Post-thyroidectomy hypocalcemia and related complications: A review

Aymen Al-Roubaie
General surgery department, Goulburn valley health, Victoria, Australia
Corresponding author email: aymenfadhil@gmail.com, aymen.al-roubaie@gvhealth.org.au

Abstract---The incidence of post-thyroidectomy hypocalcemia is high while the factors involved include age (> 50 years), type of operation, operative time, neck dissection, histology of the surgical specimen and vocal fold paralysis. Low ionic calcium concentrations are indicative of the presence of symptoms of hypocalcemia and the need for oral calcium. Progression to definitive hypoparathyroidism occurs only in patients with clinical manifestations of post-thyroidectomy hypocalcemia. In general, the problem with post-surgical hypoparathyroidism resides in the surgical procedure itself. The most common are related to neuronal hyperexcitability, which explains the paresthesias, cramps and numbness, which usually start in the perioral region and on the fingertips. Muscle spasms and muscle stiffness are also common. When severe, hypocalcemia can lead to life-threatening spastic tetany, laryngospasm, and seizures. The current manuscript aimed to present a review of the bibliography on thyroidectomy and negative impact of its complications on human health, mainly because of a higher risk for developing hypocalcemia. To achieve the study goal, this review covered most recent published articles from 2017 onward.

Keywords---post-thyroidectomy hypocalcemia, related complications, patients.

Introduction

Thyroidectomy is the main therapeutic method for neoplastic and hyperplastic thyroid diseases (Galesanu, Niculescu, Apostu, & Romeo, 2018; Manatakis, Bakavos, Soulou, Dimakis, & Tseleni-Balafouta, 2019), and it is also used in the treatment of selected cases of functional diseases (Jongekkasit, Jitpratoom, Sasanakietkul, & Anuwong, 2019). It is one of the most frequently performed operations in the world, with an incidence of acceptable complications and sequelae, which, however, can be extremely uncomfortable, disabling and, rarely,
lethal (Boutzios, Tsourouflis, Garoufalia, Alexandraki, & Kouraklis, 2019; Reinhart et al., 2018). There are anatomical and metabolic complications that are peculiar to it and others that are common to all types of operation (Kaptanoglu, 2022; Panduranga Rao, 2022). The anatomical complications are related to damage to the recurrent laryngeal nerve and/or the external branch of the superior laryngeal nerve (Jin & Sugitani, 2021; Mahyoub et al., 2021).

Throughout the time that the metabolic complications are related to changes in calcium ion concentration and thyroid function (Z. Chen et al., 2021; Chincholikar & Ambiger, 2018; Metere, Biancucci, Natili, Intini, & Graves, 2021). Among the complications common to different surgical procedures, bleeding, surgical wound infection and seroma formation stand out (Khadra, Bakeer, Hauch, Hu, & Kandil, 2018; Voruganti, 2022). Serum calcium is found bound to proteins (50.0%), free or ionized (45.0%) and bound to organic complexes (5.0%)(Babu, 2021; Dhahri et al., 2021; D. H. Kim et al., 2021; Pelle, 2017).

Calcium homeostasis is mediated mainly by parathyroid hormone (PTH), calcitonin and 1,25-dihydroxycholecalciferol (vitamin D) (Tageldin & Martin, 2020). The magnesium ion is directly related to calcium, and the abrupt drop in its concentration leads to a decrease in the production and release of PTH, in addition to exacerbating the clinical manifestations secondary to hypocalcemia. Phosphorus concentration is inversely proportional to calcium, being also mediated by PTH and vitamin D2 (Mahmoud F Sakr, 2022c; A. Shifrin, 2020).

Hypocalcemia is one of the most feared complications after thyroidectomy. Although its control is reasonably easy, it can generate late consequences, such as early cataracts and changes in bone metabolism, determining the onset or worsening of osteoporosis (more important in women, precisely those most submitted to thyroidectomy), in addition to, often prolong the period of hospitalization, increasing treatment costs (Pillai, Foster, & Ashraf, 2022; Mahmoud F Sakr, 2022c; A. Shifrin, 2020).

During thyroidectomy, damage to the parathyroid glands may occur, either by direct manipulation or by injury to their vascular pedicle, with a drop in serum PTH concentration and, consequently, of calcium. The incidence of postoperative hypocalcemia varies considerably according to data from the world literature (Daba, Weldemichael, & Mulugeta, 2019; Y. Kim, Kim, Lee, & Ahn, 2018; Yamamoto et al., 2022). Most cases are secondary to temporary hypoparathyroidism, with recovery in three weeks to six months. However, 0.0% to 33.0% of patients will have definitive hypoparathyroidism (Daba et al., 2019; Y. Kim et al., 2018; Short Textbook of Surgery, 2010; Yamamoto et al., 2022).

In the postoperative period, if not investigated, hypocalcemia may go unnoticed, as it is often asymptomatic. Phosphorus and magnesium ions, which interfere with calcium metabolism, can also change after thyroidectomies and exacerbate the clinical manifestations of hypocalcemia (Short Textbook of Surgery, 2010). A more abrupt and intense drop in calcium concentration contributes to the onset of symptoms. It is not yet known at what calcium concentration the patient may have symptoms and even if this is of any clinical importance (Liu et al., 2020).
Since the first documented successful operation in the early 1880s, several studies have been trying to define, without reaching a consensus, which are the predictive factors for hypocalcemia (C. Patel & Shetty, 2020; Slough et al., 2021). Many factors may be involved in the development of post-thyroidectomy hypocalcemia, including extensive operations, neck dissection, women with preoperative hyperthyroidism, and/or a surgical procedure performed by an inexperienced surgeon (Pâdurar, Ion, Carsote, Andronic, & Bolocan, 2019; Radakrishnan et al., 2021; Spartalis et al., 2019).

However, not all patients with these factors will develop hypocalcemia, probably because, for that, other causes compete. The identification of these causes seems fundamental for their prevention. The evolution and consequences of asymptomatic hypocalcemia also need to be further investigated. The hypocalcemia with related complications induced by thyroidectomy, and influence of them on human health are presented in this review paper.

**History of thyroidectomy**

The anatomy of the thyroid gland was initially described by Leonardo da Vinci in 1500, and by Andréas Vesalius, in 1543, as quoted by Giddings (Giddings, 1998; Ignjatović, 2010). From that date, until mid-1872, thyroid surgery was reserved for selected cases of voluminous goiter with upper respiratory and digestive obstruction, as mortality rates were around 40.0% (Giddings, 1998; Ignjatović, 2010). Advances in surgical techniques, anesthesia and technology applied to medicine have determined a significant reduction in post-thyroidectomy complications (Al-Hussain et al., 2020; Ale, Isichei, & Misauno, 2020; Alghamdi, 2019).

According to Liorente et al., (2021) and Linos and Chung (2012), the improvement of antisepsis techniques, hemostasis, the refinement of the surgical technique and the discovery of the function of the parathyroid gland in the late 19th and early 20th centuries (Linos & Chung, 2012; Llorente, Laguado, Prats, Martinez, & Barrasa, 2021). These developments in thyroidectomy reduced post-thyroidectomy mortality to approximately 8.0% (Linos & Chung, 2012; Llorente et al., 2021). In the same way, the Emil Theodor Kocher received the Nobel Prize in recognition of his work on the physiology, pathology and surgery of the thyroid gland (Mudry & Orloff). Currently, the mortality rate is less than 1.0%, reaching 0.0% in many services (Gado, 2019; Linos & Chung, 2012).

**Parathyroid gland and consequences of its resection**

According to several researchers, the parathyroid glands were described in 1839 by Albers, but their physiological importance remained obscure for almost 60 years, until Kohn showed, in 1896, that they originate from the third and fourth arches. gill and that its morphology, function and embryology are different from those of the thyroid (Gado, 2019; Linos & Chung, 2012; Mokrysheva & Krupinova, 2019; A. S. L. Yu et al., 2015). Two years later, Welsh described the first anatomical details of the parathyroid glands in humans, with particular reference to their location and vascularization (Mokrysheva & Krupinova, 2019; M.F. Sakr, 2022). Not long after, in 1907, Halsted and Evans demonstrated that
the superior and inferior parathyroid glands are generally irrigated by the inferior thyroid artery and, occasionally, the superior glands receive irrigation from both thyroid arteries (Mokrysheva & Krupinova, 2019; M.F. Sakr, 2022).

According to Sakr et al., (2022), the complete anatomy of the parathyroids was only described in 1938, by Gilmour, whose work, carried out on cadavers, showed the presence of four glands in 87.0% of the cases and a variation of two to six glands in 13.0% remaining (Mahmoud F Sakr, 2022a). He also reported that the inferior glands were close to or associated with the thymus in 32.0% of the cases and that there was a greater association of supernumerary parathyroid glands in cadavers with bicornuate thymus. Saint and Chopra (2018) reported that tetany as a complication of thyroidectomy was described by Kocher in 1883, being initially attributed to thyroid insufficiency (Saint & Chopra, 2018).

