**Topic:** TSHR-Ab AND GRAVES’ OPHTHALMOPATHY

**Title:** Thyrotropin receptor autoantibodies are independent risk factors for Graves’ ophthalmopathy and help to predict severity and outcome of the disease.

**Authors:** Eckstein AK, Plicht M, Lax H, Nenhauser M, Mann K, Lederbogen S, Heckman C, Esser J, & Morgenthaler NG (Essen & Berlin, Germany)

**Reference:** Journal of Clinical Endocrinology and Metabolism 91: 3464-3470, 2006

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**SUMMARY**

**Context:** Little is known about the relationship between TSH-receptor antibody (TSHR-Ab) and the severity and course of ophthalmopathy.

**Objective:** The objective of this study was to examine whether TSH-receptor antibody [TSH binding inhibitory antibodies (TBII)] levels are associated with the severity of Graves’ ophthalmopathy (GO) over the entire course of the disease.

**Methods:** Each evaluation consisted of determination of the Clinical Activity Score (CAS), a symptom severity score, and measurement of serum TSHR-Ab by radio-receptor assay (normal: <1.5 IU/L). Patients with a CAS >2 at any time were offered oral or intravenous glucocorticoids. Patients who had impaired ocular motility or in whom a CAS increased after withdrawal of glucocorticoid therapy were treated with orbital irradiation.

**Patients:** A total of 159 patients with GO were followed for 12-24 months. One year after the first symptoms of GO, all patients were classified into mild or severe GO according to their clinical manifestations. TBII were measured every 3 months after onset of GO. Receiver operating characteristics plot analysis was performed to assess the power to discriminate both patient groups by TBII (specificity > 90%).

**Results:** TBII levels and prevalence at each time point during follow-up were significantly higher in patients with a severe course of GO compared with patients with a mild course of GO. Prognostic statements on the course of the disease were possible for about half of the GO patients at all time points (except for the first). If at first presentation and at consecutive time points, TBII levels were less than 5.7, 2.6, 1.5, 1.5, 1.5 and 1.5 IU/L, the patients had a 2.3- to 15.6-fold higher chance of a mild course. If 5-8 months after GO onset and at consecutive time points, TBII were above 8.8, 5.1, 4.8, 2.9 and 2.8 IU/L, the patient had a 8.7- to 31.1-fold higher risk of a severe course. This relationship of TBII to the severity was independent from age and smoking.

**Conclusions:** Follow-up measurements of TBII allow, in half of the patients, assessment of the prognosis of GO and therefore, could be of additional help for the disease management.

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**COMMENT**

Graves’ ophthalmopathy (GO) is clinically relevant in approximately 40% of patients with Graves’ disease (if eyelid signs are included). Several factors are known to increase the risk of GO, namely tobacco smoking, gender, type of treatment of hyperthyroidism, older age, stress and drugs. Present retrospective study proposes
that measurement of TSH receptor antibody (TSHR-Ab) may help predict the evolution of GO severity. A high TSHR-Ab soon after the onset of GO and that remains persistently high, would predict the severity of the course of GO. Thus, determination of the level of TSHR-Ab could influence the management of the disease. Surprisingly, severity of GO was determined later, after a follow-up period of 11-14 months, after various antithyroid treatments and also after many patients had been treated with glucocorticoids, irradiation or both. Half of the patients were in the grey zone, probably because of the non-uniform classification of patients, heterogeneity of the group, different antithyroid treatments used, modification of the degree of GO severity and activity of the disease during follow-up. Other prospective follow-up studies are needed to confirm the present hypothesis.

(Chantal Daumerie, M.D.; Ph.D.)

See Figure below

![Figure 3](image-url)

**Fig. 3.** Cutoff TBII levels for the prediction of a good course of GO (gray line) and for the prediction of a bad course of GO (black line). For patients with a TBII level within the gray zone, no prognostic statement for the course of their GO is possible.
**Topic:** THYROGLOBULIN MEASUREMENTS IN THE FOLLOW-UP OF THYROID CANCER PATIENTS

**Title:** Monitoring thyroglobulin in a sensitive immunoassay has comparable sensitivity to recombinant human TSH-stimulated thyroglobulin in the follow-up of thyroid cancer patients.

**Authors:** Smallridge RC, Meek SE, Morgan MA, Gates GS, Fox TP, Grebe S, & Fatourechi V (Mayo Clinic of Medicine, Jacksonville & Rochester, USA)

**Reference:** Journal of Clinical Endocrinology and Metabolism 92: 82-87, 2007

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**SUMMARY**

**Context:** Most thyroglobulin (Tg) assays have a sensitivity of 0.5-1 ng/ml. A minority of patients with undetectable T\textsubscript{4}-suppressed Tg levels have a recombinant human TSH (rhTSH)-stimulated Tg above 2 ng/ml and identifiable residual disease.

