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REVIEW

An outline concerning the potential use of recombinant human thyrotropin for improving radioiodine therapy of multinodular goiter

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Abstract Radioiodine (^{131}I) treatment for nontoxic and toxic multinodular goiter (MNG) is an alternative therapeutic procedure used especially for patients with contraindication for surgery. Several studies have been conducted in recent years assessing the use of recombinant human TSH (rhTSH) in increasing ^{131}I uptake in MNGs. This procedure also decreases the activity level of the administered ^{131}I, changes the distribution of ^{131}I in the thyroid, lowers the absorption dose, and dramatically reduces the volume of the goiter (50–75% of the baseline volume). A major disadvantage, however, is the induction of hypothyroidism in a relatively large number of patients. A transient increase in thyroid volume and tenderness was noted in the first week of treatment. Also a short period (2–4 weeks) of hyperthyroidism was observed in most patients with potential consequences particularly for the elderly. Still, there has been no evidence to date that the adverse effects outweigh the positive results of using rhTSH. The use of rhTSH in benign goiter disease has not yet been approved worldwide, but its positive activity in MNG is remarkable and promising.

Keywords Radioiodine · Recombinant TSH · Multinodular goiter · Hyperthyroidism · Hypothyroidism

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Introduction

The therapeutic management of nontoxic multinodular goiter (MNG) is highly controversial [1]. Thyroid surgery and levothyroxine suppressive therapy are considered treatments of choice in several countries [2]. Levothyroxine suppressive therapy has been increasingly disfavored due to low efficacy and potential risks for bone loss and atrial fibrillation [3]. Surgery efficiently reduces the goiter size, but is associated with greater short-term morbidity than radioiodine (^{131}I) therapy [4]. Nevertheless, ^{131}I was largely used in the past to reduce thyroid volume in patients with nodular or diffuse goiter when surgery was not feasible.

Patients with nontoxic MNG require treatment when compressive symptoms are present. These symptoms can include dysphagia, odynophagia, and feeling of throat compression. Additionally, patients may present with extrathoracic airway obstruction, resulting in impaired airflow. The treatment of choice is usually thyroidectomy, but ^{131}I has been occasionally employed with significant reduction in thyroid volume and amelioration of symptoms and signs of compression. Data have consistently demonstrated that virtually all patients ultimately develop decrease in goiter size and improvement in compressive symptoms after therapy with ^{131}I [3, 5–12]. Studies have shown a mean thyroid volume reduction of ~40% within the first year after ^{131}I therapy—mostly during the first 3 months—and 50 to 60% reduction after 3–5 years [7, 8, 11]. Previous published experience showed that treatment response is directly proportional to the administered ^{131}I dose and inversely related to the initial goiter size [13]. Nodular or diffuse nontoxic goiters display a rather low and irregular radioiodine uptake (RAIU), mainly in areas with high dietary iodine intake, requiring a relatively

higher dose of ^{131}I to obtain a significant reduction in thyroid volume [7, 8, 11]. Therefore, it is of interest to explore new strategies to augment ^{131}I concentration by nodular goiters, but with reduced radiation exposure, to enhance thyroid volume reduction.

Recombinant human TSH (rhTSH) has been shown to be effective in increasing RAIU by the normal thyroid gland [14] and clinical studies have confirmed that rhTSH can be safely used for therapeutic purposes [15].

Origin and biological properties of rhTSH

TSH is a glycoprotein hormone that contains about 15% carbohydrate and is composed of two noncovalently linked peptide subunits—an alpha and a beta subunit. The alpha subunit is similar to that of the follicle-stimulating hormone, luteinizing hormone, and chorionic gonadotropin. The beta subunit is unique and thus determines the hormone's biological specificity. The carbohydrate structure does, however, differ between natural human TSH and recombinant human TSH.

The assessment of the ability of the thyroid tissue to increase accumulation of iodide in response to TSH elevation can be performed by radioiodine uptake followed by scintiscan after withdrawal of thyroid hormone therapy for about 4 weeks or by exogenous bovine TSH administration in cancer patients previously thyroidectomized [16]. Several factors, however, have discouraged the use of this heterologous hormone, including the occurrence of allergic reactions and loss of potency after repeated administration, caused by production of TSH antibodies that neutralizes its action [17, 18]. As a result, human TSH extracted from cadavers was tested [19], but further abandoned after occurrence of Creutzfeldt-Jakob disease associated with use of pituitary human growth hormone [20]. Once the beta subunit of the human TSH was cloned, the encoded protein could be overexpressed in a cell system (Chinese hamster ovary cells) by transfection with human alpha and beta subunits of genomic DNA [21, 22]. This technique allowed the obtainment of high quantities of rhTSH with similar biological properties of native TSH and made the extensive use of exogenous TSH possible. The currently available rhTSH agent has a biological potency of about 4 IU/mg [23].