As mentioned by several studies, Slough et al., (2021) and Sakr, (2022b) demonstrated that tetany appeared after parathyroid ablation, even when the thyroid was left intact (Mahmoud F Sakr, 2022c; Slough et al., 2021). Lebrun et al., (2020) commented that Parhon and Urechie demonstrated, in 1908, the possibility of alleviating the manifestations of tetany through the intravenous infusion of calcium (Lebrun, De Block, & Jacquemyn, 2020).

However, the association between tetany and a drop in plasma calcium was only established experimentally in the following years as reported by Gao et al., (2019) (Gao, Li, Miao, & Lun, 2019). Two manuscripts mentioned that, in 1926, Lahey described the first case in which inadvertently resected or ischemic parathyroid glands were re-implanted in the neck muscles at the same operative time (Iorio et al., 2018; Mahmoud F Sakr, 2022b). The first large series of patients undergoing parathyroid re-implantation, with clinical, physiological and histological confirmation of the functioning of the grafts were demonstrated deeply by Macksey (2011) and Ziai et al., (2022) (Macksey, 2011; Ziai, Dixon, Berman, Campisi, & Wasserman, 2022).

**Operative technique**

Knowledge of the surgical anatomy of the thyroid is of fundamental importance in reducing the morbidity of this procedure. The location and anatomical variation of the recurrent laryngeal nerve, the external branch of the superior laryngeal nerve and the parathyroid glands must be well known by the surgeon (Freeman, Sewell, Hales, & Randolph, 2021; Gemsenjaeger, 2011; G.W. Randolph, 2020; Gregory W Randolph, Kamani, Wu, & Schneider, 2021; Sittel & Guntinas-Lichius, 2017; Tjahjono, Nguyen, Phung, Riffat, & Palme, 2021).

After individualization, the superior thyroid vessels are ligated very close to the superior pole of the thyroid, to avoid injury to the external branch of the superior laryngeal nerve. The middle thyroid vein is ligated next to the gland and, with this, the thyroid lobe is mobilized medially (Freeman et al., 2021; Gemsenjaeger, 2011; G.W. Randolph, 2020; Gregory W Randolph et al., 2021; Sittel & Guntinas-Lichius, 2017; Tjahjono et al., 2021). Meticulous dissection is performed in the tracheoesophageal groove, with visualization of the recurrent laryngeal nerve, until its penetration into the larynx. Particular attention should be paid to the
parathyroid glands. The branches of the inferior thyroid artery must be ligated close to the thyroid capsule, avoiding devascularization of the parathyroids. Damage to the pedicle, hematoma or direct injury to the parathyroid gland implies its resection and its reimplantation in the neck musculature. The thyroid lobe is released from the trachea and then resected. After rigorous hemostasis, the median raphe, platysma and skin are closed (Freeman et al., 2021; Gemsenjaeger, 2011; G.W. Randolph, 2020; Gregory W Randolph et al., 2021; Sittel & Guntinas-Lichius, 2017; Tjahjono et al., 2021).

Surgical anatomy of the parathyroid glands

The parathyroids are small, oval-shaped endocrine glands, each measuring about 6 mm in length and 3 mm in width. They are usually found near the posterior surface of the thyroid (Oertli & Udelsman, 2012; G.W. Randolph, 2020). The identification of the parathyroid glands varies according to the operative technique, the underlying disease and the surgical difficulty. Some surgeons systematically locate all parathyroids during the operation (Oertli & Udelsman, 2012; G.W. Randolph, 2020). Anatomical studies show that 80.0% to 86.0% of the superior parathyroids and 90.0% to 95.0% of the inferior ones receive vascularization of the inferior thyroid artery (Mishra, Agarwal, Parameswaran, & Singh, 2022; Nistor et al., 2020).

Rarely, the superior thyroid artery is primarily responsible for supplying the superior parathyroid (0.6% on the right and 2.8% on the left). In 2.3% of the cases, the glands receive irrigation from the ima, laryngeal or esophageal thyroid arteries or from their anastomoses (Mishra et al., 2022; Nistor et al., 2020). The superior parathyroid gland is more frequently identified (69.0% of the cases) than the inferior (0% of cases), with no difference between sides (Mishra et al., 2022; Nistor et al., 2020). Normally, the human being has four parathyroids, this number varying, sometimes, from one to eight glands. In studies involving hundred patients, they found 0.9% of cases with a single gland, 2.0% with two, 7.6% with three, 85.3% with four and 4.2% with five or more glands (Alveryd, 1968; Rovena, Xheladin, Etmond, Leka, & Mitrushi; Sitges-Serra, Lorente-Poch, & Sancho, 2018).

Perioperative parathyroid viability is based on clinical assessment (gland staining). If blackened, it should be considered unfeasible and, consequently, resected and reimplanted. The surgeons suggest a small section of the gland capsule in cases of doubtful viability. When bleeding occurs, vascularization is probably preserved. They consider the clinical assessment of parathyroid viability based only on the gland color to be subjective, due to the possibility of different or even contradictory opinions regarding the same case. However, to date, there is no other more sensitive technique. (Mishra et al., 2022; Nistor et al., 2020; Oertli & Udelsman, 2012; G.W. Randolph, 2020).

Activity of the parathyroid glands

Each parathyroid gland functions individually and independently and, under normal conditions, has little or no proliferative activity. Even when broken down into fragments, they maintain hormone production (Bilezikian, Marcus, & Levine,
Each parathyroid has its point of regulation defined by the plasma concentration of calcium, and the release of PTH is unpredictable, varying from gland to gland. If one or more glands are resected, the remaining ones may or may not hyperplasia and, consequently, PTH production will gradually increase or remain insufficient (Bilezikian et al., 2001; Licata & Lerma, 2012; Peissig et al., 2018; M.F. Sakr, 2022; Spartalis et al., 2020; Taterra et al., 2019).

Normally, in states of chronic hypocalcemia and vitamin D deficiency, such as in renal failure, parathyroid cells multiply. The activity of the parathyroid glands varies by 50.0% during the 24 hours of the day and, consequently, both calcium and phosphorus show a daily variation from 0.2 mmol/l to 0.4 mmol/l. Several studies suggested standardizing the time for blood collection to minimize the impact of this variation on patient assessment (Bilezikian et al., 2001; Licata & Lerma, 2012; Peissig et al., 2018; M.F. Sakr, 2022; Spartalis et al., 2020; Taterra et al., 2019).

**Post-thyroidectomy complications**

The incidence of post-thyroidectomy complications has greatly decreased in recent years, but it still causes great inconvenience to patients (Alqahtani et al., 2020; Bawa et al., 2021; Păduraru et al., 2019; Saleem, Saleem, & Saleem, 2018; Sidani, Islam, & Nwariaku, 2022). Postoperative hematoma, in general, occurs up to eight hours after the surgery, being rare after this period. It affects approximately 1.4% of thyroidectomized patients (Alqahtani et al., 2020; Bawa et al., 2021; Păduraru et al., 2019; Saleem et al., 2018; Sidani et al., 2022). The incidence of surgical wound infection varies from 0.0% to 2.7% of thyroidectomies and usually manifests itself from the fourth postoperative day onwards. As it is a clean operation, the infection results from poor asepsis technique or contamination of seromas or hematomas (Alqahtani et al., 2020; Bawa et al., 2021; Păduraru et al., 2019; Saleem et al., 2018; Sidani et al., 2022). According to recent published studies, temporary paralysis of the recurrent laryngeal nerve occurs in 0.0% to 5.0% of patients undergoing their first thyroid operation (Alqahtani et al., 2020; Bawa et al., 2021; Păduraru et al., 2019; Saleem et al., 2018; Sidani et al., 2022). Definitive paralysis has an incidence ranging from 0.0% to 3.1%, reaching 10.5% in reoperations (Freitas, Levenhagen, Constantino, Paroni, & Martins, 2020; Alvaro Sanabria et al., 2019). It should be considered, however, that in some cases, nerve preservation is not possible due to its involvement by the tumor. Injury to the external branch of the superior laryngeal nerve is probably underestimated, since vocal fold function and laryngeal vestibule sensitivity are not always analyzed pre- and postoperatively (Alqahtani et al., 2020; Bawa et al., 2021; Păduraru et al., 2019; Saleem et al., 2018; Sidani et al., 2022).

Many times the clinical manifestations resulting from the lesion of this nerve are discreet, often going unnoticed. For this reason, the incidence found in the literature is so variable (0.3% to 58.0%) (Alqahtani et al., 2020; Bawa et al., 2021; Păduraru et al., 2019; Saleem et al., 2018; Sidani et al., 2022).
Postoperative hypocalcemia

Hypocalcemia is the most frequent post-thyroidectomy complication (Păduraru et al., 2019). According to McMurran et al., (2020) and Sessa et al., (2022), post-thyroidectomy hypocalcemia is a complex phenomenon with multiple causes (McMurran, Blundell, & Kim, 2020; Sessa et al., 2022). Even if the parathyroid glands and their vascularization are preserved, hypocalcemia can occur (M.F. Sakr, 2022). Serum calcium appears in three forms: free or ionized (45.0%), bound to organic acid complexes (5.0%) and bound to proteins (50.0%). Ionic calcium is the metabolically active form, with important participation in biological functions such as neuronal activity, muscle contractility, hormone secretion and cell mitosis (Baldassarre, 2014).

