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Incidence of hypocalcemia in total thyroidectomy

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Abstract---Background and objectives: Hypocalcemia is a common complication in patients after total thyroidectomy. This study was undertaken to identify risk factors for post thyroidectomy hypocalcemia. To evaluate the risk factors of post total thyroidectomy hypocalcemia, in order to enable early management, avoid complications, and treat accordingly. Method: A longitudinal study was performed from January 2019 to February 2022. All cases of total Thyroidectomy were included which totaled 27. Ionized serum calcium with Parathyroid Hormone, serum, magnesium, serum phosphate and vitamin D were all measured for every patient preoperatively then postoperatively once, and serum calcium was measured every eight hours for the first 48 hours. Results: Our results showed an overall significant difference in the readings of calcium at different times, the mean of pre-operative reading of serum calcium was (9.6 mg/dl), which was greater than the mean of calcium measured 24 hours post-operative that was (8.72 mg/dl) with ($p < 0.001$), and the incidence of hypocalcemia was 51.9% of hypocalcemia after total thyroidectomy. Parathyroid Hormone level was the only risk factor for developing post total thyroidectomy hypocalcemia ($p < 0.001$), other risk factors were

none of them significant. Conclusions: This study demonstrates that there are markers like (Parathyroid hormone, Magnesium, Phosphate and Vitamin D) which are risk factors for post operative total thyroidectomy hypocalcemia, regardless of other patient factors, surgical techniques, or pathologies. Parathyroid Hormone was an obvious diagnostic marker for hypocalcemia after thyroidectomy.

Keywords---thyroidectomy, hypocalcemia, parathyroid hormone.

Introduction

The etiology of postoperative hypocalcemia after total Thyroidectomy is multifactorial, although the most important component is surgical trauma to the parathyroid glands. Total Thyroidectomy may cause hypoparathyroidism due to the unnoticed removal of the parathyroid gland or damage to its blood supply. Several factors influence surgical trauma: experience of the surgeon, careful tissue manipulation, the number of parathyroid glands identified and preserved, and extent of the surgery (intrathoracic goiter, central lymphadenectomy, reinterventions). Postoperative hypocalcemia is divided into temporary cases (most common), and permanent postoperative hypocalcemia, incidence of 0.2–10%¹. Hypocalcemia may be asymptomatic (biochemical) or symptomatic (clinical). Asymptomatic hypocalcemia patients have serum Ca^{2+} levels lower than the normal range with no clinical symptoms, but symptomatic hypocalcemia patients have stinging pain or paresthesia, convulsions, muscle spasms, mental changes, arrhythmia and/or Chvostek's sign, Trousseau's sign, or QT interval prolongation. Symptomatic hypocalcemia patients may or may not have low serum Ca^{2+} and may require Calcium and vitamin D supplementation². Hypoparathyroidism is the most commonly recognized predictive factor for postoperative hypocalcemia^{3,4}. Measuring Parathyroid Hormone and other items like blood Ca at the same time⁵ could predict post-thyroidectomy hypocalcemia (sensitivity 91-100%, specificity 83-100%). Parathyroid gland (PG) injury, ischemia, and accidental removal are major causes of hypoparathyroidism^{6,7}. They occur typically during total thyroidectomy, removal of a large portion of the thyroid, malignant disease, a long disease course before surgery, or neck lymphadenectomies⁸. Hypoparathyroidism has been categorized as transient or persistent. Parathyroid Hormone also activates α -hydroxylase in renal juxtaglomerular cells and converts 25-hydroxyvitamin D (25-OH-D) into 1,25(OH)₂D, which is the activated form, and stimulates Ca^{2+} absorption in the intestines and Ca^{2+} reabsorption in the renal tubules. Therefore, factors that regulate synthesis and/or secretion of Parathyroid Hormone not only directly regulate function of Parathyroid Hormone for modulating blood Calcium but also control Calcium homeostasis by regulating 1,25(OH)₂D synthesis.

