



Post thyroidectomy hypocalcemia: physopathological considerations and prevention by homolateral sternocleidomastoid implant of a complete devascularized parathyroid gland

Abstract

Postoperative hypocalcemia incidence range after thyroid surgery from 1-2 to 61.9%. Such a wide oscillation of values in literature cannot fail to raise doubts about the method of detection and the composition of the different experiences. We here refer to the personal experience gained over the course of 3 years (from January 2020 to December 2022); 320 consecutive thyroid surgeries: 79 M, 241 F, (mean 49.11aa), 59 near total thyroidectomies, 213 total thyroidectomies, 48 recurrence interventions (of which 18 for neoplastic pathology with central or latero-cervical emptying) performed in 258 cases for benign pathology and in 62 cases for cancer. In a smaller group of 50 cases of low parathyroid vascularization after dissection, we selected 12 cases of absolutely no color signal of parathyroid vascularization at early and late acquisition and in those cases, we proceeded to a homolateral sternocleidomastoid muscle implant. The entire sample of 320 patients can therefore be subdivided, according to the extent of the demolition, to the method of opotherapy substitution with L-Thyroxine and to muscle implant of a devascularized parathyroid in 4 groups: I group 59 patients near total thyroidectomy; II group 155 total thyroidectomies with L-Thyroxine from 15-30th p.o. day; III group 94 patients total thyroidectomy with L-Thyroxine from the first p.o. day and finally IV group 12 patients total thyroidectomy with an homolateral muscle implant of a devascularized parathyroid.

In the first group the incidence of early hypocalcemia was 5 cases, equal to 8.47%, the incidence of protracted hypocalcemia was 0 cases, equal to 0%. In the second group the incidence of early hypocalcemia was 33 cases, equal to 21.29%, the incidence of protracted hypocalcemia was 7 cases, equal to 4.51%. In the third group (94 cases) the overall incidence of hypocalcemia was practically nil, with only 2 cases of early hypocalcemia, equal to 2.12% and no case of protracted hypocalcemia. In the fourth group the incidence of hypocalcemia is 1 case of early hypocalcemia 8.33% and no case of protracted hypocalcemia.

We suggest that p.o. hypoparathyroidism doesn't look to be influenced by total or near total thyroidectomy and that an early thyroid hormonal replacement therapy should be started, whenever possible, post total thyroidectomy. The surgical muscle implant of a completely devascularized parathyroid gland approach is certainly an interesting method, not without limits and criticisms, in an attempt to limit the iatrogenic impact in the determinism of post-thyroidectomy hypocalcemia.

Keywords: thyroidectomy, hypocalcemia, parathyroid, parathyroid implant

Introduction

Postoperative hypocalcemia represents a far from rare occurrence in thyroid surgery, yet the real extent of the phenomenon and its causes,

in hindsight, are difficult to establish: the rich literature on the subject, which remains current. If you look at the numerous statistical revisions found in the literature there is an extreme

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variability of figures that place its incidence within limits ranging from 2 to 61.9%. Such a wide oscillation of values cannot fail to raise doubts about the method of detection and the composition of the cases: some of the oldest in fact consider only the cases of tetany, i.e. those in which the clinical phenomena of hypocalcemia occur (tingling, s. of Troussou, s. of Chvosteck) which, as is well known, usually represent the most severe expression of hypocalcemia, but which are also possible for calcemic levels slightly below the norm and in whose pathogenesis, Magnesium seems to be involved, while on the other hand there are cases of hypocalcaemia without clinical signs of alarm [1, 2].

Other cases include demolition interventions of variable amplitude (total and subtotal thyroidectomies) and, even when they consider only subtotal resections, they can include interventions that are profoundly different from each other in terms of residual width, always difficult to evaluate and standardize even in the same area of school and of technique. Others proceed to a determination of the calcemia p.o. at fixed intervals and for a limited period of time and still others do not take into account factors related to the nature of the thyroid disease or to that of any concomitant diseases such as diabetes, renal and hepatic insufficiency etc.

