THYROID CANCER IN CHILDREN

Children with differentiated thyroid cancer achieve adequate hyperthyrotropinemia within fourteen days of levothyroxine withdrawal.

Kuijt WJ & Huang SA (Boston, USA)


SUMMARY

Context: The preparation for radioiodine administration recommended by the current pediatric literature is a 6-week withdrawal that typically includes the transient administration of $T_3$. Compared with adults, $T_4$ clearance rates and serum TSH to free $T_4$ ratios are higher in children, implying that pediatric patients can achieve adequate hyperthyrotropinemia with shorter levothyroxine withdrawals.

Objective: The objective of this study was to determine whether children with differentiated thyroid cancer achieve adequate hyperthyrotropinemia using an abbreviated levothyroxine withdrawal protocol.

Design: The study design was a retrospective analysis of 15 consecutive levothyroxine withdrawals performed without $T_3$ at the Children’s Hospital Boston.

Patients: Eleven children with differentiated thyroid cancer were included. The average age at the time of withdrawal was 12.5 ± 0.8 years.

Main Outcome Measurement: Serum TSH concentrations obtained after the discontinuation of levothyroxine were analyzed to determine the time interval required to achieve a serum TSH level greater than 25 µU/ml for each patient.

Results: Adequate hyperthyrotropinemia was documented in all children tested by day 14. The mean interval required to achieve a serum TSH level above 25 µU/ml from a suppressed serum TSH was 12.3 ± 0.7 days.

Conclusions: Shorter withdrawals minimize hypothyroid morbidity and the theoretical risk of decreased $^{131}$I residence time from excessive hyperthyrotropinemia. These benefits are amplified in children due to their high incidence of distant metastases. We propose an abbreviated 2-week withdrawal protocol to facilitate the adjunctive therapy and surveillance of children with follicular cell-derived cancers.

COMMENT

Once more in medicine it is shown that children are not just “small adults”. In this study, the authors showed that all children reached TSH > 25 µU/ml within 2 weeks of levothyroxine withdrawal (compared to 42% of adults in another study). Since a more prolonged withdrawal does not give additional benefits and, on the contrary, may be detrimental (morbidity of hypothyroidism, increased
iodine turnover from prolonged activation of the TSH receptor resulting in a decreased $^{131}$I residence time), a 2-week withdrawal is proposed for children who are prepared for diagnostic and/or therapeutic reasons.

At present time, the experience with recombinant human TSH (rhTSH) in children with DTC is scarce. Sonia Iorcansky et al. (Buenos Aires, Argentina) showed that the mean TSH levels achieved in children after the injection of $2 \times 0.9$ mg of rhTSH were remarkably similar to the values previously reported in adults, suggesting that dose adjustments were not generally required in children and teenagers who undergo stimulation with rhTSH administration for radioiodine scanning and/or serum-stimulated thyroglobulin determination (JCE&M, 90; 6553, 2005). Therefore and somewhat contra-intuitively, the TSH rise after the withdrawal of levothyroxine is different in adults and children, but equal TSH rises can be obtained after fixed dose rhTSH injections. In that respect children behave as “small adults”!

(Annick Van den Bruel, M.D.)
Topic: FOLLICULAR THYROID TUMORS

Title: Fractional allelic loss of tumor suppressor genes identifies malignancy and predicts clinical outcome in follicular thyroid tumors.

Authors: Hunt JL, Yim JH, Carty SE (Cleveland, Ohio, USA)

Reference: Thyroid 16: 643-649, 2006

SUMMARY

Background: Thyroid follicular tumors can be challenging diagnostically and clinically, because the cytologic and histologic features can be subtle and prognosis is also difficult to predict.

Study: The authors analyzed thyroid follicular tumors with known long-term follow-up for a molecular panel of tumor suppressor genes to determine whether this molecular approach has prognostic significance. Microdissection and DNA extraction were performed from tumor and normal tissue. Polymerase chain reaction (PCR) was performed for 13 short tandem repeats at or near tumor suppressor genes. PCR product was detected using semiquantitative capillary gel electrophoresis and fractional allelic loss (FAL) was calculated.

Patients and material studied: The study included eight adenomas, three minimally invasive carcinomas, four angio-invasive carcinomas, and three widely invasive carcinomas with a mean follow-up of 77 months. Three patients died of disease and an additional two are alive with disease/recurrence/metastasis.

Results: The mean FAL for benign tumors (14 %) was significantly different from that of malignant tumors (56 %; P < 0.001). Patients with a follicular tumor who had no evidence of disease recurrence had a mean FAL of 22 % and those with disease recurrence or death from disease had a mean of 78 % (P < 0.002).

Conclusions: Based on these results, a tumor suppressor gene panel for allelic imbalance in follicular-derived tumors may correlate with both malignancy and outcome in patients with follicular-derived carcinomas of the thyroid.

COMMENT

Follicular thyroid tumors can be diagnostically challenging because the diagnosis of carcinoma rests on the finding of potentially subtle or rare foci of either capsular or vascular invasion. This is particularly true for cytology obtained preoperatively by fine needle aspiration, a highly useful technique (in expert hands and eyes), but that cannot easily differentiate between benign and malignant follicular cell proliferation. Furthermore, prognostic markers for follicular-derived tumors of the thyroid, after surgical removal of the cancer, are not presently available. Molecular markers have been explored recently (such as PAX8-PPARγ translocation; cyclin D1; nm-23; telomerase; p53) but none has so far proven to have strong prognostic value.
In the present study, the authors have used a genotypic approach to investigate a tumor suppressor gene panel. The main finding of their study was that increasing histologic aggressiveness correlated with the fractional allelic loss. These results support the concept that malignant follicular neoplasms accumulate allelic loss mutations as they increase in malignant potential and behaviour. In this study also, fractional allelic loss correlated well with clinical patient outcome. Present results clearly represent an advance in our understanding, although we will need larger series with long-term follow-ups to elucidate whether molecular assays such as the one described herein will be of help to clinicians (and pathologists) in order to predict tumor behaviour in patients with follicular carcinomas.

