

Radioiodine treatment of hyperthyroidism in patients with low thyroid iodine uptake

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Abstract

BACKGROUND: The aim of the study was to analyze the effectiveness of radioactive ¹³¹I in hyperthyroid patients with confirmed lowered iodine uptake as compared to patients with an uptake of over 30%.

MATERIAL AND METHODS: We retrospectively analyzed 53 consecutive patients aged from 29 to 84 (mean age 60 years) suffering from hyperthyroidism caused by Graves' disease or toxic nodular goitre. The patients were divided into 2 sub-groups: the 1st with a maximum iodine uptake of $18.7 \pm 3.2\%$ (range, 11–23%) — 24 patients; the 2nd with a maximum iodine uptake of $27.1 \pm 2.1\%$ (range, 24–30%) — 29 patients. The control group consisted of 50 patients treated with ¹³¹I with an iodine uptake of over 30%. Each patient was evaluated before, and 6 months after, treatment for fT₃, fT₄ and TSH with ECLIA; TRAb with RIA; ultrasound with a 7.5 MHz linear probe. The volume of the thyroid gland was determined using the Gutekunst method. All these factors underwent statistical analysis and were considered along with the results of clinical examinations.

RESULTS: Clinical remission of hyperthyroidism was evident in 79.3% of both sub-groups, in total (83.3% and 75.3%, respectively). TSH was normalized in 62.3% of these patients (54.2% and 69.0%, respectively). The mean range of TSH levels increased from $0.081 \mu\text{U/ml}$ to $4.0 \mu\text{U/ml}$ after therapy; that is, from $0.087 \mu\text{U/ml}$ to $4.97 \mu\text{U/ml}$ in the 1st sub-group and from $0.076 \mu\text{U/ml}$ to $3.3 \mu\text{U/ml}$ in the 2nd sub-group. The volume of the thyroid gland was uniformly significantly lower, with a mean range of 40.5 ml before treatment and 21.7 ml afterwards.

The results seen in both sub-groups were similar; only age and dose of radioiodine were slightly higher in the 1st, while mean uptake was higher in the 2nd. By comparison of these results to those of the control patients, we observed that the values of TSH, as well as thyroid volume and evidence of clinical remission, reflected those found in the control group.

The mean dose of ¹³¹I was lower in the control group, that is 11.3 m Ci, as compared to the sub-groups as a whole, specifically, 15.7 mCi. The mean age of patients in the control group was slightly less than that of the study group (50.8 and 60, respectively).

CONCLUSIONS: 1. The results of the treatment of patients with a low iodine uptake are similar to the results obtained in the group of patients with iodine uptake above 30% and therefore low iodine uptake should not be a contraindication for isotope I-131 therapy. 2. Additionally, we have demonstrated that a statistically significant decrease in thyroid volume is observed in all patients after the iodine isotope treatment which indirectly proves the effectiveness of the prescribed treatment, and that low thyroid iodine uptake is more frequently observed in elderly patients and in patients treated with iodine or anti-thyroid drugs.

Key words: 131-I therapy, hyperthyroidism,
low iodine uptake

Introduction

The treatment of hyperthyroidism using the I-131 isotope is a generally accepted and recognised method. However, the methods for establishing treatment doses have been under discussion

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since the early '40s, when, for the first time, I-131 was used in medical treatment. The majority of medical centres use doses calculated individually for each patient [1, 2]. The method for establishing the dose is most frequently based on describing an absorbed dose, taking into consideration the size of the thyroid gland, the thyroid iodine uptake and the period of effective half-life of the isotope in the thyroid gland. Some centres use fractional doses, and the amount depends on the character of the goitre. According to some authors, low thyroid iodine uptake limits the possibility of successful treatment, or even makes it impossible. In their opinion, an absorbed dose, which is too small, does not give a prognosis for effective treatment [11].

In the Department of Endocrinology, University of Medical Sciences in Poznań, the treatment of patients with hyperthyroidism using radioactive iodine has been conducted since 1957. Our observations have shown that low thyroid iodine uptake is not a contraindication for this type of treatment; however, it should be taken into consideration while establishing the dose of radioiodine.

The aim of this paper was to analyse the 131-I treatment efficiency in patients with hyperthyroidism with proven low thyroid iodine uptake below 30%, and to compare the results of the treatment obtained in this group to the results in the control group. Informed consent was given by all treated patients and the study was approved by the Ethical Committee.

