

NUCLEAR MEDICINE, MEDICAL CENTRE, ZAJECAR, YUGOSLAVIA

## THE SIGNIFICANCE OF TSH RECEPTOR ANTIBODIES AND THYROID MICROSOMAL ANTIBODIES IN GRAVES' DISEASE

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### INTRODUCTION

Graves' disease is an autoimmune disease with etiology that is not completely understood. Numerous experimental investigations and clinical observations have primarily elucidated the role of the humoral stimulatory factors in the disease (LATS, TSI, etc). These autoantibodies (TRAb) react with TSH receptor and produce postreceptor stimulatory effects, that lead to hyperfunction of the thyroid. It is thus understandable why sensitive and specific techniques such as radioreceptor assays, cAMP generated in thyrocytes, etc. detect high levels of these autoantibodies in more than 85%, in patients with untreated Graves' disease<sup>1-3</sup>. The incidence and serum level of TRAb decrease during thyrosuppressive therapy<sup>4,5</sup>, and are almost always negative in stable remission<sup>6,7</sup>. Transplacental passage of TRAb from mother to foetus, results in genesis of neonatal hyperthyroidism<sup>8</sup>. This model for the role of TRAb in autoimmune hyperthyroidism is partly complicated by the fact that not all TSH receptor antibodies are stimulatory, and some of them block the TSH receptor and suppress the effects of TSH on the thyroid<sup>1,9</sup>.

In addition to TRAb, which has a mostly established role, a variety of others antibodies (e.g. microsomal and thyroglobulin antibodies, anti DNA antibodies, antibodies to »second colloid antigen« etc.) occur in Graves' disease<sup>10</sup>. The most consistent findings are of thyroid microsomal antibodies directed against thyrocyte peroxidase<sup>11,12</sup>.

The subject of this study was the investigation of thyroid autoantibodies, - TSH receptor antibodies (TRAb) and thyroid microsomal antibodies (TMAb) – at different stages of Graves' disease.

### MATERIALS AND METHODS

#### *Patients*

Blood samples were obtained from 114 patients with Graves' disease (34 patients prior to treatment: 20 at first appearance and 14 in relapse; 49 patients under medicament treatment: 43 treated with methimazole and 6 with propylthiouracil; 55 patients in stable remission: 43 after medicament treatment, 5 after treatment with <sup>131</sup>I and 7 after surgical treatment; and 3 patients with spontaneous hypothyroidism, 5 to 14 months after cessation of methimazole).

The diagnosis of Graves' disease was based on history, clinical examination, thyroid hormone levels (Delfia, Pharmacia-Wallac) and in some cases on <sup>131</sup>I thyroid uptake.

#### *Methods*

Antibodies to the TSH receptor were measured by commercially available TRAK-assay (Henning, Berlin). Intra-assay variation was CV=7,1% and inter-assay variation was CV=9,3%. Cut-off value was 15 U/l.

Antibodies to thyrocytes microsoms (TMAb) were measured by RIA (TMS-Bridge, Serono). Intra-assay variation was CV=6,2% and inter-assay variation was CV=7,6%. Cut-off value was 50 U/ml.

Blood samles were collected by venipuncture, centrifuged, and serun was stored at -20<sup>0</sup>C.

### RESULTS

Findings of TRAb and TMAb in patients with Graves' disease before treatment are shown on Table 1.

**Table 1.** TSH RECEPTOR ANTIBODY (TRAb) AND THYROID MICROSOMAL ANTIBODY (TMAb) FINDINGS IN UNTREATED PATIENTS WITH GRAVES' DISEASE

Positive findings	Graves' disease Untreated n = 20	Graves' disease Relapsed n = 14	Graves' disease Total n = 34
TRAb	90%	85%	87%
TMAb	70%	64%	67%

Incidence of positive findings in patients with Graves' disease under medical treatment are shown in table 2. Based on clinical examination and thyroid hormone levels, patient data are classified as hyperthyroid, euthyroid and hypothyroid.

**Table 2.** TSH RECEPTOR ANTIBODY (TRAb) AND THYROID MICROSOMAL ANTIBODY (TMAb) FINDINGS IN UNTREATED PATIENTS WITH GRAVES' DISEASE DURING MEDICAL TREATMENT

Positive findings	Euthyroid n = 25	Hyperthyroid n = 13	Hypothyroid n = 11
TRAb	32%	100%	88%
TMAb	32%	62%	54%

Findings of TRAb and TMAb in patients with Graves' disease in remission are shown i table 3.

