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Editorial: What's New in *Clinical Thyroidology*?

Jerome M. Hershman

We celebrate the silver anniversary of *Clinical Thyroidology*, now in its 25th year of publication and in the its third year of its current format. We are introducing several new features and hope that you, the readers, find them useful.

First let me pay tribute to Stephanie Lee, who is rotating off of our group of editors. Stephanie has provided many useful insights into the literature on thyroid cancer and many valuable suggestions for improving *Clinical Thyroidology.*

Three new associate editors have joined us. Elizabeth Pearce specializes in iodine deficiency and maternal and child health with regard to thyroid function and has a broad array of expertise in thyroidology. Cord Sturgeon will keep us up to date on the thyroid surgery literature. Wendy Sacks will present a new feature: Thyroid Cancer Tumor Board, which will be based on cases reviewed at the Cedars-Sinai Medical Center. Her case presentations and discussions will highlight management of difficult cases, such as those that many of you deal with regularly.

We also expect to publish a few clinically instructive case reports and encourage you to submit them. There will be no submission fee or page charge. We expect that *Clinical Thyroidology* will be indexed in Google Scholar this year, so your authorship will be recognized.

I encourage you to provide feedback about our articles, especially with regard to the Analysis and Commentary. There is room for differences of opinion that could be instructive to the readership, and I will be pleased to publish letters to the Editor.

Lastly, I want to thank the American Thyroid Association for encouraging innovation in *Clinical Thyroidology* and for providing the budget to maintain the journal.

Back to Contents

Clin Thyroidol 2013;25:3–5.

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A Single PTH Measurement on the First Postoperative Day Predicts the Need for Calcium and/or Calcitriol Supplementation following Total Thyroidectomy

Cord Sturgeon

Cayo AK, Yen TW, Misustin SM, Wall K, Wilson SD, Evans DB, Wang TS. Predicting the need for calcium and calcitriol supplementation after total thyroidectomy: results of a prospective, randomized study. Surgery 2012;152:1059-67. Epub October 13, 2012.

SUMMARY

Background

Hypocalcemia from temporary hypoparathyroidism is a common postoperative sequela of total thyroidectomy. Identification of reliable predictors of postoperative calcium and vitamin D requirements would benefit patients by mitigating the risks of postoperative hypocalcemia while reducing unnecessary calcium and/or calcitriol supplementation. The authors of this study hypothesized that a single intact parathyroid hormone (PTH) measurement on the first postoperative day would reliably predict the need for postoperative calcium supplementation. They tested their hypothesis via a single–institution, randomized, prospective trial. They also sought to develop an algorithm for calcium and calcitriol supplementation for patients at risk for postoperative hypoparathyroidism. Although several other studies have evaluated the utility of postthyroidectomy PTH measurements, this is the first hypothesis-driven, randomized, prospective trial on the subject.

Methods

The authors conducted a prospective, randomized trial at a single institution over a 23-month period beginning in February 2010. Patients who were undergoing completion thyroidectomy or total thyroidectomy were included in the trial, and 143 completed the trial. Vitamin D levels were supplemented preoperatively. Routine calcium and vitamin D were not given in the immediate postoperative period. PTH was measured on the morning of the first postoperative day. The patients were stratified by PTH level and then randomly assigned into one of five groups with standard calcium and calcitriol doses. If PTH was >10 pg/ml, no supplementation was given. If PTH was <5 pg/ml, the patient was randomly assigned to calcium supplementation or calcium and calcitriol supplementation. If the PTH was 5 to 10 pg/ml, the patient was randomly assigned to either calcium supplementation or no supplementation. Demographic and clinical data were recorded, including preoperative and postoperative calcium, vitamin D, and PTH levels. Univariate and multivariate logistic-regression analyses were performed to determine the factors associated with symptomatic hypocalcemia or PTH <10 pg/ml.

