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The incidence of recurrence and hypothyroidism after radioiodine treatment in patients with hyperthyroidism in Trakya, a mild iodine deficiency area, during the period 1991–2003

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Objective: The purpose of this retrospective study was to evaluate the incidence of recurrence and the success of radioiodine treatment (RIT) in the Trakya region of Turkey, an area with mild iodine deficiency, and to compare the effect of dose regimen selection (fixed (FD) or calculated dose (CD)) on treatment success. ***Material and Methods:*** The study sample included 148 patients (40 male, median age 50) treated with radioiodine between the years 1991–2003. Patients were categorized into three diagnostic groups: Graves' disease (GD) (n = 65), solitary toxic adenoma (TA) (n = 29), and toxic multinodular hyperthyroidism (TMH) (n = 54), and each divided into two subgroups according to treatment method; the first group was treated with a FD of 370 MBq (10 mCi), and the second with CD. ***Results:*** The largest group was GD (44%), followed by TMH (36%). Median duration of follow-up was 28 months (range 6–147). FD was given to 52.7% of all patients and CD was given to 47.3%. There was a partial difference in the dose regimen between all groups, but did not reach statistically significant levels (FD vs. CD: 65%–35%; 38%–62%; 46%–54%; GD, TA, TMH respectively, $p > 0.05$). Total cure rate in FD and CD was 46 (59%) and 37 (52.9%), respectively. The rates of hypothyroidism for GD, TA, and TMH groups were 28 (43.1%), 6 (20.7%) and 16 (29.6%), respectively. The incidence of hypothyroidism did not vary significantly between any groups ($p > 0.05$). At the end of the follow-up period, a total of 104 patients (70.3%) were treated successfully. There was no significant difference in the cure rate between any groups ($p > 0.05$). ***Conclusions:*** The treatment success in all groups and subgroups did not differ significantly between FD and CD. Our lower cure rate than in previous studies may be related to iodine deficiency. Higher doses of radioiodine may be required to increase final treatment success in endemic goiter areas. If this true, dosimetry and calculated dose regimen would be required in all groups of patients instead of an FD concept. However, our findings should be verified in larger series of patients, with longer follow-up period, and urinary iodine concentration measurements.

Key words: radioiodine therapy, iodine deficiency, Graves' disease, toxic adenoma, toxic multinodular goiter

INTRODUCTION

Since its introduction in the 1940's, radioiodine therapy (RIT) has become an increasingly used treatment for adults with hyperthyroidism. The aim of RIT is to restore euthyroidism by radiating and eliminating autonomous or immunogenic hyper-functioning thyroid tissue. Radioiodine can be considered as an appropriate and cost effective therapy in hyperthyroidism, although the decision regarding treatment should be taken on an individual basis, considering the cause and severity of disease, and the wishes of the patient. Hypothyroidism may be considered as an inevitable consequence of RIT rather than a side effect.[1]

Turkey is an iodine deficiency area.[2] The overall goiter

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prevalence is thought to be 30%, and visible goiter prevalence is 6.7%. It was also found that goiter prevalence did not fall below 2% in any region, and in some regions it may even increase up to 50%.[3] Turkey is geographically a mountainous region with volcanic properties, and so lack of iodine in the soil is an expected finding underlying endemic goiter.[4] In iodine deficiency areas, a progressive increase with age in goiter prevalence, thyroid nodularity, and functional autonomy was observed. Hyperthyroidism was twice as high as that reported in iodine-sufficient areas, mainly due to an increased frequency of toxic nodular goiter.[5] A higher prevalence of functional autonomy in thyroid tissue replete with iodine is below 1%.[6–8]

Several factors have been considered to influence the outcome of RIT, such as the administered radioiodine dose, patient's primary disease, gender, and age.[9,10] The purpose of this retrospective study was to evaluate the incidence of recurrence and the success of RIT in the Trakya region of Turkey, an area with mild iodine deficiency, and to compare the effect of dose regimen selection (fixed or calculated dose) on treatment success.

