# THYROID STIMULATING HORMONE EVALUATION BETWEEN THREE AND FOUR WEEKS OF LEVOTHYROXINE WITHDRAWAL IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA

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***Abstract***

Most patients with differentiated thyroid cancer (DTC) would require radioactive iodine (RAI) ablation therapy with I-131. Before RAI ablation therapy, levothyroxine is withheld for four to six weeks to increase TSH to over 30 mIU/L. Most people develop hypothyroidism on levothyroxine withdrawal. Reducing levothyroxine withdrawal from four to three weeks would enhance health and hypothyroidism symptoms. This study aims to evaluate the thyroid-stimulating hormone level after three and four weeks of levothyroxine withdrawal in patients with DTC in the Northern Malaysia population. All DTC patients undergoing RAI ablation therapy from January 2018 to November 2019 were enrolled. TSH levels were evaluated three and four weeks after discontinuing levothyroxine. Clinical data were analysed using IBM SPSS (Statistical Package for the Social Sciences) version 26.0.0. One hundred four patients with a mean age of 47.06 years were recruited. Most patients (77.88%) had papillary thyroid carcinoma (PTC) and were female (80.77%) and Malay (53.85%). By week three of levothyroxine withdrawal, 88.46% of patients had TSH levels above 30 mIU/L, with an average of 66.89 mIU/L, and at week four, 99.04% of patients had TSH levels above 30 mIU/L. Cohen's kappa measurement of the agreement was 0.139 between weeks three and four. A TSH level greater than 30 mIU/L was detected in 88.46% of patients who had discontinued levothyroxine for three weeks and 99.04% after four weeks. It is recommended to review the TSH level at 3 weeks instead of 4 weeks in patients who could not tolerate hypothyroidism symptoms.

**Keywords:** Thyroid cancer, Thyroxine withdrawal period, Three versus four weeks, TSH levels

## *Introduction*

Radioactive iodine ablation (RAI) is the treatment of choice for differentiated thyroid cancer (DTC) after total thyroidectomy or near-total thyroidectomy. This therapy is not required when the size of a tumour is less than 1 cm; there is no proof of metastasis, no capsular invasion, and no evidence of unfavourable histology such as tall, columnar, or diffuse cells sclerosing type and no record of radiation exposure (1). The principle of radioiodine therapy is the ability of the remnant and cancer cells to take radioactive iodine (iodine-131) via the sodium iodide channel. Although cancerous thyroid tissues exhibit hypofunction compared with non-cancerous thyroid tissues, the former can maintain physiological function and have minimal radioiodine uptake. For an effective radioiodine therapy, the thyroid stimulating hormone (TSH) level must be more than 30 mIU/L. Several approaches for achieving this aim are utilised globally, including the withdrawal of levothyroxine for three to four weeks, triiodothyronine for two weeks, and intramuscular thyrogen injection.

The standard method is four-week abstinence from levothyroxine to induce endogenous TSH and generate short-term hypothyroid symptoms. Patients at Hospital Pulau Pinang are instructed to discontinue levothyroxine for four weeks prior to RAI therapy. Due to its expensive cost, thyrogen is reserved for a select group of patients, including those who cannot tolerate hypothyroidism due to their occupation, those who are unable to attain a stimulated TSH after four weeks of levothyroxine withdrawal, and those with pituitary disease.

Since triiodothyronine is not commonly available in local hospitals, the first alternative continues to be utilised most frequently. This study aims to minimise the withdrawal duration for levothyroxine in Northern Malaysian patients with DTC from four weeks to three weeks. However, this study did not affect the hospital's standard operating procedures.

## *Methods*

This prospective observational study with a universal sampling method was conducted in the Department of Nuclear Medicine, Penang General Hospital, Malaysia, for 23 months (January 2018 to November 2019) with a 10% dropout rate. The calculated sample size is 95 subjects.

