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Evaluation of the Incidence and Risk Factors of Hypocalcemia and Hypoparathyroidism after Total and Partial Thyroidectomy

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Abstract

Background: Thyroidectomy techniques have evolved over the last 150 years. Postoperative hypocalcemia and hypoparathyroidism are common. Previous studies have focused on identifying risk factors for hypocalcemia and hypoparathyroidism after thyroid surgery, with inconclusive results. To address this, we aimed to conduct a study to assess the incidence and risk factors of postoperative calcium and hypoparathyroidism after total and subtotal thyroidectomy.

Aim: We investigated how vitamin D levels affect postoperative calcium, hypocalcemia, and hypoparathyroidism in patients undergoing total or subtotal thyroidectomy.

Methods: Patients were included over a one-year period. The data collected included information on demographic characteristics, medical history, surgical details, pre- and post-operative calcium and parathyroid hormone levels, neck dissection, type of disease, and surgery. The statistical analyses utilized paired t-tests, Wilcoxon signed-rank tests, and binary logistic regression in R Studio.

Results: The study included 39 patients with an average age of 61.5. Most patients were male (35 out of 39, 89.7%). Three patients underwent partial thyroidectomy. After the operation, the levels of calcium, corrected calcium, PTH, albumin, and phosphorous significantly decreased. Factors that varied statistically between patients with normal and hypocalcemia were PTH and magnesium levels. Several factors emerged as statistically significant predictors for post-thyroidectomy hypocalcemia and hypoparathyroidism. Factors that statistically predicted the development of hypocalcemia were parathyroidectomy, pre and postoperative parathyroid hormone level, corrected calcium levels, neck dissection, preoperative vitamin D, and postoperative magnesium levels. Besides, neck dissection and pre-operative vitamin D levels predicted the development of hypoparathyroidism.

Conclusion: By assessing pre-operative PTH and corrected calcium levels and adopting a customized surgical approach to minimize parathyroid gland damage, we can lower the risk of postoperative hypocalcemia.

Conflicts of Interest: The Authors declare no conflicts of interest.
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Introduction

Thyroidectomy techniques have undergone significant advancements over the past 150 years (1). Along with the increasing prevalence of thyroid disorders, the number of patients

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undergoing thyroid surgery has also risen (2). Total thyroidectomy is the recommended procedure for a significant proportion patients with both malignant and benign thyroid pathologies, including thyroid cancer, Graves' disease and multiple nodular goiters (3, 4).

Hypocalcemia is the most common complication post-thyroidectomy, with rates varying widely from 0.5% to 50% (5).

This condition typically arises within 24 to 48 hours post-operation (6). The multifactorial causes of postoperative hypocalcemia most frequently include iatrogenic injury to the parathyroid glands during surgery, which can result in mild and transient hypocalcemia in up to 50% of cases and rarely permanent hypocalcemia in up to 4% of cases (7-9). Several clinical studies have focused on identifying risk factors or developing models to predict hypocalcemia after thyroid surgery, with most research focusing on total thyroidectomy patients. Previous studies have explored the association of low parathyroid hormone (PTH) levels, preoperative levels of calcium, magnesium, and phosphate, with postoperative hypocalcemia (10-12).

Despite these efforts, definitive predictors of post-operation hypocalcemia are yet to be established. Given the role of vitamin D in calcium metabolism and the limited and conflicting research on the correlation between vitamin D levels and calcium levels, we aimed to conduct a study to assess the impact of vitamin D levels on postoperative calcium and hypoparathyroidism and the occurrence of hypocalcemia and hypoparathyroidism in total and subtotal thyroidectomy patients. Furthermore, the effect of other preoperative variables on post-operative calcium levels and the occurrence of hypoparathyroidism were measured.

Methods

We conducted a prospective study on patients who underwent thyroidectomy in a year period in a tertiary hospital.

The research study strictly adhered to the ethical principles outlined in the Declaration of Helsinki and received formal approval from the ethics committee. Prior to their participation, all patients were extensively briefed about the study protocol and voluntarily provided written consent to partake in the research endeavor.