To complicate matters there is also the distinction between transient hypocalcemia and permanent hypocalcemia: there seems to be no doubt about the definition of transient hypocalcemia; this should be defined as the condition that runs out within the first week or so, with a peak of incidence at the IV day, the definition of permanent hypocalcemia finds a wider variety of limits: 6 weeks, 3 months, 6 months, but there are descriptions of cases with persistent hypocalcemia over 6 months or hypocalcemia arising with dramatic effects even after years of surgery on the thyroid [3, 4]. It is therefore not surprising that, on the basis of these premises, the most different pathogenetic hypotheses have been formulated on the onset of duration and extent of the phenomenon in the attempt to identify the characteristics detecting patients at risk.

It is only during the 90s that a systematic approach to the problem begins, with prospective studies aimed at verifying the validity of the various pathogenetic hypotheses.

Background

At the present time, it's necessary to premise that a p.o. hypocalcemia of moderate intensity and

short duration is shown to be the prerogative of every surgery, as an effect of the only surgical trauma, provided of a certain entity and it looks to be related to the degree of major or minor hemodilution resulting from it; the hypocalcemia resulting from thyroid operations, instead of it, is a phenomenon of significant, greater incisiveness and it's on its pathogenesis that the different interpretative hypotheses have been addressed [5-7].

- Parathyroid deficiency: it represents the most certain cause of p.o. hypocalcemia and recognizes its origin in the inadvertent removal or damage of parathyroids. This damage can be produced by different thermic or mechanical traumas and new technology seems not to avoid those complications. Some interesting application seems to slightly reduce this kind of damages by avoiding or reducing in proximity of the anatomical parathyroid localization, the use of hemostatic devices instead of a hemostatic gel or pad [8, 9]. Regardless of the proposed technical measures, such as the section of vascular peduncles on their respective branches, close to the gland, the same anatomical dislocation of the parathyroid glands normally protects them from a decisive lesion [10]. One such occurrence would require all parathyroids to be detected in the thyroid parenchyma. More controversial because it is less provable is the hypothesis of ischemic injury or mechanical trauma whose ill-quantifiable effects would be expressed with a transitory functional deficit of the parathyroids which results in a hypocalcemia of variable duration in proportion to the extent of damage [11]. The hypo-parathormone level that would be responsible for this has been demonstrated by some AAs, while others have not registered any reduction [12]. Of circulating parathormone (PTH) [13-15]. Parathyroid deficiency, according to other hypotheses, could derive from a decreased lymphatic and venous drainage caused by the intervention or from a vascular damage produced by an autoimmune mechanism in the area of the healing processes of the thyroid loggia [16, 17]. This hypothesis would have the advantage of explaining p.o. hypocalcemia increased incidence of patients operated on an autoimmune basis such as the one from Basedow hyper-thyroids, or norm functional goiter, with chronic autoimmune thyroiditis like Hashimoto [18, 19]. Probably the explanation could

be the excision or damage of a prevalent parathyroid: this could explain, the cases where there is a usual identification of 2-3 parathyroids, but hypocalcemia occurs the same [20].

- Excess of calcitonin invoked as a hypocalcemizing factor in relation to the surgical manipulations of the gland. Calcitonin blocks calcium bone resorption with a mechanism counteracted by PTH; in the postoperative thyroid the ischemic or traumatized parathyroids according to the previous hypothesis would not be able to oppose the hypocalcemia induced by the excess of calcitonin. However, statistical analyzes aimed at demonstrating excess calcitonin did not confirm this hypothesis [21].
- Thyroid deficiency: represents one of the most obvious, but perhaps even more underrated, causes of hypocalcemia p.o; the thyroid hormones favor the reabsorption of calcium from the bones with a predominant effect also towards PTH, so much so that, in hypothyroid subjects, this mobilization cannot be obtained either from the physiological elevation of the PTH blood levels, nor from the administration of exogenous PTH [22-25]. In confirmation of these findings there is the reverse trend observed by Di Gesù in the postoperative period between increasing levels of PTH and decreasing levels of T3, T4 and blood calcium. An indirect support would instead come from the observation that continuing without interruption, in the p.o. administration of L-thyroxine prevents or reduces the incidence of p.o. hypocalcemia. On the other hand, all these findings are not in contrast with one of the most accredited hypotheses in the past: the "hungry bone syndrome" attributed the p.o. hypocalcemia to the abrupt abolition of the intense bone resorption of calcium induced by the high preoperative levels of T3 and T4 [26, 27]. However, this hypothesis is based on two assumptions that are easily refuted:
- That p.o. hypocalcemia has higher incidence among hyperfunctioning thyreopathies: this prevalence has not always been demonstrated, while other AAs. Found a greater incidence among the standard-fitting forms[28-30].
- That the hyperfunctioning thyreopathies come to the intervention in a condition of incorrect hyperthyroidism that is a

condition that is normally impossible to verify, since the indispensable condition for planning the intervention in such cases is precisely the hormonal normalization.

