PREVALENCE AND ASSOCIATED FACTORS FOR THE DEVELOPMENT OF HYPOTHYROIDISM WITHIN ONE YEAR OF RADIOACTIVE IODINE THERAPY AMONG PATIENTS WITH HYPERTHYROIDISM IN HUSM.

by

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LIST OF ABBREVIATIONS

GD	Grave's disease
TNMG	Toxic multinodular goiter
RAI	Radioactive iodine therapy (^{131}I)
ATD	Antithyroid drug
^{131}I	Iodine
RAUI	Radioactive iodine uptake
HUSM	Hospital Universiti Sains Malaysia
PTU	*Prophylthiouracil*
mCi	Millicurie
antiTPO	Antithyroperoxidase antibody
AMA	Antimicrosomal antibody
TSH	Thyroid stimulating hormone
T4	Thyroxine
fT4	Free T4
T3	Triiodothyronine
fT3	Free T3
MBq	Millibecquerel
RSNA	Radiological Society of North America
BTA	British Thyroid Association

ABSTRAK

Prevalen dan faktor-faktor penyumbang kepada terjadinya kekurangan hormon tiroid di kalangan pesakit yang berlebihan hormon tiroid yang menjalani rawatan terapi radioaktif iodin dalam tempoh setahun selepas rawatan di HUSM.

Latar belakang:

Terdapat kajian-kajian terdahulu dilakukan berkenaan masalah terjadinya kekurangan hormon tiroid di kalangan pesakit berlebihan hormon tiroid yang menjalani rawatan radioaktif iodin. Tetapi kajian seperti kurang dilakukan di kalangan populasi setempat. Kajian seperti ini penting untuk mengetahui permasalahan susulan akibat kejadian masalah kekurangan hormon tiroid selepas rawatan radioaktif iodin. Disamping itu, kami dapat membuktikan sama ada beberapa faktor penyumbang seperti umur, jantina, punca masalah berlebihan hormon tiroid, kehadiran autoantibodi, dos radioaktif iodin yang digunakan dan sama ada pesakit diberi ubat antitiroid selepas rawatan radioaktif iodin, boleh menyumbang kepada masalah kekurangan hormon tiroid selepas rawatan radioaktif iodin.

Oleh itu, objektif kajian ini adalah untuk menentukan prevalen kejadian kekurangan hormon tiroid di kalangan pesakit-pesakit yang yang mendapat terapi radioaktif iodin dan untuk melihat kaitan antara data seperti umur, keturunan, jantina, punca-punca berlebihan hormon tiroid, dos radioaktif iodin yang digunakan dan penggunaan ubat antitiroid selepas

rawatan radioaktif iodin sebagai faktor penyumbang kepada terjadinya kekurangan hormon tiroid selepas terapi radioaktif iodin.

Methodologi:

Kajian in merupakan kajian retrospektif yang melibatkan penelitian rekod-rekod pesakit. Kajian ini melibatkan pesakit berlebihan hormon tiroid yang menjalani rawatan radioaktif iodin di Klinik Perubatan Nuklear, HUSM dan mendapat rawatan susulan di Klinik Pakar Perubatan dari tahun 2002 hingga 2011. Data yang menepati kriteria di ambil sebagai populasi kajian. Ciri-ciri pesakit seperti umur, jantina, punca permasalah berlebihan hormon tiroid, kehadiran autoantibodi, dos radioaktif iodin yang digunakan dan sama ada pesakit diberi ubat antitiriod selepas terapi dicatat dan dianalisis.

Keputusan :

Terdapat 167 pesakit telah dikenal pasti mengalami masalah berlebihan hormon tiroid. Tetapi hanya seramai 137 orang pesakit telah dikenalpasti menepati kriteria untuk kajian. Prevalen permasalahan kekurangan hormon tiroid selepas terapi radioaktif iodin sebanyak 32.9%. Didapati jantina dan penggunaan ubat antitiroid selepas terapi radioaktif iodin berkait dengan terjadinya kekurangan hormon tiroid (P=0.028 dan P <0.001). Faktor-faktor lain seperti umur, bangsa, punca permasalahan berlebihan hormon tiroid dan dos radioaktif iodin yang digunakan tidak menjadi faktor penyumbang kepada terjadinya kekurangan hormon tiroid selepas terapi radioaktif iodin. Jantina perempuan didapati kurang kebarangkalian untuk mendapat kekurangan hormon tiroid berbanding lelaki (0.406 ,95%CI 0.181,0.908) dan pesakit yang diberi ubat antitiroid selepas radioaktif iodin kurang kebarangkalian untuk mendapat kekurangan hormon tiroid (0.188, 95%CI 0.081,0.438).

Kesimpulan:

Prevalen masalah kekurangan hormon tiroid selepas terapi radioaktif iodin dalam jangka masa setahun adalah 32.9%, lebih rendah jika dibandingkan dengan kajian-kajian terdahulu. Faktor seperti umur, bangsa, punca berlebihan hormon tiroid dan dos radioaktif iodin adalah tidak signifikan. Mereka yang jantina perempuan dan diberi ubat antiroid selepas terapi radioaktif didapati kurang kebarangkalian mereka untuk mendapat kekurangan hormon thyroid selepas terapi (OR 0.406 dan OR 0.188).

