UNIVERSITI SAINS MALAYSIA

EVALUATION OF DIFFERENCE IN LEVOTHYROXINE WITHDRAWAL PERIOD AND ITS EFFECTS ON THE LEVEL OF THYROID STIMULATING HORMONE AND QUALITY OF LIFE IN DIFFERENTIATED THYROID CARCINOMA PATIENTS

by

DR MOHAMMAD FITRI BIN KHALIL

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DECLARATION

I hereby declare that this research was sent to Universiti Sains Malaysia (USM) for the degree of Master of Medicine in Nuclear Medicine. It has not been sent to other universities. With that, this research can be used for consultation and photocopied as reference.

Sincerely,

DR. MOHAMMAD FITRI BIN KHALIL
(P-IPM0022/16)

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ABBREVIATIONS

ATA	American Thyroid Association
CT	Computerised tomography
DTC	Differentiated Thyroid Carcinoma
ETE	Extrathyroidal extension
FTC	Follicular Thyroid Carcinoma
IM	Intramuscular
I-WBS	Iodine-131 Whole Body Scan
I-131	Iodine-131
JEPeM	Jawatankuasa Etika Penyelidikan Manusia
mcg	Microgram
mCi	Millicurie
mIU/L	mili-International Unit per Litre
ml	Millilitre
MREC	Medical Research Ethics Committee
n	Frequency
PET	Positron emission tomography
PI	Primary Investigator
PTC	Papillary Thyroid Carcinoma
QoL	Quality of Life
SD	Standard Deviation
SPECT	Single photon emission tomography
T3	Triiodothyronine
T4	Thyroxine
TFT	Thyroid Function Test
TPO	Thyroid Peroxidase
TSH	Thyroid Stimulating Hormone

ABSTRAK

Tajuk: Penilaian tentang perbezaan kesan durasi penghentian pil tiroksin terhadap tahap hormon merangsang tiroid dan kualiti hidup pesakit kanser tiroid.

Pendahuluan: Kebanyakan pesakit yang menghidap kes kanser tiroid memerlukan rawatan radioiodin. Persediaan yang perlu sebelum rawatan radioiodin adalah penghentian pil tiroksin selama empat minggu supaya nilai hormon perangsang tiroid (TSH) melebihi 30 mIU/L. Semasa tempoh penghentian pil tiroksin selama empat minggu, kebanyakan pesakit akan mengalami simptom hipotiroidisma. Disebabkan itu, pengurangan tempoh penghentian pil tiroksin daripada empat minggu kepada tiga minggu diharap dapat meningkatkan lagi tahap kesihatan dan kualiti hidup pesakit.

Objektif: Tujuan kajian ini dijalankan adalah untuk menilai dari segi perbezaan kesan durasi penghentian pil tiroksin terhadap tahap hormon perangsang tiroid (TSH) dan kualiti hidup pesakit yang menghidapi kanser tiroid.

Kaedah: Pesakit kanser tiroid yang memerlukan rawatan radioiodin telah dimasukkan ke dalam kajian ini. Ujian darah fungsi tiroid dibuat dan borang soalselidik SF-36 diberikan kepada pesakit pada minggu ke-3 dan ke-4 selepas penghentian pil tiroksin. Data klinikal seterusnya dianalisis menggunakan IBM SPSS versi 26.0.0

Keputusan: Seramai 104 orang pesakit telah menyertai kajian ini dengan purata umur 47.06 tahun. Kebanyakan yang terlibat terdiri daripada wanita (80.77%) dan berbangsa Melayu (53.85%). Pesakit kanser tiroid jenis papilari adalah majoriti sebanyak 77.88%. Bagi tahap kanser tiroid, tahap 1 merupakan kumpulan yang tertinggi iaitu 67.31%, manakala tahap 3 adalah kumpulan yang terendah iaitu hanya 6.73% pesakit. Semasa minggu ketiga penghentian pil tiroksin, sebanyak 88.46% pesakit kanser tiroid berjaya mendapat nilai TSH melebihi 30 mIU/L, manakala sebanyak 99.04% pada minggu keempat. Analisis menggunakan Cohen kappa antara minggu ketiga dan minggu keempat adalah 0.139. Dengan menggunakan borang soal selidik SF-36 untuk menilai kesan pemberhentian pil tiroksin kepada kualiti hidup pesakit, didapati markah minima pada minggu ketiga berkurangan secara signifikan pada minggu keempat dalam semua

komponen kualiti hidup (semua $p < 0.050$). Tiada kaitan yang kukuh dikenalpasti antara tahap penyakit kanser tiroid dan nilai TSH pada minggu ketiga dan keempat.

Kesimpulan: Seramai 88.46% pesakit telah berjaya mencapai nilai TSH melebihi 30 mIU/L pada minggu ke 3 selepas penghentian pil tiroksin. Walaubagaimanapun, penghentian pil tiroksin pada minggu ke 4 adalah lebih berkesan berbanding minggu ke 3. Kesan sampingan hipotiroidisme didapati berkurangan pada minggu ke 3 berbanding minggu ke 4 penghentian pil tiroksin. Secara keseluruhannya, kesihatan dan kualiti hidup pesakit adalah lebih baik pada minggu ke 3 berbanding minggu ke 4 penghentian pil tiroksin.

