Post-thyroidectomy hypoparathyroidism, what should we keep in mind?

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AIM: *Hypoparathyroidism and the resulting hypocalcemia is a common iatrogenic complication following surgical procedures to the neck, and commonly, to the thyroid gland. The aim of this study was to review the available literature to summarize current data related to the development of hypoparathyroidism after thyroid surgery.*
MATERIALS AND METHODS: *An analysis of the surgical literature was performed using the search engine EMBASE and PubMed with particular reference to the principal risk factors related to the post-thyroid surgery hypoparathyroidism. Moreover the medical records of 345 patients, who underwent thyroid surgery at the Section of Endocrine Surgery - Department of Medical and Surgical Sciences, Advanced Technologies "G. Ingrassia" University of Catania, Italy, were also examined.*
RESULTS: *The definition of hypoparathyroidism varies widely in literature. There is a wide range of reported incidences of transient and permanent postoperative hypoparathyroidism in literature. Extensive surgery, malignant disease and concomitant central and/or lateral neck dissection, autoimmune or Grave's' disease and re-operation represent the most recognized risk factors. A wide consensus exists about transplanting a parathyroid gland when it seems to be nonviable.*
DISCUSSION: *Although many improvements have been done in surgical technique, hypoparathyroidism seems to be one of the most common complication after total thyroidectomy. In this study we discuss the diagnosis methods and the importance of its early prediction regardless it is transient or permanent. Recovery time is under discussion: some author consider a gland permanent injury if restoring functionality does not occur within 6 months other 12 months. To assess the parathyroid gland function some authors have been using postoperative PTH level as a useful tool for predicting hypocalcemia.*
CONCLUSIONS: *Many efforts are required to address the problem of a consensus on best define these complications. An early low PTH level after total thyroidectomy is associated with a high risk of permanent hypoparathyroidism and normal levels usually exclude long-term parathyroid glands dysfunction. However, the cost of the PTH assay may limit its widespread application. Despite the reassuring presence of new therapeutic strategies, intra-operative preservation of the parathyroid glands is the best prophylaxis to avoid postoperative hypocalcemia after total thyroidectomy.*

KEY WORDS: Hypoparathyroidism, Thyroid surgery

Introduction

Hypoparathyroidism and the resulting hypocalcemia is a common iatrogenic complication following surgical procedures to the neck, and commonly, to the thyroid gland [1-3] and have been reported as post-operative complication since the early descriptions of thyroid surgery from the days of Emil Theodor Kocher [4]. In spite of many improvements in surgical techniques to avoid hitting and damaging the parathyroid glands, hypoparathyroidism remains a significant postoperative morbidity after total thyroidectomy. This specific complication, as well as recurrent laryngeal nerve injury, is feared, because it may give rise to significant and sometimes permanent, disability for the patient [5]. Postoperative hypocalcemia negatively impacts a patient's quality of life, not only with a prolonged hospitalization, the need for life-long

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calcium supplementation, but also increasing the risk of medical disputes.

Considerable efforts have been spent preventing post-operative hypoparathyroidism after thyroidectomy, but its consequences remain widely undervalued [6-7]. The amount of publications on post-surgical hypoparathyroidism suggests that the problem has a high impact on health and social life either for patients and surgeons. Costs to society in terms of medical treatment, follow-up, including frequent and repeated laboratory testing and treatment and sick leave, are considerable [8]. Many factors may be involved in the onset of hypocalcemia and hypoparathyroidism after thyroid surgery, including total thyroidectomy, reoperation, neck dissection, preoperative hyperthyroidism, autoimmune and inflammatory thyroid disease and surgical procedure performed by inexperienced surgeons [9-12]. However not all patients with these factors will develop such complication, probably because in order for it to happen, concur other causes, whose identification seems fundamental to its prevention.

The aim of this study was to review the available literature to summarize current data related to the development of hypoparathyroidism after thyroid surgery. With this in mind, were analyzed the main risk factors involved in the onset of this complication and the difficulties related to defining its correct incidence. Moreover the medical records of 345 patients who underwent thyroid surgery at our Department were also examined comparing the data with those reported in the literature. Attention was paid to all those technical factors useful to avoid the possibility of to prevent injury of the parathyroid glands. The present study might lead to a better management of patients undergoing total thyroidectomy.