ABSTRACT

Prevalence and associated factors for the development of hypothyroidism within one year of radioactive iodine therapy among patients with hyperthyroidism in HUSM.

Background:

Many studies had been done regarding the incidence of hypothyroidism post RAI therapy and the associated factors for its development in patients with hyperthyroidism. However there are limited studies done in our local population and there was no similar study done in HUSM in the past. Knowing the prevalences and associated factors for the development of hypothyroidism post RAI is important to predict the possible outcomes of the patients undergoing this mode of therapy.

This study objectives were to determine the prevalence of hypothyroidism post radioactive iodine therapy and to determine the association of age, race, gender, aetiology of hyperthyroidism, dose of radioactive iodine used, presence of autoantibodies and usage of antithyroid drug post RAI with the development of hypothyroidism post RAI therapy.

Methodology:

The study was a retrospective study performed from September 2012 to November 2012. The participants were patients with hyperthyroidism who received radioactive iodine

therapy in Nuclear Medicine Clinic, HUSM since 2002 till 2011 and continued follow up under Klinik Pakar Perubatan. All the records were reviewed. Patients' data and results, including age, race, sex, aetiology of hyperthyroidism, presence of autoantibodies, dose of RAI used, usage of antithyroid drug and serial thyroid function test post therapy were included in the analysis.

Results:

Total of 167 patients screened and 137 subjects were enrolled in the study. The prevalence of hypothyroidism within one year of RAI therapy seen was 32.9%. The study showed that, gender and usage of antithyroid drug post RAI were significantly associated with the development of hypothyroidism post RAI therapy (P=0.045 and P <0.001). However, other factors; age, race, dose of RAI and aetiology of hyperthyroidism statistically not significant as associated factors for development of hypothyroidism. Female gender had less chance to develop hypothyroidism compared to male (0.406 ,95%CI 0.181,0.908) and those who on antithyroid drug had less chance to become hypothyroid (0.188, 95%CI 0.081,0.438) post RAI compared to patient who was not on antithyroid drug after RAI therapy.

Conclusion:

We found that the prevalence of hypothyroidism post RAI therapy within one year post RAI are lower compared with previous studies. High precentage of study subjects remained hyperthyroid. Factors such as age, race, aetiology of hyperthyroidism and dose of RAI were not significant as associated factors for the

development of hypothyroidism. Female gender and those who on antithyroid drug post RAI had less chance to developed hypothyroid post RAI therapy (OR 0.406 and OR 0.188).

CHAPTER 1

INTRODUCTION

1.INTRODUCTION

1.1 Study background and rationale.

Hyperthyroidism is a disorder that occurs due to excess production of thyroid hormones. This condition affecting about 2% women and 0.2% men (Wood and Franklyn, 1994). In United State about 1% of the population has hyperthyroidism (Golden et al., 2009). It is a condition having multiple aetiologies, manifestations and potential therapies. A detail medical history will provide the clinical sufficient to suggest the diagnosis of hyperthyroidism.

The proper treatment of hyperthyroidism depends on recognition of symptoms and signs of the disease and the aetiologies of the disorder. The most common cause of hyperthyroidism worldwide and including Malaysia, is Grave's disease(GD). Other causes include toxic multinodular goiter(TMNG), toxic adenoma and thyroiditis. The treatment of hyperthyroidism is directed toward lowering the serum concentrations of thyroid hormones to reestablish a eumetabolic state. The diagnostic workup begins with a thyroid stimulating hormone level test. There are three available modalities of treatment all of which are effective. These include antithyroid drugs, radioactive iodine (RAI ^{131}I) therapy and thyroid surgery. In United State, RAI is treatment of choice in patients without contraindication (Reid and Wheeler, 2005). The main complication of RAI therapy is hypothyroidism. Many reports have documented that incidence of hypothyroidism is significant during the first year or two after treatment

with RAI. The were sufficient evidence that risk factors such as dose of RAI, presence of autoantibodies, aetiology of hyperthyroidism, administration of antithyroid drug and goiter size, individually influence the outcome following RAI therapy.

The aetiology of hyperthyroidism is an important factor influencing the outcome after RAI therapy. A higher incidence of hypothyroidism has been reported in patients with Grave's disease compared with toxic multinodular goiter and solitary thyroid nodule. A higher rate of single dose treatment failure was observed in patients with multinodular goiter compared with Grave's disease and solitary toxic nodules (Bertelsen et al., 1992). Toxic multinodular goiter is relative resistant to RAI therapy requiring doses higher than widely appreciated and unlike Grave's disease hypothyroidism is relatively uncommon (Tzavara et al., 2002).

