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The influence of non–radioactive iodine (^{127}I) on the outcome of radioiodine (^{131}I) therapy in patients with Graves' disease and toxic nodular goitre

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Abstract

BACKGROUND: The aim of the study was to achieve an effective target dose in the thyroid by increasing the effective half-life (Teff) of ^{131}I by use of iodide (^{127}I) two days after ^{131}I therapy in patients with hyperthyroidism with low Teff.

MATERIAL AND METHODS: The study was carried out in two groups. Group A — 41 patients, and Group B — 14 patients, all the patients were with hyperthyroidism with Teff less than 3 days qualified for ^{131}I therapy. Only group A patients received 600 μg of iodide a day for 3 days, two days after ^{131}I therapy. Radioiodine uptake (RAIU) after 24 and 48 hours, thyroid scintiscan and ultrasonography were done before and after 12 months of ^{131}I therapy.

RESULTS: In group A a significant increase was seen in the Teff (5 days on average) resulting in an increase in the energy target dose by 28% and 37%, in patients with Graves' disease (GD) and toxic nodular goitre (TNG), respectively. After one year of therapy

50% of GD and 93% of TNG patients achieved euthyroidism; 28% of GD and 3% of TNG patients were in hypothyroidism. In Group B, all the patients had radioiodine treatment failure and received a second therapeutic dose of ^{131}I.

CONCLUSIONS: Administration of ^{127}I after ^{131}I treatment can lead to an increase in its effective half-life. This will also increase the absorbed energy dose in thyroid tissue, thereby improving therapeutic outcome without administration of a higher or second dose of ^{131}I. This may minimize whole-body exposure to radiation and reduces the cost of treatment.

Key words: non-radioactive iodine-127, toxic nodular goitre, Graves' disease, radioiodine therapy

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Introduction

Radioiodine therapy (RIT) is considered as the most comfortable and economical approach of hyperthyroidism treatment caused by Graves' disease (GD) or toxic nodular goitre (TNG). Such treatment is indicated in patients with/or without functional autonomy to normalize thyroid function, and to reduce thyroid volume [1, 2]. The outcome of radioiodine (^{131}I) therapy depends mainly on the absorbed energy dose in the thyroid tissue [3–5]. The energy dose depends on the amount of accumulated radioiodine per gram of diseased thyroid tissue. The administered activity can be chosen as a standard dose of radioiodine or calculated by pre-testing of the ^{131}I kinetics [6]. The rate of iodine turnover in the gland is measured by the effective half-life (Teff). Effective half-life determination and the uptake of ^{131}I is important for calculating the therapeutic dose as the Teff may vary from 1 to 8 days [7] while ^{131}I uptake ranges from < 10% to > 80%. Turnover of iodine in the hyperactive thyroid is often increased for no apparent reason, resulting in a reduction of the Teff value. Another variable is the local iodine supply of the patient population.

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The disadvantage of excessively high radioiodine administered activities is that the whole body may be exposed to unnecessary additional radiation. With lower radioiodine doses there is a risk of treatment failure [8]. To minimize such effects it is necessary to increase the effective half-life and decrease the therapeutic dose of ^{131}I. The administered activity, the resulting target doses in the thyroid gland, and the therapeutic outcome depend on the uptake of radioiodine. One cause of reduced ^{131}I uptake and shortened effective half-life is pre-treatment with ATDs, which may have an additional radio-protective effect, or the use of other medication which can change radioiodine kinetics; both can influence the outcome of ^{131}I therapy [9, 10]. Discontinuation of ATDs starting two or three days before ^{131}I therapy is now widely accepted [10]. Another possible explanation for a short effective ^{131}I half-life during therapy is low concentration of iodine in the intra-thyroid pool and the increased thyroid hormone secretion in hyperthyroidism. The consequence is a rapid turnover of both alimentary iodine and radioiodine ^{131}I.

