

The Incidence of Hypothyroidism Following the Radioactive Iodine Treatment of Graves' Disease and the Predictive Factors Influencing its Development

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Abstract

The purpose of this study is to evaluate and compare the incidence of hypothyroidism following different fixed radioactive iodine-131 (¹³¹I) activities in the treatment of Graves' disease (GD) and to investigate the predictive factors that may influence its occurrence. This retrospective analysis was performed on 272 patients with GD who were treated with ¹³¹I, among whom 125 received 370 MBq and 147 received 555 MBq. The outcome was categorized as hypothyroidism, euthyroidism, and persistent hyperthyroidism. Multiple logistic regression analysis was performed to identify significant risk factors that affect the development of hypothyroidism. The incidence of hypothyroidism following the first low activity was 24.8% with a high treatment failure rate of 58.4%, compared with 48.3% and 32% following high activity. The overall cumulative incidence of hypothyroidism following repeated activities was 50.7%, out of which 73.9% occurred after the first activity and 20.3% after the second activity. The higher ¹³¹I activity ($P < 0.001$) and average and mild enlargement of the thyroid gland ($P = 0.004$) were identified as significant independent factors that increase the rate of incidence of hypothyroidism (Odds ratios were 2.95 and 2.59). No correlation was found between the development of hypothyroidism and the factors such as age, gender, presence of exophthalmos, previous antithyroid medications, and the durations, and Technetium-99m (Tc-99m) pertechnetate thyroid uptake. In view of the high treatment failure rate after first low activity and lower post high activity hypothyroid incidence, high activity is recommended for GD patients, reserving the use of 370MBq for patients with average sized and mildly enlarged goiter; this increases patient convenience by avoiding multiple activities to achieve cure and long-term follow-up.

Keywords: Graves' disease, hypothyroidism, radioactive iodine therapy

Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism, which is responsible for approximately 50-60% of the cases.^[1] The use of iodine-131 (¹³¹I) in the treatment of GD is increasing, particularly as a first-line treatment,^[2] as it is easy to administer (simple), relatively

inexpensive, reliable, safe, and highly effective with a cure rate approaching 100% after one or more activity.^[3] Hypothyroidism is recognized as a major side effect of ¹³¹I treatment for hyperthyroidism.^[4]

Different methods have been used for determining the given activity, which varied from fixed activity to adjusted calculations in proportion to the size of the gland, iodine uptake, and turnover.^[5] The latter aims to optimize the therapeutic results, increasing the probability of cure and providing the lowest possible radiation to the rest of the body.^[6] There is little evidence that using a calculated activity has any advantage over a fixed-activity regimen in preventing hypothyroidism^[7] or improving the cure rate;^[8] however, it significantly

Access this article online

Quick Response Code:



Website:
www.wjnm.org

DOI:
10.4103/1450-1147.167582

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increases the cost of the therapy owing to increase in complexity of the procedure.^[9] Keeping in mind that the radioactive iodine therapy is relatively inexpensive, the increase in its cost to determine the administered activity must be clearly justified.^[9] According to the literature and our socioeconomic circumstances, we have adopted a protocol using the fixed-activity approach for the treatment of GD in our department.

The biological response of the gland is unpredictable even after application of a relatively accurate radiation dose to the thyroid gland. Although the incidence rate of early-onset hypothyroidism was reduced with calculated ¹³¹I activities, the incidence rate of late-onset hypothyroidism was high.^[3,9,10] In contrast, large ¹³¹I activities resulted in a high incidence rate of early-onset hypothyroidism^[9,11] and have been recommended by some clinicians to obviate the need for long-term follow-up.

Other risk factors, such as the presence of thyroid antibodies,^[12,13] etiology of hyperthyroidism,^[14] administration of antithyroid drugs,^[15,16] and goiter size,^[17,18] can also influence the outcome of ¹³¹I treatment.

