

# Post-thyroidectomy hypocalcemic syndrome: predictive value of early PTH.

## Preliminary results



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### Post-thyroidectomy hypocalcemic syndrome: predictive value of early PTH. Preliminary results

*AIM: The aim of this study is to determine an early measured serum PTH cut-off value below which it is possible to predict post-thyroidectomy hypocalcaemia outbreak.*

*MATERIALS OF STUDY: Ninety-three consecutive patients having a benign thyroid pathology were submitted to total thyroidectomy. In all the patients serum post-surgery intact PTH and total calcium were measured within an hour from weaning. 65 patients were measured a second time 18 hours from surgery.*

*We searched for a correlation between the post-surgery PTH values at 1 and 18 hours from surgery with the calcemia at 1 and 18 hours from surgery. We carried out a one-year follow-up for each patient. Hypocalcemia developed in 26 patients (27.95%). It was transitory in twenty-two patients (23.65%) and permanent in 4 patients (4.3%).*

*No correlation was found between PTH1 and Ca1 ( $p=0.8$ ). Statistically relevant correlation ( $p=0.008$ ) was found between PTH1 and Ca2. The correlation between PTH2 and Ca2 ( $p=0.001$ ) turns out to be even more relevant.*

*We also calculated a found that 9.5 pg/dl was PTH1 cut-off value below which it is possible to predict hypocalcemia onset ( $p=0.001$ ).*

*DISCUSSION AND CONCLUSIONS: Early post-surgery PTH measuring is a highly predictive test of post-surgery hypocalcemia. We identified a PTH1 cut-off value of 9.5 pg/dl, below which hypocalcemia onset is extremely frequent.*

*This assessment permits us to establish an adequate drug prophylaxis, thus avoiding the related symptoms. We can also perform one-day surgery thyroidectomy in patients showing normal PTH values.*

**KEY WORDS:** Hypocalcemia, PTH, Thyroidectomy.

### Introduction

The most common cause for secondary hypocalcemia is thyroidectomy. Predisposing factors to post-thyroidectomy hypocalcemia are surgery extent (sub-total or total thyroidectomy compared to lobectomy) and thyroid pathology (thyrotoxicosis, carcinoma, thyroiditis).

Post-surgery hypocalcemia is a common and often transitory event, incidental to thyroid or parathyroid surgery, determined by a iatrogenic damage on the parathyroid glands and resulting in transitory or permanent hypoparathyroidism<sup>1</sup>. International literature reports highly variable transitory hypocalcemia incidence, between 54% and 38%, and permanent hypocalcemia between 0.5% and 2% (Tab. I).

We distinguish a symptomatic hypocalcemia, with extremities and peribuccal paresthesias until tetanus crisis together with pain, neurological symptoms and at times cardiac arrhythmia at 24-48 hours from surgery, and an asymptomatic hypocalcemia.

The definition of reference parameters that may have a

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TABELLA I - Hypocalcemia incidence in literature.

Author	Transient hypocalcaemia %	Permanent hypocalcaemia %
Pattou (1998)	5.4	0.5
Delbridge (2003)	-	1-2
Rosato (2004)	8.3	1.7
Pisanu (2005)	9.7	0.7
McLeod (2006)	25	-
Stanley (2006)	22	-
Lombardi (2006)	38	0.9
Sywak (2007)	18	-
Asari (2008)	24	1.7
Vaiman (2008)	-	2

predictive value for hypocalcemia onset, would permit an adequate drug treatment, avoiding clinical symptoms hypocalcemia.

The aim of this study was to determine an early measured serum PTH cut-off value below which it would be possible to predict hypocalcemia outbreak.

### Materials and methods

Ninety-three consecutive patients having a non-flogistic benign thyroid pathology (17 M and 76 F), in state of euthyroidism, were submitted to total thyroidectomy by the same surgical team. In all the patients serum post-surgery intact PTH and total calcium were measured within an hour from weaning. 65 patients were measured a second time 18 hours from surgery.

We defined as hypocalcemia a total calcium inferior to 8 mg/dl in at least one drawing. Less than six-month-long hypocalcemia were defined as transitory and the longer ones as permanent. The normal PTH values, measured with Hitachi/Modular DPE SWA (Roche Diagnostic, Mannheim, Germany) set, fall within a range between 10 and 65 pg/ml.

