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*The usefulness of thyroid size and TSH receptor antibody (TRAb)  
determinations in predicting the effectiveness of thiamazole  
and <sup>131</sup>I treatment for Graves-Basedow's disease*

The treatment of thyrotoxicosis in Graves-Basedow's disease is symptomatic. It is relevant to determine the parameters to predict its effectiveness.

The aim of the study was to evaluate the usefulness of determining thyroid sizes, TRAb levels and their correlation as the markers of the conservative treatment effectiveness in Graves-Basedow's disease.

MATERIAL AND METHODS

The study was conducted in 100 patients with Graves-Basedow's disease, 79 women and 21 men aged 19–78,  $\bar{x}$ -46. The findings were analyzed in individual groups according to the forms of therapy. Group I – (n=55) the patients treated with thiamazole in the initial dose of 40–60 mg/24h. Once clinical euthyrosis was reached, the doses were reduced to the maintenance ones. Group II – (n=45) the patients subjected to <sup>131</sup>I therapy who had been earlier treated with thyreostatics,  $\bar{x}$ -2.5 years without achieving permanent euthyrosis. The iodine doses were determined individually. The accepted suitable dose absorbed in the thyroid was 120 Gy/g. The control group (n=20) included healthy volunteers without clinical and biochemical features of thyroid diseases, 15 women and 5 men, whose age ranged from 22 to 45 years,  $\bar{x}$ -34.

The study analyzed the thyroid sizes, TRAb levels and their correlation. The thyroid sizes were measured by ultrasonography using the Logiq 500 BE Medical System with the linear probe 6.6 MHz 64mm. The examinations were conducted before treatment. The TRAb levels were determined by radioimmunoassay using TRAK-assay (Henning). The reference range was 0–9U/l. Statistical analysis – the parameters were expressed as the arithmetic mean and standard deviation. The statistical significance was calculated by using Statistica. The values were considered statistically significant at  $p < 0.05$ .

## RESULTS

## EVALUATION OF THE CONTROL GROUP (N=20)

The ultrasound examinations revealed homogenous, normoechogenic thyroid parenchyma. The thyroid size was  $\bar{x}$ -14.45±2.37 ml. The TRAb value was  $\bar{x}$ -2.75±2.06 U/l.

## EVALUATION OF THE THIAMAZOLE PATIENTS (N=55)

The patients were divided into 2 groups according to the hormone levels determined 18 months after the beginning of treatment: Group I – 32 patients (58%) with the thyroid function normalized (euthyrosis), Group II – 23 patients (42%) with unsuccessful treatment (hyperthyrosis).

The thyroid size. The thyroid sizes were compared in individual groups. The biggest size was found in the patients with hyperthyroidism still observed 18 months after the beginning of the treatment, and was statistically significant compared to that in the euthyrosis group ( $p < 0.01$ ) and that in the controls ( $p < 0.001$ ). The data are presented in table 1.

Table 1. Comparison of the thyroid sizes (ml) in the clinical groups treated with thiamazole

Examined group	Thyroid size	
	$\bar{x}$	$\pm$
Control group	14.45	2.37
Euthyrosis	31.65 a, b	11.74
Hyperthyrosis	41.09 a	13.94

a-  $p < 0.001$  compared to the control group, b-  $p < 0.01$  compared to the hyperthyrosis group

The TRAb levels. In the patients treated with thiamazole, the initial TRAb level was found to be statistically significantly higher in the hyperthyroidism group than in the euthyrosis group and controls ( $p < 0.001$  for both parameters). After 12 and 18 months of therapy the antibody levels in this group were still higher compared to the euthyrosis and control groups. The results are compiled in table 2.

Table 2. Differences in TRAb levels (U/l) in the individual clinical groups of patients treated with thiamazole

TRAb level	Control group	Euthyrosis	Hyperthyrosis
Before treatment	$\bar{x}$ -2.75± 2.06	$\bar{x}$ -29.13± 19.14 A, B	$\bar{x}$ -54.39± 31.23 A
After 12 months		$\bar{x}$ -9.87± 8.33 B	$\bar{x}$ -39.96± 33.40 A
After 18 months		$\bar{x}$ -4.45± 2.94 B	$\bar{x}$ -40.17± 33.06 A

A –  $p < 0.001$  compared to the control group, B –  $p < 0.001$  compared to the hyperthyrosis group

The correlation between the thyroid size and TRAb level was analyzed. It was found to be positive before treatment ( $R=0.34$ ,  $p<0.05$ ) as well as 12 and 18 months after the beginning of the therapy ( $R=0.45$ ,  $p<0.001$ ;  $R=0.32$ ,  $p<0.05$ , respectively).