**Objective:** The objective was to determine whether a Tg assay with improved sensitivity could eliminate the need for rhTSH stimulation when baseline Tg is below 0.1 ng/ml.

**Design:** A retrospective study of two academic endocrine practices was conducted.

**Population:** A total of 194 patients undergoing rhTSH stimulation participated in the study.

**Results:** Of the 80 patients with Tg below 0.1 ng/ml, two (2.5%) had rhTSH-stimulated Tg above 2 ng/ml. One other patient with stimulation to 0.3 ng/ml and negative \textsuperscript{123}I scan had an ultrasound-detected malignant lymph node resected. None had \textsuperscript{131}I/\textsuperscript{123}I imaging after rhTSH stimulation suggestive of local recurrence or distant metastasis. If T\textsubscript{4}-suppressed Tg was 0.1-0.5 or 0.6-2.0 ng/ml, rhTSH Tg was above 2 ng/ml in 24.2 and 82.4%, respectively.

**Conclusions:** Patients with differentiated thyroid carcinoma and a T\textsubscript{4}-suppressed serum Tg below 0.1 ng/ml rarely have a rhTSH-stimulated Tg above 2 ng/ml, and none of these patients had \textsuperscript{131}I or \textsuperscript{123}I imaging after rhTSH stimulation suggestive of local recurrence or distant metastasis. The authors recommend monitoring such patients with a T\textsubscript{4}-suppressed Tg level and periodic neck ultrasonography. An increase in T\textsubscript{4}-suppressed serum Tg to a detectable level or the appearance of abnormal lymph nodes by physical or ultrasound examination should prompt further investigation.

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**COMMENT**

The development of Tg assays and recombinant human TSH (rhTSH) have provided the means for clinicians to detect residual (or recurrent) thyroid cancer. The combined use of serum Tg and whole body scan (WBS) after stimulation with rhTSH is particularly effective in identifying small residual foci of thyroid tissue (either normal glandular remnants and/or cancer). This study is based on the experience of the Mayo Clinic group, using a serum Tg assay with a clinical detection limit of 0.1 ng/ml, i.e. a sensitivity considerably lower than the 0.5 to 1.0 ng/ml levels reported in
other studies. The data showed that in 80 patients with T₄-suppressed (i.e. under treatment) Tg below 0.1 ng/ml, Tg remained undetectable in 47/80 patients (59%) after rhTSH; furthermore in 78/80 patients (97.5%), stimulated Tg was below 2 ng/ml. Only one of 80 patients had treatment for recurrent disease. Thus, a rare patient may have detectable disease despite a very low serum Tg (and in their case negative imaging by scintigraphy), emphasizing the importance of neck ultrasonography in the follow-up of patients with differentiated thyroid cancer (DTC).

What is proposed in this report is that by using a sensitive Tg-immunoassay with a very low cut-off, it is possible to follow patients with DTC and a T₄-suppressed Tg below 0.1 ng/ml without the need to perform rhTSH stimulation. If T₄-suppressed Tg levels are detectable, the recent guidelines of ATA/ETA should be followed because 24-82% of such patients have a rhTSH-stimulated Tg above 2 ng/ml, hence prompting additional work-up to identify residual cancer.

Two last comments: a) the testing laboratory has to ensure consistent assay performance over time; and b) patients should always be tested with the same highly sensitive Tg assay. Finally, additional studies using Tg assays with improved sensitivity and longer follow-up are needed before deciding universally that monitoring such patients with a low risk cancer grade could be recommended by carrying out a yearly T₄-suppressed Tg measurement and periodic neck ultrasound imaging, but without rhTSH stimulation. (Daniel Glinoer, M.D.; Ph.D.)

See Figure below

Upper panel: the results from Mayo Clinic (Florida): only 1 of 47 patients with a baseline Tg (‘pre’) below 0.1 ng/ml had a rhTSH-stimulated Tg (‘post’) above 2 ng/ml.

Lower panel: the results from Mayo Clinic (Rochester): in 15/33 patients (45.4%), baseline Tg (‘pre’) below 0.1 ng/ml remained undetectable after rhTSH (‘post’) and in 17/33 patients (51.3%) stimulated Tg levels were less than 2 ng/ml.
Title: Sodium/Iodide Symporter (NIS) gene expression is the limiting step for the onset of thyroid function in the human fetus.

Authors: Szinnai G, Lacroix L, Carré A, Guimiot F, et al. (Paris, France)

Reference: Journal of Clinical Endocrinology & Metabolism 92: 70-76, 2007

SUMMARY

Context: Terminal differentiation of the human thyroid is characterized by the onset of follicle formation and thyroid hormone synthesis at 11 gestational weeks (GW).