Although hypothyroidism is predictable sequale of radioactive iodine therapy, the time of its occurrence can be many years later. An early detection of hypothyroidism will allow prompt treatment. The rate of hypothyroidism at 12 months after RAI therapy at doses 10-20 mCi was 50% (Ekpebegh et al., 2008). In a study done by Ahmad et al (2002), the prevalence of hypothyroidism post RAI therapy was 55.8% at 1 year. Grave's disease, presence of autoantibodies, no antithyroid treatment prior therapy, nonpalpable thyroid gland and high dose of RAI 550 MBq (15mCi) were identified as significant independent risk factors for the development of hypothyroidism post RAI therapy.

This study was designed to determine the prevalence and associated factors (age, gender, race, aetiology of hyperthyroidism, presence of autoantibodies, dose of RAI used and usage of antithyroid drug post RAI) for the development of hypothyroidism among patients with hyperthyroidism within one year of RAI(^{131} I) therapy in Hospital Universiti Sains Malaysia.

1.2 OVERVIEW OF HYPERTHYROIDISM.

1.2.1 Definition

Thyroid hormone plays a significant role in pace of many processes in our body. Hyperthyroidism usually begins slowly but in some patients these changes can be very abrupt. It is hypermetabolic condition which associated with elevated levels of free thyroxine (fT4) and/or free triiodothyronine (fT3) and a low level of serum TSH (Iagaru and Mcdougall, 2007).

Thyroid hormone influences almost every tissue and organ system in the body and caused increased tissue thermorgenesis and basal metabolic rate. Most profound effects of increased thyroid hormone level a are on the cardiovascular system (Klein and Danzi, 2007). The complications of untreated hyperthyroidsm include loss of weight, osteoporosis, atrial fibrillation, embolic events, cardiovascular collapse and death (Burch and Wartosky, 1993).

1.2.2 Aetiology

In United State the prevalence of hyperthyroidism is approximately 1.2% (0.5% overt hyperthyroidism and 0.7 % subclinical).There are multiple causes of hyperthyroidism, the commonest is Grave's disease which approximately 60%-80% of the thyroid disease. The annual incidence of Grave's disease was found to be 0.5 cases per 1000 person during a 20 year period with peak age in person aged 20-40years. Others including toxic multinodular goiter and toxic adenoma (Ajjan and Weetman, 2007). Establishing the accurate aetiology of hyperthyroidism is important as this influences treatment strategy and is usually achieved by combination of clinical assessment, thyroid function, including thyroid autoimmune screening and radionuclide scan.

In general, hyperthyroidism can occur if; i) the thyroid is inapropriately stimulated by trophic factors, ii) there is constituitive activation of the thyroid hormone synthesis and secretion leading to autonomous release of excess thyroid hormone, iii) thyroid stores of preformed hormone are passively released in excessive amounts owing to autoimmune, infections, chemical, or either endogenous (struma ovarii, metastatic differentiated thyroid cancer) or exogenous (factitious thyrotoxicosis) (Bahn et al., 2011).

Grave's disease is an autoimmune disorder characterized by hyperthyroidism, diffuse goiter, ophtalmopathy and rarely dermopathy. The hyperthyroid state and goiter formation in Grave's diseasse are cause by stimulation of the thyroid by TSH receptor antibodies production of these antibodies is primarily within the thyroid gland

itself increasing thyroid hormone production. The female to male ratio among patients with graves disease is between 5:1 and 10:1. It can occur at the any age but the peak incidence is between 40 and 60 years of age (Brent, 2008).

Toxic multinodular goiter, also known as Plummer's disease, is the underlying condition in 15% to 20% of hyperthyroidism cases; and can be 10 times more common in iodine deficient areas. It is typically more insidious in onset than Grave's disease and occurs in patients older than 40 years with long standing goiter. The male and female ratio for toxic multinodular goiter is 1:2-4.

Toxic adenoma are found most commonly in younger patients and in iodine deficient areas (Reid and Wheeler, 2005). Other causes which can lead to hyperthyroid state include subacute thyroiditis, lymphocytic thyroiditis, post partum thyroiditis, drugs induced hyperthyroid such as amiodarone and iodine and tumour.

1.2.3 Diagnosis

The diagnosis of hyperthyroidism can be confirmed by laboratory test that measure the amount of thyroid hormones; free thyroxine (fT4), free triiodothyronine (fT3) and thyroid stimulating hormone(TSH). Reliable measurement of thyroid hormones is important tool for diagnosis and follow up of the thyroid diseases. In our study

centre, HUSM, those parameters were measured using Cobas E411 analyzer which is an immunoassay analyzer manufactured by Roche Diagnostics. The reference range are TSH : 0.3 -4.2 mIU/L, fT4 :12-22 pmol/L and fT3 :3.9-6.7 pmol/L.