ABSTRACT

Title: Evaluation of difference in levothyroxine withdrawal period and its effects on the level of thyroid stimulating hormone (TSH) and quality of life (QoL) in differentiated thyroid carcinoma patients.

Introduction: Most patients with DTC require radioactive iodine (RAI) ablation therapy using I-131. The preparation prior to RAI ablation includes withdrawal of levothyroxine for at least four weeks in order to raise the TSH level of more than 30 mIU/L. During 4 weeks of levothyroxine withdrawal, most patients develop symptoms of hypothyroidism. Reducing the period of levothyroxine withdrawal period from 4 weeks to 3 weeks could improve patient's overall health and QoL.

Objective: To evaluate the difference in levothyroxine withdrawal period and its effect on the level of TSH and QoL.

Methods: DTC patients who require RAI ablation therapy was recruited into this study. Thyroid function test and SF-36 questionnaire were conducted at week 3 and week 4 of levothyroxine withdrawal period. Clinical data was analysed using IBM SPSS version 26.0.0.

Results: A total of 104 patients with the mean age of 47.06 years were recruited. Most of them were female (80.77%) and Malays (53.85%). Papillary thyroid carcinoma accounted for 77.88% of the patients. Stage 1 disease was the largest group with 67.31% whilst stage 3 was the smallest group with 6.73%. At week 3 of levothyroxine withdrawal, 88.46% of the patients were able to achieve TSH level of more than 30 mIU/L with means of 66.89 mIU/L, compared to 99.04% at week 4 of levothyroxine withdrawal. Cohen kappa measurement of agreement between week 3 and week 4 was 0.139. There was a significant reduction in the quality of life in week 4 compared to week 3 in all components ($p < 0.050$). There were no significant association between the staging of the disease and TSH level at week 3 and week 4.

Conclusion: 88.46% of the patients had achieved TSH level of more than 30 mIU/L after 3 weeks of levothyroxine withdrawal. However, 4 weeks of levothyroxine withdrawal is still more

superior compared to 3 weeks. There was better QoL in the overall health and quality of life in week 3 compared to week 4.

1.0 Introduction

Radioactive iodine ablation (RAI) is the treatment of choice for differentiated thyroid cancer (DTC) following total thyroidectomy or near total thyroidectomy. RAI is not required when the size of tumour is less than 1 cm in and does not have proof of metastasis, no capsular invasion, no evidence of unfavourable histology such as tall cell, columnar cell or diffuse sclerosing type and no record of exposure to radiation (Luster et al., 2008). 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. However, cancerous thyroid tissue is hypofunction compared to non-cancerous thyroid tissue, but it is still able to maintain physiological function and therefore have minimal radioiodine uptake. In order for radioiodine therapy to be effective, thyroid stimulating hormone (TSH) level must be more than 30 mIU/L. To achieve this level there are few methods that are currently being practiced worldwide. It is either by withdrawal of levothyroxine for 3 to 4 weeks, triiodothyronine withdrawal for two weeks or by administration of intramuscular thyrogen. The standard procedure is 4 weeks levothyroxine withdrawal to incite endogenous TSH, thus producing short-term hypothyroid symptoms. In our setting in Hospital Pulau Pinang, patients were ordered to stop levothyroxine for 4 weeks preceding to RAI therapy. During the period of levothyroxine withdrawal, patients may suffer from hypothyroid symptoms which could affect quality of life. Quality of life can be measured using tools such as the SF-36 questionnaire which includes physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. Due to the high cost, intramuscular thyrogen is reserved for specific patients such as those unable to tolerate hypothyroidism in view of their nature of work, unable to achieve a stimulated TSH after 4 weeks of levothyroxine withdrawal and those with pituitary disease. Triiodothyronine is not readily available in the local hospital setting. Due to this, the first option is still mostly applied. The aim of this study is to determine whether patients can achieve TSH level of more than 30 mIU/L after 3 weeks versus

4 weeks of levothyroxine withdrawal. We also want to compare the quality of life (QoL) using the SF-36 questionnaire between 3 weeks and 4 weeks of the thyroxine withdrawal period. This research does not alter the existing standard operating procedure of our hospital.

2.0 Literature review

2.1 Definition, Histopathology and Demographics

DTC can be defined as carcinoma deriving from thyroid tissue's follicular epithelium. It still retains its fundamental biological characteristics of a normal thyroid tissue, including the manifestation of the sodium iodide symporter (NIS), which is important for exclusive iodine uptake (Luster et al., 2008). It also has the capability to create thyroglobulin and react towards TSH (Elisei et al., 2017). Primary thyroid tumours are categorised by the World Health Organisation (WHO) into papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), poorly differentiated carcinoma, anaplastic thyroid carcinoma, medullary thyroid carcinoma and other rare thyroid tumours (Hedinger et al., 1989). DTC includes papillary and follicular type (Haugen et al., 2016) which comprises more than 90% of all thyroid cancers (Sherma, 2003).