EVALUATION OF THE PATIENTS TREATED WITH  $^{131}\text{I}$  (N=45)

On the basis of the TSH and FT4 levels determined 18 months after the therapy, the patients were divided into 3 groups: Group I – 12 patients (27%) with normalized thyroid function (euthyrosis), Group II – 15 patients (33%) with hypothyroidism (hypothyrosis), Group III – 18 (40%) patients with ineffective treatment (hyperthyrosis).

The thyroid size. The biggest thyroid size was observed in the patients in whom the  $^{131}\text{I}$  was ineffective, compared to the euthyrosis group ( $p<0.01$ ), in the hypothyrosis group ( $p<0.05$ ) and in controls ( $p<0.001$ ). These data are presented in table 3.

Table 3. Comparison of the thyroid sizes in the individual clinical groups of patients treated with  $^{131}\text{I}$

Examined group	Thyroid size	
	$\bar{X}$	$\pm$
Control group	14.45	2.37
Euthyrosis	37.92 20.69	b,c
Hypothyrosis	43.47 18.09	a,d
Hyperthyrosis	56.56 24.19	a

a -  $p<0.001$  compared to the control group; b -  $p<0.01$  compared to the control group; c -  $p<0.01$  compared to hyperthyrosis; d -  $p<0.05$  compared to hyperthyrosis

Table 4. Differences in TRAb levels (U/l) in the individual clinical groups treated with  $^{131}\text{I}$

TRAb level	Control group	Euthyrosis	Hypothyrosis	Hyperthyrosis
Before treatment	$\bar{X} -2.75 \pm 2.06$	$\bar{X} -36.67 \pm 15.45$ a, b	$\bar{X} -62.33 \pm 46.35$ a, b	$\bar{X} -103.61 \pm 43.90$ a
After 12 months		$\bar{X} -9.58 \pm 5.82$ b	$\bar{X} -7.67 \pm 3.45$ b	$\bar{X} -63.33 \pm 29.77$ a
After 18 months		$\bar{X} -6.08 \pm 3.73$ b	$\bar{X} -7.07 \pm 5.17$ b	$\bar{X} -77.18 \pm 44.92$ a

a -  $p<0.001$  compared to the control group, b -  $p<0.001$  compared to hyperthyrosis

The TRAb levels. The comparative assessment of the examined clinical groups shows statistically significant differences in antibody levels depending on the therapeutic effects. Before the  $^{131}\text{I}$  administration, the highest antibody levels were observed in group III, i.e. with hyperthyroidism ( $p<0.001$  compared to group I, II and controls). The statistically significant differences in TRAb levels were still observed 18 months after the beginning of  $^{131}\text{I}$  therapy.

The above mentioned results are listed in table 4. In the patients treated with  $^{131}\text{I}$ , the correlation between the thyroid size and TRAb level was studied. The positive correlation was found before treatment ( $R=0.35$ ,  $p<0.05$ ) as well as after 12 and 18 months ( $R=0.40$ ,  $p<0.05$ ;  $R=0.31$ ,  $p<0.05$ , respectively).

## DISCUSSION

In Graves-Basedow's disease, there is no explicit relation between the size of the thyroid gland and severity of hyperthyroidism. This suggests that the thyroid growth may result not only from the stimulating action of the TSH receptor but also from the mechanism, which does not depend on the receptor-antibody binding (2). After TGAb was discovered (the protein stimulating the thyroid growth which does not affect the production of hormones), a new mechanism of the thyroid enlargement was implicated, which does not involve the receptors and adenocyclase stimulation but probably phosphorylation of protein tyrosine (10). The goitre size in Graves-Basedow's disease is not exclusively the result of increased number and volume of the alveolar cells. It is also related to the increased colloid amount, higher blood volumes in the gland and lymphocyte infiltrations. Moreover, some other factors responsible for the proliferation of the thyroid cells are known which include epidermal growth factor (EGF), insulin and insulin-like growth factor (IGF-1), cytokins and prostaglandins (7,8).

