ORIGINAL STUDY

Success Rate of Radioiodine Treatment of Hyperthyroidism in Qatari Patients.

***Darwish S. M., *Ghadban W. K., * Zirie M. A., **Al-Khateeb D. A.**

** Department of Endocrinology/ metabolism and Internal Medicine*
*** Department of Nuclear Medicine*

Abstract

To evaluate the response rate of hyperthyroidism to radioactive iodine treatment (RAI) and the mortality rate post RAI treatment in a Qatari cohort the records were analyzed retrospectively of 113 hyperthyroid Qatari patients (23 male, 90 female) treated with RAI (I-131) in the Endocrine Clinic, Hamad Medical Corporation, between 1984 and 2002. 90 (79.6 %) had diffuse goiter, 14 (12.4%) multinodular goiter, 6 (5.3%) single nodular goiter and 3 (2.7 %) unknown etiology. Follow up ranged from two to ten years with free thyroxin and thyroid stimulating hormone being recorded at diagnosis; six months and one year post RAI treatment and yearly thereafter.

The incidence of hypothyroidism was 64.4% after six months post RAI treatment and 75.9% at one year. Euthyroid state was high in patients who did not receive antithyroid drugs, whereas the hypothyroid state was higher in a group with pre-treatment antithyroid medication (80% versus 62.8%). The euthyroid state was more in diffuse hyperthyroidism 22.4%, while 84.6% of multinodular goiter became hypothyroid after six months of RAI treatment. Mortality rate was not increased post RAI treatment as compared to general population.

Conclusion: The incidence of hypothyroidism was 75.9% at one-year post RAI treatment and the rate of hypothyroidism increased with the length of follow up to 10 years (86.7%). There was no linear relation in response rate to increasing doses of RAI treatment groups.

Introduction:

There are various treatments for hyperthyroidism but none is ideal. The goal of radioactive iodine treatment (RAI) is to cure the hyperthyroidism and achieve long-term control [1]. RAI has been used to treat hyperthyroidism for more than sixty years because it is clinically effective, safe, and cost-effective compared to the therapeutic alternatives [2].

Sustained euthyroidism would be the most desirable outcome, without post-ablative hypothyroidism and the need for life-long thyroid hormone replacement. However it is well accepted that there is no single RAI dose or method of treatment that can reliably accomplish that goal and the development of hypothyroidism seems to be inevitable and unpredictable by any clinical factors [1-3]. Several issues are still controversial, such as the influence of antithyroid drugs on the outcome, and it has been suggested that propylthiouracil (PTU) but not methimazole may reduce the effectiveness of RAI treatment [4,5]. Another controversy is the increased mortality from all causes as well as that due to cardiovascular and cerebrovascular disease and fracture among hyperthyroid patients treated with RAI therapy [6].

The indigenous Qatari population shares a similar genetic susceptibility and racial background. With the objective of evaluating the response rate of hyperthyroidism to RAI treatment, the optimum effective dosage, the effect of pre-treatment with thyrostatic medications, the death rate post-RAI treatment, and to describe the cause(s) and methods of effective control we studied retrospectively all cases of hyperthyroidism in Qataris treated with RAI between 1984 and 2002.

Method:

The records were reviewed of 113 hyperthyroid Qatari patients treated with RAI (I-131) in the Endocrine Clinic, Hamad Medical Corporation, between 1984 and 2002. Data collected and analyzed included gender, age, free thyroxin (FT4), thyroid stimulating hormone (TSH), co-morbid conditions, etiology of the hyperthyroidism and medication such amidrone and lithium that were potential interference factors for the success of RAI treatment *[Table 1]*. The records followed patients for two to ten years. Patients were classified into three diagnostic groups, [1] Graves disease (diffuse goiter), [2] toxic multinodular goiter hyperthyroidism and [3] solitary toxic adenoma *[Table 2]*.

The RAI dosage was divided in to five groups *[Fig.1]*. FT4, TSH were recorded at diagnosis then post-RAI treatment at six

Address for correspondence:
Dr. Sara Darwish. *Department of Endocrinology\ Metabolism and Internal Medicine, Hamad Medical Corporation, P.O Box 3050, Doha, Qatar. Tel. +974 4392315. Fax + 974 4392273. E-mail:* ***saradarwish2000@yahoo.com.***

months, one year and then at yearly intervals up to ten years. The TSH was measured with Beckman Access hypersensitive TSH, a two-sided immunoenzymatic "sandwich" immunoassay and the FT4 with a Beckman Access two-step enzyme immunoassay.

