

CLINICAL THYROIDOLOGY

VOLUME 20 • ISSUE 1

FEBRUARY 2008

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Clinical Thyroidology

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CLINICAL THYROIDOLOGY

VOLUME 20 • ISSUE 1

FEBRUARY 2008

It is always difficult to assume the responsibility for an important project, particularly when it has been in the hands of a highly capable and thoughtful person—which is exactly where I find myself today. As many of you may already know, Dr. Robert Utiger stepped down as the Editor-in-Chief of *Clinical Thyroidology* in December 2007. Bob is a long-time friend of mine and many others in the American Thyroid Association and all of us know how diligently he worked on this journal. As Editor-in-Chief of *Clinical Thyroidology* from 2000 to 2007, this journal grew both in recognition and use. Since 2001, a total of 17, 843 PDF files of *Clinical Thyroidology* have been downloaded from the American Thyroid Association website in addition to copies of the journal sent to our members by mail. Dr. Utiger was exceedingly well suited for the task of Editor-in-Chief of *Clinical Thyroidology*, having previously served as Editor-in-Chief of the *Journal of Clinical Endocrinology and Metabolism* from 1983 to 1989, and as Deputy Editor of the *New England Journal of Medicine* from 1989 to 2000 and as Editor of the Endocrinology section of *Year Book of Medicine*, and Co-Editor-in-Chief of *Thyroid: a Fundamental and Clinical Text*, 6th 7th 8th and 9th editions from 1991 to 2005. It is difficult to walk in the footsteps of such a highly qualified editor.

My goals as the Editor-in-Chief of *Clinical Thyroidology* are to maintain the high level of quality set for this journal by Dr. Utiger and to involve as many of you as possible as commentators for the journal. The American and the European Thyroid Associations are rich resources of scholarly opinion that I intend to tap over time.

Dr. Jennifer Sipos, a thyroidologist and member of the American Thyroid Association, will serve as Associate Editor of *Clinical Thyroidology*. Dr. Sipos brings the perspective of an expert in the clinical management of thyroid disorders.

The American Thyroid Association is now in the process of becoming a new CME provider. In this capacity, we will have the opportunity to provide CME credits to physicians for a variety of activities. Our plan is to make CME credits available to readers of *Clinical Thyroidology*. The details for this will be posted on the ATA website as they become available, but we would like to hear from you about this new idea.

We encourage you join us in extending our readership to students, fellows and other physicians.

We look forward to receiving your suggestions and opinions about the journal.

Ernest L. Mazzaferri, MD, MACP

The prognosis of patients with sporadic medullary thyroid carcinoma is worsened if the tumor carries a *RET* mutation

Elisei R, Cosci B, Romei C, Bottici V, Renzini G, Molinaro E, Agate L, Vivaldi A, Faviana P, Basolo F, Miccoli P, Berti P, Pacini F, Pinchera A. Prognostic significance of somatic *RET* oncogene mutations in sporadic medullary thyroid cancer: a 10 years follow up study. *J Clin Endocrinol Metab* December 11, 2007 doi:10.121/jc.2007-1714.

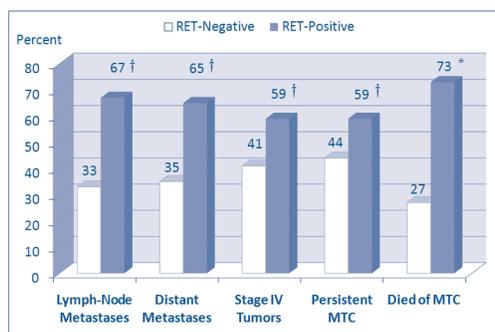
SUMMARY

Background Medullary thyroid carcinomas (MTCs) that have somatic *RET* mutations constitute up to half of nonfamilial MTCs. These tumors may be more aggressive than those lacking the mutation. This study evaluated the relationship between the presence of *RET* mutation in the tumor with outcome in patients with sporadic MTC.

Methods The study subjects were 100 patients (median age, 49 years; range, 20 to 83) with sporadic MTC followed for 3 to 32 years (mean, 10). All were treated by total thyroidectomy and central neck dissection. Before 1990, tumor tissue was embedded in paraffin, but thereafter it was frozen in liquid nitrogen immediately after acquisition and maintained at 80°C. *RET* exons 10, 11, 13, 14, 15, and 16 were sequenced using polymerase chain reaction. Basal and pentagastrin-stimulated serum calcitonin measured at 6 and 12 months and then 3 to 5 years later were negative in 7% of the patients. Detectable serum calcitonin and negative imaging studies (computed tomography, magnetic resonance imaging, and octreotide scan) served to categorize a condition as persistent biochemical disease. During follow-up, 70% of the patients had lymph-node metastases and 30% had distant metastases. Seven patients were free of disease, 28 had persistent disease, and 8 died of MTC.

Results A *RET* mutation was found in 43% of the tumors. The majority (34 of 43, 79%) had an M918T mutation, which was more frequent in large tumors ($P = 0.03$) and

when lymph-node metastases were present ($P < 0.001$). The other 9 patients had mutations in exons 10, 11, and 15. Most (16%) were at codon 634 of exon 11; four were C364R, two were C634W, and one was C364Y. One patient (2%) had a deletion of 48 base pairs in exon 10, and another (2%) had a two-base missense mutation at codon 883 in exon 15 that substituted alanine (GCT) for phenylalanine. No mutations were found in exons 13 or 14. The relationship between *RET* mutations, clinical features, and outcome is shown in the Figure. Patients with a *RET* mutation, compared with those without it, had more lymph-node metastases (67 vs. 33%, $P < 0.001$), more distant metastases (65 vs. 35%, $P = 0.02$), a more advanced tumor stage at the time of diagnosis ($P < 0.001$), more persistent disease (59 vs. 44%, $P < 0.001$), and a greater number of



Relationship between *RET* mutations, clinical features, and outcome. † $P < 0.001$, * $P < 0.01$ with and without *RET* mutation MTC = medullary thyroid carcinoma. Drawn from the data of Elisei et al.

deaths from MTC (73 vs. 27%, $P < 0.001$). On multivariate analysis, only advanced tumor stage at diagnosis ($P < 0.001$) and any *RET* mutation ($P = 0.01$) independently correlated with outcome. Survival curves showed significantly more deaths in patients whose tumor had a *RET* mutation ($P < 0.006$).

Conclusion Among patients with MTCs, those whose tumor has a somatic *RET* mutation are more likely to have lymph-node metastases and an advanced tumor stage at the time of diagnosis, and a greater rate of persistent tumor and a lower survival rate, as compared with those whose tumor does not have a *RET* mutation.

COMMENTARY

Elisei and colleagues present convincing data on the relationships between the presence of a somatic *RET* mutation, mainly at codon 918, and more extensive disease at presentation and with a poor outcome. In the past, this relationship has been challenged by several researchers, and because somatic *RET* mutations were found in only some parts of the tumor, it has been considered as a secondary event that may occur during tumor progression. To confirm the present findings, the next step will probably be to compare gene

expression in tumors with a somatic *RET* mutation with tumors without *RET* mutation and with MTCs that occurred in patients with familial multiple endocrine neoplasia and a germline *RET* mutation. Another interesting study would be to explore the relationship between the presence of somatic *RET* mutation and the progression rate of tumor assessed either by the Response Evaluation Criteria in Solid Tumors (RECIST) or by calcitonin and carcinoembryonic antigen doubling times.

As stated by the authors, a somatic *RET* mutation at codon 918 should be

routinely sought in all sporadic MTC tissues. Its presence should indicate meticulous follow-up, and in cases of advanced or recurrent disease, treatment should preferably be initiated at an early stage. Ongoing studies with *RET* tyrosine kinase inhibitors will show whether and to what extent tumor response to these new treatment methods is related to the presence of a somatic *RET* mutation.

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Thyrotropin-stimulated thyroglobulin testing is unnecessary once a patient meets the American and European Thyroid Association criteria for being free of disease

Castagna MG, Brilli L, Pilli T, Montanaro A, Cipri C, Fioravanti C, Sestini F, Capezzone M, Pacini F. Limited value of repeat recombinant human thyrotropin (rhTSH)-stimulated thyroglobulin testing in differentiated thyroid carcinoma patients with previous negative rhTSH-stimulated thyroglobulin and undetectable basal serum thyroglobulin levels. *J Clin Endocrinol Metab* 2008;93:76-81.

SUMMARY

Background Measuring thyrotropin (TSH)-stimulated serum thyroglobulin (Tg) is the most specific way to evaluate Tg levels in the follow-up of patients with differentiated thyroid cancer. Yet there is uncertainty about the necessity of repeating this in low-risk patients once the TSH-stimulated Tg is undetectable. This study evaluated the necessity of repeatedly performing this test in such patients.

Methods The study subjects were 85 patients with thyroid cancer, 75 with papillary cancer (88%), and 10 with follicular cancer (12%); 21 were males and 64 were females. The mean age (\pm SD) was 47.3 \pm 16.4 years (range, 14 to 75). All were initially treated with total thyroidectomy and thyroid remnant ablation. The first follow-up with recombinant human TSH (rhTSH)-stimulated Tg and neck ultrasonography was performed 1 year after initial therapy on all patients considered to be free of disease, defined as an undetectable baseline serum Tg (<1 ng/ml), absent anti-Tg antibodies, and a negative physical examination, neck ultrasonography, and chest x-ray. The second rhTSH-stimulation was performed a median of 29 months later (range, 12 to 84) on 67 patients found on the first rhTSH test to have no evidence of disease.

Results On the first rhTSH test, 68 of 85 patients (80%) had an undetectable Tg (<1.0 ng/ml), and all

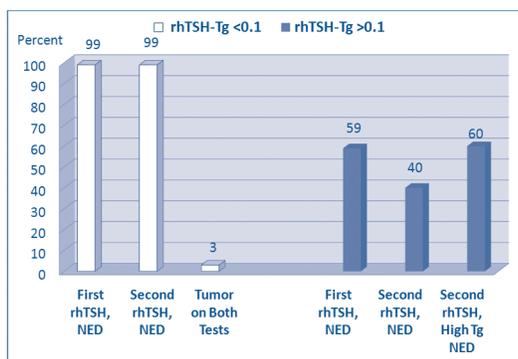


Figure. The differences in outcome with and without an undetectable rhTSH-Tg. NED = no evidence of disease. Drawn from the data of Castagna et al.

but one (98.5%) had negative ultrasonography, meeting the criteria for being free of disease. One patient (1.5%) had a tumor identified by ultrasonography with a false negative rhTSH-stimulated Tg <1.0 ng/ml. Another 17 (20%) patients had a Tg >1.0 ng/ml in response to rhTSH, and 7 (41.2%) had tumor. The median peak Tg in this group was 2.4 ng/ml (range, 1.1 to 14.8).

On the second rhTSH test, 98.5% of patients who were initially free of disease in the first test remained

so, but one patient (1.5%) had a metastatic lymph node manifest by rhTSH-stimulated Tg >1 ng/ml and a positive ultrasonogram. In the group with a first rhTSH-stimulated Tg >1.0 ng/ml, 10 patients initially had a negative ultrasonogram, 4 of whom (40%) had an undetectable second rhTSH-stimulated Tg and negative ultrasonogram. Of the remaining six patients in this group, 60% had a serum Tg that decreased in one patient, increased in three, and remained stable in two. On multivariate analysis, only the result of the first rhTSH-stimulated Tg was found to be an independent prognostic indicator.

Conclusion Patients with low-risk differentiated thyroid cancer rarely have recurrent disease when rhTSH-stimulated Tg is negative and do not require further rhTSH-stimulated serum Tg testing.

COMMENTARY

Tumor recurs in about 80% of patients with low-risk differentiated thyroid carcinoma. The American Thyroid Association (1) and the European Thyroid Association (2) describe disease-free status as no clinical or imaging evidence of disease, undetectable serum anti-thyroglobulin antibodies, and undetectable serum Tg during TSH suppression and stimulation. Until now it has not been entirely clear when in the course of follow-up one can stop performing TSH-stimulated Tg measurements, usually done with recombinant human TSH. For patients, repeating this test is both costly and

worrisome because it sends the message that there is a high likelihood of residual disease. Castagna et al. provide strong evidence that once a patient with low-risk differentiated thyroid cancer meets the criteria for being free of disease, it is no longer necessary to continue rhTSH-stimulated Tg testing. Nearly 99% of the patients with an rhTSH-stimulated Tg <0.1 ng/ml were found to be free of disease after the first test and the second test changed almost nothing. The few neck lymph-node metastases were identified by neck ultrasonography. The authors recommend that further rhTSH testing should be done only when the initial rhTSH test is positive. This is good advice from internationally recognized

leaders in thyroid cancer research that should change practice.