(Daniel Glinoer, M.D.; Ph.D.)

See Figure below

Legend: Fractional allelic loss in percent (ordinate) in adenomas (FA) was less than 20%, in minimally- and angio-invasive carcinomas (MI) ranged between 10-85%, and in widely invasive carcinomas was 65-100%.
Topic: PITUITARY-THYROID FEEDBACK REGULATION

Title: Atypical expression of Type 2 iodothyronine deiodinase in thyrotrophs explains the thyroxine-mediated pituitary thyrotropin feedback mechanism.

Authors: Christoffolete MA, Ribeiro R, Singru P, et al. (Boston, USA)

Reference: Endocrinology 147: 1735-1743, 2006

SUMMARY

Background: Thyroxine (T₄), the main product of thyroid secretion, is a critical signal in plasma that mediates the TSH-negative feedback mechanism. As a prohormone, T₄ must be converted into T₃ to acquire biological activity; thus, type 2 iodothyronine deiodinase (D2) is expected to play a critical role in this feedback mechanism. However, the mechanistic details of this pathway are still missing because, counterintuitively, D2 activity is rapidly lost in the presence of T₄ by a ubiquitin-proteasomal mechanism.

Results: In the present study, the authors demonstrate that D2 and TSH are coexpressed in rat pituitary thyrotrophs and that hypothyroidism increases D2 expression in these cells. Studies using two murine-derived thyrotroph cells (TtT-97 and TαT1) demonstrate high expression of D2 in thyrotrophs and confirm its sensitivity to negative regulation by T₄-induced proteasomal degradation of this enzyme. Despite this, the expression of the Dio2 gene in TαT1 cells is higher than their T₄-induced D2 ubiquitinating activity. As a result, D2 activity and net T₃ production in these cells are sustained, even at free T₄ concentrations that are several-fold above the physiological range. In this system, free T₄ concentrations and net D2-mediated T₃ production correlated negatively with TSHβ gene expression.

Conclusion: These results resolve the apparent paradox between the homeostatic regulation of D2 and its role in mediating the critical mechanism by which T₄ triggers the TSH-negative feedback mechanism.

COMMENT

In present investigation, the presence of D2 in thyrotrophs was clearly demonstrated in rat pituitary sections and in two rodent thyrotrophic cell models. Furthermore, the study confirmed the sensitivity of the expression of D2 in thyrotrophs to the negative regulation by proteasomal degradation of this enzyme induced by T₄.

Over a quarter of a century ago (1977), Reed Larsen & Enrique Silva were the first investigators to show that the pituitary feedback regulation of the thyroid gland was mediated by thyroid hormones, and more specifically by circulating T₄ (and not T₃). The regulatory mechanism involves the specific activity of an enzyme (the iodothyronine deiodinase, D2) that rapidly catabolizes T₄ into T₃ in thyrotrophs, thereby inducing T₃ local production that, in turn, acts negatively on the TSHβ gene and turns off TSH secretion in response to minor elevations in serum T₄.

This discovery was central in our understanding of the finely-tuned regulation of the thyroid gland and the pivotal role of the pituitary gland as a “thyrostat”, i.e. an amplification system that allows TSH secretion to be modulated (positively or negatively) in response to...
small changes in circulating free T₄ concentrations.

What makes the thyrotrophs a special kind of cells, in this respect, is the fact that these cells are equipped with a highly T₃-responsive gene (the TSHβ gene) and express very high levels of D2, the key deiodinase that activates thyroid hormone and mediates the signal transduction between serum T₄ and the binding of T₃ to nuclear thyroid hormone receptors. The expression of D2 in thyrotrophs is at the core of the T₄-mediated TSH feedback mechanism. D2-mediated net T₃ production is low at lower T₄ concentrations and high at high T₄ concentrations. This discovery also paved the way to our better understanding of the local regulatory role of thyroid hormones in peripheral target cells (such as the placenta, fat, muscle and other tissues) by locally-occurring specific deiodination pathways.

(Daniel Glinoer MD, PhD)

See Figure below

The figures show the decrease in D2 activity (mRNA and activity above; production below) in response to T₄
**Topic:** TSH-RECEPTOR ANTIBODIES AFTER ANTITHYROID DRUG TREATMENT FOR GRAVES’ DISEASE

**Title:** Serum thyrotropin receptor antibodies (TRAb) concentrations in patients with Graves’ disease before, at the end of methimazole treatment, and after drug withdrawal: evidence that the activity of TRAb and/or thyroid response modify during the observation period.

**Authors:** Carella C, Mazziotti G, Sorvillo M, et al. (Napoli, Italy)

**Reference:** Thyroid 16: 295-302, 2006

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**SUMMARY**

**Aim and methods:** The authors performed a retrospective analysis of serum thyrotropin receptor antibody (TRAb) concentrations in 58 patients with Graves’ disease (GD) at the onset of the disease, at the end of 18 month with methimazole (MMI) treatment, and after MMI withdrawal in order to evaluate the correlation between the presence of these antibodies and the relapse of hyperthyroidism. Sixty healthy subjects were enrolled as a control group.