RhTSH has an amino acid structure identical to human pituitary TSH. However, its glycosilation is somewhat different because it is produced in a nonhuman cell line. In rat studies, it has been shown that the metabolic clearance rate of rhTSH is significantly reduced when compared with that of human TSH. This is probably because rhTSH is highly sialylated, in contrast to the sulfated forms of human TSH. In this respect, rhTSH more closely resembles human TSH found in prolonged primary hypothyroidism, which is also highly sialylated and has a lower metabolic clearance rate [23].

The effects of rhTSH on thyroid function were initially tested in in vitro model systems. In a human fetal thyroid cell system, rhTSH is able to activate the TSH receptor and induce secretion of thyroglobulin (TG) and proliferation of thyroid epithelial cells [24]. Several animal studies were conducted to evaluate the pharmacological and toxicological potentials of rhTSH. These trials included single-dose and repeat-dose studies in primates—Cynomolgus and Rhesus monkeys [21, 25]—and rodents [26, 27]. After a single injection of rhTSH in Cynomolgus monkeys, a rapid clearance phase half-life of 35 min is followed by a post-distribution clearance phase half-life of 9.8 h [21]. Braverman et al. [25] confirmed this effect of rhTSH in humans. In addition to a significant stimulation of T4 and T3 secretion, a doubling of the 6- and 20-h thyroid ^{123}I-uptakes were observed in Rhesus monkeys following 3 daily intramuscular injections of 2 units ($\sim$0.4 mg) of rhTSH. It has also been demonstrated that rhTSH increases serum T4 in mice pretreated with T3 to achieve suppression of endogenous TSH. This response was used as the basis for development of a TSH bioassay [26, 27]. Colzani et al. [27] found that rhTSH is a potent stimulator of T4 secretion in mice, but produces little or no change in serum T4 levels in normal, untreated rats. Using a similar protocol as East-Palmer et al. [26] the response to rhTSH was again tested in rodents pretreated with T3 with resulting significant increase in serum T4 levels, probably due to suppressed endogenous TSH secretion.

The effects of rhTSH in normal human subjects

The first study to examine rhTSH response in healthy subjects evaluated 6 normal volunteers free of clinical or laboratory features of thyroid disease after a single 0.1 mg intramuscular injection of rhTSH. The response was a rapid increase in serum T3 and T4 levels (54% and 89%, respectively) within 4 to 8 h after the injection, with peak levels at 24 h. Serum TG levels peaked at 48 h and returned to baseline about 3 days later [28]. The expected elevation in serum TSH levels also occurred rapidly, with peak levels at 4 h and a plateau that lasted for 1 day. After 3 weeks, all changes in hormone levels were normalized. Stimulation of thyroid function by rhTSH was also evident when assessed by RAIU. Using the same study design as Ramirez et al. [28], Torres et al. [14] measured RAIU before and after a single 0.9 mg dose of rhTSH in 5 normal individuals. The RAIUs varied widely, ranging from 22 to 300%, with an average doubling after rhTSH administration. These investigators [14] also tested the effect of higher doses of rhTSH on thyroid hormone secretion.

Doses of 0.3 and 0.9 mg produced qualitatively similar changes in serum T3, T4, and TG when compared with 0.1 mg. Quantitatively, T4 and T3 responses to 0.3 and 0.9 mg of rhTSH were similar, but greater than those observed after 0.1 mg.

The enhanced RAIU that follows rhTSH administration has also been observed in individuals pretreated with sodium iodide, a RAIU inhibitor [29]. Lawrence et al. [29] measured the changes in 16-h RAIU following rhTSH 0.9 mg administered 8 or 32 h before ^{123}I. Thyroid RAIU increased by a mean of 62% and 97% at 8 and 32 h, respectively, confirming the importance of time interval between rhTSH stimulation and the effect obtained. However, rhTSH was unable to normalize thyroid RAIU after iodide administration, since there was only a mean increase to 6% (from 3%), compared with 19% before iodide ingestion. Another study, which determined the optimal time for ^{131}I administration after 0.1 mg rhTSH, showed that marked increases in RAIU occurred when ^{123}I was given 24 h after rhTSH administration to euthyroid volunteers. There were smaller increases when ^{123}I was given 48 h later and no increase when given 72 h after rhTSH [30].