The diagnosis is based on the histological examination of the thyroid tissue. PTC has a typical feature with larger cell nuclei compared to the normal thyroid cells, transparent at the centre, a ground glass nuclei (Chan & Saw, 1986) and some have calcium deposits which are also called "psammoma bodies" (Johannessen & Sobrinho-Simoes, 1980). Approximately 50 to 60% of PTC are multifocal and can affect both lobes in 30% of cases, which are in contrast with FTC that is commonly unifocal and well encapsulated with vascular and capsular invasion which make it distinguished from benign follicular adenoma (Elisei et al., 2017). Due to this, FTC requires adequate tissue sampling of the capsule and it can be further classified into minimally invasive or widely invasive (Hedinger et al., 1989).

PTC has few variants which have been distinguished as the classical variant with papillary structure, the follicular variant where the cells are organised in colloid follicles (Rosaí et al., 1983), the diffuse sclerosing variants (Carcangiu & Bianchi, 1989), the columnar variants as well as tall cell

with features of classic papillary pattern but comprised by cells that are elongated and contains granular as well as eosinophilic cytoplasm (Evans, 1986).

The most common endocrine tumour is thyroid cancer with increasing incidence within the last 30 years with a mean of 12/100000 women and 4/100000 men (Elisei et al., 2017). Based on the Malaysian National Cancer Registry Report 2007-2011, thyroid cancer is ranked ninth among female population and seventeenth among male population, with a lifetime risk of 1 in 884 males and 1 in 336 for females (Omar & Ibrahim Tamin, 2011). Incidence of thyroid cancer in Penang is 1.1% in men and 4.0% in women (Moore et al., 2010). Although incidence has been increasing about 10% each 5 years in both sexes, the mortality is declining by 17% for women and 8% for men every 5 years (Davies & Welch, 2006). The detection of microcarcinomas with exceptional prognosis may have explained this phenomenon (Baudin et al., 1998). DTC is rare among children. The incidence peaks at the age of 40 to 50 years in both sexes (Elisei et al., 2017). Most of the patients suffering from DTC survive from 30 to 40 years after diagnosis. However age of more than 60 years, follicular histo type, male gender, larger size of primary tumour and presence of metastasis are all the unfavourable prognostic (Elisei et al., 2010).

2.2 Clinical Presentation

The usual presentation of thyroid cancer can be in the form of thyroid nodule, solitary or within a multinodular goitre. Positive family history or any radiation exposure in childhood further upsurges malignancy likelihood. Other signs such as presence of palpable neck nodes, rapidly enlarging thyroid nodule, dysphagia or hoarseness further increase the probability of malignancy. Thorough medical history and physical examination can aid towards the diagnosis before proceeding with imaging modalities (Elisei et al., 2017).

2.3 Diagnosis

2.3.1 Ultrasonography (US)

Upon discovering thyroid nodule on palpation, it is mandatory to perform thyroid ultrasonography (US) as it is the most precise mean to determine gland volume, size, number, structure (cystic / solid / mixed), distinguish from other extrathyroidal masses, evaluate lymph nodes metastasis and finally to guide fine needle aspiration cytology (FNAC) (Elisei et al., 2017). The sonographic pattern can be divided into high suspicion, intermediate suspicion, low suspicion, very low suspicion and benign. All carry their probable malignancy risk and the recommended fine needle aspiration cut-off (Haugen et al., 2016).

Table 2.1 Sonographic patterns estimated risk of malignancy and fine needle aspiration guidance for thyroid nodules.

Sonographic pattern	**Ultrasound features**	**Estimated risk of malignancy (%)**	**FNA size cut-off (largest dimension)**
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with one or more of the following features: irregular margins (infiltrative, micro-lobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of ETE.	> 70 - 90[a]	Recommend FNA at ≥1 cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins without microcalcifications, ETE, or taller than wide shape.	10 - 20	Recommend FNA at ≥1 cm
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, without microcalcification, irregular margin or ETE, or taller than wide shape.	5 - 10	Recommend FNA at ≥1.5 cm

Very low suspicion	Spongiform or partially cystic nodules without any of the sonographic features described in low, intermediate, or high suspicion patterns	< 3	Consider FNA at ≥2cm. Observation without FNA is also a reasonable option
Benign	Purely cystic nodules (no solid component)	< 1	No biopsy[b]

US-guided FNA is recommended for cervical lymph nodes that are sonographically suspicious for thyroid cancer (see Table 7). [a]The estimate is derived from high volume centres, the overall risk of malignancy may be lower given the interobserver variability in sonography. [b]Aspiration of the cyst may be considered for symptomatic or cosmetic drainage. ETE, extrathyroidal extension.

Reprinted from Diagnostic Applications of Nuclear Medicine: Thyroid Tumours. Nuclear Oncology: From Pathophysiology to Clinical Applications, 545-583.

2.3.2 Fine-Needle Aspiration Cytology (FNAC)

FNAC in combination with ultrasonography lead to a rapid, accurate and inexpensive mean to further evaluate thyroid nodules, by having a sensitivity of 65% to 95%, specificity up to 96%, accuracy 98% (Livolsi & Gupta, 1992) and a negative predictive value up to 99% (Poller et al., 2008).