There is no doubt that the thyroid gland is the main organ producing antibodies and thyrologists agree that prognosis in patients with big goitres should be more cautious than in other cases. It is generally believed that markedly increased thyroid gland indirectly indicates a high degree of stimulation and substantial sensitivity of thyrocytes to the action of the thyroid stimulator (11). Our examinations showed that the thyroid size was significantly bigger in the group of patients unsuccessfully treated with thiamazole than that in the euthyreosis patients ( $p<0.01$ ). Similarly, in the patients treated with  $^{131}\text{I}$ , the biggest thyroid sizes were found in the group with hyperthyroidism ( $p<0.01$  compared to euthyreosis, and  $p<0.05$  compared to hypothyreosis).

Elevated levels of TRAb were found in over 80% of patients with Graves-Basedow's disease and they are sensitive markers of the disease (3,12). Moreover, there is no doubt that TRAb determinations are useful in monitoring the effectiveness of hyperthyroidism therapy. Bliddal et al. (1) believe that the TRAb level is significantly decreased during the first 6 months of treatment and further decrease has no clinical implications. Heberling et al. (4) observed a decrease and partial normalization of the antibody levels already 3 months after the therapy onset. The majority of authors, however, believe that the changes in TRAb levels predicting the recovery occurred after 12-month treatment with thyreostatics. According to Rasmussen (9), normalization of antibody levels at 12 months is associated with permanent remission in 62% of the patients. Similar findings were presented by Komyia et al. (6).

Our studies in the group successfully treated with thiamazole showed a statistically significant decrease in TRAb levels after 12 months of therapy and normalization after 18 months. In the patients without euthyreosis after 18 months, the TRAb levels remained elevated. The changes in TRAb levels after  $^{131}\text{I}$  treatment also allow monitoring its effectiveness. Kaise et al. (5) in their 18-month-follow-up found elevated TRAb levels in 61% of the hyperthyroidism patients and only in 16% of those with euthyreosis or hypothyroidism. The highest values of antibodies before iodine administration were observed in the group with hyperthyroidism. These values were statistically significantly different compared to the euthyreosis and hypothyreosis groups ( $p<0.001$  for both parameters). In the patients with hyperthyroidism, the antibody levels did not normalize during the 18-month follow-up. In the groups treated with thyreostatics and radioactive iodine, the positive correlation between the thyroid size and TRAb level was found before treatment as well as 12 and 18 months after the onset of administration.

The above findings demonstrate that the thyroid sizes and antibody levels are the parameters which should be taken into consideration while predicting the effectiveness of conservative treatment of hyperthyroidism in Graves-Basedow's disease.

### CONCLUSIONS

1. The TRAb levels and thyroid sizes are important parameters that should be included in the prognosis of the treatment effectiveness.
2. The TRAb level correlates with the thyroid size.

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### SUMMARY

The aim of the study was to assess the usefulness of determining the thyroid size, TRAb level and their correlation as markers for predicting the effectiveness of conservative treatment in Graves-Basedow's disease. The study included 100 patients with Graves-Basedow's disease;

group I treated with thiamazole, group II treated with  $^{131}\text{I}$ . The biggest thyroid size,  $\bar{x} -42.09 \pm 13.94\text{ml}$ , was found in the group unsuccessfully treated with thiamazole and was statistically significant compared to that in the euthyrosis group,  $\bar{x} -31.65 \pm 11.74\text{ml}$  ( $p < 0.01$ ) and controls  $\bar{x} -14.45 \pm 2.37\text{ml}$  ( $p < 0.001$ ). It is noteworthy that the initial TRAb level in the group with persistent hyperthyroidism was higher ( $\bar{x} -54.39 \pm 31.21\text{U/l}$ ) than that in the euthyrosis group ( $\bar{x} -29.13 \pm 19.44\text{U/l}$ ) and controls ( $\bar{x} -2.75 \pm 2.06\text{U/l}$ ),  $p < 0.001$  for both parameters. Elevated antibody levels were also found after 12 and 18 months of treatment. Moreover, in the  $^{131}\text{I}$  patients, the biggest thyroid size before iodine administration was found in the group with persistent hyperthyroidism,  $\bar{x} -56.56 \pm 24.19\text{ml}$ . It was statistically significantly different compared to the thyroid size in the euthyrosis patients  $\bar{x} -37.922 \pm 20.69\text{ml}$  ( $p < 0.001$ ) and in the hypothyrosis patients,  $\bar{x} -43.47 \pm 18.09\text{ml}$  ( $p < 0.05$ ). Before  $^{131}\text{I}$  administration, the highest antibody levels were observed in the group with persistent hyperthyroidism,  $\bar{x} -103.61 \pm 43.90\text{U/l}$  ( $p < 0.001$ ) compared to euthyrosis, hypothyrosis and control groups. The significance of differences in TRAb levels in the examined groups was still observed 18 months after  $^{131}\text{I}$  administration. In the groups of patients treated with thyreostatics and radioactive iodine, the positive correlation between the thyroid size and TRAb level was found before as well as 12 and 18 months after the onset of treatment. Conclusions: 1. The TRAb levels and thyroid sizes are important parameters that should be considered in predicting the effectiveness of treatment. 2. The TRAb level correlates with the thyroid size.