The effects of 0.9 mg rhTSH on thyroid function and volume were further investigated in nine healthy euthyroid male subjects [31]. Thyroid RAIU was higher when compared with baseline when it was given 24 h after rhTSH administration, but the increment was lower at 48 h and absent at 72 h. Mean thyroid volume increased by 23% at 24 h after rhTSH stimulation, and by 35% at 48 h. After 4 days, however, mean thyroid volume had reverted to baseline values. The authors in this study indicate the need of further dose–response studies to clarify potential hazard effects before routine use in the context of ^{131}I therapy and goiter. Together, these studies demonstrate that rhTSH can mimic endogenous human TSH in its ability to stimulate thyroid function and RAIU by thyroidal cells as well as increase TG levels (Table 1).

The use of rhTSH for improving ^{131}I therapy of nontoxic multinodular goiter

Increased uptake and goiter volume reduction

In recent years, pretreatment with rhTSH has been used in patients with MNG, which typically have only a fraction of the normal RAIU, to increase ^{131}I uptake in the goiter and allow treatment with lower doses of ^{131}I to induce thyroid volume reduction [32–34]. Accordingly, in a study of 15 patients with nontoxic MNG, pretreatment with a single low dose of rhTSH (0.01 or 0.03 mg 24 h before ^{131}I administration) resulted in a doubling of RAIU [35]. In addition, the single dose of rhTSH caused a more homogeneous distribution of ^{131}I by stimulating more uptake in relatively cold areas than in hot areas, particularly in patients with low serum TSH levels [36].

Various studies have demonstrated the effect of rhTSH on ^{131}I therapy for MNG. Twenty-two patients with MNG were treated with ^{131}I 24 h after administration of 0.01 or 0.03 mg rhTSH [32]. In this study, the dose of ^{131}I was

Table 1 Effect of recombinant human TSH on thyroid function, thyroid radioiodine uptake, and thyroid volume in normal subjects

No. of subjects	Dose of rhTSH (mg)	Peak increase in serum thyroid hormones (%)	Peak increase in serum thyroglobulin (%)	Time interval between rhTSH and radioiodine (^{123}I or ^{131}I)	Thyroid RAIU mean increase (%)	Thyroid volume mean increase (%)	Study (references)
6	0.1			NI	NI	NI	Ramirez et al. [28]
6	0.1	T4: 54 T3: 89	NI	NI	NI	NI	Torres et al. [14]
6	0.3	T4: 94 T3: 136	1035	NI	NI	NI	
6	0.9	T4: 99 T3: 99	1890	24 h	6 h RAIU: 116 24 h RAIU: 78	NI NI	
9§	0.9	T4: 61 T3: 81	NI	8–32 h	16 h RAIU: from 3 to 6 (baseline 18)	NI	Lawrence et al. [29]
9	0.9	Free T4: 207 Free T3: 230	1230	NI	NI	After 24 h: 23 After 48 h: 35	Nielsen et al. [31]
5	0.1	T4: 57 T3: 84	186	24 h	24 h RAIU: 88	After 48 h: 10	Pena et al. [30]
10	0.1			48 h	24 h RAIU: 36		
10	0.1			72 h	24 h RAIU: none		

NI, not investigated; §, under iodine excess; RAIU, radioiodine uptake; adapted from [15]

adjusted to the increase in uptake induced by rhTSH, aimed at 100 μCi/g thyroid tissue retained at 24 h. Pretreatment with 0.01 and 0.03 mg rhTSH resulted in reductions in the ^{131}I dose by a factor of 1.9 and 2.4, respectively. One year after treatment, there was a reduction in thyroid volume of 35% and 41% in the two groups, respectively. Despite delivering a good therapeutic response, the administration of ^{131}I 100 μCi/g of thyroid tissue corrected for 24-h RAIU raises concerns of irradiation of the surrounding neck structures and potential risk for stomach, bladder, and breast cancer, which have been reported after ^{131}I therapy for toxic nodular goiter [37–39]. In another study [33], 16 patients with MNG were treated with a fixed dose of ^{131}I (30 mCi) 72 h after pretreatment with 0.3 mg rhTSH, or 24 h after pretreatment with 0.9 mg rhTSH. The two regimens were equally effective, leading to a 30 to 40% reduction in thyroidal volume at 3 to 7 months.