Serum TSH measurement has the highest sensitivity and specificity of any single blood test used in the evaluation of suspected hyperthyroidism and should be used as measurements for assesing thyroid hormone excess (Master and Simon, 1996). In overt hyperthyroidism usually both serum free T4 and T3 estimates are elevated and serum TSH is undetectable. However in milder hyperthyroidism, serum free T4 and T3 estimates can be normal , only serum T3 may be elevated and serum TSH will be <0.01 mu/l (or undectable). These laboratory findings have been called T3 toxicosis and may represent the earliest stages of disease.

Beside doing thyroid fuction test, if the underlying cause of hyperthyroidism is not established on the basis of clinical findings there is role of doing 24 hour radioactive iodine uptake (RAIU). In Graves's disease it is associated with elevate uptake. Meanwhile, in toxic multinodular goiter, 24 hour RAIU demonstrates an enlarged thyroid with multiples nodules and area of increased and decreased isotope uptake (Fogelman et al., 1986).

Test for antibodies against thyroid specific antigen are used in the diagnosis of autoimmune thyroid disorders (Saravanan and Dayan, 2001). Antibodies to thyroglobulin, antimicrosomal and thyroid peroxidase may be present but this are not a diagnostic test for Grave's disease. All these tests are available in our study centre. These autoantibodies level are significant when the level were above the reference range. The reference range in HUSM for antimicrosomal (AMA), antithyroglobulin and antithyroperoxidase (antiTPO) antibodies are < 100 Iu/ml, < 115Iu/ml) and <34 Iu/ml respectively.

TABLE 1.2.3: Prevalence of thyroid autoantibodies (in percent) in different aetiology.

Aetiology	TSHR Ab	Tg Ab	TPO Ab
General population	0	5-20	8-27
Grave's disease	80-95	50-70	50-80
Hashimoto thyroditis	10-20	80-90	90-100
Relative of patient	0	40-50	40-50

#Larsen;William textbook of endocrinology,10th edition 2003

TSHR Ab=TSH receptor antibody

Tg Ab=thyroglobulin antibody

TPO Ab=thyroperoxidase antibody

Table above showed the prevalence of presence of autoantibodies in different aetiologies. Unfortunately the diagnostic and prognostic value of these thyroid autoantibody measurements is hampered by differences in the sensitivity and

specifity of current methods. Currently, there is no reliable clinical marker that can predict relapse. Determination of TSH receptor antibodies is useful inpredicting recurrence of Grave's disease. When values remain high at the end of drug therapy, early relapse is virtually unavoidable.

In some centres, clinicians use level of the autoantibodies to monitor patients' respond to treatment. TSH receptor antibodies (TRAb) are seen in most patients with Grave's disease, 75% to 90%. Testing usually done for a specific type of stimulating TRab that goes by several different names, including thyroid stimulating immunoglobulin (TSI) or TSH stimulating antibodies (TSAb). Thyroid stimulating immunoglobulin (TSI) can be detected in majority patient with Grave's disease but the absence of these antibodies does not rule out GD (Braverman and Utiger, 2004). When monitoring TSI, elevated levels may help predict relapse of GD and lowered TSI may indicate that GD treatment is working (Roti et al., 1998). In a study done by Ahmad et al (2002), they found that patient who had significant level of thyroid autoantibodies had increased chance to develope hypothyroidism post RAI (OR 3.51).

Other modality which help for the diagnosis of hyperthyroidism is by doing ultrasound and doppler of the thyroid gland. Ultrasound of thyroid does not generally contributed to the differential diagnosis of hyperthyroidism but increased colour doppler flow may helpful in confirming the diagnosis of thyroid hyperactivity (Bogazzi and Vitti, 2007).

1.2.4 Treatment.

The treatment of hyperthyroidism depends on cause and severity of the disease as well as on the patient's age, goiter size, comorbid condition and treatment desires.The goal of therapy is to correct the hypermetabolic state with fewest side effect and lowest incidence of hypothyroidism. Three forms of therapies are available for treating patients with hyperthyroidism which are initiation of anti thyroid drugs, RAI therapy and surgical intervention.

In our study centre, antithyroid drug was a primary therapy for hyperthyroidism. Medication that used to treat hyperthyroidism were thionamides (methimazole/carbimazole) or prophylthiouracil (PTU). If patients developed complication to antithyroid drug, contraindicated for antithyroid and relapsed, RAI therapy is the alternative option. For patients with TMNG, there are two effective and relatively safe treatment options; RAI (^{131}I) therapy and thyroidectomy.

In the United State, radioactive iodine therapy has been the therapy most preferred by physician. In Europe and Japan, there has been a greater physician preference to antithyroid drugs as initial treatment option for their patients (Wartofsky et al., 1991). In Grave's disease, patients with high likelihood of remission (especially females with mild disease, small goiter, negative or low titer TRAb), the elderly or others with comorbitidies increasing surgical risk or with limited life expectancy, antithyroid drug a particular modality as treatment (Bahn et al., 2011).

