The magnesium role in the post-thyroidectomy hypoparathyroidism

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The Authors take as a starting point their previous study ("Hypocaleemia and hypoparathyroidism after total thyroidectomy: a clinical biological study and surgical considerations"), in which they examined serum calcium and phosphorous levels variations after total thyroidectomy in two patients groups (one of control). In this study they examine the magnesium possible role in hypocaleemia. They conclude that post-thyroidectomy hypocalcemia certainly has a multifactorial etiology and underline as symptomatic patients often present a contemporaneous calcium and magnesium decrease. Besides they observe that clinical signs persist in several cases when the hypocalcemia only is treated, whereas they regress before when both ions calcium and magnesium, are treated. The authors conclude that it may be difficult attribute the hypocalcemia signs to deficiency of one both these ions at times, but the postoperative hypomagnesemia must be considered in every case of neuromuscular hyperexcitability not differently justifiable, especially if it is associated with cardiac arrhythmias and hydroelectrolytic balance alterations.

KEY WORDS: Hypocalcemia - Hypomagnesemia - Hypoparathyroidism - Thyroidectomy.

Hypocalcemia is a frequent complication of total thyroidectomy, due to injury to the parathyroid glands. This study is based on a previous scientific article made at the Endocrine Surgery Department of the Messina Polyclinic Hospital, called "Hypocaleemia and hypoparathyroidism after total thyroidectomy: a clinical biological study and surgical considerations".

In that paper, we examined the serum calcium and phosphorous levels variations in 312 patients undergone total thyroidectomy (TT); these biological parameters were compared to those of 100 patients who underwent extrathyroid surgery (control group).

This analysis made possible to distinguish the transient post-operative hypocalcemia without any clinical sign, due to haemodilution, from that due to postoperative hypoparathyroidism after total thyroidectomy.

Our protocol included magnesium dosage as well, with the aim of examining the magnesium possible role in post-thyroidectomy hypocalcemia.

Materials and methods

Patients

Our study was carried out in 905 patients, 784 females (86.6%) and 121 males (13.4%), whose age ranged between 21 and 77 years, median age 49.25 ± 20.13, undergone total thyroidectomy (TT) for thyroid pathologies (Tabella I) and in a control group of 300 patients, 216 females (72%) and 84 males (28%), whose age ranged between 22 and 78 years, median age 53.66 ± 19.8 years, undergone extrathyroid surgery under general anaesthesia.

All patients were operated by the same surgeon from 1997 to 2004.

The two groups were homogeneous with regard to age, weight, height and duration of operation.

Their characteristics were reported in Table II.

Statistical analysis

Data were represented as average and average's standard error.

Methods

Euthyroid patients with benign thyroidopathies only were included in this study, because thyroid hormones influence parathyroid metabolism and the operations for neoplastic pathology are more difficult and more radical.

Patients with factors affecting their serum calcium or magnesium levels were excluded, particularly:

- patients undergone treatment interfering with calcium (calcium-antagonist, thiazides, calcitonin, vitamin D, steroid
TABLE I.—Thyroid pathologies undergone total thyroidectomy at the Endocrine surgery Department of the Messina Polyclinic Hospital (1997-2004).

<table>
<thead>
<tr>
<th>Thyroids</th>
<th>N.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euthyroid multinodular goiter</td>
<td>389</td>
</tr>
<tr>
<td>Adenomatous goiter</td>
<td>136</td>
</tr>
<tr>
<td>Hyperthyroid multinodular goiter</td>
<td>12</td>
</tr>
<tr>
<td>Hyperthyroid adenoma with Plummer disease</td>
<td>102</td>
</tr>
<tr>
<td>Basedow disease</td>
<td>10</td>
</tr>
<tr>
<td>Recurrent goiter</td>
<td>18</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>48</td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>57</td>
</tr>
<tr>
<td>Follicular carcinoma</td>
<td>60</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>12</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>6</td>
</tr>
<tr>
<td>Anaplastic carcinoma</td>
<td>3</td>
</tr>
<tr>
<td>Osseous carcinoma</td>
<td>3</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1</td>
</tr>
<tr>
<td>Follicular adenoma</td>
<td>36</td>
</tr>
<tr>
<td>Hyperthyroid adenoma with thyroiditis</td>
<td>1</td>
</tr>
<tr>
<td>Oncotic adenoma</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>905</td>
</tr>
</tbody>
</table>

TABLE II.—Patient’s characteristics.