Objective: This study aimed to investigate the ontogeny of thyroglobulin (Tg), thyroid peroxidase (TPO), sodium/iodide symporter (NIS), pendrin (PDS), dual oxidase 2 (DUOX2), thyroid stimulating hormone receptor (TSHR), and thyroid transcription factor 1 (TITF1), forkhead box E1 (FOXE1) and paired box gene 8 (PAX8) in the developing human fetus.

Design: Thyroid tissues from 45 human embryos and fetuses (7-33 GW) were analysed by quantitative PCR to monitor mRNA expression for each gene and by immuno-histochemistry to determine the cellular distribution of TITF1, TSHR, Tg, TPO, NIS, and the onset of T₄ production. A broken line regression model was fitted for each gene to compare the log-linear increase in expression before and after the onset of T₄ production.

Results: TITF1, FOXE1, PAX8, TSHR, and DUOX2 were stably expressed from 7 to 33 GW. Tg, TPO, and PDS gene expressions were detectable as early as 7 GW and were correlated with gestational age (P < 0.01). The slope of the regression line was significantly different before and after the onset of T₄ synthesis at 11 GW (P < 0.01). NIS expression appeared last and showed the highest fit by the broken line regression model of all genes (correlation age: P < 0.0001; broken line regression: P < 0.0001). Immuno-histochemical studies detected TITF1, TSHR, and Tg in unpolarized thyrocytes before follicle formation. T₄ and NIS labelling were only found in developing follicles from 11 GW on.

Conclusion: These results imply a key role of NIS for the onset of human thyroid function.

COMMENT

The developing human thyroid gland undergoes a series of complex changes during embryogenesis in order to become functional. Morphogenesis is completed when the thyroid reaches its definitive pretracheal position – at 7 weeks gestation – but, at this early stage, the gland is mainly composed of undifferentiated thyrocyte precursors. Three morphological differentiation stages can be distinguished: precolloid, beginning colloid, and follicular growth stage. Differentiation includes several changes: the polarization of thyrocyte precursors (with basal & apical poles), followed by follicle formation (allowing colloid to be accumulated), and the expression of thyroid-specific functional genes, such as thyroglobulin ‘Tg’ (the matrix on which
thyroid hormone can be produced), thyroperoxidase ‘TPO’ (the enzyme needed to catalyse iodine incorporation onto the Tg matrix), thyroid-stimulating hormone receptor ‘TSHR’ (main regulator – at the basolateral thyrocyte membrane level – of thyroid growth & function, via hypothalamic-pituitary control), and sodium/iodide symporter ‘NIS’ (the pump needed to trap iodide from the circulation).

The present study is fascinating as it is the first attempt to investigate the sequence of this molecular program of human thyroid differentiation. The results show essentially that a precisely timed expression program exists. DUOX2 expression is stable already at 7 weeks gestation. A second group of genes (Tg, TPO, PDS) are expressed at low levels first, then increase significantly before 11 weeks gestation, and their increased expression is correlated with the onset of thyroid function. NIS is the last gene to appear, and its expression is the most strongly correlated with the rapid onset of thyroid hormone synthesis at 11 weeks gestation. This expression pattern suggests that NIS expression is the rate limiting step for the onset of thyroid function in man. In other words, all parts of the complex puzzle must first be in place for iodide to be actively trapped and organized within an already organized thyroid gland, allowing thyroid hormone to be produced.

It is important to note that this study is purely qualitative, as it does not allow to assess which quantitative fraction of the overall fetal thyroid hormone environment is related to the onset of T\(_4\) synthesis at such early embryonic stage (first trimester of gestation). Therefore, the presence of T\(_4\) in the anatomical structures bathing the developing embryo (amniotic and coelomic fluid) remains presumably mostly due to maternal transfer of thyroid hormone. Even though fetal T\(_4\) synthesis may be starting around 11-12 weeks, it is not until 16-20 weeks gestation that the fetal hormone contribution to this crucial environment may become relevant.

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

See Figure below
**Title:** Preoperative evaluation of thyroid pathology in patients with primary hyperparathyroidism.

**Authors:** Ogawa T, Kammori M, Tsuji E, Kanauchi H, Kurabayashi R, Terada K, Mimura Y, & Kaminishi M (Tokyo, Japan)

**Reference:** Thyroid 17: 59-62, 2007

**SUMMARY**

**Background:** In parathyroidectomy, it has been recognized that a shift to a minimally invasive procedure may be accompanied by a possibility of missing thyroid pathology. However, only a few findings concerning preoperative thyroid evaluation have been reported.

**Aim:** The authors investigated the prevalence of concomitant thyroid pathology by preoperative neck ultrasonography (US) in patients with primary hyperparathyroidism.

**Design:** There were 85 patients (66 women; 19 men; mean age 57 years) in the study group. The mean preoperative calcium level was 11.2 mg/dl and the mean intact PTH level was 206 pg/ml. All patients underwent neck US following fine-needle aspiration biopsy (FNAB).