All patients with DTC requiring RAI ablation therapy (either for the first time or as a follow-up) were included. Patients over 18 who had undergone a whole or near-total thyroidectomy and whose histopathological examination was verified to be DTC met the inclusion criteria. Pregnancy was the excluding factor.

The principal investigator evaluated all RAI therapy referrals. Patients were either referred as new DTC cases or existing patients needing a second RAI dose for ablation.

Prior to RAI treatment, the standard procedure consisted of levothyroxine withdrawal for four weeks and intake of seafood-containing foods for two weeks. Week four was scheduled for admission to the radioiodine unit. A series of blood tests were taken, including a thyroid function test (TFT). Patients with TSH of more than 30 mIU/L were given RAI ablation treatment on day one. On days one and two, 0.9 mg intramuscular thyrogen was administered to patients having a TSH less than 30 mIU/L. RAI ablation treatment was administered on day three to patients having a TSH level of less than 30 mIU/L, and I-WBS was performed on day five for all patients. TFT was performed during both weeks three and four. Approximately 3–5 mL of blood was taken via venepuncture in the treatment room and stored in a plain tube before being sent to the hospital's endocrine laboratory. All study participants, or their legal guardian, provided informed written consent prior to study enrolment.

Statistical analysis was performed using SPSS IBM software. Descriptive studies were used to summarise the demographics of the patients. A paired t-test was used to evaluate the proportion of patients whose TSH levels at 3 and 4 weeks were less than or greater than 30 mIU/L. A Pearson chi-square test was used to compare the TSH levels at the end of weeks three and four of levothyroxine discontinuation therapy.

## *Ethical statements*

The study was performed in accordance with the declaration of Helsinki. This study was approved by Jawatankuasa Etika Penyelidikan Manusia, USM (JEPeM code: USM/JEPeM/18010084) and Medical Research and Ethics Committee (NMRR code: NMRR-17-3021-39298).

## *Results*

### *Demographic and Clinical Data*

One hundred four patients were enrolled in the study. The median age of patients was 47.06 years. Most of the patients were female, with 80.77 % (n = 84), and male patients contributed only 19.23 % (n = 20) in this study. Among the DTC patients, 77.88% (n = 81) had papillary thyroid carcinoma (PTC), and the rest had follicular thyroid carcinoma (FTC) (22.12 %) (n = 23). The majority of the patients had stage 1 disease with 67.31 % (n = 70). The demography and clinical data are summarised in table 1.

**Table 1:** Demographic and clinical data

| **Variables** | | **N (%)** |
|---|---|---|
| **Age** | | **Mean (SD): 47.06 (14.92)** |
| **Ethnicity** | Malay | 56 (53.85) |
| | Chinese | 30 (28.85) |
| | Indian | 16 (15.38 |
| | Siamese | 1 (0.96) |
| | Indonesian | 1 (0.96) |
| **Gender** | Male | 20 (19.23) |
| | Female | 84 (80.77) |
| **Types of DTC** | Papillary Thyroid Carcinoma | 81 (77.88) |
| | Follicular Thyroid Carcinoma | 23 (22.12) |
| **Disease staging** | Stage 1 | 70 (67.31) |
| | Stage 2 | 18 (17.31) |
| | Stage 3 | 7 (6.73) |
| | Stage 4 | 9 (8.65) |

DTC=Differentiated Thyroid Carcinoma

***TSH levels between weeks 3 and 4 of levothyroxine withdrawal.***

At week 3, 88.46 % (n = 92) of patients had TSH levels greater than 30 mIU/L. Only 12 patients (11.54 %) had a TSH level below 30 mIU/L. At week 4, 99.04 % (n = 103) of patients had achieved a TSH level greater than 30 mIU/L. One patient (0.96 %) did not achieve a TSH level greater than 30 mIU/L./L. These results are shown in Figure 1.

As shown in Table 2, a paired T-test was used to compare TSH levels between weeks 3 and 4 of levothyroxine withdrawal.

