Research Article

Outcomes Associated with Treatment of Hyperthyroidism with Radioiodine; A Single Center Retrospective Study

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Abstract

Background: Hypothyroidism and hyperthyroidism are prevalent conditions with potentially crippling health consequences that globally affect all populations. Hyperthyroidism is overproduction and persistent release of thyroid hormones that can be stratified into a number of subtypes with varying magnitudes and treatment outcomes. Despite of decades of treatment of hyperthyroidism with radioiodine, the success of treatment is still debatable and influenced by many factors.

Objective: To determine outcomes associated with treatment of hyperthyroidism with radioiodine.

Methods: All patients screened for thyroid disease at King Abdullah Medical City, Makkah in between 2012-17 were included in the analysis (N = 353). Eighteen questions were used to assess the presence or absence of symptoms associated with hyperthyroidism. 251 out of 353 patients were found eligible for screening with thyroid-stimulating hormone, free triiodothyronine (fT3) and free thyroxin (fT4). On the basis of laboratory analysis, 73 patients were eligible for the differing RAI therapeutic regimens. Treatment outcomes were assessed 6 months after the patients received RAI therapy, at which time they were classified as being hypothyroid, euthyroid, or hyperthyroid.

Results: Females were predominantly affected by hyperthyroidism (75.2%) compared with males (24.8%). However, males were significantly more likely than females to have Graves' ophthalmopathy ($p < 0.01$), anxiety ($p < 0.05$), and insomnia ($p < 0.05$). A total RAI dose of $\leqslant$ 15 mCi was effective in eliminating most hyperthyroidism: $\leqslant$ 12 mCi, 26/29 = 89.7%; 12.1–15 mCi, 28/30 = 93.3%. Using bivariate analysis, the association of treatment effectiveness with each of the symptoms and comorbidities revealed significant correlations only for diabetes mellitus (rho = −0.428, $p < 0.001$).

Conclusions: Our data suggests that radioiodine remains an effective option of treating hyperthyroidism in most of the patients who qualify for it.

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Introduction

Thyroid hormones are essential for growth, reproduction, neuronal development, and regulation of energy metabolism.[1] Hypothyroidism and hyperthyroidism are prevalent conditions with potentially crippling health consequences that globally affect all populations. Although iodine nutrition is a key determinant of thyroid disease risk, ageing, body mass index (BMI), smoking status, genetic predisposition, diabetes mellitus, and ethnic origin all influence thyroid disease etiology.[2]

Hyperthyroidism can be considered as an overproduction and persistent release of thyroid hormones that can be stratified into a number of subtypes with different epidemiologies, clinical presentations, prognoses and treatment outcomes. For example, those individuals with subclinical and overt hyperthyroidism were shown to exhibit more high-grade coronary stenosis, plaque burden, and high-risk plaque features compared with patients with euthyroidism,[3] such studies demonstrate that hyperthyroidism might lead to coronary vascular degeneration and plaque instability. Consequently, it is important to understand the current incidence and prevalence of hyperthyroidism in the population because it is a potential risk factor for hypercholesterolemia, cardiovascular disease, osteoporosis, and neuropsychiatric disease states.[4] In exceptional circumstances, thyroid storm and hyperthyroidism in pregnancy (and during the postpartum period) have been recorded and require careful assessment and treatment.[5]

The prevalence of overt hyperthyroidism has been reported to range from 0.5% to 0.8% in Europe and 0.5% in the United States,[6] while in a recent study the prevalence of hyperthyroidism in Korean patients undergoing treatment was 2.76/1,000 population, with a female preponderance.[4] In one of the largest cohort studies conducted in Europe, the prevalence of hyperthyroidism was estimated to be 4.3% (5.6% in women; 3.0% in men).[2] A study of hyperthyroidism in children showed annual incidence of 4.58/100,000 person-years (95% CI: 3.00–6.99/100,000).[9] A population-based study in Taiwan revealed that incidence of hyperthyroidism increased from 0.97 per thousand persons in 2004 to 1.06 in 2010, with the major proportion of hyperthyroidism being attributable to Graves' disease (GD) (95%), followed by toxic nodular goiter (2%), and other causes (3%).[8] GD is an autoimmune hyperthyroid disease caused by stimulating antibodies against the TSH receptor, which dysregulates normal control of thyroid hormone production.

Prevalence studies of hyperthyroidism in the Kingdom of Saudi Arabia (KSA) are lacking, although a small retrospective, observational study of Omani patients with hyperthyroidism due to GD, toxic multinodular goiter, and solitary toxic adenoma revealed that a significant proportion of patients experienced malignancy.[9] Therefore, a proper initial evaluation of patients with hyperthyroidism in KSA is required as part of long-term clinical management since complications can be significant.