**Results:** Before MMI treatment, the best cut-off TRAb value for identifying patients with GD was 1.45 UI/L (specificity 100%; sensitivity 98.3%). At the end of MMI treatment, serum TRAb concentrations were significantly lower than those measured at baseline, but they were still significantly higher than those found in the control subjects. At the end of MMI treatment, 44 patients (75.9%) had positive TRAb values (>1.45 UI/L). After MMI withdrawal (median of 15 months), 34 patients (58.6%) became hyperthyroid, 4 patients (6.9%) became hypothyroid, and 20 patients (34.5%) remained euthyroid. There was a significant correlation between serum TRAb concentrations at the end of MMI treatment and the percentage of patients who became hyperthyroid and the time of appearance of hyperthyroidism. All 4 patients with TRAb values below 0.9 UI/L at the end of MMI treatment remained euthyroid throughout the follow-up period. Among the 27 patients who had serum TRAb values higher than 4.4 UI/L, 23 developed hyperthyroidism and 4 hypothyroidism. The TRAb values between 0.9 and 4.4 UI/L did not discriminate between the 27 patients (46.6%) who remained euthyroid from those who had relapse of hyperthyroidism. Thus a different TRAb cut-off at the end of treatment was calculated to identify patients who became again hyperthyroid. This TRAb cut-off value was 3.85 UI/L (sensitivity 85.3%; specificity 96.5%). All but 1 patient who had serum TRAb values above 3.85 UI/L became hyperthyroid after MMI was withdrawn (positive predictive value 96.7%). In these patients, relapse of hyperthyroidism was independent of the changes in serum TRAb concentrations and occurred after a median period of 8 weeks (range 4-48 weeks). Hyperthyroidism also developed in 5 of 24 patients who had serum TRAb concentrations lower than 3.85 UI/L at the end of MMI treatment. In these 5 patients the relapse of hyperthyroidism occurred after a median period of 56 weeks (range 24-120 weeks) and was always accompanied by an increase in serum TRAb concentrations.

**Conclusions:** TRAb persist in the blood of most patients with GD after 18 months of MMI treatment. Both the frequency and the time of appearance of hyperthyroidism are closely correlated with serum TRAb concentrations at the end of MMI treatment. Our data would suggest that TRAb maintain stimulating activity after a full course of MMI treatment in the large majority of patients with GD. However, it is likely that the potency of these antibodies and/or the thyroid response to them change during treatment, as suggested by the different values measured in euthyroid control subjects and in euthyroid patients after MMI treatment.
COMMENT
Present investigation is a retrospective study of 58 patients with newly diagnosed Graves’ disease (GD) treated with a full course of antithyroid drugs (ATD). The study shows that TRAb persists in most patients and that the time of recurrence of hyperthyroidism is closely correlated with serum TRAb values at the end of MMI treatment. At the end of MMI treatment, mean serum TRAb was 4.4 UI/L (i.e. 3-fold lower than values at diagnosis), still significantly higher than in control subjects. Furthermore, 76% of patients still had a positive TRAb value (> 1.45 UI/L). There was a significant correlation between TRAb value at the end of MMI and recurrence of hyperthyroidism (in 59%) and development of hypothyroidism (in 7%).

In this study, the TRAb radioreceptor assay that was used did not permit discrimination between stimulating, blocking or neutral antibodies. However, the data suggest that the antibodies maintain stimulating activity after a full course of MMI treatment in a majority of patients. Because most remitting patients and approximately 1/3 of those with a relapse had TRAb values overlapping the ‘normal range’ at the end of MMI treatment, the authors conclude that measurement of these antibodies is not useful in predicting the clinical course after MMI withdrawal. However, they also indicate that persistence of TRAb in the blood of patients with GD, after ATD therapy has been discontinued, may play a role in the relapse of hyperthyroidism, especially in patients who maintain a TRAb value above 4.4 UI/L.
(Daniel Glinoer MD, PhD)

See Figures below
**Topic:** DRUG EFFECTS ON THYROID FUNCTION

**Title:** Metformin may inhibit thyrotropin (TSH) secretion in patients with hypothyroidism treated with thyroxine.

**Authors:** Vigersky RA, Filmore-Nassar A, Glass AR (Washington DC, USA)


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**SUMMARY**

**Context:** Drug-drug interactions are common but often are discovered only long after initial drug release. Metformin has been available in the United States for 9 years and elsewhere for many years, but as of yet there are no reports that the drug modifies thyroid hormone economy.

**Objective:** The objective of the study was to describe the clinical and biochemical findings of 4 patients with chronic hypothyroidism, previously euthyroid on fixed doses of l-T4 for several years, in whom the metformin was initiated.

**Design:** This was a retrospective review.

**Setting:** The study was conducted at a tertiary care military hospital (Walter Reed Army Medical Center) providing care to active-duty soldiers, sailors and marines, retirees of the armed forces, and their eligible dependents.

**Participants:** Four patients with chronic hypothyroidism who were placed on metformin participated in the study.

**Intervention, Main Outcome Measurement:** Serum TSH, free T4, and free T3 levels were measured during metformin treatment.

**Results:** Initiation of treatment with metformin (three for diabetes mellitus and one for non-alcoholic steato-hepatitis) caused suppression of TSH to subnormal levels without clinical symptoms of hyperthyroidism in any patients. There was no change in free T4 or free T3 in patient 1.

**Conclusions:** No other potential causes of TSH suppression, including medication changes or interference in the TSH assay, could be identified. The mechanism of the fall in serum TSH in these four patients is unclear at present time. Should these findings be confirmed in larger prospective studies, metformin’s ability to suppress TSH without causing clinical or chemical hyperthyroidism might render this drug a useful adjunct to the treatment of patients with thyroid cancer.

