Hypothyroidism at one year following radioactive iodine therapy; Incidence and associated factors: Report from a tertiary Nigerian Hospital

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Citation

Abstract
Background: Although hypothyroidism is a predictable sequelae of radioactive iodine therapy, the time of its occurrence can be many years later. An early induction of hypothyroidism will allow for the prompt detection and treatment of hypothyroidism.

Aim: To determine the rate and determinants of hypothyroidism at one year following radioactive iodine (RAI) therapy.

Design: Retrospective review of patients case records.

Methods: Data on demographic, clinical and biochemical variables were obtained. Primary outcome was thyroid status as hypothyroid or not hypothyroid at 12 months following RAI treatment. Statistical analysis was with SPSS version 10. The level of statistical significance was taken as p < 0.05.

Results: Seventy-seven (77) subjects, 63 females received RAI. Their mean age was 41.8 ± 12 years with range of 18-72 years (n=77). Thyroid function status at 12 months post RAI was available for 31 subjects. The incidence of hypothyroidism in these 31 persons was 50%. Thyroid volume was significantly greater in those who were hypothyroid by 12 months compared with those not hypothyroid at 12 months. Both groups had similar proportions of subjects with Graves's disease, toxic and non-toxic goiter. The proportions of subjects treated with 10mci, 15mci or 20mci of RAI and those with raised microsomal antibodies were similar in both groups.

Conclusion: The rate of hypothyroidism at 12 months after RAI therapy at doses of 10-20mci was 50%. The tendency to be hypothyroid by 1 year was less increased thyroid volume.

INTRODUCTION
Radioactive iodine (RAI) therapy is employed in the treatment of various thyroid disorders. These include differentiated thyroid carcinoma [1], thyrotoxicosis due to Graves's disease and nodular goiter [2] and recently for thyroid size reduction in cases of sporadic non-toxic goitre [3] and hashimoto's thyroiditis [4]. In Grave's disease RAI has achieved superior cure rates compared with thionamides or surgery when measured by proportions of patients who remained euthyroid or hypothyroid for at least 1 year [5].

In Nigeria, RAI had been administered only at the Eko Hospitals Plc, a privately owned tertiary hospital where it has been used since 1999. The experience with the use of RAI at the Eko Hospitals Plc from the period 1991 to 1999 has been published [6]. It is however, now available in two state owned tertiary hospitals; National Hospital Abuja and the University College Teaching Hospital Ibadan.

Predictably, hypothyroidism accompanies the administration of RAI with annual incidence rates ranging from 6% [7] to 69 % [8]. It may however, manifest many years after the administration of even small doses of RAI [9]. A lifelong follow up is thus necessary after the administration of RAI therapy to allow for the early detection of hypothyroidism, as it may be insidious in presentation. Therein lies the
argument for an early induction of hypothyroidism as against
euthyroidism.

An early occurrence of hypothyroidism may obviate the
occurrence of recurrent hyperthyroidism that may follow an
initial euthyroid status. Furthermore, hypothyroidism may
even occur many years after an initial euthyroid state. This is
of particular concern in our environment where patients
cannot readily afford the cost of repeat doses of RAI as cost
of medical care still remains largely an out of pocket
expense.

In earlier series from the Eko Hospitals PLC comprising of
22 patients treated from 1991 to 1999, 2 subjects were
treated with 5mci (222 MB) of RAI, the lowest dose of RAI
administered. While one became euthyroid only 2.5 years
after receiving RAI the other remained hyperthyroid even 5
years later. While some patients treated 10 to 12 mci of RAI
were hypothyroid within 1 year others treated with a similar
dose remained hyperthyroid 3 years later. The implication is
that of possible delayed hypothyroidism. Patients may not
appreciate the necessity for continued compliance with
follow up visits where they continue to remain euthyroid
long after receiving RAI therapy particularly where the cost
of follow up visits are borne by the patient. The high default
rate post RAI therapy in the previous study from this center
may be a further justification for an early induction of a
hypothyroid status. This will allow for its earlier detection
and prompt commencement of thyroid replacement therapy
before patients default with follow up visits.

The factors that have been associated with the early
induction of hypothyroidism include female sex, Graves's
thyroid disease and small thyroid size. In this report, we
examined the incidence of hypothyroidism at 1 year of
administration of RAI and assessed for factors
that may predict the occurrence of hypothyroidism within 1
year of administration in our cohort of patients who were
treated from the year 2000 till before 26th September 2007.

**MATERIALS AND METHODS**

This is a retrospective review of case records of patients
treated with RAI for thyroid disease at the Eko hospitals Plc
from the year 2000 till date. Subsequent analysis was done
to determine the incidence of hypothyroidism at one-year
post RAI therapy. This latter analysis was limited to patients
who were followed up for at least 12 months and for whom
their thyroid function status was available at 12 months post
RAI therapy. Subjects who became hypothyroid within 1
year but who were not followed up to at least 12 months
were excluded. Subjects who were hypothyroid at the
administration of RAI were similarly excluded. The subjects
who were hypothyroid at the administration of RAI were
those with thyroid carcinoma who had total thyroidectomy
and subsequent administration of RAI when hypothyroid.
The care of patients before, during and after the
administration of RAI is as per previously published.