On the other hand, phosphorus concentration is inversely related to calcium and is regulated by calcium, Parathyroid Hormone and vitamin D. Parathyroid hormone decreases phosphate reabsorption at the proximal convoluted tubule. Phosphate ions in the serum form salts with calcium that are insoluble, resulting in decreased plasma calcium. The reduction of phosphate ions, leads to in more ionized calcium in the blood. Magnesium not only plays a direct role in Ca^{2+}

absorption (reabsorption) but is also directly involved in synthesis and/or secretion of Ca regulators, such as PTH and $1,25(\text{OH})_2\text{D}$. Hypomagnesemia stimulates PTH secretion, and hypermagnesemia inhibits PTH secretion. PTH increases blood Ca by mobilizing bone Ca into the blood and enhancing Ca^{2+} reabsorption in distal renal tubules^{9,10}. Therefore, factors that regulate synthesis and/or secretion of PTH not only directly regulate function of PTH for modulating blood Ca but also guide Ca homeostasis by regulating $1,25(\text{OH})_2\text{D}$ synthesis. In addition to Ca^{2+} , Mg^{2+} is a cation important to PTH synthesis and/or secretion. The role of Mg^{2+} in PTH synthesis and/or secretion is similar to that of Ca^{2+} ^{12, 13, 14}.

Vitamin D is a fat-soluble vitamin that participates an important role in calcium homeostasis, including helping calcium absorption from the gastrointestinal tract. Vitamin D deficiency may lead to a compensatory hyperparathyroidism, with the increased PTH levels offsetting insufficient gastrointestinal calcium absorption by enhancing renal calcium reabsorption, thus maintaining normal calcium levels¹⁵. The classic effect of vitamin D is to facilitate the intestinal absorption of calcium by mediating active calcium transport across the intestinal mucosa. Vitamin D acts in this system by both genomic and nongenomic mechanisms^{16, 17}. The aim of this study is to identify risk factors for post operative Thyroidectomy hypocalcemia in comparison with these markers (Parathyroid Hormone (PTH), serum phosphate, serum magnesium (Mg) and Vitamin D).

Patient and Methods

During the study period from January 2019 to February 2022, through a longitudinal study design only selected patients who underwent total Thyroidectomy. Patients excluded from the study were those who underwent subtotal Thyroidectomy, revision Thyroidectomy and patients with central compartment neck dissection. In our study patients were operated by three different surgeons because of small number of cases. In the majority of patients, the parathyroid gland preserved, while in few cases we remove the parathyroid gland and implant it in sternocleidomastoid muscle.

Ionized serum calcium with PTH, serum magnesium, serum phosphate and vitamin D were all measured for every patient preoperatively before a few hours by the nurse lab. Then post operative serum calcium level measured every eight hours in first 48 hours, PTH, magnesium and phosphate were checked only after 24 hours post operatively, then follow up done only for PTH three month after operation, all blood samples taken to one laboratory without use of tourniquet. None of the patients took any oral or intravenous calcium. All study participants provided written informed consent to indicate their agreement for the clinical data to be used in clinical research.

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 26). Paired sample t test was used to compare two readings assessed before and after the operation. Fisher exact test was used to independency test between three or more readings (of the same patients) measured at different time periods (before and after the operation). A chi-square test was used to compare

two readings of the same patients (done after the Fisher exact test). A p value of ≤ 0.05 was considered as statistically significant for PTH.

Results

Twenty-seven patients underwent total thyroidectomy and were included in the study. Their mean age (SD) was 43.2 (13.7) years, the median was 40 years, and the age range was 22-71 years. The largest proportion of the sample (37%) were aged 30-39 years, and the majority (81.5%) were females. Around half (48.1%) of the sample work in sedentary jobs (office work), and 44.4% were housewives. According to the data, post-operative hypocalcemia developed in 14 patients (51.9%), and 26 patients (96.3%) were diagnosed with asymptomatic hypocalcemia but only one case developed symptomatic hypocalcemia after 24 hours post operation.

There was overall significant difference in the level of calcium at different times ($p < 0.001$) which shown in Figure 1. The mean of pre-operative reading of calcium (9.6 mg/dl) was significantly ($p < 0.001$) higher than the means of calcium measured 24 hours post-operative (8.72 mg/dl).

