Abstract. This article reviews epidemiology, risk factors and treatment modalities of postsurgical hypoparathyroidism (PHypo). PHypo occurs after total thyroidectomy due to injury of parathyroid glands and/or their blood supply or after parathyroidectomy. PHypo results in hypocalcemia because parathyroid hormone (PTH) secretion is impaired and cannot mobilize calcium from bone, reabsorb calcium from the distal nephron and stimulate renal 1α-hydroxylase activity. It usually appears in the first days after surgery and it can be symptomatic or asymptomatic. Risk factors are low level of intraoperative PTH and presence of parathyroid gland in the pathological specimen. Patients usually present with paresthesia, cramps or tetany, but the disorder may also manifest acutely with seizures, bronchospasm, laryngospasm or cardiac rhythm disturbances. Standard treatment is vitamin D analogues and calcium supplementation.

Parathyparathyroidism (PHypo) is a relatively uncommon disease. Its main characteristics are hypocalcaemia, elevated serum phosphorus levels and low or inappropriately normal plasma levels of parathyroid hormone (PTH) (1, 2). It is most possible to occur following a bilateral neck exploration during parathyroidectomy, after total thyroidectomy or during a reoperation for thyroid or parathyroid diseases. It is accidentally caused either by the removal or the damage of parathyroid glands during a surgical procedure at the neck or most frequently due to direct injury or devascularization of the parathyroid glands. Patients usually present with symptoms, such as cramps, paresthesia, tetany and rarely with more severe symptoms, such as seizures, laryngospasm, bronchospasm or cardiac rhythm abnormalities. The symptoms can be presented acutely after surgery or can occur later; if symptoms remain six months after surgery, the postoperative PHypo is considered as permanent. The prevalence varies according to different studies, expertise and surgeons’ experience.

Pathophysiology

Parathyroid secretory reserve is abundant, thus, significant injury must occur before PHypo develops. It is estimated that one normal gland is adequate for the preservation of calcium homeostasis (1). The central function of PTH is to regulate ionized [Ca^{2+}] levels by concerted effects on three principal target organs: bone, kidney and intestinal mucosa. In a normal individual, PTH stimulates bone resorption and the release of Ca^{2+} into the circulation. In the kidney, PTH promotes Ca^{2+} reabsorption and inorganic phosphate (Pi) excretion in the urine. Furthermore, PTH stimulates the hydroxylation of 25-hydroxyvitamin D₃ at the 1-position, leading to formation of the active form of vitamin D (calcitriol). Vitamin D increases intestinal absorption of dietary Ca^{2+} and renal reabsorption of filtered Ca^{2+}. In bone, vitamin D increases bone resorption with a resulting increase in the release of Ca^{2+} and Pi into the circulation.

PHypo results in hypocalcaemia because PTH secretion is impaired and cannot mobilize calcium from bone. Moreover, in the kidney, lower PTH levels result in lower Ca^{2+} reabsorption and lower Pi excretion in the urine and reduced
or absent hydroxylation of 25-hydroxyvitamin D$_3$ at the 1-
position, leading to less formation of calcitriol. As a
consequence of insufficient 1,25-dihydroxyvitamin D,
(1,25[OH]$_2$Vitamin D), intestinal absorption of calcium is
reduced. The biochemical findings in PHypo are shown in
Figure 1.

Prevalence

Hypocalcaemia is a common complication after thyroid
surgery. It usually occurs in the first days after surgery and it
can be symptomatic or asymptomatic. The frequency of
transient PHypo after thyroid surgery is between 6.9 and 49%-
(3-6), whereas that of permanent PHypo varies between 0.4% and
33% (1, 7). Most studies underline the significance of
expertise and experience.

