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Original

Single, very low dose (0.03 mg) of recombinant human thyrotropin (rhTSH) effectively increases radioiodine uptake in the I-131 treatment of large nontoxic multinodular goiter

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Abstract

BACKGROUND: Radioiodine therapy (RIT) in patients with large nontoxic multinodular goiter (MNG) recently becomes more common method in comparison to surgery (especially in elderly patients and with contraindications because of severe chronic diseases other systems). Repeatedly low thyroid radioactive iodine uptake (RAIU) decreases effectiveness of RIT or makes it impossible. The recombinant human thyrotropin can increase RAIU and improve the results of RIT.
The aim of the study was to assess the influence of a single very low dose (0.03 mg) of rhTSH on RAIU and thyroid function in euthyroid (MNG-EU) and subclinical hyperthyroid (MNG-SC) patients with a large multinodular goiter.
MATERIAL AND METHODS: 40 patients (14 male, 26 female, age 57–80 yr) with large non-toxic MNG over 80 grams and with baseline RAIU < 40% were included into the double-blind randomized study and divided into two groups: rhTSH-group and control group. First group received the single intramuscular injection of 0.03 mg rhTSH and the second received placebo. The RAIU were measured 24 and 48 hours after the rhTSH and then all the patients were administered therapeutic doses of I-131. TSH and free thyroxine levels were measured at 1st and 2nd day after the injection of rhTSH and later, at 4 and 8 weeks after the RIT.
RESULTS: The mean RAIU increased significantly from 30.44 ± 7.4% to 77.22 ± 8.7% ($p < 0.001$). There were no statistically significant differences in RAIU between euthyroid (MNG-EU) and subclinically hyperthyroid (MNG-SC) patients. The peak of serum TSH was noticed 24 hours after rhTSH injection and in MNG-EU patients it has remained within normal range, similarly as fT4. In the MNG-SC group the administration of rhTSH resulted in a significant increase in the TSH values after 24 hours, whose mean level slightly exceeded the upper limit of the normal range with normalization at 48 hours. 8 weeks after the RIT, the TSH and fT4 levels did not exceed the normal range and did not differ in a statistically significant way.
Conclusions: Even the single very low dose of rhTSH increases the values of RAIU in significant way, in euthyroid and subclinically hyperthyroid patients. The administration of rhTSH is well-tolerated. Neoadjuvant administration of a low dose (0.03 mg) of rhTSH before I-131 seems to be an optimal method of management which may increase the effectiveness of RIT and decrease the exposure of the patients to absorbed doses of ionizing radiation.

KEY words: rhTSH, large goiter, multinodular goiter, radioiodine therapy, I-131, radioiodine uptake

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Background

Radioactive iodine (I-131) therapy (RIT) has been a significant part of the treatment of benign thyroid disorders for over 70 years [1]. The main indication for the use of I-131 is hyperthyroidism in the case of adenoma (nodular goiter), multinodular goiter (MNG) and Graves' disease (GD). In nodular goiter, oral administration of

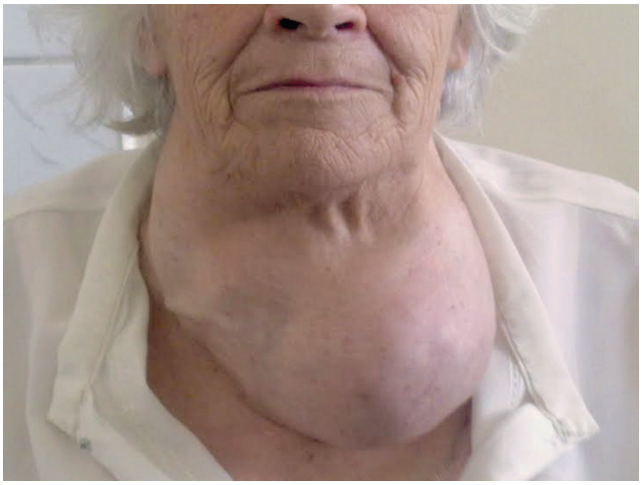

Figure 1. Large MNG (H.M., 71 years old — author's collections)

antithyroid drugs (ATD) is aimed only at appropriate preparation of the patients for RIT, which is performed when malignant lesions have been ruled out. The efficacy of RIT in these cases depends on the patient's condition as well as on appropriate preparation for treatment [1–3].

In GD, RIT is a second-line method of treatment, preferred in the case of ineffective antithyroid therapy or disease recurrence. Taking into consideration the immunosuppressive effects of ATD, the administration lasting at least 1.5 years is associated with an approx. 50% probability of achieving long-term remission [1, 4].

RIT has been increasingly often used in the treatment of patients with MNG (Figure 1). Since I-131 was first used in order to reduce thyroid volume approx. 20 years ago, RIT has been growing in popularity and becoming an attractive alternative to surgical treatment [1, 5–8]. Advanced age and concomitant diseases, such as arrhythmia or circulatory failure, may hinder general anesthesia or constitute a contraindication for thyroidectomy. Due to the fear of undesirable consequences of surgery, many patients do not consent to this type of treatment [8, 9].