Material and methods

Patients

We retrospectively analysed 53 consecutive patients (44 women and 9 men) aged from 29 to 84 (mean age 60 ± 13) admitted to our clinic for 131-I therapy because of hyperthyroidism. All of the patients came from the same iodine-deficient area. In all patients, antithyroid drugs had been administered before RAI therapy with a mean duration of treatment of one year and were withdrawn at least 2 weeks before 131-I therapy. 14 patients were diagnosed with Graves' hyperthyroidism on the basis of clinical findings, suppressed TSH levels, elevated fT4 and fT3 serum concentration and abnormally high elevated serum thyrotropin receptor antibody (TRAb) levels. 39 patients were diagnosed with toxic nodular goitre on the basis of clinical and biochemical findings of hyperthyroidism in the presence of a nodular goitre. The patients were divided into two groups. The first group included 24 individuals with maximum iodine uptake of $18.7 \pm 3.25\%$ (range, 11–23%); the second group included 29 individuals with iodine uptake of $27.1 \pm 2.1\%$ (range, 24–30%). The control group consisted of 50 consecutive patients treated with I-131, with iodine uptake of more than 30%. Within the control group, 11 patients were diagnosed with toxic nodular goitre and 39 patients with Graves' hyperthyroidism.

Methods

Radioiodine uptake — was measured by a previously calibrated scintillation counter (Polon, Warsaw, Poland) 24 h after administering a tracer dose of iodine-131 ($10 \mu\text{Ci}$). Measurement was performed for 2 minutes with the patient positioned upright and the anterior surface of the neck 20 cm from the detector.

Scintigraphy — was performed using a γ -camera (Nucline TH/33, Hungary). The images were interpreted using both computer screen (256 grey scale) and film by an experienced nuclear medicine physician.

Thyroid ultrasonography — using Aloka SSD 1100 with a linear probe of 7.5 MHz (Tokyo, Japan) was performed in every patient for exact determination of thyroid volume with the ellipsoid formula: width [cm] \times length [cm] \times thickness [cm] $\times \pi/6$ for each lobe.

Biochemical and immunological investigation — each patient underwent the following examinations: registration of serum fT3, fT4 and TSH concentrations with the ECLIA method and serum TSH receptor antibodies (TRAb) levels measurement with RIA method.

Dose calculation — the individual delivered dose (D) for 131-I therapy was calculated by the following formula: $D \text{ (mCi)} = \text{constant} \times \text{target dose (Gy)} \times \text{thyroid volume (ml)} / \text{iodine uptake at 24 h (\%)} \times \text{effective half-life of 131-I (days)}$. The target dose was 50 Gy.

Outcome assessment — all patients were followed up by clinical assessment and were checked by ultrasonography as well as for fT3, fT4, TSH, and TRAb levels 6 months after radioiodine therapy. They were classified into three groups according to their thyroid function as hypothyroid (elevated serum TSH concentration and low serum fT3 and fT4 concentration), euthyroid (normal serum fT3, fT4 and TSH concentration) or hyperthyroid (suppressed TSH levels and raised serum fT3 and fT4 concentration). No side-effects of radioiodine were noted at follow-up examination.

Statistical analysis of the obtained results was conducted using the non-parametric Mann-Whitney test for the unpaired values, and the Spearman test for the paired values.

Results

In 79.3% of examined patients (83.3% and 75.9% in both subgroups respectively) the absence of clinical features of hyperthyroidism (responders to RAI therapy) was observed 6 months after treatment. Similar results were obtained in the control group ($p > 0.05$) (Table 1).

In the group of patients with low iodine uptake, continuing low TSH values (persistent hyperthyroidism) were observed in 20.7% (11) of cases, whereas in the control group, in 24% (12) of patients. Incorrect high TSH values occurred in 17% (9) of examined patients, and in the control group in 16% (8) of patients. Normalized TSH values were observed in 62.3% (33) of the examined patients (54.2% and 69% in both subgroups respectively), and in 60% (30) of patients from the control group. Average TSH values in both tested groups increased from $0.081 \mu\text{U/ml}$ before treatment, to $4.0 \mu\text{U/ml}$ after treatment ($p < 0.0001$). In respective subgroups: group I — from $0.087 \mu\text{U/ml}$ to $4.97 \mu\text{U/ml}$, and group II — from $0.076 \mu\text{U/ml}$ to $3.3 \mu\text{U/ml}$ (Figure 1).

