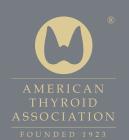
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Clinical Thyroidology

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Clinical HYROIDOLOG

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EDITORS' COMMENTS

Clinical Thyroidology was "launched in 1988 by Dr. Ridha Arem for the purpose of informing endocrinologists about the best clinical studies in thyroidology—wherever published—and providing commentary about those studies. As founding editor, Dr. Arem nourished the journal wisely, so that it became a valuable source of information about new studies in the field." This statement is quoted from the editorial of Bob Utiger in March 2001 when the journal became a publication of the American Thyroid Association and Bob Utiger became the Editor-in-Chief. Three issues were published each year. Utiger's summaries and incisive commentaries based on his encyclopedic knowledge of thyroidology made very informative and pleasurable reading. In 2008, Ernie Mazzaferri took over the editorship and introduced more detailed reviews of outstanding clinical papers. His reviews included colorful figures of the data that were a very significant addition to the review. Ernie's commentaries were also tempered by a wealth of experience, especially in the area of thyroid cancer. Clinical Thyroidology became a monthly in 2009. Following in the footsteps of these giants in thyroidology is a difficult task. Nevertheless, I am honored to have been selected by the Publications Committee and Board of the American Thyroid Association to be the Editorin-Chief of Clinical Thyroidology.

I am especially fortunate to have four outstanding Associate Editors: Albert Burger, Stephanie Lee, Jorge Mestman, and Steve Spaulding. The broad expertise of these editors will enlarge the scope of literature that will be summarized. The journal will continue as a monthly publication. It will revert back to the more concise one-page summaries of outstanding papers with commentaries, as exemplified under the Utiger editorship. The basis for this decision is my belief that the readers are very busy people who want to understand the main points and conclusions of a paper as quickly as possible. They want to know whether the information can be integrated into their clinical practice, whether the paper is a harbinger of an advance that may eventually see the light of day for clinicians, or whether the paper provides an advance in pathophysiologic understanding. To fulfill the interests of the readers, the editors (who are also the authors of the reviews) plan to present summaries of 6 to 10 articles each month. I welcome feedback from readers and will be happy to publish letters to the Editor concerning the material presented. Clinical Thyroidology will continue to list important review articles without commentary.

For endocrinologists with a special interest in thyroidology (I assume that this includes all clinical endocrinologists), I hope that Clinical Thyroidology will become a "must-read" each month. After all, the best things in life are free.

- Jerome M. Hershman, MD

MANAGEMENT OF PAPILLARY THYROID MICROCARCINOMA

Durante C, Attard M, Torlontano M, Ronga G, Monzani F, Costante G, Ferdeghini M, Tumino S, Meringolo D, Bruno R, De Toma G, Crocetti U, Montesano T, Dardano Angela, Lamartina L, Maniglia A, Giacomelli L, Filetti S, on behalf of the Papillary Thyroid Cancer Study Group. Identification and optimal postsurgical follow-up of patients with very low-risk papillary thyroid microcarcinomas. J Clin Endocrinol 2010;95:4882-8.

SUMMARY • • • • •

BACKGROUND

Small papillary thyroid cancers (PTC) are being found with increasing prevalence. The appropriate follow-up for papillary thyroid microcarcinoma (PTMC) is unclear. In addition, there is still some controversy with regard to how aggressively these patients should be treated. The purpose of this retrospective study by an Italian consortium was to test the hypothesis that clinical criteria could be used to identify patients with very low recurrence rates and to define the best method for follow-up.

METHODS

From nine centers in Italy, a group of 312 patients (89% female) with PTMC were identified who had the following seven characteristics: no family history of thyroid cancer, no previous head and neck irradiation, tumor staging T1 (1 cm or less), N0M0, no extracapsular extension, unifocal, no aggressive variants of the papillary cancer, and not locally invasive tumor. Each patient had undergone complete or nearly complete thyroidectomy. The patients were followed yearly for at least 5 years. The decision to ablate remnants with radioactive iodine was left to individual management at each institution. Patients were usually treated with suppressive doses of levothyroxine. Annual follow-

up included physical examination, serum thyrotropin (TSH), thyroglobulin, antithyroglobulin, and cervical ultrasonography with special attention to lymph nodes.

RESULTS

Three fourths of the patients had PTMC found incidentally at surgery for multinodular goiter. One fourth were diagnosed preoperatively by fine-needle aspiration biopsy. Eighty-eight percent were female. Follow-up ranged from 5 to 23 years (median, 6.7). The median tumor size was 5 to 6 mm (range, 0.5 to 10). Radioactive iodine (RAI) remnant ablation was performed in 44% and not in 56%; it was performed mainly in those diagnosed preoperatively who tended to have larger tumors. The follow-up serum thyroglobulin was <1 ng/ml in 97% of the patients. Both the first and the last follow-up cervical ultrasounds were negative in all patients. A negative ultrasound at 1 year gave a negative predictive value of 100% for recurrence. No patient had persistence or recurrence of thyroid cancer.

CONCLUSION

By appropriate risk stratification, a limited followup can be used in patients with PTMC who had no significant risk factors for recurrence. Neck ultrasonography is the key element in this follow-up.