Optimal target energy dose in the thyroid can be achieved with a high level of ^{131}I uptake and long Teff in the thyroid. An adjunct medication for prolongation of the effective half-life is lithium [11, 12] and non-radioactive iodine (^{127}I). Lithium is not suitable for routine use because of potential side effects and the narrow therapeutic range. The effective half-life depends on the iodine supply as well as on T24 and T48 radioiodine thyroid uptake [13–15] and can be prolonged by raising the alimentary iodine supply. Intake of 600 μg of inactive iodide orally may increase the levels of iodine in the intra-thyroidal pool, making more inactive iodine available for hormone synthesis. In consequence, the radioiodine turnover, hormone biosynthesis, and release of ^{131}I from thyroid should decrease, all of which lead to prolongation of the effective ^{131}I half-life during radioiodine therapy [14].

The aim of the study was to achieve an effective target dose in the thyroid by increasing the effective ^{131}I half-life in the thyroid by use of ^{127}I two days after ^{131}I therapy in patients with hyperthyroidism with low effective half-life.

Material and methods

The study was carried out in two groups of patients treated with ^{131}I: Group A and Group B

Group A consisted of 41 patients (32 female and 9 male) with hyperthyroidism. There were 14 patients with Graves' disease and 27 patients with toxic nodular goitre. Mean age was 57.6 ± 16.9 years. In all patients the effective half-life was less than 3 days and ranged between 1.5 and 2.9 days.

Group B consisted of 14 patients (10 female and 4 male), 8 of them with GD, 6 with TNG. Mean age was 55.8 ± 12.9 years. In all patients the effective half-life was less than 3 days and ranged between 1.4 and 2.8 days.

Anti-thyroid drugs were used in patients with overt hyperthyroidism to achieve euthyroidism in those with GD and subclinical hyperthyroidism in those with TNG. ATDs were discontinued five days before ^{131}I treatment. None of the patients had recently taken any medication known to affect thyroid function or RAIU. Patients had not received iodine-containing agents in the last six months. Ophthalmological examination of GD patients excluded the presence of active Graves' ophthalmopathy.

Before ^{131}I administration all patients underwent clinical examinations composed of history and physical examinations. All patients with GD were in euthyroid state clinically and biochemically, with serum levels of thyroid-stimulating hormone (TSH) > 0.1 μIU/ml (normal range 0.2–4.5 μIU/ml), free triiodothyronine (fT$_3$), and free thyroxin (fT$_4$) within normal ranges. All patients with TNG were in subclinical hyperthyroidism with levels of TSH < 0.1 μIU/ml, fT$_3$, and fT$_4$ within normal ranges. Fine-needle aspiration biopsies were used routinely before radioiodine treatment in all patients with dominant nodules within the thyroid gland, to rule out malignant changes. Thyroid scan and ultrasonography were performed before ^{131}I therapeutic dose administration to assess the size of the thyroid nodules and the volume of the thyroid gland.

In a fasting state all patients underwent a RAIU using 2 megabecquerels (MBq) of ^{131}I. Thyroid ^{131}I uptake at 24 and 48 hours was carried out and the results used to calculate diagnostic effective half-life (T$_{eff}$ D) (using semi logarithmic paper).

The therapeutic activities of ^{131}I (A in MBq) were calculated using Marinelli's formula [16]:

$$A\ (MBq) = \frac{\textit{Weight of target thyroid tissue (g)} \times \times\ \textit{absorbed dose (Gy)} \times 24.94}{\textit{Maximum uptake (\%) at time 0 [Tmax]} \times \times\ \textit{effective half-life (days)}}$$

Two days after ^{131}I therapeutic dose administration, only group A patients received 200 μg of inactive potassium iodide (^{127}I) three times a day for three days. Afterwards, the therapeutic effective half-life (T$_{eff}$ T) was calculated using T$_{120}$ and T$_{144}$ RAIU.

Maximum thyroid uptakes and the effective half-lives of ^{131}I were determined after a diagnostic dose (TmaxD) as well as after therapeutic dose of ^{131}I (TmaxT) (Figure 1).

Group B patients did not receive inactive potassium iodide.