<table>
<thead>
<tr>
<th>Group</th>
<th>Thyroid</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>905</td>
<td>300</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>538 F/82 M</td>
<td>97 F/53 M</td>
</tr>
<tr>
<td>Age (anni)</td>
<td>48,6±14,1</td>
<td>42,6±22,4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66,8±7,34</td>
<td>69,1±6,23</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164,5±7,23</td>
<td>165,7±6,49</td>
</tr>
<tr>
<td>Operation’s time(min)</td>
<td>86±15,56</td>
<td>78±41,41</td>
</tr>
<tr>
<td>Infused liquids (ml/day)</td>
<td>5,2±0,86</td>
<td>4,6±1,3</td>
</tr>
</tbody>
</table>

hormones) or magnesium (aminoglycosides, cisplatinum, cyclosporin); — patients with other pathologies as hepatic or renal insufficiency, tumors, recent haemotransfusions.

In all patients serum calcium, phosphorous, magnesium and protein levels were determined the day before the operation.

The plasmatic ions were determined by colorimetric enzymatic method.

Our surgical technique for total thyroidectomy under general anesthesia provides methodical search, identification, preservation of parathyroid glands and recurrent nerves.

After the parathyroid glands identification, we report their number and characteristics on special form.

In case of large goiters with mediastinal extension the identification of the parathyroid glands is extremely difficult, if not impossible, therefore operating benign pathologies, we avoid obtaining an "oncologic" radicalization.

If there is accidental ablation or devascularization of one or more parathyroid glands (one in 15 cases and 2 in 6 of our series) we proceed with their reimplantation between muscular bundles of the sternocleidomastoid muscle.

In postoperative period we determine serum calcium, phosphorous, magnesium and proteins postoperative levels in all patients daily, till the fourth day after the operation, which coincides with their discharge to diagnosing and treating a possible post-thyroidectomy hypoparathyroidism opportunely.

The follow-up is always carried out after eight days from the operation.

In those patients presenting transient postoperative hypoparathyroidism signs (during less than 10 days), the follow-up is daily and is carried out till the disappearance of the same and the normalization of the biological values, as well as in patients with tetanic crisis and prolonged postoperative hypoparathyroidism (over 10 days).

In this case we observed that the signs resolution and laboratory parameters normalization were even over six months.

In any case for a proper evaluation of the postoperative hypoparathyroidism we used both clinical and biological criteria.

Clinical criteria

The patients who have shown post-operative hypoparathyroidism were classified including them in several clinical situations from the more serious, the tetanic crisis to the less, the latent tetany and the neural hyperexcitability.

Tetanic crisis

In this group were included all the patients showing more or less evident tetany signs: trismus, eyelid’s and mouth’s retraction, dysphagia, opithotonus, hidrosis, tachycardia, urine retention, abdominal respiratory and members muscles late involvement.

Latent tetany

Patients of this group presented neuromuscular irritability signs, hyperexcitability of deep tendon reflex, muscular cramps and fibrillation.

Pathognomonics of this category are the Trousseau’s and Chvostek’s signs.

In this condition it is necessary also to look for electrocardiographic signs as QT extension.

Besides it, more infrequent but important other clinical situations have been reported in the ECG, as atrial and ventricular paroxysmal dysrhythmia and alternating repolarization.

The cardiac arrhythmias occurs owing to the ATPase enzyme activity decrease they were examinated in serious hypocalcemia and were shown in hypomagnesemia with hypokaliemia but also they are present in isolated hypomagnesemia.

Nervous iperexcitability

It is a sign of various neuron distress due to hypocalcemia, wich appears with : hirritability, disorientation, psychosis, ataxia ,vertigo, nystagmus.

Asymptomatic hypocalcemia

It is a laboratory’s evidence exclusively without clinical signs.
Biological criteria

In our study we considered as hypocalcemic all those patients who had serum calcium values between 8,2 and ≤7,5 mg/dl; we also distinguished, in accord to literature, the moderate hypocalcemia (between 8,2 mg/dl and 7,5 mg/dl) from serious hypocalcemia (if < 7,5 mg/dl).

The hypomagnesemia was considered moderate when the magnesium values were < 1,7 mg/dl; serious if they were < 1,5 mg/dl.

First it is necessary to distinguish between postoperative hypocalcemia and postoperative hypoparathyroidism.

The postoperative hypocalcemia is a transient and moderate serum calcium level (≤ 10%) decrease, but lasting for more than 3 days, without any clinical signs of hypoparathyroidism nor variations of serum phosphorous or magnesium levels.