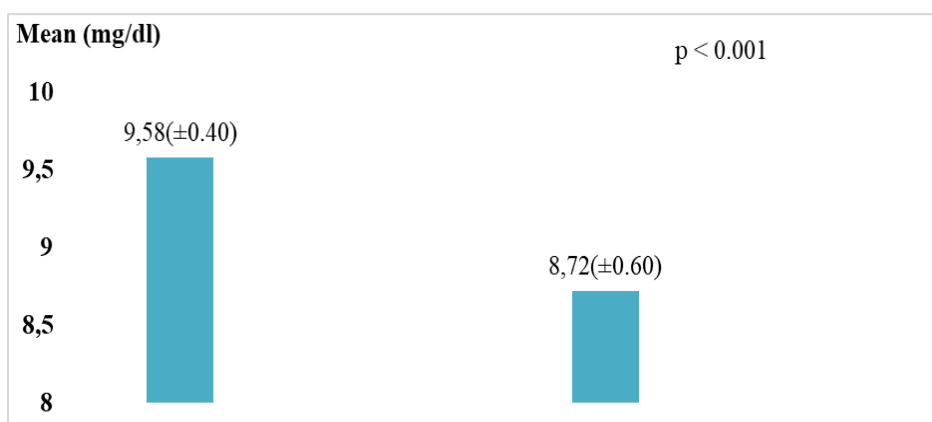


Figure 1. Means of serum Calcium measured preoperatively and after 24hr post-operative

At 24 hours post operative calcium level majority of cases developed hypocalcemia 14 patients (51.9%) as it shown in figure 1, in comparison with other serum calcium reading post operatively which taken after zero hour and 8 hours post op were less than 14 cases developed hypocalcemia. Therefore, we compared our study between hypocalcemia cases within 24 hours post operative with other risk factor in our study (Mg, PTH, Ph and Vitamin D)

Table 1. post operative calcium level 24 hours post operatively

		Cases	Cases in %
Calcium within 24hr	Abnormal	14	51.9%
	Normal	13	48.1%

The association between calcium and PTH levels measured 24 hours after the operation demonstrated in Figure 2. The majority (33.33%) of patient with low PTH, had low Ca level, and only 5 patients (18.52%) with normal PTH level had hypocalcemia, which showed the significant risk factor for developing of hypocalcemia ($p < 0.001$).

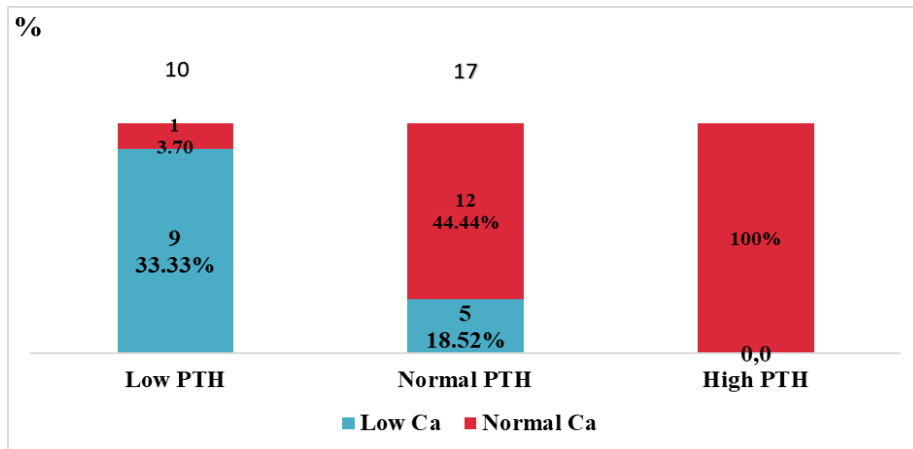


Figure 2. Calcium levels by PTH levels, 24 hours after the operation

Regarding other risk factors Mg and Phosphate as showed in Figure 3 and Figure 4 didn't show any significant relation with hypocalcemia. Only one case with high phosphate (4.55%) (measured 24 hours after the operation) had low Ca, while those with normal phosphate level 10 patients with hypocalcemia (45.45%), therefore the p value was not significant ($p = 0.5$). Also, it is evident only one patient with low Mg developed hypocalcemia (4.5%), and 10 patients (45.45%) of those with normal Mg, developed hypocalcemia, therefore overall risk factor of Mg was not significant ($p = 1.0$).

