

# Perioperative calcium and vitamin D supplementation in patients undergoing thyroidectomy - literature review

A – Study Design

B-Data Collection C-Statistical Analysis

D-Data Interpretation

E-Manuscript Preparation
F-Literature Search
G-Funds Collection

Anna Grzegory<sup>ADEF</sup>, Lech Pomorski<sup>ADF</sup>

Department of General and Oncological Surgery, Medical University of Lodz, Poland

Article history:

#### **ABSTRACT:**

Introduction: Postoperative hypocalcemia is a narrow but significant problem for patients undergoing thyroid and parathyroid surgery. It is the most common complication after thyroidectomy. It is associated with transient or permanent hypoparathyroidism. It could potentially be life-threatening for patients and increases the costs of hospitalization. The aim of the study was to evaluate the results of studies that routinely administrated calcium and/or vitamin D during the postoperative period.

Materials and Methods: In this article, a literature review -15 studies that used routine perioperative calcium (7 studies), vitamin D (2 studies) and calcium with vitamin D (11 studies) supplementation was performed. Supplementation effectiveness in prevention of postoperative hypocalcemia was compared to no prophylaxis in 10 studies. Five studies compared the effect of combined administration (calcium and vitamin D) to calcium alone. The number of papers dealing with this problem is not particularly high.

Results: Supplementation significantly decreased the rate of laboratory and symptomatic hypocalcemia. It was also effective in reducing the severity of symptoms. The combination of calcium with vitamin D was the most effective strategy. No hypercalcemia or parathyroid hormone inhibition was observed in the supplemented groups. Routine supplementation was less expensive than performing laboratory tests in the course of treatment of hypocalcemia.

Conclusions: The results of analyzed studies showed the clinical and economic advantage of routine perioperative prophylactic supplementation of vitamin D and/or calcium as compared to no prophylaxis. However, the majority of studies showed a significant range of variability in patients' characteristics. Numerous studies did not evaluate the preoperative 25-hydroxycholecalciferol level – a risk factor for postoperative hypocalcemia.

Discussion: The use of routine prophylactic supplementation of calcium and vitamin D in the perioperative period can be useful in everyday clinical practice. Further research is needed to draw clear guidelines regarding prophylactic calcium and vitamin D therapy for patients after thyroidectomy.

### **KEYWORDS:**

hypocalcemia, hypoparathyroidism, calcium, vitamin D, thyroidectomy, perioperative period

Due to the health and economic consequences of postoperative hypocalcemia, it is necessary to disseminate knowledge about non-invasive methods of limiting it that can be used in everyday clinical practice such as routine perioperative calcium and vitamin D supplementation.

Thyroidectomy is one of the most commonly performed procedures in endocrine surgery in Poland – over 20 000 per year (according to Polish National Health Fund). The risk of the following complications is connected with this procedure: bleeding, laryngeal nerve damage and above all – most common – hypoparathyroidism (HP). Postoperative hypocalcemia (PH) occurs in 1.6-54% of operated patients and in most cases it is transient [1, 2]. It can be caused by surgical injury: parathyroid ischaemia, unintended parathyroidectomy (e.g. resection of the parathyroid gland located within the thyroid lobe – i.e. intraglandularly) or hemodilution [3, 4].

Risk factors include: perioperative level of native parathyroid hormone (PTH), calcium level variations [5], female gender, surgery on patients with thyroid cancer, hyperactive goiter, intraoperative parathyroid injury and parathyroid autotransplantation [6]. One of the most commonly assessed parameters is the blood level of vitamin D. Authors of many publications consider vitamin D as hypocalcemia risk factor [6, 7, 8, 9, 10]. Studies which analyzed blood concentration of 25-hydroxycholecalciferol (25-OHD) of the inhabitants of Lodz and the rest of Poland, indicate significant deficiencies in 42.2%-81.1% of the examined population [11, 12]. PH occurs subclinically – can be assessed only by laboratory

tests, or symptomatically. It can be transient or permanent. The permanent form of PH leads to decreased life quality, increased incidence of renal complications or even psychic disturbances [13, 14, 15, 16]. The occurrence of early PH prolongs hospital stay and increases treatment costs [2, 14]. Many investigators attempt to find noninvasive methods which would allow to prevent postoperative HP. In studies referred to below, the following approaches were compared: efficacy of routine, prophylactic supplementation of calcium salts or vitamin D, and combined supplementation of calcium and vitamin D, used in various regimens in patients with benign and malignant thyroid diseases (Tab. I, Tab. II).

