

# The Effect of Calcium Supplements on Levothyroxine after Total Thyroidectomy: Results from a Single Centre, Retrospective Study in Kelantan, Malaysia

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**Abstract— Introduction:** Thyroid hormone replacement (levothyroxine) needs to be prescribed and calcium supplements may be administered with levothyroxine to overcome hypocalcaemia following total thyroidectomy. Evidences have shown that there is an interaction between those two. Therefore, we aimed to assess the effect of calcium supplements on levothyroxine after total thyroidectomy. **Methods:** A retrospective study was conducted from 1 April to 30 September 2022 involving all patients who underwent total thyroidectomy in Hospital Raja Perempuan Zainab II, Kelantan, Malaysia from 1 January 2019 to 31 December 2020. They were prescribed either levothyroxine or levothyroxine with calcium supplements for at least three months after the surgery. Those with incomplete data were excluded. Thyroxine (T4), thyroid stimulating hormone (TSH) and calcium levels were compared between patients receiving levothyroxine with and without calcium supplements using independent t-test in Statistical Package for Social Sciences (SPSS) version 22.0. A statistically significant test result was set at a P-value of less than 0.05. **Results:** A total of 50 patients were included in the study. They were mostly prescribed levothyroxine with calcium supplements (74%, n=37). When compared, those taking both medications had significantly lower T4 [11.56 (4.04) pmol/L vs 15.68 (7.59) pmol/L; P=0.017] and higher TSH [9.66 (12.44) vs 1.13 (1.54); P<0.001] levels. However, there was no significant difference of calcium levels between patients receiving levothyroxine with and without calcium supplements [2.13 (0.22) vs 2.13 (0.16), P=0.929]. **Conclusion:** Calcium supplements were observed to have an effect on levothyroxine after total thyroidectomy. Thus, it is important for healthcare providers and patients to be aware of the interaction between levothyroxine and calcium supplements.

**Keywords—** Levothyroxine, thyroxine, thyroid stimulating hormone, calcium, thyroidectomy.

## I. INTRODUCTION

Kelantan is one of the states in Malaysia that has a high incidence of goiter [1] and increasing thyroid cancer cases [2]. The surgical department of the state general hospital, Hospital Raja Perempuan Zainab II had performed 723 thyroid surgeries over a period of seven years [3]. Among them is thyroidectomy, a surgical intervention used to reduce the problems associated with various thyroid diseases such as thyroid malignancy, retrosternal goiter, uncontrolled hyperthyroidism, Hashimoto's disease and hypothyroidism with suspicion of superimposed lymphoma by resecting the thyroid gland partially or entirely [4].

Despite its low mortality rate, patients can develop complications such as comprehensive hematoma, sepsis, bilateral recurrent nerve paralysis and recurrent laryngeal nerve palsy [5]. However, the most common complication following thyroidectomy is hypocalcemia [6]–[8]. The incidence of post-thyroidectomy hypocalcemia can vary from 2% to 83% [7].

Levothyroxine is a synthetic thyroxine hormone prescribed for hypothyroidism or thyroid hormone replacement therapy, especially in patients undergoing total thyroidectomy [9], [10]. It is absorbed mainly in the small intestine, precisely at the duodenum, the ileum and the jejunum [11], [12]. In Malaysia healthcare facilities, it is available in tablet dosage form only [13]. Many factors may influence the absorption of

levothyroxine, such as gastric pH, the presence of food, concomitant medications or supplements and the nature of the disease [11].

To overcome hypocalcemia, calcium supplements may be administered alongside levothyroxine. However, they have been shown to interact with levothyroxine by lowering its absorption. A prospective cohort study by Singh et al. (2000) discovered that mean thyroxine (T4) levels were significantly lowered upon taking calcium and increased after calcium withdrawal. They observed that concomitant administration of levothyroxine and calcium also significantly increased mean thyroid stimulating hormone (TSH) levels which declined following calcium withdrawal [14]. A retrospective population analysis by Irving et al. (2015) also found that after six months on levothyroxine and calcium supplements, 4.4% of patients in the calcium group had a significant increase in TSH levels of more than 5  $\mu$ unit/L [15].

Even though clinically significant interaction between levothyroxine and calcium supplements can alter the safety and efficacy of the treatment, they still seem to be generally underestimated by patients, physicians and pharmacists [10]. Considering this and the fact that such literature is lacking in the local setting, we aim to evaluate the effect of calcium supplements on levothyroxine following the surgery in Hospital Raja Perempuan Zainab II, Kelantan, Malaysia. It is important that healthcare providers understand the potential interaction between both medications as it can help to improve the management of patients after total thyroidectomy.