Until recently, the administration of L-thyroxine was another conservative method of treatment aimed at reducing the size of the goiter (especially small-sized goiter). Due to the low effectiveness, the lack of permanent effects of the therapy and the presence of adverse effects (e.g. cardiac arrhythmia and osteopenia), it is not currently considered to be a standard method of goiter treatment [1, 9].

The occurrence and development of symptoms associated with thyroid enlargement takes place over a long period of time as the goiter grows gradually, usually at a rate of 0–20% per year. At the early stage of the disease, the patients usually feel well and do not report any problems with their general well-being. As the thyroid increases in volume, local symptoms develop, including the sensation of compression in the neck area, difficulty swallowing, dyspnea associated with tracheal deviation and compression. Cough or hoarseness, associated with the compression of the thyroid tissue on the recurrent laryngeal nerve, are less frequent. In the case of untreated goiter, the probability of hyperthyreosis increases by 10% every five years; hyperthyreosis leads to the development of numerous symptoms associated with other organs and systems [1, 9–11].

Treatment with the use of I-131 leads to a decrease in the goiter volume. Consequently, the compression is eliminated or significantly reduced. This method is non-invasive and well-tolerated by the patients [10].

However, large goiters, especially in patients over the age of 60, may be accompanied by low iodine uptake of the tissue (RAIU) and heterogeneous radioisotope uptake, which has a negative influence on the effectiveness of RIT and results in the need for repeated use of I-131. In such cases, the duration of RIT is extended and the dose of radiation absorbed by the body increases [5, 9, 11, 12].

Recombinant human thyrotropin (rhTSH) is used at a dose of 2 x 0.9 mg in the adjuvant therapy of various thyroid cancers after thyroidectomy. Exogenous thyrotropin increases the iodine uptake in the remains of thyroid tissue and possible distant metastases, allowing for radioactive iodine therapy [13, 14].

There have been reports on the positive influence of rhTSH on the outcomes of RIT in large non-toxic MNG through increasing RAIU and improving the homogeneity of I-131 uptake. Even very low doses of exogenous thyrotropin stimulate thyroid cells and may cause a significant increase in RAIU, thus improving the effectiveness of RIT. Consequently, the use of the first therapeutic dose of I-131 might allow for the reduction of the volume of nodules with a good uptake of the isotope as well as the surrounding overgrown thyroid tissue. However, excessive activation of the remaining thyroid tissue may result in the stimulation of hormone production and release, thus inducing hyperthyroidism and leading to the occurrence of a number of symptoms. So far, a dose of rhTSH effective before RIT and safe in patients with a preserved enlarged thyroid has not been determined [15–17].

The aim of the study was to assess the influence of a single very low dose (0.03 mg) of rhTSH on the iodine uptake and homogeneity of the thyroid uptake of I-131 as well as the thyroid metabolic state in euthyroid (MNG-EU) and subclinical hyperthyroid (MNG-SC) patients with a large nodular goiter.

Material and methods

After obtaining the approval of the Bioethics Committee and written consents of the patients, we started a prospective double-blind randomized study involving 40 subjects. The study enrolled patients who sought medical advice at the Nuclear Medicine Department and met the criteria of the study, according to the order in which they had presented to the clinic. The inclusion criteria were: the presence of non-toxic MNG over 80 ml in volume and RAIU not exceeding 40% at 24 hours after the administration of I-131.

During the first qualification visit, the patients underwent history-taking and physical examination. Considerable importance was placed on the presence and severity of the symptoms, such as compression signs, difficulty swallowing, dyspnea on exertion/at rest, cough, hoarseness. The patients with paroxysmal atrial fibrillation or other severe forms of cardiac arrhythmia and those with chronic obstructive pulmonary disease or asthma were excluded from the study. Pregnancy was ruled out in the women of childbearing age. In order to assess the thyroid metabolic state with radiometric methods, the levels of TSH and free thyroid hormones in the serum were measured. T3-toxicosis and concomitant autoimmune thyroid diseases were ruled out through the determination of thyroid peroxidase antibodies and TSH receptor antibodies.

The assessment of goiter volume was based on a thyroid ultrasound where the total volume of the gland is the sum of the

Table 1. Characteristics of the rhTSH-group and control group

		Total	rhTSH-group	control group	p
No. of patients		40	20	20	
Female		26	12	14	
Male		14	8	6	
Mean age (years)		65	65	65	
MNG-EU	No. of patients	22	10	12	
	Mean level of TSH [uIU/ml]	0.45 ± 0.2	0.48 ± 0.2	0.43 ± 0.2	0.681
	Mean level of fT4 [pmol/l]	18.2 ± 1.6	18.3 ± 1.9	18.5 ± 1.3	0.832
MNG-SC	No. of patients	18	10	8	
	Mean level of TSH [uIU/ml]	0.08 ± 0.06	0.07 ± 0.07	0.09 ± 0.06	0.799
	Mean level of fT4 [pmol/l]	19.6 ± 1.6	19.5 ± 2.2	19.2 ± 1.2	0.712

volumes of both lobes, calculated with the use of the following formula: lobe volume = length x width x depth x 0.5. The data obtained during the ultrasound also provided indirect information concerning the structure and type of the nodules. Chest radiography allowed for the assessment of possible deviation or the degree of compression of the trachea. The patients in whom the width of the trachea (in its narrowest part) was less than 0.5 cm were excluded from the study.