The Incidence

The incidence of post-surgical hypoparathyroidism is difficult to define and the literature review shows a considerable variation in the reported data. Hypocalcaemia after thyroidectomy ranges in fact between 1 to above 50% [13-19]. Separately considering, transient and permanent, hypoparathyroidism are reported to be 6.9 to 38 % for the former, and 4 to 10.6 % for the latter [2,10,13] but at the worst, these rates were as high as > 60 and 33 %, respectively [20,21]. It should however be emphasized that in the surgical centers with experienced endocrine surgeons and in the hands of most high-volume thyroid surgeons, the risk of transient and permanent postsurgical hypoparathyroidism can decrease to 1,6 -2 % and < 1% respectively [5,22-25].

Which definition to use

As can be noted a common problem in the reporting of the incidence rate of hypoparathyroidism is the significant influence of the definition used. The review of the literature reveals a wide range of criteria and parameters that have been used to define postoperative hypoparathyroidism including biochemical, clinical, symptomatic and even related to the duration of the treatment [1,21].

Commonly reference is made to the levels of serum calcium, considering a condition of hypocalcemia level below 8 mg/dl on the first day after surgery and PTH levels below the reference value of 10 to 65 pg/ml. Moreover, many Authors, based on their clinical experience, have chosen to use as a benchmark the need for vitamin D and/or calcium treatment due to hypocalcemia, regardless of the PTH values [26-27]. Others consider hypoparathyroidism intact parathyroid hormone serum (iPTH) <1.6 pmol/L (normal range: 1.6-6.9 pmol/L) or the presence of postoperative clinical hypocalcemic symptoms with or without a serum calcium levels of less normal range [9].

Traditionally post-thyroidectomy hypoparathyroidism is classified as either transient and permanent but there is not a constant or rational use in defining "transient" or "permanent" a postoperative hypoparathyroidism [17]. The main controversy regards the exact cut-off duration that is used for those definitions, as well as the appropriate duration of resulting follow-up. Different time points have been used to determine when postoperative hypoparathyroidism should be classified as permanent. While most of the literature considers 6 months postoperatively as a cut-off time to differentiate between transient and permanent [3,9,15] some consider postoperative parathyroid glands injury to be permanent if recovery of function as not occurred 1 year after surgery [1,25,27]. Interestingly transient hypocalcaemia following thyroidectomy generally responds to replacement therapy within a days or weeks [28] and recovery of parathyroid function is generally observed in a significant number of patientsin three weeks to six months [8,13].

Using an earlier time point could result in classifying some patients as permanently hypo-calcemic when they could still show resolution of their condition [15,29]. Moreover in the opinion of some authors recovery of parathyroid function is possible as late as over 2 years after thyroid surgery [30].

The pathogenesis

Although parathyroid function is restored in most cases, recovery is sometimes insufficient due to irreversible injury, devascularization, obstruction of venous drainage or inadvertent excision of the parathyroid glands [31,32]. Their preservation is therefore a challenge even for experienced surgeons, because when the parathyroid glands are thought to be viable during surgery, normal postoperative parathyroid function is not always guaranteed. As reported the damage to three or more parathyroid glands

is what usually causes the occurrence of hypoparathyroidism [16,33] and recently studies showed that the number of parathyroid glands left in situ is an important factor influencing postoperative hypocalcaemia [8,33,34]. Despite several anatomical studies describing neck anatomy, only few of these have characterized the detailed anatomic and vascular relationship between the thyroid and parathyroid glands [35,36]. The extreme variations in the locations of these anatomical structures have in fact compounded the issue.

