



Original Article

Hypothyroidism and its associated factors after radioactive iodine therapy among patients with hyperthyroidism in the Northeast Coast State of Malaysia



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Received 23 December 2017; revised 6 June 2018; accepted 10 June 2018; Available online 18 July 2018

المخلص

أهداف البحث: تهدف هذه الدراسة لتحديد حدوث قصور الغدة الدرقية والعوامل المرتبطة بها في غضون عام واحد بعد العلاج باليود المشع.

طرق البحث: أجريت دراسة بأثر رجعي بين المرضى الذين يعانون من قصور الغدة الدرقية الذين حصلوا على العلاج باليود المشع في عيادة الطب النووي، مستشفى جامعة ساينز ماليزيا، كلنتان. تم تضمين المعلومات الديموغرافية للمرضى، والجنس، وسبب فرط نشاط الغدة الدرقية، ووجود الأجسام المضادة، وجرعة العلاج باليود المشع واستخدام دواء ضد نشاط الغدة الدرقية بعد العلاج باليود المشع.

النتائج: من بين 167 مريضا تم فحصهم، تم ضم 137 مريضا للدراسة. كان معدل الإصابة بقصور الغدة الدرقية خلال عام واحد بعد العلاج باليود 32.9%. ووجد أن السيدات أقل احتمالا لحدوث قصور الغدة الدرقية بعد العلاج باليود المشع 0.406. وأن استخدام دواء ضد نشاط الغدة الدرقية بعد العلاج باليود المشع يرتبط بشكل كبير مع حدوث أقل لقصور الغدة الدرقية بعد العلاج باليود المشع 0.188.

الاستنتاجات: أظهرت الدراسة ارتفاع حالات الإصابة بقصور الغدة الدرقية خلال عام بعد العلاج باليود المشع. يرتبط الجنس واستخدام دواء ضد نشاط الغدة الدرقية بعد العلاج باليود المشع بشكل كبير مع حدوث قصور الغدة الدرقية.

الكلمات المفتاحية: قصور الغدة الدرقية؛ بعد العلاج باليود المشع؛ فرط نشاط الغدة الدرقية؛ مرض جريف

Abstract

Objectives: The aim of this study was to determine the incidence of hypothyroidism and its associated factors within one-year post radioactive iodine (RAI) therapy.

Methods: A retrospective study was conducted among patients with hyperthyroidism who received RAI therapy at Nuclear Medicine Clinic, Hospital Universiti Sains Malaysia (HUSM), Kelantan. Data regarding patients' demographics, gender, aetiology of hyperthyroidism, presence of autoantibodies, dose of RAI used and usage of antithyroid drug post RAI therapy were included in the analysis.

Results: Of a total of 167 screened patients, 137 subjects were eligible for this study. The incidence of hypothyroidism within one year of RAI therapy was 32.9%. Women were found to be less likely to develop hypothyroidism post RAI therapy (adjusted odds ratio, 0.406; 95% confidence interval: 0.181–0.908; $p = 0.028$). The usage of antithyroid drug post RAI was significantly associated with a lower incidence of hypothyroidism post RAI therapy (adjusted odds ratio, 0.188; 95% confidence interval: 0.081–0.438; $p < 0.001$).

Conclusion: This study showed a high incidence of hypothyroidism within one-year post RAI therapy. Gender and usage of antithyroid drug post RAI therapy are significantly associated with the development of hypothyroidism.

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Peer review under responsibility of Taibah University.



Keywords: Graves' disease; Hyperthyroidism; Hypothyroidism; Post radioactive iodine therapy

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Introduction

Hyperthyroidism affects about 2% of women and 0.2% of men.¹ It is a hypermetabolic state characterised by elevated levels of free thyroxine (fT4) and/or free triiodothyronine (fT3) and a low level of serum thyroid stimulating hormone (TSH).² Weight loss, osteoporosis, atrial fibrillation, and embolic events are some of the complications associated with hyperthyroidism. The most profound effect of hyperthyroidism is on the cardiovascular system.³ The causes of hyperthyroidism include toxic multinodular goitre (TMNG), toxic adenoma, and thyroiditis. However, the most common cause of hyperthyroidism is Graves' disease and the annual incidence of Graves' disease was found to be 0.5 cases per 1000 persons, with a peak incidence among persons aged 20–40 years.^{4,5}