1.3 RADIOACTIVE IODINE THERAPY(RAI ^{131}I)

1.3.1 Overview

Radioactive iodine (^{131}I) therapy was used since 1941. Radioactive iodine therapy is safe treatment modality and are established effective for patients with various aetiologies of hyperthyroidism. It is the most commonly used modality to treat hyperthyroidism in United State but it is not yet routinely used as first line therapy for Grave's disease in Europe and also in Malaysia. It is inexpensive, highly effective, easy to administer, tissue specific and its safety has been proven in all age group. It is painless, effective, economical and quick. RAI therapy may be used either as initial therapy or after treatment with medication.

1.3.2 Indication for RAI

The main indication for using RAI is failure of or occurance after antithyroid drug therapy. Treatment of Grave's disease with ATD is associated with high grade of relapsed. It is known approxiamately 50% to 70% of patients with GD will relapse after completing a standard course of 1 to 2 years of antithyroid drug (Weetman, 2000). Such patients will benefit from radioactive iodine therapy. Besides that, patients with allergic reaction to antithyroid drug and developed complication such as agranulocytosis or rash, or in whom time and prevention of long term sequelae is critical importance (in elderly patients with thyrocardiac disease or recurrent periodic paralysis), RAI therapy is the alternative.

For patients with toxic multinodular goiter or toxic adenoma, medical treatment is generally more difficult and will not produce permanent remission. For patients with TMNG, there are two effective and relatively safe treatment option; RAI therapy and thyroidectomy.

1.3.3 Mechanism of action of RAI

Iodine 131(^{131} I) is beta emitting radionuclide with maximum energy of 0.61 MeV,an evarage energy of 0.192 MeV and is notable for causing mutation and death in cells that it penetrates and other cells up to several milimiters away. All the isotopes of iodine are rapidly taken up in thyroid follicles. Organs other than thyroid take up ^{131} I but the thyroid is the only organ where the organification occurs. The absortion and organification of ^{131} I beta radiation by the thyroid results in highly localized destruction of those follicles. Initially RAI distrupts thyroid hormone biosynthesis follwed by necrosis of follicles cells and associated blood vessels. The spesificity of RAI for those tissues has promote this procedure as a therapeutic alternative to surgical procedure, its applicability to patients who are poor surgical risks. It has a radioactive decay half life of about 8 days resulting in euthyroidism usually within 6 to 18 weeks. It is administer orally as iodine (^{131} I) in solution or as a capsule iodine.

1.3.4 Dose RAI

There are two common approaches for determining the dose of RAI dose. One is to prescribed a fixed dose and the other one is to calculate a dose based on size of thyroid gland and percentage uptake at 24 hours. Although RAI therapy is well

established, the approach to dosing remains controversial. This is due to differing goals of treatment (control of hyperthyroiism vs avoidance of hypothyroidism). There is little evidence that using a calculated dose has any advantage over fixed dose regime in terms of preventing hypothyroidism (Peter et al., 1997). A fixed dose regime is more convenient to use.

Many studies done to evaluate the outcome various doses of RAI therapy among patients with hyperthyroidism. Kendall et al (1984), used RAI 555 MBq(15mCi) and demonstrated that 64% of their patients were hypothyroid and 30% were euthyroid 1 year after therapy. In a study comparing with two doses of RAI of 185 MBq (5mCi) and 370 MBq (10mCi), they found the incidence of hypothyroidism at 1 year was 71.4% in higher dose group and 66.4% in low dose group (Allahabadia et al., 2001).

1.4 Hypothyroidism post RAI therapy.

Hypothyroidism occured because of deficiency of thyroid hormones resulting in hypometabolic state. The main consequence of radioactive iodine therapy is post therapy long term hypothyroidism. RAI produces radiation thyroiditis and fibrosis resulting in euthyroidism usually within 6 to 18 weeks. Hypothyroidism may however manifest many years after the administration of even small doses of RAI. Early detection of hypothyroidism is important because it is easy to treat but if we missed to diagnosed and failed to monitor patients for evident of hypothyroidism, it can course life threatening condition. If left untreated, the symptoms of hypothyroidism will usually progress. Severe form of untreated hypothyroidism patients, they might end up with cardiac failure or coma. Hypothyroidism is completely treatable. A lifelong

follow up is necessary after the administration of RAI therapy to allow for the early detection of hypothyroidism. Appropriate laboratory evaluation is critical to established the diagnosis and cause of hypothyroidism in the most cost effective way.

All patient with who received RAI therapy must be follow up within the first 1 to 2 months after RAI therapy. They should assess clinically and biochemically. RAI results in resolution of hyperthyroidism in approximately 55% of patient at 3 months and 80% of patients at 6 months with average failure rate of 15%. Goiter volume is decreased by 3 months and futher reduction can be seen over 24 months (Faber et al., 1998). Base on recommendation from Management Guideline of American Thyroid Association and American Association of Clinical Endocrinologists (2011), follow up within 1-2 months after RAI therapy needed to assess patients clinically and biohemically by assessment of free T4, free T3 and TSH. This should be repeated at 1-2 month intervals until stable result are obtained. If hyperthyroid persistent beyond 6 months following ^{131} I therapy, retreatment with radioactive iodine is suggested.

