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Clinical and Biochemical Factors Affecting Postoperative Hypocalcemia After Near-Total Thyroidectomy

Czynniki kliniczne oraz biochemiczne wpływające na pooperacyjną hipokalcemię po prawie całkowitej tyroidektomii

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. The most common complication which occurs after thyroidectomy is postoperative hypocalcemia due to parathyroid gland damage. It usually appears 24–48 hours postoperatively, but there are clinical and biochemical factors which may contribute to its earlier diagnosis.
Objectives. The aim of this study was to assess clinical and biochemical factors which can influence postoperative hypocalcemia after near-total thyroidectomy.
Material and Methods. The material consisted of 103 patients with benign nodular goiter. In all patients the blood samples were taken 4 times and levels of total calcium, magnesium, inorganic phosphorus, parathormone and thyroid-stimulating hormone were measured. One day before surgery and during the first three days postoperatively patients were asked about symptoms of hypocalcemia and the presence or absence of a Trousseau sign was observed.
Results. There was no statistically significant connection between the symptoms of hypocalcemia and the age of patients and preoperative hyperthyroidism. Patients with symptomatic hypocalcemia had longer operating time, resected tissue weighed more and hospitalization time was longer than in patients without symptoms of hypocalcemia. Concomitant occurrence of hypocalcemia and hypomagnesemia postoperatively was found in 16% of patients. Changes in parathyroid hormone concentration measured 10 min after thyroid excision were more sensitive and specific for detecting patients with symptomatic hypocalcemia after surgery than total calcium concentration.
Conclusions. Measurement of intraoperative parathormone level 10 min after thyroidectomy is a highly sensitive and specific factor for detecting postoperative hypocalcemia. If we connect this parameter with some other clinical features, it will be possible to predict postoperative hypocalcemia more accurately and introduce supplementation as early as possible (**Adv Clin Exp Med 2013, 22, 5, 675–682**).

Key words: hypocalcemia, hypomagnesemia, parathyroid glands, thyroidectomy, hypoparathyroidism.

Streszczenie

Wprowadzenie. Najczęściej występującym powikłaniem po tyroidektomii jest pooperacyjna hipokalcemia wskutek zniszczenia gruczołów przytarczycznych. Pojawia się zwykle 24–48 godzin po zabiegu chirurgicznym, istnieją jednak kliniczne oraz biochemiczne czynniki mogące prowadzić do jej wcześniejszego rozpoznania.
Cel pracy. Określenie czynników klinicznych oraz biochemicznych mających wpływ na pojawienie się hipokalcemii po prawie całkowitej tyroidektomii.
Materiał i metody. Analizie poddano 103 pacjentów z łagodnym wolem guzkowym. U wszystkich badanych osób pobrano 4-krotnie krew i oznaczono stężenie wapnia całkowitego, magnezu, fosforu nieorganicznego, parathor-

monu oraz hormonu tyreotropowego. Jeden dzień przed zabiegiem chirurgicznym oraz przez 3 kolejne dni po zabiegu pacjenci byli pytani o obecność objawów hipokalcemii oraz wykonano próbę Trousseau.
Wyniki. Nie stwierdzono statystycznie istotnej zależności między wystąpieniem objawów hipokalcemii a wiekiem pacjentów i przedoperacyjnie rozpoznaną nadczynnością tarczycy. U pacjentów z objawową hipokalcemią zabieg chirurgiczny trwał dłużej, usunięta tkanka ważyła więcej i czas hospitalizacji był dłuższy niż u pacjentów bez objawów hipokalcemii. Jednoczesne występowanie hipokalcemii i hipomagnezemii w okresie pooperacyjnym stwierdzono u 16% pacjentów. Zmiany w stężeniu parathormonu, stwierdzone 10 min po usunięciu tarczycy, były bardziej czułe i swoiste dla wykrycia pacjentów z objawową hipokalcemią niż zmiany w stężeniu wapnia całkowitego.
Wnioski. Śródoperacyjne oznaczanie parathormonu 10 min po usunięciu tarczycy jest wysoce czułym i swoistym czynnikiem dla wykrycia pooperacyjnej hipokalcemii. Jeśli połączy się to oznaczenie z innymi czynnikami klinicznymi, będzie możliwe dokładniejsze przewidywanie wystąpienia pooperacyjnej hipokalcemii i jak najszybsze włączenie suplementacji (**Adv Clin Exp Med 2013, 22, 5, 675–682**).

