

Hypoparathyroidism after total thyroidectomy: prospective evaluation and relation with early hypocalcemia



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AIM: Definitive hypoparathyroidism (hypo-PTH) represents one of the most dangerous complication after total thyroidectomy. Partial or total lesion or accidental removal of parathyroid glands is an unpredictable adverse event, although real incidence is not well defined, such as management of this deficit. We started a prospective evaluation of patients treated with total thyroidectomy in our centre, to identify incidence of hypo-PTH, symptomatic or not, in relation to incidence of early postoperative hypocalcemia in our experience.

METHODS: We prospectively evaluated 177 patients treated for benign and malign pathology, measuring calcium before surgery and calcium and PTH at least three months after surgery. Postoperative hypocalcemia was observed in 37.3% of cases. Eight patients (4.5% of cohort) presented low level of PTH, at mean follow-up of 9.1 months. Positive predictive value for postoperative hypocalcemia was 12.1%, while negative predictive was 95.4%; confirming high sensitivity (100%) and low specificity (65.4%) for detecting hypo-PTH.

DISCUSSION: All patients with late hypo-PTH presented hypocalcemia on early analysis, while no case with normal postoperative calcemia accounted with hypo-PTH: this may indicate calcemia as valid prognostic factor of good gland production, when is in the range. Moreover, isolated analysis is too limited to determine real predictability.

CONCLUSION: Technical standardization represents the best method for prevention of hypo-PTH. Early hypocalcemia is a prognostic factor, even with a low specificity, of deficit of PTH-production. This observation must be related to other known prognostic factors. Postoperative normal calcemia should be a positive prognostic factor of an acceptable PTH-function, supported by large cohorts.

KEY WORDS: Hypocalcemia, Parathormone, Thyroidectomy

Introduction

Technical evolution and improvement of standardization have determined safety and low rate of complication after

total thyroidectomy (TT), mostly in referred centres for endocrine surgery¹. However, a group of postoperative complications can lead to severe and definitive multiorgan deficiency, or chronic conditions². Of these, definitive hypoparathyroidism (hypo-PTH) represents one of the most dangerous, and often unforeseen, because of damage related to chronically induced hypocalcemia (bone reabsorption, kidney stones, renal failure) and of acute conditions (cardiologic and neuromuscular symptoms)³. Partial or total lesion or accidental removal of parathyroid glands is an unpredictable adverse event,

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relating either to anatomical condition, either to technical problem in localization and preservation of all glands^{4,5}.

A lot of publications analysed this complication, also on large groups, searching for risk factors and early therapy used for an adequate retake of residual parathyroid tissue^{6,7}. Real incidence of definitive hypo-PTH is not well defined; similarly, a standardized therapeutic scheme for treating this deficit is lacking⁸. Many authors mostly take account to postoperative hypocalcemia, mistaking the real incidence of PTH deficiency with a transient function impairment. In addition, timing of measurement of serum iPTH (intact PTH) is variable among different studies, confusing a postoperative stupor (quite frequent) with a real damage of glands⁹.

On this basis, we started a prospective study on a group of patients treated with TT during the first months of 2013, in a high-volume centre, to identify the true incidence of post-TT hypo-PTH, treated with standardized protocol, focusing on immediate onset of postoperative hypocalcemia.

Aims of our study were a fair assessment of the incidence of this complication, and of the meaning of serum calcium and late serum iPTH assays, in relation with other parameters, after TT, to predict the real risk of late gland hypofunction, also in relation to a high technical standardization realized in our centre of reference.

Material and Methods

We prospectively evaluated patients treated with TT for benign and malign pathology from January to July 2013. All patients were enrolled after multidisciplinary evaluation, in relation to failure of medical therapy and of symptoms, for benign pathology, or to high neoplastic suspicion. Laboratory evaluation also included dosage of serum iPTH, calcium, phosphor, and renal function parameters (urea and creatinine). After surgery, dosage of serum calcium on first postoperative day, histological evaluation of gland, need for lymphadenectomy, and rate of early (within 30 days from surgery) and late (above 30 days from surgery) complications were considered for statistical relation with hypo-PTH. From four to six months from surgery calcium metabolism was evaluated, adding also dosage of iPTH. Lesser range for calcium was considered 8 mg/dl, while for iPTH was 4 pg/ml. In all cases of hypocalcemia, we used a standardized protocol for replacement, for symptomatic and asymptomatic cases. Long-time replacing therapy was subsequently adjusted and tailored by endocrinologists.

We included in late evaluation, at last follow-up, level of iPTH and, in case with persistent hypocalcemia, a report of symptoms. We compared postoperative hypocalcemia to late hypo-PTH; these cases were also compared to histological and anthropometric parameters.