As mentioned, rhTSH was administered 24 h before ^{131}I therapy in most studies. However, results from a study published by Duick and Baskin [34] suggest that the time interval may be even longer to achieve a maximum stimulation of the thyroid RAIU.

Tracheal compression and pulmonary function

Many elderly patients have significant intrathoracic extension of the MNG, which may cause tracheal compression with subsequent airflow reduction (Figs. 1, 2). Bonnema et al. [12] evaluated upper airway obstruction by flow volume loops in 23 patients with very large goiter. In 1/3 of the patients, there was impairment of the forced inspiratory flow at 50% of the vital capacity (FIF50%). The authors found a significant correlation between FIF50% and the smallest tracheal cross-sectional area (Fig. 3). Reduction of the MNG volume after high dose of ^{131}I had a remarkable effect in enlarging tracheal cross-sectional area and consequently improving inspiratory capacity in these patients.

Transient hyperthyroidism after ^{131}I ablation

Other studies using different doses of rhTSH and showing comparable RAIU increases with lower doses, demonstrated significant goiter reduction, but also transient hyperthyroidism after ^{131}I therapy [40–43]. A study in which 34 patients with large MNGs were randomized to receive ^{131}I therapy

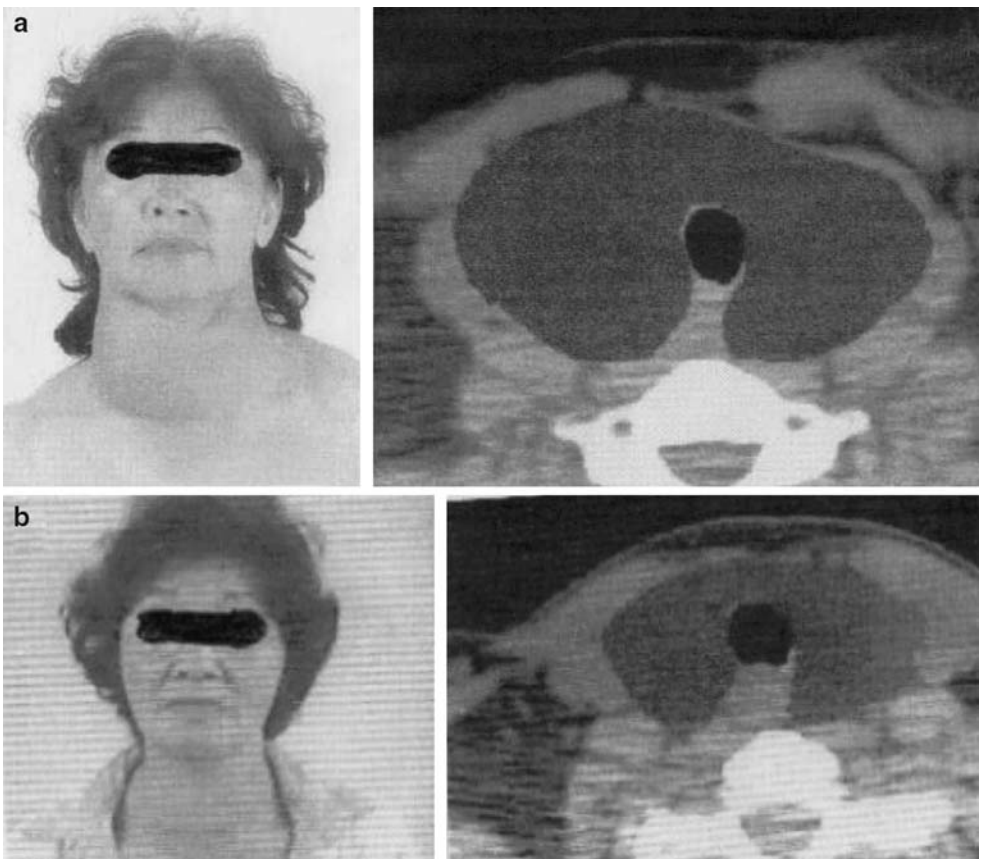

Fig. 1 (**a**) Patient JSS, F, 61 years old with a goiter volume at baseline of 320.4 cm^3 and overt hyperthyroidism. (**b**) The same patient after 36 months of radioiodine preceded by rhTSH with normal thyroid tests and a reduced thyroid volume (to 86.4 cm^3). Details about clinical and laboratory data may be found in Table 1, patient #18 in Ref. [50]