The ^{131}I was orally administered to the patients as Na^{131}I in gelatine capsules. The absorbed dose ranged between 150 and 300 gray (Gy) for TNG, and 120–200 Gy for GD, and was proportional to thyroid volume. Before radioiodine therapy the thyroid gland volume ranged between 20–100 g, measured by thyroid
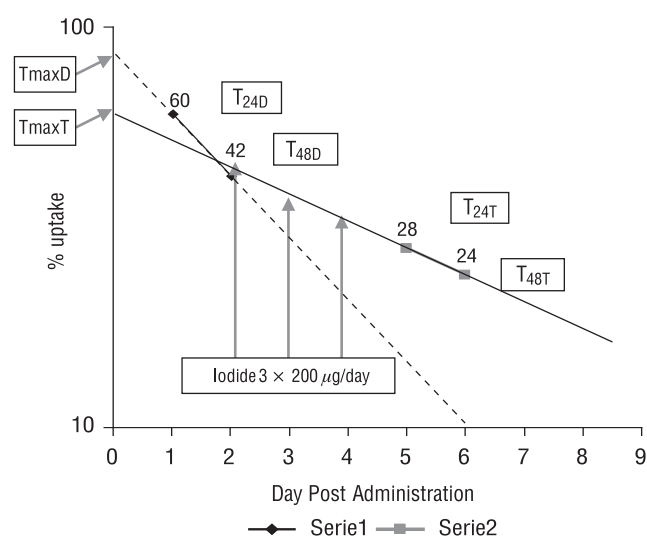

Figure 1. Changes of thyroid radioactivity curves after administration of radioiodine I^{131}: 1. diagnostic dose (Serie 1, D) and 2. Therapeutic dose (Serie 2, T) — 3 days after administration of iodide 600 ug/d (from the 3rd to the 5th day of therapy).

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scintigraphy and ultrasound. The used therapeutic activities of ^{131}I ranged between 200 and 800 MBq.

In the studied groups, we evaluated:

— thyroid hormones, fT_4, and fT_3 serum levels — using radio-immuno assays kits;

— TSH serum levels — by means of immunoradiometric assay kits.

All these parameters were measured before therapy, after 2 weeks, one month, and monthly, up to 12 months after radioiodine therapy. Thyroid scan and ultrasonography were performed after 6 and 12 months to assess the influence of RIT on the size of the thyroid nodules and the volume of the thyroid gland.

Statistical analysis using Student's paired and unpaired t-test was performed.

The protocol of the study was approved by the medical ethical committee of the Medical University of Bialystok, and written informed consent was obtained from all participants. The average duration of follow-up was 12 months.

Results

The results of thyroid RAIU after ingestion of [127]I showed a significant increase in the Teff T as a result of the decrease in the radioiodine turnover in the thyroid gland. Typical changes in decay curves are seen in figure 1. The lowest effective half-life (1.5 days) mean of 2.8 ± 0.69 days was observed in patients with GD before the RIT. After the [127]I administration in all patients there was a significant increase in Teff T (5 days on average) resulting in 28% and 37% increases in the energy target dose in patients with Graves' disease and patients with TNG, respectively. Figure 2 shows the average Teff D before and Teff T after [127]I administration.

In group A — diagnostic effective half-life (3.1 ± 0.65 days) was significantly (p < 0.01) shorter than therapeutic effective half-life (5.4 ± 0.64 days) (Table 1). Teff D among patients with Graves' disease (2.8 ± 0.69 days) was shorter than in pa-

Table 1. The results of the most important parameters in both groups. (X ± SD). There are no statistically significant differences between groups