### STATISTICS.

We submitted this data to statistical inference, searching for a correlation between the post-surgery PTH values at 1 and 18 hours from surgery with the calcium at 1 and 18 hours from surgery (respectively PTH1-PTH2 and Ca1-Ca2). To study early PTH and calcium as predictors of hypocalcemia, we used Receiving Operator Curves and calculated area under the curve.

We carried out a one-year follow-up for each patient.

### Results

Hypocalcemia developed in 26 patients (27.95%). It was transitory in twenty-two patients (23.65%), being 88.4% of the cases, and permanent in 4 patients (4.3%).

In male patients the hypocalcemia incidence was of 17.6% (3 patients), nearly half compared to female patients, who had the incidence of 30.2% (23 patients). No correlation was found between PTH1 and Ca1 ( $p=0.8$ ) (Tab. II). Statistically relevant correlation ( $p=0.008$ ) was found between PTH1 and Ca2 (Tab. III). The correlation between PTH2 and Ca2 ( $p=0.001$ ) (Tab. IV) turns out to be even more relevant.

Early serum PTH measuring was proved of high sensibility and specificity with a positive predictive value of 95.24% and a negative predictive value of 98.61%.

This data has been further elaborated through ROC curves (Receiver Operating Characteristics) to calculate a

TABELLA II - Correlation between PTH1 and Ca1.

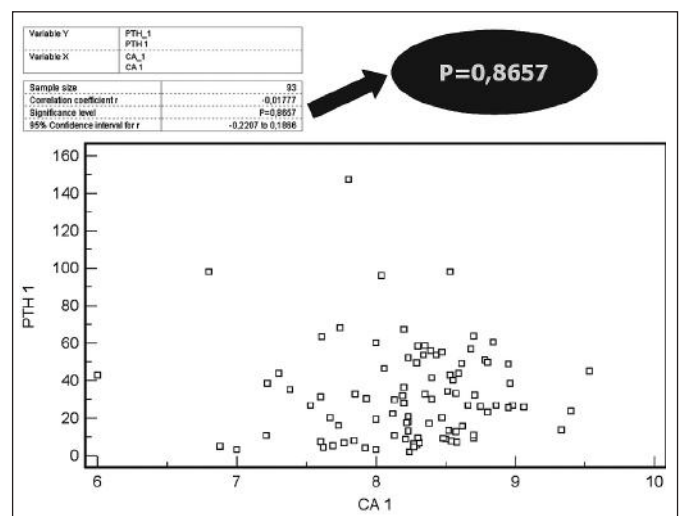


TABELLA III - Correlation between PTH1 and Ca2.

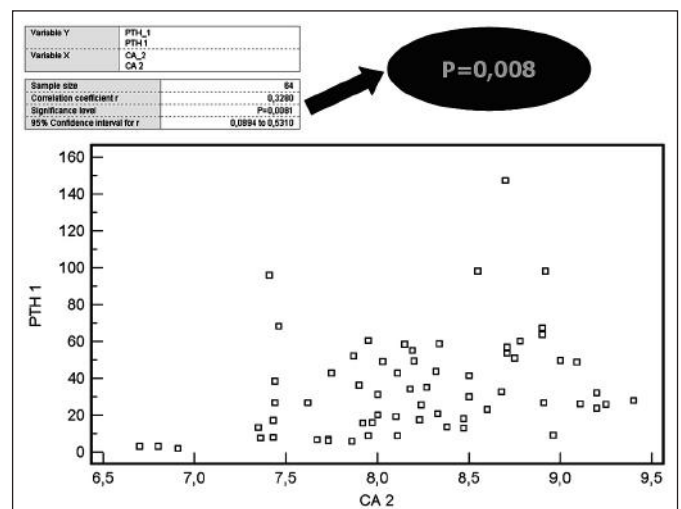


TABELLA IV - Correlation between PTH2 and Ca2.