Radioiodine treatment, properties and technique:

Patients with mild to moderate hyperthyroidism were treated with radioiodine without pre-treatment with antithyroid medications. Those with severe hyperthyroidism, associated with cardiovascular diseases or with old age were pre-treated with carbimazole or PTU. Usually anti-thyroid medications were discontinued 48-72 hours prior to RAI treatment and were restarted within 5-7 days post RAI in the high- risk group. Adrenergic blocking drugs were maintained throughout the treatment. Thyroid gland scintigraphs and uptakes were obtained using a gamma camera with a pin hole collimator 20 minutes after the injection of technetium 99m pertechnitate (tech99m pert),

Dose strategies:

The practice was to use delivered millicurie/gram giving 60 mCi/gm thyroid tissues. RAI uptake was estimated by neck sodium iodine probe, after 24 hours of oral dose of I -131, thyroid uptake was used mainly to differentiate low uptake hyperthyroid (thyroiditis) from high uptake hyperthyroidism (diffuse or nodular goiter). From 1995 we used a fixed millicurie (mCi) dose regimen: 10 mCi is usually given for small and medium size glands, and 15 mCi for large glands, multinodular goiter and autonomous nodules. The thyroid uptake function was estimated by using tech 99m pert based on gamma camera technique.

Results:

Hypothyroidism (TSH >=7) developed in 67 (64.4%) patients six months after RAI treatment. The cumulative incidence at one year was 75.9%. Subsequently, the hypothyroidism incidence was increased by 2% yearly up to five years. There was no increase in the incidence of hypothyroidism from six to nine years after RAI therapy then the incidence increased by 1.8 % in the tenth year post RAI therapy *(Figure 2)* suggesting that even patients who have been euthyroid for years post RAI therapy should continue to be monitored for long periods to detect latent hypothyroidism.

Analysis of the data six months post RAI showed no linear relationships in the various groups between the doses of RAI used and the incidences of hypothyroidism (TSH>=7 mIU/L) and euthyroid (0.2-6mIU/L); (Table3). The euthyroid state was higher in the group without pre-treatment with anti-thyroid medication (21.3% versus 10% in the group with prior anti-thyroid treatment) whereas the hypothyroid state (TSH>=7) at six months post RAI treatment was significantly higher in pre-treatment with anti-thyroid medication groups (80 %) compared with non-pre-treatment anti-thyroid medication (62.8%). *(Table 4)*

Regarding the etiology of thyrotoxicosis the analysis showed that most of the cases (84.6%) of multi-nodular goiter ended in hypothyroidism (TSH>=7) compared to 62.4% and 50% of cases in the diffuse goiter and single nodular goiter groups. In the single nodular goiter group 33.3% did not respond well to RAI and continued to be hyperthyroid *(Table 5)*.

During the post RAI period, two cases of malignancy were recorded: one with colonic cancer diagnosed at 72 months, and one with breast cancer diagnosed at 14 months. Two patients died post RAI treatment (1.8%): one due to breast cancer at 28 months and the second due to a cause other than vascular disease or malignancies at 48 months *(Table 6)*.

Discussion:

The use of radioiodine in hyperthyroidism is increasing, particularly as a first line therapy for Graves disease [5]. Hypothyroidism following treatment results from radiation damage to cellular metabolic function. Its onset is delayed for several years in many patients and in consequence the rate of hypothyroidism increases with length of follow up and even after ten years shows no signs of a plateau [7, 1]. In our study, we found similar results and trends have been reported also in the literature where the cumulative incidence of hypothyroidism at one year was 75.9% and then the annual incidence was around 2% for five years followed by no increase up to eight years post RAI but increasing again by 1.8% in the ninth and tenth years post RAI treatment. There is possibility of higher incidence of hypothyroidism after one year of follow up in Qatari patient due to decreased compliance of clinic attendance for the following nine years post RAI; this may have given the lower incidence. *(Figure 2)*

Although there is a general consensus that RAI is a safe and effective treatment for hyperthyroidism, debate remains in the term of optimal RAI treatment doses that cure the disease without ending in hypothyroidism. However, most series report that the majority of cases post RAI develop permanent hypothyroidism and very few develop durable euthyroidism [3].