Embryologically, the parathyroid glands arise in the third and fourth pharyngeal arches before descending into the neck. Their final position is variable, with 8.5% located ectopically, 6.3 % in the mediastinum and 0.2 % within the thyroid tissue [37,38]. Classically the parathyroid glands are located close to the posterior side of the thyroid, within the pre-tracheal fascia and fat, near to the upper and lower poles and are intimately related to the course of the recurrent laryngeal nerves. Up to 13-15% of population can have supernumerary parathyroid glands and 3-5% can have less than four [29]. It is therefore evident that, over the skill and scrupulousness of the surgeon, the highly variable location of the parathyroid glands decides the incidence and degree of parathyroid damage. Therefore, many surgeons are interested in how to predict hypocalcemia in order to start treatment early to prevent serious complications and avoid delaying the patient's discharge from the hospital.

Can we predict hypocalcemia?

The patients who undergo thyroid surgery are usually early discharged and reliable markers allowing early prediction of hypoparathyroidism have been carefully sought [39-41]. Monitoring serum calcium levels is a traditional method for detecting post-thyroidectomy hypocalcemia although some authors advocate calcium monitoring in selected patients only [42], or calcium monitoring only during the first postoperative 24 hours. Absolute concentrations of serum calcium alone seems anyway not sufficient to predict its development [1,28].

The incidence of post-operative hypoparathyroidism appears to be r.educed with PTH monitoring and some studies indicate that PTH levels, measured during or shortly after surgery, have a high predictive value [43,44]. Most of these studies suggested that intact parathyroid hormone (iPTH) assays performed within hours of the surgery may shorten hospital stays by identifying patients with hypocalcemia who require medical attention.

However, there is an ongoing controversy about the predictive power of post-surgery PTH levels for chronic hypoparathyroidism and the exact kinetics after surgery is still uncertain. When a low PTH is found after surgery, it is also not clearly elucidated what that will mean to the patient in the long term. Several studies have detected an early postoperative drop in serum intact parathyroid hormone concentrations in patients presenting a serum calcium level of less than 8mg/dl at 24 h or more after surgery [45]. Others supported the use of postoperative iPTH and the % of iPTH decline in predicting postoperative hypocalcemia, but the results are still inconclusive, and no definite laboratory cut point or guideline have yet been established [46]. Moreover it should be considered that a single measurement of iPTH showed in some studies conflicts with a lack of sensitivity or specificity [14]. Usually intra-operative parathyroid hormone (ioPTH) levels are not routinely measured in thyroid surgery, although they are widely used in parathyroid surgery as an indicator for parathyroid gland dysfunction [47]. According to our clinical experience and as reported by many other Authors measuring the serum parathyroid hormone (PTH) immediately after surgery is a sensitive and specific method of assessing the function of the parathyroid glands and for identifying patients at risk for hypocalcemia [15,20,23,25,43,48,49]. As also observed by us, it should however be remembered that the decrease in iPTH precedes the decline in calcium which reaches the trough level approximately 24 hours after surgery. This might lead to delay in diagnosis and treatment of postoperative hypocalcemia. However, the cost of the iPTH assay may limit its widespread application and not all hospitals will have the ideal laboratory equipment to perform this test as needed and to obtain the results in a short time [50].

Let's look at the risk factors

Although hypocalcaemia is the most common postoperative complication of thyroidectomy there is limited evidence in the literature of how risk differs in different groups of patients. Various biological, clinical, and surgical factors may influence the development of hypoparathyroidism following thyroid surgery, some of which have been generally accepted. However, establishing these risk factors continues to be a challenge. Our analysis focused on the most commonly risk factors reported in the literature.

Malignant Thyroid Disease and Lymphadenectomy

Surgical procedures performed for malignant thyroid diseases and the consequent lymphadenectomy represent possible risk factors for a iatrogenic removal of the parathyroid glands [32,51,52]. The optimal extent of thyroid surgery has been long debated by surgeons. The operation should be radical to achieve good disease control, but minimizing potential post-thyroidectomy complications is equally important [53,54]. The higher incidence of hypocalcaemia after more extensive surgical procedures is well established in the literature [9,10,12]. On the other hand some Authors recommend routine Central Lymph