The main mediator of calcium homeostasis is PTH. This is synthesized in the ribosomes of the parathyroid glands as pre-proparathyroid (115 amino acids), converted to pro-parathyroid (90 amino acids), transported through the rough endoplasmic reticulum and stored in secretory granules, as a mature hormone, with 84 amino acids (Gardella, Nissenson, & Jüppner, 2018; Hurjui et al., 2020). It is synthesized and secreted at a rate inversely proportional to the serum concentration of ionic calcium. Secretion is regulated by the interaction of extracellular calcium and specific receptors present on the surface of parathyroid cells (Gardella et al., 2018; Hurjui et al., 2020).

In addition to calcium (the main regulator), PTH synthesis is dependent on phosphorus and vitamin D. Increased phosphorus concentration can induce hypocalcemia, increasing PTH synthesis, while increasing vitamin D concentration inhibits the transcriptional activity of parathyroid cell genes, decreasing PTH synthesis (Gardella et al., 2018; Hurjui et al., 2020). In the kidneys, PTH increases calcium reabsorption in the tubules proximal and distal (normally the kidneys filter and reabsorb large amounts of calcium – 250 mmol/day), increases phosphorus excretion and stimulates the conversion of 25-hydroxycholecalciferol into vitamin D, which, in turn, acts on the bones (increasing resorption bone) and gastrointestinal mucosa (increasing calcium absorption) (Rifai, 2017; Stipanuk & Caudill, 2018).

In bones, PTH stimulates the release of calcium, increasing the activity and number of osteoclasts (Rifai, 2017; Stipanuk & Caudill, 2018). Fluctuations in serum calcium concentration cause rapid changes in PTH secretion, which, within minutes, interfere with tubular calcium reabsorption and osteoclast activity, increasing or decreasing bone resorption (Rifai, 2017; Stipanuk & Caudill, 2018). In contrast to this feed system -fast back, there is another, slower, adjustment of serum calcium, which occurs in one to two days and results from the action of vitamin D in the gastrointestinal tract, stimulating calcium absorption (Rifai, 2017; Stipanuk & Caudill, 2018).

Postoperatively, patients with hypoparathyroidism have deficient secretion of PTH and, consequently, loss of action of this hormone in bones and kidneys. Bone resorption and calcium release from skeletal stores are decreased. There is also a reduction in renal tubular reabsorption of calcium. However, due to hypocalcemia
and low filterable load, urinary calcium excretion is low (Rifai, 2017; Stipanuk & Caudill, 2018).

PTH deficiency also determines a reduction in phosphate clearance, with hyperphosphatemia being a common finding. PTH deficiency and hyperphosphatemia prevent renal production of vitamin D, the low circulating level of which results in decreased intestinal calcium absorption and bone resorption. Thus, patients with postoperative hypoparathyroidism may develop hypocalcemia, hyperphosphatemia, hypomagnesemia and metabolic alkalosis (Rifai, 2017; Stipanuk & Caudill, 2018).

**Definition and clinical manifestations of hypocalcemia**

Hypocalcemia is defined as serum calcium concentration below the normal level (Acton, 2012). Reduction in total serum calcium may not reflect the reduction in ionic calcium, and, consequently, clinical manifestation may not occur (Acton, 2012). Due to the lack of PTH stimulation (PTH half-life is 3 to 5 minutes), blood calcium levels gradually decrease. Therefore, clinical manifestations usually appear in the first 24 to 48 hours after surgery, and they are infrequent before and after this period (Acton, 2012; P. Del Rio et al., 2019; di Filippo, Doga, Frara, & Giustina, 2021; Pepe et al., 2020).

In some patients, the manifestations of hypocalcemia are mild and sometimes imperceptible or absent. Some studies described up to 87% of asymptomatic hypocalcemia after total thyroidectomy in which a meticulous dissection of the parathyroid glands was performed (Barbier et al., 2022; Bove et al., 2020; Hanks & Inabnet, 2015; Marino & Sutin, 2012; Rajan et al., 2020). These studies reported that 83.0% of thyroidectomized patients developed postoperative hypocalcemia, and 13.0% had signs and symptoms, requiring calcium replacement (Barbier et al., 2022; Bove et al., 2020; Hanks & Inabnet, 2015; Marino & Sutin, 2012; Rajan et al., 2020). According to their findings, dosage of ionic calcium instead of total calcium increases the accuracy of the results, since patients with other comorbidities and malnourished patients may have hypoalbuminemia and, consequently, alterations in the serum concentration of total calcium (Barbier et al., 2022; Bove et al., 2020; Hanks & Inabnet, 2015; Marino & Sutin, 2012; Rajan et al., 2020). The adjustment of total calcium values based on the albumin concentration may not adequately reflect the ionic calcium concentration, as changes in pH, differences in the albumin-globulin ratio and magnesium concentration may alter these values (Barbier et al., 2022; Bove et al., 2020; Hanks & Inabnet, 2015; Marino & Sutin, 2012; Rajan et al., 2020). Several studies suggested that ionic calcium levels alone are safe to investigate hypoparathyroidism and that ionic calcium levels can also be correlated with the clinical picture resulting from hypocalcemia, identifying patients at risk (Abdelhamid & Moussa, 2020; Laft, Jawad, & Numan; Thachil, Joseph, & David, 2021).

Classic manifestations of hypocalcemia result from neuromuscular junction hyperexcitability and include: paresthesia or tingling around the mouth, hands and/or feet, myalgia, tachycardia, lethargy, irritability, seizures, laryngospasm or
bronchospasm, QT interval prolongation on electrocardiogram, arrhythmias and even death (Abdel-Aziz, ELFeky, & AboSeda, 2018; Jacoby, 2020; NUMBNESS, 2018; Root & Levine, 2021). Allgrove and Shaw (2015) and Mutahar (2020) associated serum calcium levels with the presence and severity of signs and symptoms, and the acute drop in calcium levels can lead to a more exuberant clinical picture (Allgrove & Shaw, 2015; Mutahar, 2020).

Trouseau's and Chvostek's signs allow demonstrating the existence of latent tetany (Brunner, Smeltzer, Bare, Hinkle, & Cheever, 2010; Busch, Bradley, & Guardiola, 2022; Figueiredo & Joliat, 2020). Chvostek's sign is investigated by percussion of the facial nerve in its path, anterior to the pinna, and in cases of hypocalcemia, contraction of the ipsilateral perilabial muscles is observed (Omerovic, 2019; Singer & Terris, 2021; Vakharia & Topor, 2021). This sign can be positive in up to 10.0% of normal people (Omerovic, 2019; Singer & Terris, 2021; Vakharia & Topor, 2021).

Trouseau's sign is more specific and consists of the observation of generalized contraction of the forearm muscles and wrist flexion after application, for 3 minutes, of the sphygmomanometer with a pressure of about 20 mmHg above the systolic pressure (Dennis, Bowen, & Cho, 2012; Mistry & Rao, 2021; M. Patel & Hu, 2020; Schnur, Sinawe, Yoham, & Casadesus, 2021). The clinical signs and symptoms described are suggestive of hypocalcemia, and laboratory confirmation is made by measuring ionic calcium. The confirmation of hypoparathyroidism is laboratory, demonstrating undetectable blood concentrations of PTH or below the normal level (Dennis et al., 2012; Mistry & Rao, 2021; M. Patel & Hu, 2020; Schnur et al., 2021).

Classification of hypocalcemia

Hypocalcemia is classified as transient and permanent (Qin et al., 2021). Transient hypocalcemia (symptomatic or not) occurs when calcium levels return to normal within six months postoperatively (Stack & Bodenner, 2016). It is seen in 1.3% to 83.0% of cases. According to several studies, mild to moderate transient hypocalcemia can occur both after thyroidectomies and in other operations such as neck dissection and abdominal operations, often without PTH decline (Mercante et al., 2019; Philips et al., 2019; Stack & Bodenner, 2016; Unsal et al., 2020). It is usually associated with hemodilution. Postoperative hypocalcemia is usually a benign condition and does not predict permanent hypoparathyroidism (Mercante et al., 2019; Philips et al., 2019; Stack & Bodenner, 2016; Unsal et al., 2020).

Definitive hypoparathyroidism occurs when the patient maintains PTH levels below normal for a period longer than six months, requiring oral calcium administration (Bruno et al., 2021; Díez et al., 2020). Some authors still divide it into chronic hypocalcemia (persistence after six months) and definitive (after one year) (Ram, Khan, & Aziz; Alvaro Sanabria, Kowalski, & Tartaglia, 2018; Teisseyre, Moranne, & Renaud, 2021).

Permanent functional hypoparathyroidism is defined by the need for oral calcium administration to a patient with apparently normal PTH levels (E. Kim, Ramonell,
Obiarinze et al., (2021) believes that there may be normalization of parathyroid function up to two years after thyroidectomy (Obiarinze, Fazendin, Iyer, Lindeman, & Chen, 2021). Definitive hypoparathyroidism occurs in 0.0% to 33.0% of patients undergoing thyroidectomy (Diez et al., 2021; Linos & Chung, 2012).