The ideal ¹³¹I activity regimen remains controversial and the major drawback for a high activity is the high incidence of hypothyroidism. Therefore, the aim of this study is to examine the outcome in GD patients treated with two different fixed activities of ¹³¹I in our center between 2000 and 2010, and to evaluate the incidence of hypothyroidism after each activity and identify the significant risk factors influencing hypothyroidism in a multiple logistic regression model for further optimization of ¹³¹I treatment for GD patients at our center.

Patients and Methods

In the retrospective evaluation, 272 hyperthyroid patients with GD were referred to the nuclear medicine unit, Kasr Al Ainy Hospital (NEMROK), Cairo University, during the period from January 2000 to January 2010 for ¹³¹I therapy as the first or as the second treatment modality (following medical or surgical treatment). The Medical Ethics Committee of our institution approved the protocol. The diagnosis of GD was primarily based on clinical (hyperthyroid manifestations and diffusely enlarged thyroid gland) and laboratory data, including high serum free T4 level [free thyroxine (FT4); reference values, reference value (RV) = 0.9 - 1.8 ng/dL] and low serum thyrotropin levels [thyroid stimulating hormone (TSH); RV = 0.41 - 4.5 μ IU/mL]. The patients who had thyrotoxicosis due to toxic multinodular goiter (Plummer disease), toxic autonomous adenoma, GD associated with (cold) nodule were examined by scan or by palpation, and the patients who did not

complete the follow-up within 6 months were excluded from the study. Patients with previous history of thyroidectomy, pregnancy, and breast-feeding were also excluded from the study. Data were retrieved from the thyroid clinic database that included the following: The patient's age at the time of diagnosis, gender, symptoms, activity, duration of antithyroid drug intake if given before ¹³¹I therapy, clinical data for the presence of palpable nodules, the presence or absence of eye signs, TSH level, and data of thyroid scan using ^{99m}Tc pertechnetate that was done 20 min after intravenous injection of 185 MBq of the tracer to evaluate the associated nonfunctioning (cold) nodule (defined as a focal area that did not concentrate the tracer, unlike the rest of the thyroid gland). The quantitation of thyroid uptake (based on images of the gland and syringe counts before and after radiopharmaceutical injection) was done using the methodology previously described by Maisey *et al.*^[19], and it was simplified for routine use. The RVs for ^{99m}Tc pertechnetate uptake range from 0.3% to 4%.^[20] Gland sizes were determined by combining clinical examination (palpation) and thyroid scan and were divided into normal (impalpable), mild (palpably enlarged but not visible), and moderate or markedly enlarged (palpable and visible goiter) size. In view of our socioeconomic circumstances, the simple fixed activity protocol has considerable cost-saving advantages; we have adopted this protocol for the treatment of GD in our institution. The patients were divided according to the given ¹³¹I activity into the following two groups: Group 1, in which patients received 370 MBq (125 patients) (46%), and group 2, in which patients received 555 MBq (147 patients) (54%). Antithyroid drugs, if given before the therapy, were withdrawn a week before the therapy and for a minimum of 1 week after the therapy to avoid any drug influence on the therapeutic effectiveness. Iodine-containing medications were also discontinued several weeks before the therapy; in addition, the patients were started on a low-iodine diet for 10 days before the therapy and fasted before and for 2 h after giving the activity to achieve higher absorption. The patients were advised to avoid physical contact and transfer of secretions to others for several days after treatment. Regular clinical and laboratory follow-up to evaluate therapeutic efficacy was done and the patients were classified according to the outcomes into euthyroidism: Absence of signs or symptoms of hyperthyroidism or hypothyroidism with normal serum TSH value without levothyroxine therapy; resistant to therapy: Persistence of thyrotoxic manifestation and suppressed TSH value or by requirement of the repetition of ¹³¹I therapy within 3-6 months of the therapy; and hypothyroidism: Presence of symptoms or signs of hypothyroidism, together with elevated TSH value on two occasions 4 weeks apart, which require permanent treatment with levothyroxine.

Patients with elevated TSH but normal T4 or with a modest reduction in T4 were treated with thyroid replacement that was later withdrawn to reassess the thyroid status to exclude transient hypothyroidism. ¹³¹I treatment was considered to be successful if the patient was either euthyroid or hypothyroid in the absence of hypothyroid drugs within 6 months of the therapy.

