COMPARISON BETWEEN THE EFFECT OF ONE-WEEK AGAINST TWO-WEEK IODINE RESTRICTED DIET ON THE POST RADIOIODINE THERAPY OUTCOME AMONG HYPERTHYROIDISM PATIENTS IN A REGIONAL NUCLEAR MEDICINE REFERRAL CENTRE

by

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ABBREVIATIONS

I-131	Iodine-131
ICCIDD	International Council for the Control of Iodine Deficiency Disorders
MNG	Multinodular Goitre
RAIU	Radioactive Iodine Uptake
T_3	Triiodothyronine
T_4	Thyroxine
TFT	Thyroid Function Test
TSH	Thyroid Stimulating Hormone
TRAb	Thyroid Receptor Antibodies
UNICEF	United Nations Children's Fund
WHO	World Health Organisation

UNITS

KeV	Kilo electronvolt
MeV	Mega electronvolt
MBq	Mega Becquerel
mCi	milli Curie
mGy	milli Gray
µg/L	microgram per Litre
mIU/L	milli-International Units per Litre
pmol/L	picomole per Litre
<	less than

ABSTRAK

Pendahuluan: Rawatan menggunakan radioaktif Iodin-131 merupakan satu kaedah yang terbukti kegunaannya dalam rawatan penyakit kelenjar tiroid termasuklah penyakit bukan barah tiroid yang berkaitan hipertiroid dan juga penyakit kanser tiroid. Persediaan merangkumi amalan pemakanan diet sekatan iodin sebelum menjalani rawatan untuk menghasilkan keadaan kekurangan zat iodin dalam tubuh adalah penting dan boleh mempengaruhi hasil rawatan radioiodin. Walaubagaimanapun, tiada garis panduan khusus berkaitan amalan pemakanan untuk penyakit bukan barah tiroid, kaedah semasa yang diamalkan di kebanyakan pusat perubatan nuklear di Malaysia adalah untuk menasihati pesakit agar mengamalkan pemakanan diet sekatan iodin selama satu minggu untuk pesakit hipertiroid berbanding dua minggu untuk pesakit kanser tiroid.

Objektif: Tujuan kajian ini adalah untuk menilai kesan amalan pemakanan diet sekatan iodin selama satu minggu berbanding dua minggu terhadap paras serum hormon perangsangan tiroid (thyroid stimulating hormone, TSH) dan hormon tiroksin bebas (free thyroxine, T_4) selepas rawatan radioiodin serta kesan keberhasilan rawatan tersebut.

Kaedah: Pesakit hipertiroid yang dirujuk untuk pertama kali menjalani rawatan radioiodin dibahagikan secara rawak kepada dua kumpulan mengikut tempoh amalan pemakanan diet sekatan iodin selama satu minggu atau dua minggu. Terdapat sejumlah 83 orang pesakit yang terlibat (n=44 dalam kumpulan satu minggu, n=39 dalam kumpulan dua minggu). Ujian air kencing untuk paras iodin yang diambil sebelum rawatan telah digunakan untuk menilai kepatuhan pesakit terhadap amalan pemakanan tersebut. Hasil rawatan yang diingini adalah

fungsi tiroid normal atau hipotiroid pada bulan ke-9 setelah rawatan. Data demografik dan klinikal pesakit telah dikumpulkan dan dianalisa.

Keputusan: Kebanyakan pesakit adalah perempuan dengan purata umur 42 tahun dan memiliki kebengkakan kelenjar tiroid bedasarkan pemeriksaan klinikal. Pada rawatan susulan bulan ke-9, kebanyakan pesakit (83%) mencapai status tiroid yang diingini (fungsi tiroid normal atau hipotiroid). Tiada perkaitan signifikan yang dapat diperolehi di antara tempoh amalan pemakanan dengan nilai purata T_4 (p=0.057) dan serum TSH (p=0.746) serta keberhasilan rawatan tersebut (p=0.294). Walaubagaimanapun, pesakit lelaki adalah 6.22 kali ganda berkemungkinan untuk memperolehi hasil rawatan yang tidak diingini (hipertiroid) berbanding peaskit wanita dan pertambahan paras iodin dalam air kencing sebelum rawatan adalah berkait dengan pertambahan kemungkinan untuk memperolehi hasil rawatan yang tidak diingini (hipertiroid).