1.5 Prevalence of hypothyroidism post RAI and associated factors.

Radioactive iodine therapy is a leading cause of hypothyroidism especially in Grave's disease. The frequency of hypothyroidism post RAI therapy is depent on multiple factors and one of factor is the dose of RAI administered. Hypothyroidism frequently develops in the first year after treatment (with spontaneous return to euthyroidism in some patients), but it may not be manifest until years later in others. Its cumulative

occurence after the first year continues to rise with 0.5 -2% annually. Various treatment schedules have been devised with the hope of diminishing the incidence of RAI induced hypothyroidism, but in general a lower incidence of hypothyroidism is invariably associated with a higher prevalence of persistent hyperthyroidism that required retreatment. Hypothyroidism occurs less often (6-13%) after RAI therapy in toxic multinodular goiter (Wiersinga and Degroot, 2002).

In a retrospective study done by Ghabhan et al (2003), they analyzed 360 patients who received RAI therapy (dose 5mCi till 15mCi). They found the incidence of hypothyroidism was 55.8% at 6 months and 67.9% at one year. The cumulative incidence of hypothyroidism was 55.8% at one year and 86.1% at 10 years in study done by Ahmad et al (2002). In their study, Grave's disease (odd ratio: 4.29), presence of thyroid autoantibodies (odd ratio: 3.51), no antithyroid treatment given prior to RAI (odd ratio: 2.5), non palpable goiter (odd ratio:2.48) and high dose of RAI (odd ratio:1.90), were identified as significant independent risk factors for occurance of hypothyroidism post RAI therapy.

In India (2010), one study done among 158 hyperthyroidism patients who treated with RAI therapy and completed follow up in one year, they found 98.8% recovered (74.2% became hypothyroid and 22.6% euthyroid) and 1.2% remained thyrotoxic. The incidence of hypothyroidism was 23% in first trimester, 43.7% in second trimester, 4.4% in third trimester and 3.1% in forth trimester post therapy (Shinto et al., 2010).

1.6 Antithyroid drug post RAI.

Limited studies were available with regards to the use of antithyroid drugs post RAI therapy and development of hypothyroidism. In the previous studies, patients became euthyroid sooner than those who received no antithyroid drug post RAI therapy. Since the antithyroid drugs may hasten the return to euthyroid state, it is also possible that post RAI exacerbation of thyroid function as well as the incidence of thyroid storm might be prevented. With more rapid normalization of thyroid function following antithyroid drug use post RAI, hyperthyroid patients will also have lesser hyperthyroidism symptoms and a better sense of well being.

In one study done in Philliphines found, patients who received antithyroid drugs post RAI therapy reported having lesser hyperthyroidism symptoms compared to those received RAI per se and this observation was significantly noted on first and third week of antithyroid drugs initiation (Gafate and Mercado-Asis, 2008). Resuming antithyroid drug post RAI therapy is not associated with an increase risk of recurrence of hyperthyroid state or progression to hypothyroidism unless given within a week before or after radioactive iodine where there is an increased failure rate of therapy and reduced the hypothyroidism rate respectively (Mumtaz et al., 2009).

CHAPTER 2
OBJECTIVE

CHAPTER 2: OBJECTIVES

2.1 RESEARCH QUESTIONS

1)What is the outcome of RAI therapy in patients with hyperthyroidism within one year ?

2)What is the prevalence of hypothyroidism among patients with hyperthyroidism within 1 year of RAI therapy?

3)What are the associated factors for the development of hypothyroidism among patients with hyperthyroidism who received RAI therapy?

2.2 OBJECTIVES

2.2.1 GENERAL OBJECTIVES

To assess the outcome of RAI therapy in patients with hyperthyroidism who received RAI within one year.

2.2.2 SPECIFIC OBJECTIVES

2.2.2 a) To determine prevalence of hypothyroidism within one year of RAI therapy in patients with hyperthyroidism.

2.2.2 b) To determine the associated factors (age,gender,aetiology of hyperthyroidism, presence of thyroid antibodies,dose of radioactive iodine and usage of antithyroid drug post therapy) for the development of hypothyroidism in patients with hyperthyroidism who received RAI therapy.

CHAPTER 3

METHODOLOGY

CHAPTER 3: METHODOLOGY

3.0 METHODOLOGY

3.1 Study design:

Retrospective record review study.

3.2 Study setting and population:

This study was conducted from September 2012 till November 2012 at Hospital Universiti Sains Malaysia (HUSM) which is tertiary centre and a teaching hospital, at the East Coast of Peninsular Malaysia. All patients with hyperthyroidism who were follow up at Klinik Pakar Perubatan, HUSM and received RAI therapy in Nuclear Medicine Clinic HUSM from 2002 till 2011 were selected for this study. Patients' medical records were reviewed. The demographic data (age, gender and race), presence of autoantibody, etiology of hyperthyroidism, dose of RAI used and usage of antithyroid drug post RAI were documented. Thyroid function test result of each patient was reviewed. Patients were categorized into hypothyroid group or non hypothyroid group. Reference ranges for thyroid fuction test were free T3:3.9-6.7 pmol/l, free T4:12-22 pmol/L and TSH: 0.27-4.2 miu/L. These test was analyzed by using Cobas e 411 analyzer technique. The Cobas e 411, is immunoassay analyzer was manufactured by Roche Diagnostics and it is fully automated random access system for immunoassay analysis.