Ernest L. Mazzaferri, MD, MACP

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Undetectable thyroglobulin and absent anti-thyroglobulin antibodies before ¹³¹I ablation do not predict disease-free survival

Phan HT, Jager PL, van der Wal JE, Sluiter WJ, Plukker JT, Dierckx RA, Wolffenbuttel BH, Links TP. The follow-up of patients with differentiated thyroid cancer and undetectable thyroglobulin (Tg) and Tg antibodies during ablation. *Eur J Endocrinol* 2008;158:77-83.

SUMMARY

Background Thyrotropin (TSH)-stimulated serum thyroglobulin (Tg) is a key test in the follow-up of patients with differentiated thyroid cancer. However, the test is altered by antithyroglobulin antibodies (anti-TgAb) and the timing of Tg measurements. This retrospective study weighs the information from Tg and Anti-TgAb measurements and tumor histologic characteristics in predicting persistent or recurrent disease.

Methods The study subjects were 94 patients chosen from a cohort of 346 patients on the basis of undetectable TSH-stimulated serum Tg and Anti-TgAb levels performed just before thyroid ¹³¹I remnant ablation. Patients were 16 to 89 years of age; 79 (84%) were female and 15 (16%) male. The median follow-up was 8 years (range, 1 to 17). Of the 94 patients, 64 (68%) had papillary cancer, 28 (30%) follicular cancer, and 2 (2%) Hürthle-cell cancer, 95% of whom had ¹³¹I uptake in the thyroid bed on the whole-body scan after surgery. The American Joint Committee on Cancer (AJCC 6th edition) tumor classification was stage I in 40 patients (43%), stage II in 29 (31%), stage III in 12 (13%), and stage IV in 13 (14%). Over time, TSH was measured by two assays with functional sensitivities of 1.5 ng/ml and 0.6 ng/ml, and two Anti-TgAb assays with different reference ranges. Patients underwent levothyroxine withdrawal to measure TSH-stimulated Tg.

Results All 94 patients had ¹³¹I uptake in the thyroid bed on the preablation and/or the postablation whole-body scans. Eight of 94 patients (9%) were found to have metastases during follow-up, all of whom were at high risk according to the AJCC classification. Three had metastases to neck and/or mediastinal lymph nodes and five had metastases to bone and/or lung, each with different clues to the diagnosis.

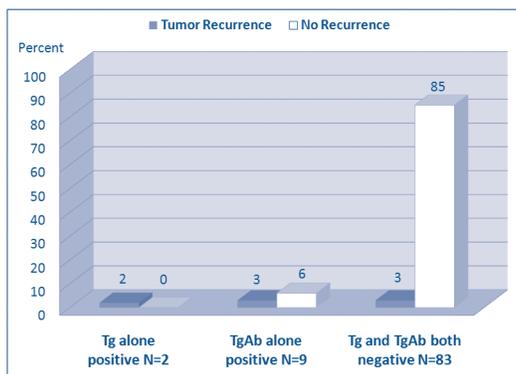


Figure. Tumor recurrence rates in patients with different Tg and anti-TgAb levels measured at the time of thyroid remnant ablation. Tg = thyroglobulin; anti-TgAb = antithyroglobulin antibody. Drawn from the data of Phan et al.

Tumors were identified by a positive TSH-stimulated Tg alone in 2 of 94 patients (2%), and by a positive Anti-TgAb test in 3 of 94 (3%), while 3 others (3%) had neither a positive serum Tg test nor an elevated serum Anti-TgAb level (Figure). None of the remaining 83 (85%) patients with undetectable TSH-stimulated serum Tg level and negative serum Anti-TgAb titers had a recurrence. Disease-free survival was significantly shorter in patients with positive Tg and/or Anti-TgAb as compared with patients who had persistently undetectable serum Tg or Anti-TgAb (standardized survival, 0.62 vs. 0.93; P<0.002). Neither undetectable serum Tg and Anti-TgAb (P = 0.7) nor histologic tumor features nor Tg immunostaining predicted recurrence. Only rising Tg or positive serum Anti-TgAb predicted tumor over time.

Conclusion Undetectable Tg and Anti-TgAb levels at the time of remnant ablation does not predict disease-free status; however, prognosis is worse in patients in whom a detectable Tg and/or Anti-TgAb develops during follow-up, which is associated with a shorter than usual disease-free survival.

COMMENTARY

There are major pitfalls to measuring serum Tg levels accurately, particularly assay interference by Anti-TgAb and heterophile antibodies. Probably the most common difficulty in practice is that Tg is often not measured in the same laboratory, a practice often beyond the control of both patient and physician alike. This inhibits critical comparative analyses of Tg levels over time, making them virtually useless(1). Still, despite using different Tg and anti-TgAb assays Phan et al. found sequential Tg measurements to be helpful. It is well known that quantitative anti-TgAb levels alone are a surrogate marker of tumor, which also must be measured in the

same assay. Phan et al. found that TSH-stimulated Tg measurements performed just before thyroid ¹³¹I remnant ablation provide little useful prognostic information, although this may in part be due to the use of two different Tg and anti-TgAb assays over time.

Timing of Tg measurements is critical. Two studies found that TSH-stimulated serum Tg measurements predicted survival if Tg was determined 6 (2) to 12 (3) months after initial therapy.

Ernest L. Mazzaferri, MD, MACP

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Thyroid ¹³¹I remnant ablation is unnecessary in carefully selected patients with papillary thyroid carcinomas 2 cm or smaller

Rosário PW, Borges MA, Valadão MM, Vasconcelos FP, Rezende LL, Padrão EL, Barroso AL, Purisch S. Is adjuvant therapy useful in patients with papillary carcinoma smaller than 2 cm? *Thyroid* 2007;17:1225-8.

SUMMARY

Background The American Thyroid Association guidelines for the management of papillary thyroid cancer suggest that low-risk patients may not necessarily require remnant ablation. However, no prospective studies have compared the outcomes of such patients, who generally have a good prognosis.

Methods This is a nonrandomized study of 136 selected patients with a single papillary thyroid cancer 2 cm or smaller without extrathyroidal invasion, lymph-node metastases, or involvement of the tumor margins in patients without a history of head and neck irradiation or familial thyroid cancer. All patients were treated with total thyroidectomy without central neck compartment (level VI) dissection, after which 42 patients (31%) were treated with thyroid hormone alone (group 1) and 36 patients (27%) were treated with 1.1 GBq (30 mCi) of ¹³¹I (group 2). Both groups received posttherapy levothyroxine. In group 1 and group 2, respectively, the mean (±SD) patient ages were 49.2±5.6 and 45.8±5.4 years (P<0.05); mean tumor sizes 10±2 and 10.8±2.3 cm; and the numbers of tumors ≤1.0 cm 24 of 42 (57%) and 56 of 94 (60%). Serum thyroglobulin levels were determined by an immunometric assay with a functional sensitivity of 0.8 ng/ml, and antithyroglobulin antibody (anti-TgAb) was measured in an assay with a detection limit of 1 IU/ml. Serum thyroglobulin levels were measured during levothyroxine

withdrawal when thyrotropin (TSH) was >30 mU/L. Posttreatment imaging was done with whole-body scans using radioiodine levels of 185 MBq (5 mCi) and with Technetium-99m (^{99m}Tc) methoxyisobutylisonitrile scans (^{99m}Tc-MIBI) and neck ultrasonography. Patients were considered to be free of disease when the serum thyroglobulin was ≤1 ng/ml and the serum TgAb <1 IU/ml and imaging studies were negative. Mean follow-up in group 1 and group 2, respectively, was 7.2±2.1 and 5.3±2 years (P<0.05).

Results Complete remission was found in 35 of 42 (83%) of patients who did not receive ¹³¹I and 84 of 94 (89%) patients treated with ¹³¹I (P = 0.4). Serum TgAb remained detectable in 11 patients (7.1% of group 1 and 8.5% of group 2), and serum thyroglobulin remained at >1 ng/ml in six patients, but serum levels of both markers declined by more than 50% during follow-up. Results of a postoperative whole-body scan, which were available in 74 (54%) patients, were negative and the ¹³¹I thyroid bed ¹³¹I uptake was <1% in 68 patients (92%). Serum TSH levels were >0.5 mU/L in 50% or more of the measurements made during levothyroxine treatment in both groups.

Conclusion Patients with selected very-low-risk papillary thyroid cancers 2 cm or smaller show no benefit with ¹³¹I thyroid remnant ablation.

COMMENTARY

The American Thyroid Association (ATA) guidelines (1) and the European Thyroid Association (ETA) consensus guidelines (2) for the management of differentiated thyroid carcinoma are in accord concerning the management of low-risk papillary thyroid carcinomas, although until recently the precise definition of low risk was not quite the same in both guidelines. However, the revision of the ATA guidelines underway now, to be published later this year, will likely closely match the European terms used to define low-risk patients. In general, three risk groups can be defined. Very-low-risk patients who have unifocal microcarcinoma 1 cm or smaller with no extension beyond the thyroid capsule and without lymph-node metastases. In this group, there are no clear benefits of and no indications for ¹³¹I ablation. ¹³¹I treatment should be considered for the high-risk group of patients with or at risk of having persistent or recurrent disease because it reduces the recurrence

rates, and perhaps improves survival, and permits early detection of persistent disease. The (intermediate) low-risk category includes all other patients, which would roughly describe the group studied by Rosário et al. Both the ATA and ETA acknowledge that the benefits of ¹³¹I in the latter group remain controversial, especially in those with a single tumor with none of the following: lymph-node metastases, extracapsular thyroidal invasion, multifocal tumor, a history of head and neck irradiation, and a family history of papillary thyroid cancer. When any of these variables are present, ¹³¹I therapy offers some benefit. Rosário et al.'s study group had many of the same features, including no extrathyroidal invasion, no lymph-node metastases, and tumor-free margins on histologic examination in patients without a positive family history of papillary thyroid cancer and head and neck irradiation. It is not stated how many patients with 2-cm papillary thyroid cancers were excluded from the original study group, but one would expect that the number is

large, considering that the high rates of multifocal tumor, lymph node metastases and extrathyroidal tumor extension in patients with low risk papillary thyroid cancer. One surprising finding in the Rosário study is the fact that most patients had TSH-stimulated serum Tg levels <1.0 ng/ml. Most contemporary studies find that residual thyroid tissue is present in about 95% of patients undergoing total thyroidectomy, which usually increases Tg levels to >1 ng/ml.

Ernest L. Mazzaferri, MD, MACP

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2. Pacini F, Schlumberger M, Dralle H, et al. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *Eur J Endocrinol* 2006;154:787-803.

Patients with elevated serum TSH levels are more likely than usual to have malignant thyroid nodules with advanced tumor stage

Haymart MR, Repplinger DJ, Levenson GE, Elson DF, Sippel RS, Jaume JC, Chen H. Higher Serum TSH level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. *J Clin Endocrinol Metab* December 26, 2007. doi:10.1210/jc.2007-2215.

SUMMARY

Background Previous studies of the relationship of serum thyrotropin (TSH) levels as a predictor of malignancy in thyroid nodules have reached differing conclusions. This is a large retrospective study of the relationship between serum TSH levels and the rate of thyroid cancer found in patients with surgically excised thyroid nodules.

Methods Study subjects are 843 consecutive patients with preoperative serum TSH measurements selected from a cohort of 1198 patients who had surgery for thyroid nodules between May 1994 and January 2007. The study cohort comprised 681 women (81%) and 162 (19%) men, 108 (16%) of whom were taking levothyroxine, which in the early years of the study had been prescribed for suppression of thyroid nodule growth and for overt hypothyroidism. Half of the patients had unilateral thyroidectomy (603 of 1198) and half had total thyroidectomy.

Results Differentiated thyroid carcinoma was found in 241 of 843 patients (29%), with papillary thyroid cancer being the most prevalent (87%). Malignant nodules were found in 63 of 162 (39%) men and in 178 of 618 women (26%), and were more prevalent in younger patients (mean age [±SEM], 46±1 vs. 50±0.7 years, P<0.01). Mean nodule size was smaller in malignant than in benign nodules (2.1±0.1 vs. 2.8±0.08 cm, P<0.001). Preoperative TSH was significantly higher in patients with malignant than with benign nodules (2.5±0.3 mIU/L vs. 1.6±0.1, P<0.001, (Figure).

