# Laboratory Indicators for Predicting Hypocalcemia After Total Thyroidectomy. A Study from A Tertiary Hospital in Saudi Arabia

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**Original Article**

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## ABSTRACT

**Background:** Hypocalcemia is a common complication after total thyroidectomy and it is the most important factor for discharging a patient who underwent total thyroidectomy. Therefore, tools are needed to identify the risk of hypocalcemia in patients who are undergoing total thyroidectomy.

**Aim:** The present study aimed to examine various preoperative parameters for predicting hypocalcemia.

**Patients and Methods:** A prospective study evaluated consecutive patients who had fulfilled the surgical indications for total thyroidectomy, at two Saudi tertiary hospitals during 2017–2018. Standardized preoperative assessment that includes routine laboratory testing and measuring the corrected serum levels of calcium, vitamin D, phosphorus, and magnesium. At 6 hour after the surgery, all laboratory parameters were re-tested. The different variables were tested using Pearson's correlation analysis, the related-samples T-test, the independent-samples T-test, and repeated measures analysis of variance.

**Results:** Total of 90 patients who underwent total thyroidectomy. The mean age of 41 ± 12 years, and included 20 men (22.2%) and 70 women (77.8%). The preoperative labs parameters (e.g., phosphorus, magnesium, albumin, vitamin D, and PTH) had poor predictive values for differentiating between the patients with and without hypocalcemia.The only significant difference was observed for postoperative PTH ($p=0.037$), and the postoperative magnesium and phosphorus levels were not statistically significant ($p=0.200$ and $p=0.997$, respectively).

**Conclusion:** Our study showed that postoperative PTH levels reliably predicted postoperative hypocalcemia. We also found that hypocalcemia was not reliably predicted by age, sex disease type, or the preoperative and postoperative values for vitamin D, phosphorus, and magnesium.

**Key Words:** Calcium, hypocalcemia, thyroidectomy.

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## INTRODUCTION

The Hypocalcemia is a common complication after total thyroidectomy[1], and is mainly related to parathyroid gland insufficiency[2].Postoperative hypocalcemia can be divided into temporary cases (the most common), and permanent postoperative hypocalcemia, which has an incidence of 0.2–10%[1]. However, aside from bleeding, hypocalcemia is the most important factor for discharging a patient who underwent total thyroidectomy. Patient who are not at-risk for developing hypocalcemia can be safely discharged in one day[2], although patients with hypocalcemia may require long-term calcium supplementation[1].Therefore, tools are needed to identify the risk of hypocalcemia in patients who are undergoing total thyroidectomy.

Intraoperative and postoperative measurements of parathyroid hormone (PTH) levels are effective for predicting the development of hypocalcemia, and patients with normal PTH levels can be discharged in the first day after surgery[3]. In addition, PTH, calcium, and vitamin D control the serum concentration of phosphorus[4], which accounts for 1% of total body weight and is mainly contained in the skeletal system[4].Thus, serum phosphate concentrations can serve as a biological marker for parathyroid insufficiency and hypocalcemia[2]. Compared to PTH, serum phosphate testing is less expensive, more readily available, and faster[2]. However, it remains challenging to identify patients who have a high risk of post-thyroidectomy hypocalcemia. Therefore, many studies have examined various perioperative parameters

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(e.g., vitamin D, magnesium, and phosphorus) to determine whether they can be used as laboratory indicators for hypocalcemia[5].

## AIM OF THE STUDY:

The present study aimed to examine various preoperative parameters (e.g., serum phosphate and magnesium levels) for predicting hypocalcemia in patients who were undergoing total thyroidectomy.

## PATIENTS AND METHODS:

This prospective study evaluated consecutive patients who had fulfilled the surgical indications for and were preparing to undergo total thyroidectomy. All surgeries were performed by the same senior head and neck surgeon at two Saudi tertiary hospitals (King Abdulaziz University Hospital and King Fahad Medical City) during 2017–2018. At these centers, all patients who undergo total thyroidectomy also complete a standardized preoperative assessment (1 day prior) that includes routine laboratory testing and measuring the corrected serum levels of calcium, vitamin D, phosphorus, and magnesium. At 6 h and 12 after the surgery, all laboratory parameters were re-tested except vitamin D. We exclude patients who has reimplantation of parathyroid gland, or parathyroid glands was identified in final histopathology. The study's design was approved by the ethical review board of King Saud University.