The postoperative hypoparathyroidism, instead, is considered a condition in which the serum calcium levels decrease is < 7,5 with clinical signs of hypocalcemia.

Particularly in hypoparathyroidism is not necessary to the two conditions co-exist, but they can be independents.

Besides in postoperative hypoparathyroidism there are:

- serum phosphorous levels increase (≥4,5 mg/dl);
- serum magnesium levels frequent delayed (<1,7 mg/dl).

For statistical analysis data were compared by K2 method, considering significative statistical differences for P=5%.

Results

In 905 total thyroidectomies for benign euthyroids pathologies on the whole of 1003 operations, parathyroid glands were identified in 796 patients (87,9%).

Particularly were observed: one parathyroid in 118 patients (18,5%), two in 136 patients (16,2%), three in 116 (13,2%), four in 344 (39,2%), five in 7 patients (0,8%).

In 27 cases (12,1%) no parathyroids were observed.

Between the identified glands, the 60,5% were upper parathyroids.

In 21 patients (2,3%) after the accidental excision of one or more parathyroids (particularly: one in 15 cases and two in 6 cases) they were reimplanted between the muscular bundles of the sternocleidomastoid muscle.

At hystological examination on the removed thyroid, parathyroid glands were observed in 10 patients (1,7%), upper parathyroids in 7 cases, inferior in 3 cases.

The parathyroids were identified like small, oval-shaped and brown organs, included in paraffin wax and coloured with hematoxilyn- eosin.

The 85% of 300 control group patients showed modest hypocalcemia and/or hypomagnesemia due to haemodilution, because of fluids infused in operative and postoperative period (mean value= 5L/die).

This hypocalcemia was asymptomatic in all cases and went back to normal in the course of 3 days after the operation.

The same mild hypocalcemia was observed in the group of thyroidectomy undergone patients too; it is a biological hypocalcemia, which means without clinical signs, in 795 patients (87,8%).

In this group the hypocalcemia was even so mild that it was inferior to 1%.

It was always observed not later than first postoperative day and appeared normal in the course of 3 days.

In these cases the magnesium levels always was within normal lower bounds, therefore no pharmacological treatment was necessary (Figures 1, 2).

Hypomagnesemia was observed in 75% of hypocalcemic patients with symptomatic hypoparathyroidism.

In 66 patients (7,2%), 59 females (median age 49,88± 9,18) and 7 males (median age 38,7±14,2) although all the parathyroids glands were identified and preserved, clinical signs of latent tetany and nervous hyperexcitability appeared in the early postoperative period (within six hours).

The symptomatology consisted in extremities paresthesias and tremblings and/ or muscular cramps.

The same patients presented normal serum calcium levels (average value 9,2 mg/dl) in preoperative period, while the magnesium levels were at the normal lower bounds.

Besides normal serum magnesium levels match against the moderate hypocalcemia in the postoperative period (Figure 3). These patients were treated with calcium and vitamin D by mouth with complete remission of clinical signs after 5 days on average.

Others 22 patients (2,4%) showed hypoparathyroidism signs with normal serum calcium levels, but at the normal lower bounds (average value of 8,3 mg/dl) and always lowers than preoperative values( average value 9,8 mg/dl).

In these patients we always observed severe hypomagnesemia (<1,5 mg/dl)

This group was treated with calcium by mouths and intravenous magnesium aspartate immediately, with only oral magnesium sulphate by mouths soon after (Figure 4).

In these 7 patients we observed clinical signs remission with serum magnesium levels normalization and increase of calcium levels within the 5 th day.

We observed typical signs of postoperative hypoparathyroidism with evident tetany in 7 patients only (0,7%), all females (median age 53,4 ± 14,82) undergone thyroidectomy for large goitre with mediastinal extension.

In 3 of these patients the parathyroid glands were not identified neither in the intraoperative period nor after the operation on the removed thyroid.

In others 4 patients the glands were identified (4 on 4), but in 3 cases one was accidentally excided and reimplantated between the muscular bundles of sternocleidomastoid muscle, in one patient the removed glands were two.

In 6 cases the tetany occurred within 5 hours after the operation, in only one patient it appeared at 11 th hour after the operation.

In these 7 patients we observed severe hypocalcemia, which decreased at 3 th day after the operation (average value 5,35 mg/dl) always associated with moderate hypomagnesemia.

Also the serum magnesium levels like those of calcium levels decreased till the 7 th postoperative day progressively (average value 1,6 mg/dl) (Figures 5, 6).