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**COMMENT**

The four patients described in this retrospective study were 2 males and 2 females (age range: 58-75 yrs), chronically treated with l-T4 after radiiodine ablation for Graves’ disease (1), for Hashimoto’s thyroiditis (1), and after thyroidectomy (2). Patient 1 was given 1500 mg of metformin daily and it was found (eight months later) that his serum TSH had decreased from 1.6 to 0.11 mU/L. Patient 2 was given 500 mg of metformin daily and it was found (two months later) that her serum TSH had decreased from 0.64 to 0.31 mU/L. Patient 3 was given 1000 mg of metformin daily...
and it was found (interval not given) that his serum TSH had decreased from 1.3 to 0.36 mU/L. Finally, patient 4 was given 500 mg of metformin daily and it was found (three months later) that her serum TSH had decreased from 1.9 to 0.39 mU/L. Thus, this is a small study of only 4 patients, with inherent weaknesses mainly because it was retrospective. Serum free T\textsubscript{4} was not measured before metformin administration. Patients were studied at different time points while taking different doses of metformin. Overall, the changes in serum TSH were rather small. If true, the effects of metformin to reduce serum TSH could be explained by interferences on l-T\textsubscript{4} biodisponibility, changes in thyroid hormone binding proteins properties, alterations in thyroid hormones peripheral metabolism, or by central inhibition of TSH secretion (dopamine-like effect). Despite the limitations, this study has the interest of showing that drugs may interfere with thyroid function and obviously needs confirmation by a large prospective study before accepting the highly speculative conclusion of the authors.

(Daniel Glinoer, MD; PhD)

See Table below

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)/gender</th>
<th>Underlying disease</th>
<th>Dose of (l-T_4) ((\mu)g)</th>
<th>Duration of DM (yr)</th>
<th>Metformin (mg/d)</th>
<th>Baseline (fT_4) (pmol/liter)</th>
<th>Post-Met (fT_4) (pmol/liter)</th>
<th>Baseline TSH ((\mu)U/ml)</th>
<th>Post-Met TSH ((\mu)U/ml)</th>
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<td>Normal</td>
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<tr>
<td>1</td>
<td>58/M</td>
<td>Graves' disease treated with I-131</td>
<td>160</td>
<td>N/A</td>
<td>1500</td>
<td>15.3–23.9 (n = 5)</td>
<td>13.4</td>
<td>1.19–1.90</td>
<td>0.11</td>
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<tr>
<td>2</td>
<td>67/F</td>
<td>Hashimoto's</td>
<td>150</td>
<td>1500</td>
<td>13.2</td>
<td>18.0</td>
<td>1.4</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>66/M</td>
<td>Thyroidectomy for MNG</td>
<td>125</td>
<td>1000</td>
<td>1.66\textsuperscript{a}</td>
<td>1.3</td>
<td>0.36</td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>75/F</td>
<td>Thyroidectomy for PTC</td>
<td>175</td>
<td>5</td>
<td>35.6</td>
<td>24.7</td>
<td>0.39</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

M, Male; F, female; DM, diabetes mellitus; MNG, multinodular goiter; PTC, papillary thyroid carcinoma; Met, metformin; N.D., not done; \textsuperscript{a} Analog assay with normal range 1.01–1.79 ng/dl.
**Topic:** THYROXINE ADMINISTRATION TO EUTHYROID PREGNANT WOMEN WITH THYROID AUTOIMMUNITY FEATURES

**Title:** Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications.

**Authors:** Negro R, Formoso G, Mangieri T, Pezzarossa A, et al. (Lecce, Italy)


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**SUMMARY**

**Context:** Euthyroid women with autoimmune thyroid disease show impairment of thyroid function during gestation and seem to suffer from a higher rate of obstetrical complications.

**Objective:** The authors sought to determine whether these women suffer from a higher rate of obstetrical complications and whether l-T4 treatment exerts beneficial effects.

**Design:** This was a prospective study.

**Setting:** The study was conducted in the Department of Obstetrics and Gynecology.

**Patients:** A total of 984 pregnant women were studied from November 2002 to October 2004; 11.7% were thyroid peroxidase antibody positive (TPOAb(+)).

**Intervention:** TPOAb(+) patients were divided into two groups: group A (n = 57) was treated with LT(4), and group B (n = 58) was not treated. The 869 TPOAb(-) patients (group C) served as a normal population control group.

**Main Outcome Measures:** Rates of obstetrical complications in treated and untreated groups were measured.

**Results:** At baseline, TPOAb(+) had higher TSH compared with TPOAb(-); TSH remained higher in group B compared with groups A and C throughout gestation. Free T4 values were lower in group B than groups A and C after 30 wk and after parturition. Groups A and C showed a similar miscarriage rate (3.5 and 2.4%, respectively), which was lower than group B (13.8%) [P < 0.05; relative risk (RR), 1.72; 95% confidence interval (CI), 1.13-2.25; and P < 0.01; RR = 4.95; 95% CI = 2.59-9.48, respectively]. Group B displayed a 22.4% rate of premature deliveries, which was higher than group A (7%) (P < 0.05; RR = 1.66; 95% CI = 1.18-2.34) and group C (8.2%) (P < 0.01; RR = 12.18; 95% CI = 7.93-18.7).

**Conclusions:** Euthyroid pregnant women who are positive for TPOAb develop impaired thyroid function, which is associated with an increased risk of miscarriage and premature deliveries. Substitutive treatment with l-T4 is able to lower the chance of miscarriage and premature delivery.
EDITORIAL

Usefulness of l-T4 administration in euthyroid pregnant women with thyroid autoantibodies.

A group of 984 euthyroid pregnant women with thyroid autoantibodies (TPO-Abs) was investigated with the aim to assess whether these women would benefit from l-T4 administration to improve pregnancy outcome and reduce the rates of miscarriage and premature delivery.

Measurements of TPO-Abs and thyroid function tests were carried out at the first prenatal visit, repeated at 20 and 30 weeks of gestation and 3 days after delivery. One hundred and fifteen women (11.7%) were shown to have positive thyroid autoantibodies (‘TAI positive’). An interesting observation was that TAI-positive women were significantly older than the control population.