Node Dissection in order to prevent a future recurrence, citing the high risk of positive lymph nodes, the accuracy of staging, better outcomes, reduced postoperative thyroglobulin levels and a lower morbidity rate associated with the first operation [53,55,56]. Particularly, as reported in a recent meta-analysis, the incidences of transient and permanent hypocalcemia in a group that underwent prophylactic central neck dissection were 26.0 and 2.0 %, respectively, compared with 10.8 and 1.2 %, respectively, in a group that did not undergo prophylactic central neck dissection [57]. Others Authors reports worse results related to neck dissection of level VI ranging up to 54.6% and 17.4 % of postoperative transient and permanent hypoparathyroidism respectively [14]. Although one study found no correlation [31], central node dissection, especially when bilateral, was reported to be a risk factor of permanent hypoparathyroidism with an incidence that increase from 0 to 23% in reoperation [9]. Analyzing our series we observed a direct relationship between diseases requiring more aggressive treatment and incidence of hypocalcemia however, we must note that even the definition of central compartment lymphadenectomy varies between surgeons and studies. Central neck dissection could contribute to hypoparathyroidism to some degree via disruption of the supplying vessels of the parathyroid glands.
Therefore, as previously reported [58], the patients who require CLND must be carefully selected and the surgical technique during the dissection may be the most important factor in preserving the parathyroid glands.

Thyroid Volume and Operative Time

Actually few authors relate thyroid volume and operative time with postoperative hypocalcemia. Due to the controversy over these factors in the literature [41,59] we should always consider the possibility that surgery in case of a large and/or substernal goiter is usually associated with longer operative time and, consequently, with a higher incidence of hypocalcemia [60]. Therefore operative time should always be considered in conjunction with the type of surgical procedure.

Reoperation

Several types of surgery are employed in the treatment of benign thyroid disease, including hemi-thyroidectomy with or without the resection the isthmus, subtotal removal of one or both lobes, as well as total or near-total resection of the thyroid gland. Apart the aforementioned problem, resulting from the extent of surgery in case of malignant disease and correlated to the onset of hypoparathyroidism, completion thyroidectomy may be required both for benign thyroid disease than when carcinoma is diagnosed at postoperative histological examination of thyroid tissue surgically removed. Although even less extensive operations can evolve with decrease in serum calcium, the extent of surgery is directly related to the severity of hypocalcemia as well as its incidence [7]. Completion thyroidectomy may results in a higher risk operation with the occurrence of parathyroid glands injury, if compared with primary surgery, due to the presence of distorted anatomy inflammation, bleeding, friability of tissues, adhesion and scar tissue. All these factors hinder the identification of parathyroid glands and pose a higher risk of injury to the parathyroid vascular pedicle [61]. Opinions concerning the frequency of complications following less or more extensive surgery on the thyroid gland cited in the literature differ. Actually thyroidectomies in which both sides of the neck were manipulated were certainly associated with significantly higher incidence of hypocalcemia [9,61]. On the other hand, an unquestionable advantage of a wide extent of thyroid resection is a lower rate of multinodular goiter recurrence compared to subtotal thyroidectomy [1]. After all, unrecognized prior reduction in parathyroid function, such as following prior central neck surgery, that as reported increases the risk of hypoparathyroidism after additional surgery, should not be underestimated [25].

Energy-Based Device

Different modalities can perform hemostasis in thyroid surgery. Choosing the best procedure often depends on the experience of the surgeon [62,63]. Energy based devices (EBD) have been developed, implemented and increasingly applied in thyroid surgery because they can provide a combined dissection and hemostatic effect. Although some reports have pointed out the benefits in reducing procedure-associated time, less operative blood loss, decreased postoperative drain, the need for postoperative analgesics therapy and hospital stay [64,65], only a few prospective studies in the literature indicated the possible benefits and harms of these devices concerning the post-operative hypoparathyroidism [66].
Thunderbeat (Olympus), Harmonic Scalpel (Ethicon) and Liga Sure (Medtronic-Covidien) are the most widely used hemostatic tools. The damage of the parathyroid glands, during the use of energy based devices may be explained referring to the physics underpinning the functioning of these instruments, such as the high temperatures and lateral thermal spread which can extend up to 2 mm. [67]. Considering the wide availability of EBD we should expect in the near future an increasing incidence of complications caused by thermal spread if a strict standardized use is not applied. However, the studies that have compared energy based devices in thyroid surgery, yielding substantial evidence and reference value, have reported similar results and post-operative morbidities rates [68,69]. Therefore we can conclude that the use of

EBD during thyroid surgery has shown potential advantages despite a potential drawback is the increased health care costs. It is important to prevent the divergence of energy during the use of energy-based devices. The parathyroid glands should be kept at a distance from energy based devices during thyroidectomy.