Statistical methods

Data were analyzed using IBM SPSS advanced statistics version 20 (SPSS Inc., Chicago, IL, USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher’s exact test) was used to examine the relation between qualitative variables. The ROC curve was used to identify the best threshold for thyroid uptake to discriminate the success and failure of the radioactive iodine (RAI)-131 therapy. Multivariate analysis was done using forward stepwise logistic regression method for the significant factors affecting development of hypothyroidism on univariate analysis. Odds ratio with 95% confidence interval (CI) was used for risk estimation. *P* < 0.05 was considered significant.

Results

Pre-therapy clinical characteristics and commonly presenting symptoms for the patients are listed in Table 1. Out of the 272 patients, 173 (63.6%) were females and the remaining 99 (36.4%) were males. Two hundred and fifteen patients (79%) were ≤50 years while the remaining 57 patients (21%) were in the older age group (>50 years), with a mean age 40.8 ± 12.4 (range 16-70 years). Two hundred and twenty one (81.3%) patients received methimazole before ¹³¹I therapy and 82 (30.1%) had clinical evidence of ophthalmopathy. Mean % pretherapy ^{99m}Tc pertechnetate thyroid uptake was uptake 16.5 ± 11 (range 3.8–52).

Thyroid uptake was analyzed using the ROC curve to discriminate the group of patients who achieved success with the treatment (euthyroidism or hypothyroidism) from the group that remained hyperthyroid (treatment failure) and we found a thyroid uptake threshold of 12.5% with a sensitivity of 60% and specificity of 47.6% for treatment success, area under curve was 0.58 [Figure 1]. We were unable to find an adequate cutoff value for the baseline TSH level.

One hundred and two patients (37.5%) developed hypothyroidism following the first activity of ¹³¹I and 50 patients (18.4%) became euthyroid. One hundred and twenty patients (44.1%) had persistent thyrotoxicosis and required second activity of ¹³¹I,

following which 28 patients (23.3%) developed hypothyroidism, 76 (63.3%) became euthyroid, and 16 (13.3%) patients required a third activity of ¹³¹I. The third activity controlled 13 patients with development of hypothyroidism in 6 (37.5%) of them and euthyroidism in the remaining 7 (43.8%). The fourth activity controlled the remaining three patients, out of whom two developed hypothyroidism and the third one became euthyroid.

The results of Chi-square analysis are presented in Table 2a and b. The activity and the goiter size were the factors that significantly affect the development of

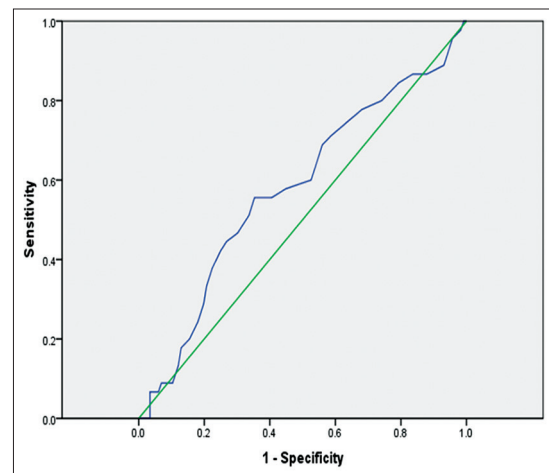


Figure 1: Receiver operating characteristic curve for ^{99m}Tc pertechnetate thyroid uptake in relation to response to radioiodine therapy