There are three main methods of managing hyperthyroidism, which are surgery (thyroidectomy), radioactive iodine-131 (RAI) therapy, and anti-thyroid medication (ATD) including both thionamide and non-thionamide drugs.[12] While there are clear benefits to each of the types of treatment employed, side-effects are common. In this single center retrospective study within the KSA, we aimed to assess the frequency, efficacy, and outcomes associated with varying doses of RAI therapy to treat hyperthyroidism since a number of recent studies have provided conflicting outcomes concerning this and other interventions.[10-11]

Methods

All patients screened for thyroid disease (N = 353) between 2012 and 2017 at King Abdullah Medical City, Makkah, Saudi Arabia were included in initial analysis. The sample was stratified into five age-groups: 16–30 years (23.8%), 31–40 years (21.2%), 41–50 years (20.7%), 51–60 years (18.1%), and >60 years (16.1%). Eighteen questions or items were used to assess the presence or absence of symptoms associated with hyperthyroidism. Closely related symptoms were grouped into the following five categories: (a) GO (2 items), (b) Graves' dermopathy (2 items), (c) cardiac symptoms (3 items), (d) sweating or heat intolerance (3 items), and (e) increased appetite or weight loss (2 items). The remaining symptoms were assessed as a single item: anxiety, diarrhea, goiter, hypertension, insomnia, and tremors.

Diabetes mellitus, chronic kidney disease, ischemic heart disease, and other comorbidities were also recorded. Blood tests for TSH, free triiodothyronine (fT3) and free thyroxin (fT4) were conducted on all of the patients using radioimmunoassay (RIA) technique. Thyroid ultrasound tests were performed on a proportion of patients who were found to have high fT3 and fT4 levels. Most of those patients showed thyroid abnormalities on the ultrasound images.

All those symptomatic patients in whom evaluation led to biochemical evidence of hyperthyroidism i.e. high fT3, fT4 and low TSH, were referred for thyroid uptake scan. Cases with focal or diffusely high uptake were selected for radioiodine after explaining the whole procedure in detail. Excluded patients included those who had already received RAI therapy in past, had hyperthyroidism secondary to other causes (e.g., thyroiditis or drugs) with low uptake on thyroid uptake scan, who failed to comply with follow-up after RAI therapy, and women who were found pregnant (by performing serum beta human chorionic gonadotropin test) or breast-feeding . Seventy three patients were found eligible for RAI therapy in accordance with the inclusion and exclusion criteria, for whom the 6-month outcome data was collected. Of the 73 eligible patients, sixty-nine patients received a single dose of RAI therapy and four patients received two doses. In total, four patients received a dose of ⩽10 millicuries (mCi), 25 received a dose of 10.1–12 mCi, 30 received a dose of 12.1–15.0 mCi, and 14 received a dose that was >15 mCi. Given the small sample of patients who received ⩽ 10 mCi, these patients were combined with the group of patients who received 10.1–12 mCi to form a "⩽ 12 mCi" group. Treatment outcomes were assessed biochemically by performing serum thyroid function tests , 6 months after the patients received RAI therapy, at which time they were classified as being euthyroid (normal TSH, fT3 and fT4), hypothyroid (high TSH with low fT3 and fT4), or hyperthyroid (Low TSH with high fT3 and fT4).

Results

After the initial biochemical screening, 214 patients found to have low TSH values. A total of 187 of the 214 (87.4%) patients who had low TSH levels also had high fT3 and fT4 levels, which indicated hyperthyroidism. Of these 187 patients, females were predominantly affected by hyperthyroidism (75.2%) compared with males (24.8%). However, males were significantly more likely than females to have GO ($p < 0.01$), anxiety ($p < 0.05$), and insomnia ($p < 0.05$). Thyroid ultrasound tests were performed on 127 of the 187 (67.9%) patients with high fT3 and fT4 levels, and identified structural abnormalities in 90.5% of such cases. These included patients with diffuse enlargement of the thyroid gland (18.9%), multiple nodules (68.5%), and single nodules (3.1%). A total dose of ⩽15 mCi was effective in eliminating 9 out of 10 cases of hyperthyroidism: ⩽ 12 mCi, 26/29 = 89.7%; 12.1–15 mCi, 28/30 = 93.3%. Doses >15 mCi were less effective: 8/14 = 57.1%. A chi-square test showed that the differences in outcomes among the three RAI doses were statistically significant (χ 2 = 10.6, $p < 0.01$). After treatment, 64.4% (47) of the patients became hypothyroid, 20.5% (15) became euthyroid while 15.1 % (11) remained hyperthyroid. Eighty percent of patients given a dose of 12.1–15.0 mCi were classified as hypothyroid, compared with 65.5% of those given a dose of ⩽ 12 mCi, and 28.6% of those given a dose of >15 mCi (Table 1). None of our patients were taking substances that could inhibit RAI from entering the thyroid gland. Sample size did not permit the use of logistic regression to analyze the contribution of other variables to the outcomes, therefore bivariate and partial Spearman correlations were used. Correlation analysis revealed that RAI dose was moderately associated with effectiveness (rho = −0.247, $p < 0.05$). The correlation was nearly identical when gender and age were added as control variables (rho = −0.242, $p < 0.05$). The association of treatment effectiveness with each of the symptoms and comorbidities by bivariate analysis revealed significant correlations only for diabetes mellitus (rho = −0.428, $p < 0.001$) and chronic kidney disease (rho = −0.281, $p < 0.05$). When these were used as control variables in separate partial correlations of