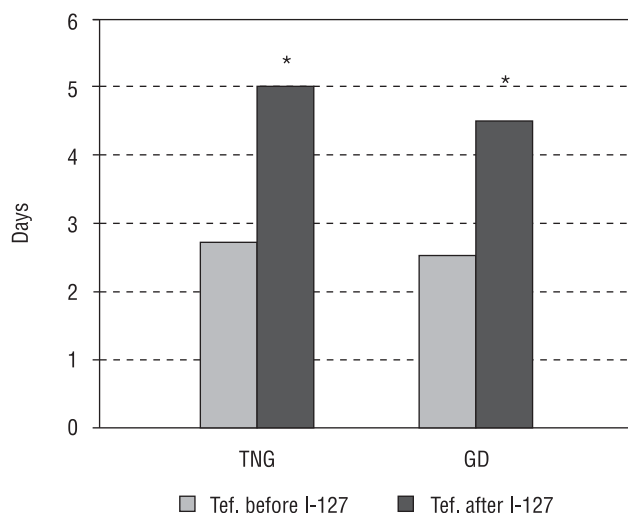|	Group A (n = 41)	Group B (n = 14)
Mean age (years)	57.6 ± 16.9	55.8 ± 12.9
Duration of hyperthyroidism	5.3 ± 6.5	6.4 ± 2.2
Thyroid volume [ml]	36.5 ± 25.7	51.7 ± 23.4
Thyroid volume [ml] (1 year after RIT)	26.2 ± 14.4	41.4 ± 23.1
RAIU T24h%	51.9 ± 13. 2	53.2 ± 10.2
RAIU T48h%	39.8 ± 11.6	43. 9 ± 9.3
[131]I half-life D1	3.1 ± 0.65	2.8 ± 0.61
[131]I I half-life D2	5.4 ± 0.64	–
Administered ^{131}I activity MBq	425.2 ± 195.1	525.7 ± 168.1
Absorption dose Gy	80–300	80–300

Figure 2. The effect of RIT and administration of 600 ug iodide over 3 days (Group A). (From the 3rd to the 5th day of therapy) on the effective half-life in patients with TNG and GD. *statistically significant increase compared to pre-therapeutic value.

tients with TNG (3.1 ± 0.62 days). Mean value of Teff T in group A was 5.4 ± 0.64 days.

Within Group B, diagnostic effective ^{131}I half-life was shorter than Teff D in Group A (2.8 ± 0.61 days). The change of [131]I Teff D in comparison to Teff T in Group A was statistically significant (p < 0.01).

The mean thyroid volume before RIT amounted to 36.5 ± 25.7 g in the whole group and was 36.5 ± 25.7 g in group A, and 51.7 ± 23.4 g in group B. Results of thyroid ultrasound and thyroid scintigraphy after 12 months of ^{131}I therapy showed a significant decrease in thyroid volume; 47% on average in patients with GD and 40% in patients with TNG (Figure 4 and Table 1). Volume of thyroid gland after RIT amounted to 26.2 ± 14.47 g in group A and 41.4 ± 23.1 g in group B.

The value of T24 was 51.9 ± 13.2% in the whole group; 51.9 ± 13.2% in group A and 53.2 ± 10.2% in group B. T48 value was 39.8 ± 11.6% in group A and 43. 9 ± 9.3% in group B.

The administered activity was 425.2 ± 195.1 MBq in the whole group; 425.2 ± 195.1 MBq in group A and 525.7 ± 168.1 MBq in group B (Table 1).

Examples of characteristic thyroid scan of patients with TNG and GD, before and after RIT with adjunct use of [127]I, are shown in Figure 4.

The average concentrations of fT4 and fT3 were, in general, higher in Group A than in Group B. The observed differences were statistically significant in both parameters. In group A we observed a decrease in serum concentrations of fT_3 in both GD and TNG patients, after 2, 5, and 6 months of radioiodine therapy in comparison to the values in first month of observation (Figure 6). The fT4 values were highest in the 3rd month and lowest in the 8th month after therapeutic ^{131}I dose administration (Figure 5). Serum TSH concentration returned to normal values after five months in most of the GD as well as TNG patients (Figure 7).