**DIAGNOSIS OF THYROID DISEASE**

Subjects in this study were categorized into the following
diagnoses: Grave's, toxic nodular goiter, non-toxic goiter and
indeterminate. Grave's disease was made based on the
presence of one of the following: diffuse goiter,
ophthalmopathy, and TSH receptor antibodies. Toxic nodular
goiter was made based on the absence of opthalmopathy and
the presence of irregular goiter on palpation or thyroid
ultrasound scan findings consistent with nodules in addition
to biochemical frank or sub-clinical hyperthyroidism. Non-
toxic goiter was diagnosed based on the absence of
biochemical frank or subclinical hyperthyroidism and lack of
infiltrative eye signs.

**MEASUREMENT OF THYROID SIZE**

This was done subjectively by WHO grading and objectively
by ultrasonography. The WHO grading is as follows: 0; not
apalpable, not visible with the neck extended, 1a; palpable but
not visible with the neck extended, 1b; visible with the neck
extended, 2; small goiter visible with the neck in normal
position, 3; large goiter. Thyroid volume was derived from
the ultrasound measurements of length (L), breadth (B) and
width (W) all in centimeters using the formula; L x B x W x
0.52 with the result expressed in milliliters. The derived
thyroid volume obtained were the sum of the individual
volumes of both thyroid lobes. The volumes of the isthmus
and pyramidal lobes were excluded.

**STATISTICAL ANALYSIS**

Results are expressed as mean ± SD, range and number of
observations for variable of interest. The statistical package
used is SPSS version 10. The means of continuous variables
were compared with the student's t test while categorical
variables were compared with the Chi square test. The level
of statistical significance was taken as p < 0.05.

**RESULTS**

Seventy-seven subjects had received RAI from the year 2000
till date. This excluded a batch of 10 subjects who received
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RAI for various indications on the 26th of September 2007, which was at the time of writing this report. These 77 subjects consisted of 63 females and 14 males. Their mean age was 41.8 ± 12 years (18-72) (n=77). The diagnosis of thyroid disease was available for 73 subjects: Graves's disease in 54 subjects, TNG in 5, NTG in 8, carcinoma in 4. The cause of thyroid disease was indeterminate in 2 subjects. The indications for RAI was recorded for 75 subjects and were failed drug therapy in 22, relapse post thyroidectomy in 20, size reduction for cosmetic reasons in 12. Six patients had RAI therapy for relapse of hyperthyroidism post thionamide therapy while 3 and 2 subjects were administered RAI for thyrotoxic heart failure and relapse of hyperthyroidism post RAI respectively. Five subjects had RAI as first line treatment of thyrotoxicosis while all 4 with carcinoma had RAI after thyroidectomy. one subject received RAI after developing neutropenia while on carbimazole therapy.

Two subjects with Graves's disease presented with unilateral proptosis in whom computerized tomogram scan revealed extraocular muscle hypertrophy in one person. The second subsequently progressed to bilateral proptosis. The histology of the four cases of thyroid carcinoma were follicular in two, papilary in one and mixed follicular-papillary in one. One patient with euthyroid Graves's disease received RAI therapy for reduction of thyroid size gland. One patient who had not seen her periods 6 weeks after receiving RAI and had a positive pregnancy test subsequently delivered a normal baby. She had used a condom as the contraceptive method.

Subsequent analysis was limited to the thirty-one subjects without thyroid carcinoma who met the following criteria: i. not hypothyroid at administration of RAI, ii: were followed up for at least 12 months, iii: thyroid function status was known at 12 months after RAI therapy. Fifteen (48.4%) of these 31 patients were hypothyroid by 12 months of follow up. Six other subjects who were hypothyroid within 12 months following RAI were excluded from this analysis as they were followed up for less than 1 year. Fourteen (93.3%) of the 15 patients who became hypothyroid by 12 months following RAI were females while all 16 subjects (100%) not hypothyroid by 1 year post RAI therapy were females. The respective mean ages and weights for hypothyroid versus non-hypothyroid subjects were 37.8±13.2 vs 40.5±12.4 years, p=0.6 and 71.2±14.1 vs 67.5±14.0, p=0.6.

Table 1 shows that both groups of patients have similar proportions of subjects with Graves disease, toxic and non-toxic goiter. Furthermore, neither group differed in the proportions treated with 10mci, 15mci or 20mci of RAI nor were there any significant differences in the percentages with elevated microsomal antibodies. However, those becoming hypothyroid had a significantly greater proportion with goiter. Thyroid volume was also significantly greater in those who were hypothyroid compared with the non-hypothyroid subjects.

The profiles of subjects who became hypothyroid by 12 months post RAI are shown in table 2 while table 3 highlights the profile of subjects who were not hypothyroid at 12 months following RAI treatment.