When all 108 patients taking levothyroxine preoperatively were removed from this analysis, the serum TSH results remained essentially unchanged. Patients were stratified by serum TSH levels based on cutoff values in population studies in order to decrease the likelihood of very high TSH levels skewing the data. The lower and upper ends of normal were considered, respectively, to be TSH <0.06 mIU/L and ≤ 5.0 mIU/L. Using these cutoffs, the majority of patients were euthyroid and the distribution of TSH levels loosely followed a bell-shaped curve. The likelihood of malignancy increased with rising serum TSH levels, both as a continuous variable and within stratified ranges. The malignancy rate was 16% when the TSH was <0.06 mIU/L, as compared with 52% when the TSH was ≥5.0 mIU/L (P = 0.001). Thyroid cancer was found in 25% of patients with a TSH of 0.40 to 1.39

mIU/L, and in 35% of patients with a TSH of 1.40 to 4.99 mIU/L (P = 0.002). Independent risk factors for the diagnosis of thyroid cancer were male gender, age, nodule size, and increasing TSH levels, being 2.5-fold with TSH 1.40 to 2.49 mIU/L, 3.5-fold with TSH 2.50 to 4.99 mIU/L, and 4.5-fold with TSH ≥5.0 mIU/L, (P≤0.01) for all variables. TSH levels were significantly higher in patients with stage III and IV disease than in patients with stage I and II tumors (TSH, 4.9±0.24 mIU/L vs. 2.1±0.24, P = 0.002).

Conclusion Patients with elevated serum TSH levels are more likely to have malignant thyroid nodules with advanced tumor stage than individuals with lower TSH levels.

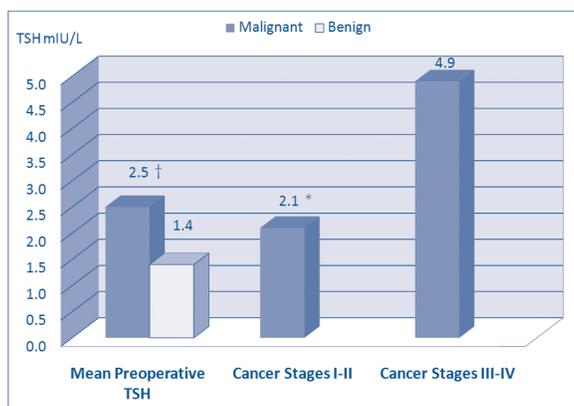


Figure. Mean postoperative serum TSH in patients with and without malignant thyroid nodules, and in patients with low and high tumor stage. †P<0.001 for the comparison of TSH levels in malignant and benign nodules; *P<0.001 for the comparison of serum TSH in low and high cancer stages.

COMMENTARY

Boelaert et al.(1) performed a retrospective study on 1,500 patients similar to that of Haymart et al. except in their study the diagnosis was based upon fine-needle aspiration biopsy cytology. They found that the risk of malignancy in a thyroid nodule increased in parallel with the serum TSH levels, much as found by Haymart et al. The odds ratio for the diagnosis of malignancy increased with a serum TSH of 1.8 to 5.5 mIU/L, compared to a TSH <0.4 mIU/L (OR 11.8 95% CI 3.23 to 8.63; P<0.001). The effect

was greater in males and younger patients and those with clinically solitary nodules.

The observations are much the same in the Haymart et al. study, however, their study makes an even stronger case for the hypothesis that high serum TSH levels increase the rate of malignancy in a parallel fashion as TSH rises, and is associated with more advanced stage papillary thyroid cancer at the time of diagnosis. The key part of this study is that all the patients underwent surgery and the histopathology diagnosis was verified as papillary thyroid carcinoma. This is a robust study that reaches two

important conclusions, one of which is new: malignant thyroid nodules in patients with high TSH levels are likely to be advanced stage papillary thyroid cancer.

Ernest L. Mazzaferri, MD, MACP

Reference

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Thyroid nodules 4 cm or larger should be considered for thyroid lobectomy

McCoy KL, Jabbour N, Ogilvie JB, Otori NP, Carty SE, Yim JH. The incidence of cancer and rate of false-negative cytology in thyroid nodules greater than or equal to 4 cm in size. *Surgery* 2007; 142:837-44.

SUMMARY

Background Determining whether a thyroid nodule is benign or malignant is usually done with the cytologic examination of cells obtained from the nodule by fine-needle aspiration biopsy. The main limitation of the procedure is the risk of a false-negative result, and the likelihood of a false-negative result increases with the size of the nodule. In this study, patients with thyroid nodules 4 cm or larger were operated on, regardless of the results of ultrasound-guided fine-needle aspiration biopsy.

Methods The study subjects were 223 patients (median age 55 years; range 22 to 89) who had thyroid nodules 4 cm or larger as the only indication for surgery. Lobectomy was done unless there were clinical indications for total thyroidectomy. Fine-needle aspiration biopsy (FNA) was performed in 149 patients (67%) only if it might have altered the extent of surgery.

Results Patients underwent 245 operations; including lobectomy and isthmusectomy (48%), total thyroidectomy (40%), and reoperative thyroidectomy (3%). Completion thyroidectomy was done when cancer was identified in the lobectomy specimen (9%). Other than nodule size, there were one or more indications for surgery in 43% of the patients, including cytology that was indeterminate (14%), atypical (5%) or malignant (1%); compressive symptoms (40%); previous head and neck irradiation (5%); or a family history of thyroid cancer (1%). In all, 81 (36%) of the patients had a multinodular goiter and 64 % had a single nodule.

The nodule was benign in 139 (62%) of the patients and malignant in 84 (38%). Most (56%) were papillary cancers, some of which were follicular (32%) or tall-cell variants

(5%). The others were Hürthle-cell (26%), follicular, (14%) and medullary (2%) cancers, and one (2%) was a thyroid lymphoma. Of the 84 patients with malignant nodules, 34 (40%) had a papillary microcarcinoma (tumors 1 cm or less in diameter), 33% of which were multifocal. The rate of thyroid cancer was not related to tumor size in this study, but cancer was significantly more common in patients with than without Hashimoto's thyroiditis (56 vs. 34%, $P < 0.001$).

Of 149 patients who underwent FNA, the preoperative cytology was classified as benign in 71 (48%), malignant in 3 (2%), indeterminate in 43 (29%) and nondiagnostic in 32 (21%). Two had follicular cancer, six had follicular variant of papillary cancer, and one had medullary cancer. When multifocal papillary microcarcinomas were included, the false-negative diagnosis rate increased from 13% to 16%. Of 24 patients with nodules 4 cm or larger that yielded indeterminate cytology, eight (33%) had thyroid cancer, including one with classic papillary cancer, five with follicular variant of papillary cancer, and one each with follicular cancer and Hürthle-cell cancer. Indeterminate Hürthle-cell tumors were found to be malignant in three of eight patients (38%). Five of 11 patients (45%) with tumors 4 cm or larger yielding atypical cytology had papillary cancers, including one each with classic, tall-cell, and, follicular variant of papillary cancer, and one with Hürthle-cell cancer. In all, 40% of the tumors with indeterminate cytology were malignant.

Conclusion The incidence rates of false-negative cytology on fine-needle aspiration biopsy of thyroid nodules are higher than usual in nodules 4 cm or larger. Patients with nodules of this size should be considered for diagnostic lobectomy, regardless of cytology results.

COMMENTARY

The management decisions for patients with thyroid nodules remain complex. The risk a nodule may be a harmful thyroid cancer is usually the deciding factor in most patient's evaluations. This risk is first assessed by cytology obtained from fine needle aspiration. McCoy and colleagues report data suggesting cytology obtained from nodules >4cm may at times be inaccurate, primarily due to misinterpretation of cellular findings. They suggest all nodules >4cm be removed.

While the above recommendation has also been proposed by others, such a blanket statement should be taken with

caution for several reasons. Importantly, several other studies have suggested very low false-negative rates from ultrasound-guided aspirations (1). Furthermore, there are few credible published data to suggest a previous benign nodule may undergo malignant transformation. Thus, such a strong recommendation for standard removal of all nodules >4cm must stem from inaccurate interpretation of cytology. Given this, a single-institution investigation utilizing only a single cytopathologist, such as that from McCoy et al, is informative but not absolute. This is especially the case for investigations that are retrospective and may harbor a selection bias – both true for this article.

Until a larger, prospective, multicenter

trial is conducted to better define clinical practice, it seems reasonable to consider either surgical resection, as well as a more conservative approach, for the treatment of large (>4cm) thyroid nodules confirmed cytologically benign via ultrasound-guided aspiration performed in a high-volume clinical setting.

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Recombinant human thyrotropin-stimulated ^{131}I therapy of multinodular goiter reduces thyroid volume but causes thyroiditis and hypothyroidism

Paz-Filho GJ, Mesa-Junior CO, Olandoski M, Woellner LC, Goedert CA, Boguszewski CL et al. Effect of 30 mCi radioiodine on multinodular goiter previously treated with recombinant human thyroid-stimulating hormone. *Braz J Med Biol Res* 2007; 40:1661-70.

SUMMARY

Background When ^{131}I is the only therapy available for patients with benign goiter, high doses of ^{131}I may be required because its uptake is usually not high. This study evaluated the efficacy and safety of a single 0.1-mg dose of recombinant human thyrotropin (rhTSH) and 30 mCi (1110 MBq) of ^{131}I .

Methods The study subjects were 17 patients with multinodular goiter, of whom 15 (88%) were women; the mean age (\pm SD) was 59 ± 13.1 years. Six had subclinical or overt hyperthyroidism. A single 0.1-mg injection of rhTSH was given the day before ^{131}I therapy. Blood samples were collected repeatedly for measurements of serum thyrotropin (TSH), free thyroxine, triiodothyronine, antithyroid peroxidase and anti-thyroglobulin and TSH receptors.

Results After rhTSH stimulation the 24-hour ^{131}I uptake increased from 18% to 50% ($P < 0.001$) and the scintigraphic uptake changed from heterogeneous to diffuse pattern. By 12 months, the thyroid volume measured by CT declined 46%, but neither the ^{131}I activity, corrected for thyroid mass,

nor the post-recombinant rhTSH-stimulated ^{131}I uptake were related to the thyroid volume reduction.

By the second month, serum TSH remained below the normal range in nine patients (53%). By the third month, the incidence of hypothyroidism was 41%, which gradually increased to almost 53% within 1 year. Titers of serum TSH-receptor antibody, absent before treatment, were high after 12 months in five patients. Autoimmune hyperthyroidism developed in a 71-year-old woman, requiring another 30 mCi (1110 MBq) of ^{131}I . Three patients had at least one symptom or sign of hyperthyroidism, during the first 10 days after ^{131}I therapy; they were treated for a short time with a β -blocker. Painful thyroiditis developed in five patients (29%) 1 week or more after ^{131}I therapy, but none had respiratory or compressive symptoms.

Conclusion Treatment of patients with a multinodular goiter with a single 0.1-mg dose of rhTSH and 30 mCi (1110 MBq) of ^{131}I significantly reduces thyroid volume, but can cause hypothyroidism, painful thyroiditis, and occasionally autoimmune hyperthyroidism.

COMMENTARY

The concept of rhTSH-stimulated ^{131}I therapy in patients with benign nodular goiter has been evaluated in a number of studies. This Brazilian study is mainly a confirmatory one. The key issues (impact on thyroid iodine uptake, goiter reduction, and adverse effects) have been addressed in previous trials. It is well known that rhTSH can increase the iodine uptake by thyrocytes more than twofold. The study confirms that the effect on thyroid iodine uptake is inversely correlated with the baseline uptake, meaning that the patients with the lowest thyroid iodine uptake benefit most from rhTSH stimulation. Since patients were asked to follow a low-iodine diet for 2 weeks before therapy, it is unclear whether the increase in the thyroid iodine uptake is due entirely to the rhTSH stimulation.

The goiter reduction by mean 46% after 12 months was of the same magnitude as in a comparable study by the same group, but with the distinction that two doses of 0.1 mg rhTSH were given in the previous one (1). This supports the experience from previous trials that a dose exceeding 0.1 mg probably is superfluous and only leads to more adverse effects. Since the study lacks a control group it

is impossible to determine how much of the goiter reduction that can be ascribed to the rhTSH pre-stimulation. However, previous randomized studies (2;3) showed a significantly greater goiter reduction when radioiodine therapy was preceded by rhTSH.

The irradiation of the goiter was highly variable among patients due to the use of a fixed radioactivity (30 mCi [1110MBq]). The correlation between the applied thyroid dose (calculated on the pre-therapeutic iodine kinetics) and the goiter reduction was statistically insignificant. This observation, in accordance with other trials (1), is interesting and suggests that rhTSH exerts its effect not only through the changes in the iodine kinetics. In addition, the thyrocyte might be preconditioned by rhTSH making it more susceptible to radiation.

Like in other studies (2;3) adverse effects were frequently observed. No difference was found between euthyroid patients and those pre-treated with methimazole. Thus, the concept of rhTSH stimulated radioiodine therapy might include also individuals with a subnormal TSH, which is a common finding among patients with goiter. Although the results of this and other trials are encouraging a

routine implementation of rhTSH stimulated radioiodine therapy should await results from ongoing phase II/III trials.