The two commonly used protocols are dosimetry and fixed dose regimen. In our hospital we used dosimetry between the year 1984–1994, and fixed dose regimen since 1995 up to the present. We grouped I-131 into different doses: 5-7 mCi, 7.1-9 mCi, 9.1-11 mCi, 11.1-13 mCi, and 13.1-15 mCi. We found no linear relation in the rate between subgroups *(Table3)*. Even though Sankar and colleague found that an empirical low dose of RAI therapy to avoid hypothyroidism results in the majority

of patient having persisting hyperthyroidism[8],in our study we found no significant difference between subgroups in the rate of persisting hyperthyroidism.

The probability of hypothyroidism following RAI is greater than three times in patients with diffuse goiter compared with solitary Toxic Nodule (STN) or Multinodular Goiter (MNG). A higher rate of single-dose treatment failure was observed in patients with MNG compared with diffuse goiter and STN. Toxic MNG is relatively resistance to RAI treatment requiring doses higher than widely appreciated and, unlike diffuse goiter, hypothyroidism is relatively uncommon.[9]

Aftab and colleague found 77.4% patients with diffuse disease became hypothyroid compared with 39.3% and 33.3% with STN and MNG respectively. They found that the single-dose treatment failure rates were similar in these three groups, whereas euthyroidism was significantly higher in patients with STN and MNG compared with diffuse disease. The low incidence of hypothyroidism and increased rate of euthyroidism in STN and MNG, observed in some studies, may well be due to the fact that the suppressed normal extra nodular tissue is protected by its inability to concentrate RAI [9]. In our study the incidence of hypothyroidism was higher in MNG (84.6%) while treatment failure was higher in STN (33.3%). 22.4% of diffuse goiters were euthyroid. *(Table5)*

Evidence suggests that anti-thyroid drug (ATD) treatment prior to RAI leads to a reduction of early–onset hypothyroidism and an increased rate of single dose RAI treatment failure. These studies suggest a radioprotective effect of ATD treatment when given prior RAI compared with RAI given alone [9] whereas others did not observe similar effects of these compounds [4]. In our study we could not find a significant difference in treatment failure but we found an increased incidence of hypothyroid among ATD groups. *(Table 4)*.

We found also hypothyroidism to be more common in Qatari patients with MNG treated with RAI, as well as among hyperthyroid patients that had received ATD prior to RAI therapy. This can be a characteristic of the Qatari population although the small sample size is a limiting factor and a larger sample is needed to confirm this finding. In some studies mortality from a number of causes increased in hyperthyroid patients treated with RAI [6] but we detected no such increase.

Conclusion:

The incidence of hypothyroidism was 75.9% at one-year post RAI treatment and the rate of hypothyroidism increased with length of follow up and up to 10 years (86.7%). There is no linear relation in response rate to increasing doses of RAI treatment groups. Hypothyroidism was higher among MNG (84.6%) while treatment failure was higher in STN (33.3%).

Table 1: Characteristics of Patients.

Characteristics	%
Sex	
Male	23 (20.4%)
Female	90 (79.6%)
Age	
15-25	13 (11.5%)
26-35	46 (40.7%
36-50 35 (31%)	
>50	19(16.8%
Exophthalmos	
Yes	33 (29.2%)
NO	77 (68.1 %)
Unknown	3 (2.7%)
Co-morbid Conditions	
Coronary artery disease	5 (4.4%)
Hypertension	18(15.9 %)
Others	18(15.9 %)
None	70(61.9 %)
Unknown	2 (1.8 %)
Pretreatment with Antithyroid medication	
Yes	11(9.7%)
No	99(87.6%)
Unknown	3 (2.7 %)
Pretreatment surgery	
Yes	6 (5.3%)
No	103 (91.2 %
Unknown	4 (3.5 %)

Table 2: Etiology of patients receiving RAI treatment

Etiology	Frequency
Diffuse	**90 (79.6 %)**
Single nodular	**6 (5.3 %)**
Multinodular	**14 (12.4 %)**
Unknown	**3 (2.7 %)**
Total	**113 (100%)**

Figure 1: percentage distribution of patients by radioactive iodine treatment doses received.