Słowa kluczowe: hipokalcemia, hipomagnezemia, gruczoły przytarczyczne, tyroidektomia, niedoczynność gruczołów przytarczycznych.

Vocal cord palsy and postoperative bleeding are complications which occur immediately after thyroidectomy, but the most common one is postoperative hypocalcemia due to parathyroid gland damage. It usually appears 24–48 hours postoperatively and requires strict monitoring, being the main factor which determines the length of hospital stay. Because of this fact, an effective method for detecting patients with developing hypocalcemia is being sought, which will enable immediate therapy and shorter hospitalization. The evaluation of calcium concentration changes has proven to be inaccurate, because postoperative hypocalcemia can be the result of hemodilution [1, 2].

There has been a broad discussion in literature about the utility of parathormone (PTH) in detecting postoperative hypocalcaemia. Studies have found that in patients after thyroidectomy with tetany symptoms, the concentration of PTH was indeterminable and in hypocalcemic patients it was much lower [1, 2]. Only one official recommendation exists, from the Australian Endocrine Surgeons Society in 2007, which recommends the measurement of parathormone concentration as a means of postoperative hypocalcemia evaluation [3]. A general agreement of investigators on this topic does not exist, thus it is essential to thoroughly analyze the utility of PTH and several other factors which can influence postoperative hypocalcemia.

Material and Methods

The material consisted of 103 patients with benign nodular goiter, who were operated on in the Department of Minimally Invasive Surgery and Proctology at Wroclaw Medical University in Poland between 2008 and 2010. The study group consisted of 87 patients (78 women and 9 men) aged 24–75 (53.1 ± 11.6) years, who underwent NTT (near-total thyroidectomy). In the control group, there were 16 patients (14 women and 2 men) aged 20–71 (40.3 ± 14.3) years, who had undergone a removal of only one lobe with the isthmus (lobectomy). The study group was divided into three subgroups (Table 1) according to the result of a check for the Trousseau sign and the presence of

Table 1. Partition of study group. The group without symptoms of hypocalcemia (GBB), the group with positive Trousseau signs (GBT) and the group with positive Trousseau signs and symptoms of hypocalcemia (GBH)

Tabela 1. Podział grupy badanej. Grupa bez objawów hipokalcemii (GBB), grupa z dodatnim objawem Trousseau (GBT) i grupa z dodatnim objawem Trousseau i objawami hipokalcemii (GBH)

Group (Grupa) / Parameter (Parametr)	GBB n = 63	GBT n = 16	GBH n = 8
Gender – women, % (Płeć – kobiety, %)	87%	94%	100%
Age – years (Wiek – lata)	54 ± 11.5	51.6 ± 13.3	49.1 ± 9.5
Trousseau sign (Objaw Trousseau)	–	+	+
Symptoms of hypocalcemia (Objawy hipokalcemii)	–	–	+

symptoms of hypocalcemia. In the control group, the Trousseau sign and symptoms of hypocalcemia were not present.

In all the patients the blood samples were taken 4 times. One day before the surgery the levels of total calcium, magnesium, inorganic phosphorus, parathormone and TSH (thyroid-stimulating hormone) were measured. At 10 min and 24 hours postoperatively the levels of total calcium, magnesium, inorganic phosphorus and parathormone were assessed. At 48 hours postoperatively the levels of total calcium, magnesium and inorganic phosphorus were measured. Serum parathormone and TSH levels were measured using a Siemens® Immulite 2000 analyzer and serum calcium, magnesium and inorganic phosphorus levels using an Olympus® AU 640 analyzer. The excised thyroid tissue was weighed after the operation on a Radwag® RS 232 electronic scale (precision of measurement: d = 0.01 g).