Each patient underwent thyroid scintigraphy with the assessment of the I-131 distribution and RAIU 24 and 48 hours after the oral administration of an I-131 diagnostic capsule with an activity of 2 MBq. Only patients with RAIU less than 40% were included in the study.

The study group consisting of 40 patients was randomly divided into two groups of 20 patients each, i.e. a control group and rhTSH-group (Table 1).

Patients from both groups received intramuscular injections in equal volume (1 cm^3 each). In the control group, the injections contained physiological saline (0.9%) while the patients from the rhTSH-group received a solution of 0.03 mg of rhTSH in physiological saline. The study used recombinant human thyrotropin in the form of Thyrogen (by Genzyme).

Immediately after the injections, both groups again received diagnostic doses of I-131 and underwent another thyroid scintigraphy with the assessment of iodine uptake at 24 and 48 hours.

Next, 48 hours after the administration of rhTSH/placebo, all patients received orally capsules with I-131 with an appropriate therapeutic activity whose value had been calculated on the basis of Marinelli's formula [18], taking into consideration new RAIU values (and the absorbed dose of 180 Gy [1]). Prior to radioactive iodine therapy, the patients underwent obligatory fine needle biopsy of the focal lesions, conducted according to the accepted standards, namely the Polish Recommendations of 2010, based on the standards of the American and European Thyroid Association.

The administered activity of I-131 could not exceed 800 MBq as this is the maximum activity approved for outpatient treatment in Poland. The mean therapeutic activity of I-131 was 715.79 ± 101.45 MBq in the rhTSH-group and 768.42 ± 74.93 MBq in the control group. The therapeutic doses of I-131 used in both groups did not differ in a statistically significant way.

All patients were further followed up. Follow-up visits at 4 and 8 weeks after the administration of radioactive iodine consisted of a physical examination, history-taking and the measurement of TSH and fT4 levels.

The normality of distribution was assessed by the Shapiro-Wilk W-test. Two groups with normal distribution were compared with Student's t-test and a test for two variances. The significance level was set at $\alpha = 0.05$.

The data presented in the present paper are preliminary results of the study in which observations and examinations of patients will be continued for over a year. The study also involves a comparison of the effectiveness of RIT in patients from the rhTSH and control groups through the assessment of the degree of goiter reduction based on the data from history and physical examination and most importantly on the results of the following imaging studies: ultrasound at 6, 12 and 18 months and iodine thyroid scintigraphy at 12 months after the treatment.

Results

After intramuscular injections of 0.03 mg of rhTSH and a repeat thyroid scintigraphy, the RAIU increased very significantly (over two times) from 30.44 ± 7.4% to 77.22 ± 8.7% ($p < 0.001$) (Figure 2). The differences between the mean RAIU before and after the administration of rhTSH were 49.2 ± 6.7% in the MNG-SC group and 44.4 ± 9.5% in the MNG-EU group and did not vary in a statistically significant way ($p = 0.21$) (Table 2, Figure 3).

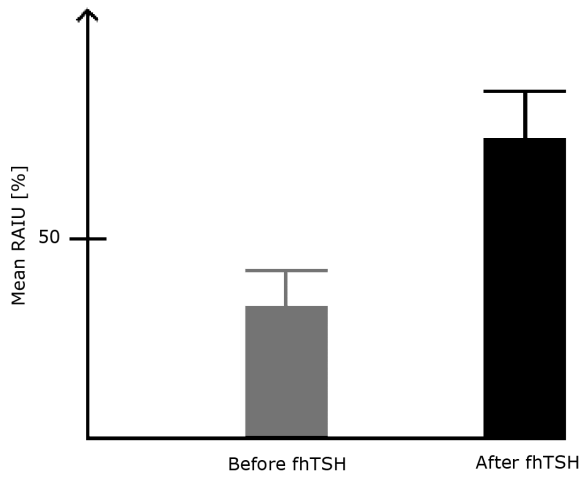

Figure 2. Thyroid uptake of I-131 (RAIU) in the rhTSH-group before and after rhTSH administration

Table 2. Comparison of RAIU in patients with MNG-SC and MNG-EU — rhTSH-group

rhTSH-group	MNG-SC	MNG-EU	p
RAIU before rhTSH (%)	29.5 ± 8.4	31.4 ± 6.4	0.586
RAIU after rhTSH (%)	78.7 ± 8.7	75.8 ± 8.8	0.524
p	< 0.001	< 0.001	

In the control group, the mean RAIU was 29.4 ± 7.5% at baseline; after placebo administration, it slightly changed and was 30.2 ± 7.8% (ns).

In the rhTSH-group, the level of serum TSH increased following the administration of exogenous thyrotropin and peaked at 24 hours after the rhTSH injection. In patients who had been in the euthyroid state at baseline, mean THS values at 24 and 48 hours after rhTSH administration did not exceed the upper limit of the normal range, i.e. 4.5 uIU/ml (Table 3).

