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Correlation between thyroid volume and humoral thyroid autoimmunity after radioiodine therapy in Graves' disease

Zależność pomiędzy objętością gruczołu tarczowego a stężeniem przeciwciał przeciwtarczycowych w chorobie Gravesa–Basedowa po terapii radiojodem

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Abstract

Background: Graves' disease is an autoimmune disorder with the presence of TSH receptor autoantibodies (TRAb). TRAb are produced mainly by lymphocytes infiltrating the thyroid gland. The aim of this study was to investigate the influence of the reduction of thyroid volume (TV) on TRAb level after radioiodine (RAI) administration in a group of patients with Graves' disease.

Material and methods: A retrospective chart review of 36 patients with Graves' disease (age range 18–67 yrs; Me 46 yrs; mean age ± SD 43 yrs ± 13.0 yrs) treated with RAI administration (the mean dose of RAI ± SD was 46.1 mCi ± 21.7 mCi) was performed. Data concerning TV, TRAb, TSH, and fT4 was collected immediately before administration of radioiodine and 18–36 months thereafter. Data was collected before the first administration of RAI and 18–36 months after the last administration of RAI for patients treated with repeated doses of RAI.

Results: Before treatment, mean male (n = 4) TV was 27.9 ml ± 9.6 ml and mean female (n = 32) TV was 20.6 ml ± 12.7 ml. Mean TV was 2.4 ml ± 1.7 ml (males) and 5.3 ml ± 10.9 ml (females) after therapy. There was an extremely significant difference between mean TV before RAI administration and after 18–36 months. There was an extremely significant difference between the mean serum level of TRAb before and 18–36 months after RAI therapy. No significant correlation between percentage reduction of TV and percentage reduction of serum level of TRAb was found.

Conclusions: 1. Decrease of thyroid gland volume after radioiodine therapy is followed by a significant decrease of the level of TRAb after 18–36 months. 2. TRAb concentration is positively correlated with thyroid gland volume. 3. Percentage reduction of TRAb is not correlated with percentage reduction of thyroid volume. **(Pol J Endocrinol 2012; 63 (1): 10–13)**

Key words: *Graves' disease, hyperthyroidism, TSH-receptor autoantibodies, iodine radioisotopes*

Streszczenie

Wstęp: Choroba Gravesa–Basedowa jest autoimmunologicznym zaburzeniem z obecnością przeciwciał przeciwko receptorowi dla TSH (TRAb, *TSH receptor autoantibodies*). TRAb są wytwarzane głównie przez limfocyty naciekające gruczoł tarczycowy. Celem pracy było zbadanie wpływu redukcji objętości tarczycy po terapii jodem radioaktywnym na stężenie TRAb w grupie pacjentów z chorobą Gravesa i Basedowa.

Materiał i metody: Przeprowadzono retrospektywną analizę dokumentacji medycznej 36 pacjentów z chorobą Gravesa–Basedowa (przedział wieku 18–67 lat; Me 46 lat, śr. wiek ± SD 43 lata ± 13,0 lat) leczonych jodem radioaktywnym (RAI, *radioiodine*) (śr. dawka I^{131} ± SD 46,1 mCi ± 21,7 mCi). Dane dotyczące objętości tarczycy (TV, *thyroid volume*), TRAb, TSH, fT4 zostały zebrane przed podaniem jodu radioaktywnego oraz 18–36 miesięcy po podaniu. W przypadku pacjentów leczonych powtórnymi dawkami RAI dane zostały zebrane tuż przed podaniem pierwszej dawki oraz 18–36 miesięcy po podaniu dawki ostatniej.

Wyniki: Przed podaniem RAI średnia objętość tarczycy wśród mężczyzn (n = 4) wynosiła 27,9 ml ± 9,6 ml, a wśród kobiet (n = 32) 20,6 ml ± 12,7 ml. Średnie objętości tarczycy 18–36 miesięcy po terapii wynosiły odpowiednio wśród mężczyzn i kobiet 2,4 ml ± 1,7 ml oraz 5,3 ml ± 10,9 ml. Stwierdza się istotną statystycznie różnicę między początkową objętością tarczycy oraz objętością gruczołu 18–36 miesięcy po leczeniu jodem radioaktywnym. Znajduje się istotną statystycznie różnicę między początkowym stężeniem TRAb oraz stężeniem TRAb 18–36 miesięcy po leczeniu radiojodem. Nie stwierdza się istotnej statystycznie korelacji pomiędzy procentową redukcją objętości tarczycy oraz procentową redukcją stężenia przeciwciał przeciwko receptorowi dla TSH.