The operative technique was similar to the one described by Erbil et al. Near-total thyroidectomy was performed in two ways. In the case of the presence of a dominant nodule in one of the lobes, a lobectomy was performed on this side and near-total resection on the contralateral lobe. In patients without a dominant nodule and in multiple nodules, a bilateral NTT was performed. The amount of remnant thyroid tissue was intended to be less than 1 g (1 cm^3). Lobectomy was defined as a total excision of one lobe with isthmus [4].

One day before the surgery and during the first 3 days postoperatively all the patients were asked about symptoms of hypocalcemia and the presence or absence of a Trousseau sign was observed. If during the postoperative period hypocalcemic symptoms were observed, the patients were given calcium and magnesium supplements.

Statistical analysis was performed using Statistica 8 and MedCalc software. The significance of differences between two variables was determined using a Student's *t*-test or Mann-Whitney U test according to the distribution of the variables. The analysis of variance (ANOVA) or its nonparametric equivalent were used to compare the parameters in 4 groups. Variables which did not have the normal distribution were logarithmized with the natural logarithm (log), which in most cases enabled further analysis. The significance of differences between qualitative variables was determined using a chi-squared test. The ROC curves were created to define the cut-off points for calcium and PTH to predict symptoms of hypocalcemia. Statistical significance was accepted at $p < 0.05$ level. In the case of performing multiple comparisons, a *post hoc* test and then Bonferroni correction were used, accepting a statistical significance less than 0.05 divided by the number of repetitions evaluated for this variable.

The study was approved by the Regional Ethical Committee at Wroclaw Medical University.

Results

There was no statistically significant connection between the symptoms of hypocalcemia and the age of patients, the number of intraoperatively visualized parathyroid glands, preoperative hyperthyroidism and serum TSH level. Patients with symptomatic hypocalcemia had significantly longer operating times, the resected tissue weighed more and hospitalization time was longer than in patients without symptoms of hypocalcemia (Table 2).

The Trousseau sign was found during at least one examination in 24 patients (23%) and symptoms of hypocalcemia in 8 patients (8%). Hypocalcemia and the symptoms of hypocalcemia were not found during the first 24 postoperative hours and were not observed in the control group (Fig. 1), but a significant drop in PTH level was observed 10 min after thyroid resection in the group with symptoms of hypocalcemia (Fig. 2). The concomitant occurrence of hypocalcemia (serum calcium < 8.4 mg/dL) and hypomagnesemia (serum magnesium < 1.9 mg/dL) in any postoperative period was found at least once in 18 patients (16%), and was significantly more frequent in the group with symptoms of hypocalcemia (Fig. 3). There is no need to evaluate the postoperative serum level of inorganic phosphorus because significant differences between the groups of patients were not observed (Fig. 4).

The comparison of ROC curves for parathormone and calcium levels in the intraoperative examination 10 min after gland excision revealed that changes in parathyroid concentration are more sensitive and specific for detecting patients with symptomatic hypocalcemia after surgery than total calcium concentration (Fig. 5). During further postoperative evaluation, neither of these parameters was better at detecting symptoms of hypocalcemia (Fig. 6).

Discussion

Subtotal thyroidectomy used to be the standard treatment for benign nodular goiter. Nowadays, near-total and total thyroidectomy are becoming the most common operations for benign diseases of the thyroid gland [4–9]. But more extensive surgery may be connected with more frequent

Table 2. Demographic and clinical features of the control group (GK), the group without symptoms of hypocalcemia (GBB), the group with positive Trousseau signs (GBT) and the group with positive Trousseau signs and symptoms of hypocalcemia (GBH)

Tabela 2. Charakterystyka demograficzna i kliniczna grupy kontrolnej (GK), grupy bez objawów hipokalcemii (GBB), grupy z dodatnim objawem Trousseau (GBT) i grupy z dodatnim objawem Trousseau i objawami hipokalcemii (GBH)