Results

A total of 112 patients (78%) had a PTH ≥10 pg/ml on postoperative day 1. The remaining 31 patients were stratified and randomly assigned into supplementation groups. Five patients with PTH <5 pg/ml and 15 patients with PTH 5 to 10 pg/ml received calcium alone. Seven patients with PTH <5 pg/ml received calcium and calcitriol. Four patients with PTH of 5 to 10 pg/ml received no supplementation. In 10% of patients with a PTH ≥10 pg/ml and 48% with PTH <10 pg/ml, symptoms of hypocalcemia were reported within the first 72 hours after surgery. The specificity of PTH <10 pg/ml for symptomatic hypocalcemia was 86%. On multivariate analysis, young age and postoperative PTH were independent predictors of postoperative

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hypocalcemia. More extensive surgery did not predict a PTH <10 pg/ml. A total of 55% of patients with a PTH <10 pg/ml on postoperative day 1 were on calcium and calcitriol at 1 week after surgery, whereas no patients with a PTH ≥10 pg/ml on postoperative day 1 were on routine calcium or calcitriol at 1 week after surgery.

Conclusions

Symptomatic hypocalcemia developed in only 10% of patients with PTH ≥10 pg/ml and all were treated successfully with calcium supplements as needed. Symptomatic hypocalcemia developed in 48% of patients with PTH <10 pg/ml . Multivariate analysis yielded no independent predictors of PTH <10 pg/ml on postoperative day 1. The authors conclude that a PTH of ≥10 pg/ml on postoperative day 1 is a strong predictor of postoperative eucalcemia and have limited the use of routine calcium supplementation to patients with a PTH <10 pg/ml on postoperative day 1.

ANALYSIS AND COMMENTARY

This study suffers from some limitations that are clearly discussed in the manuscript. The most significant issue is that after randomization, the number of patients for each PTH <10 pg/ml treatment group was very small, limiting the ability to generate meaningful statistical analyses for these groups. In particular, there did not appear to be any predictors of PTH <10 pg/ml on postoperative day 1, including extent of surgery and number of autotransplanted glands. Nonetheless, the conclusion that PTH ≥10 pg/ml is a strong predictor of postoperative eucalcemia is not affected by this.

This study is the first randomized, prospective trial on the subject and expands on a prior retrospective study by the same authors wherein they determined that PTH on postoperative day 1 was more reliable in predicting independence from vitamin D supplementation than calcium on postoperative day 1 (1). In that study, they concluded that a PTH of >5 pg/ml on postoperative day 1 was indicative of not needing routine postoperative vitamin D supplementation. In a complementary study, Landry et al. retrospectively evaluated 156 patients who underwent thyroidectomy and concluded that calcium supplementation could be limited to the patients with a PTH of <6 pg/ml on postoperative day 1 (2). Sywak et al. measured PTH at 4 and 23 hours after surgery to determine whether either was predictive of hypocalcemia and found that both were predictive and performed equally well (3). Lombardi et al. more extensively evaluated the timing of postoperative PTH measurements by comparing PTH levels drawn at the end of surgery with those drawn at 2, 4, 6, 24, and 48 hours after surgery (4). They found that PTH <10 pg/ml measured 4 or 6 hours after surgery was 100% sensitive and 100% specific for predicting symptomatic hypocalcaemia. Wiseman et al. demonstrated in a cohort of 423 consecutive patients that an algorithmic approach to postoperative calcium replacement, based on PTH measured 1 hour after thyroidectomy, could reduce the risk of severe postoperative hypocalcemia (5). Finally, guidelines have also been developed by the Australian Endocrine Surgeons that cover the topic of postoperative PTH measurement and early discharge (6). In their literature review, they found that a normal PTH had a positive predictive value for eucalcemia of 92.3%. They recommend that all patients undergoing thyroidectomy have PTH drawn 4 hours after surgery and state that patients with a normal PTH can be safely discharged on the first postoperative day either with or without supplements. Patients with undetectable PTH, on the other hand, should be started early on calcium and calcitriol.

After reviewing the literature, it seems clear that measurement of postoperative PTH is useful in predicting the need for calcium and vitamin D analogs following total thyroidectomy. Several studies have

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evaluated the utility of postoperative PTH to prognosticate short- and long-term parathyroid function, and each has come to a similar conclusion. A normal postoperative PTH is a strong predictor of postoperative eucalcemia. This is particularly important now that thyroidectomy is performed as an outpatient procedure in many specialized centers, and the ability to stratify patients into groups of low and high probability of postoperative hypocalcemia could substantially impact the discharge protocol. Questions still remain, however, regarding the cost-effectiveness of routine postoperative measurement of PTH, with one study suggesting that routine calcium and vitamin D supplementation is actually less costly than selective replacement based on PTH levels (7).

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Does High-Normal Thyroid Function Increase Risk for Atrial Fibrillation?