The risk of developing post-thyroidectomy hypocalcemia was evaluated in relation to risk factors including magnesium, vitamin D, albumin, PTH, and phosphorous. Besides, the risk of developing hypoparathyroidism was assessed. All the cases who underwent total or subtotal thyroidectomy and aged more than 18 years were included. Patients who consumed vitamin D or Calcium supplement were excluded. Furthermore, patients with any disorders that led to calcium disturbances such as pre-operative hypocalcemia, hypomagnesemia, and low PTH levels, paraneoplastic syndrome, chronic kidney disease, and pre-existing parathyroid disease, were excluded. Besides, patients with history of previous neck dissection, neck radiation, and any thyroid or para-thyroid surgery were excluded. The surgical procedures were carried out by a single otolaryngologist, who followed standardized protocols. After the surgeries, the patients refrained from eating overnight and were given a maintenance fluid infusion without calcium. Postoperatively, patients remained hospitalized for a minimum of two nights, during which blood was drawn on the first and postoperative day for calcium, magnesium, PTH, phosphorous, and albumin levels. Two examinations related to hypocalcemia, Trousseau, and Chvostek will be conducted before and after the operation. Any signs of hypocalcemia were recorded.

Data analysis was performed using R. The paired t-test and Wilcoxon signed rank test were utilized to compare pre- and post-operative laboratory data levels, as appropriate. Besides, we categorized patients based on type of surgery, post-surgical calcium and PTH levels and compared these groups. Binary

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logistic regression was conducted to assess potential factors influencing the incidence of hypocalcemia and hypoparathyroidism following thyroidectomy.

Results

Thirty-nine consecutive patients were included in this study. The average age of included patients was 61.5±9.78. Majority of cases were male (35:4, 89.7%). None of the patients had positive Trousseau, and Chvostek tests in their evaluations. Only three patients had partial thyroidectomy.

All the laboratory investigations before surgery was normal. Majority of patients had multinodular goiter. The frequency and percentage of are listed in Table 1.

Table 1. Table 1 shows the distribution of the thyroid pathology among the cases.

Variable		Frequency	Percentage
Disease	Multinodular goiter (MNG)	20	51.3
	Papillary thyroid carcinoma (PTC)	18	46.1
	Right lobe single nodule	1	2.6
neck dissection (central)		9	23.1
Post-operative vitamin D	Hypo	11	28.2
	Normal	23	59
	Hyper	5	12.8
Post-operative PTH	Hypo	29	74.4
	Normal	10	25.6
Post-operative albumin	Hypo	5	12.8
	Normal	34	87.2
Magnesium	Hypo	5	12.8
	Normal	34	87.2
Phosphorus	Normal	29	74.4
	Hyper	10	25.6
Calcium	Hypo	9	23.1
	Normal	30	76.9
Corrected calcium	Hypo	11	28.2
	Normal	28	71.8

After conducting Shapiro-wilk test, it was revealed that except for vitamin D and corrected calcium levels, other variables were not normally distributed. For the variables with normal distribution, paired t test was conducted, otherwise, Wilcoxon signed rank test was performed. The results are demonstrated in Table 2.

Table 2: shows the mean, standard deviation, and the result of statistical analysis.

Variable	Mean	Standard deviation	p-value
Vitamin D (pre-operation)	29.08	5.93	0.1752
Vitamin D (post-operation)	26.78	9.62	
PTH(pre-operation)	31.8	10.94	0.000
PTH(post-operation)	12.21	15.32	
Albumin (pre-operation)	4.62	0.45	0.0014

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Albumin (post-operation)	4.315	0.66	
Magnesium (pre-operation)	1.94	0.13	0.043
Magnesium (post-operation)	1.76	0.33	
Phosphorus (pre-operation)	3.90	0.72	0.049
Phosphorus (post-operation)	4.26	0.97	
Calcium (pre-operation)	9.54	0.51	0.0063
Calcium (post-operation)	8.98	1.03	
Corrected calcium (pre-operation)	9.09	0.46	0.0025
Corrected calcium (post-operation)	8.81	0.73	

As shown in Table 2, after the operation, the level of calcium, corrected calcium, PTH, albumin, and phosphorous significantly decreased.
Based on the type of thyroidectomy (total/partial), patients were divided into two groups. No pre-operative laboratory test differed between two groups. After conducting t-test, it was revealed that there was no statistically significant difference in any of variable (Table 3).

Table 3 show the mean, standard deviation, and resulted p-value for variables categorized based on type of thyroidectomy.

Variable	Mean(partial thyroidectomy)	Standard deviation (partial thyroidectomy)	Mean (total thyroidectomy)	Standard deviation (total thyroidectomy)	p-value
Vitamin D	27	1.41	26.77	9.87	0.923
Parathyroid hormone	10.1	12.86	12.32	15.58	0.691
Albumin	4.55	0.35	4.303	0.679	0.648
Magnesium	1.85	0.07	1.96	0.33	0.78
Phosphorus	3.95	1.34	4.278	0.97	0.78
Calcium	9	0.42	8.98	1.06	0.923
Corrected calcium	8.75	0.21	8.81	0.75	0.648

Table 4: show the mean, standard deviation, and resulted p-value for variables categorized based on developing hypocalcemia after surgery.