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Statin treatment may reduce thyroid size and the formation and size of thyroid nodules

Cappelli C, Castellano M, Pirola I, De Martino E, Gandossi E, Delbarba A, Salvi A, Rosei EA. Reduced thyroid volume and nodularity in dyslipidaemic patients on statin treatment. *Clin Endocrinol (Oxf)* 2008;68:16-21.

SUMMARY

Background Drugs of the statin class not only decrease serum lipid concentrations but also have antiproliferative actions in some tissues, including the thyroid. In this study, the effect of these drugs on thyroid volume and the frequency and size of thyroid nodules was determined.

Methods The study subjects were 135 patients with dyslipidemia (74 women, 61 men; mean age, 62 years) who had been treated continuously with a statin for at least 5 years and 137 control patients (76 women, 61 men; mean age, 62 years) living in an area of mild iodine deficiency. The control group included 28 normal subjects. All the patients in the statin group had hypercholesterolemia and were euthyroid when statin therapy was started. Most of the control group had hypertension, ischemic heart disease, or syncope. More patients in the statin group had a family history of thyroid disease (13 vs. 3%). When studied, the mean body-mass index and thyroid function were normal in both groups, and many patients were taking other drugs, but not amiodarone or lithium.

Thyroid volume was measured and the number and size of thyroid nodules were assessed by ultrasonography. The results were interpreted by one investigator, who was unaware of group assignment. A thyroid nodule was defined as a mass of any size distinguishable from the surrounding thyroid tissue. Nodules that were completely echo-free were not counted.

Results The patients in the statin group had smaller thyroid glands and fewer and smaller thyroid nodules than did those in the control group (Table). Thyroid volume remained

lower in the statin group after adjustment for body-mass index, and nodule volume remained lower after adjustment for thyroid volume. More patients in the statin group were taking other drugs (97 vs. 39%); they included angiotensin-converting-enzyme inhibitors (42 vs. 26%), β -adrenergic antagonists (40 vs. 16%), calcium-channel antagonists (33 vs. 11%), hypoglycemic drugs (18 vs. 3%), and insulin (14 vs. 1%). In analyses in which the patients were stratified by types of drugs, angiotensin-converting-enzyme inhibitors and calcium-channel antagonists were associated with fewer thyroid nodules. By logistic-regression analysis, statins were the only drugs associated with fewer thyroid nodules.

Table. Thyroid Volume and Nodules in the Statin and Control Groups.

	Statin	Control
Thyroid volume (ml)	13.4	15.9*
Prevalence of nodules (%)	36	68*
Single nodule (%)	19	39*
Multiple nodules (%)	18	29*
Nodule volume (ml)	0.7	1.3*
Nodules per patient	0.7	1.1*
Range of nodule size (mm)	3-21	2-30

*P<0.01, as compared with the statin group.

Nearly all of the patients in the statin group were taking simvastatin or atorvastatin. The absence of nodules was not related to either drug or to the dose, but was related to longer duration of treatment.

Conclusion Patients treated with statin drugs have smaller thyroid glands and fewer and smaller thyroid nodules, as compared with patients not so treated, suggesting that the drugs have an antiproliferative action on the thyroid gland.

COMMENTARY

The findings that statin therapy is associated with a smaller thyroid gland and fewer and smaller thyroid nodules are intriguing, although clearly not compelling. The clinical characteristics

of the statin and control groups differed considerably. Nodules seemingly as small as 1 or 2 mm in size were counted, and the counts were done by only one ultrasonographer. Biopsies apparently were not done, and therefore the nature of even the larger nodules is not known.

Nonetheless, accepting the results for what they are, it is worth noting there are few things that reduce thyroid size without reducing thyroid function, and even fewer that prevent the formation of thyroid nodules and limit their growth.

Robert D. Utiger, MD

There is no benefit of substitution of triiodothyronine for thyroxine in preparation of patients with thyroid carcinoma for further study or therapy

Leboeuf R, Perron P, Carpentier AC, Verreault J, Langlois MF. L-T₃ preparation for whole-body scintigraphy: a randomized-controlled trial. *Clin Endocrinol (Oxf)* 2007;67:839-44.

SUMMARY

Background Many patients with thyroid carcinoma undergo diagnostic radioiodine (¹³¹I or ¹²³I) scintigraphy or ¹³¹I therapy after initial thyroidectomy, which to be useful or effective must be done when serum thyrotropin (TSH) concentrations are high. High concentrations may be achieved by stopping thyroxine (T₄) therapy or switching to triiodothyronine (T₃) therapy and then stopping it, the rationale for the latter being that serum TSH concentrations will rise more rapidly after T₃ is stopped. This study was done to compare the effect of the two withdrawal regimens on symptoms and signs of hypothyroidism and serum TSH concentrations.

Methods The study subjects were 17 patients with thyroid carcinoma (7 women, 10 men; mean age, 64 years in the T₃-treatment group, vs. 46 years in the placebo group). They had undergone total thyroidectomy and were treated with T₄, which was to be stopped for diagnostic whole-body scintigraphy or ¹³¹I therapy. When T₄ (dose not given) was stopped, patients were randomly assigned to receive two 25-µg capsules of T₃ or placebo daily for 3 weeks. This treatment then stopped, and the planned scintigraphy or therapy was done 2 weeks later.

The patients were evaluated using the Billewicz scale at the time T₄ was stopped and every 2 weeks thereafter until the planned procedure was completed. This scale is based on assessment of eight symptoms and six signs of hypothyroidism (minimum and maximum possible scores, respectively, -53 [euthyroid] and +19 [hypothyroid]). The assessments were done by the same investigator, who was unaware of treatment-group assignment. Serum TSH was measured weekly.

Results The mean Billewicz score in the two groups was similar when T₄ was stopped (baseline), after 2 weeks of T₃ or

placebo, and at the time of scintigraphy or treatment 2 weeks after T₃ or placebo was stopped (Table).

	Base-line	2 Weeks (T ₃ or Placebo)	3 Weeks (T ₃ or Placebo)	2 Weeks after T ₃ or Placebo
Billewicz score				
T ₃ treatment group	-43	-39	-	15
Placebo group	-43	-31	-	13
Serum TSH (mIU/L)				
T ₃ treatment group	2.1	2.1*	2.1*	97
Placebo group	1.7	40*	80*	135

*Values extrapolated from Figure 2b of Leboeuf et al.

The mean serum TSH concentration was normal in both groups at baseline. It did not increase in the T₃-treatment group until after T₃ was discontinued, and was approximately 25 mIU/L 1 week later and 97 mIU/L 2 weeks later (Table). In contrast, the mean serum TSH concentration was approximately 40 mIU/L after 1 week in the placebo group, approximately 80 mIU/L at 3 weeks when the placebo was stopped, and 135 mIU/L 2 weeks later. The mean time to reach serum TSH concentrations of ≥30 mIU/L after stopping T₄ was 17 days, and it was 11 days after stopping T₃ (P = 0.07).

Conclusion Among patients with thyroid carcinoma treated with T₄ who are to undergo scintigraphy or ¹³¹I therapy, stopping T₄ for 5 weeks resulted in no more symptoms and signs of hypothyroidism than stopping T₄ and giving T₃ for 3 weeks and then stopping it for 2 weeks. Serum TSH concentrations were similar in the two groups 5 weeks later, but they rose more rapidly when T₄ was stopped. Therefore, studies or treatment can be done sooner without intervening hypothyroidism.

COMMENTARY

The practice of performing diagnostic radioiodine scintigraphy or giving ¹³¹I therapy only when serum TSH concentrations are 25 to 30 mIU/L is well established and physiologically sound. These concentrations can be reached in several ways, including cessation of T₄, substitution of T₃ for T₄ for several weeks and then cessation of T₃, reducing the dose of T₄ by 50%, and administration of recombinant TSH.

The T₃ substitution protocol was introduced because it was thought that serum TSH concentrations would rise more rapidly after T₃ was stopped than after T₄ was stopped, because T₃ is cleared more rapidly. Hence, the duration of tissue hypothyroidism and the likelihood of symptoms and signs of hypothyroidism, or their duration if any occurred, would be shorter. Notwithstanding the appeal of this approach, the data presented by Leboeuf et al. clearly indicate that cessation of

T₄ alone results in no more symptoms and signs of hypothyroidism in 5 weeks than does cessation of T₃ for 2 weeks. Furthermore, serum TSH concentrations reach values suitable for scintigraphy or ¹³¹I therapy almost as soon after T₄ is stopped as after T₃ is stopped. In short, substituting T₃ for T₄ has no benefits, is more complicated than simply stopping T₄, and lengthens the time after T₄ is stopped before scintigraphy or treatment can be done.

Robert D. Utiger, MD

An increase in liver enzymes in thyrotoxic patients may not be due to antithyroid drugs alone

Kubota S, Amino N, Matsumoto Y, Ikeda N, Morita S, Kudo T, Ohye H, Nishihara E, Ito M, Fukata S, Miyauchi A. Serial changes in liver function tests in patients with thyrotoxicosis induced by Graves' disease and painless thyroiditis. *Thyroid* 2007;17:1-5.

SUMMARY

Background Abnormal liver-function tests may be a sign of drug-induced hepatitis or cholestatic jaundice, or may be altered by thyrotoxicosis alone. This prospective study examines the extent to which thyrotoxicosis alone alters liver-function tests.

Methods The study subjects were 30 patients with Graves' disease, 27 patients with painless thyroiditis, and 35 age- and sex-matched healthy controls. Five patients with Graves' disease (17%) were treated with either 100 or 300 mg of PTU (propylthiouracil) and 25 patients (83%) were treated with 15 to 30 mg of MMI (methimazole); the drugs were gradually tapered to maintain a euthyroid state. Patients with silent thyroiditis were observed without treatment. Liver-function tests obtained were albumin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, γ -glutamyl transpeptidase, lactic dehydrogenase, alkaline phosphatase and, creatine kinase.

Results Most untreated patients with Graves' disease (77%) and over half the patients with silent thyroiditis (52%)

had one or more abnormal liver-function tests that were significantly higher than normal ($P < 0.5$ to $P < 0.001$). Serum

creatinine kinase was lower than normal ($P < 0.001$) in 57% of the patients with Graves' disease and in 59% of the patients with silent thyroiditis. One month after antithyroid drugs were started, significant elevations ($P < 0.001$) in serum alanine aminotransferase and alkaline phosphatase were observed in 53% of the patients with Graves' disease and remained so for as long as 5 months (Fig. 1). Almost 40% of the patients with silent thyroiditis had significant ($P < 0.05$ to $P < 0.001$) elevations in serum alanine aminotransferase and serum alkaline phosphatase that remained elevated for as long as 5 months, albeit at lower levels than those in patients with Graves' disease (Fig. 2). Serum free thyroxine levels were significantly higher than normal at entry into the study but gradually returned to normal within 3 to 5 months.

Conclusion Elevations of serum alanine aminotransferase and alkaline phosphatase in patients with Graves' disease or silent thyroiditis may not be due to antithyroid drugs but may be induced by thyrotoxicosis.

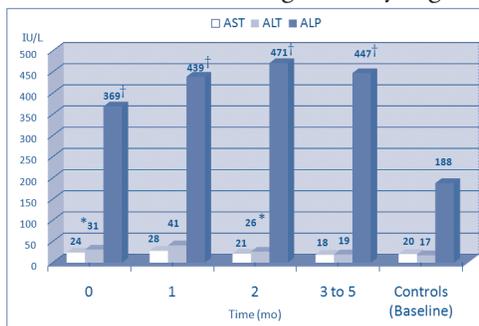


Figure 1. Liver-function test values from months 0 to 5 during treatment of patients with Graves' disease. Comparisons are between Graves' disease and healthy controls. † $P < 0.001$; * $P < 0.05$. ALP = alkaline phosphatase; ALT = serum alanine aminotransferase; AST = aspartate aminotransferase. Both figures drawn from the data of Kubota et al.

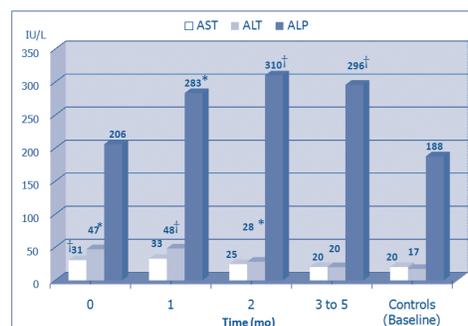


Figure 2. Liver-function test values in patients with thyrotoxicosis caused by silent thyroiditis. Comparisons are between patients with thyrotoxic silent thyroiditis and normal controls. See Figure 1 legend for symbols and abbreviations.