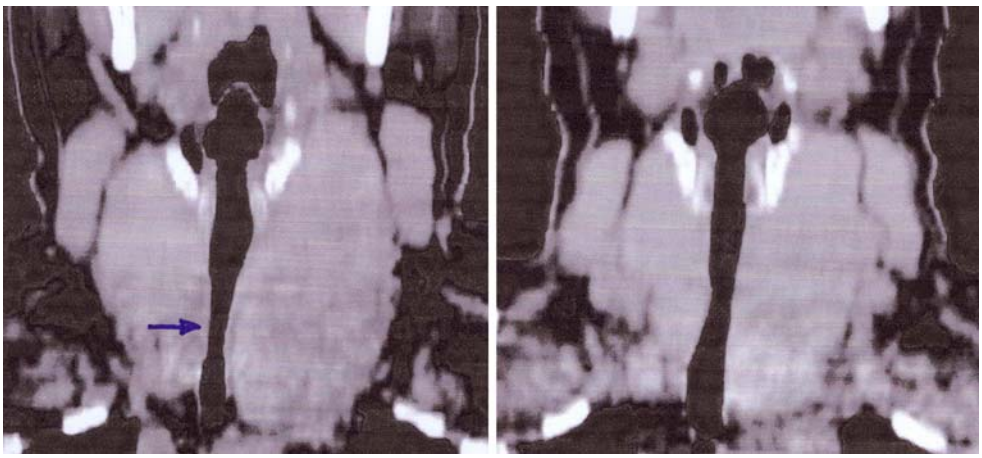

Fig. 2 Reconstruction in coronal plan before (left panel) and two years after rhTSH and RAI ablation (right panel). Note the decrease of thyroid volume and marked relief of tracheal compression. (Courtesy of Eloisa Gebrin, M.D., Department of Radiology, University of São Paulo Medical School)

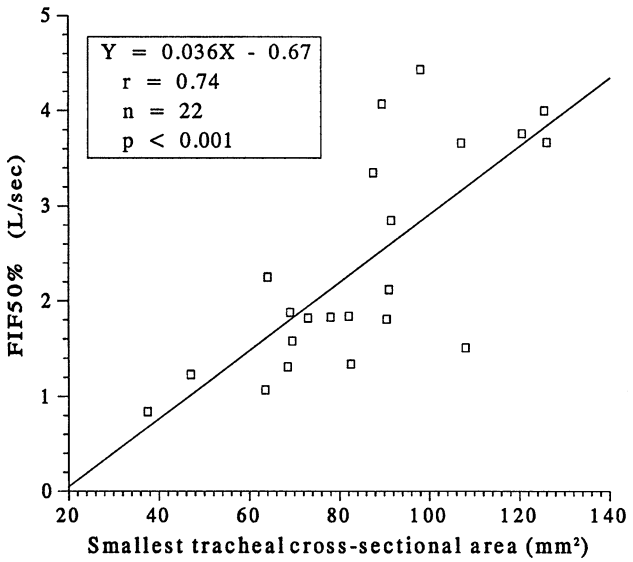

Fig. 3 Correlation between forced inspiration flow at 50% of pulmonary vital capacity (FIF50%, L/sec) and the smallest cross-sectional area of trachea before RAI ablation in patients with very large multinodular goiters. The tracheal cross-sectional area significantly increased from 84.3 ± 4.8 mm^2 to 98.2 ± 26 mm^2. Consequently, there was a concomitant increase in FIF50% values. (reprinted from Bonnema et al. [12] with permission from The Endocrine Society, J Clin Endocr & Metabolism)