Patients were diagnosed as having or not having postoperative hypocalcemia based on their laboratory values. Hypocalcemia was defined as corrected calcium levels of ≤1.95mmol/L. All data were analyzed using SPSS software (version 20.0; SPSS Inc., Chicago, IL). The different variables were tested using Pearson's correlation analysis, the related-samples T-test, the independent-samples T-test, and repeated measures analysis of variance.

## RESULTS:

We included 90 consecutive patients who underwent total thyroidectomy. The patients had a mean age of 41.24 ± 12.6 years, and included 20 men (22.2%) and 70 women (77.8%). The most common histopathological diagnoses were multinodular goiter (54.4%) and papillary carcinoma (37.8%) (Table 1). However, comparisons of the different age groups and sexes did not reveal significant differences in the histological findings (Table 2).

The average values for the preoperative and postoperative parameters, and mean changes over time, were compared between the groups with and without hypocalcemia (Table 3 and Figure 1). However, there were no significant differences according to age group, sex, and histopathological diagnosis. Furthermore, the preoperative labs parameters (e.g., phosphorus, magnesium, albumin, vitamin D, and PTH) had poor predictive values for differentiating between the patients with and without hypocalcemia. The only significant difference was observed for postoperative PTH ($p=0.037$) and postoperative calcium ($p<0.001$).The postoperative magnesium and phosphorus levels were not statistically significant ($p=0.200$ and $p=0.997$, respectively).

The abilities of PTH and vitamin D levels to predict hypocalcemia were assessed using receiver operating curves. Vitamin D had a relatively poor predictive power (area under the receiver operative characteristic curve: 0.52), which may be related to the absence of a significant difference between the patients with and without hypocalcemia. However, PTH levels provided a moderate fair predictive power (AUC= 0.733, p=0.038, 95% CI=0.527 to 0.925). The sensitivity and specificity values for various cut-off points are shown in Table 3.

**Table 1:** Patient characteristics

| | N with complete data | N(%) or mean (SD) | Range |
|---|---|---|---|
| Age in years, mean (SD) | 90 | 41.24 (12.6) | 9–69 |
| Age groups, n(%) | 90 | | |
| ≤30 years | | 21 (23.3) | |
| 31–40 years | | 23 (25.6) | |
| ≥41 years | | 46 (51.1) | |
| Sex, n(%) | 90 | | |
| Male | | 20 (22.2) | |
| Female | | 70 (77.8) | |
| Histopathological report, n(%) | 89 | | |
| Follicular carcinoma | | 6 (6.7) | |
| Multinodular goiter | | 49 (54.4) | |
| Papillary thyroid carcinoma | | 34 (37.8) | |
| Pre-operative parameters | | | |
| Parathyroid hormone | 88 | 5.84 (2.1) | 2.48–13.76 |

| | | | |
|---|---|---|---|
| Vitamin D, [nmo/L] | 84 | 53.60 (28.7) | 11.6–127.0 |
| T-CA, [mmol/L] | 88 | 2.34 (0.10) | 2.13–2.64 |
| C-CA, [mmol/L] | 79 | 2.30 (0.10) | 2–2.6 |
| Albumin, [g/L] | 86 | 42.34 (3.60) | 28–49.4 |
| Phosphorus, [mmol/dL] | 81 | 1.10 (0.21) | 0.62–1.74 |
| Magnesium, [mmol/L] | 77 | 0.84 (0.14) | 0.69–1.81 |
| Creatinine, [mmol/L] | 83 | 64.61 (14.6) | 39–104 |
| Post-operative parameters | | | |
| Parathyroid hormone, [pmol/L] | 90 | 3.37 (2.48) | 0.22 –11.3 |
| Calcium, [mmol/L | 89 | 2.21 (0.18) | 1.65–2.80 |
| Magnesium, [mmol/L] | 83 | 0.75(0.10) | 0.52–1 |
| Phosphorus, [mmol/dl] | 81 | 1.24 (0.33) | 0.1–2 |
| Hypocalcemia, n (%) | 89 | 9 (10.0) | |

SD: standard deviation.