Elizabeth N. Pearce

Selmer C, Olesen JB, Hansen ML, Lindhardsen J, Olsen AM, Madsen JC, Faber J, Hansen PR, Pedersen OD, Torp-Pedersen C, Gislason GH. The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. BMJ. November 27, 2012 [Epub ahead of print].

SUMMARY

Background

Patients with subclinical and overt hyperthyroidism are known to be at increased risk for the development of atrial fibrillation (1–5). However, the risk for incident atrial fibrillation had not previously been assessed in a very large population across the whole spectrum of thyroid function.

Methods

The study population consisted of 586,460 adult Danish primary care patients (mean age, 50.2 years; 61% women) who underwent thyroid-function testing in Copenhagen between 2000 and 2010. Patients were followed until the end of 2010 or until they moved from the study area or died. Individuals with prevalent atrial fibrillation or treated thyroid dysfunction at baseline were excluded, as were patients with a history of amiodarone, digoxin, or vitamin K use. Information about comorbidities and mortality was obtained from national Danish registries. The primary outcome was new-onset atrial fibrillation, ascertained by inpatient International Classification of Diseases, 10th Revision (ICD-10) codes. Time-dependent Poisson regression analyses were adjusted for age, sex, calendar year, an index of comorbidities, and socioeconomic status. The reference range for serum TSH was 0.2 to 5.0 mIU/L. Individuals with serum TSH <0.2 mIU/L and elevated FT_4 were considered to have overt hyperthyroidism and those with TSH <0.2 mIU/L and normal FT_4 were considered to have subclinical hyperthyroidism; conversely, individuals with serum TSH >5.0 mIU/L and low FT_4 were considered to have overt hypothyroidism and those with serum TSH >5.0 mIU/L and normal FT_4 were considered to have subclinical hypothyroidism. Sensitivity analyses were performed to account for changes in both thyroid function and thyroid treatment status over time, with adjustment for atrial fibrillation risk factors including baseline history of hypertension, heart failure, myocardial infarction, valvular hear disease, and diabetes.

Results

At baseline, 96% of patients were euthyroid, 0.3% had overt hyperthyroidism, 2% had subclinical hyperthyroidism, 2% had subclinical hypothyroidism, and 0.7% had overt hypothyroidism. Individuals were followed for a mean of 5.5 years, over which time 17,154 (2.9%) were diagnosed with new atrial fibrillation while hospitalized. As compared with euthyroid individuals, the risk for atrial fibrillation was increased in patients with overt hyperthyroidism (adjusted incidence rate ratio [IRR], 1.41; 95% CI, 1.22 to 1.63) and patients with subclinical hyperthyroidism (IRR, 1.30; 95% CI ,1.18 to 1.43) as well as in individuals with high-normal thyroid function (defined as serum TSH 0.2 to 0.4 mIU/L with normal FT_4; IRR, 1.12; 95% CI, 1.03 to 1.21). Risk for atrial fibrillation was found to be decreased in overt (IRR, 0.67; 95% CI, 0.50 to 0.92) and subclinical (IRR, 0.88; 95% CI, 0.79-0.97) hypothyroidism as compared with the euthyroid subjects. Sensitivity analyses did not substantially alter the results, although treatment of subclinical and overt hyperthyroidism was associated with a slight attenuation of atrial fibrillation risk.

Conclusions

This study demonstrates a linear inverse association between atrial fibrillation incidence and serum TSH. Even among euthyroid patients, lower serum TSH values were associated with a significantly increased risk for atrial fibrillation.

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ANALYSIS AND COMMENTARY

A major strength of this study is its very large sample size. Important limitations include the potential for misclassification of outcomes given the limitations of ICD-10 codes and the fact that only in-hospital atrial fibrillation diagnoses were ascertained. Findings in this largely white and sociodemographically homogeneous population may not be generalizable to other settings. Information was not available regarding potentially important covariates such as body-mass index, smoking status, thyroid antibody status, serum lipid levels, and echocardiographic parameters. Future observational studies with more information about covariates could better characterize risk factors for atrial fibrillation among individuals with low serum TSH, although it is unlikely that larger samples will be studied in the future. Overall, further research is needed to determine the effects of treatment of subclinical hyperthyroidism on the risk for atrial fibrillation.