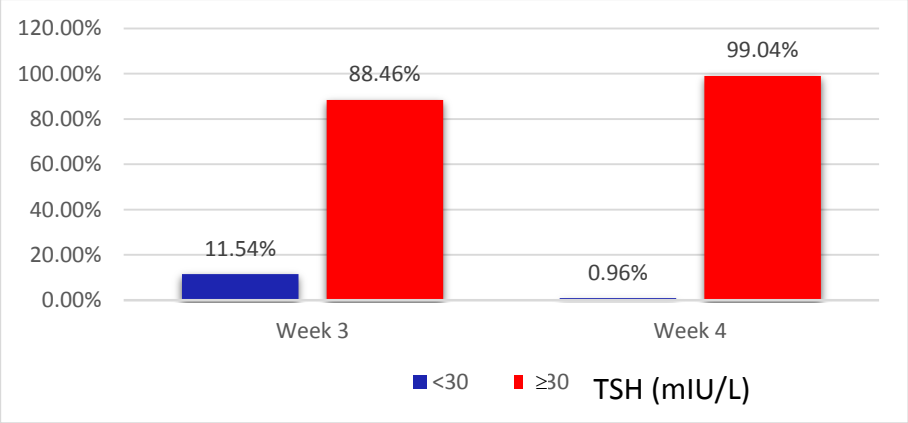


**Figure 1:** The proportion of TSH levels at weeks 3 and 4 of levothyroxine withdrawal

**Table 2:** Comparison of mean TSH levels between weeks 3 and 4 of levothyroxine withdrawal

| Variables | Mean (SD) | N | Mean differences (95% CI) | t-statistics (df) | p value |
|---|---|---|---|---|---|
| **TSH level week 3** | 66.89 (28.72) | 104 | 20.90 (16.84, 24.96) | 10.213 | <0.001 |
| **TSH level week 4** | 87.79 (19.21) | 104 | | | |

TSH-Thyroid Stimulating Hormone

As shown in Table 3, Cohen's Kappa was used to compare the TSH levels between weeks 3 and 4 (< 30 or ≥ 30 mIU/L). At week 3, twelve patients had TSH levels below 30 mIU/L, but by week 4, only one had TSH levels below 30 mIU/L. At both weeks, 92 of the 104 patients had TSH levels similar to and above 30 mIU/L.

The measure of concordance was used to determine the significance of the TSH level at week 3 relative to the gold standard (week 4). Cohen's kappa measurement of agreement revealed a value of 0.139, indicating that TSH levels at weeks 3 and 4 exhibited only a slight degree of agreement.

**Table 3:** Comparison of TSH levels (< 30 and ≥ 30 mIU/L) between weeks 3 and 4 of levothyroxine withdrawal

| | | | TSH week 4 (mIU/L) | | Total | Measure of Agreement (kappa) |
|---|---|---|---|---|---|---|
| | | | **< 30** | **≥ 30** | | |
| **TSH week 3 (mIU/L)** | **< 30** | **Count** | 1 | 11 | 12 | 0.139 |
| | | **% within TSH week 3** | 8.3% | 91.7% | 100.0% | |
| | **≥ 30** | **Count** | 0 | 92 | 92 | |
| | | **% within TSH week 3** | 0.0% | 100.0% | 100.0% | |
| **Total** | | **Count** | 1 | 103 | 104 | |
| | | **% within TSH week 3** | 1.0% | 99.0% | 100.0% | |

* kappa Agreement
0.01 – 0.20 Slight agreement
TSH-Thyroid Stimulating Hormone

The patients whose TSH levels were less than 30 mIU/L during weeks 3 and 4 of levothyroxine withdrawal were listed in Table 4. Most of the patients were female, and all were diagnosed with PTC. Staged one was predominant.

Most of these patients were receiving their initial RAI treatment. Seven of them were younger than 55 years of age, while the remaining five were older than 55 years of age. At weeks 3 and 4, only one of the 12 patients could not achieve a TSH greater than 30 mIU/L, with a value of 28.7 mIU/L.