In group A, four (28%) out of 14 patients with GD, required oral l-thyroxin replacement therapy because of hypothyroidism, seven patients (50%) achieved euthyroidism, two patients were in sub-
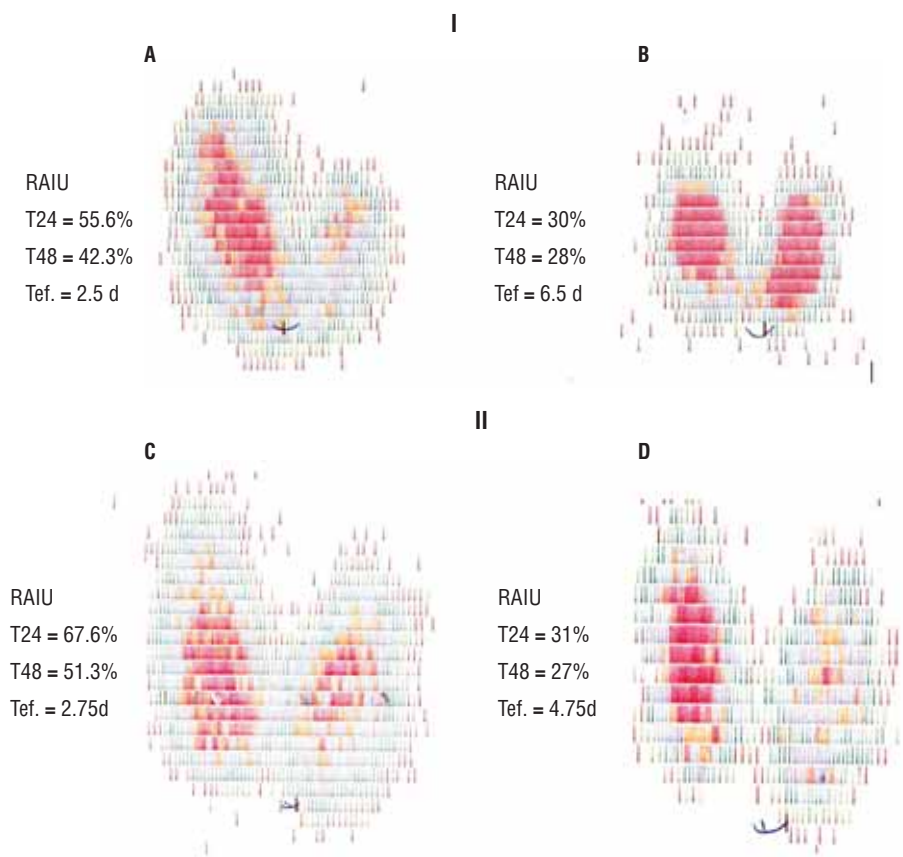
I

A

RAIU

T24 = 55.6%

T48 = 42.3%

Tef. = 2.5 d

B

RAIU

T24 = 30%

T48 = 28%

Tef = 6.5 d

II

C

RAIU

T24 = 67.6%

T48 = 51.3%

Tef. = 2.75d

D

RAIU

T24 = 31%

T48 = 27%

Tef. = 4.75d

Figure 3. Examples of thyroid scans of patients with TNG and GD before and 12 months after RIT. I. Patient with TNG. **A.** Thyroid scan before RIT.
B. Thyroid scan 12 months after RIT (600 MBq). II. Patient with GD. **C.** Thyroid scan before RIT. **D.** Thyroid scan 12 months after RIT (400 MBq).
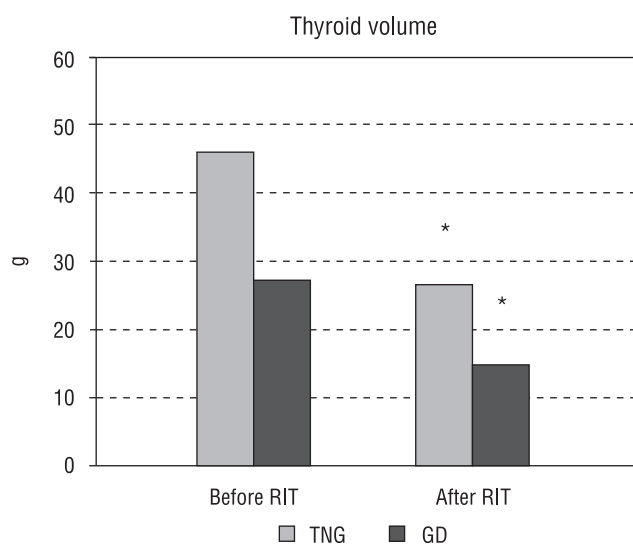

Figure 4. The effect of RIT and administration of 600 ug iodide over
3 days (Group A) (From the 3rd to the 5th day of therapy) on thyroid
volume (measured 12 months after RIT) in patients with TNG and GD.
*statistically significant decrease compared to pre-therapeutic volume.

euthyroidism, one patient was in subclinical hyperthyroidism, and
none were qualified for a second dose of [131]I.