In the MNG-SC group, with a decreased mean TSH level of 0.07 uIU/ml at baseline, the administration of an analogous dose of rhTSH resulted in a significant increase in the TSH values, whose mean level slightly exceeded the upper limit of the range considered normal and was 4.97 uIU/ml at 24 hours, undergoing normalization at 48 hours after the administration of thyrotropin. Despite the significant increase in TSH levels in the patients with subclinical hyperthyroidism at baseline, mean thyrotropin levels at 24 hours after rhTSH administration in the MNG-EU and MNG-SC groups did not differ in a statistically significant way. In the control group (both MNG-EU and MNG-SC) the mean serum TSH levels were comparable before and at 24 and 48 hours after the administration of physiological saline (Table 3, Figure 4).

Four weeks after RIT, laboratory tests performed during the first follow-up visit showed a temporary decrease in thyrotropin levels in all patients. Mean TSH values in the MNG-SC patients (from both the control and rhTSH-group) were below the lower limit of the normal range, reaching 0.03 and 0.04 uIU/ml, respectively, while

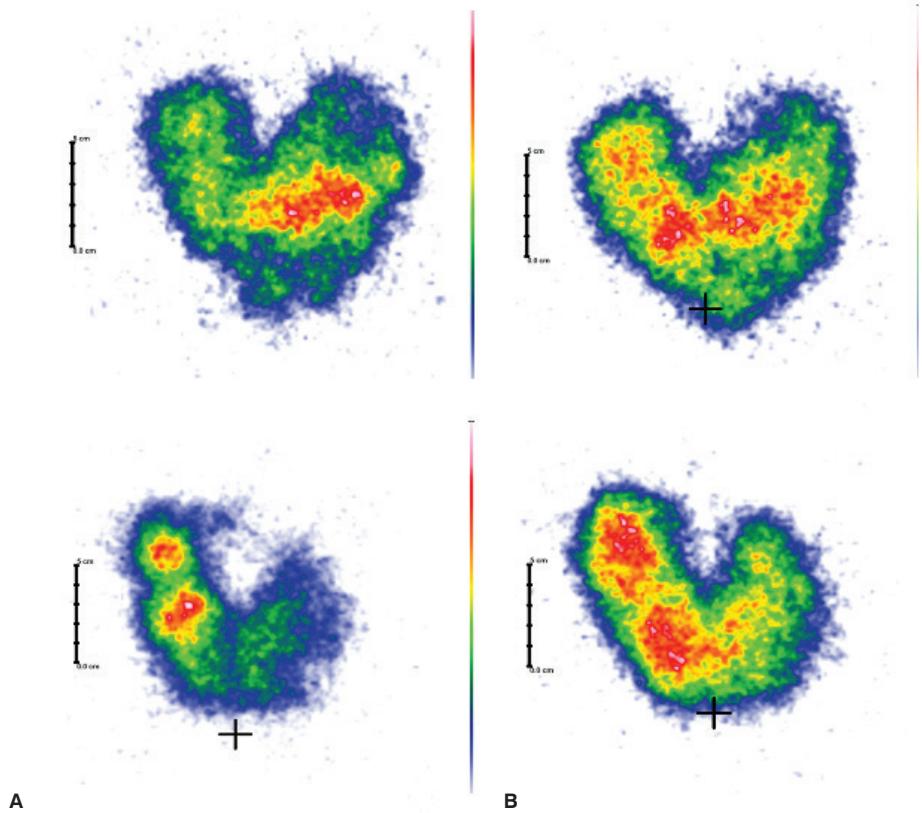

Figure 3. Examples of thyroid scintigraphy images obtained 24 hours after the administration of I-131 with an activity of 2 MBq. **A.** Before rhTSH administration; **B.** 24 hours after rhTSH administration

Table 3. Comparison of mean values of TSH in patients from the rhTSH-group (MNG-SC vs. MNG-EU)

		Serum TSH (uIU/ml)				
		Before rhTSH/placebo	24 h after rhTSH/placebo	48 h after rhTSH/placebo	4 weeks after rhTSH/placebo	8 weeks after rhTSH/placebo
rhTSH-group	MNG-SC	0.07	4.97	1.88	0.04	0.2
	MNG-EU	0.48	4.16	2.09	0.4	0.68
P		p = 0.09	p = 0.048	ns	p = 0.006	p = 0.012

the MNG-EU patients showed values lower as compared with the baseline levels, but within the normal range. During the next follow-up visit, at 8 weeks after RIT, the mean levels of serum TSH were comparable between the groups (rhTSH- and control group), with no statistically significant differences (Table 4, Figure 5).

Elevated TSH levels stimulate the release of fT4 and may result in a worse general condition of the patients. Consequently, the assessment of serum fT4 levels in patients after rhTSH administration was important. As early as at 24 hours after the injection of recombinant thyrotropin, the level of free thyrotropin increased, exceeding the limit of normal values, but fT4 levels exceeded the upper limit of the normal range only slightly. In the MNG-SC group, the mean level of free thyroxine was 23.67 pmol/ml and did not differ in a statistically significant way from the mean values obtained in the MNG-EU group (22.53 pmol/ml; normal range 0.2–22.5 pmol/ml). In the group of patients with subclinical hyperthyroidism at baseline, overt hyperthyroidism was observed also at 48 hours after rhTSH administration, while in the subjects who had been in the euthyroid state at baseline this indicator was normalized (Table 5, Figure 6).