Parameter (Parametr) / Group (Grupa)	GK n = 16	GBB n = 63	GBT n = 16	GBH n = 8
Gender – women, %) (Płeć – kobiety, %)	87%	87%	94%	100
Age – years (Wiek – lata)	40.3 ± 14.3	54 ± 11.5 [x]	51.6 ± 13.3 [x]	49 ± 9
Preoperative diagnosis of hyperthyroidism – %) (Przedoperacyjnie rozpoznana nadczynność tarczycy – %)	13%	27%	31%	–
TSH (thyroid-stimulating hormone) preoperatively – μIU/mL (TSH (hormon tyreotropowy) w badaniu przedoperacyjnym – μIU/mL)	1.4 ± 1.3	1.27 ± 2	1 ± 0.9	1.2 ± 1.1
Time of operation – min (Czas trwania operacji – min)	59 ± 9	84 ± 19 [x]	83 ± 23 [x]	103 ± 12 [x,y,z]
Number of visualized parathyroid glands (Liczba uwidocznionych gruczołów przytarczycznych)	0.7 ± 0.4	1.7 ± 0.9 [x]	1.8 ± 1 [x]	2.1 ± 0.6 [x]
Weight of resected thyroid tissue – g (Waga usuniętej tkanki tarczycowej – g)	16.94 ± 6.56	36.2 ± 25.5	42.9 ± 38 [x]	63 ± 51.2 [x,y]
Length of hospital stay – days (Długość hospitalizacji – dni)	2.7 ± 0.4	3.1 ± 0.3	3.3 ± 1.1 [x]	5.8 ± 1.2 [x,y,z]

The significant differences between groups were marked with letters:
(Istotne różnice między grupami oznaczono literami):
x – $p < 0.01$ vs. GK.
y – $p < 0.01$ vs. GBB.
z – $p < 0.01$ vs. GBT.

complications and parathyroid glands are especially endangered: their postoperative insufficiency occurs in 1.6 to 50% of cases [1, 4, 10–13]. According to the literature, the causes of parathyroid gland insufficiency are multiple and associated mostly with their iatrogenic injury, extent of surgery, surgeon's experience, retrosternal goiter, neck lymphadenectomy, thyroid cancer and the number of correctly functioning parathyroid glands left *in situ*. Parathyroid gland insufficiency may be the result of its blood supply damage, gland infarction or intraoperative removal. On the one hand, some authors recommend intraoperative visualization of all parathyroid glands, but on the other hand, unnecessary dissection in their area may lead to the destruction of their blood supply [6, 10, 14–18].

We did not find any statistically significant connection between the symptoms of hypocalcemia and the age of patients and preoperative hyperthyroidism, which was also observed by other authors [19, 20]. In contrast to our results, other authors did not find any association between thyroid size and postoperative hypocalcemia [20]. We think that a higher weight of resected tissue and, resulting from that, significantly longer operating times were associated with technical problems during surgery, which additionally endangered the fragile parathyroid tissue.

Removal of only one lobe of the thyroid gland (the control group) in comparison to NTT (the study group) was associated with significantly shorter operation time and hospital stays and significantly higher serum calcium and PTH levels postoperatively. If there are indications for lobectomy, this is a much safer procedure in comparison to NTT with regards to postoperative hypocalcemia [21]. Glinoer et al. compared changes in postoperative serum calcium and PTH levels after lobectomy and bilateral thyroidectomy in a group of 135 patients. Hypocalcemia associated with lobectomy was a very rare phenomenon without clinical importance and disappeared in most cases without supplementation. What hypocalcemia there was, was nonspecific, associated mainly with hemodilution and might be diagnosed after any other operation. On the contrary, hypocalcemia

Figs. 1–4. The significant differences between groups were marked with letters:
x – p < 0.01 vs. GK,
y – p < 0.01 vs. GBB,
z – p < 0.01 vs. GBT.

Periods:
t0 – 1 day before surgery,
t1 – 10 min after thyroidectomy,
t2 – 24 hours after thyroidectomy,
t3 – 48 hours after thyroidectomy.