Table 2.2 The Bethesda system for reporting thyroid cytopathology: Diagnostic categories and risk of malignancy

Diagnostic category	**Estimated / predicted risk of malignancy by the Bethesda system %[a]**	**Actual risk of malignancy in nodules surgically excised, % median (range)[b]**
Nondiagnostic or unsatisfactory	1 - 4	20 (9 – 32)
Benign	0 - 3	2.5 (1 – 10)
Atypia of undetermined significance or follicular lesion of undetermined significance	5 - 15	14 (6 – 48)
Follicular neoplasm or suspicious for a follicular neoplasm	15 - 30	25 (14 – 34)
Suspicious for malignancy	60 - 75	70 (53 – 97)
Malignant	97 - 99	99 (94 – 100)

[a]As reported in The Bethesda System by Cibas and Ali (1076).

[b]Based on the meta-analysis of eight studies reported by Bongiovanni et al. (103). The risk was calculated based on the portion of nodules in each diagnostic category that underwent surgical excision and likely is not representative of the entire population, particularly of nondiagnostic and benign diagnostic categories.

Reprinted from Diagnostic Applications of Nuclear Medicine: Thyroid Tumours. Nuclear Oncology: From Pathophysiology to Clinical Applications, 545-583.

2.3.3 Computerised Tomography (CT) Scan

CT scan may be useful in identifying the disease extension in advanced thyroid cancers. With addition of contrast, neck CT scan can be useful to delineate disease extension especially at the larynx, trachea and oesophagus as well as nodal assessment and involvement of muscle and blood vessels (Haugen et al., 2016). Compared to the neck ultrasound, CT has a better sensitivity to evaluate central and lateral compartment neck nodes if both of these modalities examined together, but no differences if examined separately (Ahn et al., 2008). Furthermore the combination of ultrasound neck and CT scan neck was greater to any modalities alone in nodal disease staging prior operation (Lesnik et al., 2014).

2.3.4 MRI

Cervical nodal metastasis can also be detected with MRI of the neck. However, the respiratory artefact results in difficulty to interpret especially for low volume nodal disease (Kaplan et al., 2009).

2.4 Staging

For thyroid cancer, the most used staging system is the tumour-node-metastasis (TNM) classification system defined jointly by the Union for Internationale Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) (Elisei et al., 2017) which is centred on the histopathologic depiction in tumour size, local lymph node metastasis and distant metastasis. The latest TNM classification is the 8th edition appeared in 2017 and is shown in the table below.

Table 2.3 TNM AJCC 8th Edition for Thyroid Cancer

T Category	T Criteria
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤2 cm in greatest dimension limited to the thyroid
T1a	Tumour ≤1 cm in greatest dimension limited to the thyroid
T1b	Tumour >1 cm but ≤2 cm in greatest dimension limited to the thyroid
T2	Tumour >2 cm but ≤4 cm in greatest dimension limited to the thyroid
T3*	Tumour >4 cm limited to the thyroid, or gross extrathyroidal extension invading only strap muscles
T3a	Tumour >4 cm limited to the thyroid
T3b	Gross extrathyroidal extension invading only strap muscles from a tumour of any size
T4	Includes gross extrathyroidal extension into major neck structures
T4a	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, oesophagus, or recurrent laryngeal nerve from a tumour of any size
T4b	Gross extrathyroidal extension invading prevertebral fascia or encasing carotid artery or mediastinal vessels from a tumour of any size

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No evidence of regional lymph nodes metastasis
N0a	One or more cytological or histologically confirmed benign lymph node
N0b	No radiologic or clinical evidence of locoregional lymph node metastasis
N1	Metastasis to regional nodes
N1a	Metastasis to level VI or VII (pretracheal, paratracheal or prelaryngeal / Delphian or upper mediastinal) lymph nodes. This can be unilateral or bilateral disease
N1b	Metastasis to unilateral, bilateral or contralateral lateral neck lymph nodes (level I, II, III, IV or V) or retropharyngeal lymph nodes

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

When age at diagnosis is …	And T is …	And N is …	And M is …	Then the stage group is …
< 55 years	Any T	Any N	M0	I
	Any T	Any N	M1	II
≥ 55 years	T1	N0 / NX	M0	I
	T1	N1	M0	II
	T2	N0 / NX	M0	I
	T2	N1	M0	II
	T3a / T3b	Any N	M0	II
	T4a	Any N	M0	III
	T4b	Any N	M0	IVA
	Any T	Any N	M1	IVB

Reprinted from Tuttle, R.M., Haugen, B. and Perrier, N.D., 2017. Updated American Joint Committee on cancer/tumour-node-metastasis staging system for differentiated and anaplastic thyroid cancer: what changed and why. (Tuttle et al., 2017)

2.5 Radioiodine ablation therapy (RAI) therapy

Thyroidectomy with subsequent radioiodine ablation therapy remains a standard treatment for DTC. The aims of DTC therapy are to increase overall as well as disease specific survival, lessen risk of persistent or recurrent disease plus concomitant morbidity, allow precise disease staging and risk stratification and thus minimise treatment associated morbidity and unwarranted therapy (Haugen et al., 2016).

Recommended approach aimed at DTC patient treated with thyroidectomy is centred on 2015 ATA (American Thyroid Association) Initial Risk Stratification System.