COMMENTARY

It has been known for decades that liver-function abnormalities are common in hyperthyroid patients. Prospective studies showed that serum alkaline phosphatase levels increase as thyroid function improves after therapy, but this phenomenon is primarily due to increases in the bone isoenzyme rather than the liver isoenzyme. More recently, it has been shown that temporary increases in transaminases frequently occur following PTU therapy, thought to be due to transient PTU-induced hepatitis. The study by Kubota et al. showed that increases in transaminases occurred with MMI as well as PTU. Not only that, but a similar although less dramatic increase in liver enzymes occurred in patients with

resolving silent thyroiditis who were taking no medication at all. Thus, a rise in liver enzymes may be due, in some unknown way, to the restoration of the euthyroid state. However, this study should not be taken to mean that increases in liver enzymes, especially with PTU therapy, are always part of the natural history of recovering hyperthyroidism. A recent randomized, prospective, controlled trial comparing PTU to MMI showed that almost 30% of PTU-treated patients had a more than twofold increase in transaminases, versus only 7% of patients treated with MMI (1). This study suggests that transaminase elevations are caused by PTU and that they are not exclusively part of the recovery process. Whether it is worthwhile to monitor liver function after antithyroid drugs are instituted

is debatable, and no current clinical practice guidelines recommend doing so. Nevertheless, for PTU, the case for routine monitoring is stronger than it is for MMI. In light of the study by Kubota et al., if transaminases does rise during routine monitoring, the drug may not be the culprit.

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Aplasia cutis can occur in one of monozygotic twins of a mother treated with methimazole during pregnancy

Iwayama H, Hosono H, Yamamoto H, Oshiro M, Ueda N. Aplasia cutis congenita with skull defect in a monozygotic twin after exposure to methimazole in utero. *Birth Defects Res A Clin Mol Teratol* 2007;79:680-4.

SUMMARY

Background Aplasia cutis is a rare congenital anomaly characterized by an absence of skin, usually of the scalp, and sometimes also the underlying tissue, including bone. It has been described in infants whose mothers were treated with methimazole or carbimazole, but not propylthiouracil, during their pregnancies, but whether the drugs cause the anomaly is not known. This report describes the occurrence of aplasia cutis in one of a pair of monozygotic twins whose mother was treated with methimazole during pregnancy.

Case Report A woman who was pregnant with monochorionic diamniotic female twins was treated for transient gestational hyperthyroidism with methimazole between the 11th and 17th weeks of pregnancy. The dose was 30 mg daily for 3 days and 15 mg daily thereafter. The first twin was delivered at 36 weeks' gestation. She weighed 1778 g, was 45 cm long, and had a head circumference of 32 cm. There was a midline 7-by-5 cm defect in the scalp, skull, and dura in the parieto-occipital region of the head. The

other twin was born at full gestation; at delivery, she weighed 2135 g, was 42 cm long, and had a head circumference of 32 cm; she had no congenital anomalies.

Neurologic examination of the affected twin was normal. X-rays of the skull and computed tomography of the brain confirmed the bony defect, and were otherwise normal. The scalp defect was cleansed daily, and trafermin, a recombinant human fibroblast growth factor, was sprayed on it to stimulate growth of skin over the defect. The infant's course was complicated by an infection of the scalp defect with methicillin-resistant *Staphylococcus aureus* (blood and cerebrospinal fluid cultures were negative) that was treated successfully with multiple antibiotics and povidone-iodine dressings. By day 44, the defect was covered by ingrowth of skin from its margins, but the skull defect persisted.

Conclusion Monozygotic twins exposed to methimazole during gestation may be discordant for aplasia cutis, suggesting that exposure to methimazole alone may not be sufficient to cause the anomaly.

COMMENTARY

Two types of congenital anomalies have been described in infants whose mothers were treated with an antithyroid drug during their pregnancies. One is aplasia cutis. As described above, the defect is usually limited to the skin of the scalp, and it is small and closes spontaneously. In this context, the infant described by Iwayama et al. had an unusually severe defect. Other anomalies are uncommon in these infants. The other type is what has been called methimazole embryopathy, consisting of one or more of the following—choanal atresia, esophageal atresia, tracheoesophageal fistula, omphalocele, hypoplastic nipples, facial dysmorphism, and developmental delay.

All these anomalies have occurred only in infants exposed to methimazole or carbimazole, with one exception, an infant exposed to propylthiouracil who had choanal atresia(1). The association between methimazole-carbimazole and the anomalies suggests a cause-and-effect

relationship. However, the association is based on case reports, and studies of birth registries have provided little evidence linking the drugs and either type of anomaly(2,3). An alternative explanation for the occurrence of these anomalies is that they are associated with maternal and or fetal hyperthyroidism. One study found a higher frequency of anomalies in the infants of mothers with untreated hyperthyroidism (3 of 50, 6%) than mothers with hyperthyroidism treated with methimazole (2 of 117, 2%) (4).

The varying nature of the anomalies reported in infants exposed to methimazole-carbimazole, the lack of a dose response to the drugs, and their varying effect on twin pregnancies all point to the unpredictability of any teratogenic actions the drugs may have. That unpredictability underscores the wisdom of treating pregnant women with hyperthyroidism with propylthiouracil, if any antithyroid drug therapy cannot be avoided. It is important to keep in mind, however, that its safety may be more apparent than real, because it has been

given to fewer patients worldwide than has methimazole.

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Glucocorticoid therapy should be the mainstay for all cases of amiodarone-induced thyrotoxicosis

Bogazzi F, Bartalena L, Dell'Unto E, Tomisti L, Rossi G, Pepe P, Tanda ML, Grasso L, Macchia E, Aghini-Lombardi F, Pinchera A, Martino E. Proportion of type 1 and type 2 amiodarone-induced thyrotoxicosis has changed over a 27-year period in Italy. *Clin Endocrinol (Oxf)* 2007;67:533-7.

SUMMARY

Background Type 1 amiodarone-induced thyrotoxicosis (AIT) is a form of iodine-induced hyperthyroidism that occurs in patients with preexisting nodular goiter or Graves' disease that generally is difficult to treat, often requiring several antithyroid drugs, glucocorticoids, or surgery, while type 2 AIT is a destructive thyroiditis that generally responds fairly rapidly to glucocorticoid therapy. However, the two forms of AIT sometimes overlap, making therapeutic choices difficult. The object of this study was to retrospectively assess the prevalence of the two forms of AIT over a 27-year period.

Methods The study subjects were 215 consecutive patients with untreated AIT who had been treated with long-term amiodarone. The diagnosis of AIT was based on clinical findings and increased serum free thyroxine (FT₄) and triiodothyronine (T₃) concentrations, undetectable thyrotropin (TSH) levels, and increased urinary iodine excretion levels. Patients with preexisting thyroid disorders were classified as having type 1 AIT; however, some had mixed or indefinite forms of AIT, in which case they were classified as having type 2 AIT. Patients with type 1 were treated with thionamide drugs (35%), sometimes with perchlorate (22%) or perchlorate and glucocorticoids (21%). After patients with type 1 AIT became euthyroid, 46% were treated with ¹³¹I, and 30% underwent total thyroidectomy. The diagnosis of type 2 AIT was based on an absence of serum antithyroglobulin antibodies and antithyroid peroxidase antibodies, and ultrasonographically absent or small goiter (or impalpable before 1983) and absent or small thyroid nodules (<1 cm), low or suppressed thyroidal ¹³¹I uptake, and absent hypervascularization on color-flow

Doppler studies. Almost all patients with type 2 AIT were treated with glucocorticoids, but 8% were treated with thionamide drugs alone or combined with glucocorticoids and 5% were treated with thyroidectomy.

Results Among 215 patients with AIT, 70 (33%) were categorized as having type 1 and 145 (67%) as having type 2; 146 (68%) were men and 69 (32%) were women. Of the type 1 group, 37 (53%) were men and 33 (47%) were women; however, of the type 2 group, 109 (95%) were men and 36 (5%) were women (P<0.001). Mean age (±SD) did not differ in patients with type 1 and 2 AIT, (65±10 vs. 63±13 years). The following were significantly higher in type 1 AIT: serum antithyroglobulin antibodies, antithyroid peroxidase antibodies, thyroid volume, and thyroidal 3-hour and 24-hour ¹³¹I uptake (all P<0.001). The following were significantly higher in type 2 AIT: FT₄/T₃ ratio, due mainly to higher FT₄ levels, and the cumulative dose of amiodarone (121.2±13.4 vs. 74±19.8 g (P<0.001), due mainly to the longer duration of treatment with amiodarone in type 2 than type 1 AIT (both P<0.001).

During the 27-year follow-up period from 1980 to 2006, the annual mean incidence of type 1 AIT remained almost the same, decreasing from a mean of 3.6 to 2.5 cases per year, while type 2 cases increased from 2.4 to 12.5 per year (P<0.001). The percentage of type 2 cases during this time increased linearly from 60% to 89% of the cases (P<0.001).

Conclusion As a result of the rising incidence of type 2 AIT-induced thyrotoxicosis, glucocorticoid therapy should be considered a mainstay in the management of all cases of AIT-induced thyrotoxicosis.

COMMENTARY

This group from Pisa has been in the forefront of investigating the complex problem of amiodarone-induced thyroid dysfunction. By far the most complex problem is type 1 AIT, which is often difficult to reliably identify and treat because of the high iodine levels that suppress the thyroidal ¹³¹I uptake that poses both diagnostic and therapeutic problems. It also dampens the therapeutic response to thionamide drugs, which must be given in larger than usual doses. Moreover, some drugs advised for treatment, perchlorate and iopanoic acid, are no longer available in the United States. By contrast type-2 AIT-induced thyrotoxicosis usually responds to glucocorticoid therapy within 1 to 2

weeks, with dramatic results. This study will likely be welcomed by clinicians. It provides strong support for the authors' recommendation that glucocorticoid therapy should become the mainstay of treatment of AIT-induced thyrotoxicosis.

Still, uncertainties exist about several issues. Mixed forms of AIT may not respond to either glucocorticoids or antithyroid drugs (1). It is not certain that amiodarone must be discontinued in patients with thyrotoxicosis and serious arrhythmias. One study (2) was unable to document a difference in outcome among patients in whom amiodarone was stopped and those who continued taking the drug. Bogazzi et al. found that patients with type 2 AIT received a higher cumulative dose of amiodarone over a more extended period compared

with patients with type 1, suggesting that the iodine load may be involved in the pathogenesis. Why type 2 AIT has increased so dramatically remains uncertain, but probably involves more rapid identification of patients with type 1 and greater physician awareness of the adverse effects of amiodarone.

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Most children with acquired hypothyroidism have little or no weight change in response to levothyroxine therapy

Lomenick JP, El Sayyid M, Smith WJ. Effect of levo-thyroxine treatment on weight and body mass index in children with acquired hypothyroidism. *J Pediatr* 2008;152:96-100.

SUMMARY

Background Studies in adults with hypothyroidism have shown that patients do not routinely lose weight after thyroid hormone-replacement therapy. However, such studies have not been done in children. This study evaluated short-term and long-term weight and body-mass index (BMI) changes in children with hypothyroidism treated with levothyroxine.

Methods The study subjects are 68 children all but one of whom had Hashimoto's thyroiditis. The subjects were retrospectively chosen from a group of 213 patients after meeting the following criteria: age less than 18 years at the time of the initial diagnosis of primary hypothyroidism, initiation of levothyroxine treatment on the first office visit, and at least one follow-up visit after levothyroxine therapy was initiated. At each visit, thyrotropin (TSH) was obtained, weight was recorded to the nearest 0.1 kg, and height was measured to the nearest 0.1 cm, from which the BMI was determined using the formula: weight in kilograms divided by the square of the height in meters. Study subjects were divided into two groups based on their weight at the second clinic visit compared with the first visit: those who lost weight (group 1; n = 21) and those who had no change or gained weight (group 2; n = 47). Obesity was defined as a BMI more than the 95th percentile for age and gender, and overweight was defined as a BMI more than the 85th to 95th percentile.