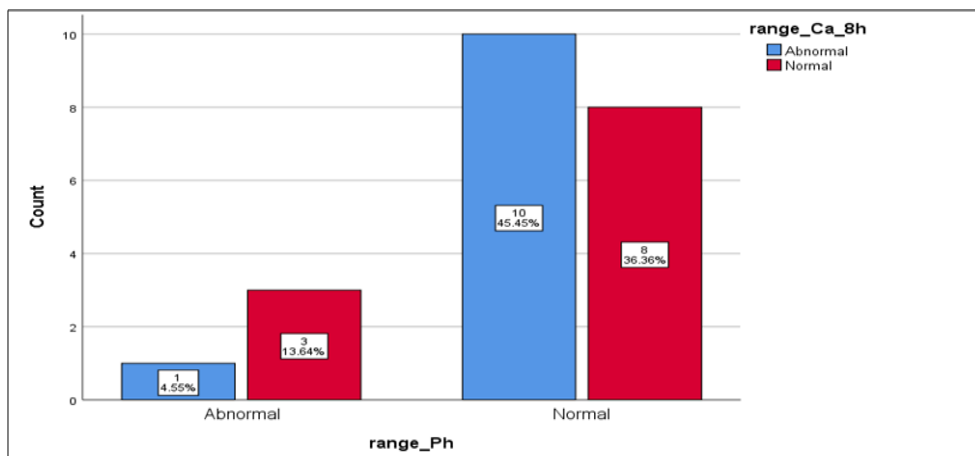


Figure 3. Calcium levels by Phosphate levels, 24 hours after the operation.

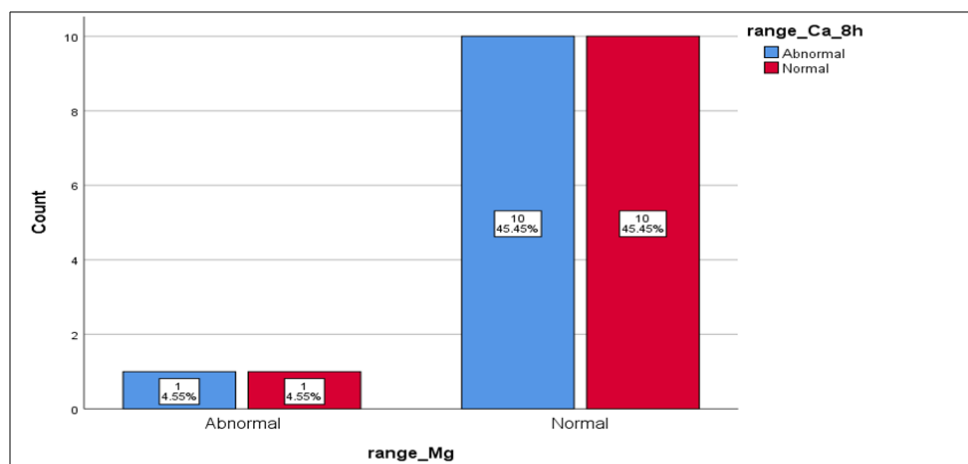


Figure 4. Calcium levels by Magnesium levels, 24 hours after the operation.

Our results showed no significant relationship between Vitamin D and post operative hypocalcemia p value (1.0). out of 27 cases 21 patients had preoperative low vitamin D level, out of those 21 patients 11 patients developed post operative hypocalcemia. 6 patients had normal vitamin D level and 3 out of them developed post operative hypocalcemia which showing in Figure 5.

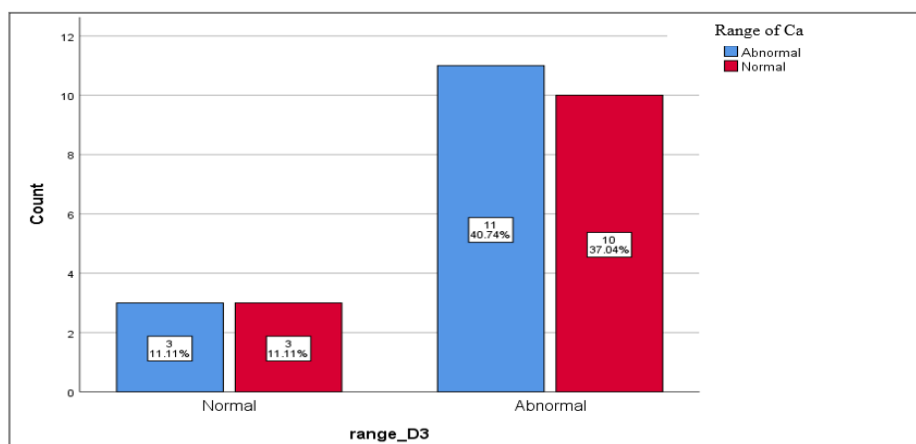


Figure 5. Calcium levels by Vitamin D levels, 24 hours after the operation.