Incidence of hypocalcemia and hypo-PTH were statisti-

cally compared with t-student test and singularly compared with anthropometric and postoperative data. A $p < 0.05$ was used as significance level. Postoperative hypocalcemia was then analysed as predictive test for hypo-PTH.

Results

A total of 177 patients submitted to TT were enrolled among considered period (January 2013 - July 2013). Anthropometric and operative data are synthetized in Table I. No case of renal failure, nor preoperative deficit of PTH, was observed in our cohort. Anthropometric and operative data are synthesized in Table I. Total extracapsular thyroidectomy is a standardized procedure¹, such as in our Surgical Unit, with a significant reduction of operative time, compared with oldest resections: first, after ligation of superior vascular pedicle, we identify and isolate recurrent nerve and parathyroid glands in usual position, advantaged by enucleation of lobe; then, we complete lobar resection with ligation of inferior vascular pedicle and section of thyrotracheal ligaments. Same passages were performed on the other side. In all cases searching for parathyroid glands was basilar before enucleation of each lobe.

Analysed cases did not presented major intraoperative complications; no reoperation was performed. Metallic stitches, for skin closure, and drain were removed on first postoperative day, in all cases, except for 5 patients, in which stitch removal was completed on second postoperative day. Main hospital stay resulted of 1.18 days (range 1-4 days). Hormonal therapy, with 50 mcg of Levo-thyroxine, was started at morning of first postoperative day: dosage was modified after three weeks by endocrinologist, in relation to serum analyses and to neoplastic findings. Mean follow-up of entire cohort was 10.4 months (range 7-13 months). No patient was lost to follow-up.

Considering minor complications, a subcutaneous or deep seromas was observed in 15 cases (8.4%), under skin incision, up to 15 ml, treated with conservative approach. In two cases (1.1%) a unilateral deficit of recurrent nerve was observed, progressively solved with medical therapy and rehabilitation.

Histological examination revealed malignancy in 19 cases (10.7% of cohort), 13 of whom were papillary and 6 follicular neoplasms; other 158 patients (89.3% of cohort) presented a multinodular goitre or an adenomatous lesion. Lymphadenectomy associated to TT was completed in 13 patients (7.3%).

Mean postoperative serum calcium were 8.4 mg/dl (range: 6.5 - 9.1). Comprehensive data of serum calcium at 4-6 months of follow-up are exposed in Table I. Postoperative hypocalcemia was observed in 66 patients (37.3% of entire cohort), with a mean value of 7.2 mg/dl (range: 6.5-7.9). Symptoms, consisting of paresthesia,

TABLE I - Analysis of cases with permanent hypoparathyroidism

	Sex	Age (years)	PTHi (pg/ml)	Follow-up (months)	Symptoms	Post-surgery calcaemia (1 st day; mg/dl)	Oral supplementation/die
P.R.	F	42	9.0	7	Yes	7.7	1000 mg calcium carbonate 0.5 mcg calcitriol
D.B.D.	F	48	8.5	7	No	7.2	3000 mg calcium carbonate 0.5 mcg calcitriol
Z.M.D.	F	62	6.7	8	No	6.7	2000 mg calcium carbonate 0.5 mcg calcitriol
T.A.	F	50	8.4	8	No	7.2	1000 mg calcium carbonate 0.25 mcg calcitriol
N.C.	F	32	7.4	9	Yes	6.9	2000 mg calcium carbonate
P.G.	F	68	3.0	10	No	7.3	1000 mg calcium carbonate 0.5 mcg calcitriol
L.R.	F	66	6.5	11	Yes	7.0	0.5 mcg calcitriol
B.E.	M	44	7.0	13	No	7.8	1000 mg calcium carbonate 0.5 mcg calcitriol
Media		51.5	7.1	9.1	3/8 cases	7.2	

tetania and Chvostek sign, were observed in about one third of cases (Table II). A standard protocol was adopted for patients with hypocalcemia: oral assumption of 3000 mg/24 hour of calcium carbonate combined with calcitriol (dosage of 0.5 mcg for die), for asymptomatic cases; intravenous infusion of calcium gluconate in 10% solution, equivalent to 5640 mg of calcium gluconate every 24 hours, until to the resolution of symptoms, for symptomatic cases. All patients were discharged with recovery of parameters, according to the international protocol, adding replacing tailored domiciliary therapy. Oral replacing therapy was maintained in 10 cases, at last follow-up, because of persistent hypocalcemia, with or without symptoms. Eight patients (4.5% of entire cohort) presented low level of serum iPTH (see Table II), at mean follow-up of 9.1 months (range 7-13), considered definitive hypo-PTH cases: three of these presented related symptoms when suspending oral supplementation. Long-term oral therapy was variable among patients, according to response to dosage and to severity of symptoms, different for metabolic response and individual variation.