COMMENTARY • • • • •

This retrospective study found that PTC <1 cm without risk factors indicative of more aggressive disease that are treated by thyroidectomy did not recur, regardless of whether radioiodine ablation had been used. The authors recommend that postoperative surveillance of these patients can be based exclusively on ultrasonography and that this can be discontinued after 5 years. It is interesting that they did not use

recombinant TSH as a basis for prognosis. They do not recommend RAI ablation for these patients, and this is consistent with the recent ATA guideline for low-risk PTMC. It should be emphasized that the conditions to be included in the study, as noted above, excluded all of the factors that might contribute to more aggressive disease.

In contrast with these conclusions and the data from this study, there are reports of patients with PTMC

who have recurrent disease. Arora et al. at New York Presbyterian Hospital compared 66 patients with PTMC and 136 patients with larger PTC (1). Recurrence was found in 17% of the patients with PTMC patients and in 21% with larger PTC; this was not a significant difference. PTMC recurred in 11 patients. Eleven of those with PTMC had recurrence. but 8 had multifocal tumors, 6 had lymph-node metastases, 3 had angiolymphatic invasion, and 2 had distant metastases. Patients with these features would have been excluded from the Italian study. Tzettov et al. in Israel reported a series of 225 patients with differentiated thyroid carcinomas < 1 cm (98% PTMC) (2); the median size was 7 mm. Multifocal disease was found in 50%, bilateral disease in 32%, extrathyroidal extension in 16%, lymph-node metastases in 26%, and distant metastases in 2.4%; 96% were treated by total thyroidectomy. Not surprisingly, 11% had recurrent disease, as compared with 32% of 543

patients with macroscopic differentiated thyroid cancer at the same institutions.

Putting this together, I conclude that the follow-up recommended by Durante and colleagues is appropriate for patients with PTMC who have no features of aggressive disease but that more extensive follow-up is necessary for patients with PTMC who have findings indicative of more aggressive disease. The patients with aggressive PTMC require aggressive therapy and careful monitoring for recurrence.

All PTMC cannot be put into the same basket. It is necessary to individualize therapy in patients with these small tumors based on the findings at initial clinical evaluation, pathology, and routine follow-up in the first year.

- Jerome M. Hershman, MD

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CALCITONIN SCREENING FOR MEDULLARY THYROID CARCINOMA

Chambon G, Alovisetti C, Idoux-Louche C, Reynaud C, Rodier M, Guedj A-M, Chapuis H, Lallemant JG, Lallemant B. The use of preoperative routine measurement of basal serum thyrocalcitonin in candidates for thyroidectomy due to nodular thyroid disorders: results from 2733 consecutive patients. J Clin Endocrinol Metab. September 29, 2010. doi:10.1210/jc.2010-0162.

SUMMARY • • • • • • •

BACKGROUND AND METHODS

The utility of routinely measuring basal calcitonin (CT) levels "under appropriate conditions" was assessed on 2733 consecutive patients from southern France who had nodular thyroid disorders and who were already scheduled to undergo thyroid surgery. Thyroid and cervical ultrasonography was performed, but fine-needle aspiration (FNA) biopsies were not performed on lesions <10 mm. A total of 43 patients had a basal CT level >10 pg/ml, which triggered additional preoperative, intraoperative or postoperative procedures or tests, and all these patients underwent at least a total thyroidectomy.

RESULTS

Of the 43 with high CT levels, 12 were found to have some form of medullary thyroid cancer (MCT): 7 were larger tumors (mean diameter, 2.5 cm), while 5 were

called "micro-MCT" or "subclinical latent MCT" (mean diameter, 4.4 mm). All of the remaining 31 patients with high CT levels had benign C-cell hyperplasia when detailed immunohistochemical examination of the entire gland was performed. These 31 patients had no cervical lymph nodes on preoperative ultrasound, and their serum CT levels had normalized when assayed at least 6 weeks postoperatively. None of the patients with an elevated basal CT level turned out to have *ret* proto-oncogene mutations, and pentagastrin stimulation testing did not provide any additional diagnostic information. Two of the 2690 patients with normal basal CT levels had a focus of micro-MCT on detailed immunohistochemistry. In conclusion, all the macro-MTCs could have been detected by ultrasonography, FNA, and/or histopathology at surgery, but basal CT screening did pick up five (of seven) patients with micro/subclinical latent MTC, one of whom had clinically unappreciated central compartment nodes.

COMMENTARY • • • • •

Similar to a number of previous studies that have used basal CT determination to screen all patients with nodules, MCT was found in $\sim 0.5\%$ of cases. The positive predictive value of the CT screening was only about 25%. The ATA has not taken a position for or against routine screening (1), based on the total associated costs and in view of the large fraction of false positive tests, which do have associated risk (note that approximately three fourths of the patients with elevated CT levels in this study underwent total thyroidectomy for an apparently benign disease). Still, the central compartment nodes of one patient

with subclinical latent micro-MCT probably would have been missed if the screening CT had not been performed. In another three cases, the nodule was not on the side where the MCT was found, so the simple lobectomy that probably would have been performed would have missed the MCT, if the high CT level had not been recognized preoperatively. However, data are lacking to support the idea that C-cell hyperplasia without germline mutation or subclinical latent MCT develop with time into macro-MTC, so it isn't clear whether those latter three cases would ever have developed clinical symptoms.