Table 1: *Treatment Outcomes Associated with Radioactive Iodine (RAI) Doses. Percentages in Parentheses.*

Outcome (%)	Total Dose (mCi)			Total
	<12	12.1–15.0	>15	
Hypothyroid	19 (65.5)	24 (80.0)	4 (28.6)	47 (64.4)
Euthyroid	7 (24.1)	4 (13.3)	4 (28.6)	15 (20.5)
Hyperthyroid	3 (10.3)	2 (6.7)	6 (42.9)	11 (15.1)
Total	29	30	14	73

RAI dose and effectiveness, chronic kidney disease (rho = −0.232, $p < 0.05$) had little effect on the correlation, although diabetes mellitus reduced the correlation substantially (rho = −.0180, $p > 0.10$). These data suggest that diabetes mellitus may have an independent effect on thyroid status after treatment.

Discussion

Hyperthyroidism is a common endocrinopathy worldwide as well as in Saudi Arabia with Grave's disease being the commonest cause followed by multinodular toxic goiter and toxic adenoma and the literature research revealed scarcity of the studies done locally regarding utilization of RAI for the treatment of this condition.[12-15]

The treatment of choice for relapsed hyperthyroidism is radioiodine, although the optimum protocol remains unknown when considering this intervention on its own. Fixed dose RAI is increasingly popular, but responses may vary.[10,17] A number of variables have previously been shown to influence outcomes after RAI treatment and these include severity of hyperthyroidism at diagnosis, goiter size, previous anti-thyroid medications, BMI, ethnicity, and diabetes mellitus.[2,17,18] In the KSA, thyroid dysfunction has been shown to be very prevalent among type 2 diabetic patients, with the most significant risk factors being family history of thyroid disease, female gender, and >10 years duration of diabetes.[14] In the present study, we demonstrated that diabetes mellitus may have an independent effect on thyroid status after RAI treatment. Given that hyperthyroidism increases the risk of cardiovascular disease-related hospitalization, and the risk is sustained for up to two decades after treatment with RAI or surgery,[17] we consider that a total dose of 12.1–15 mCi of RAI should be used to convert those with hyperthyroidism to a state of hypothyroidism (Table 1). Hypothyroidism during RAI follow-up has been shown to predict better cardiovascular outcome.[17]

A number of studies have suggested that RAI treatment is associated with development or exacerbation of pre-existing GO.[19-21,22] We found that males with hyperthyroidism were significantly more likely than females to develop GO in both the natural disease course and after treatment. To our knowledge, ours is the first study to demonstrate this. Since this complication can be very debilitating, one may intuitively expect the condition to confer a higher prevalence of anxiety and insomnia, which was evident in those men with disproportionate propensity to GO.[23,24] In effect, these data acted as an internal validation of our study variables with respect to outcome.

Although this study was limited in size and by its single center location, we corroborated previous studies confirming that hyperthyroidism is a predominantly female phenomenon.[2,4,10] The limited sample size, including loss to follow-up, prevented performance of multivariate analysis and assessment of patient demographics and symptoms with outcomes. It is likely that with a larger cohort, we would be able to ascertain significant differences in outcomes, should they exist. In this single center retrospective study within the KSA, we confirmed previous study findings in relation to frequency, efficacy, and outcomes associated with varying doses of RAI therapy. Our data provide valuable demographic and clinical information, which should aid decision-making pertaining to treatment of hyperthyroidism, especially in those countries disproportionately burdened by type 2 diabetes mellitus.

Moreover, the out result are found comparable to local and international studies.[12-15]

Conclusion

Radioiodine remains an effective option of treating hyperthyroidism in most of the qualifying patients within six months after the RAI dose. As most of our patients have shown to develop hypothyroidism after RAI, close follow up with thyroid function test is advisable for prompt recognition and treatment of hypothyroidism

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