Figure 1
Table 1: Comparison of diagnosis, doses of RAI and selected clinical parameters among subjects who were hypothyroid at 12 months (Group A) versus those not hypothyroid at 12 months (Group B)
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DISCUSSION

Only 31 of the 77 subjects receiving RAI were followed up for more than 1 year at the Eko hospitals Plc. This high rate of “default” may be partly due to some patients continuing to follow up with the doctors who referred them specifically to receive RAI therapy. The female preponderance of our subject population is explained by Graves’s disease being the commonest thyroid disorder for which patients received RAI.

The 50% rate of hypothyroidism at 12 months amongst our patients who were followed up for at least 1 year is similar with that described in two other studies [12, 13]. In one of these studies [13] with a rate of hypothyroidism at 1 year of 55%, only those with toxic adenoma were included and patients received doses of RAI in the range of 25–40 mci, which were much higher than the 10-20 mci our patients received. The second study [14] with a rate of 54.4% at year consisted of subjects with diffuse and nodular goiter. Our rate of hypothyroidism is however, much lower than the 6% and 9.6% reported in two Chinese studies [15, 16].

Although Graves disease, female gender, severity of hyperthyroidism, large thyroid gland and 10 mci rather than 5 mci of RAI have been shown as independent determinants of being hypothyroid within one year of receiving one dose of RAI therapy [10]. Our results indicate that only the size of the thyroid may be a determinant of early onset hypothyroidism as those who were not hypothyroid at 1 year were more likely to have a goiter in addition to larger thyroid volumes than those becoming hypothyroid (table 1). The reason for the absence of effect of dose in our study may be because no patient has received less than 10 mci of RAI since the year 2000. It is notable that all 3 subjects with toxic nodular goiter, followed up for at least 12 months were not hypothyroid within 1 year of receiving RAI. The relative protection from hypothyroidism in TNG may be because RAI is concentrated in the autonomous nodules which are then destroyed, thus permitting the subsequent recovery of the suppressed parts of the gland, unlike with toxic Graves with diffuse uptake of RAI and wide spread destruction of thyroid follicles.

Although RAI was administered in some subjects for thyroid size reduction, monitoring for size reduction was performed subjectively as there were no consistent measurements of thyroid dimensions post RAI therapy to assess for interval changes. Two patients with NTG who had RAI therapy amply demonstrate the limitations with RAI therapy for size reduction after 1 dose of RAI. Patient 9NO (table 2) with a WHO grade 2 goitre (volume of 20 mls) and AS not included in tables 2 and 3 as he was followed up for less than 1 year but had a huge goiter (164.9 mls). Indeed AS had been advised to have surgery but declined because of concerns with blood transfusion, as he is a Jehovah witness. Both patients had not observed any significant reduction in thyroid size as at time of last follow up. Although both patients received 20mci of RAI, NO was hypothyroid at 5 months follow up while AS was euthyroid at 8.5 months post RAI, which was the time of last follow up visit. Indeed another patient with Grade 2 goitre who had previously

Figure 2
Table 2: Profile of patients who were followed up for at least 12 months that were hypothyroid within 12 months of RAI therapy.

<table>
<thead>
<tr>
<th>Initials</th>
<th>Age</th>
<th>High (years)</th>
<th>Diagnosis for RAI</th>
<th>Diagnosis for RAI Analysis sheet</th>
<th>Dose of RAI (mci)</th>
<th>Initial grade of goitre</th>
<th>Goitre grade on 12 months follow-up</th>
<th>Thyroid size grade</th>
<th>Thyroid uptake grade</th>
<th>Time to be euthyroid (months)</th>
<th>Percent of follow-up (months)</th>
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<td>NA</td>
<td>10</td>
<td>Grade 1</td>
<td>Grade 1</td>
<td>Grade 1</td>
<td>Grade 1</td>
<td>12.5 months</td>
<td>12.5</td>
</tr>
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</table>

Figure 3
Table 3: Profile of patients who were followed up for at least 12 months that were not hypothyroid within 12 months of RAI therapy.

<table>
<thead>
<tr>
<th>Initials</th>
<th>Age</th>
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accepted RAI therapy for NTG subsequently declined when she was told that the goiter would not disappear within a week as she had expected.

This study attempts to update the only published report \[6\] with the use of RAI therapy in Nigeria. The conclusions are limited by the small sample size of subjects and that data on variables of interest were not available for all subjects.

CONCLUSIONS

Radioactive iodine therapy at doses of 10-20mci rendered half the patients hypothyroid within 1 year of therapy. Large thyroid volumes were associated with a lower rate of hypothyroidism at 1 year. We suggest higher doses for patients with large goiters to enable an earlier attainment of hypothyroidism and commencement of RAI before patients default from continued follow up visits.

ACKNOWLEDGEMENTS

We are grateful to the invaluable assistance from Sister A A Adebise, the nursing sister in charge of the Endocrine Clinic at the Eko Hospitals in helping to retrieve the case records of our study patients.

References

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