

Correlation of free T4 level at diagnosis and 03, 06 months after fixed dose radioiodine therapy among the hyperthyroid patients

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Abstract

Introduction and Background: The outcome of radioiodine therapy is influenced by factors such as age, gender, goitre size, severity of hyperthyroidism and radioiodine uptake and turnover among the hyperthyroid patients.

Objective: This study aimed to identify the correlation between Free T4 values at diagnosis and 03, 06 months after fixed dose radioiodine therapy among the hyperthyroid patients.

Methodology: This was a prospective observational study. 57 Patients, after 10 mCi fixed dose radioiodine therapy for hyperthyroidism were followed up at 03, 06 months intervals at Nuclear Medicine, Peradeniya during the period of years 2018 and 2019. The details on base line clinical presentation, Free T4 levels and the clinical status after the radioiodine therapy were collected using a check list. Data was analysed using the SPSS version 25 by using Pearson's correlation and independent sample t-test.

Results: There were 70.2% of Graves' disease patients and 29.8% of toxic multi nodular goitre patients among the 57 patients. The Pearson's correlation showed a weak relationship between the Free T4 value on diagnosis and 03 months after radioiodine therapy ($r=0.475$, $P=0.003$) and a moderate relationship between the Free T4 value on diagnosis and 06 months after the radioiodine therapy ($r=0.644$, $P<0.001$). The independent sample t-test showed that the patients who were hyperthyroid 06 months after radioiodine therapy had significantly high ($P=0.009$) mean Free T4 (8.64ng/dl) on diagnosis compared with the patients who were euthyroid or hypothyroid 06 months after radioiodine therapy (mean Free T4 value on diagnosis 4.77ng/dl).

Conclusion: This study has found a correlation between the Free T4 value on diagnosis and the Free T4 value 03, 06 months after radioiodine therapy and the Free T4 level on diagnosis can be used as a predictor for the outcome of radioiodine therapy. (SJDEM 2020/ Vol 10/No 2)

Keywords: Radioiodine therapy, Hyperthyroidism, FT4 level, Severity of hyperthyroidism, radioiodine therapy outcome

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Introduction

Hyperthyroidism is associated with significant morbidity and mortality ⁽¹⁾. Mortality mainly occurs due to cardiovascular complications such as atrial fibrillation and congestive heart failure in elderly while increasing the all causes of circulatory mortality ⁽²⁻⁷⁾. The main aetiology for hyperthyroidism is Graves' disease and other important causes are multinodular goitre and autonomous single thyroid nodule ^(8,9). The treatment modalities available are the antithyroid drugs, radio iodine therapy and surgery. Definitive treatment includes surgical intervention to reduce the volume of thyroid tissue or damage of the mechanisms of thyroid hormone synthesis by radioiodine (I131) administration ⁽⁸⁾. The clinical guidelines for the management of hyperthyroidism in Sri Lanka developed by the Endocrine society of Sri Lanka recommends the antithyroid drugs as the first line drugs for Graves' disease and until definitive treatment for toxic multinodular goiter and toxic adenoma. Other recommended treatment modalities are radioiodine therapy and thyroidectomy. The antithyroid drugs are prescribed for 12-18 months and in cases of relapse or failure to achieve remission with antithyroid drugs the suggestion is to refer to a specialist centre and to decide on further management with radioiodine therapy.

Radioiodine is a reactor radionuclide and its therapeutic effect is obtained by the emission of β radiation ⁽⁸⁾. Radioiodine is a safe and effective management option in hyperthyroidism. In the United States I131 is often recommended first line whereas in Europe it is the treatment of choice for relapsed hyperthyroidism ⁽¹⁰⁾. Various regimes of radio iodine administered activities are followed and certain centres use fixed dose and variable dose depending on radio iodine uptake by the thyroid gland and calculation of thyroid volume by Ultra Sound Scan. However, there is no clear advantage over the fixed dose with variable dose. ^(11, 12) The use of radioiodine for hyperthyroidism has increased with recognition of the low likelihood of success with antithyroid drugs ⁽¹³⁾. Initially the focus of I131 therapy was to achieve euthyroidism utilizing low/graded dose regimens ⁽¹⁴⁻¹⁶⁾. But the chances of developing hypothyroidism in long term is high and now a larger ablative dose is given to achieve early hypothyroidism and to replace with thyroxin ^(9, 17-19).