Hyperthyroidism - Grave's Disease - Hashimoto's Disease

Many studies suggest that the incidence of permanent hyperthyroidism, as a postoperative complication, is significantly affected by the original thyroid disease [9,13,61]. It was observed that autoimmune and inflammatory thyroid disease, whether Hashimoto thyroiditis or Grave's disease, increase the risk of postsurgical hypoparathyroidism with total thyroidectomy [70,71]. It is unclear exactly why thyroid surgery performed in a patient affected by hyperthyroidism have an increased rate of hypocalcaemia even though they have been treated in order to present with normal or partially controlled thyroid function at operation [2,9,38]. Factors that may have contributed to it should be the more difficult technique in the surgical treatment. It is in fact unsurprising as the thyroid gland in thyrotoxicosis tends to be large and very highly vascularized leading to a more challenging operation.

Female Patients

Previous studies reported conflicting results with respect to female gender as a risk factor for post thyroidectomy hypocalcemia [2,8,9,14,72]. A multivariate analysis of 5846 patients showed an odds ratio of 1.9 for transient hypocalcaemia with female gender that anyway seem to have a significantly lower incidence of permanent hypoparathyroidism than males [9]. However it should be considered that Women are much more likely to have a disease associated with a variety of hormones, such as menopausal syndrome and osteoporosis that can interact with Calcium or vitamin D levels. In order to avoid further confounding factors, evaluations of bone mineral density, and other hormone levels could be necessary. Furthermore pregnancy and lactation may all place the patients at increased risk for postoperative hypocalcemia [73,7].

Diabetes

Very little is reported in the literature on the possible effects that diabetes can have on the functionality of the parathyroid glands. The mechanism by which diabetes causes his effects is unclear. However, it can be hypothesized that the small vessel disease and the impact on angiogenesis, as is often observed in diabetes, may leave the parathyroid glands more vulnerable to hypoxia in these patients [29].

Vitamin D

It is believed that preoperative vitamin D level can predicts post-thyroidectomy hypocalcemia [75]. Although vitamin D deficiency appears to be a good predictor of postoperative hypocalcemia, since it is vital to calcium homeostasis, assessment of his level rarely is performed preoperatively. Particular attention should be paid to those cases in which disorders of calcium and vitamin D absorption and metabolism are expected, such as seen in patients who have undergone bariatric surgery [76].

What should we do to prevent hypoparathyroidism

Surgical Technique

Although a number of studies have listed many risk factors that are obtaining consensus, the need for a scoring system to appropriately assess the risks of post-thyroidectomy hypocalcemia is increasingly necessary. Probably the use of precise surgical techniques intended to preserve and identify PTG is an important key in preventing or reducing post-thyroidectomy hypocalcemia. In order to reduce the risk of hypoparathyroidism, careful dissection and protection of the parathyroid glands during thyroidectomy have been accepted as routine clinical procedure for many years [77]. Usually a total thyroidectomy is performed with a standard technique, but every effort should be made to visually identify each parathyroid close to the thyroid gland, assessing the location of the vascular pedicle to the parathyroid. Obviously is useful for this purpose the use of surgical loupes.
To avoid an impairment of the functionality of parathyroid glands, it is recommended to identify as many parathyroid glands as possible and to be meticulous during surgical dissection in order to preserve them in situ with an intact vascular supply. Is however reported that a systematic search of the parathyroid glands may, theoretically, increase the risk of them being injured, being a contributing factor to hypocalcemia [13,22,41].
The most practical approach to avoid unintentional parathyroid damage during total thyroidectomy is to keep the dissection through a safe zone away from the parathyroid glands. This can be safely achieved by keeping the plane of dissection in the sub capsular plane of thyroid. The inferior thyroid artery should be ligated at the level of its distal-most medial branches and the posterior branches of the superior thyroid artery were preserved, as far as possible, to minimize compromise of the blood supply to the parathyroid. This technical measure has lowered the incidence of hypoparathyroidism to a great exten
We must also keep in mind that is not always easy to identify the parathyroid glands intraoperatively, especially when hiding in non-orthotopic places, hence they must be presumed to be present anywhere around the