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Coronary Heart Disease May Not Be Increased in Older Patients with Subclinical Hypothyroidism

Jerome M. Hershman

Hyland KA, Arnold AM, Lee JS, Cappola AR. Persistent subclinical hypothyroidism and cardiovascular risk in the elderly: the Cardiovascular Health Study. J Clin Endocrinol Metab. November 16, 2012 [Epub ahead of print]. doi:10.1210/jc.2012-2180.

SUMMARY

Background

The effect of subclinical hypothyroidism (SCH) on cardiovascular risk has been controversial. The topic is of interest because many elderly patients have this diagnosis, especially when there is no adjustment for the upper limit of serum TSH based on age; however, if an age adjustment is applied to people over age 70, the number of individuals in this category diminishes substantially (1).

Methods

This is a study of cardiovascular risk in the Cardiovascular Health Study (CHS). TSH was measured on most of the baseline samples from the original cohort of 5888 people who were over age 65 in 1989, and tests were repeated in 1992, 1994, and 1996. Patients were followed for cardiovascular disease, including coronary heart disease (CHD), heart failure and death. Euthyroidism was defined as a TSH concentration of 0.45 to 4.50 mU/L, and subclinical hypothyroidism was defined as a TSH concentration >4.50 mU/L and <20 mU/L with a normal FT_4 concentration based on the first set of tests. Patients with cardiac disease at the initial examination were excluded.

Of the 4863 participants included in the analyses, 926 had only one set of thyroid tests, 980 had two, and 1513 had three; 1444 had measurements at all four time points. Follow-up was censored at 10 years beyond the first baseline measurements.

Results

Based on the first set of thyroid tests, 4184 subjects were euthyroid and 679 had SCH. In the euthyroid group, the mean age was 73.4 years and 45% were men; in the SCH group, the mean age was 74.1 years and 38% were men. Both differences were significant. The mean TSH was 2.1 mU/L in the euthyroid group and 6.7 mU/L in the SCH group. There were no differences between the two groups in the body-mass index, LDL cholesterol, serum creatinine, or the proportion of patients with hypertension or diabetes. The incidence of CHD was about 20% and that of heart failure about 5% in both groups. During the 10-year follow-up period, 225 (33.1%) of the participants in the SCH group and 174 (4.2%) in the euthyroid group initiated thyroid hormone medication.

No association was seen between SCH and incident CHD, heart failure, or cardiovascular mortality in multivariate models with 10 years of follow-up. Additional analyses stratified by degree of TSH elevation (4.5 to 6.9, 7.0 to 9.9, and 10.0 to 19.9 mU/L) showed no increase in risk of any of these cardiovascular events by subgroup of SCH. The number of individuals in each of the three SCH TSH categories was 483, 131, and 65, respectively. When thyroid status was updated based on subsequent TSH measurements, there was again no difference in cardiovascular outcomes between the two groups.

Conclusions

The data do not support an increased risk of CHD, heart failure, or cardiovascular death in older adults with persistent subclinical hypothyroidism.

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ANALYSIS AND COMMENTARY

Although the study is "prospective" in obtaining data on thyroid function, it is observational in that the patients were likely to have been treated by their treating physicians. It is pertinent that one third of those initially classified as having SCH were treated with thyroid hormone. This could have altered cardiovascular outcomes and calls into question the applicability of these data for treatment of older patients with SCH. Did updating the thyroid status place the patients with treated SCH into the euthyroid group? The fact that many of the euthyroid patients were treated with thyroid hormone suggests that a relatively abrupt onset of hypothyroidism was promptly treated by the managing physicians.

In a previous analysis of 3044 patients in this study, the participants with TSH >10 mU/L had a greater incidence of heart failure as compared with euthyroid participants (41.7 vs. 22.9 per 1000 person years; P = 0.01; adjusted hazard ratio, 1.88; 95% CI, 1.05 to 3.34) based on a 12-year follow-up (2). The current paper reports no increase in heart failure in SCH, including the subcategory with TSH >10 mU/L, and reconciles this difference as being due to having a larger number of CHS participants; this resulted in the difference in heart failure no longer being statistically significant. However, their Figure 2B shows an impressive increase in heart failure in those with TSH>10 mU/L after 6 years of follow-up. Their Figure 3A shows an increase in the incidence of cardiovascular deaths in the entire SCH group as compared with the euthyroid group after 6 years of follow-up.