**Results:** Of the 85 patients, 21 (24.7%) had thyroid nodules. Among 21 patients with thyroid nodules, 9 (10.6%) had malignant thyroid tumors, while 12 (14.1%) had benign thyroid nodules, including multinodular goiter. Of the 9 patients with malignant thyroid nodules, 4 had papillary carcinomas with lymph node metastases.

**Conclusion:** The prevalence of thyroid disease associated with hyperparathyroidism is high, and evaluation of the thyroid pathology by US enables the shift from bilateral neck exploration to the minimally invasive parathyroid surgery.

**COMMENT**

This article focuses on the surgical shift from open neck exploration for primary hyperparathyroidism (PHPT) due to parathyroid adenoma to minimally invasive procedures and, in turn, the greater possibility of missing associated thyroid pathology. It also focuses on the capacity of detecting such associated thyroid lesions by the use of preoperative neck ultrasonography (US). Thyroid nodules were found in 25% of patients operated for PHPT and, among these, thyroid malignancy was present in 9/21 patients (43%). Of interest, 6/9 thyroid cancers were not palpable (thus corresponding to incidentalomas). Tumor sizes ranged from 5-32 mm among the non palpable tumors, and from 20-80 mm among the palpable tumors. The prevalence of thyroid malignancies in this series was greater than the 2-6% reported in others series from the literature (perhaps because of geographical differences and/or the preoperative use of US and FNAB).

(Daniel Glinoer, M.D.; Ph.D.)
See Table below

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Location of Adenoma</th>
<th>Weight (Mg)</th>
<th>Thyroid Pathology</th>
<th>Tumor Size</th>
<th>Incidental or Palpable</th>
<th>Surgical Procedure</th>
<th>Ly Dissection</th>
<th>Lymphnode Meta</th>
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<td>Incidental</td>
<td>Tx</td>
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<td>HTx</td>
<td>C</td>
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<tr>
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<td>280</td>
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HTx: hemithyroidectomy, Tx: subtotal thyroidectomy, C: central lymphnode dissection, C + L: central and lateral lymphnode dissection.
**Topic:** NORMAL SERUM TSH & LIPIDS

**Title:** The association between TSH within the reference range and serum lipid concentrations in a population-based study: the HUNT study.

**Authors:** Asvold BO, Vatten LJ, Nilsen TI, & Bjoro T (Oslo, Norway)


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**SUMMARY**

**Objective:** The association between TSH and serum lipids in people with no apparent thyroid disease is insufficiently understood. The authors have studied the association between normal thyroid function, defined as TSH within the reference range of a general population, and concentrations of serum lipids.

**Design:** Cross-sectional, population-based study with 30,656 individuals without known thyroid disease.

**Methods:** Using general linear models, the authors calculated mean concentrations of total serum cholesterol, LDL-cholesterol, non-HDL-cholesterol, HDL-cholesterol, and triglycerides across categories of TSH.

**Results:** Within the reference range of TSH, there was a linear and significant (P for trend < 0.001) increase in total serum cholesterol, LDL-cholesterol, non-HDL-cholesterol, and triglycerides, and a linear decrease (P for trend < 0.001) in HDL-cholesterol with increasing TSH. Subgroup analyses showed statistically significant associations for all lipids in men above 50 years of age, and for triglycerides in all age groups. For women, associations were statistically significant in all age groups except for HDL-cholesterol below 50 years of age. The associations with triglycerides and HDL-cholesterol were stronger among overweight than normal weight individuals.

**Conclusion:** Within the range of TSH that is considered clinically normal, the authors found that increasing level of TSH was associated with less favourable lipid concentrations. The association with serum lipids was linear across the entire reference range of TSH.

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**COMMENT**

An important clinical consequence of hypothyroidism is its association with an increased risk of cardiovascular disease, which is thought to be mediated in part by the changes in serum lipids that often accompany hypothyroidism. For instance in subclinical hypothyroidism (SCH), defined as increased serum TSH (usually between 4-10 µU/ml) with normal serum free T4 levels, the benefit of early treatment with thyroxine has only been clearly demonstrated when serum lipids abnormalities are present. In such patients, studies have shown that thyroxine administration may be beneficial to reduce total serum cholesterol and LDL-cholesterol. A meta-analysis (in 1996) concluded that normalization of serum TSH in patients with SCH was associated with a decrease in serum cholesterol by 0.4 mMol/L on average (Tanis et al., Clin Endocrinol., 44:643, 1996). A more recent
meta-analysis also concluded that normalization of serum TSH decreased serum LDL-cholesterol by 0.26 mMol/L (Danese et al., JCEM 85:2993, 2000). Reduction in serum total and LDL-cholesterol may be larger in individuals with higher cholesterol levels prior to treatment. The observed decrease in LDL-cholesterol is estimated to decrease the risk of cardiovascular mortality by 9-31% (Meier et al., JCEM 86:4860, 2001).