(100 μCi/g of thyroid tissue) alone or following a single relatively high dose of rhTSH (0.45 mg) 24 h before ^{131}I administration, showed that patients who received rhTSH had transient elevations in thyroid hormone levels lasting one week, a greater reduction in goiter size (60% vs. 40%), and a higher incidence of hypothyroidism (65% vs. 21%) (40). In another study, 18 patients received two 0.1 mg doses of rhTSH followed by 30 mCi of ^{131}I. RAIU increased from 12 to 55%, free T4 increased from 1.3 to 3.2 ng/dL, and goiter size reduced from 97 to 65 cm^3. However, about 30% of the patients experienced painful thyroiditis and 39% had mild hyperthyroidism [41]. In a randomized trial of ^{131}I treatment calculated to deliver a thyroidal absorbed dose of 100 Gy (10 mrads) and administered 24 h after rhTSH (0.3 mg) or placebo, patients with MNG (mean goiter volume of 55 cm^3) who received rhTSH had more symptoms of hyperthyroidism and neck pain during the first week after treatment, a greater reduction in goiter size (52% vs. 46%), and a higher frequency of hypothyroidism (62% vs. 1%) [34]. Using a similar study design, Bonnema et al. [43] compared the effects of rhTSH (0.3 mg) or placebo, followed by a maximum dose of ^{131}I 100 mCi on goiter volume reduction in 29 patients with very large goiters (median volume of 160 cm^3). After 12 months, the median goiter volume (monitored by magnetic resonance imaging) was reduced by 34% in the placebo group and by 53% in the rhTSH group. In the placebo group, the goiter reduction correlated positively with the retained thyroid ^{131}I dose, whereas this relationship was absent in the rhTSH group. Adverse effects, mainly related to thyroid pain and cervical compression, were more frequent in the rhTSH group. At 12 months, goiter-related complaints were significantly reduced in both groups without any between-group difference. One patient in the placebo group and three patients in the rhTSH group developed hypothyroidism.

Recently, an uncontrolled study demonstrated the effect of rhTSH (0.1 mg, single dose) followed by ^{131}I 30 mCi 24 h later in 17 patients with MNG (mean thyroid volume of 106 cm^3). Pretreatment with rhTSH resulted in a mean RAIU increase from 18 to 50% and an increase in free T4 of 55% at 24 h. Mean T3 levels increased by 86% and peaked at 48 h, and median TG levels increased about 600% and peaked on the fifth day. Symptomatic tachycardia was promptly relieved with β-blocker administration. After 12 months, mean thyroid volume measured by computed tomography had reduced by 46%. The adverse effects observed were transient hyperthyroidism

(17.6%), painful thyroiditis (29.4%), and hypothyroidism (52.9%) (42) (Table 2).

Degree of goiter reduction, ^{131}I dose, and rhTSH

Most investigators [42] could not find any correlation of thyroid volume reduction with post-rhTSH RAIU, area under the curve of TSH, basal thyroid volume, or effective activity of ^{131}I. Also, in the placebo-controlled study by Bonnema et al. [43], no significant correlation was found, in either the placebo group or the rhTSH-treated group, between the degree of goiter reduction and the initial goiter size. However, in the placebo group, there was a correlation ($r = 0.74$) between the degree of goiter reduction and the retained ^{131}I thyroid dose, an observation in agreement with previous reports [13, 34]. At variance, Albino et al. [41] found a positive correlation ($r = 0.68$) between the degree of goiter volume reduction and the effective activity of administered post-rhTSH ^{131}I dose. This issue, therefore, needs further clarification, but overall, these studies suggest that goiter reduction may be dependent on other factors caused by rhTSH prestimulation and not only on the applied ^{131}I thyroid dose. For example, rhTSH could induce reactivation of inactive thyroid tissue or render the thyrocytes more vulnerable to ionizing radiation [43]. Generally, the dose of ^{131}I in these studies ranged from 75 to 400 μCi/g tissue, and most patients received doses between 100 and 200 μCi/g, similar to those used to treat hyperthyroidism.

Increase in goiter size immediately after ablation

It is worth mentioning the possibility of increase in goiter size with rhTSH. In a study of 10 patients with MNG who were given 0.3 mg of rhTSH, it was shown that 24 h after rhTSH, the mean goiter volume increased by 9.8% and after 48 h, by 24%, reverting to baseline at 1 week. This suggests that rhTSH may lead to significant cervical compression in patients with near obstructive goiters, when used for improving ^{131}I therapy in patients with goiter [44]. All side effects related to acute thyroid enlargement causing tenderness and dyspnea due to possible obstruction of tracheal airway were promptly resolved with corticosteroid therapy.