Ryc. 1–4. Istotne różnice między grupami oznaczono literami:
x – p < 0,01 *vs* GK,
y – p < 0,01 *vs* GBB,
z – p < 0,01 *vs* GBT.

Okresy:
t0 – 1 dzień przed zabiegiem chirurgicznym,
t1 – 10 min po usunięciu tarczycy,
t2 – 24 godz. po usunięciu tarczycy,
t3 – 48 godz. po usunięciu tarczycy.

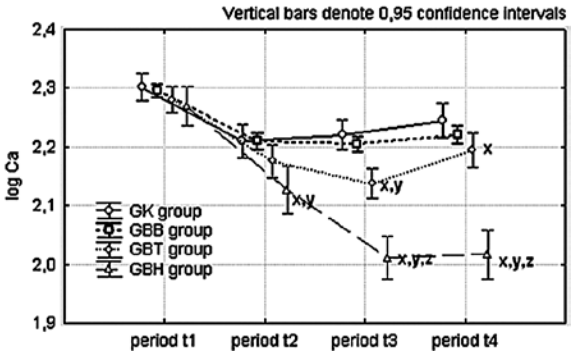

Fig. 1. Serum calcium (Ca) level in selected groups of patients

Ryc. 1. Stężenie wapnia (Ca) w surowicy w określonych grupach pacjentów

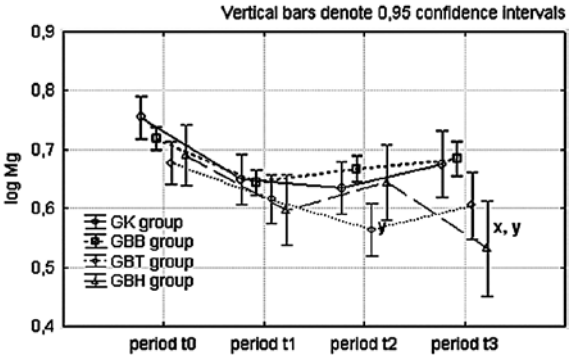

Fig. 3. Serum magnesium (Mg) level in selected groups of patients

Ryc. 3. Stężenie magnezu (Mg) w surowicy w określonych grupach pacjentów

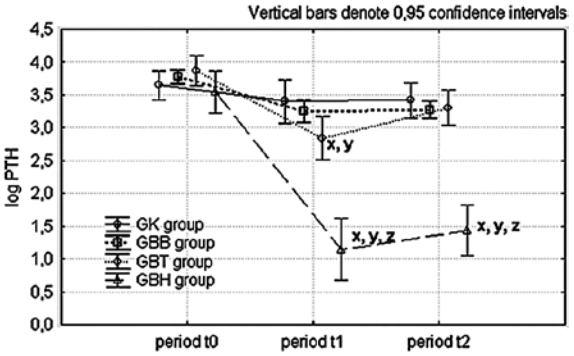

Fig. 2. Serum parathormone (PTH) level in selected groups of patients

Ryc. 2. Stężenie parathormonu (PTH) w surowicy w określonych grupach pacjentów

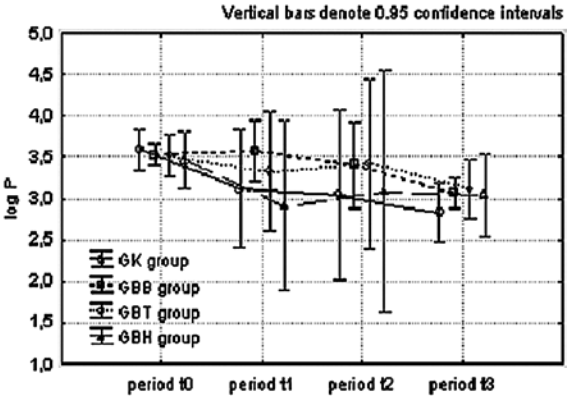

Fig. 4. Serum inorganic phosphorus (P) level in selected groups of patients

Ryc. 4. Stężenie fosforu nieorganicznego (P) w surowicy w określonych grupach pacjentów

after bilateral thyroidectomy was more common, profound and lasted longer [22].