gland while dissecting the periglandular tissue, especially during the dissection of recurrent laryngeal nerves [33] In our opinion the initial "clamp-and-tie" technique, still widely practiced, should be used especially close to the parathyroid glands. However a scrupulous and careful surgical technique during dissection and hemostasis should always be observed.

Autotransplantation

Although autotransplantation of parathyroid glands was not routinely performed, many surgeons agree that, in cases of inadvertent removal or devascularization of parathyroid glands, immediate parathyroid autotransplantation into the sterno-cleido-mastoid muscle should be used to prevent permanent hypoparathyroidism [9,30,78]. However controversial opinions are reported in some literature suggesting that autotransplantation is not always functionally successful [79,80].

Technically parathyroid glands that could not be preserved were minced into tiny fragments and autotransplanted, typically into one or more pockets of the ipsilateral sternocleidomastoid muscle, with a marking suture or clip [25]. Obviously a parathyroid gland with intact vascular pedicle and clinically viable should be left in situ. Nonetheless, its viability may be difficult to define clinically. Devascularized parathyroid glands can be recognized intraoperatively by inspection because they usually become dark brown or even black, but parathyroid tissue color alone is not a definitive test of parathyroid viability. Consideration of an intact vascular pedicle should also be assessed.

Sometimes the glands do not become discolored as their devascularization is caused only by arterial insufficiency. Viability can be determined by observing active bleeding after making small incisions with a cold knife to evaluate the blood supply to the parathyroid glands [81]. Anyhow, in our opinion, autotransplantation of a gland is not the same as careful preservation of the parathyroid with its vascular supply. Surgeons should make every effort to do the latter rather than simply relying on the former. We should not forget, in fact, that sometimes the presence of parathyroid tissue represents an unpleasant finding at histological definitive examination.

About therapy

The use of Calcium is perhaps the best therapeutic approach in case of post-operative hypoparathyroidism, and to some extent, these procedure resulted in good practical results. Because surgeons know that failure of the parathyroid glands is a potential risk of thyroid surgery, many patients are empirically treated with either calcium or calcitriol to try and avoid symptoms.

Although this supplementation can help minimize symptoms, the usual practice of post-operative routinely administering calcium supplements to all patients, may hide the real frequency of hypocalcaemia. Long-term calcium and vitamin D supplementation has its own complications, and, especially with high doses, in some patients increases the risk of constipation, promotes the development of renal calculi, renal impairment, soft tissue calcification and inhibits iron and zinc absorption from food. In addition, this practice means that a high percentage of patients take unnecessary calcium supplements.

Usually 1 to 3 grams of elemental calcium orally administered in divided doses is sufficient. Attention should be paid for patients treated with a proton pump inhibitor or elderly subjects with achlorhydria that could reduce the intestinal absorption of calcium.

Treatment of acute severe hypocalcemia after thyroidectomy consists of intravenous administration of calcium carbonate and active metabolites of vitamin D.

PTH, Ca, and Phosphate levels should anyway be checked immediately after operation and again on the days before discharge and seen for follow-up during the following week.

A new option for the successfully treatment of hypoparathyroidism, studied in the REPLACE trial is recombinant human PTH [82].

Although it is not yet approved in Europe, for the specific treatment of hypoparathyroidism, recombinant human PTH has shown promising therapeutic results in reducing calcium and vitamin D requirements, restoring normal bone metabolism and improving the patient's quality of life.

Discussion

The overall complication rate after the thyroid surgery is generally low [10], and, with increasing experience, total thyroidectomy has become an effective treatment not only for thyroid malignancy, but also for benign thyroid disease. Hypoparathyroidism is one of the most common complication after total thyroidectomy and could be permanent or transient. Permanent hypoparathyroidism is caused by removal of all four parathyroid glands or by permanent damage to their blood supply and in such a situation patients need life-long supplementation of vitamin D and calcium. Transient hypoparathyroidism is caused by reversible ischemia to parathyroid glands.