Risk Factors

Low preoperative level of serum calcium is a risk factor for
the development of transient hypocalcaemia (8). Studies have
shown that patients who received vitamin D and calcium
postoperatively suffered less from hypocalcaemia (9, 10). The
severity of hypocalcaemia seems to be remarkably higher in
those with lower than normal preoperative vitamin D levels
(11, 12). PTH level has also been suggested as a reliable
marker of postoperative permanent PHypo (13, 14). Besides,
a low level of intraoperative PTH -at any time after the
resection of the thyroid gland to ten minutes after the skin’s
closure- was related with transient hypocalcaemia (15-18).
Postoperative low serum magnesium levels were associated
with transient hypocalcaemia (19).

Furthermore, according to additional studies, women were
found to have significant higher rates of hypocalcaemia (4,
7), whereas other studies showed that gender has no
significant effect on the incidence of hypocalcaemia (20, 21).
There are conflicting data about the effect of age in the
development of postoperative hypocalcaemia (22-24).

The incidence of hypocalcaemia is higher when thyroidectomy is combined with paratracheal lymph node
dissection, whereas the size of thyroid nodule had no
influence on the prevalence of hypocalcaemia according to
some studies (21). Injury of parathyroid glands and/or
damage of their blood supply during thyroidectomy,
incidental parathyroidectomy and failed autotransplantation are independent risk factors for hypocalcaemia (20).
The surgical technique and the extent of thyroidectomy are
related to parathyroid injury, edema, infarction, ischemia or
incidental parathyroidectomy (22, 25). The extent of
thyroidectomy has a significant impact on the occurrence of
postoperative PHypo. Near total vs. total thyroidectomy has an advantage to avoid postoperative PHypo, especially
in benign thyroid diseases (26). In total thyroidectomy for
carcinoma, the posterior capsule is usually removed with
the thyroid, hence the parathyroids are at high risk for
injury, which results in higher rates of PHypo (27).
Moreover, the rate of hypocalcaemia after a reoperation is
higher than the rate after the first surgery (28, 29). The
presence of parathyroid gland in the histopathologic
specimen (i.e., unintended removal of parathyroid gland) and
the surgeon’s experience were recognized as important
risk factors for permanent PHypo (30, 31). Selective
autotransplantation of one or more parathyroid glands was
related with transient hypocalcaemia independently of the
extent of thyroidectomy and neck dissection (32-34).
Increased thyroid specimen weight is another predictor of
transient hypocalcaemia (32, 35).

Additionally, Grave’s disease is related to transient
hypocalcaemia and the presence of hyperthyroidism is a well-
established independent risk factor for the development of
postoperative hypocalcaemia (36, 37). Increased bone turnover
and difficult operations owing to increased vascularity of
thyroid gland could be possible explanations (38).

The “hungry bone syndrome” is another cause of
postoperative hypocalcaemia and can be seen after successful
parathyroidectomy in patients with severe hyperparathyroid
bone disease preoperatively or in cases of severe
hyperthyroidism. Low serum calcium levels result from
remineralization of the bone when the stimulus for high bone
turnover (e.g., high PTH or thyroid hormone levels) is
removed. Independent risk factors for the development of
hungry bone syndrome are high preoperative alkaline
phosphatase level, blood urea nitrogen, age and parathyroid
adenoma volume (39). It can typically be distinguished from
postoperative PHypo by the serum phosphorus, which is low
in the hungry bone syndrome, because of skeletal avidity for
phosphate and high in PHypo, as well as the serum PTH,
which becomes appropriately elevated in the hungry bone
syndrome. The main factors that are related to post-
thyroidectomy hypocalcaemia, according to different studies,
are summarized in Table I.

Clinical Presentation

Patients with postsurgical PHypo usually present with
paresthesia, cramps or tetany, but the disorder may also
manifest acutely with seizures, bronchospasm, laryngospasm
or cardiac rhythm disturbances (40).

Tetany, a state of spontaneous tonic muscular contraction,
is the typical clinical sign of severe hypocalcaemia. Tingling
paresthesia in the fingers and around the mouth indicate
overt tetany; carpopedal spasm is the classic muscular
component of tetany. The typical “main d’accoucheur”
posture is characterized by addition of the thumb, flexion
of the metacarpophalangeal joints, extension of the
interphalangeal joints and flexion of the wrists. These
automatic muscle contractions are painful. All muscles can participate in tetany but the most dangerous is the spasm of laryngeal muscles.