### STUDIES EVALUATING CALCIUM **SUPPLEMENTATION**

In 4 studies calcium supplementation was evaluated [17, 18, 19, 20]. It was administered in groups of patients before surgery [18] and in postoperative period [17, 19, 20]. Duration of supplementation ranged from 5 hours (intravenous supplementation) [17] to one [19] and two weeks [18, 20]. Obtained results were compared with the group without supplementation. In Oltman 2015 [18]

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the incidence of postoperative hypocalcemia in patients with Grave's Disease (GD) was compared in groups with and without supplementation and additionally in control group with other thyroid diseases without supplementation. In Roh 2009 [20] patients with papillary thyroid cancer were compared with those without central lymphadenectomy and pharmacological prophylaxis of hypocalcemia. Calcium supplementation increased the postoperative calcium level [17, 18], reduced the risk of transient laboratory hypocalcemia (LH) (24.5% vs. 44%) and symptomatic hypocalcemia (SH) (6-34.6% vs. 26-40.7%) [18, 19], as well as the risk of calcium level decrease in the postoperative period [18]. It also reduced the intensification of symptoms, discomfort and anxiety of patients [17]. In Roh 2009 [20] in a group with supplementation and central lymphodenectomy, the incidence of LH and SH was however higher than in the control group without interventions. In groups with supplementation neither hypocalcemia, nor PTH inhibition occurred [17, 20]. No statistically significant differences in remaining hypocalcemia were reported on or studied in the groups with applied prophylaxys and those without supplementation in the above mentioned studies [17, 20].

### STUDIES EVALUATING SUPPLEMENTATION OF VITAMIN D AND ITS DERIVATIVES

In the first study [21] oral calcitriol with thiazide diuretic were supplemented in the week preceding surgery. The second one [22] evaluated the efficacy of periprocedural, oral alfacalcidol supplementation. Reduction of the incidence of LH in patients with supplementation was observed – in the first 24 h 33% vs. 37%, in the next 24 h 6% vs. 14% [22]. Also the incidence of SH was reduced in the group with supplementation (5–11% vs. 22–50%) [21, 22]. Patients with severe hypocalcemia (<1.9 mmol/L) receiving supplementation achieved calcium level normalization faster [22] and the length of hospitalization stay was shorter (2.4  $\pm$  0.6 days vs. 3.6  $\pm$  1.4 days) [21]. Supplementation with alfacalcidol did not affect the occurrence of permanent hypocalcemia [22].

## STUDIES EVALUATING SUPPLEMENTATION OF CALCIUM AND VITAMIN D

The efficacy of combined supplementation of calcium and vitamin D was evaluated in eight studies [19, 20, 23, 24, 25, 26, 27, 28]. Vitamin D or its derivatives (calcitriol, alfacalcidol, cholecalciferol) and calcium were administered orally in the period ranging from a few days to a few weeks after surgery [19, 20, 23, 24, 25, 26], and in two studies – Jaan 2017 [27] and Docimo 2012 [28] - in the perioperative period. The incidence of LH was lower in the groups with supplementation (8.6%–25% vs. 32.9%-59%) [20, 23, 25, 27, 28]. The same was observed for SH incidence (1.9-23.4% vs. 4.5-54.5%) [19, 20, 23, 24, 25, 26, 27, 28]. Symptoms of hypocalcemia were milder and patients needed intravenous infusion of calcium less frequently [19, 23, 24, 27]. In Roh 2009 the incidence of hypocalcemia was lower also in the control group without lymphadenectomy (LH – 8.6% vs. 14.3%; SH - 2.0 - 6.1%) [20]. In Choe 2011 patients were divided into 4 groups with postoperative administration of: calcium with cholecalciferol or calcium with calcitriol, routinely or "on demand" [25]. In the group with supplementation "on demand", in which drugs were administered after the occurrence of the symptoms, calcium levels were higher in the patients receiving calcium with calcitriol, which suggests that it acts faster than the calcium cholecalciferol regimen.