TAI-positive women were randomly assigned to group A (who received l-T4) or group B (with no treatment). TAI-negative women served as controls. The trial design was randomized and prospective, but not placebo-controlled and not double-blind, and the medical participants to the study were kept unaware of the group to which patients belonged. A remarkable feature of this study was that TAI-positive women were significantly older than the control population.

Serum TSH levels also increased progressively in the control group but much less, from 1.1 to 2.1 µU/ml at term, as a result of mild iodine deficiency in this population. Not only was the spontaneous serum TSH increment quantitatively significantly less marked in controls, compared with group B women, but also the control and group A (treated) women were able to maintain normal serum free T_4 levels, whereas serum free T_4 levels decreased by 30% during gestation in group B women, as a consequence of the reduced functional thyroid reserve associated with chronic thyroiditis.

The most novel and important result of present study was that l-T4 administration allowed for a significant decrease in the rate of obstetrical complications. The miscarriage rate was reduced by 75% and the frequency of premature delivery by 69%. These results confirm data produced previously by other investigators who have shown an association between thyroid autoimmunity and adverse obstetrical outcome, even in the absence of thyroid dysfunction. Their importance is that for the first time in a prospective randomized study, a clear benefit of l-T4 administration was shown on the outcome of pregnancy in women with thyroid autoimmunity and without evident perturbation of thyroid function in early gestation.

An association between the risk of a miscarriage and autoimmune thyroid disease (AITD) was first reported 15 years ago and the statistical strength of this association has been largely confirmed in several population studies. AITD - without overt thyroid dysfunction - is associated
with a 3- to 5-fold increase in overall miscarriage rate. In a recent meta-analysis of all case-controlled and longitudinal studies published since 1990, the overall relative risk of miscarriage was confirmed to be increased by approximately 3-fold in women with AITD.

Finding an association does not imply a causal relationship, and the aetiology of an increased pregnancy loss in women with AITD remains largely unknown. Three hypotheses have been proposed. The first hypothesis holds that pregnancy loss is not directly related to the presence of circulating thyroid antibodies. In this view, AITD could represent only a marker of an underlying more generalized autoimmune imbalance that, in turn, would explain a greater rejection rate of the foetal graft. The second hypothesis holds that the presence of AITD could be associated with a subtle deficiency in thyroid hormone concentrations or a lesser ability of thyroid function to adapt adequately to the changes associated with the pregnant state because of a reduced thyroid functional reserve characteristic of chronic thyroiditis. The third hypothesis holds that AITD could act by delaying the occurrence of conception because of its known association with infertility. Thus, TAI-positive women tend to become pregnant at an older age (3-4 years older, on the average) and older women are more prone to pregnancy loss. These hypotheses do not contradict one another, and it remains plausible that the increased risk of pregnancy loss associated with AITD is multi-factorial, eventually resulting from a combination of several independent deleterious factors. If underlying mild thyroid deficiency plays a role to explain increased pregnancy loss, this would constitute a strong argument to screen systematically women for thyroid antibodies or mild thyroid insufficiency (before conception when they express the desire of being pregnant or as soon as a pregnancy has started) and give them the potential benefit of l-T4 treatment.

Until the present study, only three other studies have investigated whether a medical intervention would benefit women with thyroid autoimmunity. In a study by Vaquero in 2000, TAI-positive women with 2 previous first-trimester miscarriages were subdivided into women who received iv immunoglobulins during pregnancy and women who received dessicated thyroid extracts before conception and during pregnancy. Pregnancy success rate was 81% in the l-T4 group, compared with 55% in the IgG group. Negro et al. in 2005 reported the results of l-T4 administration in euthyroid TAI-positive infertile women undergoing IVF. The miscarriage rate was reduced to 33% compared with 52% in the untreated controls, but the study failed to reach statistical significance. Finally in a slightly different clinical setting, a study by Abalovich et al. in 2000 showed that it was not so much the diagnosis of overt versus subclinical hypothyroidism that mattered in relation with the outcome but mainly the adequacy of l-T4 treatment. Pregnancy outcome was compared in 27 hypothyroid women who received an adequate l-T4 treatment with 24 hypothyroid women in whom the treatment was not adequately adjusted during gestation. In pregnant women with an adequate treatment, the frequency of abortions was minimal and pregnancies carried to term without complications, while in the women with an inadequate treatment, pregnancy ended with abortion in 60-71% of the women.
What are the main lessons to be learned from present study? First, it confirmed previously known findings, namely that euthyroid women with thyroid antibodies tend to be older when becoming pregnant; that even though euthyroid in early gestation, these women tend to have a reduced thyroid functional reserve; that they have an increased risk for obstetrical complications such as miscarriage and premature delivery; and finally that when given the benefit of treatment with thyroid hormone, they normalize thyroid function and behave normally. Furthermore, the study clearly showed the benefits of l-T4 administration in pregnant women withAITD, not only to correct maternal thyroid function but also to reduce markedly the rate of undesired obstetrical events and lower their prevalence down to that found in healthy controls. There is no reason to believe that l-T4 played a role in altering underlying autoimmunity. Also, the age difference between TAI-positive and controls was not large enough to explain the different rates of miscarriage and premature birth (and even less changes in these rates after l-T4 treatment). Present study therefore leads us to conclude that among the three hypotheses evoked above, the second one, i.e. a subtle deficiency in thyroid hormone concentration and/or a lesser ability of maternal thyroid function to adapt adequately in women with AITD, was the main reason for the beneficial effects of thyroid hormone administration. If confirmed by future studies, these results would constitute an additional argument to screen pregnant women systematically for the presence of asymptomatic chronic autoimmune thyroiditis and/or mild thyroid underfunction to give such women the benefit of thyroid hormone treatment.