Table 2.4 Risk Stratification System with Proposed Modification

ATA low risk	Papillary thyroid cancer (with all of the following): • No local or distant metastases; • All macroscopic tumour has been resected • No tumour invasion of loco-regional tissues or structures

	• The tumour does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) • If ^{131}I is given, there are no RAI-avid metastatic foci outside the thyroid bed on the first posttreatment whole-body RAI scan • No vascular invasion • Clinical N0 or ≤5 pathologic N1 micro-metastases (<0.2 cm in largest dimension) Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer[a] Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including $BRAF^{V600E}$ mutated (if known)
ATA intermediate risk	Microscopic invasion of tumour into the perithyroidal soft tissues RAI-avid metastatic foci in the neck on the first post treatment whole-body RAI scan Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) Papillary thyroid cancer with vascular invasion Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension Multifocal papillary microcarcinoma with ETE and $BRAF^{V600E}$ mutated (if known)
ATA high risk	Macroscopic invasion of tumour into the perithyroidal soft tissues (gross ETE) Incomplete tumour resection Distant metastases Postoperative serum thyroglobulin suggestive of distant metastases Pathologic N1 with any metastatic lymph node ≥3 cm in largest dimension[a] Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)

Reprinted from Haugen, B. R., Alexander, E. K., Bible, K. C., Doherty, G. M., Mandel, S. J., Nikiforov, Y. E., Pacini, F., Randolph, G. W., Sawka, A. M. & Schlumberger, M. (2016). 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid, 26(1), 1-133.

Based on this risk stratification, RAI is not routinely suggested following thyroidectomy in ATA low risk DTC patient, but it is considered after total thyroidectomy for ATA intermediate risk level as well as routinely recommended for ATA high risk (Haugen et al., 2016).

2.6 Thyroid hormones synthesis

The requirements to produce thyroid hormones are a well-developed thyroid gland and a sequence of structured biochemical phases (iodine metabolism) with ample nutritional iodide consumption. Iodine mainly comes from our diet and it is absorbed into the body in about 90% into small intestines as iodide (Ziessman et al., 2013). Iodide is then transported via blood stream into the thyroid gland and taken up by the active transportation of the sodium iodide symporter. The uptake of iodide is stimulated by TSH through cyclic adenosine monophosphate-protein kinase A (cAMP-PKA). Sodium iodide transporter gene expression and post transcriptional activation are amplified by exposure to TSH (Weiss et al., 1984). With TSH, the half-life of the sodium iodide symporter is approximately 5 days and during the absence of TSH, it is further reduced to approximately 3 days (Riedel et al., 2001). Then, iodide will be transferred on apical membrane into follicular lumen, oxidised by thyroperoxidase (TPO) enzymes as well as integrated into tyrosyl residues of thyroglobulin (TG) which produces mono-iodothyrosines and di-iodothyrosines. Later, it is attached through thyroperoxidase to produce thyroxine (T4) and triiodothyronines (T3). Thyroglobulin pinocytosis and lysosomes hydrolysis result in released of T3 and T4 into the bloodstream (Kopp, 2012).

T4 is more lavish, but triiodothyronine is four times more active. T4 has a half-life of 5 to 7 days while triiodothyronine has only 1 day. About 99% of circulating thyroid hormones are bound by plasma protein and metabolised by the liver (Medscape, 2016). The supply of hormone by the thyroid gland is about one month (Ziessman et al., 2013).

2.7 Pharmacokinetics of Levothyroxine

A synthetic form of thyroxine (T4) hormone is called levothyroxine and it cannot be differentiated biochemically and physiologically from the body's natural T4 (Niazi, 2009). Adult dosage of levothyroxine is approximately 1.7 mcg/kg/day and those with heart disease or elderly may require lesser than that (Garber et al., 2012).

After consumption, levothyroxine is absorbed by the small bowel and only some by the stomach (Hays, 1988). For euthyroid patient, the time for maximum concentration (T max) is at least 2 hours and for hypothyroid patient is about 3 hours. It is taken on empty stomach because the presence of food will delay T max (Benvenga et al., 1995) (Wenzel & Kirschsieper, 1977).

T4 then undergoes deiodination by deiodinase enzymes, and loss of iodine from carbon 5 outer ring that converts T4 to T3, which is the active form. It is an important steps as the receptors inside cell nucleus devour more affinity for T3 (Mandel et al., 1993) (Pittman et al., 1971) (Robbins, 1981).

The half-life of T4 is about 7.5 days in hypothyroid state and 6.2 days in euthyroid state whereas for T3 is about 1.4 days in hypothyroid state and 1 day in euthyroid state (Nicoloff et al., 1972). About 80% of T3 and T4 are fix toward thyroxine-binding globulin (TBG) while the rest to albumin and thyroxine-binding prealbumin (Saberi & Utiger, 1974).

Food such as soy bean (Marini et al., 2012), papaya (Deiana et al., 2011), grapefruit (Lilja et al., 2005) or drinks like coffee (Vita et al., 2013) may impair levothyroxine absorption.

Drugs may also alter the pharmacokinetics of thyroid hormones, such as by affecting TSH secretion, thyroid hormones synthesis, metabolism, protein binding and also the overall effect on thyroid hormones. Due to this, levothyroxine pharmacokinetics are subjected to numerous factors such as disease, food containing seafood and concomitant medication (Colucci et al., 2013).