- Stephen W. Spaulding, MD

What fraction of patients with micro-MCT detected by intensive immunohistochemistry actually benefit from

aggressive surgery? The following paper addresses another side of this risk/benefit problem. —JMH, MD

CALCITONIN SCREENING FOR MEDULLARY THYROID CARCINOMA

Valle LA, Kloos RT. The prevalence of occult medullary thyroid carcinoma at autopsy. J Clin Endocrinol Metab. October 13, 2010. doi:10.1210/jc.2010-0959.

SUMMARY

BACKGROUND AND METHODS

A total of 24 autopsy reports containing detailed thyroid histology on approximately 7900 individuals with no clinical evidence of thyroid disease were reviewed for cases of occult MCT.

RESULTS

The weighted mean prevalence of occult medullary and papillary carcinomas of the thyroid (defined as

≤1 cm) was 0.14% for MCT and 7.6% for papillary thyroid cancer (PCT). Excluding reports that used only thick tissue sections (>3 mm), the mean prevalence of occult MTC was 0.18% and of occult PTC was 8.4%. Focusing on the studies that performed calcitonin immunohistochemistry, the MCT incidence was 0.33%. In the only two studies that assessed calcitonin immunoreactivity on thin sections through the entire thyroid, occult MCT was detected in 0.42%.

COMMENTARY • • • • •

The autopsy series that were combined for this paper spanned 35 years and came from many nations with different prevalences of nodular thyroid diseases. Diet and other environmental factors have changed as have the ways that minor thyroid nodules are detected and assessed-from 1971 when thyroid ultrasonography was in its infancy until 2006 when "thyroid incidentalomas" had burgeoned following the widespread use of MR, PET and CT scans. It is important to note that in these studies threequarters of the patients autopsied were older than 60, which may bias the data toward benign disease, since sporadic MCT commonly presents in patients in their 40s and 50s, familial MCT tends to present even earlier, while benign thyroid nodularity increases progressively with age.

Clearly, occult subcentimeter MCTs are not always benign, even though the ones detected in these autopsies were asymptomatic up to the time of death. Even so-called benign C-cell hyperplasia (>50 C-cells per 3 low-power fields) is considered to be carcinoma in situ for patients with familial MCT or MEN2, especially those with certain *ret* mutations (1). There is a clear need for up-to-date information on the behavior of occult MCT in order to conduct meaningful risk/benefit and cost/benefit analyses. Unless country- and age-specific data on the incidence and behavior of occult MCT miraculously do become available, it seems that amalgamated temporal and global data will have to do, despite questions about its applicability, particularly to younger patients.

— Stephen W. Spaulding, MD

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SHEAR WAVE ELASTOGRAPHY FOR THYROID NODULES

Sebag F, Vaillant-Lombard J, Berbis J, Griset V, Henry JF, Petit P, Oliver C. Shear wave elastography: a new ultrasound imaging mode for the differential diagnosis of benign and malignant thyroid nodules. J Clin Endocrinol Metab 2010;95:5281-8.

SUMMARY • • • • • • • • •

BACKGROUND

Thyroid elastography is an ultrasonographic technique to evaluate the stiffness of a thyroid nodule as an indicator of whether it is benign or malignant. It is based on the assumption that malignant nodules are stiffer than benign lesions. Shear wave elastography is a new technique that provides an objective assessment of the stiffness of a lesion.

METHODS

The authors used shear wave elastography and conventional ultrasound to evaluate nodules in 93 patients; 61 patients had a solitary nodule and 32 had multiple nodules. Subclinical hyperthyroidism was found in 5 patients and subclinical hypothyroidism in 3; 79 patients had thyroid surgery, including all of those with multinodular goiter and 47 of the 61 with single nodules. There was an additional control group with normal thyroid function who underwent ultrasonography and elastography. (The authors did not state whether fine-needle aspiration (FNA) of the nodules was performed.) The ultrasound machine that was used in the study was developed by SuperSonic Imagine (Les Jardins de la Duranne, Aix-en-Provence, France). It uses pushing beams to generate a shear wave and then calculates an elasticity index in kilopascals (kPa). It also displays an image in which softer tissue is blue and stiffer tissue is red.

RESULTS

Fifteen of the solitary nodules were malignant and 8 of those with multinodular goiter had 14 separate carcinomas. The ultrasound features predictive of malignancy were hypoechogenicity (sensitivity, 70%; specificity, 82%), absent halo sign (sensitivity, 93%; specificity, 41%), microcalcifications (sensitivity, 67%; specificity, 85%), and intranodular vascularity (sensitivity, 52%; specificity, 94%). The presence of dense macrocalcifications >2 mm was not predictive of malignancy, with a sensitivity of 22% and a specificity of 79.6%.

The mean (\pm SD) elasticity index was significantly higher in malignant nodules (150 \pm 95 kPa [95% confidence interval {CI}, 30 to 356]) than in benign nodules (36 \pm 30 [95% CI, 0 to 200]) and normal thyroid glands (15.9 \pm 7.6 [95% CI, 5 to 35]) (P<0.001).