Two studies showed the incidences of transient hypocalcemia and definitive hypoparathyroidism after total thyroidectomy and after different types of thyroidectomies, according to different authors (Diez et al., 2021; Linos & Chung, 2012). With their findings, the divergences of the studies in relation to the calcium dosage (ionic or total) used in the evaluation of hypocalcemia can be observed (Diez et al., 2021; Linos & Chung, 2012).

**Factors related to hypocalcemia**

**Gender and age**

Del Rio et al., (2019), as well as other authors, showed that there is no influence of patient gender on the onset of postoperative hypocalcemia (P. Del Rio et al., 2019; Palmhag, Brydolf, Zedenius, Brännström, & Nilsson, 2021; Waseem et al., 2021). In contrast, Hamid et al., (2022), Marimuthu & Murugan, (2021) and Modi & Charpot, (2021) showed a significantly higher incidence of postoperative hypocalcemia in women (Hamid et al., 2022; Marimuthu & Murugan, 2021; Modi & Charpot, 2021). Regarding age, few authors report any difference between young and elderly patients (P. Del Rio et al., 2019; Mahmoud F Sakr, 2022d; Spinelli et al., 2022). Sakr et al., (2022) noted a higher incidence of post-thyroidectomy hypocalcemia in young women (Mahmoud F Sakr, 2022d).

**Extension of the surgical procedure**

The extent of the surgical procedure is directly related to the severity of hypocalcemia as well as its incidence, although minor operations can also lead to a drop in serum calcium (Butt, Fayyaz, Qura’tulain, & Sultan, 2022; Spinelli et al., 2022; Vasileiadis, Charitoudis, Vasileiadis, Kykalos, & Karatzas, 2018).

**Partial thyroidectomy**

After partial thyroidectomy (lobectomy + isthmectomy), hypocalcemia is relatively rare, with less clinical repercussion. It is usually asymptomatic, resolving in a few days (Kazaure et al., 2021). Kazaure et al., (2021) 7 found 0.4% of cases of hypocalcemia after partial thyroidectomy, 0.1% of which were definitive, in a series of 7366 patients. Reports in the literature on post-partial thyroidectomy hypocalcemia are divergent (Al Najjar, Ghoush, Elmajed, Eldимвlawi, & Abousalha, 2021; Azaria, 2019; Mears & Treacy, 2020).

Many researchers identified 30.0% to 40.0% of patients with hypocalcemia among those undergoing partial thyroidectomy, with hypocalcemia being symptomatic in 7.0% of them (Al Najjar et al., 2021; Azaria, 2019; Mears & Treacy, 2020). In these cases, hypocalcemia is not specific and may be related to hemodilution, hypothermia, hypoalbuminemia, decreased tubular reabsorption of
calcium and increased release of calcitonin, which can be observed in other types of surgery (Al Najjar et al., 2021; Azaria, 2019; Mears & Treacy, 2020).

According to Rahim et al., (2021), hemodilution and changes in albumin or bicarbonate levels are not factors related to hypocalcemia (Rahim et al., 2021). Guo et al., (2021) and Palop et al., (2021) widely believe that postoperative hypocalcemia in patients undergoing partial thyroidectomy is due to reduced renal tubular reabsorption of calcium, and it is unlikely that PTH and calcitonin are responsible for this renal change (Guo, Zhao, Xie, Yan, & Mo, 2021; Palop, Martinez, Giménez, Samper, & Fuster, 2021).

On the other hand, four recent published studies observed a significant decrease in total calcium levels compared to the preoperative period, with ionic calcium remaining stable, as well as a decrease in albumin, but without changes in PTH and calcitonin (G. Lombardi, Ziemann, Banfi, & Corbetta, 2020; Mohamed, Qureshi, & Mohamed, 2020; Mahmoud F Sakr, 2020; Winter & Harris, 2021).

The PTH level may, in some cases, decrease in the postoperative period of partial thyroidectomy. In these cases, the most accepted explanation is the decrease in PTH release by the parathyroids, which are suppressed by manipulation (G. Lombardi et al., 2020; Mohamed et al., 2020; Mahmoud F Sakr, 2020; Winter & Harris, 2021). Bobanga & McHenry, (2021) and Patel et al., (2020) and Sakr, (2022) found 85.0% of cases of decreased PTH levels in the postoperative period, 73.0% of which underwent partial thyroidectomy, suggesting high sensitivity of the parathyroid glands to manipulation (Bobanga & McHenry, 2021; K. N. Patel et al., 2020b; Mahmoud F Sakr, 2022e). They showed a drop in PTH after all thyroidectomies, partial or total, with greater impact in larger operations, but this fact was not associated with clinical manifestations of hypocalcemia.

**Total thyroidectomy**

After total thyroidectomy, the incidence of postoperative transient hypocalcemia ranged from 8.9% to 53.0%, with 0.0% to 25.0% of definitive cases (Mercante et al., 2019; Weng et al., 2021). Philips et al., (2019) and Sakr, (2020) showed a reduction in calcium levels in the postoperative period compared to the preoperative period in all patients undergoing total thyroidectomy, with 13.0% requiring calcium replacement (Philips et al., 2019; M.F. Sakr, 2020).

There was also an increase in phosphorus levels in patients who required calcium replacement, while magnesium ion remained unchanged, suggesting hypoparathyroidism (Philips et al., 2019; M.F. Sakr, 2020). Akdeniz & Avci, (2021), Masood et al., (2019) and Sumukha, (2020) suggested total thyroidectomy, instead of subtotal thyroidectomy, as the treatment of choice for multinodular goiter with surgical indication, since there was no statistically significant difference in relation to late complications (Akdeniz & Avci, 2021; Masood, Kanaan, & Khaddouj, 2019; Sumukha, 2020).

There was a higher incidence of temporary hypoparathyroidism after total thyroidectomy, but, on the other hand, more frequent recurrence of goiter after subtotal thyroidectomy. In this case, reoperation had a higher rate of both

**Subtotal thyroidectomy**

In the postoperative period of ST (lobectomy + isthmectomy + contralateral partial lobectomy), the incidence of transient hypocalcemia ranged from 5.0% to 29.0% and that of permanent hypocalcemia ranged from 0.0% to 2.3% (Boutzios et al., 2019; Gunn, Oyekunle, Stang, Kazaure, & Scheri, 2020; Kazaure et al., 2021).

According to Brophy et al., (2019) and Pepe et al., (2020), post-subtotal thyroidectomy hypocalcemia has temporary hypoparathyroidism as its main cause (Brophy, Woods, Murphy, & Sheahan, 2019; Pepe et al., 2020). Bilateral subtotal thyroidectomy, in which part of the thyroid lobe is bilaterally preserved, is associated with an increase in goiter recurrence by 9.0% to 43.0% and with an increase in surgical morbidity in the need for reoperation (Y. S. Kim et al., 2020; G.W. Randolph, 2020; Sehnke, Schwarz, & Goretzki, 2018).

**Reoperation**

Reoperation has high complication rates compared to the first surgical procedure. The main indications for reoperation are: resection of the thyroid remnant in cancer patients; recurrent thyroid carcinoma; tumor recurrence in recurrent chain lymph nodes; recurrent goiter in symptomatic patients; recurrent thyrotoxicosis; and aesthetics (Dobrinja et al., 2021; Jukic, 2017; Kazaure et al., 2021; H. K. Kim, Ha, Han, Lee, & Soh, 2020; Margolick, Chen, & Wiseman, 2018; Semrad, Keegan, Semrad, Brunson, & Farwell, 2018).

The incidence of transient hypocalcemia varies from 3.0% to 44.1% and that of permanent hypocalcemia, from 0.0% to 11.0%. According to several studies, reoperation increases the risk of iatrogenic injury to the parathyroids by ten times (Dobrinja et al., 2021; Jukic, 2017; Kazaure et al., 2021; H. K. Kim et al., 2020; Margolick et al., 2018; Semrad et al., 2018).

Inflammatory process, bleeding, tissue friability and adhesion of structures are factors that make reoperation technically more difficult and with higher rates of complications. Therefore, it should be performed in the first postoperative days, still during the same hospitalization, or three to four months later (Dobrinja et al., 2021; Jukic, 2017; Kazaure et al., 2021; H. K. Kim et al., 2020; Margolick et al., 2018; Semrad et al., 2018).

**Neck dissection**

Of the patients with papillary carcinoma (PC) of the thyroid, 70.0% to 90.0% have microscopic metastasis in regional lymph nodes (recurrent chain) (H. K. Kim et al., 2020). Of those who do not undergo recurrent dissection, 7.0% to 15.0% develop clinically detectable metastasis, despite surgical treatment (total
thyroidectomy) associated with radioactive iodine ablation (Mancino & Kim, 2017). More recently, contrary to what was previously thought, it has been suggested that the presence of lymph node metastasis alters the prognosis, exerting an important influence on patient survival and the rate of disease recurrence (Russell, Inabnet, & Tufano, 2020).