Focal or generalized seizures can be seen in patients with hypocalcaemia. Other clinical presentations are pseudotumor cerebri, papilledema, confusion, lassitude and organic brain syndrome. The basal ganglia are often calcified in patients with long-lasting PHypo and this can be related to movement disorders.

Other manifestations of hypocalcaemia include cardiac effects (delayed repolarization, prolongation of QT, refractory congestive heart failure), ophthalmologic effects (cataract) and dermatologic effects (dry skin and brittle nails).

The signs and symptoms of hypocalcaemia are shown in Table II.

In most cases, parathyroid dysfunction after thyroidectomy resolves within a few weeks or one month after surgery (41). Postoperative PHypo is considered permanent if parathyroid gland function has not recovered within six months after surgery (4, 40, 42). Transient PHypo after neck surgery is rather usual, often termed “stunning” of the glands; chronic partial PHypo is less common, whereas chronic complete PHypo is quite rare.

Recovery of parathyroid gland function is considered when PTH levels are above 10 pg/ml and the patients did not require daily calcitriol and calcium supplementation to avoid symptoms of hypocalcaemia (31). Postoperative calcium values less than 8 mg/dl are considered as “biochemical hypocalcaemia”, while the patients presenting paresthesia in the extremities and around the mouth, with positive Chvostek’s and Trousseau’s signs, are considered as “symptomatic hypocalcaemia” (37). In another study, postoperative PHypo was defined as a documented postsurgical serum calcium level of <7.6 mg/dl, with or without symptoms, or postoperative serum calcium level of 4.0-8.4 mg/dl with neuromuscular symptoms 2 days after surgery. The study showed that a PTH level of ≤15 pg/ml or postoperative serum calcium of ≤7.6 mg/dl on the day after surgery was related to increased risk of postoperative PHypo (43). Most patients with parathyroid dysfunction after thyroidectomy return to normal function within a few weeks or one month after surgery (41, 44). When PTH levels recover to at least 10 pg/ml and hypocalcemic symptoms are absent the patient is considered euparathyroid (45). According to additional reports, recovery is considered when the patient does not require any more therapeutic calcium or calcitriol supplementation to avoid symptoms of hypocalcaemia (46, 47).
Management

The goals of therapy are to control symptoms while minimizing complications. Laboratory testing should involve measurements of serum total and ionized calcium, albumin, phosphorus, magnesium, creatinine, intact PTH and 25-hydroxyvitamin D (25(OH) vitamin D) levels. Albumin-corrected total calcium is calculated as follows:

Corrected total calcium = measured total calcium + 0.8 × (4.0 − serum albumin), where calcium is measured in milligrams per deciliter and albumin is measured in grams per deciliter.

Symptomatic hypocalcaemia is a medical emergency that requires acute intravenous administration of calcium. Ten milliliters of 10% calcium gluconate diluted in 100 ml 5% dextrose is infused intravenously over 5-10 minutes (40). This can be repeated until the resolving of patient’s symptoms. Administration of a calcium gluconate drip for longer periods may be required, particularly with persistent hypocalcaemia. The aim should be to raise the serum ionized calcium concentration into the low normal range (approximately 1.0 mM), preserve it at this level and control the patient’s symptoms. Calcium gluconate is the preferred intravenous calcium salt because calcium chloride irritates the veins and should be avoided. Oral calcium supplemetations and vitamin D analogues should also be started. Intravenous administration of calcium could cause arrhythmias and patients should be under continuous electrocardiographic monitoring (1).

Table I. Factors associated with post-thyroidectomy hypocalcaemia.