Radioactive iodine and rhTSH in the elderly with hyperthyroidism

Treatment with ^{131}I following rhTSH stimulation is also an attractive alternative in elderly patients considered poor surgical candidates or who refuse surgery. The prevalence of MNG rises in the elderly, a population in whom comorbities prevail [45]. Of even greater concern in iodine repleted areas is the development of subclinical or overt hyperthyroidism, since thyroid hyperfunction may increase the mortality risk in these patients [46]. An Italian study assessed 20 elderly patients with large goiters and compared treatment with ^{131}I (10 to 15 mCi fixed dose) following two consecutive 0.2 mg doses of rhTSH ($n = 12$; 3 patients had subclinical hyperthyroidism with TSH <0.3 μU/ml) with treatment with ^{131}I alone ($n = 8$; subclinical hyperthyroidism recorded in 5). Patients who received rhTSH had higher transient elevations in free T4 and free T3 lasting 2 weeks, a greater reduction in goiter size (44% vs. 25%). Both groups had a 17% incidence of hypothyroidism ~2 years after ^{131}I therapy. Symptomatic relief occurred in all but 1 patient following rhTSH with a 50% median reduction on thyroid volume after about 2 years [47]. In study conducted by our group, 17 elderly subjects with MNG received treatment with ^{131}I 24 h after pretreatment with 0.45 mg rhTSH and were compared with 17 elderly controls treated with ^{131}I alone. In patients pretreated with rhTSH, serum TSH and T3 levels rose to a peak level in 24 h, returning to normal at 72 h. Serum free T4 concentrations rose significantly at 48 h returning to normal at 7 days. Serum TG increased and remained elevated during the following 12 months. Patients pretreated with rhTSH had a 58% reduction in goiter volume when compared with 40% in patients treated with ^{131}I alone. Hypothyroidism was more frequent in pretreated patients (65% versus 21% in non-pretreated) after 1 year. No symptoms of hyperthyroidism were observed in these patients [40]. Four years after ^{131}I therapy, additional thyroid volume reduction was similar for patients treated with rhTSH prior to ^{131}I or with ^{131}I alone, but it was significantly more pronounced in the rhTSH group, mainly in the first year. Although no additional benefit of rhTSH was observed after a long follow-up, the initial difference in thyroid volume reduction was maintained, denoting the advantage of using rhTSH pretreatment to achieve higher thyroid volume reduction during the first treatment [48] (Table 2).

In another report of a short-term observational study, the investigators assessed the efficacy of a low-dose (0.03 mg) rhTSH stimulation on a fixed therapeutic activity of ~30mCi ^{131}I in 17 patients with large nodular goiters (12 with overt or subclinical hyperthyroidism/TSH <0.5 μU/ml and five on treatment with thionamides) [49]. RAIU increased from 26% to 43%, free T4 increased from 1.4 to 2.0 ng/dL, and goiter size decreased from 170 to 113 cm^3 by 6 months. Symptomatic relief, improved well-being and/or reduction, or elimination of antihyperthyroid drug was seen in 76% of the patients. However, 3 (18%) patients presented transient neck pain or tenderness, 1 experienced asymptomatic thyroid enlargement, and 3 became hypothyroid by 3 months (Table 2).

Table 2 Studies on the effect of recombinant human TSH on goiter reduction in multinodular goiter patients