The administered therapeutic activity of ^{131}I was generally
smaller in patients receiving [127]I, in comparison with patients from
non-iodide group. Euthyroidism in group A was achieved in 78%
of patients, hypothyroidism in 12%, and only 9% had subclinical
hyperthyroidism.

These results, as well as an improvement in the clinical condi-
tion and decrease in goitre size, were observed in all patients of
group A.

In Group B, all the patients had radioiodine treatment failure
and required further radioiodine therapy.

Discussion

Iodine obtained from food is absorbed in the digestive tract
as iodide (I-). Once in the blood stream, it diffuses rapidly into
the extracellular space then it follows two principal, competitive
pathways: uptake by the thyroid gland or excretion in urine. In
fasting subjects, radioactive tracer is observed in the neck ap-
proximately three minutes after oral administration of [131]I [17].
Absorption is complete in almost all subjects within a maximum
of two hours after ingestion. After a single ingestion of radioiodine,
thyroid uptake begins rapidly and then reaches a plateau at 10%
to 40% of the total iodine ingested in 24 to 48 hours in euthyroid
subjects [18]. Uptake varies proportionally to thyroid clearance and
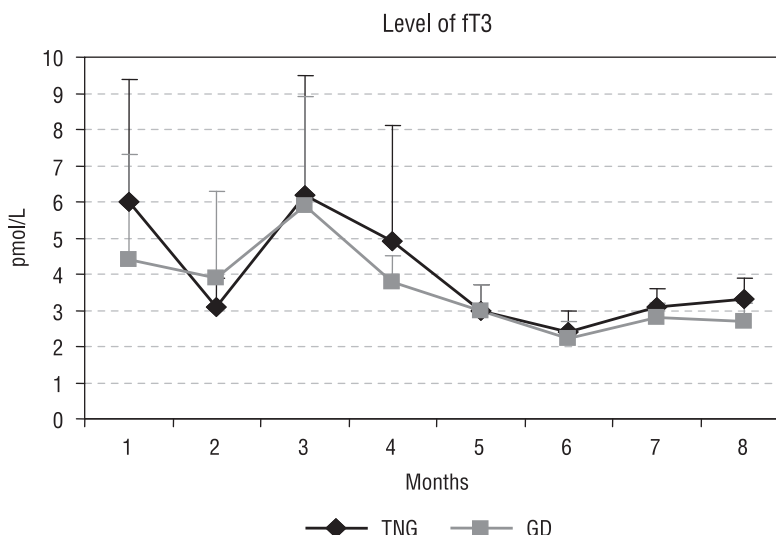plasma iodide concentration. Thyroid clearance depends on the

clinical hyperthyroidism, and one patient was qualified for another
dose of radioiodine. One patient (3%) out of 27 patients with TNG
required oral l-thyroxin replacement therapy because of hypothy-
roidism, 25 patients (93%) were successfully treated and achieved

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Level of fT3

Figure 5. The behaviour of serum FT3 levels after RIT and administration of 600 ug iodide over 3 days (from the 3rd to the 5th day of therapy) in patients with TNG and GD.