The outcome of radioiodine therapy can be influenced by factors such as age, gender, goitre size, severity of hyperthyroidism and radioiodine uptake and turnover. ⁽¹⁸⁻²²⁾ The clinical features on diagnosis also have been suggested as predictors of treatment outcome ^(18, 20,23). But most of these factors are not clinically adopted and proven useful ⁽²⁴⁾. Studies have shown patients presented with high Free T4 (FT4) at diagnosis or having a large or medium sized goitre or were on prior antithyroid medications had more radio iodine failure rates compared to patients having a low value of FT4 at diagnosis or small sized goitre or no goitre or who were

not on prior antithyroid medications and those presenting with an initial FT4 >80pmol/L on diagnosis were found to have an increased failure rate compared to those presenting with an initial FT4 of 40-79pmol/L or <40pmol/L respectively on diagnosis (16.7% v 5.0%v 2.9%, p=0.003) ⁽⁹⁾. In Sri Lanka patients are treated with radioactive iodine for hyperthyroidism and the outcome of radioiodine therapy and the factors affecting the outcome haven't been studied adequately. Even though many factors have been attributed with the outcome of radioiodine therapy most are inconclusive. The high FT4 level on diagnosis has been shown associated with therapeutic failure for radioiodine therapy compared with low FT4 level on diagnosis. If patient doesn't respond to the radioiodine therapy they may undergo a repeated dose of radioiodine which expose the patient and the environment to further radiation. Using the diagnostic FT4 value as a predictor for radioiodine therapy outcome might minimize the treatment failure for radioiodine. With this purpose, this study aimed to identify correlation between the presenting FT4 value on diagnosis and FT4 values 03, 06 months after the radioiodine therapy and also to compare mean FT4 value on diagnosis between the patients who were therapeutically success and therapeutically failure from 06 months after the radioiodine therapy.

Methods

Subjects and Materials

This was an observational descriptive study. 57 hyperthyroid patients who were referred to the Nuclear Medicine Unit, Faculty of Medicine, University of Peradeniya during the period of 2018 and 2019 for radioiodine therapy were included in the study. These patients were having Grave's disease or toxic multi nodular goitre and undergoing 10 mCi radioactive iodine therapy. The main indications for the referral by the endocrinologists or by the surgeons for the radioiodine treatment were relapsing Graves' disease or antithyroid drug resistant cases or patient's unfit for surgery. Patients who were not consenting for the study and who were undergoing less than 10 mci radioactive iodine therapy were excluded from the study.

Hyperthyroid patients undergo thyroid uptake study with Tc99m pertechnetate to determine the pathophysiology of thyrotoxicosis before radioiodine therapy and once the patients are prepared for radioiodine therapy they are given a fixed dose radioiodine of 10mCi (370MBq) at the centre as outpatient basis. Once the dose is given they are advised to get the thyroid functions tests done by 06 weeks from therapy and to continue their follow up at their specialized centers every 2 months thereafter.

Data collection and follow up

The patients after the informed written consent were followed up at the intervals of 03 months, 06 months from the radioiodine treatment for the study purpose at Nuclear Medicine Unit, Peradeniya. An interviewer administered questionnaire and a check list were used to collect the demographic details and clinical details about the patients. The demographic data included age and gender of the patients. The clinical check list included the details on aetiology, FT4 level and thyroid stimulating hormone (TSH) values at the diagnosis of hyperthyroidism, FT4 and TSH level at radioiodine therapy, the administered radioiodine dose and FT4, TSH levels at 03, 06 months after radioiodine therapy. The required data since diagnosis of hyperthyroidism till radioiodine therapy was obtained retrospectively from patient's clinic records and thyroid function reports. During the follow up study at 03, 06 months after radioiodine therapy relevant clinical data was obtained from the patient, patients' clinic notes and thyroid function reports which were performed at the respective hospitals.