As far as we are concerned, the opportunity to return to the subject occurred when we started to notice that the incidence of p.o. hypocalcemia had significantly increased by number of cases and by intensity, during the 90s. For many of us, trained to a twentieth century practice with thyroid surgery and accustomed to an almost insignificant relevance of the phenomenon in previous experience, the novelty represented a moment of reflection and analysis.

What has changed during these years? At a critical analysis carried out as the phenomenon revealed itself in its full physiognomy, nothing else was changed, if not a tendency, more and more pushed, towards wider demolitions for benign thyreopathies. In the early 90s, in fact, in order to eliminate the problem of nodular recurrence and recurrences in general for multinodular goitre, we had also adopted for these forms a thyroidectomy that was closer and closer to "near total" thyroidectomy, already by us adopted in the treatment of diffuse toxic goiter and multimodal toxic goiter.

The increased frequency of p.o. hypocalcemia it could therefore be due to the increased risk of parathyroid lesions and / or the increased parenchymal demolition caused by total thyroidectomy.

Materials and Methods

We here refer to the personal experience gained over the course of 3 years (from January 2020 to December 2022) at the Endocrine-Surgery Unit of the Division of General Surgery and Oncological Physiopathology of the University of Campania, "Luigi Vanvitelli". In this experience, including a series of 320 consecutive thyroid surgeries selected based on the completeness of post-operative data, we could compare the calculus trend p.o. in relation to age and sex, to the type of intervention (near total thyroidectomy, total thyroidectomy, etc.), to the basic thyroid pathology (norm-functional goiter, hyperfunctioning goiter, immersed goiter, recurrence, cancer etc.) and to any associated diseases (diabetes, renal failure, etc.).

The sample includes 79 males, 241 females, (mean 49.11aa), includes a total of 59 near total thyroidectomies, 213 total thyroidectomies, and 48 recurrence interventions (of which 18 for neoplastic pathology with laterocervical emptying), performed in 258 cases for benign

thyreopathies and in 62 cases for cancer.

The technique for near total thyroidectomy is an operation that involves the surgical removal of both thyroid lobes except for a small amount of thyroid tissue (on one or both sides less than 1.0 mL). Total thyroidectomy is performed by us using a standard technique and is not dissimilar in goiters and cancer except for the extension to the perithyroidal and laterocervical lymph nodes in the case of cancer where these were of increased volume. As far as the parathyroids are concerned, our technique foresees the search and the systematic recognition of at least 2 parathyroids, usually on the first side of surgical approach, and only if these are not recognizable or respectable because they are not found, the research is carried out with greater attention also on the other side, where, in this case, their recognition becomes mandatory; the valuation of integrity and recently the possibilities of the vascularization's interpretation (thanks to ICG and NIR i.o. angiography techniques) enable, in case of a completely devascularized gland, the attempt to revascularization implanting it in the homolateral sternocleidomastoid muscle.

We systematically requested to the pathologist to search for parathyroid tissue on the operative part and we carried out controls of the preoperative calcemic levels and then 12 hours after surgery, and then from day to day until discharge. The p.o. it was usually 3-4 days (median value on the 4th day), provided that outside of other reasons, it was possible to maintain calcium levels in the normal range with oral calcium therapy alone (2g / day + / - vit .D3), started for everyone since the first day po The calcium therapy was suspended in such cases after 7-10 days after an outpatient check of normal calcemic values, then repeated verification at 15, 30, 90 and 120 days and then from year to year coinciding with thyroid hormonal controls.