For a positive predictive value of at least 80%, the cutoff level of the elasticity index for malignancy was estimated as 65 kPa. The elasticity index was <65 kPa (negative) in three papillary thyroid carcinomas and one follicular tumor of uncertain malignant potential. It was >65 kPa in all follicular carcinomas and in the one medullary and one anaplastic carcinoma.

Table 1 shows the sensitivity, specificity, and positive and negative predictive values for detection of malignancy in the nodules evaluated by shear wave elastography, ultrasound, or the combination of both methods.

CONCLUSIONS

The authors recommend shear wave elastography as the first-line procedure for evaluation of thyroid nodules. When the value is >65 kPa, FNA should be performed, and if <65 kPa, the decision for FNA may be based on other ultrasound characteristics.

TABLE 1. Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for Diagnosis of Malignancy in Thyroid Nodules by Shear Wave Elastography (SWE), Ultrasound, or the Combination of Ultrasound and SWE.

Variable	SWE	Ultrasound	Ultrasound + SWE	
	%	% (95% confidence interval)		
Sensitivity	85 (72–99)	52 (73-91)	82 (67–96)	
Specificity	94 (89–99)	97 (94–100)	97 (94–100)	
PPV	80 (65–95)	82 (64–100)	88 (75–100)	
NPV	96 (92–100)	88 (82-94)	95 (91–99)	

COMMENTARY • • • •

As of this writing, elastography has been reported in 22 papers in the English literature for evaluation of thyroid nodules since the first paper using this method by a Japanese group in 2005 (1). Recently. real-time elastography, in which elasticity was graded 1 to 3, where lower numbers denoted greater elasticity, was found to be useful in further evaluation of nodules that were indeterminate or nondiagnostic on FNA. The malignant nodules were stiffer (grades 2 or 3) and the benign nodules were more elastic (grade 1) (2), but this method is very dependent on the operator. In contrast with static elastography, the results of shear wave elastography are not dependent on the operator, and they are

reported to be reproducible and quantitative. The result is not altered by a hard area in the vicinity of the nodule of interest. However, elastography may not be useful in the presence of coarse calcifications because the calcifications are stiff, causing a false positive rate as high as 25%. The technique may be especially valuable in the diagnosis of follicular thyroid cancers because these cancers often lack the ultrasound features of papillary thyroid cancer and they usually cannot be diagnosed with precision by FNA. As the authors state, large prospective studies of shear wave elastography will be needed to confirm these results and to determine the true utility of this procedure in the evaluation of thyroid nodules.

— Jerome M. Hershman, MD

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UNIVERSAL SCREENING FOR THYROID DISORDERS IN PREGNANCY

Wang W, Teng W, Shan Z, Wang S, Li J, Zhu L, Zhou J, Mao J, Yu X, Li J, Chen Y, Xue H, Fan C, Wang H, Zhang H, Li C, Zhou W, Gao B, Shang T, Zhou J, Ding B, Ma Y, Wu Y, Xu H, Liu W. The prevalence of thyroid disorders during pregnancy in China: the benefits of universal screening in the first trimester of pregnancy. Eur J Endocrinol. November 8, 2010 [Epub ahead of print].

SUMMARY • • • • • • • • • • • • •

BACKGROUND

Maternal and perinatal morbidities are wellcomplications documented of pregnancy mothers with thyroid dysfunction, both clinical and subclinical, and in euthyroid mothers diagnosed with chronic thyroiditis. Impaired fetal brain development and decreased intelligence quotient have been demonstrated in children of such mothers, and also in those mothers diagnosed with hypothyroxinemia (1,2). The vast majority of affected women are asymptomatic; therefore, in view of the potential pregnancy and progeny complications, it has been suggested that every woman be screened for thyroid dysfunction before or very early after conception. The prevalence of overt or clinical hypothyroidism in pregnancy is reported to be about 0.3%, subclinical hypothyroidism between 2% and 4%, euthyroid thyroiditis between 5% and 20%, isolated hypothyroxinemia early in pregnancy between 0.8% and 1%, and clinical hyperthyroidism <1% (3). Universal screening is a very controversial topic, the most powerful argument against it is the lack of a randomized, clinical trial showing a beneficial effect of thyroid therapy on pregnancy outcome.

METHODS

In a 4-year period, Wang et al. recruited 2899 pregnant women before 12 weeks' gestation from 10 antenatal clinics in Shenyan, China, from iodine-adequate areas. Blood samples were obtained from all women after overnight fasting for serum thyrotropin (TSH), free thyroxine (FT₄), (FT₃), thyroid peroxidase antibodies (TPOAb) and urinary iodine excretion. Gestational age was assessed by patient last normal menstrual period and confirmed by ultrasonography. All participants answered a questionnaire that gathered information about reproductive age, personal and family history of thyroid disorders, personal history

of type 1 diabetes or other autoimmune disease and history of therapeutic or neck irradiation. Any woman with a positive answer was identified as being at high risk for thyroid disease during pregnancy. First trimester–specific reference intervals for this population were previously published by the authors. The first trimester–specific reference ranges were: TSH, 0.13 to 3.93 mIU/L; FT₄, 12.0 to 23.34 pM, and TPOAb <50 IU/ml.