**Table 4:** List of patients who failed to achieve a TSH level of 30 mIU/L or higher at weeks 3 and 4 of levothyroxine withdrawal

| TSH level at week 3 (mIU/L) | TSH level at week 4 (mIU/L) | Gender | Tumour type | Stage | Age | Number of RAI |
|---|---|---|---|---|---|---|
| 22.1 | 45.5 | Female | PTC | 1 | 75 | 1 |
| 6.72 | 95 | Female | PTC | 1 | 18 | 2 |
| 29.44 | 56.1 | Female | PTC | 1 | 26 | 1 |
| 16.47 | 64.4 | Female | PTC | 1 | 25 | 1 |
| 0.596 | 98 | Female | PTC | 2 | 63 | 3 |
| 14.6 | 75.4 | Female | PTC | 1 | 38 | 1 |
| 27.22 | 98.6 | Female | PTC | 4B | 64 | 3 |
| 13.18 | 58.6 | Female | PTC | 4B | 60 | 1 |
| 12.75 | 48.5 | Female | PTC | 1 | 49 | 1 |
| 13.7 | 35.7 | Female | PTC | 2 | 60 | 1 |
| 26.57 | 38.4 | Male | PTC | 1 | 47 | 1 |
| 5.44 | 28.7 | Female | PTC | 1 | 32 | 1 |

## *Discussion*

### *Demographic and Clinical Data*

This prospective study was conducted in Malaysia to evaluate the difference in the levothyroxine withdrawal period and its effect on TSH in patients with DTC. A total of 104 patients were successfully recruited.

The mean age of patients with DTC is 47.06 years, almost similar to other studies on patients with thyroid cancer. Borget et al. (2007) compared stimulation with thyrogen and thyroid hormone withdrawal in patients with a mean age of 46.7 years (2). Chow et al. (2006) performed an almost similar study on patients with thyroid cancer and reported a mean age of 44.2 years (3). Dow et al. (1997) research on patients with thyroid cancer after levothyroxine withdrawal reported a mean age of 40 (4). Based on the current thyroid cancer trend in the United States, the mean age for diagnosis of thyroid cancer was 53 years for men and 49 years for women (5).

Females constituted the majority of included participants. In Malaysia, the female population has a higher incidence of thyroid cancer, with a lifetime risk of 1 in 336, compared with the male population, with a lifetime risk of 1 in 884 (6). Moore et al. (2010) studied the epidemiology of cancer in peninsular and island south-east Asia and revealed that specifically on Penang Island, women had more risk of developing thyroid cancer at 4/100000, whereas that of the male population is 1.1/100000 (7).

Among the recruited patients in this study, Malay ethnicity was dominant, followed by the Chinese and Indian races. For thyroid cancer incidence in Malaysia, the Malay ethnic has the highest number of reported cases for males and females, followed by Chinese and Indians (6). Another study in Kuala Lumpur also noted that Malay has the highest incidence of differentiated thyroid cancer among other races (8).

Papillary (PTC) and follicular thyroid carcinoma (FTC) accounted for the most cases in this work. Most of these studies reported more cases of PTC than FTC. A couple of studies reported a similar trend with PTC of 69% and FTC of 21%; the rest are medullary and anaplastic thyroid cancer (3) (8).

Most recruited patients had stage 1 disease, followed by stages 2, 4 and 3. According to the Malaysian cancer registry, most patients are diagnosed at stages 1 and 2 (male 48% and female 60%) (6). Golger et al. studied 3-week levothyroxine withdrawal and showed the following staging distribution: stage 1 with 65.19%, stage 2 with 27.07%, stage 3 with 7.18% and stage 4 with 0.55% (9).