The main finding of present study was to show a consistent, linear, and significant increase in concentrations of total serum cholesterol, LDL-cholesterol, non-HDL-cholesterol, and triglycerides, in both men and women, with increasing concentration of serum TSH within the reference range of 0.5-3.5 µU/ml. There was also a consistent reduction in HDL-cholesterol with increasing TSH. In a separate analysis, an additional interesting finding of present study was that, in the context of this population study, the authors had a database concerning 2.007 patients with SCH. When the data from patients with SCH were analysed with those of the normal subjects, there was a continuum for further increases in total serum cholesterol, LDL-cholesterol, non-HDL-cholesterol, and triglycerides, but no clear association with decreased HDL-cholesterol.

In conclusion, TSH levels representative of normal thyroid function may have long-term harmful effects on cardiovascular health through the association with serum lipids. However, the strengths of the associations were modest, and their clinical significance remains to be determined in prospective studies of variations of normal thyroid function related to risk of cardiovascular disease.

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

See Figures below
Title: Effects of evening versus morning thyroxine ingestion on serum thyroid hormone profiles in hypothyroid patients.

Authors: Bolk N, Visser TJ, Kalsbeek A, van Domburg RT, & Berghout A (Rotterdam, the Netherlands)


SUMMARY

Objective: Standard drug information resources recommend that L-thyroxine be taken half an hour before breakfast on an empty stomach, to prevent interference of its intestinal uptake by food or medication. The authors have observed cases in which TSH levels improved markedly after changing the administration time of L-thyroxine to the late evening. They conducted therefore a pilot-study to investigate whether L-thyroxine administration at bedtime improves TSH and thyroid hormones, and whether the circadian rhythm of TSH remains intact.

Design: Patients were studied on two occasions: on a stable regimen of morning thyroxine administration and two months after switching to night-time thyroxine (L-T4) using the same dose. On each occasion patients were admitted for 24h and serial blood samples were obtained.

Patients and measurements: Twelve women treated with L-T4 for primary hypothyroidism were investigated. They used no medication known to interfere with L-T4 uptake. Patients were admitted to hospital and blood samples were obtained at hourly intervals for 24h via an indwelling catheter. Following this first hospital admission, all women were then asked to switch the administration time from morning to bedtime or vice-versa. After two months they were readmitted for a 24h period of hourly blood sampling. Blood samples were analysed for serum TSH, free T4 and free T3, total T4 and reverse T3, serum TBG, and total protein and albumin.

Results: A significant difference in TSH and thyroid hormones was found after switching to bedtime administration of L-T4. Comparing bedtime to morning ingestion, the twenty-four hour average serum values showed: - TSH: 5.1 ± 0.9 versus 1.2 ± 0.3 µU/ml (mean ± SD) (P < 0.01); - free T4: 16.7 ± 1.0 versus 19.3 ± 0.7 pMol/L (mean ± SD) (P < 0.01); - total T3: 1.48 ± 0.05 versus 1.64 ± 0.1 nMol/L (mean ± SD) (P < 0.01).

There was no significant change in total T4, reverse T3, albumin and TBG levels, nor in the T3/rT3 ratio. The relative amplitude and time of the nocturnal TSH surge remained intact.

Conclusion: L-thyroxine taken at bedtime by patients with primary hypothyroidism is associated with higher thyroid hormone concentrations and lower TSH concentrations compared to the same L-T4 dose taken in the morning. The circadian TSH rhythm stays intact. These findings are best explained by a better gastrointestinal uptake of L-T4 during the night.

COMMENT

This is quite an interesting study with unexpected – and potentially important – findings. We always tell our patients to take their thyroxine tablet in the morning “as soon as they wake up”. We also all see a few patients who, for various reasons,
prefer to take their drug in the evening and, as long as they take it two hours (at least) after their last meal, we tell them that it is all right. And indeed, their thyroid function tests are usually OK and indistinguishable from patients who take thyroxine in the morning. Those are the dogmas we have been trained with and, in turn, train our medical students with. For the first time to our knowledge, a well-conducted study shows clear differences between morning and evening thyroxine ingestion, using the same dosage and in the same set of patients. Dogmas are there to be challenged. Is this one more dogma to throw away?

The authors speculate that the differences might be attributable to a lesser intestinal absorption of thyroxine in the morning and they provide some arguments in favour of a better degree of intestinal absorption in the evening. Is this convincing and also does it really matter? You will have to decide for yourself but I will certainly switch a few of my patients from morning to evening and see what happens.

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

See Figures below
Title: Combined clinical, thyroid ultrasound and cytological features help to predict thyroid malignancy in follicular and Hürthle cell thyroid lesions: results from a series of 505 consecutive patients.