Przydatność oceny objętości tarczycy i poziomu przeciwciał przeciw receptorom TSH (TRAb) w prognozowaniu skuteczności leczenia choroby Graves-Basedowa Tiamazolem i  $^{131}\text{I}$

Celem pracy była ocena przydatności pomiarów wielkości tarczycy, poziomu TRAb i ich wzajemnych korelacji jako wskaźników skuteczności leczenia zachowawczego choroby Graves-Basedowa. Badaniem objęto 100 osób z chorobą Graves-Basedowa: grupa I - pacjenci leczeni Tiamazolem, grupa II - pacjenci leczeni  $^{131}\text{I}$ . W grupie chorych leczonych nieskutecznie Tiamazolem objętość tarczycy była największa -  $\bar{x} -41,09$   $\bar{x} -13,94\text{ml}$  i różniła się w sposób istotny statystycznie z wielkością tarczycy w grupie z eutyreozą  $\bar{x} -31,65$   $\bar{x} -11,74\text{ml}$  ( $p < 0.01$ ) oraz grupie kontrolnej  $\bar{x} -14,45$   $\bar{x} -2,37\text{ml}$  ( $p < 0,001$ ). Zwraca uwagę wyższy wyjściowy poziom TRAb w grupie chorych z utrzymującą się nadczynnością  $\bar{x} -54,39$   $\bar{x} -31,21\text{U/l}$ , różniący się od poziomu TRAb w grupie z eutyreozą  $\bar{x} -29,13$   $\bar{x} -19,14\text{U/l}$  oraz w grupie kontrolnej  $\bar{x} -2,75$   $\bar{x} -2,06\text{U/l}$  ( $p < 0,001$  dla obu wskaźników). Po 12 i 18 miesiącach leczenia stwierdzano utrzymywanie się podwyższonych wartości przeciwciał u tej grupy chorych. Również u pacjentów leczonych  $^{131}\text{I}$  największą objętość tarczycy przed podaniem jodu stwierdzano w grupie chorych z utrzymującą się nadczynnością  $\bar{x} -56,56$   $\bar{x} -24,19\text{ml}$ . Różniła się ona w sposób istotny statystycznie od wielkości tarczycy u pacjentów w grupie z eutyreozą  $\bar{x} -37,92$   $\bar{x} -20,69\text{ml}$  ( $p < 0,01$ ) oraz w grupie z hypotyreozą  $\bar{x} -43,47$   $\bar{x} -18,09\text{ml}$  ( $p < 0,05$ ). Przed podaniem  $^{131}\text{I}$  najwyższe stężenia przeciwciał obserwowano w grupie z utrzymującą się nadczynnością  $\bar{x} -103,61 \pm 43,90$  ( $p < 0,001$  w porównaniu z grupą z eutyreozą i hypotyreozą oraz grupą kontrolną). Istotności różnic w poziomach TRAb w badanych grupach klinicznych utrzymywały się przez 18 miesięcy po podaniu  $^{131}\text{I}$ . Zarówno w grupie chorych leczonych tyreostatykiem, jak i jodem radioaktywnym zanotowano dodatnie korelacje pomiędzy wielkością tarczycy a poziomem TRAb przed leczeniem oraz 12 i 18 miesięcy po rozpoczęciu leczenia. Wnioski: 1. Poziom przeciwciał przeciw receptorom TSH oraz objętość gruczołu tarczowego stanowią ważne parametry, które należy uwzględnić przy prognozowaniu skuteczności podjętego leczenia. 2. Poziom TRAb koreluje z objętością tarczycy.