2.8 Methods to achieve TSH level more than 30 mIU/L

The aim is to have TSH of more than 30 mIU/L in preparing patient with radioiodine ablation therapy or diagnostic whole-body scan. It is recommended in the latest ATA 2015. However there is still not much certainty of this relating to optimum TSH level which is connected with long term outcomes improvement (Haugen et al., 2016). An analysis done by Fallahi et al noted a TSH of more than 25 mIU/L was significantly correlated with success of the ablation (Fallahi et al., 2012) while another two studies showed that there were no significant association with prior TSH level radioiodine ablation plus ablation outcomes (Prpic et al., 2012) (Karam et al., 2003).

After the removal of thyroid gland via total thyroidectomy procedure, RAI ablation or whole-body thyroid scan could be planned 6 weeks later. In order to elevate TSH level to more than 30 mIU/L, patient may not be given levothyroxine postoperatively. This may lead to a stimulated level of TSH after six weeks. In addition, the other method is to start with levothyroxine and later thyrogen is given (Ziessman et al., 2013).

However, both of the methods described above are not practical as it is quite difficult to obtain an appointment 6 weeks post-surgery due to long waiting queue for RAI ablation therapy. Patient needs to start with levothyroxine suppression therapy and recombinant TSH, which are expensive and only given to indicated cases. This leaves us with either levothyroxine withdrawal for 4 to 6 weeks or triiodothyronine withdrawal.

Thyrogen can be given to patients who has severe hypothyroidism symptoms, occupational related risks of having hypothyroidism such as lorry driver, those who operate heavy machinery or teacher, and those who are failed to achieve more than 30 mIU/L stimulated level of TSH despite 4 weeks of levothyroxine withdrawal. Apart from that, it is also given to patient with pituitary disease who has difficulty to increase TSH or to whom that the treatment cannot be delayed (Haugen et al., 2016). Thyrogen is given intramuscularly in two consecutive days with a dose of 0.9 mg each

(Ziessman et al., 2013). Although this may help the patient to avoid hypothyroid symptoms, it is not so practical due to its expensive price (De Danieli et al., 2016).

For triiodothyronine withdrawal, patients usually have already started on levothyroxine for at least 30 days. Levothyroxine is stopped for total of 4 weeks. Within the 4 weeks of levothyroxine withdrawal, triiodothyronine will be given only for the first two weeks and the patient is not on any thyroid hormone replacement for the remaining two weeks. According to Lee et al (2010), the mean TSH value after 2 weeks of triiodothyronine withdrawal is 73.6 mIU/L which ranges between 30.1 to 100 mIU/L (Lee et al., 2010). Triiodothyronine withdrawal seems to be able to reduce the period of withdrawal to 2 weeks but is not available in our hospital.

The most practical way to increase the TSH level is levothyroxine withdrawal. ATA suggested a period of 3 to 4 weeks for the withdrawal (Haugen et al., 2016). Few other studies have been done with the duration of withdrawal from 4 to 6 weeks and describing on the implication of short-term hypothyroidism.

Table 2.5 Study description and level of evidence of several articles describing the implications of short-term hypothyroidism on various systems.

Author	Number of patients	Duration of withdrawal	Study description
Cardiovascular effects			
Grossman et al.	11	6 weeks	Case-controlled study
Bengel et al.	10	5 weeks	Longitudinal study
Constant et al.	10	5 weeks	Longitudinal study
Fomei et al.	12	6 weeks	Longitudinal study
Botella – Carretero et al	21	5 weeks	Case-controlled study
Giusti et al	61	Variable	Case-controlled study
Neurocognition and well being			
Nagamachi et al.	24	4 weeks	Case-controlled study
Quality of life			Longitudinal repeated
Dow et al.	34	-	measures
Botella – Carretero et al.	18	5 weeks	Case-controlled study
Tagay et al.	130	4 weeks	Case-controlled study
Luster	130	4 weeks	Retrospective/questionnaire
Schroeder PR et al	228	4 weeks	Longitudinal / SF-36

Reprinted from Dumtas, L. H. & Biondi, B. (2007). Short-term hypothyroidism after Levothyroxine-withdrawal in patients with differentiated thyroid cancer: clinical and quality of life consequences. European journal of endocrinology, 156(1), 13-19.

2.9 Short form – 36 Questionnaire

The definition of health-related QoL is satisfaction or happiness within the territory of life which affect or be affected by health and this can be measured through questionnaire (Sararaks et al., 2005). One of the most comprehensively used and broadly translated and tested tools worldwide is the SF-36 which measures sickness by including eight health concepts such as physical, social and role functioning, mental health, health perception, energy fatigue, pain and general health. It has been testified as a sensitive instrument for outcome of care for abundant disease and sensitive to alterations of health among the general population (Ware Jr & Gandek, 1998) (Shiely et al., 1996). The UK version of SF-36 was initially converted to Malay by Universiti Sains Malaysia (USM) and further modified into two-phased study (1999 and 2000), validity and reliability in Malaysian context were tested among asthmatic and general population and the conclusion was SF-36 Malay version can be applied which is largely suitable for internal consistency and validity (Sararaks et al., 2005).