Ethical Consideration

Ethical clearance and permission for the study was obtained from Ethics Review Committee, Faculty of Medicine, University of Peradeniya. Patients were provided written information sheet about the study and written informed consent was obtained prior to the participation in the study.

Statistical Analysis

The details of age, gender and the diagnosis were described in percentages. Chi-square test was performed between two categorical variables. Independent sample t-test was used to check whether there was statistical difference between the mean FT4 values at diagnosis for the patients who were therapeutically success (either hypothyroid or euthyroid) and who had therapeutic failure (persisting hyperthyroidism) 03, 06 months after radioiodine therapy. Scatter plots and Pearson's correlation coefficient used to assess the relationship between the FT4 values at diagnosis and FT4 values 03, 06 months after the radio radioiodine therapy. Results were considered statistically significant at $P < 0.05$. The statistical analysis was done using the SPSS version 25.

Results

There were 57 participants in the study including 42.1% of males and 57.9% of females. The mean age of males and females were 58.75 years and 47.30 years. There were 70.2% of Graves' disease patients and 29.8% of toxic multi nodular goiter patients in the study population. The mean FT4 value on diagnosis for Graves' disease was 5.12ng/dl and 6.3 ng/dl for toxic multi nodular goiter. The independent sample t-test didn't show a significant

difference between the presenting FT4 values at diagnoses for both of these aetiologies ($P=0.5057$).

The Pearson's correlation showed no significant correlation between the FT4 value at diagnosis and the FT4 values before radioiodine therapy ($r=0.18$, $P=0.287$) and the scatter plot (Fig1) showed a very negligible correlation between these two variables ($r^2=0.032$). The scatter plot (Fig2) showed a weakly positive linear relationship between the FT4 value at diagnosis and the FT4 value 03 months after radioiodine therapy ($r=0.475$, $P=0.003$, $r^2=0.226$). There was a moderately positive linear relationship between the FT4 value at diagnosis and the FT4 value 06 months after radioiodine therapy ($r=0.644$, $P<0.001$, $r^2=0.415$) (Fig3).

The 73.68% patients, who responded to radioiodine therapy (euthyroid/ hypothyroid) after three months from radioiodine therapy (mean diagnostic FT4=4.93ng/dl, SD=3.239261) and the 22.32% of patients who were persistently hyperthyroid after three months from radioiodine therapy (mean diagnostic FT4= 6.38 ng/dl, SD=7.595734) didn't show difference in their FT4 values at diagnosis ($P=0.321$). After 06 months from radioiodine therapy, 84.21% of the patients who responded to radioiodine therapy (euthyroid/hypothyroid) with mean diagnostic FT4= 4.77ng/dl (SD=3.077156) and 15.79% of the patients who were hyperthyroid with mean diagnostic FT4= 8.64ng/dl (SD=9.597409) showed significant difference in their mean diagnostic FT4 value when compared by the independent-sample t-test ($P=0.009$).

Discussion and Conclusion

Previous studies have shown that the goiter size and the severity of the hyperthyroidism as independent indicators of response to radioiodine therapy (18-22). This study has identified that the FT4 value on diagnosis can be used as an indicator for radioiodine therapy outcome as identified in previous studies. There was significant correlation between the FT4 values at diagnosis and the FT4 values 03, 06 months after the radioiodine therapy. Further the mean FT4 value at diagnosis was significantly low among the therapeutically success patients compared to the therapeutically failed patients for radioiodine therapy 06 months after radioiodine therapy. FT4 value on diagnosis $>80\text{pmol/L}$ ($>6.22\text{ng/dl}$) has been identified associated with more treatment failure in studies (9). Three months after the radioiodine therapy, the patients with persistent hyperthyroidism had mean diagnostic FT4 value of 6.38 ng/dl and after 06 months, the patients failed radioiodine therapy had mean diagnostic FT4 value of 8.64ng/dl. Similarly another study has suggested that absence of a palpable goitre, lower presenting serum FT4 level, female gender and a larger first dose of radioiodine are associated with increased probability of cure (25). At 03 and around 06 months after the radioiodine therapy there was therapeutic success (euthyroid/hypothyroid) in patients with mean diagnostic FT4 value of 4.93ng/dl and 4.77ng/dl

respectively in this study which can be stated that having a lower FT4 level on diagnosis can increase the probability of cure (25).