Kesimpulan: Tiada perbezaan yang signifikan di antara kesan amalan pemakanan diet sekatan iodin selama satu minggu berbanding dua minggu terhadap keberhasilan rawatan radioiodin. Walaupun secara umumnya tempoh satu minggu amalan pemakanan diet sekatan iodin didapati adalah mencukupi sebagai persediaan pesakit hipertiroid, usaha untuk memastikan kepatuhan dalam mengamalkan diet sekatan iodin sebelum rawatan boleh mempengaruhi kemujaraban rawatan radioiodin. Kajian pada masa akan datang dengan jumlah sampel yang lebih besar dan meliputi faktor-faktor penyumbang yang lain patut diteruskan bagi mendapatkan keputusan yang mungkin lebih relevan.

ABSTRACT

Introduction: Therapy using radioactive Iodine-131 is an established method of treatment for thyroid diseases including hyperthyroidism related benign disorders as well as thyroid cancers. Pre-treatment dietary restriction to induce a state of iodine deficiency is considered important and may influence the radioiodine therapy outcome. Although there are no specific guidelines of dietary preparation for benign thyroid disorders, the current practice in most nuclear medicine centres in Malaysia is to advice one-week dietary restriction for hyperthyroidism patients as compared to two-week duration for thyroid cancer patients.

Objective: The aim of this study is to evaluate the effect of one-week against two-week iodine restricted diet on the post radioiodine therapy levels of serum thyroid stimulating hormone (TSH) and free thyroxine (T_4) levels as well as the treatment outcome.

Methods: Hyperthyroidism patients referred for first radioiodine therapy were randomised into two groups according to one-week or two-week dietary restriction. There were 83 patients (n=44 in one-week dietary restriction group, n=39 in two-week group). Pre-therapy urinary iodine test was done to document compliance towards the dietary restriction. Favourable therapy outcome includes euthyroid or hypothyroidism at 9 months post therapy. Demographic and clinical data were collected and analysed.

Results: Majority of the patients were females with mean age of 42 years old and had goitre clinically. At 9th month follow-up, majority of patients (83%) achieved favourable thyroid status. No significant statistical association was found between the duration of dietary restriction with mean free T_4 (p=0.057) and serum TSH (p=0.746) levels as well as therapy outcome (p=0.294). However, male patients were 6.22 times more likely to develop unfavourable post therapy outcome compared to female patients and an increasing level of pre-treatment urinary iodine was associated with increased likelihood of developing unfavourable post therapy outcome.

Conclusion: There is no significant difference between the effects of one-week against two-week iodine restricted diet on the post radioiodine therapy outcome. Although generally a period of one-week iodine restriction appears to be adequate for the preparation of hyperthyroidism patients, efforts to ensure adequate compliance and stringency should be advocated as these may possibly influence the efficacy of dietary restriction and radioiodine therapy. Future studies with larger sample size and covering other contributing factors are recommended.

1.0 INTRODUCTION & LITERATURE REVIEW

1.1 Introduction

Benign disorders of the thyroid gland usually present with alteration in the thyroid function and may well be accompanied by goitre or thyroid swelling. In general, the state of excessive thyroid hormones or thyrotoxicosis is caused by various aetiologies such as Graves' disease, thyroiditis, factitious thyroxine intake and struma ovarii, while hyperthyroidism commonly relates to a hyper-functioning thyroid gland. Nevertheless, both terms (i.e. hyperthyroidism and thyrotoxicosis) are interchangeably used (Topliss et al., 2004).

There are no official statistics available on the prevalence of hyperthyroidism in Malaysia. However, the prevalence of hyperthyroidism in neighbouring Indonesia is reported to be about 6.9% (Indonesian Society of Endocrinology, 2012). In the United Kingdom, prevalence of hyperthyroidism among women is 2% while among men is 0.2% (Collier, 2012). The most common causes of hyperthyroidism in the United States are Graves' disease, toxic multinodular goitre (MNG) and toxic adenoma (Bahn et al., 2011). In Australia, similarly Graves' disease and toxic MNG are the most common causes of hyperthyroidism (Topliss et al., 2004). Graves' disease has been estimated to affect approximately 0.5% of the general population, predominantly female in the age group of 40 to 60 years old (Abraham and Acharya, 2010). The prevalence of toxic MNG increases with age and in regions of iodine deficiency (Zainudin et al., 2012).