Table 1: Clinical characteristics of Graves’ disease patients according to radioactive iodine-131 activity

| Variables | Activity of ¹³¹ RAI (%) | | P |
|--|------------------------------------|------------|-------|
| | 370 MBq | 555 MBq | |
| Gender | | | |
| Male | 43 (43.4) | 56 (56.6) | 0.528 |
| Female | 82 (47.4) | 91 (52.6) | |
| Age | | | |
| ≤50 | 95 (44.2) | 120 (55.8) | 0.255 |
| >50 | 30 (52.6) | 27 (47.4) | |
| Presence of exophthalmos | | | |
| Yes | 39 (47.6) | 43 (52.4) | 0.727 |
| No | 86 (45.3) | 104 (54.7) | |
| Premedical treatment | | | |
| Yes | 94 (42.5) | 127 (57.5) | 0.018 |
| No | 31 (60.8) | 20 (39.2) | |
| Duration of medical treatment | | | |
| ≤1 year | 51 (45.9) | 60 (54.1) | 0.303 |
| >1 year | 43 (39.1) | 67 (60.9) | |
| Size of thyroid gland | | | |
| Average sized and mildly enlarged | 41 (55.4) | 33 (44.6) | 0.015 |
| Moderately and markedly enlarged | 68 (38.6) | 108 (61.4) | |
| % ^{99m} Tc pertechnetate uptake | | | |
| >12.5% | 18 (20.5) | 70 (79.5) | 0.074 |
| ≤12.5% | 24 (32.9) | 49 (67.1) | |

Table 2a: Comparison between responses after first activity between two groups in relation to risk factors

| Variables | Response (%) | | | P |
|--|--------------|-------------|-------------|--------|
| | Euthyroid | Hypothyroid | No response | |
| Activity | | | | |
| 370 MBq | 21 (16.8) | 31 (24.8) | 73 (58.4) | <0.001 |
| 555 MBq | 29 (19.7) | 71 (48.3) | 47 (32) | |
| Sex | | | | |
| Male | 15 (15.2) | 34 (34.3) | 50 (50.5) | 0.255 |
| Female | 35 (20.2) | 68 (39.3) | 70 (40.5) | |
| Age | | | | |
| ≤50 | 44 (20.5) | 80 (37.2) | 91 (42.3) | 0.203 |
| >50 | 6 (10.5) | 22 (38.6) | 29 (50.9) | |
| Presence of exophthalmos | | | | |
| Yes | 16 (19.5) | 27 (32.9) | 39 (47.6) | 0.591 |
| No | 34 (17.9) | 75 (39.5) | 81 (42.6) | |
| Size of thyroid gland | | | | |
| Average sized and mildly enlarged | 17 (23) | 38 (51.4) | 19 (25.7) | 0.004 |
| Moderate and markedly enlarged | 31 (17.6) | 60 (34.1) | 85 (48.3) | |
| % ^{99m} Tc pertechnetate uptake | | | | |
| ≤12.5 | 15 (20.5) | 40 (54.8) | 18 (24.7) | 0.416 |
| >12.5 | 22 (25) | 39 (44.3) | 27 (30.7) | |
| Premedical treatment | | | | |
| +ve | 41 (18.6) | 83 (37.6) | 97 (43.9) | 0.984 |
| -ve | 9 (17.6) | 19 (37.3) | 23 (45.1) | |
| Duration of medical treatment | | | | |
| ≤1 year | 19 (17.1) | 40 (36) | 52 (46.8) | 0.661 |
| >1 year | 22 (20) | 43 (39.1) | 45 (40.9) | |

hypothyroidism following the first activity where a higher percentage of patients receiving higher dose of ¹³¹I (555MBq) developed hypothyroidism (48.3%), and a lower percentage patients remained hyperthyroid (32%) compared to those who received 370 MBq (24.8% and 58.4%, respectively; $P < 0.001$), and a higher proportion of patients with normal sized and mildly enlarged thyroid gland developed hypothyroidism (51.4%) compared with patients with moderately and markedly enlarged thyroid gland (34.1%), whereas the frequency of persistent hyperthyroidism was significantly higher in the latter group of patients (48.3%) compared with the former group (25.7%; $P = 0.004$).

Multiple logistic regression analysis demonstrated that administered high activity (555 MBq) and average sized and mildly enlarged gland increase incidence of hypothyroidism by 2.95 and 2.58 times, respectively (95% CI = 1.68–5.2 and 1.43–4.67, respectively). Age, gender, presence of exophthalmos, ^{99m}Tc pertechnetate thyroid uptake, and previous medical treatment and its duration had no statistically significant effects on the development of hypothyroidism with different P values (0.847, 0.416, 0.306, 0.186, 0.968, and 0.639).