The SF-36 has been applied worldwide and since its release and systematic review and meta-analyses done by Lins and Carvalho (2016), there were 172 articles published between 1997 to 2015. The conclusion showed SF-36 was progressively described in the scientific literature and researchers need to be mindful of its possible influence on human's health (Lins & Carvalho, 2016).

For thyroid cancer patients, the SF-36 questionnaire has been utilised to portray the QoL because of its proven sensitivity (Pacini et al., 2006) (Schroeder et al., 2006). Few studies have been done by using the SF-36 towards thyroid cancer. It has been used to assessed thyroid cancer survivor's health related QoL done in Singapore by Tan et al (2007) besides in the Netherlands by Husson et al (2011) and successfully define QoL among their patients (Tan et al., 2007) (Husson et al., 2011).

Moreover, it had been used by Crevenna et al (2003) to evaluate the QoL among thyroid cancer patients during levothyroxine suppression therapy (Crevenna et al., 2003).

Scoring of the questionnaire is centred on general population norm. The points more than 50 is considered the subject having good to best health, 40 to 50 as mid ranged health while less than 40 points is the lower range of health.

2.10 Levothyroxine withdrawal and Quality of life

Serum TSH level must be more than 30 mIU/L prior RAI to warrant good iodine uptake for the therapy. Higher TSH level also increases sensitivity of thyroglobulin monitoring which needs to stimulate adequate radioiodine uptake (Ziessman et al., 2013).

Acceptance of levothyroxine withdrawal technique to increase TSH does not seem evidence-based, since literature comprehends limited data accompanying this approach (Hilts et al., 1979). ATA suggested levothyroxine withdrawn for 3 to 4 weeks prior to RAI therapy or diagnostic testing, (Haugen et al., 2016).

A few studies have shown that 3 weeks of withdrawal is as effective as 4 weeks. Liel et al (2002) reported mean interval to reach a TSH of 30 mIU/L was 17 days among 13 patients on levothyroxine withdrawal (Liel, 2002). Sanchez et al (2002) reviewed 21 patients on levothyroxine withdrawal with 90% had a TSH level more than 30 mIU/L in 3 weeks (Sánchez et al., 2002).

Golger et al (2003) concluded withdrawal from levothyroxine for 3 weeks can expedite the recognition of residual or recurrent thyroid cancer by measurement of stimulated serum thyroglobulin (Golger et al., 2003). In addition, it has bearable effect toward QoL, and loss of time work compared to 4 weeks levothyroxine withdrawal protocol. They also recommended that stage 2 to 4 patients with low thyroglobulin and TSH less than 25 mIU/L for either thyrogen or a more prolonged levothyroxine withdrawal interval to exclude residual disease (Golger et al., 2003).

Davids et al (2006) described thyroglobulin stimulation by 3 weeks (day 21) is simple, cost effective as well as recuperates QoL (Davids et al., 2006).

Retrospective study by Grigsby et al (2004) suggested preparation of patients for RAI administration can be done within 1 to 3 weeks of levothyroxine withdrawal. Major limitations of this study are its retrospective nature (Grigsby et al., 2004).

Hypothyroid symptom may vary with age and sex. Women may experience menstrual irregularities while those elderly may have a decline in cognitive function. Common hypothyroid symptoms are cold intolerance, constipation, depression, concentration difficulty, menorrhagia, myalgias, weakness, weight gain, dry skin, fatigue, hair thinning and memory impairment (Gaitonde et al., 2012). Other reported symptoms besides clinical hypothyroidism are physical discomfort, emotional dysfunction, health risks in elderly, frail or have concomitant illness as well as impaired QoL and work (Luster et al., 2005).

The greatest impairment in the QoL of thyroid cancer patients occurs during levothyroxine withdrawal which induces a hypothyroid state (Dow et al., 1997) and Luster et al (2005) reported 11 days' work absenteeism due to hypothyroidism produced by withdrawal (Luster et al., 2005).

Long-standing hypothyroidism may affect neuropsychiatric, cardiovascular, negatively influences lipid metabolism and increases atherosclerotic risk. Nevertheless these changes are reversible after euthyroid status (Biondi & Klein, 2004).

Botella-Carretero et al (2003) reported that prolonged TSH suppression and withdrawal of levothyroxine are associated with undesirable cardiovascular effect (Botella-Carretero et al., 2003). Besides that, during the period of withdrawal, cholesterol and low-density lipoprotein cholesterol may be raised and qualitative changes improve its susceptibility to oxidation (Staub et al., 1992).

Hypothyroidism is correlated with mood disturbances and changes in intellectual function (Jackson, 1998). It is postulated that thyroid hormone depletion affects the cerebral blood flow which may result in psychiatric manifestation (O'Brien & Harris, 1968). During the episodes of transient hypothyroidism, Tc-99m hexamethylpropyleneamine oxime single photon emission computed

tomography (HMPAO SPECT) showed cerebral blood flow abnormalities which resulted in thyroid dysfunction-induced mood changes (Nagamachi et al., 2004).