In cases in which the p.o. calcemic levels went down and remained below the normal range, with or without specific symptomatology and despite oral calcium therapy, we infused daily e.v. Calcium gluconate or Calcium chloride corresponding to a dose ranging from 8 to 40 mEq, in relation to the ability to reconstitute and maintain normal or subnormal calcium levels. A normo-calcemic level obtained and maintained for at least 24 hours proceeded by suspending the infusion e.v. and verifying the maintenance of a normal calcium with the oral supplement only. At this point these patients were also included in the "unhooking" protocol provided for the normal cases, as described previously. To exclude

mutual interferences of the variables considered (age, sex, type of pathology, complications such as diabetes and mediastinal immersion and the type of intervention) and to freely correlate them to the postoperative calcemic level variable, for the evaluation of statistical significance, the test chi, covariance, and correlation coefficients, a Microsoft Excel Office worksheet was used. We have defined the hypo-calcemic patients in agreement with the laboratory parameters: normal levels of ionized calcium in adults, (4.64-5.28 mg/dL) and Total Calcium (range 8.2-10.4 mg/dl); we classified the hypocalcemia in mild (not inferior to 4,0 or 7.6 mg/dl), moderate (between 3,5-4,0 or 7.5-7 mg/dl) and severe (less than 3,5 or 7 mg/dl); intravenous ions calcium infusion was planned and implemented only for moderate and severe hypocalcemia. We did not distinguish symptomatic hypocalcemia from those asymptomatic, often being the dissociated symptoms from serum calcium values, but we distinguished an early hypocalcemia (I-VII p.o. day) with peak in the II postoperative day and a protracted hypocalcemia (from 1-6 months p.o.); the former can be identified with transient hypocalcemia, the second (more or less) with permanent hypocalcemia; in all cases in which the hypocalcemia lasted more than 1 month after the intervention, the dosage of the levels of blood parathormone (PTH) and calciuria was carried out. The pathological anatomist detected the presence of parathyroid tissue on histological examination in 4 cases (all patients then norm-calcemic and none in the implant group). Convinced that one of the main factors that can affect more heavily the appearance of p.o. hypocalcemia, is the thyroid hormonal deficiency, we have adopted in the last year the rule to begin the replacement opotherapy in scalar doses with L-thyroxine since the first p.o. day. Until then, in order not to interfere with the growth of blood levels of TSH (Thyrotropin Stimulating Hormone) necessary for the diagnostic and therapeutic procedures of nuclear medicine, for any cases of incidental cancer, we started the replacement opotherapy starting 15-30 days from the intervention, having acquired the histological diagnosis and obtained a good growth of the TSH level.

The entire sample of 320 patients can therefore be subdivided, according to the extent of the demolition, to the method of opotherapy substitution with L-Thyroxine and to the radio-guided identification of the parathyroids in 4 groups:

- I group comprising 59 patients undergoing near total thyroidectomy.

- II group comprising 155 patients who underwent total thyroidectomies in which the replacement opotherapy was started from 15-30th p.o. day
- III group including 94 patients who underwent total thyroidectomy in which the replacement opotherapy was started from the first p.o. day.
- IV group comprising 12 patients who underwent total thyroidectomy in which the devascularized parathyroid gland was implanted in the homolateral sternocleidomastoid muscle.

TABLE 1 shows the distribution of the 330 cases according to the basic pathology, the type of intervention and the opotherapy method.

Results

In the first group (59 cases), regardless of the underlying pathology, however benign, the incidence of early hypocalcemia was 5 cases, equal to 8.47%, the incidence of protracted hypocalcemia was 0 cases, equal to 0%.

In the second group (155 cases) the overall incidence of early hypocalcemia was 33 cases, equal to 21.29%, the overall incidence of protracted hypocalcemia was 7 cases, equal to 4.51%. All these patients have parathormone in the low or low limits of the norm. It should be remembered however that, at least 1 case of these, presented, 10 months after the intervention, a spontaneous, as well as inexplicable, normalization of the calcemic level that remains on normal values without oral calcium support at 10 months of distance. The numerical consistency of the sample allows comparisons by age, sex, type of thyroid pathology, any associated diseases without the interference of the type of intervention and the type of replacement opotherapy.

As for age, patients can be divided into two groups > 45 years (91) <45years (64); the incidence of early hypocalcemia is respectively 26 cases equal to 28.57% and 7 cases 10.93%, significantly different between the two groups, although the incidence of protracted hypocalcemia is respectively 4 cases, equal to

4.39 % and 3 cases, equal to 4.68% with slightly appreciable difference, not significant between the two age groups.