**Table 2:** Histological reports according to age and sex

| | FC | MNG | PTC | *P-value* |
|---|---|---|---|---|
| Age group, n(%) | | | | |
| ≤30 years | 1(4.8) | 13 (61.9) | 7 (33.3) | 0.340 |
| 31-40 years | 0 | 15 (65.2) | 8 (34.8) | |
| ≥41 year | 5 (11.1) | 21 (46.7) | 19 (42.2) | |
| Sex, n(%) | | | | |
| Male | 1(5.0) | 12 (60.0) | 7 (35.0) | 0.861 |
| Female | 5 (7.2) | 37 (53.6) | 27 (39.1) | |

FC: Follicular Carcinoma, MNG: multinodular goiter, PTC: papillary thyroid carcinoma.

**Table 3:** Comparing patients with and without hypocalcemia

| | All patients n=90 | Patients with hypocalcemia | Patients without hypocalcemia | *P-value* |
|---|---|---|---|---|
| Age, mean (SD) | 41.36(12.17) | 41.44 (13.5) | 41.06 (12.6) | 0.932 |
| Age group, n(%) | | | | |
| ≤30 years | 21 (23.6) | 2 (22.2) | 19 (23.8) | 0.861 |
| 31–40 years | 23 (25.8) | 3 (33.3) | 20 (25.0) | |
| ≥41 year | 45 (50.6) | 4 (44.4) | 41 (51.2) | |
| Sex, n(%) | | | | |
| Male | 20 (22.5) | 2 (22.2) | 18 (22.5) | 0.985 |
| Female | 69 (77.5) | 7 (77.8) | 62 (77.5) | |
| Histopathological report, n(%) | | | | |
| Follicular Carcimoma | 6 (6.7) | 1 (11.1) | 5 (6.3) | 0.761sss |
| Multinodular goiter | 48 (53.9) | 4 (44.4) | 44 (55.7) | |
| Papillary thyroid carcinoma | 34 (38.2) | 4 (44.4) | 30 (380) | |
| Pre-operative parameters | | | | |
| Parathyroid hormone | 5.84 (2.1) | 5.53 (2.1) | 5.88 (2.1) | 0.637 |
| Vitamin D, [nmol/L] | 53.60(28.7) | 49.43 (27.7) | 54.08 (29.2) | 0.657 |
| T-CA, [mmol/L] | 2.34(0.10) | 2.28 (0.06) | 2.35 (0.10) | 0.053 |
| C-CA, [mmol/L] | 2.30(0.10) | 2.29 (0.07) | 2.30 (0.10) | 0.783 |
| Albumin, [g/L] | 42.34(3.60) | 42.0 (2.7) | 42.49 (3.5) | 0.698 |

| | | | | |
|---|---|---|---|---|
| Phosphorus, [mmol/L] | 1.1(0.21) | 1.14 (0.14) | 1.11 (0.21) | 0.639 |
| Magnesium, [mmol/L] | 0.84(0.16) | 0.79 (0.07) | 0.84 (0.14) | 0.311 |
| Creatinine, [mmol/L] | 64.61(14.6) | 60.37 (18.2) | 65.29 (14.2) | 0.368 |
| Post-operative parameters | | | | |
| Parathyroid hormone, [pmol/L] | 3.37 (2.48) | 1.72 (1.5) | 3.54 (2.5) | 0.037 |
| Calcium, [mmol/L] | 2.21 (0.18) | 1.84 (0.11) | 2.25 (0.14) | <0.001 |
| Magnesium, [mmol/L] | 0.75(0.10) | 0.71 (0.05) | 0.75 (0.09) | 0.200 |
| Phosphorus, [g/L] | 1.24 (0.33) | 1.25 (0.19) | 1.24 (0.34) | 0.997 |
| Change | | | | |
| Calcium, [mmol/L] | -0.14 (0.17) | -0.45 (0.11) | -0.09 (0.14) | <0.001 |
| P-value for intra-group change | <0.001 | <0.001 | <0.001 | |
| Parathyroid hormone, [pmo/L] | -2.45 (2.7) | -3.81 (2.4) | -2.33 (2.71) | 0.121 |
| P-value for intra-group change | <0.001 | <0.001 | <0.001 | |
| Phosphorus, [mmol/L] | +0.16 (0.27) | +0.11 (0.21) | +0.17 (0.28) | 0.542 |
| P-value for intra-group change | 0.001 | 0.151 | 0.004 | |
| Magnesium, [mmol/L] | –0.08 (0.13) | –0.09 (0.08) | –0.09 (0.14) | 0.995 |
| P-value for intra-group change | <0.001 | 0.004 | <0.001 | |