1.2 Brief Anatomy and Physiology of Thyroid

The thyroid gland is an essential organ and fundamental component of the complex human endocrine system. It has the ability to concentrate iodide from dietary iodine in order to produce the thyroid hormones. Apart from significant role in the regulation of protein and carbohydrate metabolisms, these thyroid hormones have important effects on our growth as well as the cardiovascular, respiratory and sympathetic nervous systems.

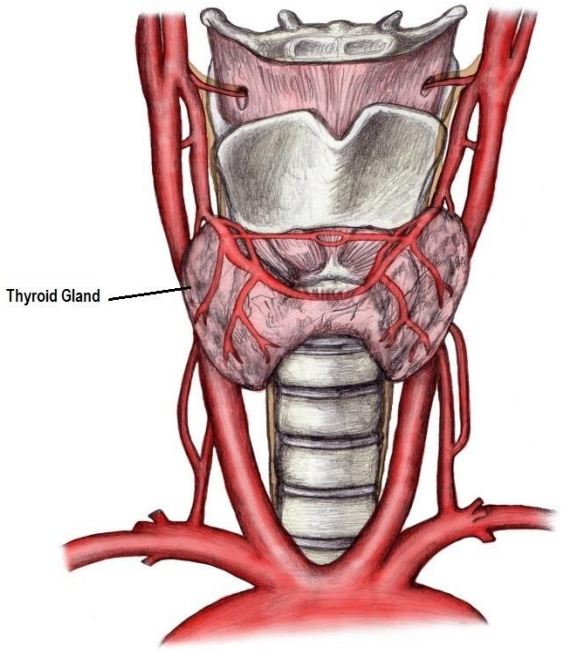

Figure 1.0: Anterior view of the thyroid gland (*adapted from Medscape.com, accessed on 1/10/2015*)

The thyroid gland consists of right lobe and left lobe connected by isthmus. It is located in the lower neck just below the thyroid cartilage at the anterior superior aspect of the trachea. The arterial supply of the gland is from the superior thyroid artery which is a branch of the external carotid artery and inferior thyroid artery which is a branch of the thyrocervical trunk. The venous drainage of the thyroid gland is by the superior, middle and inferior thyroid veins. The gland is supplied by both parasympathetic and sympathetic nerves.

The average weight of the thyroid gland is approximately 15-20 grams (Ziessman, O'Malley and Thrall, 2006). A cross-sectional postmortem study conducted in a South-Asian country reported that the mean weight of the thyroid gland for middle aged females and males to be approximately 19 grams (Nurrunabi et al, 2010). Microscopically the thyroid gland is comprised of numerous follicles of varying sizes that are enclosing colloid-filled cavities or follicular lumens (Figure 2.0).