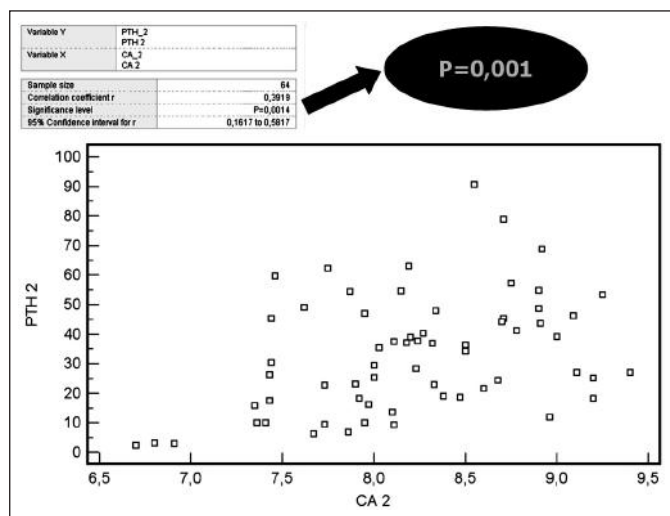
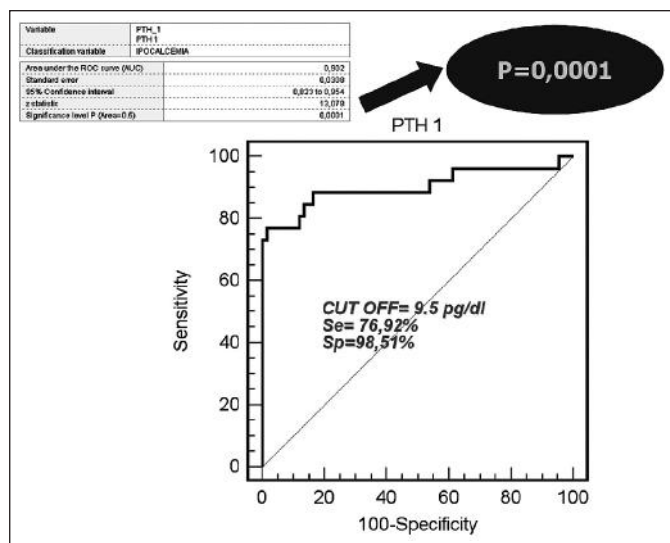


TABELLA V - PTH1 cut-off highly predictive of hypocalcaemia.



PTH1 cut-off value below which it would be possible to predict hypocalcemia onset with good approximation. The value showing the best performance on ROC curves turned out to be 9.5 pg/dl (p=0.001) with a sensibility of 76.92% and specificity of 98.52%. A comparison of PTH1 and PTH2 curves showed the two tests are relatively superimposable (p=0.2) (Tab. V).

## Discussion

The cause of incidental hypocalcemia after thyroid surgery can be manifold. It could be caused by hypoparathyroidism (transitory or permanent) due to iatrogenic damage of one or more parathyroids, stroke, accidental removal of one or more parathyroids during surgery or excessive skeletal requirement (osteodistrophy from thyrotoxicosis) 3-5.

The risk factors that can provoke accidental removal of one or more parathyroids are bilateral resection instead of unilateral one, and malignant pathology due to the higher parathyroid lesion risk during lincectomy 8. The age seems not to affect hypocalcemia onset 8.

A meticulous dissection and the surgeon's experience are risk reducing factors regarding post-thyroidectomy hypocalcemia complications 1,7.

The different rate of hypocalcemia in literature can be correlated to several factors. First, the preventive administration of calcium and vitamin D masks the real hypocalcemia incidence. Second, an actual total thyroidectomy exposes to a higher hypocalcemia risk than a near-total one which saves the small parenchymal rests near the parathyroid glands.

A PTH deficit implies a hypocalcemia due to reduction of osteoclastic bone reabsorption, of kidney calcium reabsorption and of bowel calcium absorption.

Serous calcium may get normal from some days up to some weeks after surgery, with spontaneous re-establishment of parathyroidal function (transitory hypocalcemia); in case the hypocalcemia persists for more than six months, it is configured as persistent hypocalcemia 2.

When hypocalcemia is severe, it can provoke serious complications and evident clinical symptoms that at times require administration of intravenous calcium gluconate therapy. Hypocalcemia may protract the hospital-stay and require a larger number of blood tests.