The proper treatment for hyperthyroidism depends on the identification of the symptoms and signs of the disease and its aetiologies. Antithyroid drugs, radioactive iodine (RAI) therapy and surgery are the main treatment modalities known to be effective. In 1941, RAI therapy was introduced and became popular due to its strong efficacy and safety profile.^{6,7} The nuclide used in this therapy is iodine-131 (¹³¹I).⁸ ¹³¹I is a beta-emitting radionuclide with an average energy of 0.192 MeV (maximum energy of 0.61 MeV) and tissue range of 0.8 mm.⁹ Although ¹³¹I may cause cell mutation and cell death, all the iodine isotopes are rapidly taken up into the thyroid follicles; thus, only thyroid follicles undergo organification. The absorption and organification of ¹³¹I beta radiation by the thyroid follicles result in the highly localised destruction of those follicles. ¹³¹I disrupts thyroid hormone biosynthesis and causes the necrosis of the follicles and blood vessels. The half-life of ¹³¹I is approximately 8 days and results in euthyroidism within 6–18 weeks.⁹

RAI therapy is indicated when antithyroid drug therapy fails to treat hyperthyroidism or when there is recurrent hyperthyroidism. Treatment of Graves' disease with medication is associated with 50–70% recurrence after completing a standard course of 1–2 years of antithyroid drugs.¹⁰ Patients who are allergic to antithyroid drugs and who have neither TMNG nor thyroid cancer are the best candidates for RAI therapy. RAI therapy destroys the thyroid tissue and renders patients either euthyroid or hypothyroid.⁹ Most often, hypothyroidism is a long-term effect of RAI that necessitates life-long thyroxine supplementation.⁸ Hypothyroidism frequently develops in the first year after treatment. However, hypothyroidism may also manifest several years post RAI therapy.¹¹ Thus, patients who have undergone RAI require long-term follow up.

In Malaysia, RAI has become one of the main therapeutic services available at several tertiary hospitals and institutions

with nuclear medicine facilities. Hospital Universiti Sains Malaysia (HUSM) located in Kelantan, is the only facility that offers RAI in the Northeast Coast of Peninsular Malaysia where it serves as a referral centre for the two neighbouring states, i.e., Terengganu and Kedah. The RAI administration practice varies from centre to centre with regards to the selection of cases, preparation for RAI, dosage of radioiodine, and protocol for the use of antithyroid drugs pre- and post RAI. Although there are standard international guidelines for RAI therapy, the different practices may lead to different outcomes of RAI therapy from centre to centre, especially in the incidence of hypothyroidism post RAI therapy.

A study in Bangladesh showed that the incidence of hypothyroidism one year post RAI was 35.6%.¹² A retrospective study of 360 patients by Ghabhan et al. revealed that the incidence of hypothyroidism post RAI at 6 months and one year was 55.8% and 67.9%, respectively.¹³ Ahmad et al. showed that the cumulative incidence of hypothyroidism was 55.8% at one year and 86.1% at 10 years.¹⁴ There are many factors associated with the development of hypothyroidism post RAI therapy, such as history of Graves' disease, presence of thyroid autoantibodies, usage of antithyroid treatment prior to RAI and absence of a palpable goitre.¹³ These conflicting results mandate further study regarding this issue. Thus, the objective of this study was to determine the incidence of hypothyroidism and its associated factors within one-year post RAI among patients with hyperthyroidism in the Northeast Coast Region of Malaysia.

Materials and Methods

This was a retrospective record review study from 2002 to 2011. Patients were identified from the registered list of patients who underwent RAI therapy at the Nuclear Medicine Department, HUSM and were followed-up for at least one year after the therapy.

Patients with hyperthyroidism and older than 18 years, who received RAI therapy at the Nuclear Medicine Clinic and were followed up at the Endocrine Clinic in HUSM were included in the study. Patients' younger than 18 years and/or who were followed up for less than a year post RAI at the study centre were excluded from the study.

Patients' medical records and electronic data were reviewed. The socio-demographic data (i.e., age, gender and race) of all patients together with the aetiology of hyperthyroidism, date and dose of RAI therapy given, presence of autoantibodies, and post-therapy antithyroid drug usage were charted on the case report forms. The onset of hypothyroidism was determined by reviewing the results of serial thyroid function tests taken at one week and at every three months post RAI therapy up to one-year post RAI therapy. The subjects were grouped after all the available data were collected. The sample size calculation for the study yielded an optimal sample size of 167 after considering a single proportion, and a 10% drop-out rate (Ahmad et al., 2002).

