Recombinant human TSH and radioactive therapy in the management of benign multinodular goiter

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Short title: rhTSH before $^{131}$I in benign nodular goiter
Keywords: Goiter, rhTSH, radioactive iodine
Word count for the abstract: 247
Abstract
Multinodular goiter (MNG) is a very common thyroid disorder associated with diverse goitrogenic factors, the most important being iodine deficiency. The clinical presentation of a patient with MNG can vary from a completely asymptomatic goiter to a life-threatening disease due to upper airway compression. Subclinical or overt hyperthyroidism can evolve due to autonomously hyperfunctioning nodules. In the absence of clinical, sonographic or cytological findings suggestive of malignancy, the selection of the best therapeutic option for a patient with MNG will depend on the size and location of the goiter, the presence and severity of compressive symptoms, and the presence or absence of thyrotoxicosis. There is still no consensus in terms of atoxic MNG treatment and its optimal management remains controversial; therapeutic options include levothyroxine (LT4), surgery and radioiodine. Suppressive treatment with LT4 is discouraged due to the possible risk of causing sub-clinical or overt hyperthyroidism and its low efficacy when compared with surgery or radioiodine (\(^{131}\)I). Total thyroidectomy is an effective treatment, but carry the risk of surgical complications and is often refused by the patient. \(^{131}\)I therapy is an alternative to thyroid surgery to reduce the size of benign MNGs. During the last decade, and based on the ability of recombinant human thyrotropin (rhTSH) to more than double thyroid \(^{131}\)I uptake (RAIU), this compound has been evaluated as an adjuvant to \(^{131}\)I in the treatment of MNG. Very small doses of rhTSH have been used in patients with MNG and few safety concerns have been observed.
Introduction

Radioiodine ($^{131}$I) was introduced almost three decades ago for the treatment of Multinodular Goiter (MNG) (1). Since then, $^{131}$I have have shown to be safe and effective (2, 3), resulting in significant thyroid volume (TV) reduction when compared with levothyroxine suppressive therapy, which offered no benefit (4), and improvement in obstructive symptoms (dyspnea, dysphagia) in the majority of patients (5, 6). Radioiodine treatment reduces MNG volume in approximately 40% after one year and by 50–60% after 2–5 yr (4, 5, 6, 7, 8, 9). Nonetheless, the therapeutic efficacy of radioiodine in patients with MNG depends to some extent on the radioactive iodine uptake (RAIU). Frequently, MNGs have a low and heterogeneous RAIU, requiring high $^{131}$I activities (10). The administration of recombinant human TSH (rhTSH) prior to $^{131}$I has been shown to be a potentially valuable therapeutic tool for the management of MNG (11, 12, 13, 14, 15, 16, 17, 18, 19, 20). rhTSH in a low single dose increases $^{131}$I uptake by two to fourfold and homogenizes RAIU (21, 22). The effect of rhTSH on RAIU allows the administration of lower $^{131}$I activities, with similar therapeutic effects as higher $^{131}$I activities without rhTSH prestimulation, and with lower exposure of extrathyroidal tissues to radiation. When usual $^{131}$I activities are administered after rhTSH, greater TV reduction have been observed; 33% to 62% TV reduction when rhTSH plus $^{131}$I are administered compared to 13% to 46% when placebo and the same $^{131}$I activities are given (14, 16, 17, 19, 23, 24). Overall, It has been shown that rhTSH doses lower than 0.1 mg do not cause acute increases in TV or thyroid hormone levels (25). When given 24 hours prior to the administration of fixed or calculated $^{131}$I activities, rhTSH is a safe and efficacious adjunct therapeutic approach that allows the administration of lower $^{131}$I activities (23)