The biggest discussion in relation to elective dissection or not of the recurrent chain is based on its morbidity, especially with regard to definitive postoperative hypoparathyroidism (Mallick & Harmer, 2018). According to Yan et al., (2021), Luster et al., (2019) and Mandapathil et al., (2019), recurrent neck dissection is associated with a higher incidence of postoperative hypoparathyroidism, ranging from 14.0% to 54.6% (transient) and from 4.0% to 17.4% (definite), and also the higher incidence of inadvertent parathyroid resection (Luster, Duntas, & Wartofsky, 2019; Mandapathil, Lennon, Ganly, Patel, & Shah, 2019; Yan, Xiang, Wang, & Wang, 2021).

Chang et al., (2020), Godlewksa et al., (2020) and Terris & Duke, (2016), in which 4.0% of the patients developed definitive hypoparathyroidism, suggest that recurrent dissection is not routinely performed in all cases of PC, but only in those with clinically detectable metastases or in patients at higher risk (Chang et al., 2020; Godlewksa et al., 2020; Terris & Duke, 2016).

**Identification of the parathyroid glands and reimplantation**

The relationship between the number of identified parathyroid glands and the incidence and/or severity of hypocalcemia is controversial (M.F. Sakr, 2020). Van Slycke et al., (2021) and Falch et al., (2018) stated that the incidence of temporary hypocalcemia is inversely proportional to the number of parathyroid glands found (Falch et al., 2018; Van Slycke, Van Den Heede, Brusselaers, & Vermeersch, 2021). On the other hand, Del Rio et al., (2019), Sakr, (2022) and Mencio et al., (2020) did not find any correlation between these two factors (P. Del Rio et al., 2019; Mencio et al., 2020; Mahmoud F Sakr, 2022d).

According to Ponce de León-Ballesteros et al., (2019), Sitges-Serra, (2021) and Sakr, (2022a), in situ preservation of at least one parathyroid gland is the main way to prevent hypocalcemia, with a reduction in definitive hypoparathyroidism to less than 5.0% (Ponce de León-Ballesteros et al., 2019; Mahmoud F Sakr, 2022b; Sitges-Serra, 2021).

Inadvertent resection of the parathyroid gland occurs between 1.0% and 19.0% of thyroidectomies, all of which confirm that there is no relationship between this resection and postoperative hypocalcemia when only one gland is resected and the others remain intact, with the preserved pedicle (Levine, 2018; Rajamahendran, 2018). Lee et al.78 found an incidence of 11.0% of inadvertent resection in their series of hundred patients, and in 2.0% of the cases, the gland in question was intrathyroid (S. H. Kim et al., 2020; Yao et al., 2022).

No patient evolved with permanent hypoparathyroidism. Bai et al., (2018), Ghafoor et al., (2020) and Sala et al., (2019) showed a higher incidence of inadvertent parathyroid resection in cases of reoperation and neck dissection,
with no correlation with the histological type of the disease or the size of the thyroid gland (Bai, Chen, & Chen, 2018; Ghafoor et al., 2020; Sala et al., 2019). According to Tsai et al., (2019) and Sakr, (2022b) the resection of two or more glands has proven to increase the risk of transient and permanent postoperative hypoparathyroidism (Mahmoud F Sakr, 2022d; S.-H. Tsai et al., 2019).

According to Parameswaran & Agarwal, (2018) and Myers & Snyderman (2017), when three or more parathyroid glands were identified and preserved in situ, all patients who developed postoperative hypocalcemia returned to preoperative calcium levels (Myers & Snyderman, 2017; Parameswaran & Agarwal, 2018). Lesions of the vascular pedicle of the parathyroids can occur due to tension at the time of ligation of the thyroid vessels or by their inclusion in the ligation. Damage to the parathyroid veins can lead to congestion of the gland and temporarily interfere with its function (Myers & Snyderman, 2017; Parameswaran & Agarwal, 2018).

The best way to preserve the vascularization of the parathyroid glands is the juxtacapsular dissection of the thyroid gland, with ligation of the branches of the inferior thyroid artery close to the thyroid (Myers & Snyderman, 2017; Parameswaran & Agarwal, 2018). At the end of the operation, the thyroid bed and resected thyroid should be thoroughly evaluated looking for inadvertently resected or ischemia parathyroid, which, if found, should then be reimplanted into the neck musculature (usually the sternocleidomastoid muscle) (Myers & Snyderman, 2017; Parameswaran & Agarwal, 2018).

It is fragmented and crushed before being implanted, in order to increase the contact surface with the recipient bed and, consequently, the chance of graft success and the return of its function. Implantation of a devascularized or resected parathyroid gland inadvertently can reduce the incidence of permanent hypoparathyroidism (Myers & Snyderman, 2017; Parameswaran & Agarwal, 2018). If there are signs of venous congestion or hemorrhage in the parathyroid gland, it is necessary to decompress it, incising its capsule (Myers & Snyderman, 2017; Parameswaran & Agarwal, 2018).

According to Barczyński et al., (2017), the parathyroid tissue, implanted in the muscle, is initially nourished by imbibition, starting to receive new vascularization after five or six days, when capillaries grow in the periphery of the gland (Barczyński, Gołkowski, & Nawrot, 2017). After two to three weeks, vascular connections are established between the parathyroid and the body (Barczyński et al., 2017). Three studies showed the functioning of all parathyroid grafts 15 days after surgery (Lo & Tam, 2001; Ponce de León-Ballesteros et al., 2019; Sierra et al., 1998). The percentage of graft take-up varies from 83.0% to 95.0% (Lo & Tam, 2001; Ponce de León-Ballesteros et al., 2019; Sierra et al., 1998). Jung et al., (2013) and Chen et al., (2022) indicated that, although the percentage of return to function of the parathyroid graft is high when the four glands are implanted, the PTH level reaches, at most, 70.0% of the preoperative values (C.-F. Chen et al., 2022; Jung et al., 2013).

When at least one gland is left in the bed, with a preserved pedicle, the PTH reaches at least 80.0% of the preoperative value (C.-F. Chen et al., 2022; Jung et
Several implantation methods have been proposed - the glands can be crushed, minced, sliced, injected or implanted whole - the most accepted being the use of small slices, approximately 0.3 mm (Nasiri et al., 2022; Mahmoud F Sakr, 2022b). The implantation areas commonly described are the neck muscles (mainly sternocleidomastoid), pectoral or forearm musculature. Most authors prefer the neck muscles, taking advantage of the same incision. In cases with the possibility of neck dissection in the future, with risk of resection of the muscle used for implantation, a parathyroid graft is chosen in the pectoral or forearm muscles (Nasiri et al., 2022; Mahmoud F Sakr, 2022b).

**Surgeon experience**

Many authors state that the incidence of postoperative hypocalcemia is inversely proportional to the surgeon’s experience (Ceylan & Kesici, 2022; Remer, Linhares, Scola, Khan, & Lew, 2022; Sessa et al., 2022). The surgeon’s experience is not an independent predictive factor, and the surgical extension alone, the most important predictive factor. Operations performed by residents under the supervision of experienced surgeons did not have an increased incidence of postoperative hypocalcemia (Ceylan & Kesici, 2022; Remer et al., 2022; Sessa et al., 2022).

**Thyroid disease**

According to several authors, thyroid disease is related to an increased incidence of hypocalcemia (Jagadeesan, 2020; Rivera & Lock, 2008; Suh & Shen, 2016). Diving goiter, thyroid cancer, hyperthyroidism (diffuse or multinodular toxic goiter), and bulky goiter increase the postoperative incidence of hypocalcemia (JM & NM, 2004). On the other hand, Hemmati et al., (2021), Cali et al., (2021), Brophy et al., (2019) and Grodski & Serpell, (2008) found no statistically significant difference in the relationship between diagnosis of the underlying disease and post-thyroidectomy hypocalcemia (Brophy et al., 2019; Cali, Hasani, Buffet, Menegaux, & Chereau, 2021; Grodski & Serpell, 2008; Hemmati et al., 2021).

**Thyroid volume**

Few authors relate thyroid volume to postoperative hypocalcemia (Richa, Issa, Echtay, & El Rawas, 2018; S.-Q. Xu, Ma, Su, Cheng, & Zhou, 2019). Prete et al., (2022) and Papanastasiou et al., (2019) suggest that the assessment of thyroid volume can be performed preoperatively by ultrasonography. In their studies, massive goiter was associated with longer operative time and greater blood loss and, consequently, with a higher incidence of hypocalcemia (Papanastasiou et al., 2019; Prete et al., 2022).

**Thyroid Carcinoma**

In studies conducted by Wanget al., (2021) and Bumber et al. (2020), thyroid carcinoma was the main predictive factor for the development of postoperative hypocalcemia (Bumber, Potroško, Vugrinec, Ferencaković, & Gršić, 2020; C. WANG et al., 2021). Bjornsdotthir et al., (2022), Lim et al., (2020), and Beahrs and
Ahn et al., (2019) reported a high incidence (3.0% to 6.5%) of definitive hypoparathyroidism after thyroidectomy for cancer (Ahn et al., 2019; Bjornsdottir et al., 2022; Diez et al., 2019; Lim, Jeon, Gwak, & Suh, 2020).