At the centre, the dose of sodium iodide-131 (NaI-131) used in RAI was in the range of 5–15 mCi (185–555 MBq). The dose administered was based on the estimation of thyroid gland size by a trained endocrinologist during physical examination. Patients with small or normal thyroid glands

received between 5 and 10 mCi of NaI-131, while patients with enlarged thyroid glands or nodularity received between 10 and 15 mCi of NaI-131. Oral NaI-131 was given in the liquid form and was dispensed by a nuclear radiopharmacist.

The diagnosis of hyperthyroidism was confirmed by thyroid function tests involving the determination of thyroxine (T4), triiodothyronine (T3) and TSH concentrations. These parameters were measured using the Roche Cobas e411 analyzer and the normal reference ranges used were TSH: 0.3–4.2 mIU/L, fT4: 12–22 pmol/L, and fT3: 3.9–6.7 pmol/L. An alternative method involves the measurement of radioactive iodine uptake over 24 h; the uptake is elevated in patients with Graves' disease. A TMNG is an enlarged thyroid gland with multiple nodules with areas of increased and decreased isotope uptake. However, this procedure is not routinely performed at the study centre.

Hypothyroidism is diagnosed in the presence of elevated TSH levels and low levels of fT4 and/or fT3. Hyperthyroidism is diagnosed when TSH levels are suppressed with increased fT4 and/or fT3 levels. Reference range: fT4: 3.9–6.7 pmol/L, fT4: 12–22 pmol/L and TSH: 0.27–4.2 pmol/L.¹⁵

The confidentiality of the data was strictly maintained. Data were analysed using SPSS version 20 (IBM Corp., Armonk, NY, USA). Means and standard deviations were calculated for numerical variables, while frequencies and percentages were calculated for categorical variables. The dependent variable was hypothyroidism within one-year post RAI therapy. Data were analysed using simple and multiple linear regressions.

The study protocol was approved by the Research and Ethics Committee, Universiti Sains Malaysia (USM/PPP/JEPeM [256.4 (2.13)]).

Results

There were 167 patients with hyperthyroidism who underwent RAI therapy at the study centre based on the clinic register. Thirty patients were excluded because they were followed-up at other centres. Thus, the final number of patients included in this study was 137. The ages of the study subjects were between 19 and 87 years. There were more female patients than males. The highest proportion of the study subjects were of Malay ethnicity. The aetiology of hyperthyroidism in our study was classified into three groups: Graves' disease, non-Graves' disease and unclassified group. Patients with unknown aetiology of hyperthyroidism were placed in the unclassified group. Table 1 details the socio-demographic characteristics of the study subjects.

The proportion of patients who developed hypothyroidism within one year post RAI was 32.9%. The proportions of thyroid statuses among the subjects are shown in Table 2.

Table 3 shows the univariate analysis of factors associated with the development of hypothyroidism post RAI.

Details of the gender and antithyroid drug usage post RAI significantly associated with the development of hypothyroidism among post RAI patients are shown in Table 4.

Discussion

The mean age of the study population was 47 ± 11.94 years, ranging from 19 to 87 years, and the majority of the

Table 1: Socio-demographic data of patients with hyperthyroidism who received RAI therapy (N = 137).

Variables	n (%)	mean (SD)
Age		47.39 (11.94)
Gender		
Male	45 (32.8)	
Female	92 (67.2)	
Race		
Malay	126 (92)	
Chinese	11 (8.0)	
Aetiology of hyperthyroidism		
Graves' disease	65 (47.4)	
Non-Graves' disease	20 (14.6)	
Unclassified	52 (38.0)	
Presence of autoantibodies		
Yes	25 (18.2)	
No	19 (13.9)	
No data	93 (67.9)	
Dose of RAI		
≤10 mCi	92 (67.2)	
>10 mCi	45 (32.8)	
Post therapy antithyroid drug		
Yes	102 (74.5)	
No	35 (25.5)	

subjects were Malay (92%). The large variation in age was most probably due to the delayed decision to undergo RAI therapy due to safety concerns regarding the side effects of RAI such as hypothyroidism, scarring and worsening ophthalmopathy.¹⁶ Those who were of reproductive age were concerned about the effects of RAI therapy on their reproductive system i.e., chances of pregnancy and how it would affect breastfeeding. Their concerns were quite justified. Lactating breast tissues are able to absorb significant amounts of RAI and it is advisable to avoid breastfeeding for at least six weeks post RAI to prevent RAI exposure to the infant.¹⁷ Female patients were advised not to become pregnant for at least 4–6 months post RAI and to refrain from having close contact with young children for at least 10 days post RAI.¹⁸ All the aforementioned reasons may deter the patients from deciding to undergo the RAI therapy. In our study, of 137 hyperthyroidism patients, there were 92 females and 45 males. The most common aetiology of hyperthyroidism identified in our study population was Graves' disease, which is in accordance with the majority of the subjects being female. Females are more inclined to develop Graves' disease compared to their male counterparts.

