**Topic:** WHAT HAPPENS TO TSH-RECEPTOR ANTIBODIES AFTER TREATMENT OF HYPERTHYROIDISM IN GRAVES’ DISEASE?

**Title:** TSH-receptor autoimmunity in Graves' disease after therapy with antithyroid drugs, surgery, or radioiodine: a 5-year prospective randomized study.

**Authors:** Laurberg P, Wallin G, Tallstedt L, Abraham-Nordling M, Lundell G, & Torring O (Aalborg, Denmark & Stockholm, Sweden)


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**SUMMARY**

**Background:** Autoimmunity against the TSH receptor is a key pathogenic element in Graves' disease. The autoimmune aberration may be modified by the treatment of hyperthyroidism.

**Objective:** To compare the effects of the three common therapeutic for Graves' hyperthyroidism on TSH-receptor autoimmunity.

**Methods:** Patients with newly diagnosed Graves' hyperthyroidism, aged 20-55 years, were randomized to medical therapy, thyroid surgery, or radioiodine therapy (radioiodine was only given to patients ≥ 35 years of age). L-thyroxine (L-T4) was added to therapy as appropriate to keep patients euthyroid. Antithyroid drugs were withdrawn after 18 months of therapy. TSH-receptor antibodies (TRAb) in serum were measured before and for 5 years after the initiation of therapy.

**Results:** Medical therapy (N=48) and surgery (N=47) were followed by a gradual decrease in TRAb in serum, with the disappearance of TRAb in 70-80% of the patients after 18 months. Radioiodine therapy (N=36) led to a 1-year long worsening of autoimmunity against the TSH receptor, and the number of patients entering remission of TSH-receptor autoimmunity with the disappearance of TRAb from serum during the following years was considerably lower than with the other types of therapy.

**Conclusions:** The majority of patients with Graves' disease gradually enter remission of TSH-receptor autoimmunity during medical or after surgical therapy, with no difference between the types of therapy. Remission of TSH-receptor autoimmunity after radioiodine therapy is less common.

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**COMMENT**

The authors investigated prospectively 179 patients with Graves’ disease (GD), subdivided into 2 cohorts based on age. The ‘younger’ cohort (N=60; 20-34 years) comprised patients randomized for therapy with subtotal thyroidectomy (Tx) or antithyroid drugs (ATD) given for a maximum of 18 months. The other ‘less young’ cohort (N=119; 35-55 years) comprised patients treated with Tx, ATD, or radioiodine (RI*). Finally, 40% of patients received ATD, 37% were submitted to Tx, and 23% benefited from RI* administration. The clinical outcomes of the patients from this study have already been published (Torring et al; JCEM 1996). In the present article, the authors report on the changes in TSH receptor antibody (TSHR-Ab) during a 5-year follow-up period. After treatment with ATD & Tx, TSHR-Ab titers began to decrease gradually (already within 6 months) so that, after 18 months (i.e. at the end of ATD therapy), 70-80% of patients in the 2 groups had...
negative TSHR-Ab. Conversely in the RI*-treated patients, the pattern of changes in TSHR-Ab showed first a brisk increase in titers (double after 3-6 months) during the 1st year, followed by a gradual decline with TSHR-Ab reaching a value close to the initial TSHR-Ab titers (before RI*) 15-18 months after RI* treatment. At the end of the 5-year follow-up period, RI*-treated patients still had elevated TSHR-Ab (on average), significantly higher than in the other 2 groups.

These results convey several important messages, some already known and others more puzzling. First, the rapid decline of TSHR-Ab after surgery is a known fact, believed to be directly related to the post-surgical disappearance of thyroid antigens. It is one of the main reasons for proposing to perform a ‘large’ subtotal thyroidectomy in patients with GD leaving the smallest possible thyroid residues, another reason being to avoid regrowth (and potentially a recurrence) from thyroid remnants. In spite of the beneficial autoimmune outcome, it should be remembered that some (albeit rare) patients maintain positive TSHR-Ab, even long after Tx.

Second, the transient surge of TSHR-Ab after RI* administration is another known fact, believed to be caused by sudden release of thyroid antigens triggering the autoimmune response. The new finding here was to show that even after a long follow-up period, RI*-treated GD patients tended to maintain positive TSHR-Ab titers. In another commentary on the same article (see Clin. Thyroidology, Feb 2008), Mazzaferri wrote that this finding was worrisome, especially with regard to the more common trend to treat young women using RI* in the USA (risk for the fetus during pregnancy, for instance). This risk is certainly real and worrisome, although it may probably depend also on the ‘ablation’ objective set when calculating the dose of RI* to deliver. One of the intriguing features in present results was that, if one sets the upper TSHR-Ab value at the level reached 12 months after RI* (and not at the initial level) in this group, then changes in TSHR-Ab become almost super-imposable in all groups, as if the autoimmune response declined in parallel in the 3 treatment groups, but remained higher in the RI*-treated patients because it started from much higher TSHR-Ab levels.

Third and finally concerning ATD treatment, TSHR-Ab declined from the onset of therapy, with a 12-18 months period needed to reach negative TSHR-Ab, hence the 1-1.5 year of ATD treatment classically adopted in Europe. As it is the case in most studies of this kind, some patients experienced a recurrence after ATD withdrawal, namely 16 patients (23%) in present study (a relatively low frequency), associated in most cases with a secondary increase in TSHR-Ab.

See Figure