SUBJECTS AND METHODS

Study population: The study sample included all hyperthyroid patients (n = 249) treated with radioiodine in Trakya University Medical Faculty between the years 1991–2003. The medical records of patients over 13 years of age were evaluated. Thirty-six sets of case notes could not be located, and these patients could not be traced. The maximal effect of RIT generally occurs over 4 to 8 weeks, but continued improvement in thyroid functions is often seen for as long as 6 months after RIT. Fifty-three patients with a follow-up of less than 6 months after the first dose of radioiodine and 12 patients who had thyroidectomy before RIT were excluded.

The study focused on 148 patients: 108 females (73%) and 40 males (27%), aged between 24–83 years.

Patients were categorized by clinical examination findings, ultrasonography, and thyroid scintigraphy findings, into three diagnostic groups as follows:

1. Graves' disease (GD) (n = 65 patients): GD was defined as biochemical hyperthyroidism (raised serum free T_4 concentration and undetectable TSH) together with a palpable diffuse goiter, a homogeneous thyroid scan or echopenic pattern on ultrasonography and/or extra thyroidal manifestations.

2. Solitary toxic adenoma (TA) (n = 29): TA was defined as hyperthyroidism in the presence of "hot nodule" in thyroid scan and single nodule in ultrasonography.

3. Toxic multinodular hyperthyroidism (TMH) (n = 54): The diagnosis of TMH was based on the presence of one or more thyroid nodules at palpation and/or ultrasonography and an irregular distribution of ^{131}I or technetium-99m pertechnetate on thyroid scan.

RIT: Patients were divided into two subgroups. The first group was given a fixed dose (FD) of 370 MBq (10 mCi). Administration of a calculated dose (CD) of radioiodine was used in the second group. The following formula was used[1]:

$$\text{Administered dose (mCi)} = \frac{120\ \mu\text{Ci}\ ^{131}\text{I/g of thyroid} \times \text{estimated thyroid gland weight (gram)}}{\text{24 hour radioiodine uptake (RAIU)}}$$

Like in GD groups, we used the weight of whole thyroid gland that is not corrected according to nodule presentation, in the calculated dose regimen of ^{131}I for TA and TMH groups. Thyroid weight was estimated using ultrasonography. The volume of each lobe (length × width × depth) estimated the weight of the gland (e.g., right lobe (5 cm × 3 cm × 2 cm) + left lobe (5 cm × 3 cm × 2 cm) = 60 g). Thyroid RAIU was measured 24 h after oral ingestion of 0.37 MBq of ^{131}I (24-h RAIU, normal range 30%–55%).

Although our patients are living in a mild-iodine deficiency area, we asked then to follow a low-iodine diet for the RAIU test and before RIT for one week in order to prevent any inhibiting effect of dietary iodine on the RAIU test and RIT.

Antithyroid medication was stopped 3–5 days before the radioiodine administration. Antithyroid medication, if necessary, was restarted 3–5 days after RIT. Patients were examined at the first 2 months and thereafter with a 2-month interval. If necessary, the RIT was repeated at least after 6 months.

Follow-up: Follow-up included clinical examination and determination of biochemical parameters. When assessing the long-term outcome of the treatment, patients were considered (1) hyperthyroid (biochemically hyperthyroid or still taking an antithyroid drug), (2) hypothyroid (biochemically hypothyroid ± receiving L-thyroxin), and (3) euthyroid (biochemically euthyroid). The success of therapy (cure rate) was defined as disappearance of hyperthyroidism (euthyroidism or hypothyroidism). Cure rate of patients was evaluated first at the 6th month after RIT and then at each time point during the follow-up period. Euthyroid patients who had been treated with antithyroid drugs after RIT were not evaluated for ^{131}I treatment success.

Statistical method: Values were expressed as mean ± SD. Chi-square tests and ANOVA were used for statistical analysis. A p value <0.05 was set as statistical significance.