In hypo-PTH group, a prevalence of female was observed (M/F: 1/7), similarly to entire cohort. All cases of hypo-PTH presented hypocalcemia on postoperative analysis, while in no patient with early normal serum calcium appeared deficit of iPTH. Histological examination of hypo-PTH cases identified a patient with papillary cancer, submitted to TT with central lymphadenectomy and subsequent radiometabolic therapy. Other cases presented a benign or adenomatous goiter. No significant relation with a specific histological result, neither association with perioperative complication, neither with lymphadenectomy, was observed ($p = ns$).

Positive predictive value for postoperative hypocalcemia was 12.1%, while negative predictive value was 95.4%; this parameter presented a high sensitivity (100%) and low specificity (65.4%) for detecting definitive hypo-PTH.

Discussion

A lot of studies evaluated calcium metabolism and analysis of PTH after TT; minority of them considered early parameters with long-term results of PTH secretion^{5,7,10}. Our prospective evaluation specifically led to a real and accountable incidence of permanent hypo-PTH after TT (4.% of our cohort): this value is variable in literature from 0.5% to 15% of surgical cohorts^{3,4,11}. While transitory hypo-PTH may be considered a minor complication, observed from 8 to 51% of cases, because of low risk of sever organ damage, definitive hypo-PTH is a real major complication of neck surgery, even if manageable with medical therapy. A correct diagnosis of definitive hypo-PTH must necessarily be confirmed by evaluation of serum iPTH, that stabilizes 5-6 months after surgery^{9,12}. Renal (nephrolitiasis) and bone (osteolysis, reabsorption) alterations, during chronic replacing treatment for hypocalcemia, and cardiologic acute syndrome, for transitory severe hypocalcemia, are reported^{3,13}. Searching for predictive factors and pathological findings are priorities for surgical groups, accounting for clinical evolution^{2,14}. Confirmed risk factors for definitive hypo-PTH are actually previous neck radiotherapy, and congenital absence of part or all glands^{7,11}. The most important mechanism for surgical injury of glands is consequent to arterial or venous vessel section,

with ischaemia or congestion, and oedema on tissue ^{4,14}; anyway, these alterations are frequently reversible, as demonstrated from studies on transplant of parathyroids glands on lateral region of neck, with a good restoration of PTH-secretion at six months ¹⁵.

Technical standardization and high-volume activity of referred endocrinosurgery unit, led to significant reduction of risk and detection of high-risk population ^{9,11,16}. A nearly linear relation between number of surgical procedure and complication rate has been demonstrated ¹⁷. Referring to surgical technique, indentifying all parathyroid glands is an established point in thyroidal surgery, finding them at bifurcation of superior and inferior vessels, on posterior plan ². Technically, distal ligation of inferior thyroidal vessels, without manipulation of principal trunk, seems to be associated with better trend of calcium metabolism ¹⁸, due to vascular inflow on principal parathyroids glands, located at inferior pole. Moreover, no specific technical difference for late hypo-PTH has been observed.

Despite this accuracy, deficit of gland function is possible, and often unpredictable ¹⁹. In order to excluding cases of preexistent reduction for PTH production, evaluation of calcium balance is mandatory in preoperative phase ²⁰.

Early dosage of iPTH has been considered for predicting definitive gland lesion, such as demonstrated by some authors^{21,22}; moreover, this analysis may be influenced by other factors (such as low levels of vitamin D and use of oral calcium supplements) ²³⁻²⁵. Post-TT PTH levels accurately predict hypocalcemia, but lack 100% accuracy, mostly regarding definitive hypo-PTH: absolute relation of this analysis with definitive hypo-PTH is not confirmed by all authors²⁶. Neither intraoperative evaluation reported a good sensitivity for PTH production, while its use is confirmed for surgical treatment of hyper-PTH ²⁷. Better evaluation seems to be the trend analysis of iPTH during months (mostly at one-months follow-up), also if no valid cut-off has been established ^{28,29}. Conversely, we observed, during years, a strict relation between early hypocalcemia, mostly symptomatic, and lack of recovery of PTH function. For this reason, we analysed only hypocalcemia in order to evaluating its predictability on PTH function. Postoperative hypocalcemia after TT, with transient or definitive hypo-PTH, in literature is 5-45% ^{7,9}; symptoms are present in less than half of cases. A lot of authors doubted on predictability of this factor, as isolated parameter ¹⁹, because postoperative examination may be influenced by many variables. Some endocrinologists evaluated only symptomatic hypocalcemia such as authentic predictors of late deficit of PTH ³⁰.