Table 2b: Comparison between two groups regarding the development of hypothyroidism in relation to risk factors

| Variables | Response (%) | | P |
|--|----------------|-----------------------|--------|
| | Hypothyroidism | No response or normal | |
| Activity | | | |
| 370 MBq | 31 (24.8) | 94 (75.2) | <0.001 |
| 555 MBq | 71 (48.3) | 76 (51.7) | |
| Gender | | | |
| Male | 43 (34.3) | 65 (65.7) | 0.416 |
| Female | 68 (39.3) | 105 (60.7) | |
| Age | | | |
| ≤50 | 80 (37.2) | 135 (62.8) | 0.847 |
| >50 | 22 (38.6) | 35 (61.4) | |
| Presence of exophthalmos | | | |
| Yes | 27 (32.9) | 55 (67.1) | 0.306 |
| No | 75 (39.5) | 115 (60.5) | |
| Size of thyroid gland | | | |
| Average sized and mildly enlarged | 38 (51.4) | 36 (48.6) | 0.011 |
| Moderately and markedly enlarged | 60 (34.1) | 116 (65.9) | |
| % ^{99m} Tc pertechnetate uptake | | | |
| >12.5 | 39 (44.3) | 49 (55.7) | 0.186 |
| ≤12.5 | 40 (54.8) | 33 (45.2) | |
| Premedical treatment | | | |
| Yes | 83 (37.6) | 138 (62.4) | 0.968 |
| No | 19 (37.3) | 32 (62.7) | |
| Duration of medical treatment | | | |
| ≤1 year | 40 (36) | 71 (64) | 0.639 |
| >1 year | 43 (39.1) | 67 (60.9) | |

Response to second activity

One hundred and twenty patients who did not respond to the first activity were given the second activity after a mean time of 6.77 months (minimum 3 months and maximum 12 months). Among them 59 patients received 370 MBq and 61 received 555 MBq. A significantly high proportion of patients develop euthyroidism after the second activity, which was an increase of 44.9% compared to the first activity. Hypothyroidism did not increase following the second activity where it developed in 28 patients (23.3%) compared to 37.5% after the first activity, whereas persistent hyperthyroidism was noted in 16 patients (13.3%).

Twenty five patients out of the 73 nonresponding patients in the first group received second activity of 555 MBq while 48 patients received 370 MBq. There was no statistically significant difference in the response rate (controlled versus uncontrolled) between the patients receiving 370 MBq (85.4%) and those receiving 555 MBq (92%) with P value = 0.417. Hypothyroidism developed in 11 (22.9%) and 2 (8%) patients, respectively, while euthyroidism developed

in 30 (62.5%) and 21 (84%) patients, respectively. There was no statistically significant difference in the development of hypothyroidism in relation to the given second activity, age, gender, previous medical treatment and its duration, as well as goiter size as shown in Table 3a.

Eleven out of 47 nonresponding patients in the second group received second activity of 370 MBq while the remaining 36 patients received 555 MBq. There was no statistically significant difference in the response rate (controlled versus uncontrolled) between the patients receiving 370 MBq (90.9%) and 555 MBq (83.3%) with P value = 0.537. Hypothyroidism developed in 2 (18.2%) and 13 (36.1%) patients, respectively, while euthyroidism developed in 8 (72.7%) and 17 (47.2%) patients, respectively. There was no statistically significant difference regarding the development of hypothyroidism in relation to the given second activity, age, gender, previous medical treatment and its duration, as well as goiter size as shown in Table 3b.

Thirteen patients out of the remaining 16 second activity nonresponders responded to the third activity of 555 MBq ^{131}I activity with the development of hypothyroidism in six patients (37.5%) and euthyroidism in seven patients (43.8%). The fourth activity of 555 MBq controlled the remaining three patients with the development of hypothyroidism in two patients and euthyroidism in one.