(Extracts from the Editorial (JCEM) to the article written by Daniel Glinoer, MD; PhD)
**Topic:** GRAVES’ DISEASE AND IODINE RESTRICTION

**Title:** Restriction of dietary iodine does not ameliorate the early effect of antithyroid drug therapy for Graves’ disease in an area of excessive iodine intake.

**Authors:** Hiraiwa T, Ito M, Imagawa A, Takamatsu J, et al. (Osaka & Kobe; Japan)


**SUMMARY**

**Context:** The close relationship between iodine intake and the effects of antithyroid drugs (ATD) for Graves’ disease (GD) has been well established. However, it remains unknown whether restriction of dietary iodine improves the effect of ATD.

**Objective:** The present study aimed to clarify this issue in Japanese patients with GD who routinely ingest large amounts of dietary iodine.

**Design:** The authors performed a prospective clinical study in 81 patients with newly diagnosed GD who were divided into an iodine-restricted group and a control group.

**Main Outcome Measurement:** Urinary iodine, thyroid hormones and TSH receptor antibody were measured during the first 8 weeks of ATD therapy.

**Results:** Urinary iodine concentrations in the iodine restricted group were significantly lower than in the control group (P = 0.04). However, there were no significant differences in the decrease of thyroid hormones and TSH receptor antibody between the two groups.

**Conclusions:** Restriction of dietary iodine does not ameliorate the effect of ATD therapy for GD in an area of excessive iodine intake.

**COMMENT**

Variation in iodine intake affects the efficacy of antithyroid drugs (ATD). Because Japan remains a country with an excessive iodine intake (due to a large consumption of seaweeds and kelp in the population) and a high prevalence of Graves’ disease, it was reasonable to carry out such a study with the aim to assess whether patients with GD given ATD therapy would benefit from iodine restriction.

The authors succeeded in reducing the iodine intake in their patients. In the subgroup of 31 patients put on an iodine-restricted diet, the median urinary iodine concentration (UIC) decreased from ~200 to 150 µg/gr creatinine, after 8 weeks. This may not seem much, but it is of interest that in the control group during the same period, the median UIC increased from 200 to 340 µg/gr creatinine. How can this be explained? Presumably because in the noniodine-restricted GD patients, the onset of therapy with ATD blocked the glandular uptake of iodine, thereby inducing a proportionally larger release of iodine into the urine.
Scrutinizing the changes in free T4 and free T3 concentrations over the first 8 weeks of ATD therapy in both groups, the authors found no difference in the hormone decrements. Finally, they found no change in the TSH receptor antibody titers between the 2 groups; these values remained essentially unchanged. The latter observation is not surprising, since it is well known that TSH receptor antibody titers, under ATD treatment, may take up to 6 months before a significant decrease can be seen.

There are two main weaknesses in the design of the present study. The first weakness is that despite reaching a significant degree of iodine restriction, this was clearly not enough to induce real iodine deficiency. The levels of UIC in the iodine-restricted group were still higher, on the average, that in patients with GD followed in Belgium, for instance. The second weakness was that the study was much too short. One would have liked to see how the thyroid function parameters, including the TSH receptor antibody titers, would change in the longer term, say after 6 to 12 months with ATD therapy between the two groups.

(Daniel Glinoer, M.D.; Ph.D.)

See Figure below

![Graph showing the sequential changes in median urinary iodine (Uf)/urinary creatinine (Ucr) ratio between the control and iodine restricted (IR) groups. Two-way repeated-measures ANOVA; p=0.043. Wk: week.](image-url)
**Topic:** HASHIMOTO’s DISEASE, ONCOGENES & THYROID CANCER

**Title:** RET/papillary thyroid cancer rearrangement in non neoplastic thyrocytes: follicular cells of Hashimoto’s thyroiditis share low-level recombination events with a subset of papillary carcinoma.

**Authors:** Rhoden KJ, Unger K, Salvatore G, Yilmaz Y, et al. (New Haven, USA; Neuherberg, Germany; & Napoli, Italy)

**Reference:** Journal of Clinical Endocrinology and Metabolism 91: 2414-2423, 2006

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**SUMMARY**

**Context:** RET/papillary thyroid cancer (PTC) is a marker for papillary thyroid carcinoma, but its specificity has been questioned because of the disputed identification of RET/PTC in Hashimoto’s thyroiditis (HT), oncocytic tumors, and other thyroid lesions.

**Objective:** The objective of the study was to determine 1) whether RET/PTC occurs in non neoplastic follicular cell of HT, and 2) its recombination rate in thyroid tumors.

**Design/Patients:** Forty three samples from 31 cases of HT were examined using FISH (interphase fluorescence in situ hybridization) with RET probes spanning the breakpoint region; real-time PCR to quantify RET/PTC1, RET/PTC3, and c-RET transcripts; and RT-PCR after laser capture micro-dissection to enrich samples for follicular cells. The results were compared with those similarly obtained in 34 papillary carcinomas, eight thyroid oncocytic tumors, and 21 normal thyroids.

**Results:** Normal samples showed no RET rearrangement. Sixty-eight percent (15 of 22) of HT were positive by FISH; in all thyroiditis, signals were localized to rare non neoplastic follicular cells; low-level RET/PTC was identified in 17% (5 of 29) of thyroiditis cases by real-time RT-PCR and in an additional 6 of 11 real-time negative cases after increasing the sensitivity of detection with laser capture micro-dissection. Low RET/PTC1 levels were detected in 26% (9 of 34) of papillary carcinomas with an expression pattern and proportion of FISH-positive cells similar to those of the thyroiditis. Forty-seven percent (16 of 34) of papillary carcinomas and one oncocytic carcinoma expressed high RET/PTC1 mRNA levels.