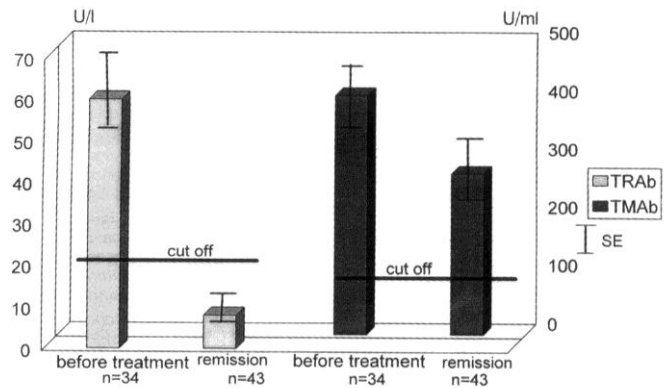
**Table 3.** TSH RECEPTOR ANTIBODY (TRAb) AND THYROID MICROSOMAL ANTIBODY (TMAb) FINDINGS IN UNTREATED PATIENTS WITH GRAVES' DISEASE IN REMISSION AFTER MEDICAL TREATMENT (METHIMAZOLE), RADIOIODINE THERAPY AND SURGICAL TREATMENT

Positive findings	Methimazole n = 43	<sup>131</sup> I n = 5	Operation n = 7
TRAb	1 (2%)	3	2
TMAb	27 (62%)	5	3

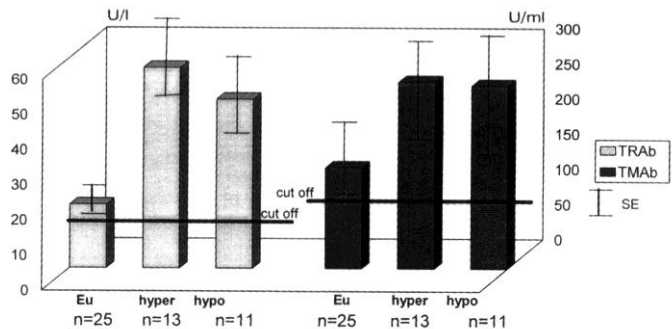
Three patients treated by methimazole before investigation, and hypothyroid at the time of investigation, all had positive findings for both autoantibodies.

The distribution of mean values for all the groups of patients is presented in Figures 1 and 2.

**Fig. 1.**  
TSH receptor antibody (TRAb) and thyroid microsomal antibody (TMAb) findings in patients with Graves' disease before the therapy and in stable remission.



**Fig. 2.**  
TSH receptor antibody (TRAb) and thyroid microsomal antibody (TMAb) findings in disease during medical treatment in relation to their metabolic status.



## DISCUSSION

The pathogenesis of Graves' disease is quite complex. Genetic factors (e.g. HLA types), cellular immunity factors, as well as humoral factors (e.g. TSH receptor antibodies), are some of the factors in the aetiopathological chain<sup>13-15</sup>. The other main thyroid autoimmune disease, Hashimoto's thyroiditis, has on the other hand, quite well elucidated aetiopathogenesis (particularly the role of cellular immunity and TMAb and TgAb)<sup>11-16</sup>. Nevertheless, the coexistence of these two autoimmune diseases (or perhaps the one disease transforming into the other) as well as presence of antibodies characteristic for the other thyroid autoimmune disease, has not yet been clarified.

In this study we have tried to examine the role of TMAb levels in Graves' disease, and compare the TMAb findings with the levels of TRAb, whose role in Graves' disease is relatively well established.

Numerous authors<sup>1,2,4,6,17</sup>, have reported similar findings: in untreated Graves' disease, TSH receptor antibody (TRAb) levels are highly positive; in response to medical treatment TRAb levels decrease, and in remission they practically disappear. The high levels of TSH receptor antibodies observed in hypothyroidism under medical treatment, or after cessation of treatment, suggest the conversion from stimulatory to blocking type of antibodies<sup>5,28,29</sup>.

This analysis did not however further contribute to elucidation of the role of thyroid microsomal antibodies (TMAb) in Graves' disease. Positive findings in untreated Graves' disease were less

frequent (67%) than was the finding of TSH receptor antibodies (87%). Under medical treatment, as with the TRAb findings, the frequency of positive TMAb findings were less frequent in euthyroid patients than in hyperthyroid patients. Positive TRAb in patients in remission was infrequent (2%), unlike positive TMAb which were frequent (62%).

The literature is also inconclusive: some findings suggest that negative TMAb before treatment, and under medical treatment are prognostically unfavorable, because in these patients the disease has a tendency to relaps after cessation of medical treatment<sup>10</sup>. Other authors, in contrast, report that patients with high TMAb levels hardly ever achieve remission<sup>20</sup>. More in agreement is the decline of TMAb under medical treatment<sup>21,22</sup>, or after successful surgical treatment<sup>23</sup>, although some publications do not support this<sup>24</sup>. Yet, some others authors done the significance of TMAb finding in prediction of relapse at the end of medical therapy<sup>25</sup>, or their predictive values for persistent hyperthyroidism after <sup>131</sup>I therapy<sup>26</sup>. There are also some studies that suggest a predictive value of TMAb in »pre-Graves' disease« in first degree relatives of patients with Graves' disease<sup>27</sup>.

With respect to our findings we make the following comments: in untreated Graves' disease the high frequency of positive TMAb confirms the autoimmune aetiology of the disease; negative findings in a minority of patients (33% in this study) does not exclude autoimmunity. The high TMAb levels in hypothyroid patients are probably in accordance with the pathogenesis of the disease (coexistence of TMAb and TSH receptor blocking antibodies?). The significance of high frequency of positive TMAb findings, in patients with Graves' disease in stable remission is not clear. We could not confirm the hypothesis of either longer remission or more frequent relapses in this group of patients: high TMAb levels before treatment had no predictive value for remission, or relapse in case of initial remission; the duration of remission could also not be predicted from the TMAb findings.

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