In the control group (both MNG-EU and MNG-SC) the mean serum fT4 levels were comparable before and at 24 and 48 hours after the administration of physiological saline (Table 6, Figure 7).

After the administration of therapeutic I-131 doses in all patient groups, the fT4 levels determined during the follow-up visits at 4 and 8 weeks did not exceed the normal range and did not differ in a statistically significant way (Table 6, Figure 7).

The patients underwent physical examination and history-taking before each assessment of the hormone levels. Physical examination did not show worsening of the patients' state. The patients did not report intensified local symptoms or worrying clinical signs accompanying the temporary increase in free thyroid hormone levels. Regular heart rate of < 100 beats per minute was found in all patients, including those with temporary overt hyperthyroidism. None of the followed-up patients were advised to take additional drugs, including beta-blockers.

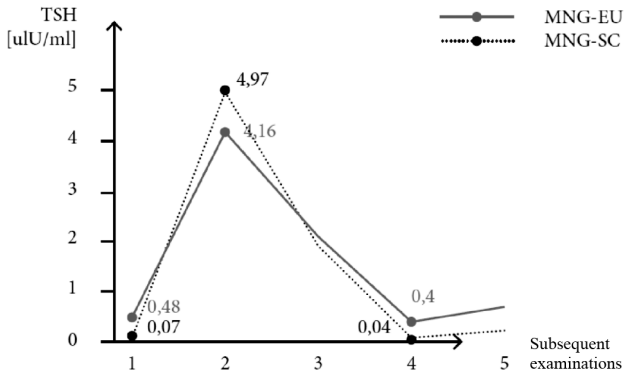

Figure 4. Comparison of mean values of serum TSH in MNG-SC and MNG-EU patients from the rhTSH-group (1. before rhTSH administration, 2. 24 hours after rhTSH administration, 3. 48 hours after rhTSH administration, 4. 4 weeks after rhTSH administration, 5. 8 weeks after rhTSH administration)

Discussion

Despite the fact that RIT has been used in the treatment of thyroid diseases for over 70 years, some authors still consider it to be an unreliable method producing no satisfying results in the case of non-toxic nodular goiter [5, 6, 19, 20]. First reports on

Table 4. Comparison of mean values of TSH in patients from the rhTSH-group and control group

		Serum TSH [ulU/ml]				
		Before rhTSH/placebo	24 h after rhTSH/placebo	48 h after rhTSH/placebo	4 weeks after rhTSH/placebo	8 weeks after rhTSH/placebo
MNG-SC	rhTSH-group	0.07	**4.97**	**1.88**	0.04	0.2
	control group	0.08	**0.09**	**0.08**	0.02	0.35
p		ns	**p = 0.000**	**p = 0.009**	ns	ns
MNG-EU	rhTSH-group	0.48	**4.16**	**2.09**	0.4	0.68
	control group	0.43	**0.45**	**0.44**	0.21	0.5
p		ns	**p = 0.012**	**p = 0.024**	ns	ns

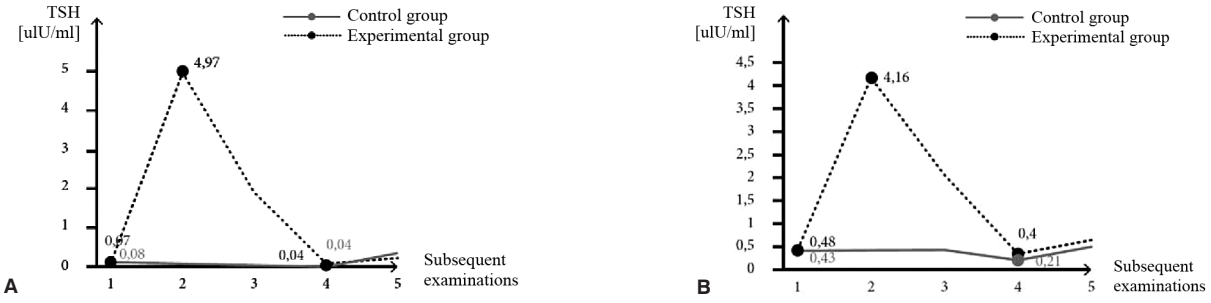

Figure 5. Comparison of mean values of serum TSH in patients from the rhTSH-group and control group (1. before rhTSH administration, 2. 24 hours after rhTSH administration, 3. 48h after rhTSH administration, 4. 4 weeks after rhTSH administration, 5. 8 weeks after rhTSH administration). **A.** MNG-SC; **B.** MNG-EU

