutional and individual surgeon protocols have been reported for biochemical testing for POH, including calcium and PTH measurements.

Since low ionized calcium levels are the main factor responsible for symptoms, postoperative measurement of serum calcium levels alone has often been used to diagnose POH and prevent symptomatic hypocalcemia. Hypocalcemia is usually defined as calcium levels below the lower limit of normal for an institution's laboratory [4], usually 8 mg/dL. Some authors proposed to use the absolute value of serum calcium levels to define hypocalcemia, others preferred to use the decreasing trend or the rate of change of calcium measurements at different time points, as a predictive tool for POH [19]. However, because trending calcium often requires sampling over a 24-hour or even longer time period and because postoperative calcium levels may be confounded by prophylactic calcium and calcitriol administration or by low preoperative vitamin D levels, most authors have underlined the role of measuring PTH, which has the advantage of a short half-life (less than 5 minutes), at various time points in the early post-thyroidectomy period [20]. Despite the differences in study design, PTH assays used and timing of PTH sampling, all studies concluded that there is a strong correlation between postoperative PTH levels and hypocalcemia. Unfortunately, it is not possible to define an absolute PTH level or relative decline having 100% sensitivity and 100% specificity [21–24]. Thus, the earliest opportunity to predict POH reliably is through the measurement of serum PTH levels during the first 24 hours after thyroidectomy, which may allow the early detection and treatment of patients at risk of POH, and subsequently allow safe patient discharge. According to the American Thyroid Association [4], a PTH level < 15 pg/mL is usually predictive of impending hypocalcemia and requires a preemptive prescription of oral calcium and calcitriol and/or serial serum calcium measurements until calcium stability has been confirmed.

15.5 Postoperative Management of Postoperative Hypoparathyroidism

The objective of postoperative correction of POH is to avoid the symptoms and complications of hypocalcemia. Several protocols have been proposed to guide calcium and vitamin D supplementation after surgery.

The empirical prophylactic approach consists in the routine prescription of oral calcium with or without oral calcitriol, without testing PTH or calcium levels [25]. This prophylactic approach has the advantage of being fast and facilitating hospital discharge after thyroidectomy; however, it has a non-negligible risk of causing severe hypercalcemia and potential renal injury. Moreover, it requires biochemical monitoring for medication tapering in all discharged patients, which affects the cost-effectiveness of this strategy.

In the presence of early/mild hypocalcemia (calcemia below 8 mg/dL) and/or PTH < 15 ng/L, oral calcium supplementation (1–3 g of calcium carbonate daily) and calcitriol (typically 0.25–0.5 mcg twice daily) might be considered. If severe symptomatic hypocalcemia develops despite oral calcium and calcitriol therapy, intravenous calcium (1–2 g of calcium gluconate) is the most expeditious but also the least durable method for raising serum calcium rapidly.

The oral dose of calcium and calcitriol or other vitamin D metabolites should be individually tailored by checking serum calcium initially every week and then every 2–3 weeks or monthly. Once stable normocalcemia is achieved and serum phosphate normalizes, the doses can be gradually reduced or, if hypocalcemia develops while tapering down calcium-vitamin treatment, the previous effective dose should be restarted.

15.6 Long-Term Management and Complications of Postoperative Hypoparathyroidism

Long-standing POH may have a substantial impact on quality of life. The long-term consequences of POH are not negligible and include nephrolithiasis, nephrocalcinosis, basal ganglia calcification, ectopic soft tissue calcification, cataracts, and potential defects in bone metabolism [26].

Bone microarchitecture in hypoparathyroid patients is abnormal, with a low bone turnover; in fact, even if the mineral content and bone mass tend to be increased, there is also an augmented bone stiffness that may increase the risk of fractures. Hypercalcemia during treatment in the presence of hyperphosphatemia determines a high calcium phosphorus product that predisposes to the risk of calciphylaxis, with vascular calcification, basal ganglia calcification, and thrombosis. Moreover, the risk of ectopic mineralization in the kidney may accelerate the risk of renal failure [17].

The goals of long-term treatment of POH are to maintain serum calcium within the normal range with the minimal amount of calcium and vitamin D supplementation, in order to reduce the complications of treatment, such as hypercalcemia,

hypercalciuria, nephrolithiasis and nephrocalcinosis [4, 17]. Chronic treatment of POH requires oral calcium and vitamin D. Vitamin D in the active form of calcitriol is essential to increase calcium absorption and can be upwards titrated to reduce the amount of calcium supplementation. Some patients remain normocalcemic only by taking calcitriol. However, in some cases calcium homeostasis cannot be completely controlled by treatment with calcium and vitamin D metabolites. For this reason, alternative approaches have been studied, including the use of recombinant human PTH that was approved by the FDA in 2015. The randomized phase III REPLACE trial [27] demonstrated that the treatment with recombinant human PTH (1–84) reduces the need of calcium and vitamin D supplementation in half of the adult patients treated, improves quality of life, and achieves a significant benefit in bone metabolism. However, further studies with various PTH fragments and analogs are ongoing to confirm their use in clinical practice.

15.7 Conclusions

In conclusion, patients undergoing bilateral thyroid surgery are at risk for POH and should be routinely tested for serum calcium and intact PTH levels in the early 24-hour postoperative period.

A meticulous intraoperative handling of PG and careful preservation of the vascular supply could minimize the risks of POH, in particular of the long-term consequences of hypoparathyroidism and chronic treatment with calcium and calcitriol supplementation.

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