Biological and clinical parameters were normal in all these within six months, but one patients who reported definitive hypoparathyroidism after one month.

Particularly the serum magnesium levels went back to normal before than calcium levels within one month approximately.
Discussion

The magnesium is subject to a complex modulation of several hormones, not totally explained till today; firstly of calcitropic hormones: vitamin D, calcitonin, parathormon (PTH), but also of thyroid and adrenal hormones, sexual steroids, glucagon and insulin.6-7

Particularly between magnesium and calcitropic hormones exist a biunivocal relation, studied in the past. The PTH acts on the intestinal and tubular magnesium absorption and on its bony release; on the other hand this ion is very important for the normal parathyroid function, that means the PTH production, but also for the vitamin D metabolism and for the receptor sensitivity of their target organs.

Finally the vitamin D, like the PTH promotes the intestinal magnesium absorption.6

From the studies on the relation between magnesium and calcitonin too, might emerge a feed-back regulation system, like that calcium-calcitonin, but of it independent and genetically determinated.7

It is known that in all patients operation undergone, therefore in the thyreopatic patient, occur hydroelectrolytic and acid-base balance alteration in reply to neurhormonal process of the surgical stress.

With regard to magnesium metabolism, it can concur in a hypomagnesemia worsening.8,9

In fact, the stress determines both an increase of circulating catecholamines, ADH, corticosteroids, insulin and taurine decrease, all factors concurring variously in determining a hypomagnesemia. Therefore, it exists a vicious circle in which stress and magnesium deficiency potentiate each other.

Besides, in all surgical patients, respiratory alkalosis, hypocalcemia, hypophosphoremia often occur associated with hypomagnesemia, due to magnesium transient transfers from the extracellular to the intracellular compartments.10

The haemodiluition, associated with others factors like a postoperative parathyroid transitory failure could have an important role in these alterations.11-13

The general anaesthia as well influences the serum magnesium due to intravenous anaesthetics, like a propofol act on cellular membranes directly and could explain intracellular magnesium variations, determining nervous hyperexcitability and cardiac arrhythmias.

These clinical signs regress with the serum magnesium levels normalization.14

We must besides distinguish between the thyreopatic and patient with hyperthyroidism.

In fact, the thyroid hormones speed up the metabolic process and are responsible for directly and indirectly dispersing magnesium mechanisms.

In hyperthyroidism, renal magnesium dispersion with hypermagnesiuria occurs and magnesium serum and erythrocyte levels at normal lower bounds we reported.15

Furthermore, the hyperthyroidism by the TSH lower levels, could inhibit parathyroid function determining hypocalcemia and also hypomagnesemia.

In fact, in thyreopatic patient the relation between magnesium and parathyroid function is fundamental for the metabolism of this ion, particularly the relation between magnesium deficiency and hypoparathyroidism.

In thyreopatic patients a decrease of PTH secretion is reported which associated with the hormonal reply to surgical stress, the haemodiluition and the action of some intravenous anestheticon cellular membranes determines a relative magnesium decrease.

Finally, not only the magnesium deficiency determines a decrease of PTH action, but also the same PTH metabolism and its action were influenced by the magnesium levels, being AMP-cyclic mediated process.

It is validated by studies on patients with secondary hypocalcemia due to hypomagnesemia.

In fact, it was observed that the serum PTH levels were influenced by the hypomagnesemia, as the sensitivity of PTH receptor and the vitamin D 3 metabolism.14-16

The iatrogenic hypoparathyroidism rate after total thyroidectomy is between 3% and 25%.1

Particularly the parathyroid injury is related to surgeon's experience and the operated pathology, with hypoparathyroidism rates till 50% after total thyroidectomy for cancer or radicalization for goitre recurrence.17

Therefore the risk of injury is proportionate to the thyroidectomy extension.

However, this surgical procedure keeps its value, as demonstrate some series of cases, in whose the hypoparathyroidism rates after parathyroid autotransplantation is 1%, with success in 99% of cases.18

The postoperative hypomagnesemia, not yet fully analysed, is frequently or rather common after total thyroidectomy, and often associated with transitory hypocalcemia.

In all cases of postoperative hypocalcemia it is necessary to carry out proper therapy because in this situation the patient is predisposed to tetany and convulsion.

This therapy consists in intravenous Calcium gluconate, calcium and vitamin D by mouth and it is more effective when the hypocalcemia isn't related to PTH levels decrease and the symptoms are only paresthesias, hyperventilation and irritability.19

Postoperative hypocalcemia aetiology is multifarious.