RESULTS

The mean (\pm SD) age of the 2899 women was 27.61 \pm 3.55 years and the median gestational age was 6 weeks (range, 4 to 12). The median urinary iodine was 177 µg/L. A little over half of the women were nulliparous; the authors classified 367 of the 2899 women (12.7%) as a high-risk group according to *The Endocrine Society Clinical Practice Guidelines*. The vast majority of the 367 women were included in the high-risk group because of a personal or family history of thyroid disease or a previous miscarriage.

Of the 2899 women with thyroid tests recorded, 294 had thyroid dysfunction, a prevalence of 10.2%; 28 (1.0%) had clinical hyperthyroidism; 217 (7.5%) hypothyroidism (8 of them diagnosed with clinical hypothyroidism); and 26 (0.9%) hypothyroxinemia. High titers of TPOAb were present in 279 (9.6%) of the 2899 women, 196 of whom were euthyroid. Of the 217 hypothyroid women, only 72 had TPOAb detected (33.2%), whereas in the hyperthyroid group, 7 of 28 (25%) were TPOAb-positive.

The prevalence of thyroid dysfunction in the 367 women in the high-risk group was significantly higher than in the non-high-risk group (15.0 vs. 9.4%, P = 0.001). However, of the 217 women with elevated serum TSH, 38 were in the high-risk group and 171 (78.8%) in the low-risk group. Of the 8 women with clinical hypothyroidism, 6 were in the

UNIVERSAL SCREENING FOR THYROID DISORDERS IN PREGNANCY

non-high-risk group. Of the 28 patients with clinical hyperthyroidism, only 7 were in the high-risk group.

There was no difference in the prevalence of hypothyroxinemia between the high-risk and the non-high-risk groups (0.9% vs. 0.9%, P = 0.928).

The authors concluded that a case-finding strategy for screening thyroid function in the high-risk group would miss about 81.6% of women with elevated serum TSH and 80.4% women with hyperthyroidism.

COMMENTARY • • • • •

The controversy about universal versus selective screening for thyroid disease and/or thyroid dysfunction in pregnancy continues. Several studies in the past decade showed that women with untreated hypothyroidism had adverse pregnancy outcomes and adverse neuropsychological and motor development in their progeny. One study showed that testing of only high-risk groups would miss one third of pregnant women with overt/subclinical hypothyroidism (4), another study showed that of 61 women with hypothyroidism, 46 (75%) were in the low-risk group, and 9 of 12 women with hyperthyroidism also belonged to the low-risk group (5). In the article by Wang et al., almost 88% of women with hypothyroidism did not have risk factors for thyroid disease. In all of these studies, the risk factors most associated with abnormal thyroid function were family and personal history of thyroid disease, other autoimmune disease, and previous miscarriage. The authors rightly point out that the main argument against universal screening is the lack of a randomized, clinical trial demonstrating a reversal of both obstetric and intellectual abnormalities with maternal thyroxine-replacement therapy.

Among other issues to consider in assessing universal vs. case finding screening, are the need for trimester-specific reference ranges for serum TSH and T_4 assays, including iodine status in a given population; the most appropriate gestational age for screening; which thyroid tests are best suited for disease detection (TSH, T_4 , TPOAb); cost-effectiveness; and the ability to institute both hormonal therapy soon after the diagnosis is confirmed and follow-up monitoring.

Proponents of universal screening stressed (3, 6) the almost universal availability to obtain a reliable, rapid turnaround and affordable serum TSH test; a simple and perhaps harmless treatment with levothyroxine; and the difficulty of obtaining proper answers to a specific questionnaire, because of the time it takes to fill it out, language barriers, and lack of understanding of medical terminology. It would be interesting to know whether the responses to the questionnaires given by obstetricians were consistent among the 10 hospitals in the study by Wang et al.

Universal screening could gain further support by the recent publication of Negro et al. (7), which concluded that universal screening, as compared with case finding, for detection and treatment of thyroid hormonal dysfunction during pregnancy did not show a decrease in adverse outcomes in a subgroup of 77 low-risk women diagnosed with subclinical hypothyroidism; 43 of them received levothyroxine treatment and 44 remained untreated. Obstetrical complications were experienced by 43% of the treated group as compared with 91% of the untreated one.

In conclusion, the few studies available confirm that case finding for detection of thyroid dysfunction in pregnancy would miss a significant number of women with thyroid dysfunction, the majority of them with subclinical hypothyroidism or with euthyroid thyroiditis.

In the meantime, health care professionals should decide, based on the evidence available, when and how to assess the need for thyroid testing in women who are planning pregnancy or are newly pregnant.

— Jorge Mestman, MD

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NATURAL HISTORY OF SUBCLINICAL HYPERTHYROIDISM

Vadiveloo T, Donnan PT, Cochrane L, Leese GP. The Thyroid Epidemiology, Audit, and Research Study (TEARS): the natural history of endogenous subclinical hyperthyroidism. J Clin Endocrinol Metab. October 6, 2010 [Epub ahead of print].