RESULTS

In our study, the largest group was GD (65 patients, 44%), followed by TMH (54 patients, 36%). TA (29 patients, 20%) was a relatively smaller group. The patients number

Table 1 Radioiodine therapy in Trakya region during the period 1991–2003; type of disease distributed according to age and gender, and follow-up

	GD	TA	TMH	p
Number of patients (%)	65 (43.9)	29 (19.6)	54 (36.5)	$p < 0.0001$
Gender				
Females	37	25	46	$p = 0.0002$
Males	28	4	8	
Female: male ratio	1.3	6.25	5.75	
Age of RIT (yrs)				
mean ± SD	43 ± 11	57 ± 12	54 ± 12	$p < 0.001$
Range	24–68	31–83	27–78	
Follow-up period (mo)				
mean ± SD	25 ± 23	37 ± 35	27 ± 21	$p > 0.05$
Range	6–147	6–134	7–122	

GD = Graves' disease, TA = Toxic adenoma, TMH = Toxic multinodular hyperthyroidism

of the groups was significantly different ($p < 0.0001$).

Although, there was no significant difference between the number of patients according to gender in GD group (= 1.3), the female/male ratio of TMH and TA groups was significantly higher than GD (TA = 6.25, TMH = 5.75, $p = 0.0002$). The mean age was 50 ± 12 years (range, 24 to 83 years). The mean age of GD was significantly lower than that of the other groups ($p < 0.001$). Table 1 summarized characteristics of the patients who were treated with radioiodine in Trakya University Medical Faculty between the years 1991–2003.

The mean follow-up was 28 ± 25 months (range 6–147) (median 20 months) for all patients. The follow-up period did not vary significantly between the groups ($p > 0.05$).

One hundred thirty-two patients (89.2%) received antithyroid medication before the RIT. Seventy of them was treated with antithyroid drug for a period of 15–18 months. In 62 of 132 patients, antithyroid drug therapy was applied for two or more periods. Remaining 16 patients (10.8%) did not receive any antithyroid medication prior to RIT. In GD group, side effects from antithyroid drugs occurred in five patients (3 leucopenia, one urticaria, and one skin eruption).

Overall RIT results

Seventy-eight patients (52.7%) were treated with FD and 70 (47.3%) with CD. There was a partial difference in the dose regimen between all groups, but not reach statistically significant levels between the three groups (FD vs. CD: 65%, 35%; 38%, 62%; 46%, 54%, GD, TA, TMH respectively $p > 0.05$). The mean dose (ranges) for GD, TA, and TMH were 9.77 ± 2.79 (3–20); 9.43 ± 4.62 (3–20); 12.07 ± 3.79 (2–20) mCi, respectively. The mean dose between the groups was significantly different ($p < 0.001$). GD and TA groups received similar mean doses, which were significantly lower than TMH ($p = 0.001$).

At the end of the follow-up, 23 (29.5%) patients were euthyroid and 23 (29.5%) were hypothyroid in FD, and 23 (32.9%) were euthyroid and 14 (20%) hypothyroid in CD.

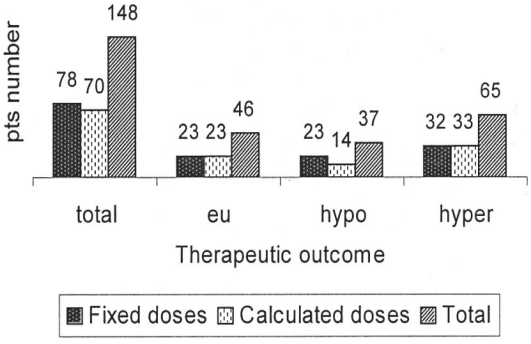

Fig. 1 RIT results according to dose schema and therapeutic outcome suggested by thyroid function at > 6 months after RIT. (pts number = patients number, eu = Euthyroidism, hypo = Hypothyroidism, hyper = Hyperthyroidism)

Total cure rate in FD and CD was 46 (59%) and 37 (52.9%), respectively. Forty-six patients (31.1%) were euthyroid and 37 (25%) were hypothyroid after RIT. Also 83 of 148 patients (56.1%) were treated successfully with RIT. Thirty-two (41%) and 33 (47.1%) patients had recurrence in FD and CD, respectively (Fig. 1).