### *TSH levels between weeks 3 and 4 of levothyroxine withdrawal.*

TSH levels of 30 mIU/L or higher are necessary for RAI therapy. To accomplish this goal, patients must stop taking levothyroxine for at least four to six weeks (10). The stimulated TSH level was reached by 88.46% of

patients after three weeks and nearly 99.04 % after four weeks. TSH levels were only examined in a handful of trials over the course of one week to six weeks following levothyroxine discontinuation. Liel et al. (2002) studied 13 patients and monitored their TSH levels every 3–4 days after levothyroxine withdrawal. RAI was administered as soon as the TSH level reached more than 30 mIU/L within an average of 17 days (11). In the present study, TSH levels were not assessed every 3–4 days, nor was the duration of TSH levels above 30 mIU/L averaged. Future studies could adopt this method, but it would be impractical due to the tight scheduling of admission for high-dose RAI; therefore, the treatment may not be administered once the TSH level reaches 30 mIU/L. Additionally, patients must come to the hospital every 3–4 days, thus incurring significant expenses.

Our study showed a similar result to a few studies (12). Sanchez et al. divided two groups of patients necessitating RAI therapy. Group 1 received thyroidectomy with RAI between 6 months and 21 years before the trial, necessitating the discontinuation of levothyroxine prior to having additional RAI ablation therapy, whereas Group 2 was treated with RAI ablation immediately after thyroidectomy. By the end of the third week, 90 percent of group I and one hundred percent of group II had met this objective (13). They concluded that the hypothalamus and pituitary take longer to respond to levothyroxine disruption the longer the thyroid hormone suppression medication is administered. Grigsby et al. did almost a similar study with the grouping with Sanchez et al. The TSH levels exceeded 30 mIU/L in 51 % of subjects after a 15–21 days withdrawal period and 93 % after 21-35 days of levothyroxine withdrawal. At the end of 35 days, 8 (7 %) of patients have not reached the TSH value of the desired level (14).

The mean TSH value in this study was 66.89 mIU/L at week three of levothyroxine withdrawal. This value is similar to a study by Golger et al. with a value of 54.5 mIU/L. This study also has almost similar findings (83% vs 88%) at three weeks of levothyroxine withdrawal. The only difference was that the cut-off point for a stimulated TSH was 25 mIU/L (9). As for stimulated TSH levels, our facility adhered to the most recent ATA 2015 standard of over 30 mIU/L (15).

A total of 12 patients were unable to achieve a TSH level of more than 30 mIU/L at week 3, but only one patient failed to achieve the targeted level at week 4. Nine out of twelve patients were receiving RAI for the first time. This study contradicts the report from Edmonds et al., who suggested that this phenomenon might be the effect of prolonged therapy with levothyroxine with a range of 4–11 years on TSH suppression therapy (16).

The TSH value of the only patient who failed to achieve 30 mIU/L was 28.7 mIU/L at week four which in some centres it would be considered enough value to give the RAI. The possible reason was that the patient was not adhering to the strict food regime since this was her first RAI, but we did not have any evidence.

Many studies and case reports described other factors that could contribute to inadequate TSH stimulation. For example, extrathyroidal functioning thyroid tissue and hypopituitarism of the pituitary gland tumour (17), the presence of the pyramidal lobe after total thyroidectomy (18) and the prevalence of anti-thyroperoxidase antibodies by increasing age (19,20) were of many reasons which could contribute to inadequate TSH stimulation after levothyroxine withdrawals.

## *Conclusion*

A TSH level of more than 30 mIU/L was achieved by 88.46% and 99.04% of DTC patients after 3 and 4 weeks of levothyroxine withdrawal, respectively. It is recommended to review the TSH level at 3 weeks instead of 4 weeks in patients who could not tolerate hypothyroidism symptoms.

## *Acknowledgement*

This study received honorarium funds from a short-term grant (Grant number: 304.CIPPT.6315176) and Myra KPI Grant; (Grant number: 1001.CIPPT.AUPS001) from Universiti Sains Malaysia.

## *Conflicts of interest*

The authors report no conflict of interest.

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