In this study, 06 months after radioiodine therapy 15.79% of the patients had therapeutic failure and their mean diagnostic FT4 value was 8.64ng/dl (>100pmol/L). This can be compared with previous studies which have shown a higher failure rate to a single dose of radioiodine (18,26,27). Hypothyroidism is inevitable after radioiodine therapy (25) and it is recommended to use a large fixed single dose of radioiodine therapy to induce hypothyroidism and replace with thyroxine. Studies have shown more therapeutic response or cure rates with 10mCi compared to 05 mCi of radioiodine therapy (18) and the cure rate for Graves' disease has been high with doses of 10-20mCi (28). Several attempts and trials were done to select the optimal dose of radioiodine dosage required for patients using various dosimetry methods have shown, that they do not improve cure rates and the rates of hypothyroidism and they are similar to those associated with fixed-dose regimens (11,12,23,29). As in many centers, (23,30,31) the Nuclear Medicine Unit, Peradeniya uses a fixed dose regimen of 10 mCi of radioiodine to the hyperthyroid patients and this study data found out that 06 months after radioiodine therapy around 84% of the patients became euthyroid or hypothyroid. The rest of the population which had therapeutic failure had a very high FT4 level on diagnosis and providing an increased fixed dose of radioiodine more than 10mCi would have resulted early hypothyroidism and therapeutic response. This might have been effective rather than waiting for few months to deliver the second dose of radioiodine therapy to achieve therapeutic response. Because, the cardiovascular and other complications due to thyrotoxicosis can be minimized by achieving early euthyroidism or hypothyroidism.

The purpose of several studies has been to determine the optimal dose of radioiodine for curing hyperthyroidism, while avoiding the development of permanent hypothyroidism. Doses were calculated on the basis of thyroid size, the uptake of radioiodine, or the turnover of radioiodine (12, 32, 33). But they didn't show a better outcome over the fixed dose regimen. Goiter size and free T4 level at diagnosis have been shown strongly associated (18) with therapeutic outcome for radioiodine. Logistic regression in a previous study has showed that the presence of palpable goiter and the severity of hyperthyroidism were significant contributing factors for the failure following a single dose of radioiodine, after dose adjusting for gender, administered activity and age of onset of hyperthyroidism. High activities of RAI can be offered to patients depending on the presence of poor prognostic factors at individual

level without offering high activities for each patient. While offering the high activities of radioiodine for therapy there should be concern on long term effects of radioiodine and the thyroxine replacement (18). Presence of poor prognostic factors such as larger goiter or severe hyperthyroidism are indicative for the therapeutic failure and these factors can be used as an indicator to increase the required radioiodine activity to induce early hypothyroidism (18). This can be supported by the findings from this study where the patients with severe hyperthyroidism required a second dose of radioiodine therapy or antithyroid drugs. Providing a single larger ablative dose has benefits such as that the patient should be prepared only once for the radioiodine therapy, cost effectiveness, lesser radiation exposure to the family and importantly the early cessation of hyperthyroid symptoms and complications. But a larger prospective study is required to assess the outcome of larger single dose of ablative therapy in patients with highly elevated FT4 value on diagnosis and in this study only 57 patients were followed up who were given 10mCi and this was a major limitation.