variable	Mean(hypocalcemic cases)	Standard deviation (hypocalcemic cases)	Mean (normocalcemic cases)	Standard deviation (normocalcemic cases)	p-value
Vitamin D	27	12.55	26.69	8.47	0.258
Parathyroid hormone	18.97	20.07	9.55	12.45	0.044
Albumin	4.8	0.44	4.125	0.65	0.345

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Magnesium	1.73	0.41	1.94	0.29	0.039
Phosphorus	3.84	0.68	4.42	1.02	0.271

Then cases were categorized based on post-operative hypocalcemia. Likewise, no variable differed significantly across groups (Table 4).
As illustrated in table 4, the only factor that varied statistically between patients with normal and hypocalcemia was PTH level. The cases were divided into categories based on the presence of post-operative hypoparathyroidism. In addition, it was found that calcium and corrected calcium levels significantly differed across the various groups, as indicated in Table 5.

Table 5: shows the mean, standard deviation, and resulting p-value for variables categorized based on the development of hypoparathyroidism after surgery.

Variable	Mean(hypopara thyroidism)	Standard deviation (hypoparathyroidism)	Mean (normal PTH)	Standard deviation (normal PTH	p-value
Vitamin D	25.05	9.75	31.77	17.04	0.222
Albumin	4.19	0.69	4.68	0.415	0.154
Magnesium	1.94	0.32	2	0.35	0.0157
Phosphorus	4.39	0.99	3.89	0.813	0.355
Calcium	8.85	1.14	9.36	0.49	0.032
Corrected calcium	8.91	0.79	8.5	0.45	0.018

To see the effect of independent variables on post-operative corrected calcium and PTH levels, binary logistic regression was conducted. The results are demonstrated in Table 6 and Table 7.

Table 6: shows the results of conducted binary logistic regression to predict post-operative calcium levels.

Variable	p-value
Type of thyroid surgery (total/subtotal)	0.994
Neck dissection	0.0334
Surgery	0.992
Type of disease	0.232
Parathyroidectomy*	0.0102
Pre-operative vitamin D levels	0.047
Post-operative Vitamin D	0.926
Pre-operative PTH levels*	0.044
Post-operative PTH levels	0.0034
Preoperative albumin level	0.0823
Post-operative albumin level	0.00651
Pre-operative phosphorus levels	0.101
Post-operative phosphorus levels	0.105
Pre-operative magnesium levels	0.721
Post-operative magnesium levels	0.031
Pre-operative calcium level	0.0858

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Pre-operative corrected calcium levels*	0.00262

As demonstrated in table 6, parathyroidectomy, pre-operative PTH, and corrected calcium levels statistically predict the post-thyroidectomy hypocalcemia development.

Table 7: shows the results of conducted binary logistic regression to predict post-operative PTH levels.

Variable	p-value
Type of thyroid surgery (total/subtotal)	0.0.439
Neck dissection	0.00585
Type of disease	0.0.0055
Parathyroidectomy*	0.0312
Pre-operative vitamin D levels	0.0288
Post-operative Vitamin D	0.0661
Pre-operative PTH levels	0.3995
Preoperative albumin level	0.0365
Post-operative albumin level	0.055
Pre-operative phosphorus levels	0.969
Post-operative phosphorus levels	0.166
Pre-operative magnesium levels	0.701
Post-operative magnesium levels	0.584
Pre-operative calcium level	0.0553
Post-operative calcium levels	0.179
Pre-operative corrected calcium levels	0.919
Post-operative corrected calcium levels	0.144

Discussion

This study is one of the few studies to measure Mg and PTH levels simultaneously in patients who have undergone total and subtotal thyroidectomy, allowing for a thorough assessment of post-operative hypocalcemia and hypoparathyroidism.

Our findings indicate that parathyroidectomy, alongside pre-operative parathyroid hormone (PTH) and corrected calcium levels are significant predictors of hypocalcemia development following thyroidectomy. These correlations are in line with previous research and highlight the delicate balance maintained by the parathyroid glands in calcium homeostasis and the inadvertent disruption caused by surgery (12-15). The predictive value of preoperative PTH level is possibly attributable to its regulatory role on serum calcium (16). Lower preoperative PTH levels may serve as an indicator of a compromised parathyroid function and predisposition to hypocalcemia. Additionally, lower corrected calcium levels preoperatively may indicate an increased risk of hypocalcemia following thyroidectomy.

Previous studies had suggested a link between low preoperative vitamin D and an increased risk of postoperative hypocalcemia (12, 14, 17, 18). Similarly, we found significant association between preoperative vitamin D levels and the development of postoperative hypocalcemia.