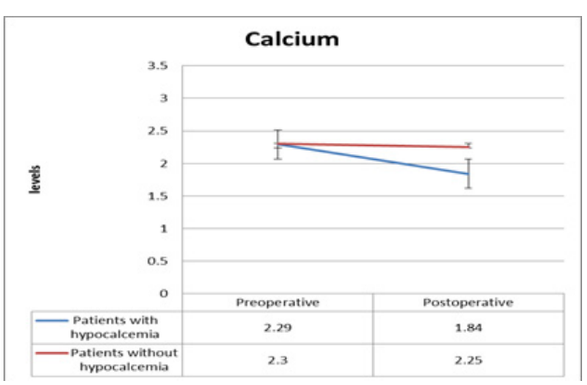
SD: standard deviation.

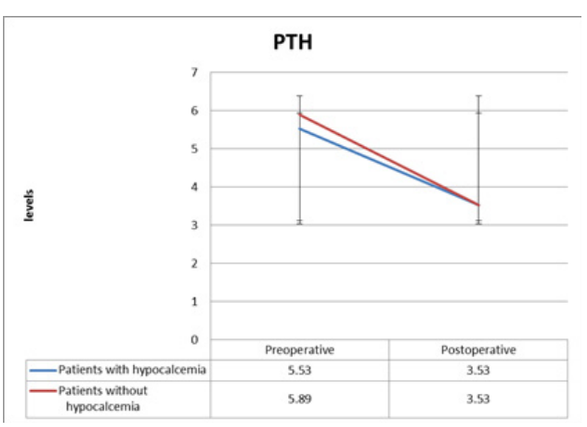
**Table 4:** Sensitivity and specificity for identifying hypocalcemia using postoperative parathyroid hormone levels

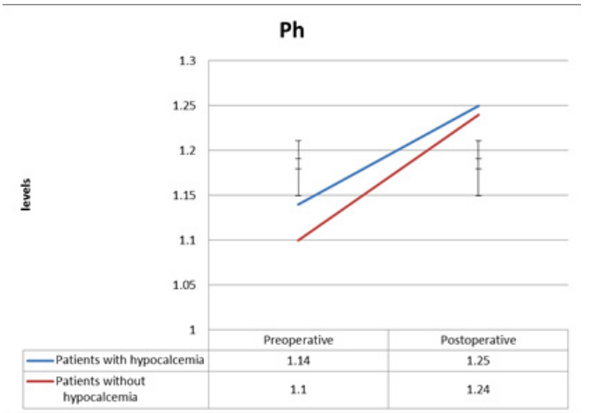
| Cut-off | PTH ≤1 | PTH≤1.5 | PTH≤2 | PTH≤2.5 | PTH≤3 |
|---|---|---|---|---|---|
| Sensitivity | 37.5% | 62.5% | 75.0% | 75.0% | 75.0% |
| 1-Specificity | 10.8% | 18.5% | 26.2% | 33.8% | 41.5% |