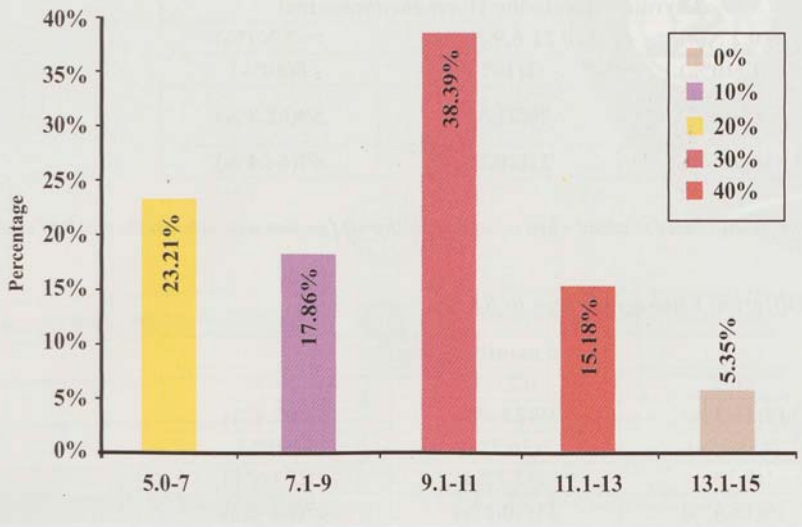

Figure 2: Cumulative frequency (%) of hypothyroidism following radioactive iodine treatment.

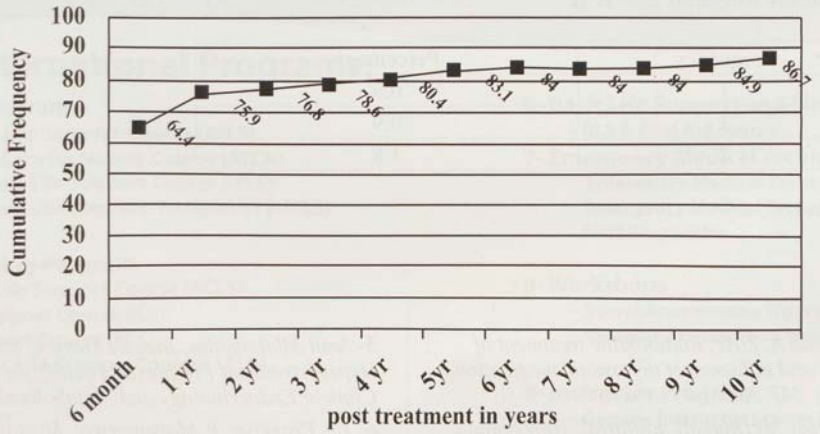

Table 3: Different Doses of Radioiodine and Response Rate

Radioiodine Doses(mCi)	Thyroid Stimulating Hormone (6months)		
	<0.2 N (%)	0.21-6.9 N (%)	>=7
5-7	3 (13%)	9 (39.1%)	11(47.8%)
7.1-9	4 (21.1%)	5 (26.3%)	10 (52.6%)
9.1-11	4 (9.8%)	6 (14.6%)	31(75.6%)
11.1-13	3 (20%)	1 (6.7%)	11(73.3%)
13.1-15	2 (33.3%)	0 (0)	4 (66.7%)
Total *	16 (15.4%)	21 (20.2 %)	67(64.4%)

** Total of 104 patients only as nine patients failed to attend when scheduled for thyroid function tests at 6 months post RAI treatment.*

Table 4: Pretreatment with antithyroid medications and response after radioactive iodine treatment

Pretreatment	Thyroid Stimulating Hormone (6months)		
	<0.2 N(%)	0.21-6.9 N (%)	>=7 N (%)
Anti-thyroid medication	1 (10%)	1(10%)	8(80%)
Non Anti-thyroid medication	15(16%)	20(21.3%)	59(62.8%)
Total*	16(15.4%)	21(20.2%)	67(64.4%)

** Total of 104 patients only as nine patients failed to attend when scheduled for thyroid function tests at 6 months post RAI treatment.*

Table 5: The Response of Different Etiology Groups to RAI.

Etiology	TSH 6 months group		
	<0.2	0.21-7	>=7
Diffuse	13(15.3%)	19(22.4%)	53(62.4%)
Single nodule	2(33.3%)	1(16.7%)	3(50%)
Multinodular	1(7.7%)	1(7.7%)	11(84.6%)
Total*	16(15.4%)	21(20.2%)	67(64.4%)

** Total of 104 patients only as nine patients failed to attend when scheduled for thyroid function tests at 6 months post RAI treatment.*

Table 6: Total mortality and the duration post RAI

Months	Frequency	Percentage
28	1	0.9
48	1	0.9
Total	2	1.8

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