SUMMARY

Objective: The cytological patterns of follicular and Hürthle cell nodules are included among the indeterminate results of fine-needle aspiration cytology, because distinction between benign and malignant lesion can only be made on histological criteria. The diagnostic value of atypia at cytology, clinical parameters and echographic patterns were examined to establish the risk of malignancy in 505 patients with follicular and Hürthle cell nodules at cytology.

Design and patients: The study included 505 consecutive patients who had undergone thyroidectomy from the period 2002-2005.

Results: Histological diagnosis of malignancy was carried out in 125 of 505 (25%) patients, the follicular variant of papillary carcinoma being the most frequent histotype. Only atypia at cytology and spot micro-calcifications at ultrasound were significantly predictive of malignancy. Male gender, normal thyroid volume, single nodularity, nodule hypoechogenicity, size and blurred margins were associated with malignancy, although not significantly. An arbitrary clinical score allowed the identification of patients with high (41%; 110 patients) and low (16%; 242 patients) risk of malignancy. Combining the clinical score with the presence of atypia at cytology, the authors could identify 30 patients (6%) in whom the risk of malignancy was as high as 63%.

Conclusion: Twenty-five percent of patients with a cytological result of follicular and Hürthle cell thyroid lesion had a final diagnosis of malignancy. Only atypia at cytology and spot micro-calcifications at thyroid ultrasound were significantly associated with malignancy. Other clinical parameters and thyroid ultrasound patterns can be used to set up a clinical score useful for predicting the individual risk of malignancy before surgery.

COMMENT

Thyroid nodules are frequent in the general population and only a minority of these nodules are likely to cause significant clinical problems. The introduction of fine-needle aspiration cytology (FNAC) in the mid-seventies (1975 in the USA, 1979 in Belgium) has allowed to markedly reduce the number of patients submitted to thyroid surgery for benign nodular lesions and increase in turn the prevalence of malignancy in surgical series. However, FNAC has its limitations, especially when the cell pattern shows follicular proliferation. Such pattern can be found in
follicular carcinoma and in the follicular variant of papillary carcinoma, but also in hyperplastic nodules within a benign goiter and follicular adenoma. Based solely on cytological criteria, the distinction between benign and malignant follicular neoplasia is not feasible without histology. Similarly, Hürthle cells (oncocyes or oxyphilic cells) can be found in Hürthle cell adenomas and carcinomas and histology is needed for the final diagnosis of an oncocytoma. Such cytological patterns (follicular proliferation and/or oncocyes) are classified among the indeterminate diagnoses or “atypia” in FNAC and, therefore, the objective of present study was to assess whether the finding of atypia at FNAC, associated with specific clinical parameters and echographic patterns could be useful to predict malignancy. The study is also of interest because of the large number of patients included (over 500) from the same institution.

Of the 505 patients, 426 had a follicular lesion and 79 a Hürthle cell lesion at FNAC. Among them, 25% had a final diagnosis of thyroid malignancy at histology. Histological diagnosis of malignancy was made in 46/101 nodules (45%) presenting atypia and in 79/404 nodules (20%) without atypia (P<0.001). In follicular nodules, malignancy was found in 40/83 samples with atypia compared with 76/343 without atypia (P<0.001). Clinical parameters were found to be of little help to identify malignancy. With regard to specific echographic parameters, only spot micro-calcifications (P=0.009) and blurred nodular margins (P=0.06) were associated with malignancy. The authors constructed an arbitrary clinical score which allowed the identification of patients with a high (41%) versus a low (16%) risk of malignancy. Combining the clinical score with the presence of atypia at cytology, the authors could identify 30 patients (6%) in whom the risk of malignancy was as high as 63%. Finally even in the subgroup with the lower risk, malignancy was found in 16% of the patients, hence confirming the appropriateness of surgical treatment for follicular and Hürthle cell neoplasia.

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

See Figure below
**Topic:** SERUM CALCITONIN MEASUREMENT IN PATIENTS WITH THYROID NODULES

**Title:** Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5,817 consecutive patients with thyroid nodules.

**Authors:** Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S, Crocetti U, Attard M, Maranghi M, Torlontano M, & Filetti S (Italy)


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**SUMMARY**

**Context:** Routine serum calcitonin (CT) measurement in patients with thyroid nodules for diagnosis of medullary thyroid carcinoma (MTC) is controversial.

**Objective:** To evaluate the diagnostic accuracy of systematic CT measurement in non-multiple endocrine neoplasia type 2 patients with nodular thyroid disease.

**Settings:** Study conducted at a national healthcare system hospital (outpatient and inpatient sectors).

**Subjects:** Consecutive patients with nodular thyroid disease (N = 5,817) were studied.

**Main outcome measures:** Serum CT levels were measured under basal conditions. When basal CT values were more than or equal to 20 and less than 100 pg/ml, testing was repeated after pentagastrin stimulation. Basal or stimulated CT levels greater than 100 pg/ml were indication for surgery.