Results Most of the subjects (81%) were female, and 57% were overweight. Mean age (\pm SD) was similar in the two groups—11.0 \pm 3.0 and 10.7 \pm 3.2 years, P = 0.8. Of the 22 patient characteristics studied, only three were significantly

different in the two groups. Children in group 1 had a longer duration of follow-up (43 \pm 3.1, vs. 1.8 \pm 1.7 years; P = 0.002) and had more severe hypothyroidism (TSH, 349 \pm 388, vs. 56.8 \pm 90.8 mU/L; P<0.003) than those in group 2; however, the degree of hypothyroidism was highly variable (TSH range, 5.5 to 1600 mU/L). Children in group 2 had the highest percentage of short/poor growth (24 vs. 0%, P = 0.002). By the second visit, 4.4 months after the first, 31% of the entire group had lost weight. The mean weight loss was 2.3 kg (range, 0.6 to 7.3, P = 0.81), and there was no statistically significant difference in weight loss or BMI between the two groups. The mean serum TSH decreased from 147 mIU/L at baseline to 5.0 mIU/L in response to levothyroxine therapy. Thirty of the 68 children (56%) had at least 2 years of follow-up, and 19 of 68 (28%) had at least 4 years of follow-up. During this extended period, weight and BMI did not change significantly compared with baseline values. Changes in weight and BMI between the two groups were also not significantly different. At the second visit, significant inverse correlations were found between the initial TSH and a change in weight (R = -0.42, P = 0.001), weight z score (R = -0.55, P<0.01, weight percentile (R = -0.44, P = 0.01), and BMI z score (R = -0.005); however, after 4 years of treatment, these correlations were no longer statistically significant.

Conclusion There is little change in body weight and BMI over an extended period when children with hypothyroidism are treated with levothyroxine. Those who initially lose weight tend to have severe hypothyroidism but sustain only a small weight loss.

COMMENTARY

Weight gain in patients with severe myxedema is largely due to the accumulation of proteinaceous fluid in body cavities. In the absence of significant metabolic derangement, body weight is regulated within narrow limits over many years and does not change significantly in patients with hypothyroidism treated with levothyroxine. Patients with less severe degrees of hypothyroidism tend to experience little or no weight gain. A retrospective study(1) of 25 adults with primary hypothyroidism found that 12 months after starting levothyroxine, patients lost an insignificant amount of weight (mean change, -0.6 kg [95% confidence interval, -2.2 to +1.1; P>0.5). Another study(2) of 18 subjects with hypothyroidism found that patients with serum thyroxine

levels of \geq 20 μ g/dl (258 nmol/L) had higher pre-morbid body weights and greater weight loss from baseline compared with subjects with thyroxine values <20 μ g/dl. Still, over the first 6 months of levothyroxine treatment, subjects with hypothyroidism showed a small decline in mean body weight but returned to pretreatment weight by 24 months.

Most of the children in Lomenick et al.'s study had significant biochemical hypothyroidism, with serum TSH levels >10 mU/L in 84% and >20 mU/L in 59% of the study subjects. Nonetheless, levothyroxine therapy resulting in near normalization of serum TSH levels did not significantly alter weight or BMI at any point at which it was measured. Given the current epidemic of childhood obesity in the United States, parents of overweight children are best advised not to blame it

on hypothyroidism. Still, some physicians sometimes prescribe unnecessary levothyroxine therapy for children with mild hypothyroidism. Dietary advice should thus be given at the onset of any treatment of hypothyroidism, and patients should be advised that treating children with mild hypothyroidism is not likely to have a therapeutic benefit on the child's weight.

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Patients with type 2 diabetes mellitus and subclinical hypothyroidism are at increased risk of nephropathy but not of retinopathy or cardiac mortality

Chen HS, Wu TE, Jap TS, Lu RA, Wang ML, Chen RL, Lin HD. Subclinical hypothyroidism is a risk factor for nephropathy and cardiovascular diseases in Type 2 diabetic patients. *Diabet Med* 2007; 24:1336-44.

SUMMARY

Background Subclinical hypothyroidism has been associated with impaired cardiac function and the development of atherosclerosis, but these relationships have not been fully explored in patients with diabetes mellitus, a group at high risk for heart disease and thyroid dysfunction. The purpose of this prospective cross-sectional and longitudinal analysis was to determine the relationship between subclinical hypothyroidism and the prevalence of retinopathy, nephropathy, and incident cardiovascular disease and mortality in type 2 diabetic patients not being treated with levothyroxine.

Methods Study subjects were 556 patients with type 2 diabetes without thyroid disease. Of this group, 41 (7%) had untreated subclinical hypothyroidism, defined as a thyrotropin (TSH) level >4.0 mU/L with a normal serum free thyroxine level. Controls were 515 (93%) euthyroid patients with type 2 diabetes. The mean duration (\pm SD) of diabetes was 9.7 ± 7.8 years in the study group and 9.6 ± 7.5 years in controls ($P = 0.9$). Men comprised 54% (22) of the study group and 66% (339) of the controls; women were 46% (19) of the study group and 34% (176) of the controls. Mean age was 67.2 ± 10.8 years in the study group and 66.3 ± 10.7 in controls ($P = 0.6$). There were no statistically significant differences between the study and control groups with respect to age, gender, duration of diabetes, smoking history, body-mass index, blood pressure, hemoglobin A_{1c}, cholesterol, triglycerides, and liver-function tests. Study subjects had higher serum creatinine levels, higher urine albumin-to-creatinine ratios, and higher initial TSH levels than controls (5.61 mIU/L; range, 4.03 to 12.5, vs. 1.34 mIU/L; range, 0.41 to 3.99). Compared with controls,

study subjects were more likely to be taking insulin (51.2% vs. 32%, $P < 0.03$) and calcium blockers (83% vs. 45%, $P = 0.001$) and were less likely to be using sulfonylureas (43.9% vs. 65.4%, $P < 0.2$).

Results There was a greater prevalence of diabetic nephropathy in study subjects than in controls (71% vs. 47%; (odds ratio [OR], 3.15; 95% confidence interval [CI] 1.48 to 6.69; $P = 0.003$). Additional adjustment for HbA_{1c}, blood pressure, body-mass index, and smoking status did not change this association (OR, 2.76; CI, 1.28 to 5.95; $P = 0.006$). The prevalence of retinopathy was 34% in study subjects and 31% in controls (OR, 1.15; CI, 0.59 to 2.26; $P = 0.7$).

During longitudinal analysis, 12 of 41 (29%) subclinically hypothyroid patients required levothyroxine; the serum TSH normalized in seven others (17%). The incidence rate of overt hypothyroidism was 8 cases per 100 patient-years. During a follow-up of 44 ± 7.4 months, 51 participants had cardiovascular events at a rate that was higher in study subjects (24%) than in controls (10%). The risk of cardiovascular events after adjusting for age, sex, HbA_{1c} and other cardiovascular risk factors was significantly higher in study subjects than that in controls (hazard ratio [HR], 2.93; 95% CI, 1.15 to 7.48; $P < 0.3$); however, this became nonsignificant after additional adjustment for urinary albumin-to-creatinine ratio (HR, 2.06; 95% CI, 0.67 to 6.36). During a 44-month follow-up, 27 participants died, 10 from cardiovascular causes, which did not differ according to thyroid status.

Conclusion Patients with type 2 diabetes with subclinical hypothyroidism are at increased risk of nephropathy, but are not at increased risk of retinopathy, cardiovascular related mortality, or total mortality.

COMMENTARY

Subclinical hypothyroidism is associated with impaired cardiac function, and in some studies has been found to increase the risk of atherosclerosis and myocardial infarction in elderly women (1). Others have not found such a risk. This study of Taiwanese patients found that the rate of cardiovascular events was increased in subclinically hypothyroid patients with type 2 diabetes; however, when controlled for urine albumin-to-creatinine ratio, this observation was no longer statistically significant. It is well known that when microalbuminuria develops in patients with diabetes, the relative risk for cardiovascular disease increases substantially. On the other hand, the finding of an increased risk

for nephropathy in patients with type 2 diabetes with subclinical hypothyroidism is convincing but of uncertain pathogenesis. The other interesting observation in this study is the rate at which overt hypothyroidism developed in subclinically hypothyroid patients. Overt hypothyroidism developed in almost 30% of patients with type 2 diabetes with subclinical hypothyroidism, while fewer (17%) converted to euthyroidism. Parle et al.(2) found similar results, with overt thyroid failure developing over a period of 1 year in 26% of 107 patients over 55 years of age who had subclinical hypothyroidism, while TSH became normal in 37% of the patients. The study by Chen et al. has important implications for patients with type 2 diabetes mellitus and subclinical

hypothyroidism who are at increased risk for nephropathy.

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Serum thyrotropin concentrations increase with age in healthy subjects

Surks MI, Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. *J Clin Endocrinol Metab* 2007;92:4575-82.

SUMMARY

Background Thyrotropin (TSH) secretion tends to increase with age, but whether the increase is a function of age or due to an increase in the frequency of mild thyroid disease is controversial. This study was done to determine whether the reference range for serum TSH concentrations changes with age.

Methods The study subjects were 16,533 participants in the National Health and Nutrition Survey III (NHANES III, 1988-1994) ≥12 years of age who had no thyroid disease and were not taking thyroid-related drugs; they constituted a thyroid disease-free group. Serum TSH, thyroxine, and antithyroid peroxidase and antithyroglobulin antibodies were measured in all these subjects. Among them, 14,376 had normal serum antithyroid antibody concentrations and 13,444 were not pregnant or taking drugs that alter thyroid function and had normal serum antithyroid antibody concentrations and no biochemical evidence of thyroid dysfunction; these 13,444 subjects constituted a reference group. The overall reference range for serum TSH was <0.4 to 4.5 mIU/L. The subjects were subdivided into subgroups according to age and serum TSH concentrations, as shown in Table 1.

Age	Percentage of Age Group with Indicated Serum TSH Value			
	<0.4 mIU/L	0.4-2.49 mIU/L	2.5-4.5 mIU/L	>4.5 mIU/L
20-29 yrs	2.7	88.8	6.5	2.0
40-49 yrs	1.2	85.1	11.5	2.4
60-69 yrs	1.6	77.5	17.3	3.5
80+ yrs	2.6	61.5	23.9	12.0

700 to 2919 subjects per group.

Results The proportion of subjects with serum TSH concentrations of 2.5 to 4.5 mIU/L and >4.5 mIU/L in the thyroid disease-free/normal serum antithyroid antibody group increased with age (Table 1). The results were similar in the larger thyroid disease-free group, which included subjects with high serum antithyroid antibody concentrations. The mean serum TSH concentrations increased with age (Table 2), and therefore the peak of the bell-shaped curves defining the distribution of serum TSH concentrations (x-axis) according to their frequency (y-axis) was shifted to higher serum TSH concentrations in the older age groups. The base of the curves widened with age, as indicated by the disproportionate increase in the 97.5 percentile value, but the curves remained symmetric, with no skewing to higher concentrations that might indicate an increased frequency of hypothyroidism. The results were similar in women and men and in subjects in different racial/ethnic groups.

Age	Mean (mIU/L)	97.5 Percentile
20-29 yrs	1.4	3.6
40-49 yrs	1.6	3.8
60-69 yrs	1.9	4.3
80+ yrs	2.4	7.5

668 to 2564 subjects per group.
2.5 percentile values not given.

Conclusion Serum TSH concentrations increase with age in subjects with no thyroid disease and normal serum antithyroid antibody concentrations.

COMMENTARY

Most surveys of thyroid function in the general population have revealed an increase in the frequency of subclinical hypothyroidism, defined as high serum TSH and normal thyroxine concentrations, with age. However, in these studies, a single reference range for serum TSH encompassing subjects of all ages was used, whether determined previously or based on the study cohort.

The finding of higher, and normally distributed, serum TSH concentrations in older subjects with no evidence of thyroid disease means that use of a single reference range for serum TSH for all adults overestimates the

frequency of subclinical hypothyroidism in older people. It also provides strong evidence that the reference range for serum TSH should not be reduced, as has been proposed,⁽¹⁾ which would overestimate the frequency of subclinical hypothyroidism even more. Given the doubtful efficacy of long-term treatment of subclinical hypothyroidism, identifying fewer cases should benefit not only individual patients but also the population as a whole.

Why are serum TSH concentrations higher in healthy older people? Possible explanations include decreased thyroid sensitivity to TSH, secretion of TSH with decreased biologic activity, and decreased sensitivity of the hypothalamus

and pituitary to inhibition by thyroid hormone. Presumably the higher concentrations are accompanied by small changes in thyroid secretion, which might be either slightly lower or slightly higher than in younger subjects, depending on which of these possibilities was the explanation.

Robert D. Utiger, MD

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Many people on thyroid hormone therapy remain hypothyroid or become hyperthyroid, including some pregnant women and women of reproductive age

Aoki Y, Belin RM, Clickner R, Jeffries R, Phillips L, Mahaffey KR. Serum TSH and Total T₄ in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999–2002). *Thyroid* 2007;17:1211–23.

SUMMARY

Background Data from the National Health and Nutrition Examination Survey (NHANES) provide a wealth of information about the thyroid health status of the U.S. population. This secondary analysis provides new and more detailed information concerning thyroid hormone abnormalities influenced by medications and the prevalence of abnormal thyroid tests among pregnant women and women of reproductive age.