The definition of hypoparathyroidism varies widely in literature in terms of calcium level, need for supplementation of calcium and/or vitamin D [21,27].

Furthermore, different time points have been used to determine when postoperative hypoparathyroidism should be classified as transient or permanent. Some consider postoperative parathyroid glands injury to be permanent if recovery of function has not occurred within

6 month [4,11,17] whereas others define permanence at 1 year after surgery [1,25,27]. However it should be remembered that using an earlier time point could result in classifying some patients as permanently hypo calcemic when they could still show resolution of their condition [15,27]. All this is reflected on a wide incidence of hypoparathyroidism reported in different series where transient and permanent hypocalcaemia ranges from 1.6-60% to 0,9-33% respectively.

The problem of early and accurate prediction of post-operative hypocalcaemia has also been discussed in great detail [2]. Early prediction also helps in identifying "at risk patients" requiring early calcium and vitamin D supplementation. Many efforts have been done to early assess the postoperative parathyroid function, and there are several reports that postoperative PTH level is a useful tool for predicting hypocalcemia [43,44]. Particular attention has been paid tolowering PTH level immediately or several hours postoperatively. The rapid PTH assay can virtually reflect real time parathyroid function because the short half-life of PTH [45].

However, intraoperative PTH assay is not available in all centers for its cost. Furthermore, operation time can be prolonged, because it needs time. Usually post-operative serum calcium levels are used to predict hypoparathyroidism and other authors reported that a gradual increase of calcium level within 24 hours postoperatively predicts normal calcium levels [28]. Regarding the correlation between postoperative hypocalcemia and the number or the viability of in situ preserved parathyroid glands many reports are available in literature [1,30,79,80]. Although physical preservation of the parathyroid glands in situ is necessary, it does not ensure normal parathyroid function owing to vascular injury of the glands. A wide consensus exists about the transplant of the parathyroid gland that seems to be nonviable 9,30,78. Moreover some surgeons, in order to prevent permanent hypoparathyroidism, advocated routine parathyroid autotransplantation [83].

Although a color change from the normal brownish-red to blue-black has traditionally been thought to be a sign of vascular involvement and impaired function [84], recent studies have questioned this method [17,33]. Others Authors have shown that bleeding from an incision of a parathyroid gland, so-called "knife" test, is an important finding suggesting intact vascularity [81,84].

Wishing to proceed to a discussion about the most common risk factors we can certainly affirmed that the risk of hypoparathyroidism increases with extent of thyroidectomy, malignant disease, concomitant central and/or lateral neck dissection, autoimmune or Graves' disease and re-operation

Particularly it is reported that the transient hypocalcemia after thyroidectomy for cancer ranges from 13.6 to 75% and permanent hypoparathyroidism ranges from 3.3to 5.8 % [9] by placing the cancer as the main predictive factor for the development of these complications [84]. Moreover the eventually associated lymphadenectomy increases the risk of hypoparathyroidism. This conclusion is supported by the findings of many Authors [51,52,57]. A significantly higher incidence of permanent hypoparathyroidism was observed in patients with hyperthyroidism but it is unclear exactly why in these patients thyroidectomies have an increased rate of hypocalcaemia [71]. Thyrotoxicosis was also found to be a significant factor in several other studies exploring hypocalcaemia [2,9,38] and many authors indicate that Grave'sdisease and Hashimoto's disease are to be considered a risk factor for postoperative hypoparathyroidism [9,17,27,61].

Reoperation may increase the risk of iatrogenic injury to the parathyroid glands [1,9,18,61]. The incidence of transient and permanent hypocalcemia is reported up to 44.1 and 11% respectively [7]. Given the high incidence of hypoparathyroidism resulting from re-operation, surgeons should not be encouraged to adopt hemi-thyroidectomy for unilateral benign disease.