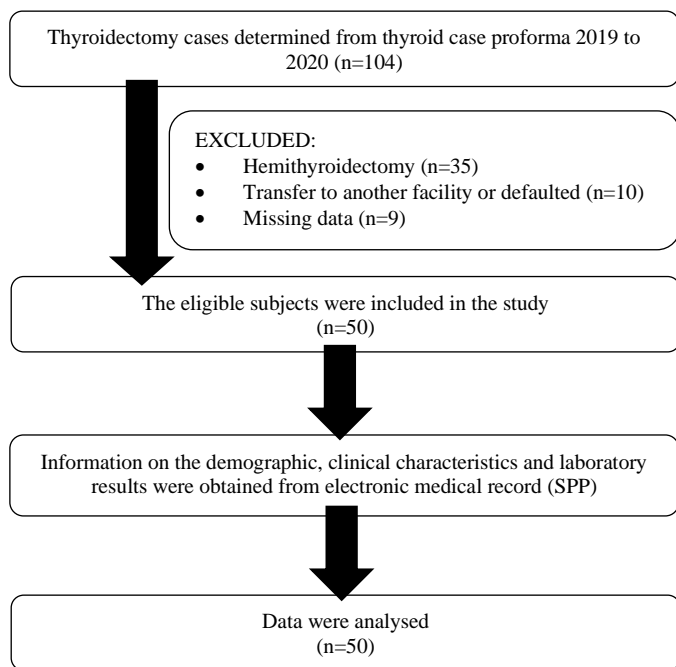
II. METHODS

A. Design and Study Population

We conducted a retrospective study between the period of 1 April to 30 September 2022 using a clinical registry which is the thyroid case proforma from surgical department, Hospital Raja Perempuan Zainab II. The inclusion criteria were all patients who underwent total thyroidectomy in Hospital Raja Perempuan Zainab II from 1 January 2019 to 31 December 2020, prescribed either levothyroxine or levothyroxine with calcium supplements for at least three months after surgery. Those with incomplete data of T4, TSH and calcium levels were excluded from the study.

B. Data Collection

Eligible subjects were determined from the thyroid case proforma based on the study criteria. Since all patients who fulfilled the study criteria were included, no sample size calculation and sampling method was applied. Information on their demographic, clinical characteristics and laboratory results were further obtained from electronic medical records which was the Patient Management System (SPP) and documented in the data collection form.



C. Statistical Analysis

The data analysis process was performed in Statistical Package for Social Sciences (SPSS) version 22.0. The demographic and clinical characteristics of the patients were described using descriptive statistics. All numerical data were presented in mean and standard deviation (SD) while categorical data were noted in frequency and percentage. T4, TSH and calcium levels were compared between patients receiving levothyroxine with and without calcium supplements using independent t-test. A P-value of less than 0.05 was determined as a statistically significant test result.

D. Ethical Approval

Our study was registered with National Medical Research Register (NMRR), Ministry of Health Malaysia with NMRR ID-22-00300-CLO. The ethical approval was obtained from Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia while the site approval to conduct the study was permitted by the hospital director. To maintain confidentiality, no identifiers were used and all subjects were remained anonymous.

III. RESULTS

A. Demographic and Clinical Characteristics

A total of 50 patients were recruited into the study. They were all Malay with mean (SD) age of 44.9 (15.2) years old, mostly female (82%, n=41) and married (86%, n=43).

The diagnosis was mainly goitre (68%, n=34) with mean (SD) length of hospitalization after total thyroidectomy was 4.9 (1.8) days. Many of them had no comorbidities (60%, n=30) but were taking concomitant medications (78%, n=39) which were not known to interfere with levothyroxine (88%, n=44). Also, the majority were prescribed levothyroxine with calcium supplements (74%, n=37) (Table 1).

TABLE 1. The demographic and clinical characteristics of the patients (n=50)

Characteristics	Mean (SD)	n (%)
Gender		
Male		9 (18%)
Female		41 (82%)
Age (years old)	44.9 (15.2)	
Race		
Malay		50 (100%)
Marital status		
Single		7 (14%)
Married		43 (86%)
Diagnosis		
Goitre		34 (68%)
Carcinoma		14 (28%)
Autoimmune		2 (4%)
Length of hospitalization after total thyroidectomy (days)	4.9 (1.8)	
Comorbidities		
Yes		20 (40%)
No		30 (60%)
Concomitant medications		
Yes		39 (78%)
No		11 (22%)
Other medications known to interfere with levothyroxine		
Yes		6 (12%)
No		44 (88%)
Group		
Levothyroxine with calcium		37 (74%)
Levothyroxine		13 (26%)

B. Comparison of T4, TSH and Calcium Levels

When compared, it was found that the mean (SD) T4 levels were significantly different between patients receiving levothyroxine with calcium and levothyroxine alone. The patients receiving levothyroxine with calcium had lower T4 level than those on levothyroxine only [11.56 (4.04) vs 15.68 (7.59), P=0.017] (Table 2).

TABLE 2. Comparison between levels of T4 between patients receiving levothyroxine with and without calcium supplements after total thyroidectomy

Group	n	Mean (SD)	Mean difference (95% CI)	t-statistics (df)	P-value
Levothyroxine with calcium	37	11.56 (4.04)	-4.12 (-7.47, -0.77)	-2.48 (48)	0.017
Levothyroxine	13	15.68 (7.59)			

Normal: 7.86 – 14.41 pmol/L; Independent t-test

The mean (SD) levels of TSH in both groups were also significantly different. The patients receiving levothyroxine with calcium had a higher TSH level than those on levothyroxine only [9.66 (12.44) vs 1.13 (1.54),  $P < 0.001$ ] (Table 3).