Methods Data collected from the NHANES were analyzed on a subsample of 4392 participants, which represented a weighted population of almost 223 million people during 1999–2002. Data on age, sex, pregnancy status, ethnicity, and use of thyroid-altering prescription medications were collected by interview. Ethnicity was categorized as non-Hispanic white, non-Hispanic black, Mexican American, and one termed “remaining race/ethnicity.” A current diagnosis of thyroid disease was based on self-reporting. Women were categorized as nonpregnant when pregnancy status could not be ascertained. Blood specimens were collected from participants and analyzed for total thyroxine (T₄) and thyrotropin (TSH).

Results The main findings in the study are that 7.3% of the total population (16,371,000) had either self-reported thyroid disease or was taking thyroid medicines or medicine that

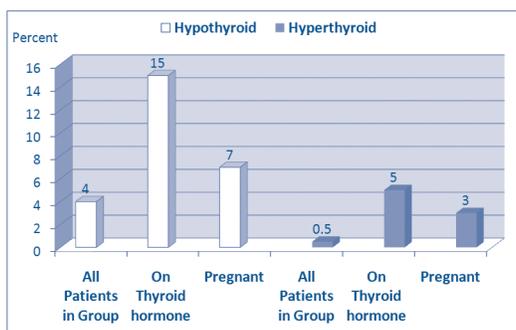


Figure. All = overall incidence of hypothyroidism or hyperthyroidism; Pregnant is pregnancy and reproductive age. Drawn from the data of Aoki et al.

potentially altered thyroid hormone levels, such as estrogen, lithium, and amiodarone. Women comprised 75% of this group. Of the total population, 3.7% were hypothyroid (0.3% overt and 3.4% mild) and 0.5% were hyperthyroid. The prevalence of both diagnoses was lower in nonwhites, and increased with age. Mean TSH values were lower in non-Hispanic blacks than in others (1.46 vs. 1.15 mIU/L). People 50 years of age or older had higher mean TSH levels than younger individuals (1.4 vs. 1.56 mIU/L).

Total T₄ levels were higher in Mexican Americans and lower in non-Hispanic blacks. Among individuals taking medicine (levothyroxine, liothyronine, and/or desiccated thyroid) for hypothyroidism, 15% had overt or mild hypothyroidism (odds ratio [OR], 4.0; P = 0.001), which was more prevalent in men (19.7 vs. 14.1%, P = 0.1); and 5.3% were hyperthyroid, a rate 10-fold that of the general population (OR, 11.4; P < 0.001). Among pregnant women and those of reproductive age, 6.9% and 2.8%, respectively, were hypothyroid and 2.9% and 0.5%, respectively, were hyperthyroid.

Conclusion A large number of patients on replacement thyroid hormone therapy are clinically hypothyroid or hyperthyroid, including women who are pregnant or of reproductive age, emphasizing the importance of monitoring thyroid function in these groups.

COMMENTARY

Most findings in this analysis of NHANES 1999–2002 confirm those of NHANES III (1988–1994)(1). In the 1988–1994 survey, only 63% of individuals with self-reported thyroid disease or taking thyroid-replacement medications had serum TSH within the reference range. The current study reports that about 9 of 157 (5.7%) thyroid hormone-treated patients were hyperthyroid and that about 28 of 157 (17.9%) were hypothyroid, mainly with subclinical hypothyroidism in patients 70 years of age or older. Many, if not most, of the latter are likely within their age-specific reference range, as it was recently reported that population TSH distribution curves shift to higher TSH concentration with age(2), and that the upper limit, the 97.5 percentile, is about 9.5 mIU/L in

thyroid disease-free individuals who are 70 years of age or older. Even using an upper limit of 4.5 mIU/L, as in the current analysis, the number estimated to be within TSH reference limits seems higher (76.4%) than in the 1988–1994 survey, suggesting that, while still not optimal, quality of care in thyroid-hormone replacement may be improving, and making less likely the authors’ suggestion that inadequate regulation of dose potency by the Food and Drug Administration contributes to these findings.

The present findings do not contribute meaningfully to discussions of prevalence of thyroid dysfunction in pregnancy because of inadequate numbers, as acknowledged by the authors. There were only 209 pregnant women in the sample, 14 (6.9%) of whom were categorized as hypothyroid and 6 (2.9%) hyperthyroid.

Some of the latter likely do not have thyroid disease, since decreased TSH often occurs during normal pregnancy.

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The rate of papillary thyroid cancer may be increased in women with Hashimoto's thyroiditis

Repplinger D, Bargren A, Zhang YW, Adler JT, Haymart M, Chen H. Is Hashimoto's thyroiditis a risk factor for papillary thyroid cancer? *J Surg Res.* October 29, 2007. doi:10.1016/j.jss.2007.09.020

SUMMARY

Background Whether the incidence of papillary thyroid cancer is increased in patients with Hashimoto's thyroiditis is debated. In this retrospective study, the incidence of papillary thyroid cancer was investigated in a large cohort of patients with and without Hashimoto's thyroiditis who underwent thyroidectomy.

Methods This study was done on 1198 patients who underwent thyroidectomy for benign thyroid disease over a 13-year period, from May 1994 to January 2007. The study group was 217 (28%) individuals with Hashimoto's thyroiditis, of whom 195 (90%) (196) were females and 20% (21) were males. The control group was 981 individuals without autoimmune thyroid disease (gender ratio not stated). The data were collected from chart reviews, but the reason for thyroidectomy is not stated. Patients and controls had a small number of tumors other than papillary thyroid cancer but this report describes only those with papillary cancer.

Results The incidence rate of papillary thyroid cancer was 230 of 981 (23%) in controls and 63 of 217 (29%) in patients with Hashimoto's thyroiditis (P = 0.05).

The gender rates of papillary thyroid cancer in patients with Hashimoto's thyroiditis was 56 of 196 (29%) in females and 2 of 21 (33%) in males. There was a significantly greater percentage of papillary thyroid cancer cases in females with Hashimoto's thyroiditis (29%) compared with females without Hashimoto's thyroiditis, (22%, P = 0.03). This trend was not significant (P = 0.2) in males. Among women with any type of thyroid malignancy, papillary thyroid cancer comprised 56 of 59 (95%) of the thyroid malignancies in those with Hashimoto's thyroiditis, and 159 of 196 (81%) malignancies in those without Hashimoto's thyroiditis (P<0.001). There were no significant differences in age, thyroid weight, and nodule size in patients with and without papillary thyroid carcinoma.

Goiter occurred in only 9% (5 of 56) patients with Hashimoto's thyroiditis but was inversely associated with thyroid cancer, occurring in 9% with and 36% without goiter (P<0.001). Tumors ≥1.0 cm were found in 65% (41 of 158) patients with Hashimoto's thyroiditis and in 29% (56 of 196) of controls (P = 0.03).

Conclusion The incidence rate of papillary thyroid cancer may be increased in women with Hashimoto's thyroiditis.

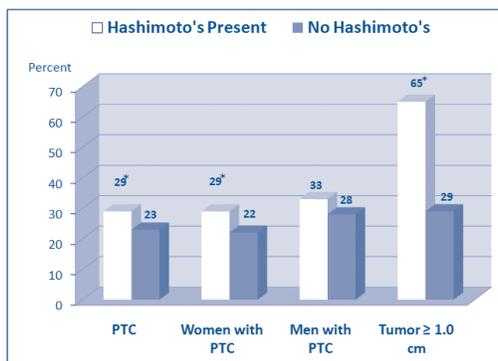


Figure. PTC = papillary thyroid cancer. *P<0.05 for the comparison of variables with and without Hashimoto's thyroiditis.

COMMENTARY

In 1955, Dailey et al.(1) first reported the association between papillary thyroid cancer and Hashimoto's thyroiditis. Although this association is uncertain, RET/PCT rearrangements have been found in follicular cells of patients with Hashimoto's thyroiditis, which might be the molecular link between the two disorders.

Larson et al.(2), provided further insight into this issue, comparing data from the SEER (Surveillance, Epidemiology and End Results) database with the demographics of a large group of patients who had undergone

thyroidectomy. They also studied molecular markers of inflammation in thyroid glands from patients with Hashimoto's thyroiditis, hypothesizing that this might provide the link between the chronic inflammation of Hashimoto's thyroiditis and thyroid cancer. They found that patients with Hashimoto's thyroiditis were three times more likely than usual to have thyroid cancer and found evidence that the PI3k/Akt pathway might be the molecular mechanism responsible for thyroid carcinogenesis in patients with Hashimoto's thyroiditis.

There appears to be enough information to warrant careful follow-up

of patients with Hashimoto's thyroiditis in whom malignant thyroid nodules might develop at a higher rate than usual.

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The autoimmune response to ^{131}I treatment of Graves' hyperthyroidism is considerably better with surgery and antithyroid drugs than with ^{131}I

Laurberg P, Wallin G, Tallstedt L, Abraham-Nordling M, Lundell G, Tørring O. TSH-receptor autoimmunity in Graves' disease after therapy with anti-thyroid drugs, surgery, or radioiodine: a 5-year prospective randomized study. *Eur J Endocrinol* 2008;158:69-75.

SUMMARY

Background Serum levels of thyrotropin (TSH)-receptor antibodies (TRAb) generally parallel disease activity in patients with Graves' disease, tending to decline and disappear after all types of successful therapy for hyperthyroidism. This 5-year prospective study compares the effects of antithyroid drugs, surgery, and ^{131}I therapy on TSH receptor autoimmunity in patients with Graves' hyperthyroidism.

Methods The study subjects were 179 patients with Graves' hyperthyroidism divided into two groups, one comprising 60 patients (33%) 20 to 34 years of age who were randomized to treatment with either subtotal thyroidectomy (leaving ~1 g of thyroid tissue) followed by levothyroxine (L-T₄) or 10 mg of methimazole four times daily, plus L-T₄ (medical therapy). The other group consisted of 119 patients (66%) 35 to 55 years of age who were treated with surgery, medical therapy, or ^{131}I . A total of 71 patients (40%) received medical therapy for 18 months, after which antithyroid drugs and L-T₄ were discontinued. A total of 67 patients (37%) were randomized to surgery, and 41 patients (23%) were randomized to ^{131}I therapy. There were no statistically significant differences in gender, the number of smokers, and baseline serum thyroid hormone levels in the three treatment groups. Serum TRAb levels were determined by a radioreceptor assay kit.

Results Before therapy, serum TRAb levels were similarly elevated in the three treatment groups. Shortly after treatment, serum TRAb levels began to fall in the medically and surgically

treated patients, and within about 1 year, declined in parallel to the upper reference limit of normal, gradually disappearing in 70 to 80% of the patients within 18 months after therapy. TRAb levels in the medical and surgical groups at 6 to 60 months after therapy were not significantly different ($P>0.05$). In patients treated with ^{131}I , the TRAb pattern was substantially different, increasing immediately after ^{131}I therapy to a peak level twofold greater than the baseline within 3 months, and then declining to an average TRAb value in the pretreatment level at about 18 months after treatment. Thereafter, TRAb values in the ^{131}I group continued to gradually decline; however, they remained well above the normal reference range and significantly higher than those in surgically and medically treated patients (Figure, $P<0.003$). After antithyroid drugs had been stopped, 16 patients (23%) experienced a recurrence, 14 (88%) with an associated increase in TRAb, one with a continuously elevated TRAb and another in whom TRAb was not measured. TRAb levels decreased in those who remained euthyroid and those in whom recurrent hyperthyroidism developed, although average TRAb levels remained significantly higher at 12 and 18 months in patients in whom recurrent hyperthyroidism had developed.

Conclusion Medical and surgical therapy are both followed by a gradual and parallel remission of serum TRAb autoimmunity, which completely disappears after 18 months in most patients, whereas ^{131}I therapy leads to a year-long worsening of TRAb with considerably less decline and persistent TRAb elevations over the ensuing 5 years.

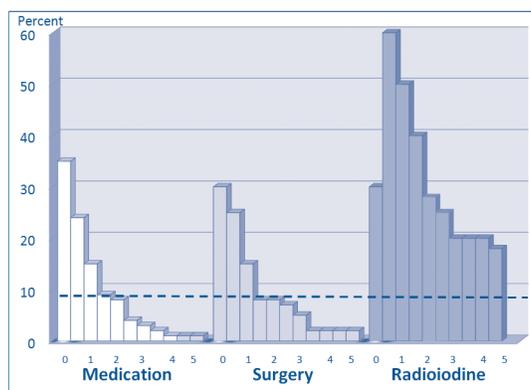


Figure. Percent change in TRAb at 6-month intervals from 0 to 5 years in the three treatment groups. The dashed line is at the upper reference range for TRAb.