According to the results of our study, the safety of the energy-based devices is proved and their use in patients with thyroid diseases could be appropriate [69]. Attention should be paid to using it at a n appropriate distance from vital anatomic structures such as recurrent laryngeal nerves and parathyroid glands. Close to this important structures, while performing thyroidectomyis highly recommended to use conventional suture ligation technique in order to prevent damage to the parathyroid glands [62].

Conclusions

In literature, there is a wide range of reported incidences of transient and permanent postoperative hypoparathyroidism. Many efforts are required to address the problem of a consensus on best define these complications. Various biological, clinical, and surgical factors may influence the development of hypoparathyroidism after thyroid surgery, some of which have been generally accepted. Extensive surgery, malignant disease and concomitant central and/or lateral neck dissection, autoimmune or Graves' disease and re-operation represent the most recognized risk factors. Preservation of the parathyroid glands during total thyroidectomy is the best prophylaxis to avoid postoperative hypocalcemia after total thyroidectomy for an endocrine surgeon. Not always is necessary to visually identify all parathyroid glands to accomplish this. Parathyroid glands lying a slight distance from the thyroid are more difficult to identify but easier to maintain functionally intact. Dissection at the sub-capsular plane of the thyroid during total thyroidectomy ensures preservation of most of the parathyroid, thereby lowering the incidence of postoperative hypocalcaemia. Understanding the complex vascular structures surrounding the parathyroid gland is crucial to prevent post-thyroidectomy hypoparathyroidism

because there is no guarantee of normal postoperative parathyroid function, even if the procedure is performed for benign disease.
In our opinion it is important for surgeons to think about second surgery that may be performed in future for various reasons when they perform hemi-thyroidectomy as an initial surgery.
A careful examination of the surgical specimen intraoperatively decreased the incidence of inadvertent parathyroidectomy during thyroid surgery.
Any parathyroid gland that looks likely to be totally devascularized can be removed during the operation and autotransplanted into well-vascularized muscles such as the sternocleidomastoid muscle.
Evaluation and management of central neck surgical patients for postoperative hypoparathyroidism may present challenges. Although the dissection of central compartment is a safe procedure, it is difficult to keep the parathyroid glands intact in case of a tumor is large, infiltrative or if there are extensive lymph node metastasis. In this case, a careful staging should be performed in order to avoid possible morbidity related to reoperation for recurrence involving lymph node.
Resolution of hypoparathyroidism is likely to be related to recovery of the parathyroid glands function. Nowadays is it difficult to predict which patients will recover and it is also unclear as to whether any specific intervention will facilitate recovery.
Furthermore, 12 months may be the most appropriate time point to define hypoparathyroidism as a permanent condition because patients with transient postoperative failure of parathyroid glands usually resolved within a year after surgery.
A low PTH level early after total thyroidectomy is associated with a high risk of permanent hypoparathyroidism and normal levels usually exclude long-term parathyroid glands dysfunction. However, the cost of the PTH assay may limit its widespread application.
Finally, hypoparathyroidism following thyroidectomy is a documented source of complaints and medical disputes. Appropriate informed consent remains a priority to emphasize particularly the importance of some primary factors responsible for the increased risk of unintended injury of parathyroid glands after thyroid surgery.

Riassunto

L'ipoparatiroidismo e l'ipocalcemia sono complicanze iatrogene relative agli interventi chirurgici sul collo ed in particolare sulla ghiandola tiroide. L'analisi della letteratura ha evidenziato un'ampia variabilità nella definizione dell'ipoparatiroidimo, del suo range di incidenza e della sua durata. Le più comuni cause sono rappresentate dalla chirurgia estesa, dalle patologie maligne e dalla dissezione del comparto centrale e laterale del collo. Altri fattori di rischio sono rappresentati dalle malattie autoimmuni e dai re-interventi. Di estrema importanza si rileva la precoce individuazione dei fattori di predittività sulla insorgenza e sulla sua classificazione in transitorio e permanente. Nonostante l' apporto di moderni presidi tecnici volti alla salvaguardia dell'integrità delle ghiandole paratiroidi e di un' accurata tecnica chirurgica, ulteriori studi sono richiesti per meglio definire questa importante complicanza.

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