Approach to the patient with MNG

MNG is defined as the enlargement of the thyroid gland, in the absence of autoimmune thyroid disease, malignancy or inflammation, and associated with more than one nodule identified clinically, sonographically or surgically. Presence of symptoms or signs of compression within the neck, concern for coexisting thyroid cancer, substernal or retrosternal extension or need for rapid
correction of the thyrotoxic state are factors that favor surgery as the treatment modality (26). Factors weighing against the choice of surgery include significant comorbidity such as cardiopulmonary disease, or other debilitating disorders. In other cases, the patient or patient’s family refuse the surgery. During more than seven decades, $^{131}$I therapy has been used to treat thyroid diseases, mainly Graves’ disease. Radioactive iodine, not only showed to cure hyperthyroid patients, but also resulted in shrinkage of the thyroid gland. Due to the effect on the gland volume, $^{131}$I has been used in the treatment of compressive nontoxic nodular goiters. In 1988, Hegedüs et al., using sonography, demonstrated for the first time that $^{131}$I treatment of nontoxic MNG lead to significant goiter volume reduction after 1 year (1). A number of studies, using ultrasonography, computed tomography, or magnetic resonance imaging for accurate measurements of thyroid volume, have shown that radiiodine therapy in patients with nontoxic, nodular goiter results in a mean reduction in thyroid volume of approximately 40% after 1 yr (1, 3, 5) and of 50–60% after 3–5 yr (3-9, 27) with improvement in obstructive symptoms in the majority of patients (5, 6). The improvement in compressive symptoms is accompanied by significant tracheal widening, as measured by magnetic resonance imaging (5), and improvement in respiratory function (28). The amount of $^{131}$I administered depends on thyroid weight and RAIU. Doses of approximately 100mCi [3.7 megabecquerels (MBq)] radioiodine/g thyroid tissue corrected for RAIU at 24 h were usually given (27). As patients with nontoxic nodular goiter usually have a rather low and heterogeneous RAIU, they require high doses of radiiodine activities (10), causing considerable irradiation of extrathyroidal organs and tissues (29), leading to hospitalization and isolation (27) in most cases. Therefore, there was interest to explore strategies to enhance RAIU in these patients. The administration of a single, low dose of rhTSH considerably increased RAIU in patients with nodular goiter (21). A dose of 0.01 mg rhTSH given 24 h before $^{131}$I administration increased 24-h RAIU from 29 to 51%, while 0.03 mg rhTSH increased 24-h RAIU from 33 to 63% (21). A single, low dose of rhTSH not only doubled 24-h radioactive iodine uptake but also caused a more homogeneous distribution of $^{131}$I within the thyroid gland in patients with a nodular goiter by stimulating $^{131}$I uptake in relatively cold areas more than in relatively hot areas (22). It has been shown that pretreatment with a single, low dose of recombinant human TSH allows dose reduction of $^{131}$I in patients with
nodular goiter (30). $^{131}$I therapy after pretreatment with a single low dose of rhTSH in patients with nodular goiter resulted in a TV reduction 1 yr after therapy, of 35% in the group pretreated with 0.01 mg rhTSH and of 41% in the group pretreated with 0.03 mg rhTSH. This was accompanied by an increase of the smallest cross-sectional area of the tracheal lumen (SCAT) of 17% and 44%, respectively (30).