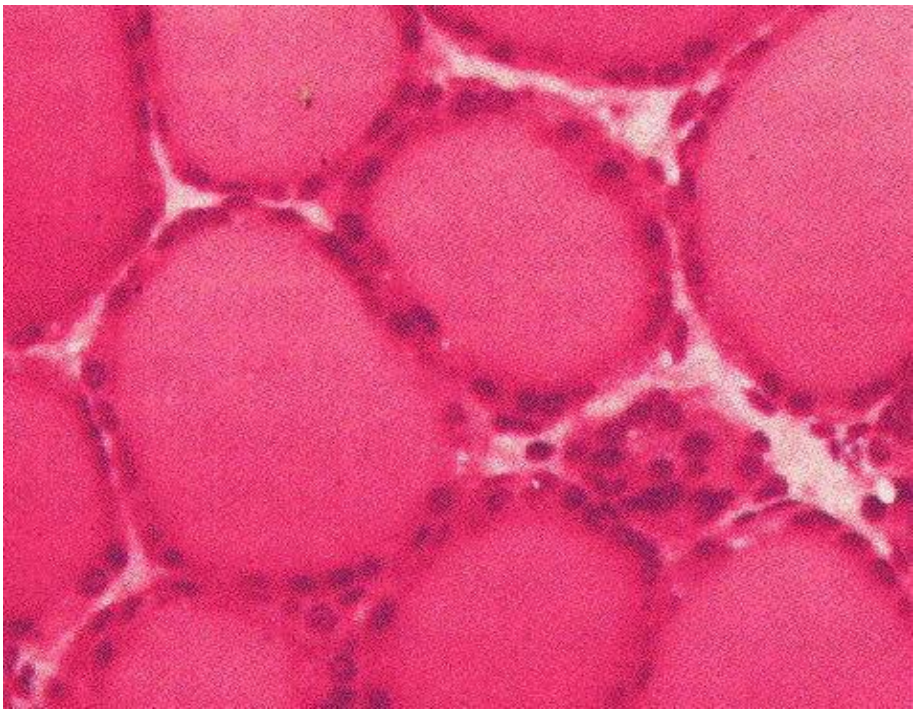

Figure 2.0: Thyroid follicles (*adapted from Medscape.com, accessed on 1/10/2015*)

After oral consumption, dietary iodine from food is promptly reduced to iodide in the upper small intestine and being distributed in the blood as an extracellular ion similar to chloride (Ziessman, O'Malley and Thrall, 2006). Iodide is subsequently trapped by the thyroid follicular cell through a high-energy carrier mediated sodium iodide thyroid pump before being converted into thyroid hormones through a series of metabolic steps (Ivanac et al., 2004). In the normal thyroid gland, synthesis of thyroid hormones through oxidation and organification process promptly follows trapping of iodide (Ziessman, O'Malley and Thrall, 2006).

The biosynthesis and secretion of thyroid hormones into the circulation are stimulated by the thyroid stimulating hormone (TSH) and inhibited by excess iodine (Cavalieri, 1997). The TSH secretion on the other hand is being principally regulated by the thyroid-pituitary feedback mechanism which is very sensitive to circulating serum thyroid hormone levels. The main thyroid hormone released by the thyroid gland is thyroxine (T_4) which then being transported to peripheral tissues by thyroid binding proteins and finally converted to the more metabolically active triiodothyronine (T_3) at the site of action (Ziessman, O'Malley and Thrall, 2006).

1.3 Management of Hyperthyroidism

Patients with hyperthyroidism may be asymptomatic but commonly present with substantial symptoms. They may experience symptoms of irritability, nervousness, palpitation, excessive sweating, heat intolerance, hand tremors and weight loss in spite of good appetite. Examples of signs of thyrotoxicosis are tachycardia, atrial fibrillation, fine tremor and goitre (Iagaru and McDougall, 2007). Patients may also present with any of the associated complications. Common complications include hypokalaemic periodic paralysis, pretibial myxoedema, thyroid cardiomyopathy and Graves' opthalmopathy (Zainudin et al., 2012). Institutional studies in Malaysia showed the prevalence of thyroid associated opthalmopathy among Graves' disease patients was approximately 34.7% (Lim et al, 2008), while hypokalaemic periodic paralysis were present in 5.0% of the cases (Tan et al, 1989).

Confirmatory diagnosis of hyperthyroidism is usually done by laboratory measurement of the serum TSH and free T_4. In fact the diagnostic accuracy improves when both parameters are evaluated particularly when hyperthyroidism is strongly suspected (Bahn et al., 2011). Measuring free T_4 is preferred compared to total T_4 as measurement of total T_4

is affected by protein binding abnormalities (Zainudin et al., 2012). However, in patients with low TSH but normal free T_4 such as in early stage of the disease or autonomously functioning thyroid nodule, only the serum T_3 level may be elevated and hence should be measured (Bahn et al., 2011).

Additional laboratory test to detect thyrotropin receptor antibodies (TRAb) is particularly useful in diagnosing Graves' disease as it is a sensitive marker of the disease. Other relevant investigations that would be helpful in the evaluation of thyrotoxicosis are radioiodine uptake study (RAIU) and radionuclide thyroid scan (Bahn et al., 2011, Zainudin et al., 2012). In our local setting, ultrasonography of the thyroid gland is also occasionally being performed in addition to the stated laboratory tests as part of the disease assessment. Thyroid ultrasound remains a valuable tool in the evaluation of thyroid disorders including estimation of thyroid volume and characterization of palpable nodules as well as in sonographic guided fine needle aspiration biopsy (Tessler and Tublin, 1999).