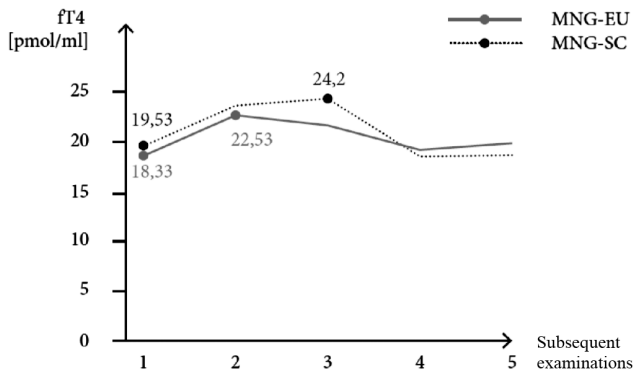

Figure 6. Comparison of mean values of serum fT4 in MNG-SC and MNG-EU patients from the rhTSH-group (1. before rhTSH administration, 2. 24 hours after rhTSH administration, 3. 48 h after rhTSH administration, 4. 4 weeks after rhTSH administration, 5. 8 weeks after rhTSH administration)

non-invasive attempts at reducing goiter volume with I-131 were published at the beginning of the 1990s [21, 22]. They suggested the possibility of treating older patients with multiple systemic diseases who were disqualified from invasive treatment. Since then RIT of non-toxic goiter appears to have been growing in popularity. However, a questionnaire conducted among the members of the American Thyroid Association and concerning the preferred methods of treatment of non-toxic goiter > 50 g in size showed that only 1% of the specialists chose RIT as a first-line method of treatment [6]. The members of the European Thyroid Association gave similar answers. However, in the Latin American countries the percentage was 7% [19]. Publications describe promising outcomes achieved after the use of radioactive iodine in the treatment of euthyroid goiter. The degree of reduction in the volume of the goiter varies from 30% to 60% in different centers and depends on the characteristics of the study group, particularly on the size of the goiter. The smaller the goiter, the easier it is to achieve a larger

Table 5. Comparison of mean values of fT4 in patients from the rhTSH-group (MNG-SC vs. MNG-EU)

		Serum fT4 [pmol/ml]				
		Before rhTSH/placebo	24 h after rhTSH/placebo	48 h after rhTSH/placebo	4 weeks after rhTSH/placebo	8 weeks after rhTSH/placebo
rhTSH-group	MNG-SC	19.53	23.67	24.2	18.5	18.6
	MNG-EU	18.33	22.53	21.55	19.1	19.8
P		ns	ns	p = 0.032	ns	ns

Table 6. Comparison of mean values of fT4 in patients from the rhTSH-group and control group

		Serum fT4 [pmol/l]				
		Before rhTSH/placebo	24 h after rhTSH/placebo	48 h after rhTSH/placebo	4 weeks after rhTSH/placebo	8 weeks after rhTSH/placebo
MNG-SC	rhTSH-group	19.53	23.67	24.2	18.5	18.6
	control group	19.21	**19.81**	**19.54**	22.65	21.45
p		ns	**p = 0.039**	**p = 0.031**	ns	ns
MNG-EU	rhTSH-group	18.33	**22.53**	**21.55**	19.1	19.8
	control group	18.49	**18.23**	**18.45**	21.65	19.44
p		ns	**p = 0.048**	**p = 0.049**	ns	ns

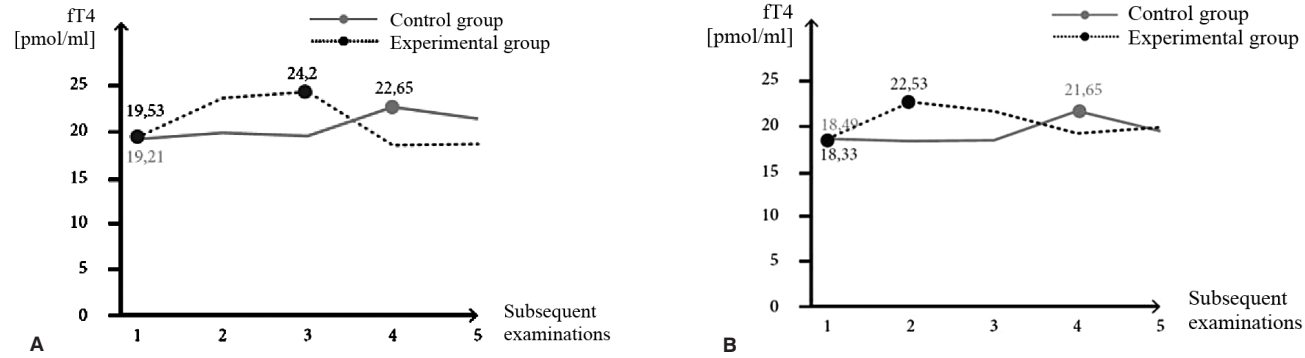

Figure 7. Comparison of mean values of serum fT4 in patients from the rhTSH-group and control group (1. before rhTSH administration, 2. 24 hours after rhTSH administration, 3. 48 hours after rhTSH administration, 4. 4 weeks after rhTSH administration, 5. 8 weeks after rhTSH administration). **A.** MNG-SC; **B.** MNG- EU