GD group

In GD group, 42 patients (65%) were treated with FD and 23 (35%) patients with CD. Of the FD, 24% were euthyroid and 36% became hypothyroid after RIT. Following CD, 26% patients were euthyroid, and 22% developed hypothyroidism. Forty % and 52% patients had a recurrence, treated with FD and CD, respectively (Fig. 2-A).

TA group

Eleven of TA (38%) patients were treated with FD and 18 (62%) with CD. Of the FD, 45% were euthyroid. After CD, 39% were euthyroid, and 28% became hypothyroidism. Fifty-five % and 33% of patients had a recurrence, treated with FD and CD, respectively (Fig. 2-B).

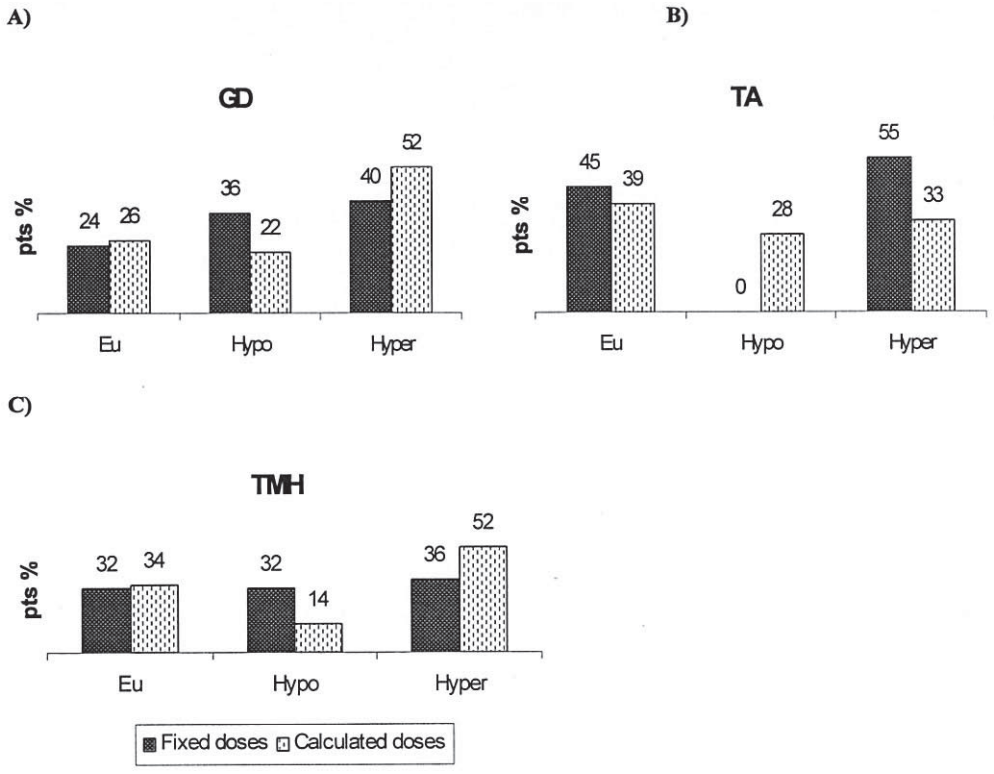

Fig. 2 RIT results at all groups according to FD and CD. A) Graves' disease, B) Toxic adenoma, C) Toxic multinodular hyperthyroidism. (Therapeutic outcome of patients; Eu = Euthyroidism, Hypo = Hypothyroidism, Hyper = Hyperthyroidism, pts % = patients percentage ratio)

TMH group

Twenty-five (46%) of TMH were treated with FD and 29 (54%) CD. Thirty-two % of patients were euthyroid, and 32% became hypothyroid after the FD. In the CD, 34% of patients were euthyroid, and 14% developed hypothyroidism. Thirty-six % and 52% of patients had a recurrence, treated with FD and CD, respectively (Fig. 2-C).