There is evident that the patients are often symptomatic when both ions, calcium and magnesium, are decreased and they stay in this situation if only hypocacemia is correct; therefore is important to correct both ions.20

In fact exists a hypomagnesiemic hypocalcemic syndrome reported in over 10% of patients.21

However, it is not possible to ascribe the symptoms to one or either of these ions deficiency prevalently.

Therefore the serum magnesium levels must be evaluate always in postoperative period, not only in case of nervous hyperexcitability not differently justifiable, but also in case of electrolytic alterations, refractories cardiac arrhythmias, severe diarrhea, concomitant diuretic therapy.22

Conclusions

In conclusion from the results obtained in this study and from other experiences reported in medical literature, we can sum up some considerations.

We reported similar variations of serum calcium and magnesium levels in both patient's groups observed.

It demonstrate the important role of fluids infused by the
haemodilution mechanism during the operation in general anaesthesia.

In the control group these electrolytes variations were not associated with clinical signs and were transitories. (<36 hours)

A particular case of postoperative hypocalcaemia was observed in patients with hypoparathyroidism after total thyroidec-
my.

This is a specific syndrome due to parathyroid iatrogenic injury after accidental glandular excision, ischemia or edema.

However the hypoparathyroidism should have a multifarious aetiology in which an important role is that of magnesium, as hypocalcaemia cofactor.

This supposition is confirmed by the hypoparathyroidism signs observed in our patients. In 87.8% of patients the hypocalcaemia was light and without clinical signs, the same was observed in 85% of control group.

It is Important as the 75% of patients with symptomatic hypoparathyroidism had a concomitant hypomagnesaemia.

Finally we must underline that in a narrow group of patients with hypoparathyroidism signs wasn’t observed hypocalcaemia, but hypomagnesaemia and normal calcium levels.

It occurs in 2,4% of patients.

In these patients there were normal calcium levels and very decreased magnesium levels (<1,5 mg/dl).

However we must analyse this result in consideration of this group presented normal postoperative calcium levels but always decreased in respect of the preoperatives (between a mean average of 9,88 mg/dl in preoperative and 8,3 mg/dl in postoperative period).

In any case we observed that in these patients clinical signs of hypoparathyroidism regress after therapy with calcium and magnesium.

On the basis of our results we reflected upon the magnesium importance in postoperative hypoparathyroidism, also if in the percentage observed the hypomagnesaemia, as only hypoparathyroidism cause wasn’t statistically significant (K2, P=5%).

Besides we must underline as in 7 patients who presented postoperative tetany the hypocalcaemia was always associated with magnesium decrease, reaching the normal lower bounds.

At last our results confirm the magnesium influence on parathyroid function and parathormone action and their mutual relation.

This influence could be determinant in case of iatrogen hypoparathyroidism, acting the ion as cofactor of hypocalcaemia, protracting and potentiating it, but not only.

In the decreased parathyroid function could acts on magnesium levels showing signs and symptoms of nervous excitability, also in the presence of normal calcium levels, apart from hypocalcaemia, as occurred in 2,4% of our patients.

Concerning this, it should interesting compare the clinical behavior of two groups of patients with symptomatic hypoparathyroidism, but with normal calcium levels, also if at the normal lower bounds, and with severe hypomagnesaemia, treating one with calcium only, other with magnesium only.

Riassunto

Ruolo del magnesio nell’ipoparatiroidismo post-tiroidecтомia

Gli Autori prendono spunto da un loro studio precedente ("Ipoparatiroidismo e ipoparatiroidismo dopo tiroidecтомia totale: uno studio clinico-biologico e di considerazioni chirurgiche"). Nel quale avevano esaminato in due gruppi di pazienti (uno di controllo) le variazioni dei livelli sierici di calcio e di fosfato dopo tiroidecтомia totale. Nel presente studio essi esaminano il possibile ruolo del magnesio nell’ipoparatiroidismo post-tiroidecтомia. Essi concludono che l’ipoparatiroidismo post-tiroidecтомia abbia sicuramente un’etologia multifattoriale e sottolineano come i sintomi sintomatici spesso presentino una diminuzione contemporanea di calcio e di magnesio. Essi osservano anche che i segni clinici persistono in diversi casi quando viene trattata la sola ipocalcaemia, mentre regrediscono più velocemente quando vengono trattati solo i segni cellulari. I risultati sono stati confrontati con quelli di altri studi clinici-biologici e chirurgici.