**Recombinant human TSH (rhTSH) use in MNG**

In patients with toxic MNG (TMNG) medical management before $^{131}$I therapy should be tailored to the patient based on the severity of the hyperthyroidism, patient age, and comorbid conditions. Worsening of hyperthyroidism with increased heart rate and rare cases of supraventricular tachycardia, including atrial fibrillation, have been observed in patients treated with $^{131}$I for TMNG or MNG (31, 32). Therefore, the use of beta-blockers to prevent post-treatment tachyarrhythmias should be considered in all patients with TMNG who are older than 60 years of age and those with cardiovascular disease or severe hyperthyroidism (33). Pretreatment with methimazole prior to radioactive iodine therapy for TMNG is indicated in patients who are at increased risk for complications due to worsening of hyperthyroidism, including elderly and those with cardiovascular disease or severe hyperthyroidism (34). rhTSH doubles or increases even more the thyroid RAIU (11, 15, 35, 36, 37), depending on the baseline RAIU, and results in a more homogeneous distribution of $^{131}$I in MNG (22). During the last decade, and based on the above observations, rhTSH has been evaluated as an adjuvant to $^{131}$I therapy, in an attempt to improve the efficacy of this treatment for MNG (11, 38, 39). Different rhTSH doses have been utilized; in some studies 0.2 mg or more (40, 41, 42, 43, 44, 45, 46), while in others 0.1 mg or less (14, 17, 20, 23, 30, 47). Since the introduction of rhTSH as an aid for $^{131}$I therapy in MNG, nine randomized controlled trials (RCT) have been published (13, 14, 16, 17, 19, 23, 24, 40, 41). Despite variations in population characteristics, groups with different patient numbers, sampling size, different rhTSH agents and dosages, radiotherapy methods, outcome analyses, and methodological biases, all RCTs have shown the superiority of rhTSH before radiiodine therapy over radiiodine alone to reduce goiter volume. Soon after the demonstration that rhTSH was an excellent adjunct therapeutic approach for
patients with MNG treatment that allowed the administration of lower $^{131}$I activities (21) we began to use it in different, safe and efficacious dosages. Our first study employed two consecutive doses of rhTSH prior to TSH (15). Because the goiter size was highly variable in our study and we used a fixed $^{131}$I activity (30 mCi; 1.11 MBq), we calculated the retained thyroid $^{131}$I activity and determined correlations with the volume reduction of the goiter. We were able to show a positive correlation between the radiation dose to the thyroid and the decrease in thyroid volume at 6 months (Fig. 1) (15). About one third of our patients receiving 0.2 mg rhTSH developed mild thyrotoxic symptoms controlled easily by the administration of a beta-blocking agent (15). In an attempt to lessen the adverse effects, the second study employed just 0.1 mg rhTSH (20). All patients with a low and heterogeneous RAIU showed an increase and homogeneous RAIU (Fig. 2) (48). Thyroid volume was significantly reduced by 46.0 ± 14.6% after 1 year. A typical example of goiter shrinkage is shown in figure 3 (48). After rhTSH administration, RAIU significantly increased from 18.1 ± 9.7 to 49.6 ± 13.4%. The ratio between post- and pre-rhTSH RAIU (RR) was calculated to indicate the fold increase in uptake in response to rhTSH. Median RR was 2.6 (1.2 to 9.2). There was an inverse correlation between RR and the pre-rhTSH $^{131}$I 24-h uptake ($r = -0.613$, $P = 0.009$), indicating that patients with lower basal uptake values achieved higher RR values. Fast et al (49) also demonstrated in a multicentric study that patients with baseline RAIU < 20% achieved a greater reduction in goiter size using MRrhTSH. Modified Release rhTSH (MRrhTSH) is equipotent to rhTSH for increasing thyroid RAIU but resulting in a lower peak plasma TSH concentration. Potentially, MRrhTSH could reduce side effects due to altered pharmacokinetics, with a delayed time to reach the maximum TSH concentration as compared with aqueous rhTSH (19). Our third study compared two different rhTSH doses (0.005mg and 0.1mg) with one placebo group (17) followed by a fixed 30mCi (1.11 GBq) activity. We demonstrated that a very low dose of 0.005 mg rhTSH was equally safe and effective as 0.1 mg rhTSH. Both doses increased the efficacy of radiiodine (15). In a multicentric RCT we compared two different MRrhTSH doses (0.01 mg and 0.03 mg) versus placebo (19). In this study a modified-release (MRrhTSH) was used. The study showed that the threshold for efficacy seems to be around 0.03 mg rhTSH, at which dose there are just minor safety concerns (19).
Side effects of rhTSH use in MNG