**Results:** Fifteen cases of MTC and seven of C-cell hyperplasia (CCH) were identified. MTCs were diagnosed in all patients with basal CT more than 100 pg/ml. The four patients with basal CT ≥ 50 and < 100 pg/ml included two cases diagnosed with MTC and two cases with CCH. In ten patients with basal CT ≥ 20 and < 50 pg/ml, histology confirmed the presence of MTC in four, four others had CCH, and the remaining two were negative for thyroid malignancy. Positive predictive values for basal CT levels in the preoperative diagnosis of MTC were: 23.1% for values ≥ 20 pg/ml, 100% for values ≥ 100 pg/ml, 25.0% for values ≥ 50 and < 100 pg/ml, and 8.3% for values ≥ 20 and < 50 pg/ml. Positive predictive values for the pentagastrin test (> 100 pg/ml) were 40% in the entire series.

**Conclusions:** CT screening of thyroid nodules is a highly sensitive test for early diagnosis of MTC, but confirmatory stimulation testing is necessary in most cases to identify true positive cases.

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**COMMENT**

Medullary thyroid carcinomas (MTC) represent 4-10% of all malignant thyroid neoplasms, and most of them (~75%) are sporadic lesions. By the time patients with MTC present with clinical disease, the condition is usually already metastatic and the outcome poor. Thus, there is a good case for attempting to reach an early diagnosis, using CT measurement, in all patients with thyroid nodules. However, the systematic use of CT measurement in the initial work up (or follow up) of nodule
patients remains controversial. The recent European thyroid cancer guidelines do advocate its use (see Europ. J. Endocrinol., 2006) while the equivalent U.S. guidelines do not (see Thyroid, 2006). The prevalence of sporadic MTC in patients with thyroid nodules is low, in the order of 0.3-1.3%. Does this low prevalence justify CT measurements in all nodular lesions? Plasma CT is a sensitive marker of CT-secreting C-cell disease and, therefore, routine determination of CT permits early diagnosis. The difficulty is that the real aim of screening nodules with CT measurement is not just the detection of smaller tumors (hence, indicating less advanced disease), but to reduce the overall morbidity and mortality of MTC, and this has unfortunately not yet been clearly demonstrated.

In the Editorial accompanying the article (by I. Borget et al.), the group of Martin Schlumberger discusses a medical economic rationale for the early detection of MTC, using CT measurement, and comes to the conclusion that “plasma CT determination in the assessment of thyroid nodule patients appears to be highly favourable compared with a number of other accepted healthy interventions”. At the same time, these authors admit that further studies are obviously needed to confirm the benefits of routine CT screening and that, until then, uncertainties will remain and clinicians should use their own judgment, based on imperfect information. (Daniel Glinoer, M.D.; Ph.D.)
Topic: PET SCAN FOR THYROID NODULES WITH INCONCLUSIVE FNA CYTOLOGY

Title: \(^{18}\)F-FDG PET reduces unnecessary hemithyroidectomies for thyroid nodules with inconclusive cytologic results.

Authors: de Geus-Oei L-F, Pieters G, Bonenkamp JJ, Mudde AH, Bleeker-Roovers CP, Corstens F, & Oyen WJG (Nijmegen, the Netherlands)

Reference: Journal of Nuclear Medicine 47: 770-775, 2006

SUMMARY

Background: Fine-needle aspiration biopsy (FNAB) is inconclusive in up to 20% of patients with solitary thyroid nodules. In these cases, hemithyroidectomy is necessary, but only 20% of the surgically resected nodules prove to be thyroid carcinoma.

Aim: To explore the potential of \(^{18}\)F-FDG PET to reduce the number of unnecessary hemithyroidectomies in the pre operative assessment of thyroid nodules with inconclusive FNAB results.

Methods: Forty-four consecutive patients, scheduled for hemithyroidectomy because of inconclusive FNAB results, participated in this prospective study. \(^{18}\)F-FDG PET of the thyroid region was performed before surgery and standardized uptake values were calculated. The final histo-pathologic diagnosis served as a standard of reference.

Results: Histo-pathologic examination of the surgical specimen revealed 7 well-differentiated thyroid carcinomas in 6 patients, all accumulating \(^{18}\)F-FDG (negative predictive value: 100%). \(^{18}\)F-FDG accumulated in 13 of 38 benign nodules. The pre-PET probability for cancer in this study population was 14% (6/44), and the post-PET probability increased to 32% PET (6/19). The percentage of unnecessary hemithyroidectomies in a hypothetical algorithm using \(^{18}\)F-FDG was only 30% (13/44), compared with 86% (38/44) without \(^{18}\)F-FDG PET. \(^{18}\)F-FDG PET reduced the number of futile hemithyroidectomies by 66% (25/38) (95% C.I.: 49%-80%; Fisher’s exact test: P=0.0038). Semiquantitative analysis using standardized uptake values did not help to further reduce this number.