Generally the treatment options available for hyperthyroidism consist of anti-thyroid drugs, surgery and radioiodine therapy. In the local setting, majority of patients are treated with thionamide anti-thyroid drugs up to 18 months before being tapered off. Hong et al. (2007) described that in Malaysia the most consumed thionamide was carbimazole (82.8%) followed by propylthiouracil (17.2%). The consumption of anti-thyroid drugs was reported to be higher locally compared to Australia which might possibly related to the local preference for drugs as the first-line therapy while radioiodine which is available only in several regional centres being typically placed as the second-line therapy (Hong et al, 2007). Prolonged usage of thionamides may cause minor and transient adverse effects such as skin rash, itchiness and mild leucopenia. However, the most dangerous side effect is agranulocytosis which can occur in approximately 0.5% of the patients (Bartalena, Bogazzi and Martino, 1996). As for surgery in hyperthyroidism, it is indicated for cases of goitre with pressure effects, suspected thyroid

malignancy, severe progressive opthalmopathy or when medical therapy fails (Zainudin et al, 2012).

1.4 Radioiodine Therapy

The oral administration of I-131 has been generally a well-recognised procedure in treating both benign and malignant disorders of the thyroid for the last 70 years (Silberstein et al., 2012). Examples of the common clinical indications for radioiodine therapy are Graves' disease, toxic nodular thyroid diseases and well differentiated thyroid cancers such as papillary and follicular carcinoma. Absolute contraindications for I-131 therapy include pregnancy and breastfeeding (Stokkel et al, 2010, Sisson et al., 2011). The use of radioiodine in treating hyperthyroidism is substantially more frequent in the United States compared to Europe and parts of Asia (Abraham and Acharya, 2010).

Both Society of Nuclear Medicine and European Association of Nuclear Medicine guidelines defined I-131 as a β-emitting radionuclide with a physical half-life of approximately 8 days with a principal γ-ray of 364 KeV and a principal β-particle with a maximum energy of 0.61 MeV, an average energy of 0.192 MeV, and a range in tissue of 0.4 mm (Silberstein et al, 2012, Stokkel et al, 2010). The thyroid gland receives the highest radiation absorbed dose. Assuming 55% thyroid uptake in a 20 gram of hyperthyroid gland, the calculated radiation absorbed dose is 790 mGy/MBq to the thyroid gland followed by 0.290 mGy/MBq to urinary bladder wall and less than 0.1 mGy/MBq to other organs (Silberstein et al., 2012).

The basis of radioiodine therapy is physiological whereby I-131 is taken up by iodide transporter of the thyroid gland and processed the same way as natural iodine. Subsequently β-particles from I-131 will deliver ionising radiation that disrupts chemical bonds throughout

the thyroid cells, inflicting devastating damage on DNA molecules and triggering cellular dysfunction causing ultimately cell death (Robbins and Schlumberger, 2005). These will lead to thyroid volume decrease and control of thyrotoxicosis (Mumtaz et al., 2009).

The reason for I-131 therapy among patients who had received anti-thyroid drugs was either because of failure of medical treatment (70%) or disease recurrence (11%) as reported in a retrospective study involving 258 patients (Sztal-Mazer et al., 2012). Around 50–90% of hyperthyroid patients are cured within one year following I-131 therapy (Bonnema and Hegedus, 2012). The goal of radioiodine therapy for hyperthyroidism is to achieve a non-hyperthyroid status either a euthyroid state or iatrogenic hypothyroidism that should be adequately compensated with oral levothyroxine (Silberstein et al., 2012). Thus, hypothyroidism post radioiodine therapy is commonly accepted to be a favourable outcome and should subsequently be treated with levothyroxine. Several studies have defined hypothyroidism following I-131 administration as low free T_4 with high TSH requiring thyroxine hormone replacement whereas euthyroid as normal thyroid function off all thyroid medication and hyperthyroidism requiring further radioiodine as a relapsing high free T_4 and suppressed TSH at one year post therapy (Lewis et al., 2013, Yau et al., 2009).

In general, the treatment with radioactive I-131 for hyperthyroidism has minimal adverse effects. Transient exacerbation of hyperthyroid symptoms due to radiation thyroiditis may occur 1–2 weeks after therapy (Mumtaz et al., 2009). However, these symptoms would usually respond to short-term beta blocker therapy if required. Thyroid ophthalmopathy may worsen or develop after I-131 therapy for Graves' disease, especially among patients who are smokers (Silberstein et al., 2012). It has been suggested by several studies that these patients should be covered with steroids (Mumtaz et al., 2009). Society of Nuclear Medicine has highlighted that based on previous multicenter trials; there is no evidence of an increased risk

of thyroid carcinoma or other cancers following radioiodine therapy for hyperthyroidism (Silberstein et al., 2012).