Calcium level normalization was achieved faster in the intervention groups [20, 23, 27]. Also the length of hospital stay in those groups was shorter (1.2  $\pm$  0.4 vs. 2.9  $\pm$  0.9) [24]. Routine administration of calcium and vitamin D was related with lower costs than performing laboratory tests [26]. Inhibition of PTH was not observed in the study or control groups [19, 20, 23, 25]. Administration of calcium and vitamin D did not influence the occurrence of permanent hypocalcemia [20, 23].

# STUDIES COMPARING SUPPLEMENTATION OF CALCIUM WITH COMBINED SUPPLEMENTATION OF CALCIUM AND VITAMIN D

The comparison of efficacy of calcium supplementation with supplementation of calcium and vitamin D was performed in 5 studies [19, 20, 29, 30, 31]. Vitamin D or its derivatives (calcitriol, cholecalciferol, alfacalcidol) were administered orally. Prophylaxis was used in the postoperative period [19, 20, 29, 30] and in Nemade 2014 in the perioperative period [31]. In the group with double supplementation LH occurred less frequently than in the group with calcium supplementation only (4.2–8.2% vs. 24.5–29.1%) [20, 31]. A similar correlation in SH incidence was observed (1.7–23% vs. 6.7–41.6%) [19, 21, 30, 31].

In Tartaglia 2005 [29] the incidence of both tetany (defined by authors as spontaneous masseter muscle contraction and carpal spasm and the presence of serious and widespread parestheses with positive Trousseau's sign) and SH were the lowest in the group with the highest calcitriol dose (2  $\mu g-0\%$  and 17.1%, 1  $\mu g-2.9\%$  and 28.%, calcium -7.4% and 22.%). Patients receiving calcium with vitamin D had milder symptoms and usually did not require intravenous calcium infusion [19, 31]. In those patients higher postoperative calcium levels were observed despite the type of thyroid disease (benign or malignant) [30]. Also normalization of calcium level in postoperative period was faster [20]. Inhibition of PTH was not observed [20, 29] and permanent hypothyroidism developed less frequently [19, 31].

Metaanalyses from Antakia 2015 [32] and Alhefdi 2013 [33] suggest that postoperative, combined supplementation of calcium and vitamin D is related with lower incidence of transitional hypocalcemia, compared to supplementation of calcium alone or no supplementation.

#### CONCLUSION

Studies claimed the advantage of perioperative, routine prophylaxis with supplementation compared to the lack of supplementation. Such an approach was also more economical. Authors demonstrated the highest efficacy of oral postoperative supplementation of calcium salts in conjunction with vitamin D.

The influence of prophylactic calcium and vitamin D supplementation on the occurrence of hypercalcemia or PTH secretion were not found.

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Tab. I. Characteristics of groups and hypocalcemia definition in included studies.