Thyroid volume in the examined group decreased in a statistically significant way in all patients, from an average 40.5 ml before treatment, to 21.7 ml after treatment ($p < 0.0001$). Analysing the patients depending on diagnosis, a statistically significant difference in the change of thyroid volume was observed (Δ). In the patients with Graves' disease, thyroid volume after treatment with radioiodine amounted to 33.4% of the initial value (from 29.42 ml to 10.0 ml), whereas in the patients with toxic nodular goitre, it amounted to 60.7% of the initial value (from 42.5 ml to 25.83 ml) (Figure 2).

In the control group, the average volume before treatment amounted to 43.4 ml and decreased in a statistically significant way to 17.4 ml ($p < 0.0001$). At the same time, the degree of the

Table 1. Clinical status before and after treatment

| | Clinical condition before treatment | | | | Clinical condition 6 months after treatment | | | |
|----------|-------------------------------------|-----|----------------|------|---|------|-----------------|------|
| | Thyreotoxicosis | | Hypothyroidism | | Euthyroidism | | Thyreotoxicosis | |
| | n | % | n | % | n | % | n | % |
| Group I | 24 | 100 | 7 | 29.1 | 13 | 54.2 | 4 | 16.7 |
| Group II | 29 | 100 | 2 | 6.9 | 20 | 69.0 | 7 | 24.1 |
| Total | 53 | 100 | 9 | 17.0 | 33 | 62.3 | 11 | 20.7 |
| Control | 50 | 100 | 8 | 16.0 | 30 | 60.0 | 12 | 24.0 |

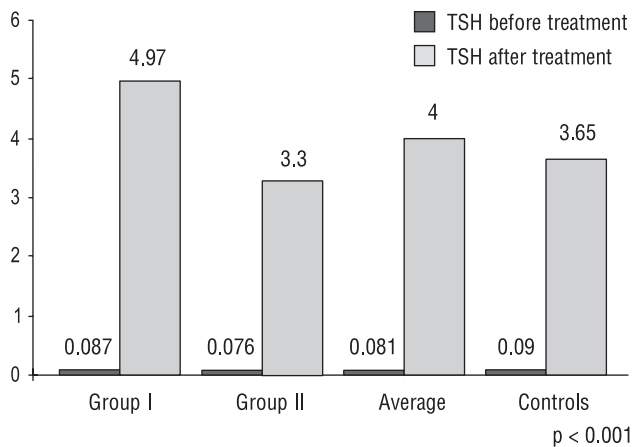


Figure 1. Change in TSH value after I-131 treatment (U/ml).

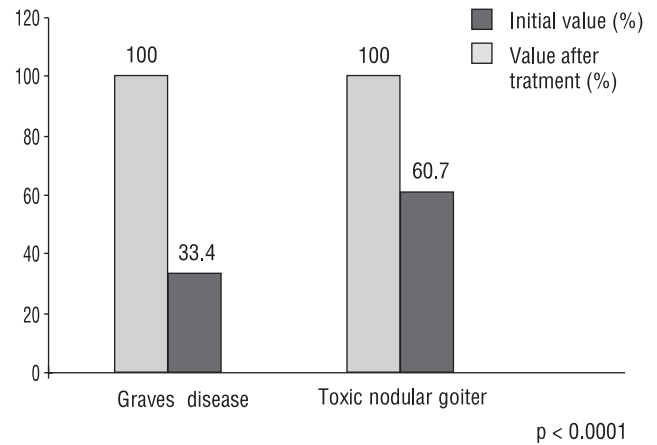


Figure 2. Change in thyroid volume depending on diagnosis.

change in thyroid volume obtained after treatment in the tested group did not differ in a statistically significant way in comparison to the control group. (Figure 3).

The average thyroid iodine uptake in the tested group (23.3%) was smaller in a statistically significant way in comparison to the control group (63.3%) ($p < 0.0001$). The average age of the patients from the control group was 50.8 and was lower in a statistically significant way than in the tested group 60.0 ($p = 0.0037$) (Table 2).

The average ^{131}I dose was smaller in the control group and amounted to 11.3 mCi, in comparison to the tested group — 15.7 mCi (Group I — 16.5 mCi, Group II — 15.0 mCi, respectively), which constitutes a statistically significant difference ($p = 0.0059$). (Figure 4).

The results obtained in the particular subgroups were similar, however; only age and dose were slightly higher in the first subgroup, with the average iodine uptake slightly larger in the second subgroup.