reduction in its volume even at low doses of I-131 [5, 19, 22, 23]. This results in considerably better effectiveness of the therapy as compared with conservative treatment with LT4 (and a lower risk of adverse effects as compared with conservative treatment). As societies age, the number of elderly patients with concomitant diseases affecting e.g. the circulatory and respiratory systems, in whom surgical treatment of non-toxic goiter is not performed, is constantly growing. Nevertheless, the occurrence of local symptoms caused by an enlarged thyroid requires the treatment, not just conducting observations [5]. The use of LT4 is impossible due to comorbidities and the administration of I-131 becomes a method of choice. Thyroid scintigraphy in patients over the age of 60 often shows low RAIU values accompanying large goiters [15, 17, 24–26]. Consequently, a single administration of a maximum dose usually does not result in the desired outcomes and the treatment requires the administration of consecutive doses of I-131, which prolongs the duration of the therapy and has a negative influence on the satisfaction with the treatment. Moreover, the irradiation of the body increases. This is why factors which could safely improve the effectiveness of RIT are constantly sought [27]. Thyrotropin is a hormone which has a positive effect on iodine uptake and radiosensitivity of thyroid tissue [28]. Increased levels of TSH also improve the homogeneity of I-131 uptake in a multinodular goiter. Descriptions of first attempts at using recombinant human thyrotropin as an adjunct in radioactive iodine therapy of MNG can be found in the literature. However, the study groups described are very heterogeneous in terms of numerous significant factors influencing the course and results of the treatment, such as the size of the goiter, iodine uptake of the thyroid tissue, thyroid metabolic state, and particularly the patterns of patient preparation and rhTSH administration. Many of the studies were not randomized and had no control groups and the majority of the publications described study groups consisting of no more than 20 patients.

Nevertheless, according to the above-mentioned paper [6], when selecting I-131 for the treatment of non-toxic MNG more than 50% of the respondents suggested the wish to use rhTSH as neoadjuvant therapy.

Human thyrotropin is routinely used as an adjunct to the treatment of differentiated thyroid cancer in the form of two 0.9 mg injections. A dose of 2 x 0.9 mg is considered safe and does not result in adverse effects such as hyperthyroidism as the patients have had their thyroid glands surgically removed [29]. The administration of exogenous thyrotropin in a patient with preserved thyroid whose size considerably exceeds the normal range may result in the induction of hyperthyreosis, which has a negative impact on the patient's condition, particularly in the case of elderly patients with numerous comorbidities. There is no consensus as to the dose of rhTSH used before the administration of I-131. The studies described so far have used doses from 0.005 mg to 0.9 mg. The injections have been performed once, 2–24 hours before the administration of I-131, or twice, at an interval of 24 hours [26, 30–34].

In our study, after the use of a single low dose of rhTSH (0.03 mg) the 24-hour RAIU increased by 144% in the MNG-EU group and by 166% in the patients with MNG-SC. There were no significant differences in iodine uptake before and after the administration of thyrotropin between the patients in the euthyroid and subclinical hyperthyroid state. One report described a significant increase in RAIU (by 87%) after the administration of a very low dose of rhTSH (0.01 mg) and the use of a 3 times higher rhTSH dose (0.03 mg) resulted in further stimulation of RAIU (by 145% as compared with the baseline values) [35]. Other authors observed RAIU increasing by 40–91% after the administration of 0.03 mg of exogenous thyrotropin [24, 25]. Romao et al. administered 0.1 mg of rhTSH and achieved a 111% increase in RAIU. The degree of stimulation of RAIU in this study was lower than in our case. After intramuscular administration of 0.1 mg of rhTSH performed twice (over two consecutive days) the mean RAIU increased from the baseline 35% only to 45% [36]. Only Albino et al. found a significantly higher (as compared with other studies) increase in RAIU as it grew 4.5 times after 0.1 mg of thyrotropin was administered twice [30]. In other papers, authors suggested the use of 0.45 mg of rhTSH, achieving a 151% increase in iodine uptake [37]. Torres et al. injected 0.9 mg of exogenous thyrotropin and found only a 75% increase in the 24-hour I-131 uptake; however, this study was conducted in healthy volunteers and should not be compared with the outcomes obtained in MNG patients [38]. RAIU values achieved after the administration of various doses of exogenous thyrotropin allow for conclusions regarding a threshold value of the dose of rhTSH above which there is no further significant increase in iodine uptake. Moreover, no significant differences were found in the values of uptake in MNG patients after the administration of 0.1 mg as compared with 0.3 mg of rhTSH [33]. In addition, scintigraphy performed 24 hours after the administration of rhTSH shows improved homogeneity of uptake, which partially translates to the above-mentioned RAIU increase [25, 39]. Increased iodine uptake not only in the nodules with a good uptake of the isotope, but also in the extranodular tissue or nodules whose previous I-131 uptake was low may result in a higher degree of goiter volume reduction after the use of radioiodine in therapeutic activities [35, 40]. Our results and previous reports do not indicate the necessity of using an rhTSH dose higher than 0.03 mg in order to achieve a significant increase in RAIU. A single low dose of 0.03 mg increases the 24-hour I-131 thyroid uptake over two times, not inducing long-term hyperthyreosis but only a slight excess of the upper limit of the reference range of fT4 levels (only in patients with subclinical hyperthyroidism).