Level of fT4

Figure 6. The behaviour of serum FT4 levels after RIT and administration of 600 ug iodide over 3 days (from the 3rd to the 5th day of therapy) in patients with TNG and GD.
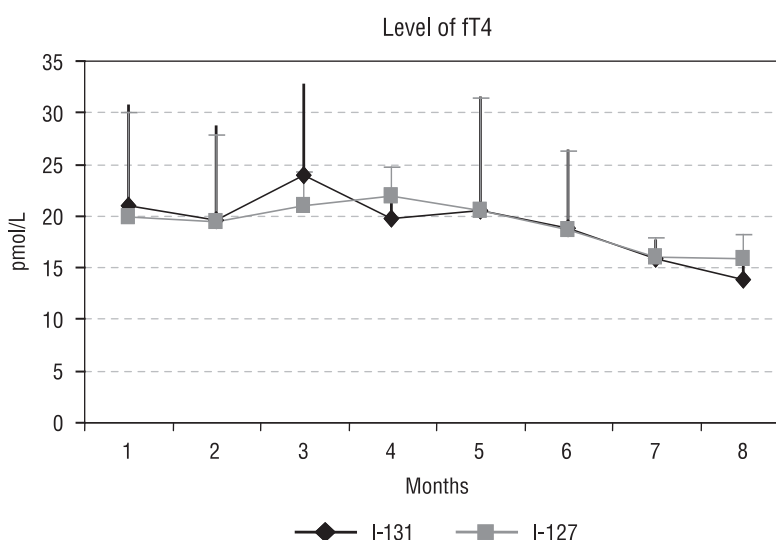
volume and function of the gland. It is adaptive and depends on plasma iodide concentration and dietary intake. As a result, when dietary iodine intake is low, thyroid uptake increases [19, 20]. During exposure to radioactive iodine, the thyroid absorbed dose increases proportionally. Thyroid uptake is higher in adolescents than adults and decreases progressively with age [21]. A normally functioning thyroid produces $100\,\mu$g levothyroxine and $10\,\mu$g tri-iodothyronine daily, and the intra-thyroidal turnover of iodine is estimated at $71.15\,\mu$g iodine/d.

The study of patients with low effective half-life to benefit from non-radioactive iodide tablets was based on experimental and clinical data [14, 22]. A low iodine diet is thought to be helpful in preparing patients for radioiodine therapy [23, 24]. The effects of inactive iodide after radioiodine therapy or radioiodine exposure are well known. In a retrospective study, Hao et al. [25] described

298 patients who had received 250 mg iodide daily, beginning five days after therapeutic ^{131}I administration. Serum levothyroxine levels and the intra-thyroid ^{131}I washout were lower than in patients not receiving additional iodine.

In the treatment of hyperthyroidism, the goal should be to minimize the amount of radiation exposed to the patients and to the environment, while eliminating the hyperthyroid state. Thyroid optimal target energy dose can be achieved by a high uptake and long effective half-life of radioiodine in the thyroid.

In the average patient, the effective half-life is often considered to be five days, which corresponds to a biological half-life of 13.2 days. Radiation dose depends not only on uptake but also on the effective half-life. For a given uptake, the longer the effective half-life, the less radioactive iodine is required to achieve a given radiation dose. Because the radiation dose to the thyroid
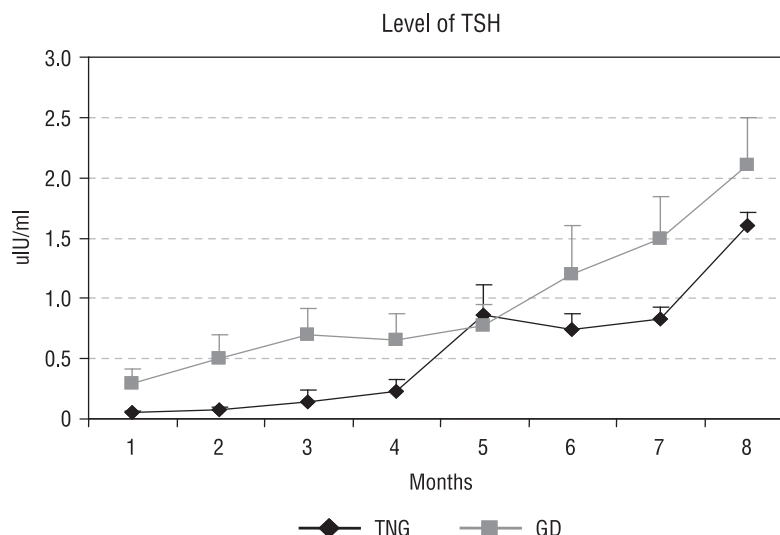
Level of TSH

Figure 7. The behaviour of serum TSH levels after RIT and administration of 600 ug iodide over 3 days (from the 3rd to the 5th day of therapy) in patients with TNG and GD.

occurs only when radioiodine is present in the thyroid, a larger amount of iodine is needed in case of fast turnover. Iodine deficiency can also cause a decrease in the radioiodine retention time in the gland. If turnover is slow, the iodine remains in the gland for a long time and a smaller amount of radioiodine is needed to achieve a given radiation dose.