3.3 Inclusion criteria:

1) Age more than 18 year old.

2) Patients with hyperthyroidism who received RAI therapy in Nuclear Medicine Clinic and follow up at Klinik Pakar Perubatan in HUSM.

3.4 Exclusion:

1) Age less than 18 year old.

2) Follow up less than one year post RAI therapy.

3.5) DATA COLLECTION:

The demographic data (age,gender and race) of all patients together with aetiology of hyperthyroidism,date and dose of RAI therapy given, presence of autoantibodies and usage of antithyroid drug post therapy were charted on data requisition form (APPENDIX A).

The onset of development of hypothyroidism also was assessed by charting the serial thyroid function result within one year of RAI therapy.

3.6 DEFINITION OF OPERATIONAL TERM:

3.6 (a) HYPERTHYROIDISM:

Hyperthyroidism is diagnosed when thyroid stimulating hormone (TSH) suppressed with raised free thyroxine (fT4) and/or free triiodothyronine (fT3) levels are above the normal reference (AACE Thyroid Task Force, 2002). Reference ranges; free T3:3.9-6.7 pmol/L, free T4:12-22 pmol/L and TSH: 0.27-4.2 pmol/L).

3.6 (b) RADIOACTIVE IODINE THERAPY (RAI ^{131}I):

It is an isotope of iodine (^{131} I) that emits radiation. It is administered orally as sodium Iodide ^{131}I, it is given dissolved in water or a capsule. It is absorded quickly by stomach and intestine then carried in to blood stream to the thyroid, where it is taken up by the gland. The radioactive iodine is rapidly incorporated into the thyroid and its radiation results in destroying the gland's cells (RSNA 2012).

3.6 (c) HYPOTHYROIDISM :

Elevated TSH and suppressed serum free T4 or free T3 or both below the normal reference range (reference ranges: free T3:3.9-6.7 pmol/L, free T4:12-22 pmol/L and TSH: 0.27-4.2 pmol/L).

3.6 (d) WITHIN ONE YEAR OF RAI THERAPY:

Onset of development of hypothyroidism among patients with hyperthyroidism who received RAI therapy up to one year post RAI.

3.7 SAMPLE SIZE CALCULATIONS:

3.7.1) OBJECTIVE (a): to determine the prevalence of hypothyroidism post RAI therapy among patients with hyperthyroidism within one year post therapy. Sample size was calculated using Single Proportion Formula.

$n = (z /\Delta)^2 p (1-p)$

Anticipated population proportion (p) = 56% (0.56)

#p=prevalence of hypothyroid =0.56 (according to study (Ahmad et al., 2002)) reported that cumulative incidence of hypothyroidism within one year was 55.8%.

n=the estimated sample

Z=1.96 for 95% confidence

Δ= Absolute precision

Level of significance = 5%

Absolute precision (Δ) = ± 8%

$n = (1.96/ 0.08)^2 \ 0.56(1.0-0.56)$

$n = 148$

Considering 10% non response rate, therefore n =163

3.7.2) OBJECTIVE (b) –To determine the associated factors (age,gender ,dose of RAI used ,present of autoantibodies and antithyroid drug post therapy)for the development of hypothyrodism following RAI therapy,Two Proportion Independent Sampling method was used to evaluate the significant of the associated factors.

variables	α	power	P_0	P_1	m	n
Gender	0.05	0.8	0.6	0.8	1	81
Aetiology	0.05	0.8	0.33	0.77	1	19
Presence autoantibody	0.05	0.8	0.48	0.8	1	34

Final sample size :

The largest sample size n=162

Considering 10% dropped out, therefore total number of patients required for this study is n =178

3.8 Ethical consideration

This study was approved by Human Research and Ethics Comittee, Universiti Sains Malaysia (USM/PPP/JEPeM[256.4.(2.13)]).

3.9 Statistical analysis

All data analysed were carried out using SPSS statistical software (version 20.0). The prevalences was calculated based on the obtained data whereby it was split into 2 independent categorical variables (hypothyroidism and non hypothyroidism)