Regarding sex, patients divided into two groups of 37 males and 118 females, present a significant difference for early hypocalcemia involving 30 cases, equal to 25.4% of females and only 3 cases, equal to 8.10 % of males, but the differences become thinner, until they become non-significant, when comparing the protracted hypocalcemia data concerning 1 male equal to 2.7% and 6 females equal to 5.08%. The comparison by type of thyroid pathology concerns:

101 cases of Multifunctional Pluri-nodular Goiter (GPN). 41 cases of Toxic Goiter (GT), including Uni-nodular Toxic Goiter, Pluri-nodular Toxic Goiter, Diffused Toxic Goiter and 13 cases of Cancer (K). The incidence of early and protracted hypocalcemia in the three classes of pathology is shown in TABLE 2.

From this it appears evident and significant a greater incidence of protracted or permanent hypocalcemia in hyperfunctioning forms and in cancers compared to the normal function forms, even if the sample's size doesn't allow strong significative considerations.

Taking into account other characteristics of the basic thyroid pathology, data on cases with mediastinal immersion were compared to those with autoimmune pathology and those related to relapse for goiter or for cancer [30]. Both these conditions appear to be characterized by a higher incidence of precocious and protracted hypocalcemia.

In the forms with mediastinal immersion, early hypocalcemia was present in 5/20 cases equal to 25.00% and protracted hypocalcemia was present in 3/20 cases equal to 15%.

In autoimmune forms (Hashimoto's Thyroiditis, Basedow) the frequency appears even greater although its significance is weakened by the numerical modesty of the sample; in fact, the incidence of premature hypocalcemia concerns 5 cases out of 12 equals to 41.66% and remains high even at a distance, when hypocalcemia still

TABLE 1. Breakdown of the 320 patients operated during the period under examination according to the basic thyroid pathology, the type of intervention and the therapeutic modalities.

	Type of Surgery	L-Tiroxina	Goiter	Cancer	Total
I Group	Near Total Thyroidectomy	15-30p.o.day	59	-	59
II Group	Total Thyroidectomy	15-30p.o.day	115	40	155
III Group	Total Thyroidectomy	1p.o. day	74	20	94
IV Group	Total Thyroidectomy and Radio guided Parathyroid Research	1p.o. day	10	2	12
Total			258	62	320

TABLE 2. Breakdown of the post-operative hypocalcemia precocious and protracted between the different types of thyroid pathology; Multifunctional Plurinodular Goiters (GPN), Toxic Goiters (GT) and Cancer (K), with their respective significance values.

	GPN		GT		K		P
	N° cases	%	N° cases	%	N° cases	%	
Early Hypocalcemia	11/101	10,89	10/41	24,39	2/13	15,38	<0,05
Protract Hypocalcemia	1/101	0,99	3/41	7,31	1/13	7,69	<0,05

affects 4 cases, equal to 33.33%.

In relapses we also observe a non-high frequency of early hypocalcemia (4 cases), equal to 8.33%, but this frequency remains high for the protracted hypoglycemia with 3 cases, equal to 6.25%.

As for the associated diseases, the only one that appeared in the sample under examination in numerical measure sufficient for a statistical analysis was diabetes with 20 cases.

The onset of early and protracted hypocalcemia in diabetic patients was not significantly different from the general trend with 5 cases out of 20 equals to 25.00% for early hypocalcemia and with 0 cases out of 20, equal to 0% for prolonged hypocalcemia.

In the third group (94 cases) the overall incidence of hypocalcemia was practically nil, with only 2 cases of early hypocalcemia, equal to 2.12% and no case of protracted hypocalcemia. The same types of thyroid pathology are present in this sample in the second group (GPN-51, GT-23, K-20, mediastinal goiter-12, autoimmune phenomena-4), although in proportionally less.

In the fourth group (12 cases of completely devascularized parathyroid gland with homolateral sternocleidomastoid muscle implantation) the overall incidence of hypocalcemia is also in the latter group, practically nil, with only 1 case of early hypocalcemia 8.33% and no case of protracted hypocalcemia. This data although promising has not yet, given the smallness of the sample, statistical validity.