Significant differences between the number of intraoperatively visualized parathyroid glands in the group of patients after near-total thyroidectomy were not found, thus it is impossible to predict the postoperative insufficiency of parathyroid glands only on the basis of the number of glands left *in situ*. It is impossible during a surgery to unequivocally decide which parathyroid glands have a damaged blood supply and need to be autotransplanted. Kuhel and Karel conducted a survey on the usefulness of changes in parathyroid gland color depending on their blood supply. They found that it is impossible to determine the blood supply of parathyroid glands only on the basis of the changes in their color [23, 24], therefore it is very important to leave as many of the parathyroid glands intact as possible *in situ*.

The discussion over the minimum number of parathyroid glands which will ensure calcium and phosphate homeostasis remains unresolved. Some authors think that only one gland is enough, but others think that there should be at least

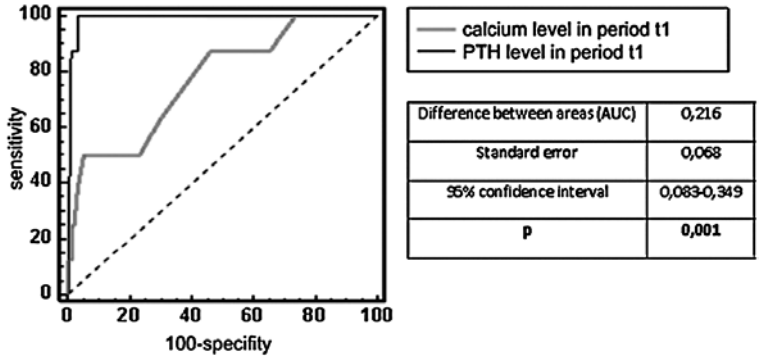

Fig. 5. Comparison of ROC curves for serum parathormone (PTH) and calcium (Ca) levels in period t1 (10 min after thyroidectomy) for prediction of postoperative symptoms of hypocalcemia. Serum PTH level is more specific and sensitive for prediction of symptoms of hypocalcemia than serum calcium level in period t1

Ryc. 5. Porównanie krzywych ROC dla parathormonu (PTH) i wapnia (Ca) w okresie t1 (10 min po usunięciu tarczycy) w celu przewidzenia pooperacyjnych objawów hipokalcemii. Stężenie parathormonu w surowicy jest bardziej swoistne i czułe dla przewidzenia objawów hipokalcemii niż stężenie wapnia w surowicy w okresie t1

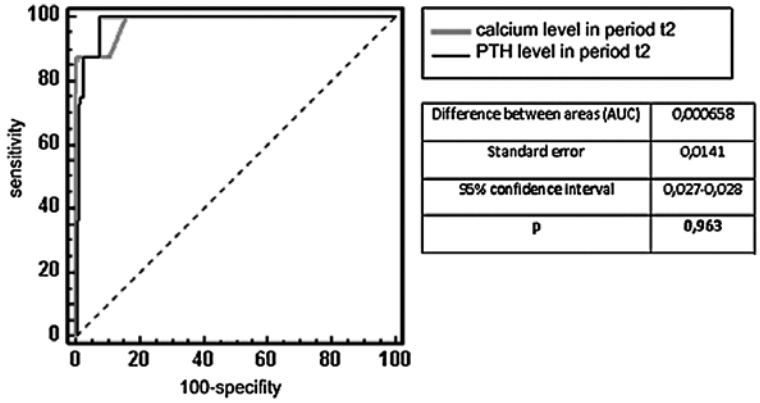

Fig. 6. Comparison of ROC curves for serum parathormone (PTH) and calcium (Ca) levels in period t2 (24 hours after thyroidectomy) for prediction of postoperative symptoms of hypocalcemia. There is no significant difference between serum PTH and calcium level in predicting postoperative hypocalcemia in period t2