Wnioski: 1. Istotne statystycznie zmniejszenie stężenia TRAb następuje po redukcji objętości tarczycy w wyniku terapii jodem radioaktywnym. 2. Stężenie TRAb wykazuje związek z objętością gruczołu tarczycowego. 3. Procentowa redukcja stężenia TRAb nie jest skorelowana z procentową redukcją objętości tarczycy. **(Endokrynol Pol 2012; 63 (1): 10–13)**

Słowa kluczowe: *choroba Gravesa–Basedowa, nadczynność tarczycy, przeciwciała przeciwko receptorowi TSH, izotopy jodu promieniotwórczego*

Introduction

TSH receptor autoantibodies are used to diagnose Graves' disease (GD), to differentiate GD from other variants of autoimmune hyperthyroidism, and to monitor therapeutic effects (after antithyroid drug treatment, thyroidectomy or radioiodine). TRAb predict relapse of hyperthyroidism in GD [1]. TRAb play a role in the pathogenesis of Graves' orbitopathy (GO) [2], and the frequency of GO increases with high TRAb serum level

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[3]. TRAb serum level is correlated with the severity and activity of GO [4, 5].

TSHR antibodies are produced mainly by lymphocytes infiltrating the thyroid gland [6]. Extrathyroidal circulating lymphocytes may also contribute to the production of autoantibodies [7]. TRAb serum level usually falls after antithyroid drug therapy and thyroidectomy [7]. Necrosis, atrophy and fibrosis of follicular cells are biological effects of radioiodine therapy. The pattern of TRAb decrease during radioiodine treatment has been observed to be different than that after surgery or the administration of anti-thyroid drugs [8]. Thyroid ablation is suspected to eliminate TRAb, possibly due to the removal of most TSH receptors or many sensitised T lymphocytes.

If the thyroid gland is the main source of autoantigens and lymphocytes producing autoantibodies, it may be suspected that the decrease of thyroid volume is followed by a decrease in the level of TRAb.

Investigations concerning the course of TRAb titre in groups of patients after total thyroidectomy and bilateral subtotal resection indicate that if more thyroid tissue is left, the risk of recurrent goitre and an unfavourable course of TRAb titre is higher [9, 10]. On the other hand, a prospective randomised study has shown that there is no difference in TRAb titre between groups of patients after total thyroidectomy and subtotal thyroidectomy (less than 4 ml of tissue left) [11]. However, thyroid tissue contribution in the production of autoantibodies is strongly suggested due to the statistically significant decrease of TRAb titre after thyroidectomy.

Aim of the study

The aim of this study was to analyse:

— if there was any difference between the serum level of TSH receptor autoantibodies (TRAb) before radioiodine treatment and after,
— if there was a positive correlation between a decrease of thyroid volume and a decrease of TRAb serum level after radioiodine therapy.

Material and methods

Patients and radioiodine therapy

This study was designed as a retrospective chart review of patients suffering from Graves' disease with hyperthyroidism who underwent radioiodine therapy. Thirty six patients (four male, 32 female; age range 18–67 yrs; Me 46 yrs; mean age ± SD 43 yrs ± 13.0 yrs) with Graves' disease were enrolled in this study. They were selected consecutively by one physician. The diagnosis was established on common clinical and laboratory criteria. Initially, all patients were treated with antithyroid drugs (ATDs) for the mean period of 28 ± 30 months (range 3–84 months). Despite the initial ATDs therapy, all patients were hyperthyroid before radioiodine administration, except one who was euthyroid (mean serum TSH 0.11 ± 0.5 mU/l, Me 0.005 mU/l; fT4 27.1 ± 22.1 pmol/l, Me 20.5 pmol/l). Twelve patients suffered from mild Graves' orbitopathy. The maximal administered single dose of radioiodine was 22 mCi. The therapy of 24 patients required repeated doses of radioiodine. The mean total dose of radioiodine was 46.1 mCi ± 21.7 mCi (range 22–88 mCi, Me 44 mCi). For further statistical analysis, all data was collected immediately before administration of radioiodine and 18–36 months thereafter. Final data of patients treated with repeated doses of radioiodine was collected 18–36 months after the last dose of I^{131}.