Conclusions: In addition to data in the literature demonstrating accurate detection of thyroid cancer by \(^{18}\)F-FDG PET, this study showed that \(^{18}\)F-FDG PET should play an important role in the management of patients with inconclusive cytologic diagnosis of a thyroid nodule. \(^{18}\)F-FDG PET reduced the number of futile hemithyroidectomies by 66%. Although PET is a relatively costly procedure, the cost outweighs the costs and risks associated with unnecessary thyroid surgery.

COMMENT

This is strongly opinionated study by Dutch colleagues, showing that in patients with thyroid nodules with inconclusive FNAB diagnosis, the use of \(^{18}\)F-FDG PET scan may help improve the preoperative diagnosis of cancer and reduce the number of what the authors refer to as unnecessary or ‘futile’ hemithyroidectomies. Clearly, 7 thyroid carcinomas were identified by preoperative \(^{18}\)F-FDG PET scan in 6 patients (3 papillary and 4 follicular). However, the authors failed to indicate why FNAB was
considered inconclusive and what the characteristics of the nodules were. Moreover, in the entire series of 44 patients, "inconclusive" cytology revealed follicular proliferation in most nodules, and in some of them atypical aspects (such as Hürthle cells, etc.). Without disposing of the complete set of clinical and paraclinical information necessary to make a preoperative diagnosis of “who should be operated” (i.e. clinical history, palpation, ultrasound data, evolution of nodule size over the previous years, etc.), my personal opinion is that I cannot join the enthusiasm of our Dutch colleagues. Thyroid surgery for follicular adenomas (almost one half of the final histologic diagnoses in this series) is not ‘futile’. We could, however, use the present results to include $^{18}$F-FDG PET scanning in specific cases where there is hesitation about the adequate management.

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

See algorithm below

![Algorithm Diagram](image-url)

**FIGURE 3.** Diagnostic algorithm including $^{18}$F-FDG PET. In existing diagnostic algorithm, nodules with inconclusive cytologic diagnosis must be removed, and hemithyroidectomy is necessary to allow reliable histologic diagnosis. In proposed diagnostic algorithm, $^{18}$F-FDG PET is implemented as shown.
**Topic:** Doctor: “I FEEL A LUMP IN MY THROAT”

**Title:** Thyroid pathology and the globus symptom: are they related? A two year prospective trial.

**Authors:** Burns P & Timon C (Dublin, Ireland)


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**SUMMARY**

**Context:** The globus sensation is a constant feeling of a lump in the throat and may be associated with thyroid enlargement.

**Objective:** A two year prospective study was set up to ascertain the relationship between thyroid pathology and globus symptoms.

**Patients and Methods:** All patients undergoing thyroid surgery over a two year period were included. Patients were questioned pre- and post-operatively. Globus symptoms scores were recorded using a visual analogue scale. The size, weight and histological features of the removed specimens were correlated and statistical analysis performed.

**Results:** Two hundred patients were included in the study; 58 were symptomatic for globus pharyngeus preoperatively, and 80% of these patients’ symptoms resolved postoperatively (P<0.0001). Patients with histological features of inflammation showed the greatest improvement.

**Conclusion:** As many as one third of patients with a thyroid mass will complain of a globus-like symptom. Patients undergoing thyroid surgery, who are symptomatic for globus pharyngeus, can expect that their symptoms will improve following surgery.

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**COMMENT**

How many times have we heard in our consultation: “Docteur j’ai la sensation d’avoir une boule dans ma gorge” (in Nederlands: dokter, ik voel een zwelling in mijn keel). The globus pharyngeus symptom refers to a complaint of a ‘lump’ sensation in the throat, with a negative physical examination of the pharynx and neck.

The present study was prospective in design and carried out in one homogeneous surgical unit. A visual analogue scale (VAS) was used to grade symptoms pre- and postoperatively (between 0 and 10). Results showed a clear decrease in symptoms postoperatively, with VAS decreasing from 5.2 to 1.1. The decrease was even more pronounced in patients with ‘inflammation’. Among those patients with globus-like symptoms, histological diagnoses were: multinodular goitre (N=30), colloid goiter (N=9), follicular adenoma (N=7), carcinoma (N=6), etc. Also, the weights of resected tissue were less than 30 g (N=17/58; 29%), 30-100 g (31/58; 53%), and greater than 100 g (N=10/58; 17%), indicating that a relatively large proportion of these patients had large goitres.

*(Daniel Glinoer, M.D.; Ph.D.)*
See Figure below

![Graph showing VAS globus scores](image)

**Fig. 1**
Patients’ mean pre-operative (pre-op) and post-operative (post-op) visual analogue scale (VAS) scores for globus pharyngeus.