<table>
<thead>
<tr>
<th>Factors</th>
<th>References</th>
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<tbody>
<tr>
<td>Female sex</td>
<td>(4, 12, 35, 71-73)</td>
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<tr>
<td>Older age</td>
<td>(11, 12, 14, 74)</td>
</tr>
<tr>
<td>Grave’s disease</td>
<td>(4, 15, 71, 75-78)</td>
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<td>Malignant pathology</td>
<td>(15, 79, 80)</td>
</tr>
<tr>
<td>Large goiter</td>
<td>(35, 81)</td>
</tr>
<tr>
<td>Long duration of surgery</td>
<td>(15, 32, 35)</td>
</tr>
<tr>
<td>Few identified parathyroid glands</td>
<td>(34)</td>
</tr>
<tr>
<td>Heavy thyroid specimen</td>
<td>(32, 35)</td>
</tr>
<tr>
<td>Lower calcium before surgery</td>
<td>(8, 15, 34, 35, 44, 82-84)</td>
</tr>
<tr>
<td>Lower calcium after surgery</td>
<td>(15, 17, 43, 79, 83-98)</td>
</tr>
<tr>
<td>Larger decline in postoperative calcium</td>
<td>(15, 79, 81, 85, 86, 88, 92, 98, 99-104)</td>
</tr>
<tr>
<td>Higher preoperative PTH</td>
<td>(84, 105, 106)</td>
</tr>
<tr>
<td>Lower intraoperative PTH</td>
<td>(14-18, 75, 79, 84, 91, 93, 94, 97, 98, 107-109)</td>
</tr>
<tr>
<td>Larger decline in intraoperative PTH</td>
<td>(17, 19, 79, 91, 93, 107, 108, 110-112)</td>
</tr>
<tr>
<td>Larger decline in postoperative PTH</td>
<td>(16, 17, 79, 84, 98, 106, 107, 109, 113, 114, 118, 125, 126)</td>
</tr>
<tr>
<td>Low perioperative calcium and PTH</td>
<td>(15, 17, 43, 94, 127, 128)</td>
</tr>
<tr>
<td>Low preoperative 25(OH)vitD</td>
<td>(11, 12, 71, 116, 129)</td>
</tr>
<tr>
<td>Low magnesium after surgery</td>
<td>(19, 106)</td>
</tr>
<tr>
<td>High phosphate after surgery</td>
<td>(17, 117)</td>
</tr>
<tr>
<td>Higher preoperative alkaline phosphate</td>
<td>(11, 12, 35, 130)</td>
</tr>
</tbody>
</table>

PTH: Parathyroid hormone.

Table II. Signs and symptoms of postsurgical hypoparathyroidism.

| Neuromuscular                  | • Paresthesias (mouth and extremities)          |
|                               | • Muscle spasms                               |
|                               | • Seizures                                    |
|                               | • Chvostek sign                                |
|                               | • Trousseau sign – main d’accoucheur           |
|                               | • Tetany (clinical or latent)                  |
|                               | • Laryngeal stridor                            |
|                               | • Bronchospasm                                 |
|                               | • Coma                                        |
|                               | • Pseudotumor cerebri                         |
|                               | • Papilledema                                  |
| Cardiovascular                | • Arrhythmia                                   |
|                               | • Hypotension                                  |
| Other                        | • Cataracts                                    |
|                               | • Xeroderma                                    |
|                               | • Congestive heart failure                     |
| Surgical neck scar            |                                             |

Patients with chronic hypocalcaemia can often tolerate severe hypocalcaemia with minimal or no symptoms. Serum calcium levels can be restored with oral calcium and vitamin
D supplementations in patients who are asymptomatic or have mild symptomatic hypocalcaemia. Although many calcium salts can be used, oral calcium carbonate is the most frequently prescribed salt. Calcium citrate, on the other hand, is more consistently helpful in patients with achlorhydria (48, 49). The usual doses of calcium are 1 to 3 grams of elemental calcium in 3 to 4 divided doses with meals to warrant best absorption. The general purpose of treatment is to preserve serum calcium in the low normal or mildly subnormal levels. The goal of chronic therapy is to maintain serum calcium levels (albumin, adjusted total calcium or ionized calcium) in the lower part or slightly below the lower limit of the reference range (target range), with patients being free of symptoms or signs of hypocalcaemia. Lower serum calcium predisposes the patient to symptoms of hypocalcaemia and cataract if the phosphate level is also high. When serum calcium concentrations are in the upper normal range hypercalcemia may occur and this is related to nephrolithiasis, nephrocalcinosis and chronic renal insufficiency. Levels of serum calcium, phosphorus and creatinine should be measured weekly to monthly during initial dose adjustments, with twice-yearly measurements once the regimen has been stabilized. A 24-hour urine calcium should be determined at least once a year once stable doses of supplements are established and should be <4 mg/kg/24 hours. All patients should be tested with slit-lamp and ophthalmoscopic examination annually to monitor for the development of cataracts (1).