COMMENTARY

It is well known that ^{131}I therapy induces a transient increase in serum TRAb levels and an exacerbation of Graves' ophthalmopathy, presumably caused by the sudden release of thyroid antigens(1), which does not happen with surgery or antithyroid drug therapy. The extent to which this occurs is graphically confirmed by the long-term randomized study by Laurberg et al., who found a striking difference in the early burst of TRAb autoimmune activity in response to ^{131}I therapy compared with the almost immediate decline in serum TRAb levels following surgery or antithyroid drug therapy (Figure). Although the immediate

increase in TRAb activity after ^{131}I therapy declined after a few months, it remained higher than normal over 5 years and was significantly higher than the undetectable levels seen in most patients treated with surgery or antithyroid drugs, which is a worrisome finding.

In 2006 Laurberg (1) proposed that the gradual remission of the autoimmune aberration that occurs when patients with Graves' disease are treated with antithyroid drugs is probably not caused by a special effect of thionamide drugs, but instead is directly linked to the euthyroid state and is independent of the drug type and dose. The present study strongly supports this view and raises questions about the use of

^{131}I therapy for Graves' disease in younger patients, which in the United States is often used for younger patients within the age range reported by Laurberg et al.

Ernest L. Mazzaferri, MD, MACP

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Carbamazepine decreases serum thyroxine in patients with normal pituitary–thyroid function and those with hypothyroidism

Simko J, Horacek J. Carbamazepine and risk of hypothyroidism: a prospective study. *Acta Neurol Scand* 2007;116:317-21.

SUMMARY

Background Patients treated with the antiepileptic drug carbamazepine may have low serum thyroxine (T₄) concentrations, which have been attributed to increased T₄ clearance. To explore further the effect of carbamazepine on pituitary–thyroid function, serum thyrotropin (TSH), total T₄, and free T₄ were measured repeatedly during carbamazepine treatment in patients who had normal thyroid function and in patients with T₄-treated hypothyroidism.

Methods The study subjects were 29 patients, of whom 19 (18 women, 1 man; median age, 47 years) had no thyroid disease and 10 (all women; median age, 42 years) had hypothyroidism caused by Hashimoto’s thyroiditis and were taking 100 µg of T₄ daily. The indications for carbamazepine therapy were partial seizures in 22 patients, trigeminal neuralgia in 4, and diabetic neuropathy in 3.

The patients were treated with 150 mg of carbamazepine daily for 3 days, 300 mg daily for 4 days, and then 450 mg daily for 7 weeks, for a total treatment period of 7 weeks. Serum TSH, total T₄, and free T₄ were measured at baseline and weekly during carbamazepine treatment. Serum carbamazepine was measured at week 7, at which time all the patients had serum carbamazepine concentrations within the therapeutic range.

Results All patients in both groups had normal baseline serum TSH, total T₄, and free T₄ concentrations. Among the patients in the no-thyroid-disease group, there was an approximately 20% fall in serum total T₄ concentrations

during the study period, accompanied by a lesser fall in serum free T₄ concentrations, and no change in serum TSH concentrations (Table). There was a similar fall in serum total and free T₄ concentrations and a larger increase in serum TSH concentrations in the patients with T₄-treated hypothyroidism, and serum TSH increased to >5 mU/L in three of them.

	Week				P Value*
	0	2	5	7	
No-thyroid-disease group					
Serum total T ₄ (µg/dl)	8.2	6.4	6.3	6.1	<0.01
Serum free T ₄ (ng/dl)	1.1	1.0	1.0	1.0	<0.01
Serum TSH (mU/L)	1.7	2.1	2.0	2.0	0.07
Hypothyroid group					
Serum total T ₄ (µg/dl)	8.6	7.5	6.7	7.1	<0.01
Serum free T ₄ (ng/dl)	1.2	1.1	1.1	1.1	<0.01
Serum TSH (mU/L)	1.7	2.2	3.0	1.7	0.01

To convert serum total T₄ and free T₄ to nmol/L and pmol/L, respectively, multiply by 12.9.
*P value for variation during weekly intervals.

Conclusion Carbamazepine causes a small decrease in serum total and free T₄ concentrations in patients with normal pituitary–thyroid function and patients with T₄-treated hypothyroidism. The compensation for the decrease is incomplete, and patients with hypothyroidism may need higher doses of T₄.

COMMENTARY

Carbamazepine and several other drugs (including phenytoin and rifampin) increase the clearance of T₄ and T₃, because they increase hepatic cytochrome P-450 enzyme activity. Adults receiving long-term therapy with these drugs have serum total and free T₄ concentrations that are slightly lower than in normal subjects, with lesser or no reduction in serum total and free T₃ concentrations. Their serum TSH concentrations are usually normal, but may be slightly high, albeit usually within the reference

range. This study indicates that the changes occur soon after the initiation of carbamazepine, and the changes then are similar to those in patients receiving long-term treatment. The effects are somewhat larger in children treated with carbamazepine; some of them have subclinical hypothyroidism(1), and children with hypothyroidism often need more T₄ when given the drug.

The slightly low serum T₄ concentrations but only minimal elevations in serum TSH concentrations in most patients treated with carbamazepine suggests that pituitary–thyroid

compensation for the increase in T₄ clearance is incomplete. One possible explanation is that the drug has T₄-agonist activity in the hypothalamus or pituitary, in addition to its effect on T₄ clearance.

Robert D. Utiger, MD

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The rate of levothyroxine therapy for patients treated with long-term lithium steadily increases over time without good evidence of therapeutic benefit

Bocchetta A, Cocco F, Velluzzi F, Del Zompo M, Mariotti S, Loviselli A. Fifteen-year follow-up of thyroid function in lithium patients. *J Endocrinol Invest* 2007;30:363-6.

SUMMARY

Background Lithium inhibits T₃ and T₄ secretion and can cause goiter, chronic autoimmune thyroiditis, and possibly hyperthyroidism. This prospective follow-up study was performed to evaluate the long-term course of thyroid dysfunction in patients treated with long-term lithium.

Methods The study subjects were 150 consecutive outpatients with bipolar disorder being treated with lithium who initially underwent a cross-sectional evaluation of thyroid function in 1989, including physical examination and measurement of thyrotropin (TSH), circulating antimicrosomal antibodies, antithyroid peroxidase, and thyroglobulin antibodies. Serum TSH was measured during follow-up. Incidence rates of hypothyroidism and hyperthyroidism were calculated from the number of patients requiring therapy for thyroid dysfunction. This is the 15-year follow-up study.

Results Annually, 5 to 10% of the patients were lost to follow-up. Of 150 patients initially evaluated, 45 (30%) completed the 15-year follow-up; however, data from 118 patients in whom TSH had been assessed at least once during follow-up were included in the incidence calculations. A total of 976 patient-years of evaluation were available, 680 (70%) in women and 296 (30%) in men. Antithyroid antibodies, which developed at a rate of 1.7% per year (1.8% in women

and 1.4% in men) increased during follow-up from 21% to 28% in women and 4% to 10% in men (P<0.02).

Eight patients (5%) were already taking levothyroxine replacement for hypothyroidism at the initial evaluation, and levothyroxine was prescribed to an additional 14 patients during follow-up. The annual incidence rate, which overall was 1.5%, was 2.1% in women and 0.3% in men (P>0.5); however, it was significantly higher in patients with circulating thyroid antibodies (6.4%), as compared with 8% without thyroid antibodies (0.8%; relative risk, 8.4; 95% confidence interval, 2.9 to 24.0) The annual incidence rate of hypothyroidism in antibody-negative women was 1.3% over 474 patient-years, while no cases of hypothyroidism were observed in antibody-negative men. When last observed, 41% of antibody-positive patients had hypothyroidism, as compared with 7% of patients without antithyroid antibodies (P<0.01). Only one case of hyperthyroidism was observed during follow-up.

Conclusion The number of lithium-treated patients being prescribed levothyroxine increased threefold over 15 years of observation and was highest in patients with antithyroid antibodies, which also increased during this period. Whether levothyroxine was therapeutically beneficial is not addressed in this study.

COMMENTARY

The main findings in this study are supported by vague criteria for hypothyroidism. Patients had annual serum TSH measurements, but serum thyroid hormone results are not reported and patients were considered to be hypothyroid when levothyroxine therapy was instituted. Nonetheless, when the same criteria were applied to all the patients, an impressive 41% of antibody-positive patients had been prescribed levothyroxine, as compared with 7% without antithyroid antibodies.

A study by Perrild et al.(1) of 100 patients with a bipolar disorder found

that goiter was more common in patients treated with lithium for 1 to 5 years (44%) or for more than 10 years (50%) than it was in patients who never received lithium (16%). Smoking significantly contributed to thyroid size and goiter. Still, thyroid volume determined ultrasonographically in nonsmoking patients was significantly related to the duration of lithium treatment. Most of the patients had normal serum TSH levels and no thyroid autoimmunity. Subclinical or overt hypothyroidism was found in only 4% and 21% of patients who were treated for 1 to 5 years and more than 10 years, respectively. It is likely that the difference in incidence and therapy

reported by Bocchetta et al. stem from the fact that subclinical hypothyroidism develops in many patients taking lithium, which likely increased the number of patients being treated with levothyroxine. This is not likely to have therapeutic benefit.

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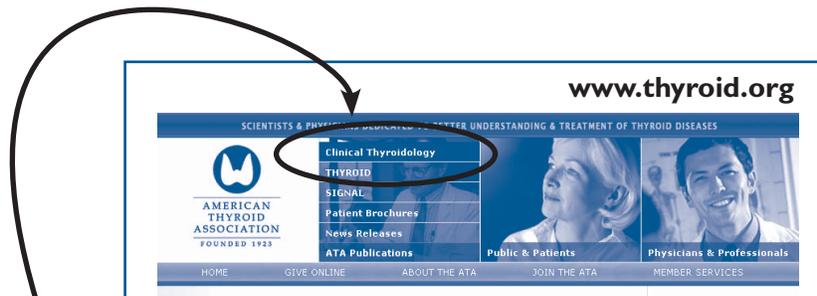
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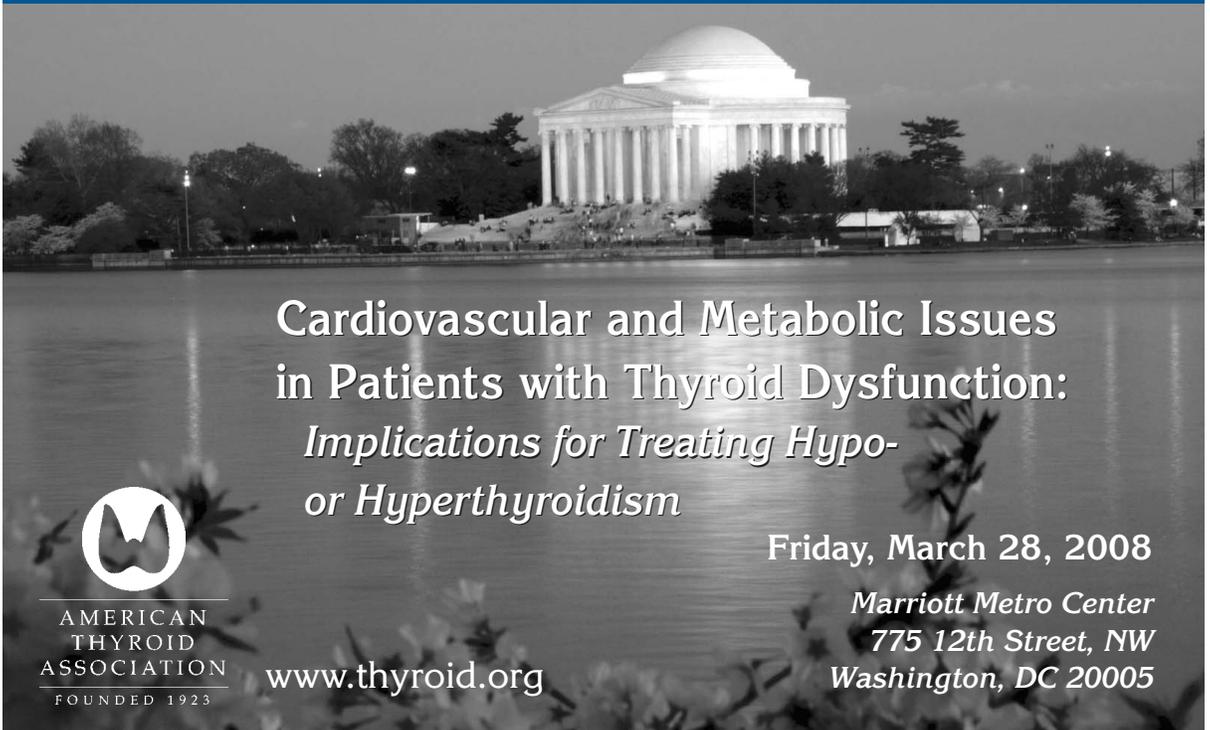
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