These studies are very difficult to perform and easy to criticize. That said, the current study does not negate the necessity of performing a randomized, controlled study of treatment of SCH in elderly individuals, with the diagnosis based on age-adjusted TSH levels, in order to determine whether therapy with thyroid hormone improves cardiovascular status and many other indicators of health and well-being.

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Patients Undergoing a Surgical Lobectomy Require a Complete Preoperative Thyroid Evaluation and Long-Term Follow-up to Detect Postoperative Hypothyroidism

Jorge H. Mestman

Verloop H, Louwerens M, Schoones J, Kievit J, Smit JW, Dekkers OM. Risk of hypothyroidism following hemithyroidectomy: systematic review and meta-analysis of prognostic studies. J Clin Endocrinol Metab 2012;97:2243-55. Epub April 17, 2012.

SUMMARY

Background

The literature shows considerable heterogeneity with regard to the reported risk of hypothyroidism after hemithyroidectomy. The aim of this systematic review and meta-analysis was to determine the overall risk of hypothyroidism, both clinical and subclinical, after surgical lobectomy and to identify risk factors for postoperative hypothyroidism.

Methods

A systematic literature search was performed using several databases, including PubMed. Original articles in which an incidence or prevalence of hypothyroidism after primary hemithyroidectomy could be extracted were included. Study identification and data extraction were performed independently by two reviewers. In cases of disagreement, a third reviewer was consulted. A total of 32 studies were included. Meta-analysis was performed using logistic regression with random effect at study level.

Results

The search of the electronic databases yielded a total of 1269 unique references that were evaluated by title and abstract. Finally, 31 publications (32 studies from 1983 to 2011) with a total of 4899 patients were included. The largest study comprised 1051 patients (1). The authors carefully selected reports in which the results of preoperative thyroid tests and surgical pathology reports, as well as thyroid-function tests performed in the years after surgery, were available.

The overall risk of hypothyroidism after hemithyroidectomy was 22% (95% CI, 19 to 27). A clear distinction between clinical (supranormal TSH levels and subnormal thyroid hormone levels) and subclinical (supranormal TSH levels and thyroid hormone levels within the normal range) hypothyroidism was provided in four studies. These studies reported an estimated risk of 12% for subclinical hypothyroidism and 4% for clinical hypothyroidism. Positive anti-TPO status is a relevant preoperative indicator for hypothyroidism after surgery. Effect estimates did not differ substantially between studies with lower risk of bias and those with higher risk of bias.

Conclusions

This meta-analysis showed that hypothyroidism will develop in approximately 1 in 5 patients after hemithyroidectomy and that clinical hypothyroidism will develop in 1 of 25.

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Patients Undergoing a Surgical Lobectomy Require a Complete Preoperative Thyroid Evaluation and Long-Term Follow-up to Detect Postoperative Hypothyroidism

Verloop H, et al.