SUMMARY • • • • • • • • •

BACKGROUND

Patients with subclinical hyperthyroidism have subnormal serum thyrotropin (TSH) with normal free thyroxine (FT₄) and free triiodothyronine (FT₃) or total T_3 concentrations, usually with no typical features of hyperthyroidism. The prevalence varies widely in different reports, ranging from 0.7% to 12.4%. The rate of development of overt hyperthyroidism in these patients has been estimated at 1% to 5% per year. The purpose of this study was to determine the rate of conversion to overt hyperthyroidism and the rate of conversion to the euthyroid state.

METHODS

The study included a population of almost 600,000 people in Tayside, Scotland, starting in 1993; eventually 46% had a TSH measurement. The patients included in the study were over age 18, nonpregnant, not receiving therapy for thyroid disease, and not taking drugs that could affect thyroid function. They had at least two measurements of TSH separated by 4 months or more that were <0.4 mU/L with normal thyroid hormone levels. Thyroid function was followed at 2, 5, and 7 years.

RESULTS

Approximately three fourths of the patients were women. The prevalence of subclinical hyperthyroidism

increased with time so that it was about 0.6% in 2006–2008. The patients were further subdivided into two groups: those with a TSH of <0.1 mU/L (417 patients) and those with a TSH of 0.1 to 0.4 mU/L (1507 patients). A third group of 100 patients could not be classified because the TSH fluctuated between the two categories. The mean (\pm SD) age at baseline was 66 ± 16 years. Of those with a TSH of <0.1 mU/L, 96% had measurement of FT₄ and 84% serum T₃, but for those with a TSH of 0.1 to 0.4 mU/L, only 20% had measurement of FT₄ and 15% serum T₃.

Frank hyperthyroidism developed within 1 year of diagnosis in 10% of those with a TSH of <0.1 mU/L. Of the patients with a TSH of <0.1 mU/L, 17% were receiving treatment for hyperthyroidism at 2 years, 37% at 5 years, and 44% at 7 years. Conversely, in this group, 51%, 40%, and 37% had no improvement at 2, 5, and 7 years, respectively. Of the group with a TSH of 0.1 to 0.4, 2.5%, 11%, and 17% were receiving treatment for hyperthyroidism at 2, 5, and 7 years; 72%, 55%, and 50% had no improvement at 2, 5, and 7 years. In the two groups together, 17%, \sim 30%, and 30% to 38% reverted to normal at 2, 5, and 7 years.

CONCLUSIONS

The authors conclude that very few patients with subclincal hyperthyroidism develop overt hyperthyroidism and that the majority revert to normal or remain subclinically hyperthyroid.

NATURAL HISTORY OF SUBCLINICAL HYPERTHYROIDISM

COMMENTARY • • • •

The strengths of this study are that it follows the largest number of subjects with subclinical hyperthyroidism reported to date and that it classifies these subjects into the two groups. The authors conclude that the rate of development of overt hyperthyroidism, 10%, is small in those with a TSH of <0.1 mU/L, but they ignore the even higher proportion in this category who were given therapy for hyperthyroidism. They base the diagnosis of hyperthyroidism on raised FT₄ and T₃ levels, but it is likely that the physicians caring for these patients decided that the TSH of <0.1 mU/L together with whatever thyroid hormone levels the patients had was a sufficient basis for the initiation of therapy. When the authors ignored those under therapy, the progression to overt hyperthyroidism was 6.1% of all patients at 1 year. They consider these patients as having incipient hyperthyroidism and

differentiate them from those with stable subclinical hyperthyroidism.

The authors tend to emphasize that most patients remain subclinically hyperthyroid or revert to normal, but I think the take-home message is that in 10% hyperthyroidism will develop within 1 year and that clinical judgment will dictate an intervention in an even higher proportion of patients as they are followed. Clearly, most of those who have slightly subnormal serum TSH levels make up the 2.5% of subjects below the lower 95% confidence limit and will probably not require intervention, but this study provides good evidence that those with serum TSH <0.1 mU/L must be followed carefully. The findings reinforce the recommendations of the Task Force on subclinical thyroid disease (1).

- Jerome M. Hershman, MD

Reference

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T₃-PREDOMINANT GRAVES' DISEASE

Ito M, Toyoda N, Nomura E, Takamura Y, Amino N, Iwasaka T, Takamatsu J, Miyauchi A, Nishikawa M. Type 1 and type 2 iodothyronine deiodinases in the thyroid gland of patients with 3,5,3'-triiodothyronine-predominant Graves' disease. Eur J Endocrinol. October 11, 2010 [Epub ahead of print].

SUMMARY • • • •

INTRODUCTION

Triiodothyronine (T_3) -predominant Graves' disease is defined by elevation of the serum free T_3 level associated with normal or low free thyroxine (FT_4) level in patients with Graves' disease who are on antithyroid drug therapy (1). This contrasts with ordinary Graves' disease in which patients on antithyroid drugs usually attain normalization of both serum FT_4 and FT_3 . The reasons for the predominance of T_3 secretion are unclear. In the euthyroid state, 80% of T_3 production is extrathyroidal, but in patients with Graves' disease, the majority of T_3 production is in the thyroid gland. This paper explores the basis for the increased production of T_3 in T_3 -predominant Graves' disease.