In our report, all patients with late definitive hypo-PTH presented with hypocalcemia on first postoperative day, while no case with normal postoperative serum calcium accounted with hypo-PTH; statistical analysis confirmed high sensitivity of hypocalcemia for gland lesion, and

high negative predictive value. Moreover, isolated analysis is too limited to determine real predictability: other parameters, such as functional or central lymphadenectomy associated with TT, neck reoperation or preoperative deficit of vitamin D related, are stronger predictors of definitive hypo-PTH and therefore should be combined with serum calcium dosage ^{26,31}. Conversely, early hypocalcemia, high indicative for hypo-PTH, may suggest gland traumatism (of different kind, from *stupor* to tissue damage, or to ischaemia). In our experience, about one third of cases of hypocalcemia presented symptoms (paresthesia, Chvostek sign, torpor): moreover, symptoms were not associated with a higher risk of hypo-PTH. Different mechanisms should be related to a different sensitivity to hypocalcemia or to metabolic compensation ^{5,19}. For this reason, asymptomatic cases with normal serum calcium can present low iPTH levels, while, conversely, severe hypocalcemia may present only with transitory reduction in PTH secretion, with normal serum iPTH. One can assume that many factors contribute to symptoms and serum fluctuation.

Our analysis of postoperative supplementation revealed, in the group with early hypocalcemia, a progressive reduction for oral calcium and vitamin D with progression of follow-up; this may be explained with gradual resolution of stupor of parathyroidal tissue, that represents the pathological finding in the majority of PTH deficit with recovery of function.

A lot of supportive scheme after thyroidal resection has been proposed, in order to reducing risk of acute hypocalcemia and encouraging production of residual glands. On this trend, many authors proposed an aggressive treatment for post-TT hypocalcemia, without obtaining significant amelioration of PTH-secretion and incidence of complication, but adding costs and risk of multiorgan calcium deposition ³. In absence of symptoms, stimulation on PTH-secretion may be supported by low levels of serum calcium, one of the strongest factors for PTH-production: for this reason a targeted and monitored replacing therapy should be encouraged ¹¹. Our postoperative protocol, adopted by international referred centers ^{12,32}, led to a reduction to minimum of acute complications, favouring also a good PTH-secretion.

Conclusion

Permanent hypo-PTH is a high-risk and underestimated condition, also after standardized surgery. Early hypocalcemia has a prognostic value for hypo-PTH, even with a low specificity. This observation must be necessarily related to other known prognostic factors and eventually to intraoperative finding of serum iPTH. However, value of postoperative normal calcemia should be a positive prognostic factor of an acceptable parathyroidal function, supported by large cohorts. Adjustment of replacing therapy must be tailored, because response to

therapy and function recovery are variable: postoperative hypocalcemia and, if confirmed, PTH trend can be used to stratify risk for developing definitive hypo-PTH.

Riassunto

L'ipoparatiroidismo definitivo (ipo-PTH) rappresenta una delle complicanze più pericolose dopo tiroidectomia totale. La lesione parziale o totale o l'eliminazione accidentale delle ghiandole paratiroidi è un evento avverso imprevedibile, anche se la sua reale incidenza non è ben definita, come pure il trattamento di questa problematica. Abbiamo dunque programmato una valutazione prospettica dei nostri pazienti trattati con tiroidectomia totale nel nostro centro, per identificare l'incidenza di ipoparatiroidismo, sintomatico o asintomatico, in relazione all'incidenza dell'ipocalcemia postoperatoria precoce nella nostra esperienza.

Lo studio è stato di tipo prospettico su 177 pazienti operati alla tiroide per patologia benigna e maligna, dosando il calcio ematico subito prima dell'intervento chirurgico e del calcio e del PTH almeno tre mesi dopo l'intervento. L'ipocalcemia postoperatoria è stata osservata nel 37,3% dei casi. Otto pazienti (4,5% di coorte) hanno presentato bassi livelli di PTH in un follow-up medio di 9,1 mesi. Valore predittivo positivo dell'ipocalcemia postoperatoria è stata del 12,1%, mentre predittivo negativo era del 95,4, confermando alta sensibilità (100%) e bassa specificità (65,4%) per rilevare un ipo-PTH.

Tutti i pazienti con ipo-PTH tardivo presentavano ipocalcemia all'analisi precoce, mentre nessun caso con normale calcemia postoperatoria ha sviluppato un ipo-PTH: questo dato potrebbe suggerire la calcemia postoperatoria come valido fattore prognostico del funzionamento delle paratiroidi quando si presenta nell'intervallo normale. Peraltro il suo dosaggio isolato è troppo limitato per costituire una reale prevedibilità.

In conclusione la standardizzazione della tecnica chirurgica rappresenta il metodo migliore per la prevenzione dell'ipo-PTH. La ipocalcemia precoce postoperatoria rappresenta un fattore prognostico, anche se con bassa specificità, di un deficit di produzione del PTH. Questa osservazione deve essere considerata insieme ad altri fattori prognostici noti.

La calcemia postoperatoria, se normale, potrebbe essere considerata un fattore prognostico positivo di una accettabile funzione postoperatoria delle paratiroidi, se confermata da ampie casistiche.

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