The rates of hypothyroidism for GD, TA, and TMH groups were 28 (43.1%), 6 (20.7%), and 16 (29.6%) respectively. The incidence of hypothyroidism did not vary significantly between any groups ($p > 0.05$).

Sixty-five of 148 patients required repeated doses of RIT. However, only 34 (52%) of patients could be treated with second RIT, because some of them did not accept additional RIT. Patients who rejected the second RIT were treated medically.

Totally, at the end of the follow-up period, 104 patients (70.3%) were treated successfully, whereas 44 (29.7%) remained hypothyroid. There was no significant difference in the cure rate, between any groups ($p > 0.05$).

DISCUSSION

Several therapeutic methods are available for the treatment of hyperthyroidism, including antithyroid drug medication, surgery and RIT.[1] The goal of treatment is to reduce thyroid hormone hyper-secretion. Among these methods, RIT has become a cornerstone in the treatment of patients with hyperthyroidism. ^{131}I is rapidly and completely absorbed and quickly concentrated, oxidized, and organified by thyroidal follicular cells. Although ^{131}I emits beta and gamma irradiation, destruction of thyroid cells occurs, because of the ionizing effects of the beta particles.[1] The effect of RIT depends on the amount of accumulated radioiodine per m*l* diseased thyroid tissue and the effective half-life of radioiodine in the diseased thyroid tissue. Although RIT has been used for hyperthyroid patients for several years, there is no consensus about the optimal radioiodine dose or the most satisfactory method of dose calculation among physicians.

Allahabadia et al.[10] studies different dose regimens and types of goiter. Single dose of radioiodine treatment with 370 MBq had a higher cure rate than those given 185 MBq (84.6% vs. 66.6%), but an increase in hypothyroidism incidence at 1 year (60.8% vs. 41.3%). In their study, although in GD group the incidence of hypothyroidism was higher than other groups, the cure rate was not significantly different between any groups, GD, TA and TNG (Graves 69.5% and TNG 71.4%). In our study, there was no difference in the treatment success between subgroups; this finding was in concordance with their results. Franklyn et al.[11] also compared the success rate of fixed and calculated doses RIT or surgery in large series. They did not find any difference in cure rate between dose

schema with single dose (90.5% CD vs. 89.7% FD), but the prevalence of hypothyroidism in the FD group was greater than in the CD one (55% vs. 16–20%). Different from our results (55%), in Malmo, a non-endemic area, the cure rate was very high (95–100%).[12] There was a recurrence only in Graves' group in the latter study.

Iodine deficiency remains an important public health problem in Turkey. Turkey has long been known as a mild iodine deficiency area according to the figures obtained from previous epidemiological studies. In Edirne, a city of Trakya region, goiter prevalence was found to be 42%,[13,14] and its population showed mild iodine deficiency; median urinary iodine concentration was 78 $\mu g/l$.[14] In regions with sufficient iodine supply, the results of RIT seem to be more satisfying than in iodine deficient areas, or—from another point of view—the radiation dose necessary to restore euthyroidism seems to be lower if the iodine supply is sufficient.[15] Trakya region is an iodine deficiency area, and this might affect hypothyroidism rate of after RIT in GD. Our hypothyroidism rate for GD group was overall 43.1%, and was lower compared with previous reports. The incidence of hypothyroidism after RIT in patients with GD was found within a range of 55% to 83% in the previous literature depending on the dose schema and follow-up period.[12,16–18] The response to RIT in GD is unpredictable. The hypothyroidism rate after RIT might be related not only to the dose of RIT, but also to immunologic factors, or others such as age and iodine deficiency.[15]