STUDY	N	N WITH SUPPLEMENTATION	TC [%]	TT (%)	TT+ CND (%)	TT + MRND (%)	AUTOTRANSPLANTATION OF PARATHYROID GLAND	DEFINITION OF HYPOCALCEMIA
Uruno 2006	547	243	78	22	78	0	-	Symptomatic hypocalcemia
Oltman 2015	123	45	12,2	100	0	0	11,4	Symptomatic hypocalcemia
Bellantone 2002	79	52	6,3	100	0	0	-	Ca < 8 mg/dl
Roh 2009	197	49	100	25	57	18	8	Ca < 8 mg/dl
Testa 2006	42	22	73,8	100	0	0	0	Ca < 2,1 mmol/l
Genser 2014	219	111	38,8	78,1	21,9	0	9,1	Ca < 2 mmol/l
Roh 2006	90	45	83,3	79	0	21	21	Ca < 8 mg/dl / Ca++ < 1,0mmol/l
Kurukahvecioglu 2007	487	243	15,6	100	0	0	-	Symptomatic hypocalcemia requiring supplementation
Choe 2011	306	154	100	0	100	0	40,2	Ca < 0,8 mmol/l / Ca++ < 1 mmol/l
Jaan 2017	60	30	57,5	81,7	13,3	0	6,7	Ca < 8,5 mg/dl
Arer 2017	106	53	13,2	94,3	5,7	0	0	Symptomatic hypocalcemia
Docimo 2015	50	50	10	100	0	0	0	Ca < 8 mg/dl
Tartaglia 2005	417	202	20,6	100	0	0	0	Symptomatic hypocalcemia
Pisaniello 2005	120	60	11,7	100	0	0	-	Ca < 8 mg/dl
Nemade 2014	48	24	14,6	100	0	-	-	Ca < 8 mg/dl / Ca++ < 1 mmol/l

N – number of patients; TC – thyroid cancer; TT – thyreoidectomy; CND – central neck dissection; MRND – modified radical neck dissection; Ca – calcium level; Ca++ – lonized calcium level.

Tab. II. Supplementation used in the studies.