**Conclusions:** Low-level RET/PTC recombination occurs in non neoplastic follicular cells in HT and in a subset of papillary thyroid carcinomas. RET/PTC expression variability should be taken into account for molecular diagnosis of thyroid lesions. Overlapping molecular mechanisms may govern early stages of tumor development and inflammation in the thyroid.

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**COMMENT**

RET/PTC is an oncogene that results from a fusion between the RET gene (coding for the tyrosine kinase receptor) and the H4 gene. As of today, 11 different fusion partners of RET have been identified, giving rise to specific RET rearrangements, among which the most common types are RET/PTC1 and RET/PTC3. The fusion results in constitutive activation of the gene, thereby...
explaining its oncogenic nature, clearly demonstrated in follicular thyroid cells. RET/PTC is found in 20-40% of adult sporadic papillary thyroid carcinomas, and its prevalence is even higher in children and patients exposed to radiation (i.e. Chernobyl).

Originally, the RET rearrangement was considered specific for papillary carcinoma. More recently, however, the specificity of RET/PTC has been challenged by observations indicating that it could also be detected in other thyroid lesions (adenomas, benign and malignant oncocytomas) and even in some non neoplastic conditions such as Hashimoto’s thyroiditis (HT). Some of these studies have led to the conclusion that RET/PTC1 and RET/PTC3 rearrangements could perhaps be found in virtually all thyroid glands affected by HT, suggesting that multiple occult papillary thyroid carcinomas coexist with this common autoimmune disease. If such conclusion was correct, it would lead to a much more aggressive attitude towards the nodules that are so frequently associated with HT. Two important limitations must, however, be kept in mind. First, these studies had substantial technical limitations, rendering their conclusion debatable. Second, clinicians know that cancer is NOT frequently associated with HT, even after patients have been followed up for 30-40 years.

Using highly sophisticated and reliable techniques, the article by Rhoden et al. conclusively showed that RET/PTC was detectable in the majority of thyroid glands with HT, but that the positivity was segregated in rare follicular cells. Furthermore, the detection level was extremely low, with a cut-off point set at 3.5%, while most investigators use a cut-off limit of 10%. If a cut-off limit of 10% was used, virtually all positive samples detected in the present study would have been considered negative.

Despite these limitations, the present article is important because it provides additional evidence that RET/PTC could be present within thyroid glands affected by HT. The significance of this low-level event, with respect to the risk of neoplastic transformation, remains to be elucidated.

As stated by Dr Nikiforov who wrote an excellent editorial to accompany the publication of this article (and from whom I borrowed most of my commentaries), “we should separate the proven findings from speculation and exert caution, particularly when the well-being of patients is at stake”.

(Daniel Glinoer, M.D.; Ph.D.)
**SUMMARY**

**Background:** Total or near-total thyroidectomy is increasingly used to treat benign thyroid conditions. Lifelong treatment with thyroxine (T4) is then required, but the optimal dose is difficult to predict. This study investigated factors that might predict the ideal T4 dose, with the aim of reducing delays in achieving normal thyroid function after surgery.

**Patients and methods:** Data on 98 patients who underwent total or near-total thyroidectomy for benign disease were reviewed retrospectively. Patient and operative variables that might predict time to achieve normal thyroid function and optimal T4 replacement dose were examined.

These data were then used to formulate an algorithm for T4 dosage, based on patients' weight, that was subsequently applied prospectively to a comparable group of 27 patients.

**Results:** The median time to achieve normal thyroid function was 14.5 (range 2-120) weeks before introduction of the algorithm, and was greater in patients needing large changes in T4 dose. In multivariate analysis, the best predictors of optimal T4 dosage were bodyweight ($r = 0.46$, $p < 0.001$) and age ($r = -0.32$, $p < 0.001$). Subsequent use of a weight-related algorithm improved time (median of 8 weeks) to achieve normal thyroid function.

**Conclusions:** The T4 replacement dosage after total or near-total thyroidectomy is largely influenced by bodyweight. Use of a weight-related algorithm improves patient care compared with use of standard T4 dose-titration methods.

**COMMENT**

Much of the literature on the requirements for l-thyroxine (T4) replacement has focused on primary hypothyroidism and these studies may not accurately predict T4 requirements after total thyroidectomy. Present study was performed by thyroid surgeons in patients operated for Graves’ disease or a multinodular goitre. The results confirm previous findings of a relationship between the final T4 dose and bodyweight as well as an inverse relationship with age. In the first part of their study a traditional dose-titration method for T4 replacement was used, with a starting dose of 100 µg/day. The duration of the subsequent titration phase to achieve normal thyroid function was largely dependent upon the magnitude of the change in T4 dose from baseline, with increments of 25-50 µg/day at intervals of 4-8 weeks. Normality was defined by a serum TSH level within the normal population range or – in previously thyrotoxic patients – a serum free T4 level within the normal population range with a subsequent normal TSH at the same dose. The median T4 dose required to achieve normal thyroid function was 1.7 µg/kg (range 1.1-3.1), which is higher than the baseline ‘standard’ dose of 100 µg (or 1.3 µg/kg). Moreover, as T4 requirements were more closely related to lean body mass than bodyweight alone, leaner patients required proportionally greater
doses of T4 per unit bodyweight, although heavier patients required higher absolute T4 doses.

These retrospective data were then used to develop a weight-related algorithm for calculating the postoperative T4 dose (in 25 µg intervals, for simplicity of dosage), that was subsequently applied to a second cohort of patients. Using their algorithm, the initial T4 dose was higher (median of 125 µg/d) and there was a significant reduction in the necessary subsequent changes to reach the final T4 dose (within 25 µg of baseline) and thus in the time needed to achieve normal thyroid function. The results of this clinical study are readily applicable to our daily practice.