Discussion

In 1941, the ^{131}I isotope was used for the first time in medical treatment. Since then, this type of therapy has been widely used in the treatment of hyperthyroidism [1, 2]. ^{131}I therapy is a safe and effective method, and with the exception of hypothy-

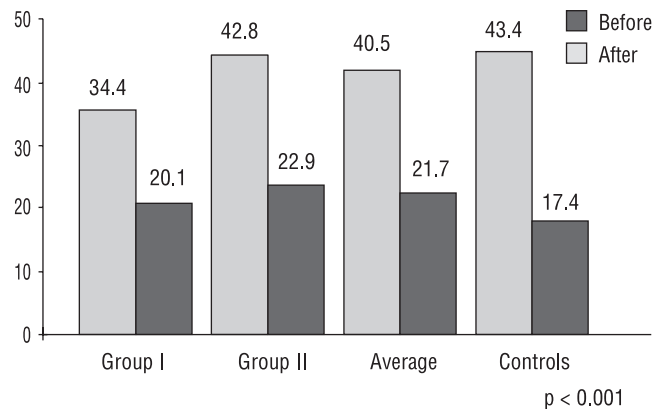


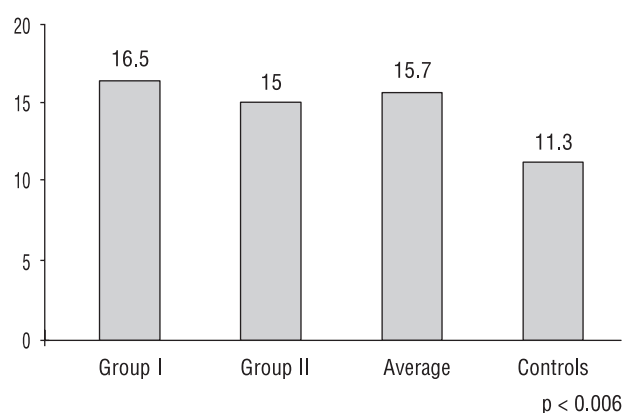
Figure 3. Change in thyroid volume after treatment (ml).

roidism no other serious side effects were observed. There is no evidence of increased risk of thyroid gland cancer caused by the radioiodine treatment. The frequency of leukaemia and other proliferative diseases is similar to those in the general population [3].

Although radioiodine therapy may sometimes cause slight post radiation thyroiditis, temporary exacerbation of thyreotoxicosis symptoms, vomiting and lack of appetite or in the case of Graves' disease and in smokers [4], ocular symptoms aggravation, all the

Table 2. Results of treatment

| | TSH [mU/ml] | | Thyroid volume [ml] | | Age (years) | Uptake I (%) | Dose [mCi] | Responders to RAI therapy (%) |
|----------|----------------|--------------|------------------------|--------------|----------------|-----------------|---------------|-------------------------------------|
| | Before | After | Before | After | | | | |
| Group I | 0.087 ± 0.039 | 4.97 ± 8.929 | 34.4 ± 20.84 | 20.1 ± 16.89 | 62.9 ± 11.4 | 18.8 ± 3.2 | 16.5 ± 9.13 | 83.3 |
| Group II | 0.076 ± 0.054 | 3.3 ± 8.163 | 42.8 ± 29.02 | 22.9 ± 17.03 | 57.5 ± 14.3 | 27.1 ± 2.1 | 15.0 ± 9.43 | 75.9 |
| Average | 0.081 ± 0.047 | 4.0 ± 8.474 | 40.5 ± 25.76 | 21.7 ± 16.86 | 60.0 ± 13.2 | 23.3 ± 4.9 | 15.7 ± 9.24 | 79.3 |
| Control | 0.09 ± 0.049 | 3.65 ± 9.021 | 43.4 ± 28.84 | 17.4 ± 15.3 | 50.8 ± 15.1 | 63.3 ± 15.7 | 11.3 ± 7.46 | 76.0 |

**Figure 4.** Average I-131 dose (mCi).

registered side effects are incomparable to the effects of thyreotoxicosis which may lead to the death of the patient. They are also incomparable to the unpredictable allergic reactions to thyreostatics, anaesthetics and surgical complications.

Despite such a long period of using this method, the optimal method for calculation of the dose is still a matter of debate. It is questionable whether the adjusted dose has any benefit over the fixed dose, and which factors should be incorporated into the dosimetric formula.

Some authors claim that patients with thyreotoxicosis should be treated with ablative fixed-doses that completely eliminate hyperthyroidism, leading to the permanent hypofunction of the organ within 1 year [5–9]. They emphasize that this is proof of the cure of thyreotoxicosis, and in a period of TSH determination using hypersensitive methods as well as widely available L-thyroxin preparations, a substitute therapy may be quickly and effectively applied without endangering patients to the unbeneficial results of hypothyreosis. Treatment using thyroxin is one of the safest and most effective methods of controlling thyroid gland function.