Our study has highlighted a particular utility of the early PTH (PTH1) assessment.

The utility of early post-surgery PTH (PTH1) measuring consists in predicting the hypocalcemia risk and consequently in establishing of an adequate drug prophylaxis to avoid onset of correlated symptoms (hypocalcemic syndrome). Furthermore, we can safely discharge patients in the first post-surgery day, thus performing a one-day surgery. To all the patients with total calcemia values below 8 mg/dl with or without symptoms, we carried out a supporting drug therapy at first instance parenteral (calcium gluconate) and oral (calcium carbonate), the latter always together with D3 vitamin, at second instance. In fact, PTH is immediately affected by surgical trauma, but it requires several hours to determine a calcemia fall. Therefore, this latter cannot be used as an early marker.

We demonstrated that hypocalcemia comes about more frequently in patients whose PTH is inferior to 9.5 pg/dl, the cut-off value emerging from our study.

To this purpose, in patients with PTH inferior to 10 pg/dl we administered calcium gluconate on the surgery day and calcium and vitamin D3 orally from the first post-surgery day until calcemia normalization.

Being the hypoparathyroidism drug therapy not always without problems, it is more rational, when possible, to prevent its onset not only by means of a more accurate surgery technique but also, when needed, with help of parathyroidal autograft in case of accidental or forced

ablation (subcapsular location) of the parathyroid/s or in presence of their trophic disorder.

In conclusion, we demonstrated that early post-surgery PTH measuring (an hour after surgery) is a highly predictive test of post-surgery hypocalcemia. In our limited sample, we identified a PTH1 cut-off value of 9.5 pg/dl, below which hypocalcemia onset is extremely frequent. This assessment permits us to establish, before the hypocalcemia onset, an adequate drug prophylaxis, thus avoiding the onset of unpleasant and at times risky correlated symptoms. We can also perform one-day surgery thyroidectomy in patients showing normal PTH values.

### Riassunto

La causa più frequente di ipocalcemia secondaria è quella conseguente a tiroidectomia. Fattori predisponenti sono l'estensione dell'intervento e la patologia tiroidea di base.

L'ipocalcemia postoperatoria è una conseguenza comune e spesso transitoria della chirurgia tiroidea e paratiroidea, determinata da un deficit iatrogeno delle ghiandole paratiroidi con conseguente ipoparatiroidismo transitorio o permanente. Le casistiche mondiali riportano incidenze di ipocalcemia transitoria molto variabili (da 5,4 a 38%) e di ipocalcemia definitiva comprese tra 0,5 e 2%.

Distinguiamo una ipocalcemia sintomatica, con insorgenza di parestesie alle estremità e peribuccali fino alla crisi tetanica accompagnata da dolori, sintomi neurologici e, talvolta, da aritmie cardiache, a 24-48 ore dall'intervento ed una ipocalcemia asintomatica, che consiste nel solo riscontro di calcemia totale < 8 mg/dl.

La definizione di parametri di riferimento che possono avere valore predittivo per la comparsa di ipocalcemia permetterebbe un trattamento farmacologico adeguato, evitando così le manifestazioni cliniche della ipocalcemia.

Questo studio è stato eseguito per determinare un *cut-off* di PTH sierico dosato precocemente al di sotto del quale sia possibile prevedere la comparsa di ipocalcemia. Novantatre pazienti consecutivi affetti da patologia tiroidea benigna non flogistica (17 M e 76 F), in stato di eutiroidismo, sono stati sottoposti a tiroidectomia totale nella stessa struttura e dalla stessa equipe operatoria. In tutti i pazienti è stato eseguito il dosaggio postoperatorio sierico di PTH intatto e calcio totale. In 65 pazienti è stato eseguito anche un secondo dosaggio 18 ore dopo l'intervento.

Abbiamo definito ipocalcemia il riscontro di una calcemia totale inferiore a 8 mg/dl in almeno un prelievo. È stata definita transitoria una ipocalcemia di durata inferiore a sei mesi e definitiva una ipocalcemia di durata superiore. Abbiamo eseguito un follow-up della durata di un anno per ciascun paziente.