ANALYSIS AND COMMENTARY

Medical indications for lobectomy or hemithyroidectomy are the presence of a single thyroid nodule or, rarely, unilateral goiter. The nodule in the vast majority of cases is benign or has suspicious or indeterminate characteristics on fine-needle aspiration cytology or is a single toxic adenoma (2). Long- term follow-up of patients after the surgical procedure is not clearly defined in the medical literature, unless it is a malignant lesion. The chances of developing hypothyroidism in such cases is not clearly defined. The authors stated that "apart from the need for regular doctor visits and blood check-ups, long-term thyroid hormone therapy may be associated with accelerated loss of bone mineral density, atrial fibrillation, changes in left ventricular function, and impairment in psychological well-being." In their systematic review of the literature, studies assessing thyroid function after hemithyroidectomy in euthyroid populations of any age were eligible for the meta-analysis. Postsurgical hypothyroidism included cases of increased serum TSH levels (subclinical and clinical hypothyroidism) and those of patients on thyroid-replacement therapy. The reported incidence of postsurgical hypothyroidism ranged from 0 to 43%. The pooled risk of hypothyroidism after hemithyroidectomy was 22%. A clear biochemical distinction between clinical and subclinical hypothyroidism was reported in only four studies (467 patients); the overall risk was 12% (95% CI, 5 to 25) for subclinical hypothyroidism and 4% (95% CI, 2 to 8) for clinical hypothyroidism. It was usually detected within the first 6 months after surgery. Older age was reported as a risk factor for the development of hypothyroidism in only four studies. Higher preoperative TSH level (within the normal range) was a significant risk factor in 13 studies. The presence of anti-TPO antibodies was reported as a risk factor for hypothyroidism in six studies (791 patients); there was a higher risk (48%) in patients with anti-TPO antibodies than in those without antibodies (19%, P = 0.001). The degree of inflammation in the resected lobe was reported in four studies (459 patients); the risk for hypothyroidism was higher (49%) in patients with a high degree of inflammation than in patients with no inflammation or a low degree of inflammation (10%; P = 0.006). The authors recognized the limitations of their study, among them the inability to assess what proportion of the reported hypothyroidism was transient or permanent, the definition of hypothyroidism among the different studies, the time of measuring TSH levels in patients in whom hypothyroidism develops, and the frequency of patient follow-up. The number and timing of laboratory measurements varied from only one TSH measurement 4 to 8 weeks after surgery to regular thyroid hormone measurements once, twice, or three times a month for years after the intervention. One study reported that in untreated patients with hypothyroidism, TSH levels progressively decreased during the first 20 months after surgery (3). Another study reported that in 33% of patients with hypothyroidism, TSH levels normalized within 28 months after the intervention (4). One study showed a risk of 17% for early postoperative hypothyroidism and 8% for persistent hypothyroidism, showing that, at least in some patients, hypothyroidism can be a transient phenomenon (5). From the results of the meta-analysis, the recommendation for clinicians caring for patients before and after lobectomy could be summarized as follows: (1) determine serum TSH and anti-TPO antibodies prior to surgery; (2) recognize that age, serum TSH in the upper limits of the reference range and elevated anti-TPO antibodies are risk factors for the development of hypothyroidism; (3) review the surgical pathology report, since the presence of chronic thyroiditis is an additional risk; (4) measure serum TSH levels on a regular basis in patients at risk, keeping in mind that in some patients serum TSH elevations are transient; and (5) realize that hypothyroidism, both clinical and subclinical, may develop years after the surgical procedure.

continued on next page

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Should 99mTcO4 Thyroid Scintigraphy Still Be Used In Investigating Thyroid Nodules In Multinodular Goiter?

Albert G. Burger

Graf D, Helmich-Kapp B, Graf S, Veit F, Lehmann N, Mann K. Functional activity of autonomous adenoma in Germany. Dtsch Med Wochenschr 2012;137:2089-92.

SUMMARY

Background

The ATA and ETA guidelines on thyroid nodules recommend considering radionuclide scanning in patients with thyroid nodules if the serum TSH is low (<0.4mU/L) or low-normal (e.g., <0.6 to 0.4 mU/L) (1,2). FNAB without prior scintigraphy is recommended for all other nodules ≥1 cm diameter examined by ultrasound. In geographic areas that formerly had or still have dietary iodine deficiency, such nodules are frequent and most often embedded within small multinodular goiters (3). It is argued that FNAB can be avoided if such nodules are scintigraphically shown to be autonomously functioning, since malignancy is exceedingly rare in this condition. In Germany, endemic goiter is decreasing in the younger population, but in elderly persons it is still a frequent finding (4,5). It is therefore understandable that in this country thyroid scintigraphy still plays an important role in the evaluation of thyroid nodules.

Methods

In a group of 476 nonselected patients with nodular goiter, nodules >1 cm were investigated by ultrasound and by scintigraphy, even though the serum TSH level was not low or suppressed. For scintigraphy 99mTcO4 was used exclusively, because ^{123}I scintigraphy is too costly for routine use. No technical details are given, but it can be assumed that the standard methods with frontal and lateral pictures was used. FNAB apparently was not done in any cases. The 99mTcO4 scans were classified as compensated (if the extranodular tissue was well visible), partially compensated or decompensated if uptake of the tracer in nonnodular areas was partially or entirely suppressed (sometimes called warm or hot nodules). In five subjects, T_3 suppression tests were performed.

Results

Of 476 patients with nodular goiters, a region of focal autonomy was scintigraphically identified in100 patients. By ultrasound and scintigraphy, 40% were 1.1 to 1.9 cm, 41% were 2 to 2.9 cm, and 15% were ≥3 cm in longest dimension. In most cases (87), scintigraphy detected only one nodule, while in the remaining 13 cases, two or more focally active areas were present. A total of 68 patients had a serum TSH >0.4 mU/L, while in the remaining 32 patients, the TSH was <0.4 mU/L. There was no strict correlation between serum TSH levels and scintigraphic findings, even though the percentage of decompensated scintigraphy (39%) was similar to those in whom the serum TSH was <0.4 mU/L (32%).