Transient post-thyroidectomy hypocalcemia for cancer ranged from 12% to 20% in most series, reaching 75.0% in some studies exhibited substituting goiter (Hamdan, Sataloff, & Hawkshaw, 2020; Mallick & Harmer, 2018). They showed, in multivariate logistic regression analysis, that substernal goiter is an independent predictive factor for postoperative hypocalcemia (Hamdan et al., 2020; Mallick & Harmer, 2018).

**Hyperthyroidism and Hypothyroidism**

Thyroid hormone acts on the bones primarily by increasing the rate of bone remodeling and, simultaneously, the fecal and urinary excretion of calcium and the reabsorption of phosphorus (Delitala, Scuteri, & Doria, 2020; Lademann, Tsourdi, Hofbauer, & Rauner, 2020; Shi et al., 2020; Tsourdi, Lademann, & Siggelkow, 2018). In the bones of hyperthyroid patients, there seems to be greater activity of osteoclasts in relation to of osteoblasts and, consequently, greater resorption than bone neoformation (Delitala et al., 2020; Lademann et al., 2020; Shi et al., 2020; Tsourdi et al., 2018).

Prolonged untreated hyperthyroidism can lead to osteodystrophy and, consequently, to post-total thyroidectomy hypocalcemia, due to rapid recalcification (bone starvation) due to the loss of hormone stimulus from thyroid (Delitala et al., 2020; Lademann et al., 2020; Shi et al., 2020; Tsourdi et al., 2018). This situation is confirmed by the high levels of alkaline phosphatase resulting from osteoblastic activity and bone formation in patients with postoperative tetany (Delitala et al., 2020; Ibrahim & Anumahb, 2021; Kusuki & Mizuno, 2019; Lademann et al., 2020; Shi et al., 2020; Tsourdi et al., 2018).

A recent study found higher levels of PTH in the preoperative period of patients with thyrotoxicosis, associating them with hypocalcemia (Abdelaziz, Essawy, Wageh, Khalifa, & Zydan, 2021). The use of antithyroid drugs leads, in a few months, to a significant recovery of bone density in patients with thyrotoxicosis, reducing the incidence of post-thyroidectomy hypocalcemia (Abdelaziz et al., 2021; Sywak, Prichard, & Delbridge, 2021; Testa, Martinelli, & Pacini, 2018a, 2018b).

Bugălă et al., (2022), Palmhag et al., (2021), Soylu & Teksoz, (2020) ,Thakur, (2021) and Şahbaz et al., (2018) considered hyperthyroidism, in multivariate logistic regression analysis, as an independent predictive factor for both transient and permanent postoperative hypocalcemia (Bugălă et al., 2022; Palmhag et al., 2021; Şahbaz et al., 2018; Soylu & Teksoz, 2020; THAKUR, 2021).

The incidence of symptomatic hypocalcemia in patients with Basedow-Graves disease (GD) was 50.0% for those clinically treated and 43.0% for those not treated, with no statistical difference between them (Bugălă et al., 2022; Palmhag et al., 2021; Şahbaz et al., 2018; Soylu & Teksoz, 2020; THAKUR, 2021). In contrast, Donahue et al., (2021) did not consider hyperthyroidism as a predictive
factor for postoperative hypocalcemia, but empirically treated all patients postoperatively with calcium carbonate and/or vitamin D (Donahue, Pantel, Yarlagadda, & Brams, 2021). Phookan et al., (2021), Moran et al., (2020) and Wojtczak et al., (2018) commented that toxic goiter, as it is more vascularized, contributes to increased perioperative bleeding, reducing the visibility of the surgical field (Moran et al., 2020; Phookan et al., 2021; Wojtczak, Aporowicz, Kaliszewski, & Bolanowski, 2018).

According to Ismailov & Khayitboyeva, (2019) and Kh, (2019), this fact justifies a higher incidence of iatrogenic injury to the parathyroid glands. In addition, parathyroid vessels may be compromised by the autoimmune process of diffuse toxic goiter (Ismailov & Khayitboyeva, 2019; Moran et al., 2020; Phookan et al., 2021; Wojtczak, Aporowicz, Kaliszewski, & Bolanowski, 2018).

Sakr, (2022) showed that the incidence of postoperative hypocalcemia was significantly higher in women with diffuse toxic goiter (Mahmoud F Sakr, 2022e). This greater predisposition of women to postoperative hypocalcemia can be partially explained by the fact that many of them have preoperative osteodystrophy, as a result not only of hyperthyroidism but also of osteoporosis (more frequent in postmenopausal women). However, there was a higher incidence of symptomatic hypocalcemia in young women, justified by the faster bone metabolism in female patients with thyrotoxicosis (Al Ibrahimi & Ahmed, 2021; Guo et al., 2021). This contribution was also pointed out by Eltyeb (2021), in 2021 (Eltyeb, 2021).

More recently, another study showed a statistically significant difference in relation to the concentration of 25 hydroxycholecalciferol - lower in women (2.38 nmol/l) than in men (3.30 nmol/l) – and concluded that the main cause of post-thyroidectomy hypocalcemia in women with diffuse toxic goiter is vitamin D deficiency (D. Kim, 2017). Less dramatic changes were seen with men. Hypothyroidism is also a cause of hypocalcemia (Tecilazich, Formenti, Frara, Giubbini, & Giustina, 2018). As the thyroid hormone participates in the renal activation of vitamin D, hypothyroidism can reduce its concentration, consequently leading to a decrease in intestinal absorption and an increase in calcium excretion (Tecilazich et al., 2018; Vibhatavata et al., 2020).

**Ligation of the inferior thyroid artery**

Ligation of the inferior thyroid artery away from the thyroid gland is controversial, although many authors consider it a risk factor for transient and permanent hypoparathyroidism (Alvaro Sanabria et al., 2018; Waseem et al., 2021). Waseem et al., (2021) and Ahmed et al., (2020) managed to significantly reduce the incidence of permanent hypoparathyroidism in their patients after modifying their operative technique, starting to connect the branches of the inferior thyroid artery very close to the thyroid capsule (Ahmed, Waseem, Zafar, & Abid, 2020; Waseem et al., 2021).

Santrac & Dzodic, (2019), Sapmaz & Kılıç, (2020) and Al Kordy et al., (2019) found no statistically significant difference between ligation of the trunk and branches of the inferior thyroid artery close to the thyroid capsule (Al Kordy, El Ewesy, & Hassan, 2019; Santrac & Dzodic, 2019; Sapmaz & Kılıç, 2020).
Srinivasan et al., (2022) and Kong et al., (2019) suggested that anastomoses between branches of this artery and branches from the trachea, esophagus and thyroid maintain the vascularization of the parathyroid glands (Kong, Wang, & Wang, 2019; Srinivasan et al., 2022).

**Calcitonin**

Calcitonin, a polypeptide consisting of 32 amino acids, is synthesized by the parafollicular cells of the thyroid gland (Giannetta et al., 2020; Shen, Wu, Zhang, & Tu, 2022). It induces a decrease in calcemia, inhibiting bone resorption by osteoclasts and increasing renal excretion of this ion (Xie et al., 2020). The regulation of calcitonin secretion is mainly done by the plasma concentration of calcium. Acute elevation or reduction of calcium levels leads, respectively, to an increase and decrease in calcitonin secretion (Hsiao et al., 2020; Xie et al., 2020). Although other factors have been described as stimulating calcitonin secretion, pentagastrin (mainly) and the administration of venous calcium are true secretagogues, being important agents for the clinical evaluation of calcitonin secretion by normal and neoplastic cells (Wondisford, 2020; Wong, Nabata, & Wiseman, 2022).

Some authors suggested that calcitonin is also responsible for the alteration of the postoperative calcium concentration in thyroidectomies (Băetu, Olariu, Nițu, et al., 2021; Băetu, Olariu, Stancu, et al., 2021; Tausanovic et al., 2021). Manipulation of the thyroid gland would lead to an increase in calcitonin secretion and, consequently, to a decline in calcium. The effect of calcitonin is expected early, as its half-life is two to 15 minutes (P. Yu et al., 2019). Li et al., (2021), Hamed & Afifi, (2019) and Sharif et al., (2018) showed that there was no significant change in postoperative calcitonin when comparing patients with hypo- or normocalcemia (Hamed & Afifi, 2019; Li, Rogers, & Rehman, 2021; Sharif, Ali, Rahman, Siddique, & Rahman, 2018).

In healthy volunteers, administration of calcitonin did not cause hypocalcemia. Chin et al., (2004) and Del Rio et al., 1987) reported a slight increase in plasma calcitonin levels in the first two postoperative days, as well as a decrease in calcium, concluding, however, that as this decrease preceded the increase in calcitonin, there was no correlation between the two findings (Chin, Gutierrez, Still, & Kosutic, 2004; A. Del Rio, Rico, Bordiu, & Novoa, 1987). Oliveira et al., (2021) detected a reduction in calcitonin levels after thyroidectomy (Oliveira et al., 2021).