L'ipocalcemia si è sviluppata in 26 pazienti (27,95%). Questa è stata di tipo transitorio in ventidue pazienti

(23,65%), costituendo l'88,4% delle ipocalcemie, e definitiva in 4 pazienti (4,3%).

Negli uomini l'incidenza di ipocalcemia è stata del 17,6%, quasi la metà rispetto alle donne; in queste ultime l'incidenza è stata del 30,2%.

Abbiamo ricercato una correlazione tra valori di PTH postoperatorio ad 1 e 18 ore con la calcemia ad 1 e 18 ore dall'intervento (rispettivamente PTH1-PTH2 e Ca1-Ca2). Tale correlazione non esiste tra PTH1 e Ca1 ( $p=0,8$ ), poiché il PTH risente precocemente dell'insulto chirurgico, ma determina riduzione della calcemia solo dopo alcune ore dall'intervento chirurgico. Esiste invece una correlazione statisticamente significativa ( $p=0,008$ ) tra il PTH1 e la seconda calcemia (Ca2). Ancor più significativa risulta la correlazione tra PTH2 e Ca2 ( $p=0,001$ ).

Il dosaggio precoce del PTH serico si è dimostrato altamente sensibile e specifico con un valore predittivo positivo di 95,24% ed un valore predittivo negativo di 98,61%.

Tali dati sono stati ulteriormente elaborati mediante l'utilizzo di ROC *curves* al fine di calcolare un *cut-off* di PTH1 al di sotto del quale si possa prevedere con buona approssimazione la comparsa di ipocalcemia. Tale valore è risultato pari a 9,5 pg/dl ( $p=0,001$ ).

A tutti i pazienti con valori di calcemia totale (Ca1 o Ca2) inferiori a 8 mg/dl con o senza sintomatologia abbiamo somministrato una terapia farmacologica di supporto.

Le cause di ipocalcemia secondaria ad intervento di tiroidectomia possono essere multifattoriali. Essa potrebbe essere dovuta ad un ipoparatiroidismo (transitorio o permanente) risultato dal danno iatrogeno di una o più ghiandole paratiroidi, da ischemia, o asportazione accidentale di una o più paratiroidi durante l'intervento chirurgico, o da eccessivo fabbisogno scheletrico (osteodistrofia da tireotossicosi).

I fattori di rischio sono la resezione bilaterale e la patologia maligna in virtù del maggior rischio di lesione paratiroidea in corso di linfectomia. L'età non sembra influenzare l'insorgenza di ipocalcemia.

Una dissezione meticolosa e l'esperienza del chirurgo sono fattori che riducono lo sviluppo di complicanze da ipocalcemia post-tiroidectomia.

Il riscontro di una incidenza di ipoparatiroidismo variabile nelle diverse casistiche può essere correlabile a più fattori come la somministrazione profilattica di calcio e vitamina D ed una tiroidectomia realmente totale che è a maggior rischio di complicanza ipocalcemia rispetto ad una near-total.

Il calcio sierico si può normalizzare da pochi giorni a qualche settimana dopo l'intervento chirurgico (ipocalcemia transitoria); quando l'ipocalcemia persiste per più di sei mesi, si parla di ipocalcemia persistente.

L'ipocalcemia severa può provocare serie complicanze e una sintomatologia manifesta che necessita la somministrazione di calcio gluconato e.v. prolungando la degenza.

L'utilità del dosaggio precoce del PTH post-operatorio (PTH1) consiste nel prevedere il rischio di insorgenza di ipocalcemia e di instaurare una profilassi farmacologica adeguata. Il PTH, infatti, risente immediatamente del trauma chirurgico, ma necessita di diverse ore per determinare una riduzione consensuale della calcemia. Quest'ultima non può essere, pertanto, utilizzata come marcatore precoce.

Abbiamo dimostrato che l'ipocalcemia si istaura più frequentemente nei pazienti con valori di PTH inferiori a 9,5 pg/dl, *cut-off* emerso dal nostro studio.

È bene, dunque, quando possibile, prevenire l'insorgenza di ipocalcemia mediante un'accurata tecnica chirurgica, ma anche con l'ausilio di autoinnesto paratiroideo in caso di ablazione accidentale od obbligata di paratiroide/i od in presenza di loro turba trofica.

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