No. of subjects	Dose of rhTSH (mg)	Time interval between rhTSH and radioiodine (^{123}I or ^{131}I)	Therapeutic dose of ^{131}I (mCi)	Peak increase in thyroid hormones (%)	Goiter reduction (%)	Time of follow-up	Goiter size estimation (Methods)	Remarks	Study (references)
12	0.01	24 h	~39 (mean)	Free T4: 47 Free T3: 41	35	1 year	MRI	0.01 mg: ^{131}I activity reduced by a factor 1.9	Nieuwlaat et al. [32]
10	0.03	24 h	~23 (mean)	Free T4: 52 Free T3: 59	41			0.03 mg: ^{131}I activity reduced by a factor 2.4; Hypothyroidism: 36%	
6	0.3	72 h	30	NI	NI	7 months	Palpation	0.3 mg: increase in 4 h RAIU 72 h after rhTSH: from 3.9 to 17	Duick & Baskin [33]
10	0.9	24 h	30	NI	30–40			0.9 mg: remission of compressive symptoms in 69% Hypothyroidism: 56%	
17	none		~96 (mean)	Free T4: 34 T3: 33	40	1 year	CT	^{131}I: Hypothyroidism: 23%	Silva et al. [40]
17	0.45	24 h	~90 (mean)	Free T4: 594 T3: 73	58			^{131}I + rhTSH: Hypothyroidism: 64%; hyperthyroidism: 100%	
18	2 × 0.1	24 h	30	Free T4: 146 T3: 191	39	6 months	CT	24 h RAIU increased from 12–53%; Hypothyroidism: 65%; hyperthyroidism: 39%	Albino et al. [41]
8	none		NM	NM	25	20 months	US + CT		Giusti et al. [47]
12	2 × 0.2	24 h	NM	Free T4: 290* Free T3: 340*	44	22 months	US + CT		
17	0.03	24 h	~30	Free T4: 46 T3: 33	34	6 months	CT	24 h RAIU increased from 26% to 43%; Hypothyroidism: 18%; hyperthyroidism: 18%	Cohen et al. [49]
29	none		14 (median)	NM	46	1 year	US	^{131}I: 24 h RAIU decreased from 32 to 29; Hypothyroidism: 11%; hyperthyroidism: 21%	Nielsen et al. [44]
28	0.3	24 h	~16 (median)	NM	62			^{131}I + rhTSH: 24 h RAIU increased from 34 to 47; Hypothyroidism: 62%; hyperthyroidism: 36%	
15	none	24 h	~42 (median)	NM	34	1 year	MRI	^{131}I: hypothyroidism: 7%	Bonnema et al. [43]
14	0.3		~38 (median)	NM	53			^{131}I + rhTSH: hypothyroidism: 21%	
17	0.1	24 h	30	Free T4: 56 T3: 87	46	1 year	CT	24 h RAIU increased from 18 to 50%; Hypothyroidism: 53%; hyperthyroidism: 18%	Paz-Filho et al. [42]

* Calculated; NM, not mentioned; NI, not investigated; MRI, magnetic resonance imaging; CT, computerized tomography; US, ultrasonography; adapted from [15].

Cardiovascular events after RAI ablation

Cardiovascular parameters to detect transient elevation of serum thyroid hormones were evaluated in 27 of 42 patients (age range 42–80 years) with large MNGs who were treated with rhTSH before receiving ^{131}I 30 mCi [50]. All patients presented a transient surge in serum levels of free T4 and total T3 into the hyperthyroid range following therapy. However, post-treatment cardiovascular evaluation did not show significant changes when compared with baseline evaluation, suggesting that treatment of MNGs with RAI after rhTSH stimulation does not affect structural and functional parameters of the heart. These findings are reassuring, particularly when considering treatment for older adults with comorbidities that preclude surgery.

Thyroid autoantibodies occurrence after ^{131}I therapy

Some studies have reported the development of thyroid antibodies associated with ^{131}I therapy [9, 41, 51]; however, a direct cause-effect linking to rhTSH has not been demonstrated. These observations have been interpreted as an immunological response caused by the release of thyroid antigens from destroyed follicular cells [51]. In a study published by our group, we found that rhTSH pretreatment had no significant effect in the development of antibodies (TSH receptor and TPO) when compared with treatment with ^{131}I alone [52].

Conclusions and comments

Given the limited experience published in the literature so far, before considering the routine use of rhTSH administration before ^{131}I treatment of MNG, several issues must be taken into consideration:

- ^{131}I treatment alone can lead to a 15–25% transient increase in thyroid volume during the first week after treatment [1];
- RhTSH administration alone occasionally can lead to a significant increase, albeit transient, in thyroid volume, of up to 100% in normal subjects within 48 h [53];
- The combination of the two modalities may lead to a substantial acute increase in thyroid volume;
- ^{131}I treatment of MNG leads to transient hyperthyroidism during the first 2 weeks after therapy and the combination with rhTSH administration can enhance this effect, with potential consequences particularly for the elderly patients [32, 40];
- The optimal dose of rhTSH for pretreatment of MNG remain to be determined. Studies have used different doses and regimens of rhTSH administration, from as low as 0.01 or 0.03 mg to as high as 0.45 mg or 0.9 mg 24 h before RAI treatment;
- There is a significant occurrence of hypothyroidism after ^{131}I treatment following rhTSH stimulation;
- Although rare, autoimmune hyperthyroidism (approximate reported incidence of 4–5%) can develop after treatment of MNG with ^{131}I [51, 54];
- Currently, rhTSH is not approved by the FDA as an adjuvant for ^{131}I treatment of goiter.

Based on these results, pretreatment with rhTSH seems a promising alternative to thyroid surgery for the management of nontoxic MNG, particularly in elderly individuals. However, the optimal dose and timing of both rhTSH and ^{131}I as well as the criteria for patient eligibility remain to be determined.

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