Lee et al (2010) compared scores replicating physical signs, social activities, mood changes, and use of medical resources, between the use of thyrogen, levothyroxine withdrawal and triiodothyronine withdrawal. There was significant difference in QoL status amid the thyroid hormone withdrawal groups (levothyroxine and triiodothyronine withdrawal) and recombinant TSH group. However no significant variance in QoL between levothyroxine and triiodothyronine withdrawal (Lee et al., 2010).

Short-term hypothyroidism rarely results in fatal outcome; however, accidents may happen in severe hypothyroidism related to muscle weakness as well as cerebellar ataxia, especially in the elderly. Chow et al (2006) studied on health related QoL in DTC patient during 4 weeks of levothyroxine withdrawal. Results showed health-related QoL declines with the times of levothyroxine withdrawal and suggested 3 weeks of withdrawal to minimize the influence on QoL. (Chow et al., 2006).

Dow et al (1997) conducted a research on 34 subjects with thyroid cancer undertaking thyroid hormone withdrawal that showed significant variations on physical and psychological levels. Overwhelming fatigue, anorexia, problems with motor skills, constipation, and fluid retention unavoidably caused impaired QoL were routinely reported. Besides that weakened motivation and lessened productivity as well as quality of work which might affect themselves and also their family and social life (Dow et al., 1997).

Disturbed psychometric functionality and poor QoL were noted in 18 women with DTC during levothyroxine withdrawal as evidence of deteriorating cognitive tests performance, verbal information, physical and mental symptoms which are mainly attributed to profound hypothyroidism during the withdrawal period (Botella-Carretero et al., 2003).

3.0 Rationale / Benefit of The Study

The research is conducted to compare level of TSH and QoL during period of levothyroxine withdrawal (3 weeks and 4 weeks) prior to RAI ablation of DTC.

Blood test for TSH level is taken at week 3 and week 4 during period of levothyroxine withdrawal. TSH level is determined at week 3 and week 4. Thus, a statistical analysis is done to see the percentage of patients who achieve the TSH level of more than 30 mIU/L in week 3 and week 4. The SF-36 questionnaire is also given at week 3 and week 4 to the patients to assess their QoL during that time. Depending on the result of this study, the nuclear medicine physician could consider 3 weeks levothyroxine withdrawal period instead of 4 weeks prior to RAI ablation therapy.

Patients who are unable to achieve TSH level of more than 30 mIU/L after 4 weeks of levothyroxine withdrawal is given IM Thyrogen as well.

3.1 Aim

To reduce the period from 4 weeks to 3 weeks of levothyroxine withdrawal in order to achieve level of TSH of more than 30 mIU/L and improve QoL.

4.0 Materials and Methods

4.1 Study Design and Location

The study design is a prospective observational study with universal sampling method. This study was carried out in the Department of Nuclear Medicine, Penang Hospital. The study period was 23 months (January 2018 to November 2019) with patient recruitment from May 2018 until May 2019.

4.2 Study Sample

All DTC patients who require RAI ablation therapy (first time or follow up) is included in this study.

4.3 Inclusion and Exclusion Criteria

Inclusion criteria:

- Above 18 years old
- Undergone total or near total thyroidectomy
- HPE confirmed DTC

Exclusion criteria:

- Pregnancy

4.4 Sample size calculation

For objective 1 and 2, sample size calculation is based on this formula of calculation:

$$n = 2\{z\,(\alpha \div 2)\,(p1(1 \pm p1) \pm p2(1 \pm pw))\} \div d2$$

$$= 2\,\{1.96 \times 0.55\} \div (0.05^2)$$

$$= 86$$

$$\approx 95$$

(with additional 10% dropout)

For objective 3, sample size calculation is based on this formula calculation (single mean):

$$n = \{z\,(\alpha \div 2)\,(\delta^2)\} \div d^2$$

$$= \{1.96^2\ (0.7^2)\} \div 0.5^2$$

$$= 75$$

$$\approx 83$$

4.5 Methodology

4.5.1 Data Collection

All referrals for RAI therapy were screened by the principal investigator (PI). Patients were either referred as new case of DTC or existing patients who require another dose of RAI for ablation.

The standard procedure prior to RAI treatment was withdrawal of levothyroxine for 4 weeks and food containing seafood for 2 weeks. Admission to the radioiodine ward was planned at week 4. Series of blood tests including thyroid function test (TFT) was taken. Those patients with TSH of more than 30 mIU/L were given RAI ablation treatment as planned. Iodine-131 whole body scan (I-WBS) was performed on day 5 after RAI ablation treatment. Patients with TSH less than 30 mIU/L were given 0.9mg IM thyrogen on day 1 and day 2. RAI ablation treatment was administered on day 3 and I-WBS were done on day 5.

4.5.2 Thyroid function test (TFT)

TFT was taken at week 3 and week 4. About 3 to 5 ml of blood was taken through venepuncture and kept inside a plain tube. This procedure was done in the treatment room. The plain tube containing the blood was then sent by senior healthcare assistant (PPK) to endocrine laboratory in the hospital. The specimen was kept at room temperature for at least 8 hours or refrigerated for at least 2 days. Specimen was rejected if the stability limit was exceeded. The specimen was processed by the medical laboratory technologist on the same day the specimen was sent. The method for performing this study was *Electrochemiluminescence.*