Widely deployed methods for determining the dose of I-131 activity for radioiodine therapy of hyperthyroidism are by prescribing (a) fixed empirical dose for all patients, (b) dose corrected for thyroid size and iodine uptake study and (c) quantity of I-131 calculated to deliver a specific radiation dosimetry to the thyroid gland (Kalinyak and McDougall, 2003). Nevertheless, there are no advantages that could be proven in using adjusted dose method as well as no differences in the time to outcome between the fixed and adjusted dose methods (Leslie et al., 2003). Similarly, Jaiswal et al. (2014) reported that there was no statistically significant difference between the success rates of the two methods at 3 months post therapy among Graves' disease patients in India. A fixed dose regime has been suggested to be simple, more convenient to use and effective to achieve treatment goals (Mumtaz et al., 2009, Yau et al., 2009).

Fixed doses of radioiodine activity for hyperthyroidism are commonly in the range of 185–555 MBq (5–15 mCi) which enable additional incremental dose of I-131 when the gland is large (Iagary and McDougall, 2007). Good therapy outcome was seen following administration of doses less than 370 MBq (10 mCi) for normal sized thyroid glands and approximately 555 MBq (15 mCi) for large thyroid glands (Shinto, Pachen and Sreekanth, 2010). Lewis et al. (2013) reported that a single standard dose of 550 MBq (14.9 mCi) to be highly effective in treating hyperthyroidism in a study that includes Graves' disease and toxic MNG.

In addition to the dosage of I-131, a number of parameters could influence the effect and outcome of radioiodine therapy. These include age and gender of the patients, thyroid size, severity of the disease and usage of anti-thyroid medications. Nevertheless, based on current knowledge, it appears clear that no single factor reliably predicts the outcome of

radioiodine therapy and these factors probably interact mutually in a complex manner (Bonnema and Hegedus, 2012).

1.5 Radioiodine Therapy in Malaysia

At present, the therapy with I-131 for thyroid diseases has become one of the main therapeutic services available in Malaysian government hospitals and institutions with nuclear medicine facilities. Locally most of the nuclear medicine centres prescribe a fixed dose of radioiodine with consideration given to the thyroid size made on clinical palpation and assessment (Zanial and Hamzah, 2015). A Summary of Consensus for the Management of Thyroid Disorders in Malaysia has recommended a fixed dose of 370–555 MBq (10–15 mCi) (Zainudin et al., 2012).

1.6 Patient Preparation and Iodine Restricted Diet

Generally a state of iodine deficiency should be induced in order to subsequently increase the I-131 uptake (Silberstein et al., 2012). Hence, as part of the preparation measures, patients are advised to avoid and stop consuming anti-thyroid drugs for 1–2 weeks, iodine containing substance such as expectorants, agar and Lugol's iodine for 2–3 weeks, multivitamin for 7 days, amiodarone for 3–6 months or longer and radiographic contrast agents for 3–4 weeks prior to radioiodine therapy and should be placed on an iodine restricted diet (Mumtaz et al., 2009).

Among patients with well differentiated thyroid cancer, a temporary low-iodine diet is recommended before they undergo I-131 treatment (Sawka et al., 2010, Li et al., 2015). In the United States, a low iodine diet with intake less than 50 µg of iodine per day for 1–2 weeks

before radioiodine ablation is recommended by the American Thyroid Association (Cooper et al., 2009). Based on available data, majority of the population in the United States are iodine sufficient (Li et al., 2015). The rationale for low iodine diet in such circumstances is it would help to deplete iodine concentration in the body and optimise radioiodine uptake in the thyroid cells (Sawka et al., 2010).

Patients being prescribed with low iodine diet are required to avoid foods which are rich in iodine (Park and Hennessey, 2004, Tamoda et al., 2005). Dietary sources with highest iodine content are marine products such as fish, shellfish and seaweed followed by egg, milk, dairy products and fortified or iodised salt (European Food Safety Authority, 2014). Other examples of food with high iodine contents are breads made with iodinated dough conditioners, chocolate as well as dried and cured food products (Park and Hennessey, 2004).