**Hypoalbuminemia and blood transfusion**

Qu et al., (2022), (Tinawi, 2021) and Cornelius, (2020) suggested that hypoalbuminemia may be the main factor in the pathogenesis of postoperative hypocalcemia, when only total calcium is measured. Patients receiving blood transfusions during or after the operation may have hypocalcemia (Cornelius, 2020; Qu, Wang, & Li, 2022; Tinawi, 2021). Citrate, used for blood conservation, chelates calcium, reducing the concentration of ionic calcium (Cornelius, 2020; Zulkufli, Jamaluddin, & Yazid, 2020).
Drug and fluid administration

Drugs and intravenous fluids can also alter calcium levels. Thiazide diuretics, vitamins A and D, lithium, and antacids may induce hypercalcemia (Bateman & Egan, 2022; Wermers & Abate, 2022), while anticonvulsants, diazepines, oral contraceptives, and steroids may favor hypocalcemia (Onset, 2019; Springer & Nappe, 2019). Rajeswari, (2017) did not, however, find a correlation between the ingestion of these drugs and the administration of fluids in the peri- and postoperative periods with the development of transient or permanent hypocalcemia (Rajeswari, 2017).

Reddy & Mohammad, (2022) and Chang et al., (2020) in a comparative study between thyroidectomies and other surgical procedures in the neck, showed that hemodilution and parathyroid dysfunction are involved in the fall in calcium (Chang et al., 2020; Reddy & Mohammad, 2022). In the perioperative period of these operations, it was mainly caused by hemodilution, while hypoparathyroidism was the main responsible for its occurrence in the postoperative period of thyroidectomies (Chang et al., 2020; Reddy & Mohammad, 2022).

According to Kandinov et al., (2021), comparing operations such as parotidectomy, laryngectomy and cholecystectomy with thyroidectomies, showed a slight decrease in total calcium in all procedures, but ionic calcium remained stable (Kandinov, Nguyen, Yuhan, Johnson, & Svider, 2021).

Urinary alteration

According to several studies conducted by different authors, variation in urinary calcium concentration was not different when comparing thyroidectomized patients with those undergoing other procedures (Edafe, Mech, & Balasubramanian, 2019; Mazoni et al., 2022; Nemade, Rokade, Pathak, Tiwari, & Sonkhedkar, 2014; Ponce de León-Ballesteros et al., 2020). The authors found that calciuria decreased after all procedures, returning to preoperative values on the second day after surgery.

Calcium cut-off value

Some studies using postoperative calcium measurements were able to predict which patients might or might not develop hypocalcemia manifestations (Mallick & Harmer, 2018; Păduraru et al., 2019; Saint & Chopra, 2018; M.F. Sakr, 2022; Spartalis et al., 2019). Some researchers had verified, through serial measurements of postoperative calcium, that a calcium curve that is always positive in the first 14 hours after the operation predicts, 100% of the time, that the patient will remain normocalcemic, and can be safely discharged from the hospital, no risk of hypocalcemia (Mallick & Harmer, 2018; Păduraru et al., 2019; Saint & Chopra, 2018; M.F. Sakr, 2022; Spartalis et al., 2019). The others also showed that early calcium measurements (12 hours postoperatively) may foreshadow symptomatic postoperative hypocalcemia (Malik et al., 2019; Sasi et al., 2022; Torabi, Avery, Salehi, & Lee, 2020).
In two studies carried out by Essa et al., (2021) and Vasudev & AV, (2020), the calcium curve that was always positive or initially negative and later positive in the first 24 hours after surgery indicated a low probability of manifestations of hypocalcemia (Essa et al., 2021; Vasudev & AV, 2020). Vasudev & AV, (2020) concluded that a stable or rising calcium curve ensures safety for patients undergoing total thyroidectomy on the first postoperative day to be discharged, as they do not present a risk of hypocalcemia (Vasudev & AV, 2020).

On the other hand, a declining calcium curve does not necessarily imply the appearance of clinical manifestations of hypocalcemia, but the patient should be considered at risk and, therefore, remain hospitalized under observation. McLeod et al., (2006) reported that patients with a positive calcium curve (12-hour calcium value minus 6-hour calcium value) have an 87.5% chance of remaining normocalcemic. In contrast, a negative calcium curve predicts hypocalcemia in 46.2% of cases (McLeod et al., 2006). Curves greater than +0.02 mmol/l/hour have a significantly high chance of predicting normocalcemia (97.0%), while values equal to 0.00 mmol/l/hour can predict it 78% of the time.

Patel et al.,(2020) and Del Rio et al., (2019) confirmed that patients with total calcium below 7.5 mg/dl have a high risk of becoming symptomatic, unlike those with calcium above this value (P. Del Rio et al., 2019; K. N. Patel et al., 2020a). Del Rio et al., (2019) and Bergamaschi et al., (1998) showed an incidence of temporary and permanent hypocalcemia, respectively, according to postoperative calcium values: 14.9% and 2.1% for calcium concentrations below 1.60 mmol/l; 4.1% and 1.1% for calcium between 1.60 and 1.80 mmol/l; and 0.8% and 0.5% for calcium between 1.80 and 2.00 mmol/l, considering calcium reference values from 2.25 mmol/l to 2.60 mmol/l (Bergamaschi, Becouarn, Ronceray, & Arnaud, 1998; P. Del Rio et al., 2019).

Paladino et al., (2021) showed that ionic calcium values below 2.00 mmol/l (2.25 mmol/l to 2.60 mmol/l) on the first postoperative day can predict hypocalcemia manifestations by approximately 50.0 % of cases (Paladino et al., 2021). According to Noordzij et al., (2007) and Richards et al., (2003), measuring ionic calcium at six hours and also one day after surgery, found a value of 1.00 mmol/l (1.12 mmol/l to 1.32 mmol/l) or less for symptomatic patients. At six hours and one day after the operation, respectively, the sensitivity of the test was 40.0% and 50.0%; the specificity of 94.0% and 79.0%; the positive predictive value of 80.0% and 56.0%; and the negative predictive value of 74.0% and 75.0% (Noordzij et al., 2007; Richards, Bingener-Casey, Pierce, Strodel, & Sirinek, 2003).

Mahmoud F Sakr, (2022), Noordzij et al., (2007) and (Lombardi et al., 2004) found a statistically significant decrease in calcium values in the postoperative period compared to the preoperative period, noting that, in normocalcemic patients, it tends to stabilize after six hours of the operation, while, in hypocalcemic patients, the decline is progressive, up to approximately 42 hours postoperatively (C. P. Lombardi et al., 2004; Noordzij et al., 2007; Mahmoud F Sakr, 2022d). On the other hand, Wang et al., (2015) and Albert Stepansky et al., (2010), performing serial calcium measurements, were unable to define whether or not patients would develop hypocalcemia (Albert Stepansky, Natan Poluksht, Philippe Hagag, & Ilan Wassermann, 2010; J.-B. Wang, Sun, Song, & Gao, 2015).
Treatment of hypocalcemia

Although several authors have identified some predictive factors for postoperative hypocalcemia, it is still difficult to predict which patients would need of calcium and vitamin D supplementation in the postoperative period to treat or prevent signs and symptoms of low plasma calcium (Barbier et al., 2022; Bove et al., 2020; Cannizzaro, Okatyeva, Bianco, Caruso, & Buffone, 2018; de Carvalho et al., 2021; McMurran et al., 2020; Pâduraru et al., 2019).

Patients with symptomatic hypocalcemia and low blood calcium levels receive oral calcium supplementation (1 to 4 grams/day) with or without vitamin D (Kellerman & Rakel, 2020). Some patients with severe hypocalcemia and/or important manifestations also receive, at the beginning, venous calcium gluconate, administered slowly, until these manifestations improve (Barbier et al., 2022). Cases of hypomagnesemia should receive magnesium supplementation in the form of magnesium sulfate by mouth. intravenous (Barbier et al., 2022).

PTH is commercially available, but its use requires daily intramuscular applications, in addition to being very expensive (Barbier et al., 2022). Calcium carbonate is absorbed in the duodenum, and 20.0% to 30.0% of this absorption is dependent on vitamin D, which is prescribed in the most active form (vitamin D - calcitriol), at a dose of 0.25 mg to 0.50 mg per day (Saha & Goswami, 2019). A low-phosphate diet is also recommended (Barbier et al., 2022). Some researchers informed their patients about the clinical manifestations of postoperative hypocalcemia and give them calcium carbonate so that they can, if necessary, that is, in the presence of symptoms, start medication (Yamaguchi et al., 2020). In this case, routine laboratory tests are not performed (Donahue et al., 2021).

On the other hand, others empirically treat patients submitted to total thyroidectomy or bilateral TS and, without requesting tests in the postoperative period, release them home early (Donahue et al., 2021; Radakrishnan et al., 2021). The efficacy and safety of these alternative treatments still need further studies, since those currently available are not fully accepted by the scientific community. For Khatiwada & Harris, (2021) and Bhettani et al., (2019), routine oral calcium supplementation in the postoperative period, in addition to being empirical, has an ineffective cost-benefit ratio, and therefore its indication is not justified (Bhettani et al., 2019; Khatiwada & Harris, 2021).