In our study population, as expected, patients with GD presented with hyperthyroidism at an earlier age than those in the other groups. The higher mean age of our patients and the clear predominance of women are in concordance with other reports on TA and TMH.[6,10,17]

Epidemiological studies have shown that in iodine deficiency areas the incidence of hyperthyroidism is significantly higher with respect to areas with normal iodine intake and that it is due to TA.[5,8,19,20] The patient population percentage in our study according to type of hyperthyroidism was as follows: GD (43.9%), TA (19.6%), and TMH (36.5%).

We found a 20.7% and 29.6% incidence of hypothyroidism and a 20.7% and 35.8% recurrence rate of RIT for TA and TMH, respectively. The incidence of hypothyroidism after RIT in patients with TMH was reported to be within the range of 3%–64% in the literature.[17,21–24] Although Trakya region is an epidemic goiter area, the incidences of hypothyroidism in TA, TMH for non-endemic goiter area were similar in our study group (25% and 19%, respectively).[12] The rate of therapy failure (persistent or recurrent hyperthyroidism) was reported to be in the range of 0%–33%.[21,25] A comparison of these studies is difficult, because study groups, RIT doses and follow-up periods were different. In our study group, the final recurrence rate in TA and TMH was 20.7% and 29.6%, respectively. The rate of hypothyroidism after RIT in TA and TMH is inversely related to the degree of ^{131}I uptake in extra nodular tissue. The ^{131}I uptake is directly dependent on the nodules, inherent iodine metabolism and autonomous tissue volume, and inversely related to the patient's iodine pool size.[26] In iodine deficiency areas, such as Trakya, the higher rate of treatment failure among TA and TMH patients might be explained by the patients' increased iodine turnover causing a decreased effective half-life of ^{131}I.

At the end of the follow-up period, among the treatment failure group (44 patients, 29.7%), some patients were treated with an additional dose of RIT. Some of them did not accept additional RIT, and some were treated medically.

The clinical presentation and biological behavior of thyroid disease in an iodine deficiency area seem significantly different from that of an iodine sufficient area, such as large goiter,[27,28] increased RAIU,[29] type of cancer and its metastatic patterns.[30] As discussed above, we observed different results from previous studies. One of the causes might be decreased RAIU. (i) Thionamids cause decreased RAIU. Thioureas conferred radioresistance due to their sulfhydryl groups, but not carbimazole (MMI). In our institute, first-line antithyroid drug preference is prophylthiouracil (PTU). It may reduce the therapeutic efficacy of subsequent ^{131}I when discontinued 5–55 days before RIT.[31] (ii) Iodine excess diminishes RAIU. Trakya is an iodine deficiency area, but unfortunately not have the official iodine supplementation. The daily intake of iodine varies from person-to-person because of using iodinize salt and certain foods. (iii) Iodine deficiency areas, Graves' disease may manifest at an earlier age and may be more difficult to treat. In this area, Graves' patients are therapy-resistant.[32] (iv) A higher prevalence of functional autonomy in thyroid tissue has been described in iodine deficiency areas,[6] and thyroid autonomy might need higher doses. In our study, the lower success rate in Graves' disease may possibly be related to concomitant functional autonomy which is caused by long-lasting iodine deficiency.

Study Limitations: The major study limitation was the relatively small size of the study population and the limited follow-up period. Additionally, urinary iodine concentration was not determined.

Conclusion: The treatment success in all groups and subgroups did not differ significantly between fixed or calculated dose schemes. Our lower cure rate than in previous studies may be related to the mild iodine deficiency present in Trakya region. Higher doses of radioiodine may be required to increase the final treatment success in endemic goiter areas. If this is true, dosimetry and calculated dose regimen would be required in all groups of patients instead of a fixed dose concept. However, our findings should be verified in larger series of patients, with longer follow-up period, and urinary iodine concentration measurements.

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