The level of FT4, T3 hormones has been correlated with the rate of treatment failure after the radioiodine therapy in many studies and in range of other studies it failed to show this relationship, but they didn't demonstrate a reverse relationship (34). Even though many studies, including this study focused on the baseline hormonal levels on diagnosis of hyperthyroidism it is argued that the status at the time of therapy is equally or even more relevant to predict the outcome of radioiodine therapy (34). The metabolic activity is high when there is more disease activity in the cell and the intracellular radioprotective antioxidative defense potentially higher in the metabolically active thyrocyte (35) and a high turnover of radioiodine has been noted with higher disease activity (34). These problems can be pertained especially to those studies that find a high disease activity associated with treatment failure (18,23,25) and high FT4 value on diagnosis is an evidence of severe hyperthyroidism and higher disease activity which showed correlation with treatment failure.

In conclusion there is a moderate correlation between the FT4 value on diagnosis and the outcome of radioiodine therapy at 06 months after the radioiodine therapy. These findings suggest that the FT4 value on diagnosis can be used as an indicator for radioiodine therapy outcome. The prognostic value of severity of hyperthyroidism or FT4 value on diagnosis has been established in previous studies and further studies are suggested to use the FT4 value on diagnosis among individual patients to select the single larger fixed radioiodine dose and to follow up for the treatment outcome.

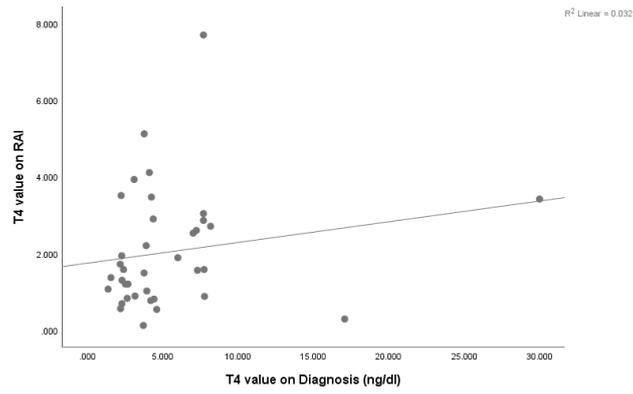


Figure 1: The Scatter plot showing the relationship between the FT4 value on diagnosis and the FT4 value before giving the Radioiodine therapy.

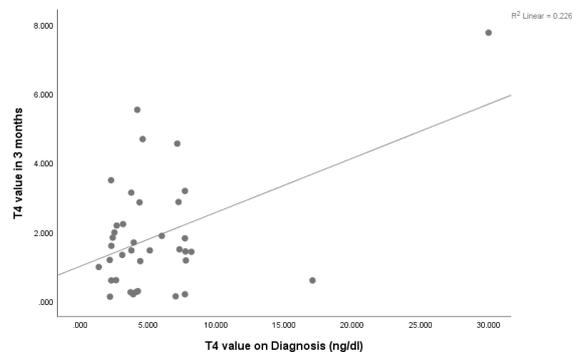


Figure 2: The Scatter plot showing the relationship between the FT4 value on diagnosis and the FT4 value before giving the Radioiodine therapy.

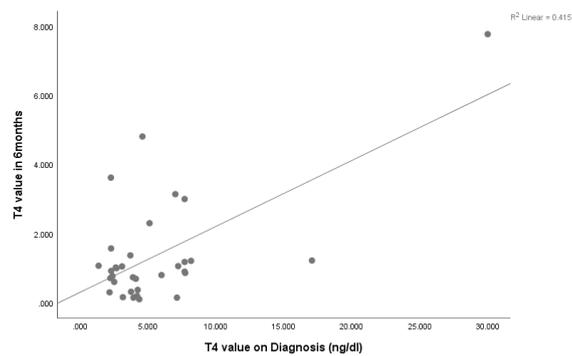


Figure 3: The Scatter plot showing the relationship between the FT4 value on diagnosis and the FT4 value at 06 months after giving the Radioiodine therapy.

Conflict of Interest

No potential conflicts of interest were disclosed.

Limitations in the study

The main limitation in this study was the sample number. The number of referred patients for radioiodine therapy was a contributing factor for this. FT4 level and TSH level were measured to assess the thyroid functions and FT3 level wasn't performed in these patients.

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