In one of the first studies on the effects of rhTSH in healthy volunteers, the administration of 0.9 mg of thyrotropin resulted in a considerable increase in thyroid hormone levels, with a 61% increase in T4 and 81% increase in T3 levels [41]. In another study, an analogous dose of TSH was also administered in subjects with a healthy thyroid and the level of free hormones fT4 and fT3 increased by 207% and 230%, respectively [42]. In both studies, the hormone release was induced after the value of TSH reached over 70–200 uIU/ml. Torres et al. were also one of the first to study the effect of rhTSH on the thyroid metabolic state of healthy volunteers in whom thyroid hormone levels increased nearly two times after the administration of 0.9 mg of rhTSH [38]. In this study, the authors suggested the use of lower doses of thyrotropin. After intramuscular administration of 0.1 mg of rhTSH, the level of T4 increased by 54% and that of T3 grew by 89%. A dose of 0.3 mg caused T4 induction similar to that after the administration of 0.9 mg; in the case of T3, the increase was even larger. This might suggest the existence of a threshold rhTSH dose; exceeding the dose does not result in larger induction of the production of free thyroid hormones. These studies on the response of a healthy

thyroid to the administration of rhTSH confirmed the necessity of seeking a new lower dose of rhTSH to be used in MNG radioactive iodine therapy. Romao et al. used an intramuscular dose of 0.1 mg of TSH and found the maximum level of TSH 24 hours after the administration of rhTSH (12 uIU/ml on average); the group treated included not only euthyroid patients, but also ones with subclinical and overt hyperthyroidism [43]. Despite the use of antithyroid drugs, the increase was significantly higher in the patients with increased baseline free hormone levels; consequently, the frequency of adverse effects typical of overt hyperthyroidism was higher in patients with overt hyperthyroidism at baseline (60.4%) than the euthyroid patients (17.8%). The authors also advise against using rhTSH in patients with subclinical hyperthyroidism in connection with a 31% frequency of side effects. In another paper, a dose of 0.2 mg was administered twice in euthyroid patients, resulting in temporary overt hyperthyroidism lasting 14 days, which is not desirable in elderly patients, particularly ones with concomitant circulatory disorders [25]. Consequently, the authors suggest routine preventive symptomatic treatment [25, 31, 44]. Studies with patients aged 42–80 years showed that a single dose of 0.1 mg of rhTSH induces hyperthyroidism, which increases the risk of left-sided diastolic heart failure three times [45]. In another group, a dose of 0.1 mg administered twice caused tachyarrhythmia in two patients [17]. In our patients, the administration of a single very low dose of 0.03 mg of rhTSH caused a 24% increase in free thyroxine levels in patients with subclinical hyperthyroidism at baseline and a 23% increase in those with MNG-EU. In the MNG-SC group, mean fT4 values only slightly exceeded the upper limit of the normal range at 48 hours after the administration of rhTSH and the first follow-up visit after the use of I-131 showed their normalization. The patients did not undergo antithyroid drug therapy before or after RIT. A dose of 0.03 mg of rhTSH seems to be safe both in patients who were in the euthyroid state at baseline and those with subclinical hyperthyroidism and the mean values of free hormones do not indicate the necessity for obligatory use of additional drugs in order to prevent possible side effects, as it was suggested in the papers cited. Additional administration of beta-blockers or other drugs having symptomatic effects, facilitating the treatment of hyperthyroidism, should be considered individually for each patient.

Many authors stress the necessity of exercising special caution during the use of rhTSH, not only due to the risk of adverse effects associated with hyperthyreosis, but also in connection with the possible occurrence of temporary goiter enlargement caused by the physiological effect of thyrotropin, which stimulates thyroid cells and increases their size, thus increasing the thyroid gland. Another factor influencing an increase in the size of the thyroid may be inflammation of the tissue occurring in some patients after the use of I-131, which may also cause temporary pain [17, 33, 46, 47]. Bonnema et al. studied 29 patients with goiters 99–440 ml in volume and found significantly more frequent side effects after the administration of 0.3 mg of rhTSH as compared with the control group; only two patients required the use of corticosteroids, which resulted in the expected improvement [31]. In another Italian center, all patients treated with rhTSH received obligatory steroids in order to avoid complications associated with temporary thyroid enlargement [17, 26]. Other authors also described cases of a temporary increase in goiter volume, occurring in as many as 24% of the patients treated with a neoadjuvant dose of 0.3 mg of thyrotropin [35]. The volume of the goiter at 24 hours after the injection increased by approx. 10%, at 48 hours by 24% and returned to the normal size after 7 days in 9 out of 10 followed-up patients. In the case of a dose of rhTSH equal to or lower than 0.03 mg, no statistically significant cases of goiter enlargement were found.

Conclusions

A single intramuscular injection of a very low dose (0.03 mg) of recombinant human thyrotropin considerably increases the degree and homogeneity of RAIU in large multi-nodular goiter, both euthyroid and subclinically hyperthyroid. The administration of rhTSH is well-tolerated and leads to similar outcomes in patients with subclinical hyperthyroidism and euthyroid individuals. Neoadjuvant administration of a low dose (0.03 mg) of rhTSH before I-131 seems to be an optimal method of management which may increase the effectiveness of RIT and decrease the exposure of the patients to absorbed doses of ionizing radiation. However, prior to recommending such administration, the effects of RIT should be thoroughly analyzed over at least one year of follow-up.

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