In our study, about one-third (45, 32.9%) of the patients became hypothyroid within one-year post RAI therapy. The

Table 2: Proportion of hypothyroidism within one-year post RAI therapy, N = 137.

Variables	n (%)
Hypothyroid	45 (32.9)
Non-hypothyroid	92 (67.1)
Euthyroid	27 (19.7)
Remained hyperthyroid	65 (47.4)

Table 3: Simple Logistic Regression on associated factors with development of hypothyroidism post RAI therapy.

Independent variable	Non-hypothyroid	Hypothyroid	Regression coefficient (β)	Crude odds ratio (95% CI)	Wald statistic (df)	p-value
Age	46.77 \pm 11.80	48.67 \pm 12.25	0.01	1.013 (0.957–1.017)	0.761 (1)	0.385
Sex						
Female	67 (74.5)	20 (44.4)	-0.76	0.466 (0.221–0.984)	4.014 (1)	0.045
Male	25 (25.5)	25 (55.6)	0.00	1		
Race						
Malay	85 (92.4)	41 (91.1)	-0.169	0.844 (0.234–3.047)	0.067 (1)	0.796
Chinese	7 (7.6)	4 (8.9)	0.00	1		
Aetiology of hyperthyroidism						
Graves' disease	42 (45.7)	23 (51.1)	-0.05	0.951 (0.445–2.033)	0.017 (1)	0.897
Non Graves' disease	50 (54.3)	22 (48.9)	-1.18	0.307 (0.790–1.183)	2.943 (1)	0.086
Unclassified	63 (68.5)	29 (64.4)	0.00	1	0.223 (1)	0.637
Dose of RAI						
≤ 10 mCi	29 (31.5)	16 (35.6)	0.18	1.199 (0.565–2.543)		
> 10 mCi			0.00	1		
Antithyroid drug post RAI						
Yes	78 (84.8)	24 (53.3)	-1.58	0.205 (0.091–0.450)	14.461 (1)	<0.001
No	14 (15.2)	21 (46.7)	0.00	1		

majority (65, 47.4%) of patients remained hyperthyroid and only 27 patients (19.7%) became euthyroid. The dose of RAI used in this study was between 5 and 15 mCi, but 92 (67.2%) of patients in this study received ≤ 10 mCi of RAI. Similar findings were reported in a study conducted in Bangladesh. The RAI dose used was between 7 and 10 mCi; 35.6% of the hyperthyroid patients developed hypothyroid within one year post RAI.¹² In a recent study conducted in Cairo, 24.8% of Graves' disease patients who received 10 mCi of RAI therapy developed hypothyroidism 6 months after therapy_ENREF_19. In India, a study among 158 patients reported that about 74.2% of patients developed hypothyroidism one year after RAI therapy; 22.6% became euthyroid and 1.2% remained thyrotoxic.¹⁹ The dose of RAI used in the study ranged from 10 to 15 mCi. More patients developed hypothyroidism most likely as a result of the higher dose of RAI used, which was more than 10 mCi compared to that used in our study. This is supported by multiple studies; Shinto et al. (2010) showed that higher doses of RAI (> 10 mCi) led to a higher proportion of hypothyroidism (97.7%) among patients post RAI, although there was no statistically significant correlation.¹⁹ A study conducted in Cairo reported that

among patients who received RAI doses of 15 mCi, 48.3% developed hypothyroidism at 6 months post RAI.²⁰

Another study reported that 67.9% of the study population developed hypothyroidism one year after receiving a 20 mCi RAI dose,¹³ which was 10 mCi higher than that used in our study. Administration of low doses of RAI is possible but may lead to treatment failure, requiring the administration of a second dose. This would then lead to a higher prevalence rate of hypothyroidism⁹; thus, different doses and methods of administration of RAI yield different outcomes.