2.0 RATIONALE & OBJECTIVES

2.1 Problem Statement and Rationale of Study

A systemic review on dietary iodine restriction prior to I-131 treatment or scanning in well differentiated thyroid cancer had advocated the use of low iodine diet for the duration of up to two weeks as part of the preparation measures (Sawka et al., 2010). In contrast, the duration of dietary iodine restriction is unclear for benign thyroid diseases although the recommendation for thyroid cancer patients may be as long as 10-14 days (Mumtaz et al, 2009). A review article by Lee (2012) has suggested a simplified low-iodine diet for 5-7 days among hyperthyroidism patients. Nevertheless, at present there is no randomised study or standardised guideline on the timing of dietary restriction for hyperthyroidism patients undergoing radioiodine therapy. Society of Nuclear Medicine, United States and its counterpart the European Association of Nuclear Medicine in their respective latest practice guidelines did not specify any duration for iodine restricted diet for benign thyroid diseases (Silberstein et al., 2012, Stokkel et al, 2010).

The current practice in Malaysia including Hospital Pulau Pinang is to advice for one-week iodine restricted diet among hyperthyroidism patients and two-week iodine restricted diet among thyroid cancer patients. Although stringency is not usually specified, the emphasis is placed on the avoidance of iodine containing food, seafood including fish, shellfish, prawn and squid, kelp and supplements that contain high iodine and iodized salt (Zanial and Hamzah, 2015). For thyroid cancer, the duration of low iodine diet is a crucial factor as iodine intake can vary by geographic region as well as individual's dietary preferences and in areas where the average estimated iodine intake is high, individuals may require a longer length of iodine restriction (Li et al., 2015). Likewise for hyperthyroidism, the one-week restriction may not be adequate for some patients with probable high dietary iodine consumption. Longer duration of iodine restricted diet is thought to enhance the state of iodine deficiency and subsequently promote better I-131 uptake by the thyroid gland

contributing towards favourable treatment outcome. Therefore, the aim of this present study was to determine the most appropriate timing of dietary iodine restriction as part of the pre-treatment preparation among hyperthyroidism patients that would eventually result in a favourable post therapy thyroid status.

2.2 Objectives of Study

2.2.1 General Objective

The primary objective is to evaluate the impact of one-week against two-week iodine restricted diet has on the post radioiodine therapy outcome (i.e. euthyroid, hypothyroid or hyperthyroid status biochemically) among hyperthyroidism patients undergoing first radioiodine therapy.

2.2.2 Specific Objectives

There are three specific objectives for this study;

i. To evaluate the TSH and free T_4 levels based on the thyroid function test (TFT) of these patients at 6^{th} and 9^{th} month post therapy.

ii. To determine the post therapy thyroid status biochemically (i.e. euthyroid, hypothyroidism or hyperthyroidism) based on the TFT values at 9^{th} month post therapy.

iii. To correlate the impact of iodine restricted diet on post therapy TFT levels and the thyroid status at 9^{th} month post therapy.

2.3 Research hypotheses

The null hypothesis for this study is that there is no significant difference between the impact of one-week and two-week iodine restricted diet on the post radioiodine therapy outcome amongst hyperthyroidism patients. The alternative hypothesis is that the two-week iodine restricted diet has a better impact (i.e. favourable biochemical status) compared to the one-week diet on the post radioiodine therapy outcome amongst hyperthyroidism patients.

3.0 MATERIAL & METHODS

3.1 STUDY BACKGROUND, DESIGN AND PERIOD

This was a randomised prospective study that was conducted in Hospital Pulau Pinang. It involved hyperthyroidism patients undergoing first radioiodine therapy at the Nuclear Medicine Department, Hospital Pulau Pinang which was one of the regional nuclear medicine centres under the jurisdiction of Ministry of Health Malaysia. Presently, Hospital Pulau Pinang is the main referral centre for the northern region of Peninsular Malaysia covering the states of Perlis, Kedah, Penang and northern Perak (Appendix F).

3.1.1 Study Period

The total study period was 17 months beginning from 1st February 2014 until 30th June 2015. The sampling frame for patient recruitment was from 1st February 2014 until 30th September 2014. Enrolled patients were being follow-up for duration of 9 months and the last review session was on 30th June 2015.