Thyroid ultrasonography [12]

The thyroid gland of every patient was examined ultrasonographically immediately before the administration of radioiodine, and 18–36 months thereafter using a linear transducer (7.5 MHz). The thyroid gland volume was estimated by the same physician using the ellipsoid formula: width (mm) × depth (mm) × length (mm) × 0.52 = volume (ml). Goitre was diagnosed when male thyroid volume exceeded 25 ml and female thyroid volume exceeded 18 ml. Percentage reduction of thyroid volume was estimated as initial thyroid volume (ml)/ /final thyroid volume (ml) ×100%.

Laboratory results

Serum TSH and free thyroxine (fT4) were measured using the electrochemiluminescence technique in Cobas E 601 (norm range TSH 0.27–4.2 mU/l; ft4 11.5–21.0 pmol/l). Estimations of TRAb were done via radioimmunoassay TRAK Human Brahms (norm < 2 IU/l). Percentage reduction of TSH receptor autoantibodies was estimated as initial TRAb titre (IU/l)/final TRAb titre (IU/l) × 100%.

Statistical analysis

Statistical analysis was performed with GraphPad InStat. The level of significance was indicated by p values. All p values of less than 0.05 were considered to indicate statistical significance.

The percentage reduction of thyroid volume underwent further analysis to refer reliable parameter of thyroid volume decrease among the group. Percentage reduction of TRAb serum level referred objective parameter of TRAb decrease and was also statistically analysed.

Results

Thyroid volume

Before treatment, mean male (n = 4) thyroid volume was 27.9 ml ± 9.6 ml (two males had a goitre), and mean female (n = 32) thyroid volume was 20.6 ± 12.7 ml (17 females had a goitre).

Table I. *Changes in thyroid volume, TSH receptor antibodies serum level before and after radioiodine therapy*
Tabela I. *Zmiany objętości tarczycy, stężenia przeciwciał przeciw receptorowi dla TSH przed i po terapii radiojodem*

Mean thyroid volume before therapy ± SD [ml]		Mean thyroid volume after therapy ± SD [ml]		p	Mean percentage reduction of thyroid volume [%]
Female	Male	Female	Male	< 0.0001	83.7
(n = 32)	(n = 4)	(n = 32)	(n = 4)		
27.9 ± 9.6	20.6 ± 12.7	2.4 ± 1.7	5.3 ± 10.9		
Mean TRAb level before therapy ± SD [IU/l]		**Mean TRAb level after therapy ± SD [IU/l]**		**p**	**Mean percentage reduction of TRAb level [%]**
23 ± 12.3		9.8 ± 11.5		< 0.0001	49.1

Mean thyroid volume was 2.4 ± 1.7 ml (males) and 5.3 ± 10.9 ml (females) after therapy. Mean percentage of thyroid volume reduction was 83.7% (Table I). Two females had a goitre (27 ml and 25 ml).

There was an extremely significant difference between mean thyroid volume before radioiodine administration and after 18–36 months (Wilcoxon matched-pairs signed ranks test, $p < 0.0001$).

TSH receptor autoantibodies (TRAb)

Before radioiodine administration, mean serum level of TSH receptor autoantibodies in the group was 23 ± 12.3 IU/l (Me 21.7 IU/l, range 3.83–41.3 IU/l). Mean serum level of TSH receptor autoantibodies after 18–36 months was 9.8 ± 11.5 IU/l (Me 4.5 IU/l, range 0.04–40 IU/l). There was an extremely significant difference between the mean serum level of TSH receptor autoantibodies before and 18–36 months after radioiodine therapy (Wilcoxon matched-pairs signed ranks test, $p < 0.0001$).

Correlation between thyroid volume and TSH receptor autoantibodies

Spearman rank correlation test showed an extremely significant correlation between thyroid volume and the serum level of TRAb ($p < 0.0001$; $r = 0.55$).

Correlation between percentage reduction of thyroid volume and percentage reduction of serum level of TRAb was not statistically significant (Spearman rank correlation, $p = 0.7$; $r = 0.07$).