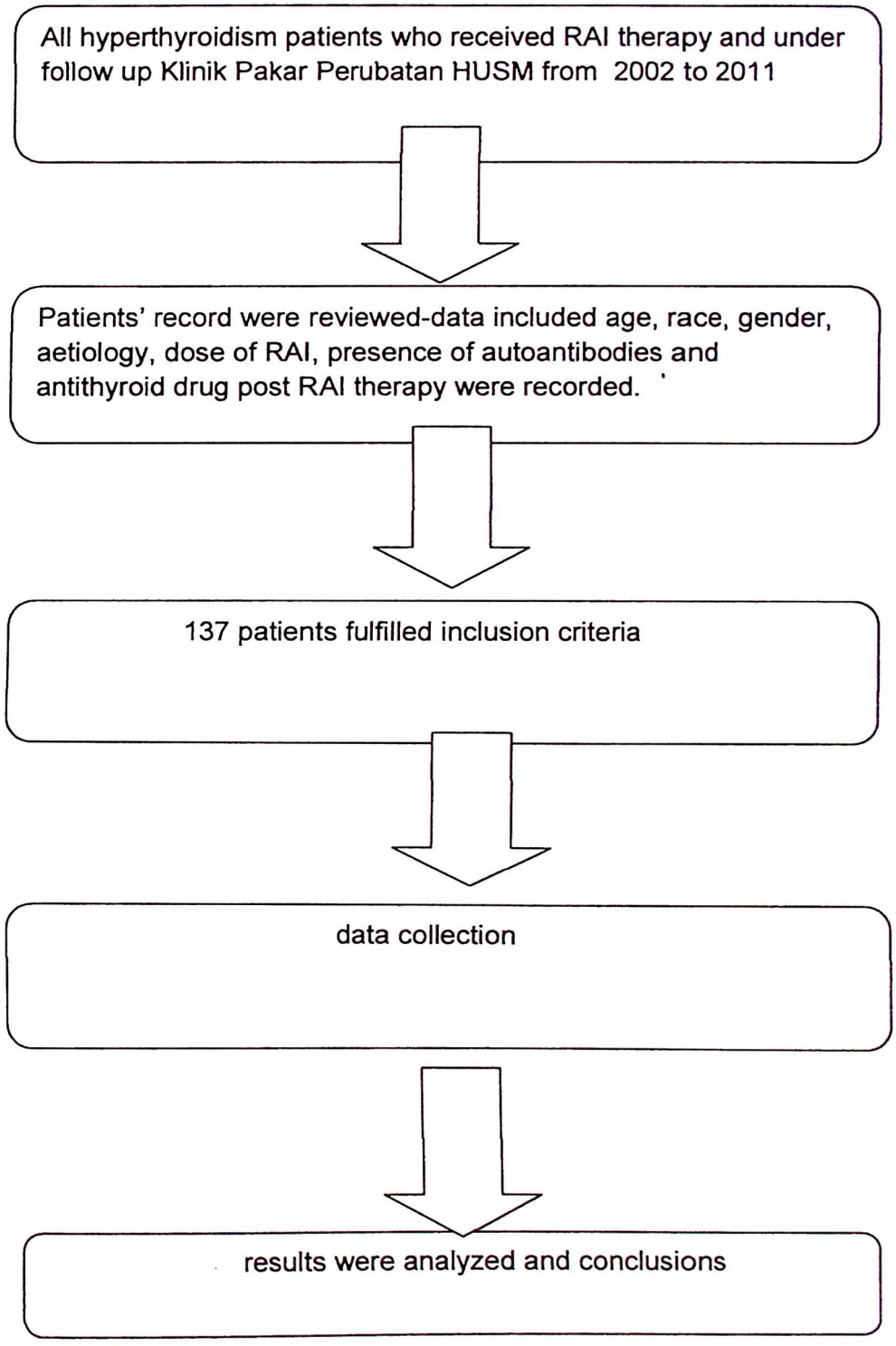
The percentage of patients who developed hypothyroidism post RAI therapy over the total patients would be considered as the prevalances. Two groups of hypothyroidism and non hypothyroidism (remained hyperthyroidism and euthyroid) were created. Association between demographic data (age,gender and race), aetiology of hyperthyroidism,dose of RAI used and usage of antithyroid drug post RAI therapy were assessed by Chi square test for normally distributed categorical variables and two tailed Fisher's exact test was applied expected cell frequencies were less than five.

After univariable analysis was done,futher analysis of significant categorical outcomes of hypothyroidism and non hypothyroidism was carried out using multiple logistic regression. Association between variables and hypothyroid group would be explored.

A *P* value below 0.05 will be considered as statistically significance.

3.10 STUDY FLOW CHART

FIGURE :STUDY FLOW CHART



CHAPTER 4

RESULTS

CHAPTER 4: RESULTS

4.0 RESULTS

4.1 DESCRIPTIVE ANALYSIS

4.1.1 DEMOGRAPHIC DATA

Total number of 167 patients were identified in this retrospective study in Klinik Pakar Perubatan (KPP), HUSM, of which 30 were excluded. The final numbers of patients included in this study were 137. Among this patients, the mean age of the subjects in the study were 47.39±11.94 years. The ages ranged from 19 till 87 years old (Figure 1). There were more female patients, 92 (67.2%) as compared to male, 45 (32.8%) patients. Malay ethnics constitued the highest proportion of the study subjects; 126 (92%) patients and 11 (8%) of them were Chinese (Table 4.1) which represent normal ethnic distribution and population in state of Kelantan.