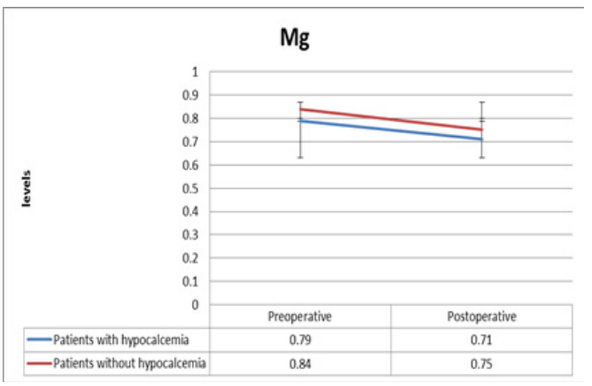
PTH: parathyroid hormone

**Fig 1:** Changes in the parameters means among patients with and without hypocalcemia






## DISCUSSION

The present study examined 90 participants (77.8% women), and the most common histopathological diagnosis was multinodular goiter, which was followed by papillary carcinoma. However, there were no histopathological differences between the different age and sex groups (Table 2). In addition, the patients with and without hypocalcemia did not exhibit any clear differences in age, sex, or histopathology. Furthermore, the preoperative and postoperative laboratory parameters (e.g., phosphate, magnesium, albumen, creatinine, and vitamin D) were not significantly useful for predicting hypocalcemia, with the single exception of postoperative PTH levels ($p=0.037$) (Table 3). In general, these findings agree with the findings from previous studies.

The risk factors for postoperative hypocalcemia include Grave's disease, the surgery's extent (including neck dissection), identifying <3 parathyroid glands, and/or the tumor being left in situ[1].Traditionally, surgeons have used serum calcium levels as the standard for identifying patients who may develop postoperative hypocalcemia, although this measure is not useful until 12 h after the surgery[1]. Furthermore, there are conflicting data regarding whether age is associated with hypocalcemia, with some studies finding that younger patients have a higher risk of developing hypocalcemia[5,6].Other studies have found that hypocalcemia is more common among older age groups[7], while we found no significant age-related differences.

The present study revealed that low postoperative PTH levels were the most reliable laboratory indicator for predicting postoperative hypocalcemia, and this finding agrees with those from other studies[1,5]. For example, Lombardi *et al*. found that low PTH levels at 4 h and 6 h postoperatively were able to predict hypocalcemia, and they concluded that a single PTH measurement may be useful for identifying patients who will develop hypocalcemia[8]. Furthermore, Lam and Kerr found that a decrease in PTH levels at 1 h postoperatively was a strong predictor of post-thyroidectomy hypocalcemia[9].Moreover, Seo *et al*. found that hypocalcemia was predicted by iPTH levels of <10.42 pg/mL at 1 h postoperatively and a >70% decrease in PTH levels at 1 h postoperatively[1].

Previous studies have reported that PTH provides a sensitivity of up to 96.4% for predicting hypocalcemia, with a specificity of 37.5–75%, although other studies have reported values that approached 100%[1,8]. We believe that these results are related to the larger patient populations from those studies, and it should be noted that mild hypocalcemia can occur even if there are normal postoperative PTH levels[10]. This is especially true in cases of vitamin D deficiency, as proposed by Pradeep *et al*.[11]. Nevertheless, our data indicate that patients with normal postoperative PTH levels are eligible for early discharge, and their hospital stay can be minimized, given their low risk of developing hypocalcemia and readmission. However, standardized approaches are needed for the early management of patients with low PTH levels, in order to prevent the development of hypocalcemia.

Although we did not detect a significant association between hypocalcemia and vitamin D levels ($p=0.657$), other studies have reported some level of correlation with hypocalcemia[7,12]. Our findings also revealed no significant association with magnesium levels ($p=0.200$). Cherian *et al*. found a high prevalence of postoperative hypomagnesemia among hypocalcemic patients (up to 80%, $p=0.41$), and they also observed an elevated risk of developing clinical signs/symptoms of hypocalcemia, which led them to recommend close postoperative magnesium monitoring for patients with hypocalcemia[13]. Another study of 333 patients revealed a significant postoperative decrease in magnesium levels ($p = 0.017$)[4]. The present study

did not detect a significant postoperative change in phosphorus 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%)[14].

The present study is limited by the small sample size and the fact that we did not consider any symptoms of hypocalcemia. Moreover, we did not consider the surgery's extent and the number of parathyroid glands that were identified intraoperatively. Therefore, larger studies in other areas of Saudi Arabia are needed to validate our findings.

## CONCLUSION

In conclusion, hypocalcemia is a common complication after thyroidectomy, and we found that postoperative PTH levels reliably predicted postoperative hypocalcemia. We also found that hypocalcemia was not reliably predicted by age, sex, disease type, or the preoperative and postoperative values for vitamin D, phosphorus, and magnesium. Therefore, early interventions to prevent hypocalcemia should be implemented in patients with low PTH levels after thyroidectomy.

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## CONFLICT OF INTEREST

There are no conflicts of interest.

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