Pâduraru et al., (2019) found that the administration of calcium in the immediate postoperative period, with or without vitamin D, effectively reduced the signs and symptoms of postoperative hypocalcemia (Pâduraru et al., 2019). Patients were discharged early and safely, and many of them had oral calcium administration suspended a few days after the operation, upon laboratory confirmation of normal serum calcium (Kazaure et al., 2021). This treatment reduced the risk of symptoms without inhibiting PTH secretion by normofunctioning parathyroids (Bashir et al., 2021).

Donahue et al., (2021), Sanabria et al., (2019) and Tartaglia et al., (2005) showed that the combined administration of calcium and calcitriol after total thyroidectomy reduces the risk of severe hypocalcemia, warning, however, that
10.0% to 13.0% of patients may still have calcium levels below 7 and 5 mg/dl on the second and third postoperative days and, respectively, clinical manifestations (Donahue et al., 2021; A Sanabria, Rojas, & Arevalo, 2019; Tartaglia et al., 2005).

**Changing the other ions**

**Phosphorus**

The adult human organism contains about 600 g of phosphorus (1.0% of body weight), of which 85.0% is in the skeleton, while the rest (15.0%) is found in the extracellular fluid, in the form of inorganic phosphate, and in soft tissues, in the form of phosphate esters (Lanham-New, Hill, Gallagher, & Vorster, 2019). The intestinal and renal absorption and excretion of phosphorus are related to the concentration of PTH. PTH increases the concentration of vitamin D, which, in turn, is responsible for stimulating the active absorption of this ion in the intestine. In the kidneys, PTH acts directly on the proximal tubules, decreasing phosphorus reabsorption and increasing phosphaturia (Bilezikian, Martin, Clemens, & Rosen, 2019; Lanham-New et al., 2019; Pham-Huy & Huy, 2022).

Serum phosphorus concentration drops more rapidly in response to PTH than increases in calcium. Thus, monitoring phosphorus in hypocalcemic patients in need of calcium supplementation may indicate, earlier, the return of parathyroid gland function (Bilezikian et al., 2019; Lanham-New et al., 2019; Pham-Huy & Huy, 2022). According to the available literature data, when serum calcium remains less than or equal to 8.0 mg/dl (8.4 mg/dl to 10.2 mg/dl) or phosphorus levels are greater than or equal to 4.0 mg/dl (2.5 mg/dl to 4.5 mg/dl), the risk of permanent hypoparathyroidism is on the order of 66.0% and 69.0%, respectively (Bilezikian et al., 2019; Lanham-New et al., 2019; Pham-Huy & Huy, 2022).

**Magnesium**

Some in vitro and in vivo studies have shown that magnesium can regulate PTH secretion in a similar way to calcium. The enzyme adenylate cyclase requires magnesium to generate cyclic adenosine monophosphate (cAMP), which, in turn, is a peripheral mediator of parathyroid cells, regulating PTH secretion. Magnesium deficiency increases the sensitivity of parathyroid cells to calcium, by reducing the activation of adenylate cyclase and, consequently, the release of PTH (Freitag et al., 1979; MAHAFFEE, COOPER, RAMP, & ONTJES, 1982; Nguyen, Tran, Nguyen, & Nguyen, 2021; Palermo et al., 2019; RUDE, OLDHAM, SHARP Jr, & SINGER, 1978; J. Xu et al., 2022).

Magnesium deficiency also reduces the effect of PTH on the kidneys and bones and increases its degradation in the liver and kidneys. Consequently, all hypocalcemic patients with magnesium deficiency will have relative hypoparathyroidism (Pepe et al., 2020). Magnesium also participates in the metabolism and action of vitamin D (Tecilazich et al., 2018). Patients with hypocalcemia and hypomagnesemia are resistant to large doses of vitamin D, caused by the reduction in both PTH and renal resistance to this hormone (Jain et al., 2021).
In addition, oral administration of vitamin D does not increase calcium levels. Hypomagnesemia associated with hypocalcemia makes patients more symptomatic, and plasma calcium correction without concomitant normalization of magnesium may maintain manifestations for longer (A. A. Khan et al., 2019). Temporary hypoparathyroidism leads to reduced renal tubular reabsorption of magnesium, and extracellular volume expansion increases the its excretion (Chincholikar & Ambiger, 2018). According to deep studies conducted by Wilson and others, approximately 10.0% of patients undergoing total thyroidectomy develop hypomagnesemia and hypocalcemia (Stojanovska et al., 2021; G. Wilson, Nistor, & Beasley, 2022; R. B. Wilson, Erskine, & Crowe, 2000).

**Hyperparathyroidism**

PTH measurement by immuno-chemiluminescence assay was described by Irvin III et al., (1999) (Irvin III, Molinari, Figueroa, & Carneiro, 1999), and has recently been considered a standard test by several authors (Bhangu & Riss, 2019; Carneiro-Pla & Pellitteri, 2021; Z. F. Khan & Lew, 2019; Leung et al., 2019). PTH measurements are performed at different times of the postoperative period - 10 minutes, one, two, four or eight hours - and its result is released in 15 minutes (Covic, Goldsmith, & Torres, 2020).

Due to the difficulty in predicting which patients will develop postoperative hypocalcemia, some authors, based on the operation and in serum calcium values, have shown a correlation between hypocalcemia and the drop in PTH in the immediate postoperative period, with statistically significant results (Covic et al., 2020; Kritmetapak & Pongchaiyakul, 2019; K Lorenz, Schneider, & Elwerr, 2020; Mak et al., 2020; S. D. Tsai et al., 2019).

PTH values below 7.0 pg/ml have high sensitivity and specificity in predicting postoperative hypocalcemia56. The recent published studies opt for pre- and postoperative PTH dosages, instead of considering its postoperative value in isolation (K Lorenz et al., 2020; Palmhag et al., 2021). According to Sakr, (2020), a PTH concentration lower than 10.0 pg/ml indicates symptomatic hypocalcemia in the postoperative period (p < 0.0001) (Mahmoud F Sakr, 2020). With this value, the sensitivity verified in the study developed by these authors was 80.0%; the specificity of 100.0%; the positive predictive value of 100.0%; and the negative predictive value of 91.0% (Mahmoud F Sakr, 2020).

Bhettani et al., (2019), Kim et al., (2015), Nagel et al., (2022), Pertsemlidis et al., (2017) and Shifrin, (2021) suggested calcium and vitamin D replacement for patients with a drop of 70.0% or more in PTH compared to the preoperative period (Bhettani et al., 2019; W. W. Kim et al., 2015; Nagel et al., 2022; Pertsemlidis, Inabnet, & Gagner, 2017; A. L. Shifrin, 2021). They also observed that intraoperative PTH values (after thyroid resection) below 10.0 pg/ml may indicate damage to the parathyroids and, consequently, the need to resect and reimplant them to prevent definitive hypoparathyroidism (Bhettani et al., 2019; W. W. Kim et al., 2015; Nagel et al., 2022; Pertsemlidis et al., 2017; A. L. Shifrin, 2021). They showed that the sensitivity and specificity of intraoperative PTH measurement in predicting biochemical and symptomatic hypocalcemia were not significantly different from calcium measurement on the day after the operation.
Some authors also report that postoperative PTH levels within the normal range are associated with a very low risk of hypocalcemia (Bhettani et al., 2019; W. W. Kim et al., 2015; Nagel et al., 2022; Pertsemidis et al., 2017; A. L. Shifrin, 2021). Sormaz et al., (2021) reported that patients with normal calcium values and PTH values above 28.0 pg/ml six hours after the operation had a very low risk of developing hypocalcemia (Sormaz et al., 2021).

According to Kim et al., (2021) and others, performing two PTH measurements (intraoperative and immediate postoperative), found that PTH values greater than 10.0 pg/ml and an increase in postoperative PTH compared to intraoperatively indicate low risk of hypocalcemia (Daskalaki et al., 2022; D. H. Kim et al., 2021; Rahman, 2021). Treating all patients with PTH < 8.0 pg/ml, measured one hour after the operation, reduced the incidence of postoperative hypocalcemia by 50.0%.

**Conclusions**

The incidence of early postoperative hypocalcemia and at 6-month follow-up is normally revealed with factors involved with hypocalcemia. The patients need calcium replacement in the postoperative period and, of these, are evolved to definitive hypoparathyroidism. There is importance of changes in magnesium and phosphorus ions in patients with postoperative hypocalcemia, with or without clinical manifestations, correlating them with changes in calcium. Hypocalcemia is a common complication after thyroidectomy surgery. Symptoms can be varied, from mild (spasms, paresthesias) to severe life-threatening symptoms (tetany, laryngospasm, convulsions, arrhythmias and cardiac arrest). Calcium replacement should be guided by symptoms and serum calcium levels. Mild cases should be treated with calcium replacement (calcium carbonate, calcium citrate) and calcitriol, both by mouth. Severe and refractory cases should be treated with the previous option + intravenous calcium replacement (formulations with gluconate and calcium chloride are the most common). Other variables that are associated with a higher incidence of hypocalcemia include types of operation, operative time, underlying disease, neck dissection and vocal fold paralysis.

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