Discussion

From the complex of data that emerged in our analysis, many are the elements called into question for p.o. hypocalcemia.

First of all, it is necessary to underline the really low incidence of postoperative hypoparathyroidism considering that only 4 cases out of 7 can be considered true hypoparathyroidisms based on PTH levels.

Secondly from the same consideration derives the protracted hypocalcemia (lasting more than a month) does not necessarily coincide with the p.o. hypoparathyroidism and it does not necessarily

coincide with permanent hypocalcemia, if we think of the case of spontaneous normalization that occurred 10 months after the intervention.

If we consider the extent of the surgical exeresis there is no doubt that total thyroidectomy affects the hypocalcemia, especially early, in greater measure, since in near total thyroidectomies this is practically absent.

If the sudden and complete hypothyroidism produced by total thyroidectomy is not provided early, the incidence of p.o. hypocalcemia both early and protracted obeys some of the most known pathogenic factors.

Total thyroidectomies for improper goiter show an incidence of p.o. hypocalcemia significantly higher (6.55%) than those carried out for norm-functional goiter (0.99%).

A higher incidence of hypocalcemia, above all protracted, is also prevalent prerogative of the forms of thyroid cancer (5.00%).

Even greater incidence seems to produce mediastinal immersion (15%) and the presence of autoimmune diseases (33.33%), although a more consistent numerical confirmation is required for the latter.

Likewise relapses in the measure of greater operating complexity express a discrete frequency of protracted hypocalcemia (6.25%).

The presence of associated diseases such as diabetes has been not significant.

All these differences disappear, however, when we proceed to an early correction of hypoparathyroidism induced by thyroidectomy.

The significant, almost absolute eradication of hypocalcemia, both early and prolonged in patients in the III group, shows that one of the most significant element to induce p.o. hypocalcemia is thyroid hormonal deficit.

The IV group, although the promising perspectives that open the intraoperative evaluation of parathyroid vascularization by ICG-NIR technology during thyroid surgery leaves some perplexities of interpretative character (low specificity, low positive predictive value), of technical character (lengthening of the operative time for the ident-

-ification of a devascularized parathyroid gland and unpredictable efficacy of the parathyroid muscle implant) and conceptual (parathyroids often found in the thyroid parenchyma or dislocated in the mediastinum).

Conclusion

It can be said with sufficient certainty that the incidence of p.o. hypoparathyroidism is almost exceptional in thyroid surgery even after total thyroidectomy, instead of that, the incidence of p.o. hypocalcemia is a far from rare event, of course more intense and frequent, more difficult and greater is the glandular demolition and therefore particularly evident after total thyroidectomy. The emergence of total thyroidectomy in an ever more significant proportion of benign pathology therefore requires the monitoring and correction of this occurrence, especially in the early post-operative phases. There is no doubt also that an early correction of hypothyroidism induced by total thyroidectomy drastically reduces the cases of both precocious and prolonged hypocalcemia, for which it is recommended the beginning of scalar dosing with L-thyroxine starting from the first p.o. day. The causes of those hypocalcemia that persist after months of surgery are many time multifactorial and obscure, especially when the thyroid function is steadily and definitely rebalanced and despite the PTH levels are within the limits of the norm. Their numerical consistency is however so limited, especially if the correction of hypothyroidism is precocious, not to allow a reliable statistical analysis. This occurrence, the possibility also at a spontaneous correction of hypocalcemia and the possibility of a hypocalcemia that develops even after months or years of normal calcium, impose a control of the calcemic level even after the traditional 6 p.o. months.

The surgical implantation of a complete devascularized parathyroid gland in the homolateral sternocleidomastoid muscle seems

an interesting method, not without limits and criticisms, to limit the iatrogenic impact in the determinism of post-thyroidectomy hypocalcemia, of course bigger sample and prospective studies need to achieve a significative statistical impact.

Declarations

■ Ethics approval and consent to participate

This study followed the ethical principles of the Declaration of Helsinki. Participation in the study was voluntary. Before inclusion in the study, surgical staff explained the purpose of the procedure and informed consent form was secured from each participant.

■ Consent for publication

We have had authorization for publication like our Hospital Privacy Policy already require.

■ Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

■ Competing interests

The authors declare that they have no competing interests.

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