The overall incidence of hypothyroidism following four activities was 50.7%, the mean number of activity is 1 ± 0.63 (range 1-4). It developed at median 6 months (minimum 3 months and maximum 48 months); 11.8% of the patients developed hypothyroidism after 3 months, and 22.8% after 6 months. The median cumulative activity for the development of hypothyroidism is 555 MBq (minimum 370 MBq and maximum 2220 MBq) [Tables 4-6]. The relation between overall cumulative incidence of hypothyroidism and age, gender, pretreatment with anti-thyroid drugs and its duration, goiter size, $^{99\text{m}}\text{Tc}$ pertechnetate uptake, and cumulative activity of ^{131}I are detailed in Table 7. Goiter size and cumulative activity are the only variables that are associated with the statistical significant incidence of hypothyroidism.

Discussion

The ideal activity of ^{131}I remains elusive. Low fixed activities are associated with the reduced early incidence of hypothyroidism and unacceptable low cure rates, while caution is required with larger activity in view of the possible long long-term effects of the T4 replacement

Table 3a: Comparison between response following the second activity in the first group (previously receiving 370 MBq) in relation to risk factors

| Variables | Response (%) | | | P |
|-----------------------------------|--------------|-------------|-------------|-------|
| | Euthyroid | Hypothyroid | No response | |
| Activity | | | | |
| 370 MBq | 30 (62.5) | 11 (22.9) | 7 (14.6) | 0.156 |
| 555 MBq | 21 (84) | 2 (8) | 2 (8) | |
| Sex | | | | |
| Male | 19 (73.1) | 4 (15.4) | 3 (11.5) | 0.899 |
| Female | 32 (68.1) | 9 (19.1) | 6 (12.8) | |
| Age | | | | |
| ≤50 | 38 (67.9) | 11 (19.6) | 7 (12.5) | 0.741 |
| >50 | 13 (76.5) | 2 (11.8) | 2 (11.8) | |
| Size of thyroid gland | | | | |
| Average sized and mildly enlarged | 9 (56.3) | 6 (37.5) | 1 (6.3) | 0.113 |
| Moderately and markedly enlarged | 32 (72.7) | 6 (13.6) | 6 (13.6) | |
| Premedical treatment | | | | |
| +ve | 37 (66.1) | 10 (17.9) | 9 (16.1) | 0.199 |
| -ve | 14 (82.4) | 3 (17.6) | 0 (0) | |
| Duration of medical treatment | | | | |
| ≤1 year | 20 (66.7) | 7 (23.3) | 3 (10) | 0.277 |
| >1 year | 17 (65.4) | 3 (11.5) | 6 (23.1) | |

Table 3b: Comparison between responses after second activity in the second group patient (previously received 555 MBq) in relation to risk factors

| Variables | Response (%) | | | P |
|-----------------------------------|--------------|-------------|-------------|-------|
| | Euthyroid | Hypothyroid | No response | |
| Activity | | | | |
| 370MBq | 8 (72.7) | 2 (18.2) | 1 (9.1) | 0.332 |
| 555 MBq | 17 (47.2) | 13 (36.1) | 6 (16.7) | |
| Sex | | | | |
| Male | 12 (50) | 8 (33.3) | 4 (16.7) | 0.892 |
| Female | 13 (56.5) | 7 (30.4) | 3 (13) | |
| Age | | | | |
| ≤50 | 20 (57.1) | 12 (34.3) | 3 (8.6) | 0.115 |
| >50 | 5 (41.7) | 3 (25) | 4 (33.3) | |
| Size of thyroid gland | | | | |
| Average sized and mildly enlarged | 1 (33.3) | 2 (66.7) | 0 (0) | 0.324 |
| Moderately and markedly enlarged | 24 (58.8) | 11 (26.8) | 6 (14.6) | |
| Premedical treatment | | | | |
| +ve | 21 (51.2) | 13 (31.7) | 7 (17.1) | 0.532 |
| -ve | 4 (66.7) | 2 (33.3) | 0 (0) | |
| Duration of medical treatment | | | | |
| ≤1 year | 9 (40.9) | 9 (40.9) | 4 (18.4) | 0.319 |
| >1 year | 12 (63.2) | 4 (21.1) | 3 (15.8) | |

therapy.^[21] In the present study, the reported failure rate following the first activity of 555MBq was similar to the rates reported by Bertelsen *et al.*^[22] (32% and 33%) and higher than those reported by other studies^[23-25] (32%, 19%,