Ryc. 6. Porównanie krzywych ROC dla parathormonu (PTH) i wapnia (Ca) w okresie t2 (24 godz. po usunięciu tarczycy) w celu przewidzenia pooperacyjnych objawów hipokalcemii. Nie stwierdzono istotnej różnicy między stężeniem w surowicy parathormonu i wapnia w przewidzeniu pooperacyjnych objawów hipokalcemii w okresie t2

3 glands [1, 4, 10, 11, 17, 25]. In a study of 200 patients after total and near-total thyroidectomy, Erbil et al. found that the number of intraoperatively identified parathyroid glands is smaller in patients with symptoms of hypocalcemia than in patients without these symptoms [10]. We found in our study that patients with symptoms of hypocalcemia had an insignificantly higher number of intraoperatively identified parathyroid glands, which confirms the hypothesis that not the number but the intact vascularization of glands plays a major role in their postoperative functioning. The identification of all parathyroid glands during surgery is very difficult due to their common ectopic location. The presence of parathyroid glands within the thyroid gland amounts to 2–5% of what is confirmed on autopsy studies [17]. The frequency of accidentally removed parathyroid glands is 5–20% and in 40–50% of cases they are located within the thyroid gland, which makes their intraoperative identification impossible, resulting in unintentional excision. In most cases only one parathyroid gland is accidentally removed, but the clinical significance of this fact and association with postoperative parathyroid gland insufficiency has not yet been explained [1, 3, 10, 12, 14, 17].

The measurement of calcium levels after thyroidectomy and the use of this parameter for evaluation of the functioning of the parathyroid glands is inadequate and leads to delayed diagnosis of their insufficiency. The significant decrease in PTH level was measured much earlier, at 10 min after thyroidectomy. It enables early recognition of hypocalcemia, whose first symptoms do not occur until

24 hours postoperatively, and early supplementation immediately after the operation [26, 27]. Aluffi et al. observed that in 67 patients, the calcium level was lower than 7.5 mg/dL 24 hours postoperatively, which is a prognostic factor for the development of parathyroid gland insufficiency ($p < 0.05$). Unfortunately, this parameter is not useful immediately after the operation, which delays early supplementation and prolongs hospitalization [28]. It appears to be more useful to measure postoperative PTH level, which is associated with its short elimination half-life of about 2 min [29]. Grodski and Serpell analyzed 27 publications which have been published since 2000 on the topic of postoperative hypocalcemia after thyroidectomy, and found that progressive and profound hypocalcemia is impossible when the postoperative PTH level remains within normal range, thus its measurement may be used to choose patients who may leave the hospital on the first postoperative day and the right moment to introduce supplementation with vitamin D_3 and calcium.

Significant differences in serum inorganic phosphorus level between the groups of patients were not observed, especially between the group with symptoms of hypocalcemia and the one without these symptoms, so changes in its level can not be used as a marker of disturbances in calcium homeostasis in the immediate postoperative period.

Concomitant occurrence of hypomagnesemia and hypocalcemia leads to the exacerbation of hypocalcemic symptoms, thus it is important to supplement both electrolytes simultaneously [30]. Despite the existence of several guidelines for postoperative supplementation with vitamin D_3 and calcium [1, 9, 25, 28], only some authors recommend supplementation with magnesium [30]. According to our observations, a postoperative decrease in magnesium level is quite common, especially in patients with hypocalcemia, thus it needs to be systematically checked and supplemented so as not to exacerbate symptoms of hypocalcemia.

The necessity for supplementing calcium and magnesium was associated with a significantly longer hospital stay. The potential danger of postoperative bleeding and recurrent nerve palsy are generally immediate postoperative issues, so it is very important to identify patients who need supplementation because only they need longer hospitalization [1].

We conclude that postoperative hypoparathyroidism after near-total thyroidectomy is quite a common complication, which should be addressed as quickly as possible to reduce the number of cases with symptomatic hypocalcemia. Supplementation should consist not only of calcium and vitamin D_3, but also of magnesium to reduce symptoms to a minimum and to shorten hospital stay.

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