(Marie Bex, MD)

See table and figures below

**Table 1** Weight-related algorithm for calculation of postoperative T4 dose

<table>
<thead>
<tr>
<th>Patient weight (kg)</th>
<th>T4 dose (µg)</th>
</tr>
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<tbody>
<tr>
<td>≤ 53</td>
<td>100</td>
</tr>
<tr>
<td>54–86</td>
<td>125</td>
</tr>
<tr>
<td>87–108</td>
<td>150</td>
</tr>
<tr>
<td>&gt; 108</td>
<td>175</td>
</tr>
</tbody>
</table>

**Fig. 1** Time to achieve normal thyroid function before introduction of algorithm in relation to change in thyroxine dose from baseline (final ‘ideal’ dose minus initial dose). Median, interquartile range and range are represented by points, boxes and whiskers respectively.

**Fig. 2** Effect of bodyweight on final weight-adjusted T4 dose before introduction of algorithm. Median, interquartile range and range are represented by points, boxes and whiskers respectively. *z = 3.45, P < 0.001 (Mann–Whitney U test)*
Topic: NODULAR GOITER AND RADIOIODINE TREATMENT

Title: Incidence of postradioiodine immunogenic hyperthyroidism (Graves’ disease) in relation to a temporary increase in thyrotropin receptor antibodies after radioiodine therapy for autonomous thyroid disease.

Authors: Schmidt M, Gorbauch E, Dietlein M, et al. (Cologne, Germany)

Reference: Thyroid 16: 281-288, 2006

SUMMARY

Background: Retrospective analysis of the incidence of postradioiodine (RI) immunogenic hyperthyroidism (i.e. Graves’ disease “GD”) in relation to a temporary increase in TSH-receptor antibodies (TRAb) without overt hyperthyroidism after RI therapy for autonomous thyroid disease.

Patients and methods: A total of 1357 patients had undergone RI treatment for autonomous thyroid disease in the institution between 2000 and 2003. On pre-treatment evaluation, 565 patients (41.6%) had solitary autonomous toxic nodule (SATN), 693 patients (51.1%) a toxic multinodular goiter (TMNG), and 99 patients (7.3%) a diffuse thyroid disease (DISS). Ultrasound examinations and thyroid scintigraphy were performed before and after RI therapy. TRAb was measured using a sensitive assay with the human TSH receptor as antigen.

Results: Fifteen of 1357 patients (1.1%) developed post-RI hyperthyroidism between 1 and 13 months after RI treatment, with clinically overt hyperthyroidism and an elevation in TRAb titers. The breakdown among the patients was as follows: SATN: 8/565, 1.4%; TMNG: 6/693, 0.9%; DISS: 1/99, 1%). Patients with elevated TPO-Ab before RI therapy had an almost 10-fold higher risk of developing post-RI immunogenic hyperthyroidism (6/57; 10.5%). A total of 13 of 999 patients with TRAb measurements after RI therapy had increased titers of TRAb and, to some extent, of TPO-Ab without development of clinically overt hyperthyroidism.

Conclusions: There is an estimated 1.1% risk of a temporary increase of TSH receptor antibodies after RI therapy for autonomous thyroid disease without development of clinically overt hyperthyroidism.

COMMENT

When radiiodine (RI) is given for a solitary toxic adenoma or a multinodular toxic goiter, the treatment is aimed at destroying the autonomous follicular thyroid cells. These dying cells release many antigenic constituents and it is therefore understandable that a transient increase (or an onset) of thyroid autoimmunity may follow RI administration. Thus, RI treatment may lead to definitive hypothyroidism by irreversible destruction of thyroid tissue, autoimmune hypothyroidism by chronic autoimmune thyroiditis (perhaps enhanced by RI administration), and finally in rare instances to autoimmune hyperthyroidism by RI-related induction of antibodies to the TSH receptor with stimulating activity. The latter condition would logically be found more frequently when RI treatment has been given for toxic autonomous lesions (i.e. adenomas), since radioiodine
tends to destroy primarily the autonomous cells and not the ‘normal’ thyroid tissue which is usually functionally ‘dormant’. In present study, the authors showed that immunogenic hyperthyroidism (Graves’ disease) was present in 1.5% of the treated patients, with a clear-cut increase in TRAb titers and various degrees of hyperthyroidism, with abnormally elevated levels of serum free T4 and free T3 ranging up to 6.3 ng/dl and 2100 pg/dl, respectively. It is also logical that the frequency of these abnormality, induced – or aggravated – by RI administration, was significantly greater in the patients who presented already features of thyroid autoimmunity before the treatment. Finally, it should be remembered that similar cases of induced thyroid autoimmunity have also been reported in patients with differentiated thyroid cancer, who received RI therapy to ablate residual thyroid tissue or distant metastases, although such occurrence remains exceptional.

(Daniel Glinoer, M.D.; Ph.D.)

See Figure below

**FIG. 1.** Development of postradioiodine immunogenic hyperthyroidism in a patient with unifocal thyroid autonomy. This patient developed postradioiodine immunogenic hyperthyroidism 3 months after radioiodine therapy for unifocal thyroid autonomy. The first scintigram with pertechnetate (top left) demonstrates focal uptake, which is confirmed by a post-therapy scintigram of iodine-131 (bottom left). Diffuse uptake into the thyroid is shown in a scintigram (top right), made 3 months after radioiodine therapy. At that time overt hyperthyroidism had developed and a second post-therapy scintigram of iodine-131 (bottom right) confirms this finding, this patient having received a second application of radioiodine.