PERIOD OF SUPPLEMENTATION	STUDY GROUP	CONTROL GROUP
perioperative (3 to 8 h after the procedure)	Ca i.v. (78-156 mg)	no supplementation
preoperative 2 weeks	Ca p.o. (3 g/d) no supplementation	no supplementation, no GD
postoperative from the 1st to the 7th day	B Ca p.o. (3 g/d) C Ca p.o. (3 g/d) + calcitriol (1 μg/d)	A no supplementation
postoperative 2 weeks	A TT + CND + Ca (3 /d) + alfacalcidol p.o. (1 µg/d) B TT + CND + Ca p.o. (3 g/d) C TT+CND no supplementation	TT, no CND, no supplementation
preoperative 1 week	calcitriol (1.5 μg/d) + thiazid diuretic p.o. (25 mg/d)	no supplementation
perioperative 1 day before and 8 days after surgery	alfacalcidol p.o. (2 μg/d)	no supplementation
postoperative 2 weeks	Ca (3 g/d) + vitamin D p.o. (1 g/d)	no supplementation
postoperative 7 days	Ca (600 mg/d) + vitamin D p.o. (400 U/d)	no supplementation
postoperative	A1 Ca (3 g/d) + cholecalciferol p.o. (20 $\mu$ g/d) routinely A2 Ca (3 g/d) + calcitriol p.o. (5 $\mu$ g/d) routinely	B1 like A1 "on demand" B2 like A2 "on demand"
perioperative 7 days before and 7 days after surgery	Ca (2 g/d) + calcitriol p.o. (1 μg/d)	no supplementation
postoperative from the 24th hour after surgery for 7 days and then reduction of doses for the next 7 days	Ca + vitamin D p.o. ≤ 70 kg 5 g/d + 1760 U/d > 70 kg 7.5 g/d + 2640 U/d	no supplementation
perioperative 3 days befor and 14 days after surgery	Ca (2 g/d) + vitamin D p.o. (800 U/d)	no control group
postoperative for approx. 15 days with gradual dose reduction	A Ca (1.5 g/d) + calcitriol (1 $\mu$ g/d) p.o. B Ca (1.5 g/d) + calcitriol (2 $\mu$ g/d) p.o.	C Ca p.o. (1.5 g/d)
postoperative from the 15th day after surgery	Ca (1500 mg) + cholecalciferol p.o. (400 U/d)	Ca p.o. (300 mg/d)
perioperative 1 week before and 2 weeks after surgery	Ca (2 g/d) + vitamin D p.o. (60000 U 3 times a week)	Ca p.o. (2 g/d)
	preoperative 2 weeks  postoperative from the 1st to the 7th day  postoperative 2 weeks  preoperative 1 week  perioperative 1 day before and 8 days after surgery  postoperative 2 weeks  postoperative 7 days  postoperative 7 days before and 7 days after surgery  postoperative 7 days and then reduction of doses for the next 7 days  perioperative 3 days befor and 14 days after surgery  postoperative 1 days after surgery  postoperative 1 days after surgery  postoperative 2 days befor and 14 days after surgery  postoperative for approx. 15 days with gradual dose reduction  postoperative from the 15th day after surgery  perioperative 1 week before and 2 weeks after	perioperative (3 to 8 h after the procedure)  preoperative 2 weeks  Ca p.o. (3 g/d) no supplementation  postoperative from the 1st to the 7th day  postoperative 2 weeks  A TT + CND + Ca (3 /d) + alfacalcidol p.o. (1 μg/d) B TT + CND + Ca p.o. (3 g/d) C TT+CND no supplementation  preoperative 1 week  calcitriol (1.5 μg/d) + thiazid diuretic p.o. (25 mg/d) perioperative 1 day before and 8 days after surgery  postoperative 2 weeks  Ca (3 g/d) + vitamin D p.o. (1 g/d)  postoperative 7 days  Ca (600 mg/d) + vitamin D p.o. (5 μg/d) routinely A2 Ca (3 g/d) + calcitriol p.o. (5 μg/d) routinely A2 Ca (3 g/d) + calcitriol p.o. (1 μg/d)  perioperative 7 days and then reduction of doses for the next 7 days  perioperative 3 days befor and 14 days after surgery  postoperative for approx. 15 days with gradual dose reduction  postoperative from the 15th day after surgery  postoperative from the 15th day after surgery  postoperative from the 15th day after surgery  perioperative from the 15th day after surgery  postoperative week before and 2 weeks after  Ca (2 g/d) + vitamin D p.o. (800 U/d)  A Ca (1.5 g/d) + calcitriol (1 μg/d) p.o. B Ca (1.5 g/d) + calcitriol (2 μg/d) p.o.  Ca (2 g/d) + vitamin D p.o. (60000 U 3 times a week)

 $i.v.-intrave uously; p.o.-orally; Ca-calcium; TT-thy reoidectomy; CND-central neck dissection; GD-Grave's \ Disease; /d-per \ day.$ 

Groups of patients included in the majority of the studies were heterogeneous in the term of presurgical diagnosis. Patients with benign thyroid diseases, including GD and hyperactive multinodular goiter, and those with tumors of the thyroid were included. None of the stu-

dies evaluated calcium and vitamin D supplementation in the short, perioperative period only, which would have enabled better control of a researcher over patient's compliance during hospitalization. Prolonged hospitalization was also enforced by the regimens of the labo-

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ratory tests. Inclusion and exclusion criteria did not eliminate many factors influencing calcium hemostasis. In the majority of the studies preoperative 25-OHD level was not evaluated [17, 18, 19, 20, 23, 24, 25, 27, 28, 29, 30, 31]. In Poland significant vitamin D deficiency is being observed. It may be necessary to assess preoperative 25-OHD levels and to implement an appropriate regimen based on the results.

Administration of routine, prophylactic supplementation of calcium and vitamin D in perioperative period can be helpful in everyday clinical practice. This may reduce the incidence of postoperative hypocalcemia and the amount of postoperative laboratory tests. Further investigation is still needed in order to determine a standard procedure.

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Corresponding author:	Anna Grzegory; Department of General and Oncological Surgery, Medical University of Lodz, Poland; e-mail: an.grzegory@gmail.com							
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