Discussion

Hypocalcemia is one of the most common complications following thyroidectomy. In our study, post-total thyroidectomy hypocalcemia developed in 51.9% (14 patients). Only one patient out of 14 patients developed symptomatic hypocalcemia after 24 hours postoperatively. This patient needs intravenous calcium with oral vitamin D, while all 26 patients were asymptomatic. According to the literature, post-total thyroidectomy hypocalcemia occurs in 50–68% of patients^{18,19} which goes with our study. The majority of patients had asymptomatic hypocalcemia and needed no treatment. The occurrence of hypocalcemia is mainly associated with hypoparathyroidism when parathyroid

glands are devascularized, injured, or dissected during surgery⁶. In addition to PTH level, in our study we selected other factors that may have an effect on the level of calcium like magnesium, vitamin D and phosphate, which may be associated with postoperative hypocalcemia. It would be helpful if we identified other risk factors that help us in post operative hypocalcemia^{20,21}. We evaluated post operative hypoparathyroidism, hypomagnesemia, hyperphosphatemia and vitamin D deficiency as risk factors for postoperative hypocalcemia, but in our study only Parathyroid showed a risk factor for post operative hypocalcemia.

According to our data, low PTH during the first 24 hours after surgery was a statistically reliable predictor of post-operative hypocalcemia ($p < 0.001$). out of 27 patients in our study 10 patients developed Hypoparathyroidism PTH level less than 15 pg/mL (37.0%) out of these 10 patients 9 patients developed hypocalcemia (90.0%). So if we compare post-operative normal PTH levels, 17 patients had normal post operative PTH level (15-65 pg/mL) 5 of them developed hypocalcemia (18.5%), other 12 patients have normal calcium level.

Regarding Mg level, our study shows post thyroidectomy hypocalcemia developed only 1 patient (4.55%) of those who had low Magnesium level, while hypocalcemia developed in 10 patients (45.5%) of those with normal Mg level, this was statistically non-significant ($p=1.0$). Wilson et al. reported that hypomagnesemia indeed had a significant relation with hypocalcemia in a prospective study in a series of 50 patients with total thyroidectomy¹⁹. As its obvious, the relationship between calcium and magnesium metabolism is complicated. Magnesium deficiency is associated with impaired secretion and affinity of PTH. Magnesium may compete with calcium, and play a mimic effect on the parathyroid cell. The "calcium" receptor stimulates secretion of PTH in the presence of elevated level of calcium. However, when hypomagnesemia, calcemic ions are relative much more than usual, secretion of PTH is inhibited¹⁹.

On the other hand, phosphorus concentration is inversely related to calcium and is regulated by calcium, PTH and vitamin D²². The reduction of phosphate ions, therefore, results in more ionized calcium in the blood. In our study none of the patients (27) developed hypophosphatemia. Only one patient had high phosphorus level which developed post operative hypocalcemia (4.45%). While 45.5% of those with normal phosphate which were 10 patients developed hypocalcemia post operative and one patient with high phosphate showed low Ca levels. Our result didn't show any significant risk factor between Ph and Ca P value (0.58). in a study by Turki Aldrees did not detect a significant postoperative change in phosphorus of 333 patient's levels ($p=0.997$), while Cho et al. evaluated 1,030 patients for 6 years and observed a 40% increase in postoperative phosphorus levels on days 1-2, which reliably predicted hyperparathyroidism (specificity: 83%)²².

Regarding Vitamin D as a risk factor, it is well known that serum calcium is regulated by the coordinated actions of PTH and activated vitamin D. PTH maintains a positive calcium balance by stimulating calcium resorption in the renal tubular and calcium release from bone²³. Reduced function of PTH and/or

vitamin D causes hypocalcemia. In the present study, the patient who developed hypocalcemia showed no relation to low levels of Vitamin D²⁴.

Conclusion

The incidence of post operative hypocalcemia after total thyroidectomy was 51.9%. None of the patients developed hypocalcemia or hypoparathyroidism after 3 months of follow up postoperatively. Our study showed post operative PTH level was the only risk factor for developing post total thyroidectomy hypocalcemia. The weakness of our study is the small number of patients. This was due to difficulty in following up with the patient due to the social, cultural nature of our society.

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