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Additionally, we did not observe any notable differences between vitamin D levels before and after the surgery.

After assessing 215 patients, it was found that 52.1% of those who underwent thyroidectomy developed hypocalcemia(19). This rate is clearly more than our study (about a third of our cases developed hypocalcemia). Other risk factors for hypocalcemia post-thyroidectomy include post-operative PTH less than 10, neck dissection, and inadvertent parathyroid resection(19). All the risk factors aligned with our study. Soares et al. demonstrated that the percentage decrease in PTH levels during the first and eighth hours after thyroidectomy, as well as magnesium levels, strongly predicted postoperative hypocalcemia (20).

Cherian et al. evaluated 50 patients who underwent total thyroidectomy. They found that hypomagnesemia is a frequent finding after thyroidectomy. Furthermore, low post-operative PTH levels were associated with post-surgical hypocalcemia(21). In our study, we observed a significant decrease in Mg levels after surgery. Interestingly, we found that both pre-operative PTH levels, and post-operative PTH levels, significantly predicted the occurrence of hypocalcemia.

Out of 607 patients who underwent total thyroidectomy, 124 patients (20.4%) developed hypocalcemia first day after thyroidectomy. Unlike our study, most of their patients were female. Their cases were younger than our patients. They concluded that combination of low PTH and the decline in PTH level more than 50% predict developing hypocalcemia (22). Likewise, we found that both pre and post-operative PTH levels correlate with developing hypocalcemia.

Moreover, we assessed the effect of variables on hypoparathyroidism development after partial/total thyroidectomy. Type of thyroid disease (MNG), neck dissection, preoperative vitamin D and albumin levels all correlated with developing post-surgical hypoparathyroidism.

Alomari et al. conducted a retrospective study on 343 patients who underwent total or partial thyroidectomy. Despite our research, the majority of their cases involved females. However, the included patients were generally younger than those in our study. Among the patients, about 38% (130 patients) developed hypoparathyroidism, with the majority of them having undergone total thyroidectomy. The study revealed that pre-operative levels of Mg, PTH, ph, Ca, and vitamin D did not correlate with the incidence of hypoparathyroidism. The only significant factor associated with the occurrence of hypoparathyroidism was the type of surgery, with total thyroidectomy showing a significant relationship with hypoparathyroidism (23). The rate of developing hypoparathyroidism among our cases (74.4%) was clearly more than Alomari et al.'s. Despite their finding, we did not observe any association between type of surgery and developing hypoparathyroidism. The reason for this discordance is that the number of patients who underwent partial thyroidectomy in our study was very low (only three patients).

Yamashita et al. found that 1,25 (OH)2D levels were a significant predictor of hypoparathyroidism. They also observed that levels of Mg, PTH, Ca, and 1,25(OH)2D significantly decreased after thyroidectomy (24). Accordingly, we found that pre-operative vitamin D levels predicted the occurrence of hypoparathyroidism. However, in our study, we found no significant difference between the levels vitamin D, while Mg, PTH, albumin, and Ca levels all declined after thyroidectomy. Viqar et al. evaluated 62 patients to assess the impact of Mg on the development of hypoparathyroidism and hypocalcemia after total or subtotal thyroidectomy. Lower Mg levels were associated with post-operative hypoparathyroidism and hypocalcemia(25). The results were in accordance with ours.

After evaluating 321 patients following hemithyroidectomy, it was found that both PTH and calcium levels decreased significantly after

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the surgery. This aligns with our findings, as we observed significant change in calcium levels following thyroidectomy. Furthermore, our results regarding PTH were consistent with this research. The study revealed that low preoperative levels of PTH and calcium were risk factors for transient hypoparathyroidism and hypocalcemia(26).

While our study had certain strengths, it also had some limitations that need to be acknowledged. One significant drawback was the relatively short follow-up period and the small sample size. It is worth noting that the majority of the patients included in the study were male.

Conclusion

In conclusion, our study provides practical insights to improve surgical planning and patient care by identifying predictive factors of hypocalcemia and hypoparathyroidism following thyroidectomy. By evaluating pre-operative PTH and corrected calcium levels, and tailored surgical approach to minimize damage to the parathyroid glands, the risk of postoperative hypocalcemia can be reduced.

Future studies are required to improve our predictive model in order to accurately calculate the risk and identify the need for monitoring and supplementation to prevent complications such as hypocalcemia, ultimately enhancing surgical outcomes and patient well-being.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Ethics

This study received ethical approval from the Ethics Committee of the Islamic Azad University, Ahvaz Branch (Approval Code: IR.IAU.AHVAZ.REC.1402.042).

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