METHODS

Studies were performed in 13 patients with T_3 -predominant Graves' disease and 18 patients with "common-type" Graves' disease. The activity and mRNA of type 1 (D1) and type 2 (D2) iodothyronine deiodinase were measured in the thyroid glands removed at surgery from the group with T_3 -predominant Graves' and the group with commontype Graves' disease.

RESULTS

The patients with T_3 -predominant Graves' disease (GD) were significantly younger and had much

larger thyroid glands as calculated by ultrasound measurements than the patients with common Graves' disease (Table 1). The thyrotropin (TSH)receptor antibody levels of the T₃-predominant GD was 40-fold greater and the thyroid-stimulating antibody was 3-fold greater than in the patients with common GD. Deiodinase 2 activity in the thyroid tissue of T₃-predominant GD was much higher than in common GD tissue. Deiodinase 1 activity was also significantly higher in the T₃predominant-GD as compared with the common-GD thyroid tissues. The activity of both deiodinase 2 and deiodinase 1 was positively correlated with the ratio of serum FT₃/FT₄ and with the TSH-receptor antibody or thyroid-stimulating antibody levels. The deiodinase type 1 mRNA was significantly greater in the T₃-predominant thyroid tissue as compared with the common GD tissue, but this was not found with regard to the deiodinase 2 mRNA. Deiodinase 1 activity was significantly correlated with the mRNA level.

The increased tissue activity of the thyroid deiodinases 1 and 2 explains the basis for the T_3 predominance as compared with ordinary GD. Presumably, the higher levels of the thyroid-stimulating antibody plays a role in this pathogenesis by stimulating the activity of both thyroid 5'-monodeiodinases, thus augmenting conversion of T_4 to T_3 .

TABLE 1. Comparison of Various Parameters in 13 T₃-Predominant Graves' Disease and 17 Patients with Common Graves' disease.

	T ₃ -Predomant Graves' Disease	Common Graves' Disease			
Age (yr)	36±12*	49±16			
TSH (mU/L)	2.5±5.0	2.0±2.0			
FT_4	0.89 ± 0.79	0.87±0.15			
FT ₃	4.7±3.6*	2.4±0.4			
FT ₃ /FT ₄	6.6±3.0*	2.7 ± 0.5			
TSH-receptor antibody	206±276*	5.0±4.7			
TSI	1124±582*	350±338			
Thyroid volume	227±126*	32±23			
Thyroid D1 (pmol/mg/hr)	403±201*	321±152			
D1 mRNA (U)	0.028±0.015*	0.016±0.014			
Thyroid D2 (fmol/mg/hr)	824±596*	195±132			
D2 mRNA (U)	0.545±0.276	0.404±234			
* Indicates significant difference. TSI = Thyroid stimulating immunoglobulin					

COMMENTARY • • • • • • • • • • • •

T₃-predominant Graves' disease was first described in 1984 by Junta Takamatsu (a coauthor of this study) et al., and shown to be a recalcitrant condition with regard to long-term cure by antithyroid drug therapy (1). The lack of remission can be predicted by the high level of TSH-receptor antibody. The frequency of this condition in relation to ordinary Graves' disease is unclear. I believe that it is relatively rare, but all of us have seen some of these patients in our practices. The current study explains the pathogenesis based on advances in our understanding of the two activating deiodinase enzymes that convert T_4 to T_3 . However, gaps in our knowledge remain. Deiodinase 1 in peripheral tissues is stimulated by high levels of T_3 , but this may contribute little to serum T_3 in this situation, since FT₄ is normal or low in T₃-

predominant GD. The transcriptional regulation of D2 is stimulated by cyclic AMP that is generated in the thyroid by the TSH-receptor antibody (2). However, T₃ causes down-regulation of type 2 deiodinase by a posttranslational mechanism involving ubiquitinmediated proteasomal degradation (2). The half-life of D2 is only 40 minutes; it is rapidly activated or suppressed. In hyperthyroidism, the activity of D2 is suppressed. The relative contribution of D1 and D2 to the thyroid's secretion of T₃ in hyperthyroidism is still unclear, and the relative contributions in this rare variant of Graves' disease still remain to be clarified. Nevertheless, the data of this recent contribution provide good evidence to show that thyroidal 5'-deiodinases are responsible for the elevated serum T₃ in T₃-predominant Graves' disease.

— Jerome M. Hershman, MD

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REVIEW ARTICLES, GUIDELINES & HOT NEW ARTICLES

REVIEW ARTICLES

- 1. Mitrou P, Raptis SA, Dimitriadis G. Insulin action in hyperthyroidism: a focus on muscle and adipose tissue. Endocr Rev 2010 Oct;31(5):663-79.
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We invite you to join the ATA!

Are You Intrigued by the Study of the Thyroid? You Belong in the ATA!

- ATA members are leaders in thyroidology who promote excellence and innovation in clinical care, research, education, and public policy.
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Call for Proposals – American Thyroid Association (ATA) Research Grants Deadline: January 31, 2011

Electronic Submission: Proposals should be submitted electronically through the research grant application feature on the ATA website, www.thyroid.org.