TABLE 3. Comparison between levels of TSH between patients receiving levothyroxine with and without calcium supplements after total thyroidectomy

Group	n	Mean (SD)	Mean difference (95% CI)	t-statistics (df)	P-value
Levothyroxine with calcium	37	9.66 (12.44)	8.53 (4.30, 12.75)	4.08 (39)	<0.001
Levothyroxine	13	1.13 (1.54)			

Normal: 0.40 – 4.00 mIU/L; Independent t-test

However, there was no significant difference of calcium levels between patients receiving levothyroxine with and without calcium supplements [2.13 (0.22) vs 2.13 (0.16),  $P = 0.929$ ] (Table 4).

TABLE 4. Comparison between levels of calcium between patients receiving levothyroxine with and without calcium supplements after total thyroidectomy

Group	n	Mean (SD)	Mean difference (95% CI)	t-statistics (df)	P-value
Levothyroxine with calcium	37	2.13 (0.22)	0.001 (-0.13, 0.14)	0.09 (48)	0.929
Levothyroxine	13	2.13 (0.16)			

Normal: 2.20 – 2.65 mmol/L; Independent t-test

#### IV. DISCUSSION

It is well known that some medications, food and dietary supplements can interfere with intestinal absorption of levothyroxine when taken simultaneously. Such reports include calcium supplements of various formulations [9], [16].

Our findings indicated that calcium supplements had a modest, significant effect on thyroid function, likely due to the malabsorption of levothyroxine when they are concomitantly administered. We found that the patients taking calcium supplements with levothyroxine had a significantly lower T4 level by 24.5%. The results were consistent with other previous literature. Singh et al. (2000) reported that concomitant administration of calcium and levothyroxine reduced mean serum T4 levels. The mean free T4 levels among their study population were 17 pmol/L at baseline, 15 pmol/L during the calcium period and 18 pmol/L (1.4 ng/dL) after calcium discontinuation ( $P < 0.001$ ). The increased T4 levels in most patients after calcium withdrawal suggested that the changes were likely due to calcium ingestion [17]. The extent of T4 level reduction was supported by Zamfirescu and Carlson (2011) who concluded that calcium supplements significantly decreased the levothyroxine absorption by about 20 to 25% [16]. It was observed that taking calcium supplements concomitantly with levothyroxine within four

hours could interrupt its absorption [18]. This is because levothyroxine takes about three hours to be completely absorbed in the intestine [10]. The interaction was relevant for all calcium supplement formulations, with each of them significantly diminished the T4 absorption area compared to levothyroxine alone [16]. In Hospital Raja Perempuan Zainab II, the calcium supplements available are calcium lactate and calcium carbonate [13].

As for TSH levels, we observed that it was higher in patients taking calcium supplements with levothyroxine compared to those taking levothyroxine alone. It was above the normal range, in concordance with a case report by Mazokopakis et al. (2008). The TSH level for their patient rose from 2.0 mIU/L to 9.8 mIU/L after taking levothyroxine and calcium carbonate [18]. Singh et al. (2000) noted that simultaneous administration of levothyroxine and calcium increased the mean TSH levels from 1.6 to 2.7  $\mu$ unit/L which declined to 1.4  $\mu$ unit/L following calcium withdrawal [17]. Irving et al. (2015) found that the elevation of TSH level after six months from baseline [1.39 (2.44) to 1.64 (2.71),  $P = 0.005$ ] was statistically significant in calcium as one of the study drugs. One-third of the patients in the trial even had TSH levels above the normal range, necessitating an incremental dose of levothyroxine during calcium therapy [15].

Finally, we observed that the calcium levels were similar between both groups. It is anticipated that with frequent monitoring, the calcium levels for patients taking levothyroxine with or without calcium supplements have no major difference. This is due to the fact that hypocalcaemia following thyroidectomy is a frequent complication [6]–[8]. A doctor will prescribed calcium supplements in patients who are risk of developing hypocalcaemia [19] which is identified as a marked decrease in blood calcium, immediately after surgery [20].

One of the limitations of our study was the small sample size obtained from a single center. We were unable to include thyroidectomy cases performed after 2020 as the COVID-19 pandemic had disrupted the delivery of surgery. Therefore, the findings were not generalizable to the whole population in Malaysia and should be interpreted carefully. Because of the retrospective design, we also encountered a great deal of missing data. Some key statistics such as medication adherence, body mass index and dietary intake were not possible to be measured from secondary data. Therefore, we recommend that future investigations should be carried out in prospective manner in multiple centers to portray the actual effect of calcium supplements on levothyroxine after total thyroidectomy.

#### V. CONCLUSION

Calcium supplements were observed to have an effect on levothyroxine after total thyroidectomy. The interaction caused lower T4 levels and higher TSH levels in patients taking both medications. Thus, it is important for patients and healthcare providers to be aware that calcium supplements can interact with levothyroxine by affecting its absorption. Continuous education can help to decrease the risk of this clinically significant interaction.

CONFLICT OF INTEREST

We declare that we do not have any personal or financial conflict of interest.

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