Sensation of thyroidal swelling can occur, but no acute compressive effects have been observed with 0.3 mg rhTSH (24). In patients with very large goiters (median volume 160 mL), a 24% transient goiter volume increase was reported to occur 24 hours after 0.3 mg of rhTSH (40). Adjunct therapies with very small doses of rhTSH (0.01 to 0.03 mg) have been evaluated in both euthyroid and hyperthyroid patients with MNG and few safety concerns have been observed (19, 20). However, one study showed that hyperthyroid patients had higher increases in thyroid hormone levels after 0.1 mg rhTSH plus radioiodine, with a higher frequency of side effects (46). Currently, the rhTSH adjunct therapy is not indicated in patients with toxic MNG (34). In patients with critical tracheal narrowing, prophylactic glucocorticoid therapy should be considered to prevent rhTSH and radioiodine-related swelling and further respiratory compromise (34). Painful transient thyroiditis may occur within the first month after treatment. Development of Graves’ hyperthyroidism (with high levels of TSH receptor antibodies) in patients with preexisting high thyroid peroxidase antibody concentrations has also been described after treatment of euthyroid MNG with RAI (50). It is important to mention that the adjunct therapy of MNG with rhTSH and $^{131}$I is not approved by the FDA or EMEA. Also, the cost-effectiveness of combined rhTSH has not been demonstrated. As an alternative to rhTSH, two recent studies showed that, in patients with MNG, methimazole-induced hypothyroidism increases endogenous TSH levels, augmenting RAIU and allowing the administration of more effective activities of radioiodine (51, 52). Until now, there has no published study comparing the efficiency and safety of exogenous TSH versus endogenous TSH.

Concluding remarks

When radioiodine therapy is preceded by recombinant human TSH (rhTSH), there is an increase in goiter volume shrinkage in patients with MNG compared to radioiodine treatment alone. This effect has been shown in short term as long term studies. It is still unknown what are the patients who respond better to rhTSH. Currently the lowest efficacy dose of rhTSH is around 0.03 mg. Studies comparing exogenous with endogenous TSH are still needed to clarify the benefits and colateral
effects of each treatment. It should be emphasized that rhTSH-stimulated $^{131}$I therapy is still an off-label treatment for MNG.

Declaration of interest

The author declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements

The author thanks to Cesar Luiz Boguszewski for his support in preparing this review

References


25. Fast S, Nielsen VE, Bonnema SJ, Hegedüs L. Dose-dependent acute effects of recombinant human TSH (rhTSH) on thyroid size and function: comparison of 0.1, 0.3 and 0.9 mg of rhTSH. Clin Endocrinol (Oxf). 2010;72:411-416.


42. M. Giusti, C. Cappi, B. Santaniello, E. Ceresola, C. Augeri, C. Lagasio, F. Minuto, Safety and efficacy of administering 0.2 mg of recombinant human TSH for two consecutive days as an adjuvant to therapy with low radioiodine doses in elderly outpatients with large multinodular goiter. Minerva Endocrinol. 2006 31 191–209.


FIGURE LEGENDS

Fig.1. Significant positive correlation between the degree of goiter volume reduction and the effective uCi/g activity of administered $^{131}$I ($r = 0.676, P = 0.002$).

Fig 2. Scintigraphy before (A) and 24 hours after the administration of rhTSH 0.1 mg in a single dose (B). Besides making the uptake of $^{131}$I more homogeneous, rhTSH increased the 24-hour uptake from 4.5 to 39.3%.

Fig 3. An example of goiter reduction. Computerized tomography with multiplanar reconstruction of a patient with multinodular substernal goiter treated with 30 mCi (1.11 MBq) radioiodine after 0.1
mg rhTSH. A1 and A2: Baseline (thyroid volume 147 ml); B1 and B2: 1 year after reatment (thyroid volume 42 ml).
FIGURES.

Figure 1

**Effective uCi/g dose of 131-I and goiter reduction**

- Correlation coefficient: $r = 0.676$
- Significance level: $p = 0.002$

Graph shows a positive correlation between the dose of 131-I in uCi/g and goiter reduction percentage.
Fig. 2
Fig. 3