Discussion

Volume of thyroid gland as the source of TSH receptors seems to have a strong influence on the level of autoantibodies. After 18–36 months of radioiodine therapy, final thyroid volume was significantly lower than initial thyroid volume. This finding has been reported in other researches covering a period of one year observation [13, 14]. Radioiodine thyroid volume reduction has to be analysed separately from surgical methods because of the different pattern of TRAb level changing. The decrease of thyroid volume is the consequence of damage to the thyroid cells and transient elevation of TRAb is described after radioiodine administration.

In our study, radioiodine destruction of the thyroid tissue was followed by a statistically significant decrease of TRAb level. This finding is similar to results referred to in other researches with more numerous groups [15]. Laurberg et al. studied 36 patients with Graves' disease treated with I^{131}. Laurberg's investigation showed one-year worsening of TRAb titre, which may be explained by the initial thyroid tissue damage and release of thyroid antigens. Contrary to our findings, TRAb level was above the norm range within five years of observation. In our study, the observation time was shorter. The crucial difference between our results may be a consequence of the different pattern of radioiodine administration. Laurberg's patients were treated with a single dose of radioiodine. Additionally, Laurberg does not report the initial thyroid volume of patients with Graves' disease, which, in the case of larger-volume thyroid gland, can predict failure in response to a single dose of radioiodine [16]. In our study, 24 out of 36 patients underwent repeated radioiodine therapy.

Total radioiodine dose may have a crucial influence on the final thyroid volume. If there is a link between percentage thyroid reduction and TRAb serum level, the dose of I^{131} may have an impact on therapeutic effect.

In our study, the decrease of TRAb serum level after therapy followed the reduction of thyroid gland volume. Regalbuto et al. analysed 55 patients with Graves' disease treated with I^{131}. Patients who responded to therapy had post-therapy thyroid volume significantly lower, and percentage thyroid volume reduction greater, than non-responders [13].

We did not find a correlation between percentage reduction of thyroid volume and percentage reduction of TRAb serum level, but the decreasing tendency of these two parameters has been observed.

Massaro et al., in a study of 32 patients with Graves' disease, found significant thyroid volume reduction after radioiodine therapy. They did not establish a correlation between percentage reduction of thyroid gland volume and functional score (TSH, fT4, fT3 serum level), but the period of observation was three to 12 months, and this seems to be insufficient [11]. A larger group of patients is needed to establish a final answer from a statistical analysis.

In our study, a positive correlation between thyroid gland volume and level of TRAb has also been found. The high level of autoantibodies may be linked to the presence of goitre.

The decrease of the level of TRAb may be incomplete even after total ablation of thyroid gland. Extrathyroid factors, like the bone marrow, may be responsible for the secondary autoimmune response and may produce autoantibodies after thyroid removal. On the other hand, it is reasonable that the extrathyroidal tissues are the source of autoantigens. It could be explained also by the fact that minimal remnants of thyroid tissue still exist even when no thyroid tissue is found. Cigrovski-Berkovic et al. described a patient with Graves' disease who underwent total thyroidectomy and persisted mildly hyperthyroid with high TRAb postoperative titre. Scintigraphy examination found pyramidal lobe and remnant thyroid tissue in the left lobe [17].

Another study showed that thyroid-stimulating hormone-receptor antibodies disappeared within six years in all eight patients with Graves' disease who underwent total radioiodine thyroid ablation due to coexistent differentiated thyroid carcinoma [12].

The percentage of cure with low dose of administered I^{131} compared to the percentage of cure with higher radiation dose is unsatisfactory [18]. It should be further investigated if total thyroid ablation could be a new guideline in Graves' disease therapy.

Post-therapeutic hypothyroidism and the necessity of L-thyroxine replacement are considered as natural consequences, rather than side-effects, of radioiodine therapy. On the other hand, radioiodine treatment of hyperthyroidism may have an influence on the increased cancer incidence [19]. Other investigations have shown that malignant thyroid lesions after radioiodine treatment of benign thyroid diseases are seldom detected [20]. Using an advanced dosimetric algorithm for activity calculation may help to achieve a balance between clinical remission and the risk of radioiodine overdose [15]. Further investigations are needed to establish the role of radioiodine therapy in the treatment of Graves' disease.

Conclusions

1) Radioiodine ablation of thyroid gland is followed by a decrease of serum circulating autoantibodies.
2) TRAb concentration is positively correlated with thyroid gland volume.
3) Percentage reduction of thyroid tissue is not correlated with the percentage reduction of serum TRAb.

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