Gender and treatment with antithyroid medication post RAI are significantly associated with the development of hypothyroidism. Our results show that females are less likely to become hypothyroid compared to male patients. Contrary to our results, Ghadhan et al. (2003) reported that gender was not significantly associated with the incidence of hypothyroidism,¹³ while Allahabadia et al. (2001) also showed that the incidence of hypothyroidism did not vary significantly between females (50.5%) and males (49.4%).²¹

This study clearly showed that the usage of antithyroid drug post RAI therapy significantly reduces the development of hypothyroidism. This finding is supported by a study conducted in Belgium which also observed lower incidence rates of hypothyroidism but higher rates of recurrence or persistence of hyperthyroidism.²² However, a meta-analysis suggested that when antithyroid drugs are given right before, with or right after RAI therapy, the incidence of treatment failure increases. A reduction in the risk of hypothyroidism also reduced when antithyroid drugs were given with or after RAI.²³ There is a plausible interaction between antithyroid drugs and the uptake of RAI.

A few studies have reported that antithyroid drug administration during RAI therapy reduces RAI absorption,^{23,24} leading to RAI treatment failure. Walter et al. also concluded that antithyroid drugs given one week post RAI had an effect on the outcome of RAI therapy; patients were less likely to develop hypothyroidism, leading to a higher rate of treatment failure.²³ This probably explains

Table 4: Multiple logistic regression of factors associated with the development of hypothyroidism post RAI therapy.

	Adjusted β coefficient	Adjusted OR ^a	95% CI	p value
Sex				
Female	-0.90	0.406	0.181, 0.908	0.028
Male	0.00	1		
Antithyroid drug post RAI				
Yes	-1.670	0.188	0.081, 0.438	<0.001
No	0.00	1		

^a A backward likelihood ratio multiple logistic regression model was applied. No interaction was found between the two variables. The Hosmer–Lemeshow test yielded a p value of 0.966, indicating a good model fit.

why a higher proportion of subjects in our study remained hyperthyroid post RAI. On the other hand, Mumtaz et al. reported that carbimazole, restarted on the seventh day after RAI, had no impact on subsequent thyroid function.⁹ This controversy remains unresolved and has been debated for decades.

In the present study, all the patients were placed on antithyroid drugs before RAI therapy to control their symptoms. The medications were stopped three to seven days before taking RAI. The decision to resume the medication post RAI therapy depended largely on the severity of the hyperthyroidism, dose of antithyroid drugs prior to RAI therapy, and the clinical judgement of the attending endocrinologist. Majority of the patients in this study were put back on the antithyroid medication seven days post RAI to alleviate their symptoms since the effects of RAI would not be immediate.

A few limitations are evident from our study. The most important limitation is that this was a retrospective analysis. Some of the data, such as the presence of autoantibodies were not available as a result of incomplete referral information received from other hospitals. The study did not include subjects from other races since Kelantan is a predominantly Malay society. Thus, recruitment of patients of other races was difficult and analysis for racial differentiation was not possible.

We recommend future studies to adopt a prospective multicentre approach in order to determine the local prevalence of hypothyroidism post RAI therapy. This will reduce the chance of missing data especially on the aetiology of hyperthyroidism. In our study, 52 patients were unclassified due to the lack of a definitive diagnosis. We also recommend higher doses of RAI to prevent treatment failure. A fixed-dose regimen, which is far more convenient, should be adopted instead of a dose regimen based on the size of the thyroid gland to evaluate the effect of RAI.^{9,25}

We also suggest a future study that assesses the cumulative incidence of hypothyroidism post RAI up to several years post therapy. The cumulative incidence of hypothyroidism among patients with Graves' disease and those with TMNG or toxic adenoma were 24% vs. 4%, 59% vs. 15% and 82% vs. 32% at 1, 10 and 25 years, respectively.²⁶

Conclusion

In conclusion, the incidence rate of hypothyroidism within one year post RAI therapy in this study was 32.9%. Female gender and the use of antithyroid drugs post RAI were significantly associated with the development of hypothyroidism.

Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

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

Authors' contributions

WMIWM is an endocrinologist that responsible for the ideas of the study, how the study will be conducted and expert opinion. SCS is responsible for data collection and preparing the proposal of the study. ND involve in analysis of the data and writing the manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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How to cite this article: Wan Mohamed WMI, Sayuti SC, Draman N. Hypothyroidism and its associated factors after radioactive iodine therapy among patients with hyperthyroidism in the Northeast Coast State of Malaysia. *J Taibah Univ Med Sc* 2018;13(5):432–437.