Table 4: Time of hypothyroidism following ¹³¹I RAI treatment

| Time in months | Frequency | Percent | Valid percent | Cumulative percent |
|----------------|-----------|---------|---------------|--------------------|
| 3 | 32 | 11.8 | 23.2 | 23.2 |
| 6 | 62 | 22.8 | 44.9 | 68.1 |
| 9 | 18 | 6.6 | 13.0 | 81.2 |
| 12 | 10 | 3.7 | 7.2 | 88.4 |
| 18 | 6 | 2.2 | 4.3 | 92.8 |
| 24 | 5 | 1.8 | 3.6 | 96.4 |
| 36 | 2 | 0.7 | 1.4 | 97.8 |
| 48 | 3 | 1.1 | 2.2 | 100.0 |
| Total | 138 | 50.7 | 100.0 | |
| Euthyroid | 134 | 49.3 | | |
| Total | 272 | 100.0 | | |

Table 5: Permanent hypothyroidism in relation to the activity order

| Order | Number | Percent |
|-------|--------|---------|
| 1 | 102 | 73.9 |
| 2 | 28 | 20.3 |
| 3 | 6 | 4.3 |
| 4 | 2 | 1.4 |
| Total | 138 | 100 |

Table 6: Cumulative activity for development of hypothyroidism following ¹³¹I RAI treatment

| Cumulative activity (MBq) | Number | Percent | Cumulative percent |
|---------------------------|--------|---------|--------------------|
| 370 | 31 | 22.5 | 22.5 |
| 555 | 71 | 51.4 | 73.9 |
| 740 | 11 | 8.0 | 81.9 |
| 925 | 4 | 2.9 | 84.8 |
| 1110 | 13 | 9.4 | 94.2 |
| 1295 | 3 | 2.2 | 96.4 |
| 1665 | 3 | 2.2 | 98.6 |
| 2035 | 1 | 0.7 | 99.3 |
| 2220 | 1 | 0.7 | 100.0 |
| Total | 138 | 100.0 | |

20%, and 19.5%) with an incidence of hypothyroidism similar to the reported by Ratcliffe *et al.*^[23] (48.3% and 48.3%) and higher than that reported by the other two ones^[24,25] (71.1% and 62.1%). The failure rate in the current study following 370 MBq was also found to be higher than that reported by Isgoren *et al.*^[26] and Allahabadia *et al.*^[27] (58.4% versus 22% and 15.4%, respectively); the latter studies reported the incidence of hypothyroidism to be 56.5% and 60.8% compared with to 24.8% in the current study. This difference in response rate may be explained by the presence of other factors interlinked with each other that may exert effect on the outcome other than the ¹³¹I activity that is not the sole factor responsible for the outcomes such as difference in absorption of radioactive iodine ¹³¹I between different regions, turnover of ¹³¹I in the thyroid gland, and varying radiosensitivity of the

thyroid tissue to ¹³¹I (biological variable) that is undefined, unpredictable, and varies from one individual to another and the measurement and size of which remain elusive factors; the latter had a significant impact on the outcome in the present study ($P = 0.004$).

The rate of cumulative incidence of hypothyroidism after repeated ¹³¹I activities in the current study is 50.7%. The highest incidence rate 44.9% occurs at 6 months posttherapy that is comparable to the rate reported by Ahmad *et al.*^[4] (38.2% after 6 months). The high ¹³¹I activity (555 MBq) and average sized and mildly enlarged goiter are identified as independent significant risk factors for increased incidence of hypothyroidism after the first ¹³¹I activity when analyzed in a multiple logistic regression analysis in the present study. In the presence of these risk factors the probability of developing hypothyroidism increased 2.95 and 2.59 times. This is in agreement with other studies that stated that ¹³¹I activity^[3,11,27] and goiter size^[18,28] are important factors influencing the development of hypothyroidism.