The American Thyroid Association (ATA) is pleased to announce the availability of funds to support new investigator initiated research projects in the area of thyroid function and disease. Topics may include, but are not limited to, Thyroid Autoimmunity, Iodine Uptake and Metabolism, Thyroid Cancer, Medullary Thyroid Cancer, Clinical Disorders of Thyroid Function, Thyroid Hormone Action and Metabolism, Thyroid Imaging, Thyroid Nodules and Goiter, Thyroid Development and the Brain. Research awards are intended to assist new investigators in obtaining preliminary data for submission of a more substantial application (i.e., to the NIH). Research grants, up to \$25,000 annually, will be awarded for two year terms based on receipt and review of a satisfactory progress report from funded investigators in the fourth quarter of the first year of funding.

Guidelines for All Research Grant Proposals: As mentioned above, research awards are targeted for funding of new investigators to obtain preliminary data for submission of a more substantial application (i.e., to the NIH). Interested investigators should submit a brief description of the proposed research by January 31, 2011.

Eligibility of Applicant and Use of Funds Guidelines:

- 1. New investigators are individuals who are less than 6 years from completion of their post-doctoral fellowship and have never been a PI on an NIH RO1 or equivalent grant (recipients of NIH R29, R21 and KO8 awards are eligible).
- 2. Faculty members (MD and PhD) are eligible.
- 3. Postdoctoral fellows are eligible if their department provides written confirmation that at the time of the award the applicant will have a junior faculty position.
- 4. Students working towards an MD or a PhD are not eligible.
- 5. Investigators and individuals who have previously received ATA, ThyCa or THANC awards are not eligible. In general, investigators who have achieved the rank of associate professor or higher are not eligible.
- 6. Applications are limited to one per individual researcher.
- 7. The funds can be used for direct costs associated with the proposal, including technician's salary, supplies or equipment but not for PI's salary.
- 8. Recipients of ATA grants must be ATA members (submit application online if not already a member). For new members, membership dues for the first year will be waived.

Proposal Requirements: The following documents must be submitted online:

- 1. Grant Proposal (A short proposal that should be no longer than 900 words or three double-spaced pages in 12 point type. These space requirements are absolute and nonconformance will preclude review.)This short proposal should include:
 - Name /affiliation of applicant, complete work/home contact information
 - Title of proposed study
 - Background to the project
 - Hypothesis and/or outline of proposed studies
 - Outline of methodology
 - Anticipated results and implications
 - A short statement of how the grant will aid the applicant
 - References (selected)
- 2. CV (NIH-style CV up to 4 pages) including evidence that the applicant is a new investigator with date of completion of postdoctoral training and current grant support (if any). In the case of postdoctoral fellows, written confirmation from the department chair must be provided that the applicant will have a junior faculty position at the time of the award. Note: Without a suitable CV, applications will not be considered.
 - Cover letter

Grant Review: The ATA Research Committee will rank proposals according to their scientific merit. Authors of selected proposals will be notified in March 2011 and invited to submit a complete grant application.

Call for Nominations for the 2011 Awards **American Thyroid Association**



Distinguished Service Award
 Sidney H. Ingbar Distinguished Lectureship

■ Van Meter Award Lecture ■ Paul Starr Award Lecture ■

■ John B. Stanbury Thyroid Pathophysiology Medal ■

The Van Meter Award Lecture established in 1930, recognizes outstanding contributions to research on the thyroid gland or related subjects. The award is given each year to an investigator who is not older than

the age of 45 in the year of the award. The Van Met award lecture during the annual meeting. An honora recipient. This award receives support from Mary	arium and expenses are	awarded to the Van Mete			
Tominee: Date of Birth					
Sidney H. Ingbar Distinguished Lectureship Awa thyroidology, in keeping with the innovation and vi- career. The Ingbar award is conferred upon an estab to thyroid-related research over many years. An hor Distinguished Lectureship Award recipient. This award of Sidney H. Ingbar.	sion that epitomized Dr blished investigator who norarium will be present	. Ingbar's brilliant investign has made major contributed to the Sidney H. Ingba	gative itions ar		
Nominee:					
The Paul Starr Award Lecture recognizes an outs honorarium will be presented to the Paul Starr Awa Boris Catz.			r.		
Nominee:					
The Distinguished Service Award (DSA) honors a contributions to the American Thyroid Association ATA Annual Banquet.		*	_		
Nominee:					
The John B. Stanbury Thyroid Pathophysiology either conceptual or technical, to the understanding thyroid disease, as evidenced by having a major impulseases. A medal, funded by Dr. John Stanbury, is Nominee:	of thyroid physiology o pact on research or clini	r the pathophysiology of cal practice related to thy			
Nominated by: (print or type)	Signature:	Date:			
Nominators must submit all of the following electromagnetion by the deadline of March 31, 2011: 1. Completed and signed Nomination Form 2. CV and brief nomination letter, emphase 3. List of 2 to 4 most significant publication papers.	m (above). sizing major accomplish	ments.	the		