3.2 STUDY POPULATION AND SAMPLE SIZE

The sampling population of this study was derived from all hyperthyroidism patients referred from within and outside Hospital Pulau Pinang for first radioiodine therapy. The sample size was calculated using PS Power and Sample Size Ver.3.0.10, 2009 (Appendix B). The required size to achieve a power of 70% and confidence interval of 95% was 101 patients. Therefore, the needed sample size for this study was 111 patients considering dropout rate of 10%. The calculation was based on 25% difference of a previous study produced by Morris et al. with standard deviation 127.7 (Morris et al., 2001). Although that study was conducted among thyroid cancer patients, it was chosen as a reference for sample

size calculation as there was no published similar study being done among hyperthyroidism patients prior to the initiation of this study.

3.2.1 Sampling procedure

The total number of patients recruited for this study based on the selection criteria were 83 patients (74.8% of the calculated sample size). Patients had been randomised and assigned into two groups using opaque-sealed envelopes containing computer generated randomisation numbers. The first group (44 patients) underwent one-week dietary restriction and the second group (39 patients) underwent two-week dietary restriction.

3.3 SELECTION CRITERIA

3.3.1 Inclusion Criteria:

- Patients undergoing first radioiodine ablation
- Patients aged between 18 years old and 65 years old

3.3.2 Exclusion Criteria:

- Patients with hyperthyroidism associated opthalmopathy
- Patients who are pregnant or breastfeeding
- Patients who have underwent recent (within 1 month) contrasted radiographic study
- Patients who have underwent previous thyroid surgery
- Patients who lost to follow up post radioiodine therapy

3.4 MINIMIZING SAMPLING ERROR

Data collection was performed by primary/principal investigator.

3.5 ETHICAL BOARD

This study has been registered with the National Medical Research Register (NMRR) of Malaysia. The protocol for this study was submitted to the Medical Research Ethics Committee (MREC) of the Ministry of Health Malaysia and has been approved by the committee (Appendix C). The study protocol was also reviewed and approved by the Research Secretariat of Advanced Medical and Dental Institute, Universiti Sains Malaysia and Research Ethics Committee (Human) of Universiti Sains Malaysia.

3.6 METHODOLOGY

The current practice in the Department of Nuclear Medicine, Hospital Pulau Pinang is to prescribe fixed dose of 555 MBq (15 mCi) for all hyperthyroidism cases referred for radioiodine therapy. Liquid I-131 is administered orally to patients as an outpatient procedure. In conjunction with local regulations, the radiation exposure rate has been calculated to be equivalent to or less than the permissible value of 6.6 mR/hour measured at one meter distance. Patients are required to attend scheduled clinic follow up sessions every 3 months for 1 year duration at the Nuclear Medicine Department, Hospital Pulau Pinang. At each session, patients are being assessed clinically on their signs and symptoms pertaining to the thyroid status and respond towards therapy apart from biochemical monitoring of the free T_4 and TSH levels taken prior to the follow up session. Patients with favourable thyroid status either biochemically euthyroid or hypothyroidism at approximately one year post therapy will

be considered as successfully treated with radioiodine. Hypothyroidism patients will be placed on life-long thyroxine hormone replacement. However, patients who are still hyperthyroid will be advised for another low dose radioiodine therapy.

3.6.1 Patient Preparations and Iodine Restricted Diet

Patient preparation will help in ensuring the effectiveness of radioiodine therapy. Briefing session and dissemination of transcribed information on the pre-treatment preparation as well as the therapy procedure are well recommended measures (Royal College of Physicians, 2007, Stokkel et al., 2010, Silberstein et al., 2012). After being randomised and assigned to their respective dietary group, patients were given pre-therapy counselling and briefing conducted by medical officers in the Nuclear Medicine Department, Hospital Pulau Pinang. A copy of the formal written departmental leaflet on the instruction and preparation list for low dose radioiodine therapy was also provided to the referring team and handed over to the patients.

Patients were instructed to stop consuming anti-thyroid drug such as carbimazole and propylthiouracil for 7 days prior to radioiodine therapy and should only resume taking the medication after 7 days following the therapy. Patients were ensured not to be on medication containing high-iodine such as amiodarone apart from having no recent history of contrasted radiographic examination. They were also advised to avoid iodine containing food and stop consuming seafood, kelp, supplements or multivitamins that contain high iodine and iodized salt for 7 or 14 days depending on their randomised dietary group. They were given a simple structured dietary recommendation and instruction tailored to local food intake prepared by the hospital dietician (Appendix D). Referral for dietician consultation was offered and aided