Other authors consider the occurrence of hypothyroidism after radioiodine treatment as a significant side effect and propose a more conservative approach where the aim is to achieve a durable euthyroid state and to avoid hypothyroidism [10]. In various publications, the percentage of patients with hypothyreosis ranges from 20% to 50%, depending on the method of dose calculation.

In our study, we calculated an individual dose for each patient and the frequency of hypothyroidism amounted to 17%, which was similar to the control group. Therefore, we postulated that

adjusted-dose regimens reduce the likelihood, or at least delay the onset, of permanent hypothyroidism.

The purpose of radioiodine treatment in patients with low iodine uptake remains questionable [11]. Some studies report that the therapeutic effect in patients with low iodine uptake is much lower than in patients with iodine uptake above 30% [12] or even that low thyroidal ^{131}I uptake makes radioiodine therapy unfeasible [13]. Unfortunately, iodine supplementation of dietary salt and the common use of preparations of vitamins containing iodine cause low iodine uptake in many patients with thyreotoxicosis. Assuming that the limit of iodine uptake, from which radioiodine therapy may be applied, is 30%, or as some authors claim 40%, a large group of patients should be disqualified from this type of treatment [11]. However, other authors have demonstrated that individuals with higher 24-h uptake value are more likely to fail to respond to radioiodine treatment and to persist in a hyperthyroid state [14]. Moreover, according to the results of a recent study [15], patients with the lowest pretherapeutic RAI uptakes show the highest success rates after RAI treatment. Our study supports these findings. The treatment effectiveness in patients with a low thyroid iodine uptake amounted to 79.2%, and was similar to the control group. Although the average therapeutic dose in the tested group amounted to 15.7 mCi and was larger than the dose administered to the control group (11.3 mCi), no higher incidence of hypothyroidism was observed. This proves that a higher dose of ^{131}I is warranted in patients with low iodine uptake and guarantees a success rate similar to those in patients with iodine uptake above 30%.

Reduction in thyroid size [16] is indirect proof of the beneficial effects of radioiodine on the thyroid gland. In our study, a statistically significant decrease in the organ volume was assessed 3 months after the therapy. The results were similar to those obtained previously in this clinic [17].

Pedersen and Kirkegaard proved that treatment effectiveness depends on the initial concentration of TSH [18]. The higher the TSH concentration before treatment, the higher the effectiveness of iodine therapy. Our tests, although carried out on a smaller number of patients, confirm those observations. In the first tested subgroup, the TSH concentration amounted to 0.087 $\mu\text{U/ml}$, and the disease remission occurred in 83.3% of patients. In the second subgroup, the TSH concentration amounted to 0.076 $\mu\text{U/ml}$ and remission was observed in a smaller number of patients — 75.8%.

Sowiński [19] proved the relationship between the initial results of T3, T4 and rT3, and the effectiveness of treatment with ^{131}I -iodine isotope. The higher the initial values of T3 and T4, the worse the therapeutic effect. An inverse dependence was observed

in rT3. It seems that for larger TSH values and lower values of T3 and T4, the clinical symptoms of thyreotoxicosis are less intensified and therefore the percentage of successful treatment in those patients is higher.

It has been shown in this research that the mean age of the patients with low thyroid iodine uptake is higher in comparison to the control group. Additionally, in some patients from this group, clinical symptoms of circulatory insufficiency and cerebral arteriosclerosis were observed, which disqualified the majority from surgical procedure. The ineffective treatment with anti-thyroid drugs, existing contraindications and the patients' fear of surgical treatment implies that many patients suffering from thyreotoxicosis are recommended for radioiodine treatment.

Summing up, therapy of hyperthyroidism in patients with a low thyroid iodine uptake is as effective as in other patients. Iodine uptake below 30% does not restrict the use of iodine therapy and, excluding the health benefits, may lower the cost of treatment in patients with thyreotoxicosis.

Conclusions

On the basis of the obtained results, the following conclusions were drawn:

1. The results of the treatment of patients with a low iodine uptake are similar to the results obtained in the group of patients with iodine uptake above 30%, and therefore low iodine uptake should not be a contraindication for isotope I-131 therapy.
2. Additionally, we have demonstrated that a statistically significant decrease in thyroid volume is observed in all patients after the iodine isotope treatment, which indirectly proves the effectiveness of the prescribed treatment, and that low thyroid iodine uptake is more frequently observed in elderly patients and in patients treated with iodine or anti-thyroid drugs.

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