Our study was based on the model of iodine metabolism published by Urbannek et al. and Dietlein et al. [14, 22, 26]. It demonstrates the dependence of effective half-life on the iodine supply and on thyroid ^{131}I, and shows that the effective half-life could be prolonged by increasing the alimentary iodine supply. In our study, the patients with short ^{131}I half-life of less than three days benefited from inactive potassium iodide tablet administration, taken 48 hours after the administration of ^{131}I therapeutic activity.

The therapeutic ^{131}I doses given to GD and TNG patients were reduced according to the individual increase in the effective half-life which led to increased absorbed doses in the thyroid. In our study the maximum reduction in thyroid volume was observed at 12 months. This maximal reduction of thyroid volume was observed earlier, at 3–6th months, by others [27, 28].

In group A thyroid RAIU measurement after [127]I intake, showed an almost 2-fold increase in effective half-life of ^{131}I in the thyroid tissue. This can be explained by the rapid hormone synthesis in Graves' hyperthyroidism and TNG, and iodine depletion in the thyroid in hyperthyroid patients with TNG and GD due to an emptying of the intra-thyroidal iodine pool. This shortens the effective half-life, because all the ingested iodine is used for biosynthesis of thyroid hormones which are in turn rapidly removed by the increased turnover. If the intra-thyroidal iodine pool is filled by increasing the iodine supply, the thyroid hormone release remains constant and the portion of radioiodine incorporated into thyroid hormones will decrease while the effective half-life of ^{131}I in thyroid increases. In our study the prolongation of the effective half-life by administration of [127]I was mostly noted in patients with GD because of intra-thyroidal iodine deficiency. In patients with initially short effective half-life, the target energy dose was increased by administration

of [127]I , and this led to the use of smaller doses of radioiodine and avoidance of further ^{131}I treatment.

The administered activity of radioiodine was lower in patients who received inactive iodide (Group A) compared to Group B patients. This method was effective, and euthyroidism was achieved in most cases, but subclinical hyperthyroidism was observed only in 9% of cases. It is worth emphasising that in our study after 12 months of radioiodine therapy only 12% of patients were in hypothyroidism, which is in contrast to the 100% noted in other studies [26].

In Group B, despite the high doses of radioiodine administered, the failure rate was higher and hyperthyroidism persisted in all the patients. These unsatisfactory results were due to the low effective half-life of [131]I.

Based on the iodine metabolism model, the clinically observed increase of the effective ^{131}I half-life by administration of [127]I has several possible explanations: an increase in the intra-thyroidal iodine pool, a decrease in thyroid clearance, or a decrease in intra-thyroid iodine turnover.

Iodination blockade by use of ATDs is a second possible cause of the short ^{131}I half-life [9], but in our group, ATD administration was discontinued five days before ^{131}I RAIU test and ^{131}I therapy. Therefore, the effects of ATDs were considerably limited in our study.

According to the results of several studies [29, 30], thyroid uptake can be blocked (at least 95%) by large doses of potassium iodide (> 100 mg) administered before, and 5 hours after, the radioiodine intake. The administration of [127]I prior to radioiodine therapy is contraindicated because it would cause an unnecessary reduction in radioiodine uptake during therapy.

Conclusions

Administration of non-radioactive iodine two days after ^{131}I therapy in patients with hyperthyroidism with short effective half-life represent a novelty of the post-therapeutic use of [127]I. This can cause an increase in ^{131}I effective half-life resulting in an increase

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in the absorbed energy dose in thyroid tissue, thereby improving therapeutic outcome without the necessity of administration of a higher or second radioiodine dose. Such a procedure will also minimize the whole-body exposure to radiation as well as reduce the total cost of therapy.

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