There remains controversy regarding the outcome following the ¹³¹I therapy in patients who received ATD. Some authors concluded that ATD treatment prior to the ¹³¹I treatment leads to a reduction of early-onset hypothyroidism^[4,10,15,16,29,30] and increases the failure rate of single ¹³¹I treatment.^[16,31-34] In contrast, other studies failed to observe an excess of persistent hyperthyroidism in patients with a history of ATD.^[24-26,35-37] The results of the present study matched the latter ones, where neither previous medical treatment with methimazole nor its duration had a statistically significant effect on the development of hypothyroidism among the whole study population or in each group separately ($P = 0.968$). Age, gender, presence of exophthalmos, and ^{99m}Tc pertechnetate thyroid uptake had no statistically significant effect on the development of hypothyroidism in the present study. This is in agreement with Ahmad *et al.*, who stated that age and gender were not significantly associated with the development of hypothyroidism in multiple logistic regression analysis.^[4]

Conclusion

In view of the different impacts of different activities of ¹³¹I on the cure rate and incidence of hypothyroidism in GD patients, which is applied to the first activity only and not to the second activity, we recommend a high activity of 555 MBq of ¹³¹I as the routine treatment first activity for all GD patients, reserving the use of 370 MBq for patients with an average sized and mildly enlarged goiter. We also recommend the careful follow-up of patients in the second trimester following ¹³¹I therapy

Table 7: Relation between cumulative incidence of hypothyroidism and different parameters

| Variables | Response (%) | | P |
|--|----------------|--------------|--------|
| | Hypothyroidism | Euthyroidism | |
| Gender | | | |
| Male | 49 (49.5) | 50 (50.5) | 0.757 |
| Female | 89 (51.4) | 84 (48.6) | |
| Age | | | |
| ≤50 | 109 (44.2) | 106 (49.3) | 0.981 |
| >50 | 29 (50.9) | 28 (49.1) | |
| Presence of exophthalmos | | | |
| Yes | 42 (51.2) | 40 (48.8) | 0.916 |
| No | 96 (50.5) | 94 (49.5) | |
| Premedical treatment | | | |
| Yes | 114 (51.6) | 107 (48.4) | 0.560 |
| No | 24 (47.1) | 27 (52.9) | |
| Duration of medical treatment | | | |
| ≤1 year | 61 (55) | 50 (45) | 0.314 |
| >1 year | 53 (48.2) | 57 (51.8) | |
| Size of thyroid gland | | | |
| Average sized and mildly enlarged | 46 (62.2) | 28 (36.8) | 0.037 |
| Moderately and markedly enlarged | 84 (47.7) | 92 (52.3) | |
| % ^{99m} Tc pertechnetate uptake | | | |
| >12.5 | 47 (53.4) | 41 (46.6) | 0.293 |
| ≤12.5 | 45 (61.6) | 28 (38.4) | |
| Cumulative ¹³¹ RAI activity | | | |
| 370 MBq | 31 (59.6) | 21 (40.4) | <0.001 |
| 555 MBq | 71 (69.6) | 31 (30.4) | |
| 740 MBq | 11 (26.8) | 30 (73.2) | |
| 925 MBq | 4 (12.9) | 27 (87.1) | |
| 1110 MBq | 13 (43.3) | 17 (56.7) | |
| 1295 MBq | 3 (50) | 3 (50) | |
| ≥1480 MBq | 5 (50) | 5 (50) | |

because of the higher incidence of hypothyroidism in this posttreatment period.

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How to cite this article: Husseni MA. The incidence of hypothyroidism following the radioactive iodine treatment of graves' disease and the predictive factors influencing its development. *World J Nucl Med* 2016;15:30-7.

Source of Support: Nil. **Conflict of Interest:** None declared.