In patients with PHypo, vitamin D2 or D3 (ergocalciferol or cholecalciferol, respectively) or vitamin D metabolites, (calcitriol or 1,25-(OH)2 vitamin D or 1 alpha-OH vitamin D), are usually required. Calcitriol is the active metabolite of vitamin D with rapid action and is frequently used for primary therapy as it maintains serum calcium, in part, by improving the efficiency of intestinal calcium absorption (50). Calcitriol is administered over a wide dosing range (0.25-2.0 μg/day) (51) and can rise serum calcium levels significantly within 3 days (52, 53). The analog alfacalcidol (1-alpha-hydroxy vitamin D3), which is quickly converted to 1,25(OH)2D3 in vivo, can be useful in clinical practice (54). Vitamin D therapy can be related to hyperparathyroidism, since active vitamin metabolites and analogs also increase intestinal phosphate absorption (48). In such cases, the hyperphosphatemia may be reduced by lessening dietary intake of phosphate (e.g., in meats, eggs, dairy products and cola beverages), whereas phosphate binders can be used in severe situations (55).

Thiazide diuretics can increase renal calcium reabsorption in patients with PHypo (56, 57). This approach may be needed to achieve a urinary calcium of <4 mg/kg/day. Furosemide and other loop diuretics should be avoided because they increase urinary calcium excretion and, thus, might decrease serum calcium levels. Other factors that may precipitate hypocalcaemia are glucocorticoids that can antagonize the action of vitamin D and its analogues. Hydrochlorothiazide may assist to limit the amount of vitamin D and calcium supplements that are required to maintain normal calcium levels in PHypo (58, 59). Limitations of thiazide diuretics are associated with the risk of developing hypokalemia and/or hyponatremia and, thus, low-sodium diet could be helpful (60).

PTH(1-34) and PTH(1-84) have been used as replacement therapy for PHypo. Treatment of PHypo with PTH is appealing because it provides the hormone that is missing. In a trial with hypoparathyroid patients, administration of PTH(1-34) once daily normalized serum and urine calcium levels (61). PTH(1-34) can maintain normocalcaemia as effectively as conventional treatment (62, 63). The addition of PTH(1-84) to conventional therapy maintains normocalcaemia and at the same time allows the reduction of vitamin D and calcium supplements dosages (64, 65). Another possible benefit, because of its phosphaturic properties, is that PTH may lessen the risk of soft-tissue deposition of calcium in the kidneys (nephrocalcinosis, nephrolithiasis) and probably in other soft tissues. Indeed PTH(1-84) has been recently approved by the Food and Drug Administration for the management of cases of chronic PHypo not adequately controlled with conventional therapy (40, 66).

Finally, parathyroid autotransplantation plays an important role in the prevention of PHypo following thyroid surgery (67). The function of reimplanted parathyroid gland can be easily checked after thyroid surgery, since glands are usually reimplanted within the sternocleidomastoid muscle (68) or in the forearm subcutaneous tissue (69). Reimplantation of devascularized or accidentally removed parathyroid glands during thyroid surgery has been advocated to decrease the risk of post-operative permanent PHypo (27, 70).

Conclusion

This systematic review summarizes our current state of knowledge on postsurgical PHypo, a major disorder of parathyroid function, and its treatment modalities. Further research should be directed on the risk factors and the pathways of the pathophysiological mechanisms that may provide additional knowledge on prevention, etiology, molecular pathogenesis and other therapeutic approaches.

References


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