Nodules with a diameter of 1 to 1.9 cm (by ultrasound) were equally distributed among the compensated, partially compensated, and decompensated scans. The larger nodules were more often partially compensated or decompensated. The echographic findings (hypodense structure, microcalcifications, etc.) did not vary with the size of the nodule.

A significantly elevated titer of thyroid anti-TPO antibodies was present in five cases. The results of the five T_3 suppression tests are not reported.

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Conclusions

In a country with prior iodine deficiency, small nodular goiters are a frequent finding. If thyroid scintigraphy is extensively used, as was done in the current study, it will reveal autonomously functioning tissue in about one third of cases). Therefore, thyroid scintigraphy may allow one to avoid FNAB in these circumstances.

ANALYSIS AND COMMENTARY

The recommendations of the ATA and ETA support the use of scintigraphy for nodules present in a multinodular goiter if the patient's serum TSH level is low-normal or suppressed, which was observed in 32% of the autonomous nodules studied here. This percentage would have been even higher if a "low-normal serum TSH" had been defined as higher than the 0.39 mU/L set in this study. Nevertheless, in a considerable percentage of apparently euthyroid patients (TSH >0.4 mU/L), 99mTcO4 scintigraphy indicated a possibly autonomously functioning area. These nodules were selected by their scintigraphic appearance. The authors consider them to be adenomas.

Presumably, thyroids in patients with multinodular goiters whose serum TSH is >0.4 mU/L do not produce excessive amounts of thyroid hormones, but some areas are merely more active than other areas within the goiter. This could correspond to cohorts of follicles that do not correspond to true, clearly circumscribed adenomas. This pathology is obviously very frequent in multinodular goiters and is a completely different entity than adenomas. Since T_3-suppression tests were not done routinely, it is even possible that these areas are not autonomously functioning (3).

Except for anecdotal observations of "functioning" thyroid cancers, "hyperfunction" is generally considered to occur only in benign thyroid lesions. Unfortunately, the authors did not perform FNABs, which is the method of choice for most thyroidologists. We are therefore missing the critical information of how many operations may have been avoided by preferring scintigraphy over FNAB. It is reasonable to assume that some FNABs would have yielded a cytologic report of indeterminate-type tissue, and some of these patients would have been sent for surgery.

From another viewpoint, one may argue that patients with thyroid autonomy are at-risk for eventual hyperthyroidism. However, the real incidence of this possibility is not known. Excluding transient Jod–Basedow syndrome due to iodine contamination, it certainly would take years, if not decades, for this course of events to occur, and simple surveillance of thyroid function by serum TSH should eliminate the risk of unrecognized hyperthyroidism.

The apparently high incidence of thyroid autonomy in Germany is striking and does not correspond to the rarer observation of thyroid autonomy in iodine-replete areas. It is likely that in Germany many of these observations correspond to autonomously functioning cohorts of follicles of varying size within multinodular goiters (3).

In practice the article reminds us that scintigraphy can still be useful in certain circumstances. However, it should not be considered as a routine procedure in all patients with nodular goiter. A patient with a multinodular goiter who lives or lived in an iodine-deficient area—or a patient who refuses FNAB—may benefit from thyroid scintigraphy, even if she or he has normal TSH values.

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Clinical THYROIDOLOGY
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The Bethesda System for Reporting Thyroid Cytopathology Is Effective for Clinical Management of Thyroid Nodules

Jerome M. Hershman

Bongiovanni M, Spitale A, Faquin WC, Mazzucchelli L, Baloch ZW. The Bethesda System for Reporting Thyroid Cytopathology: a meta-analysis. Acta Cytol. 2012;56:333-9. Epub July 25, 2012; doi: 10.1159/000339959.

SUMMARY

Background

The Bethesda System for Reporting Thyroid Cytopathology (BSRTC) resulted from a conference held at the National Institutes of Health in 2007. The system led to standardization of FNA reports based on six diagnostic categories: DC I = nondiagnostic, DC II = benign, DC III = atypia/follicular lesion of undetermined significance (AUS/FLUS), DC IV = follicular neoplasm/suspicion for a follicular neoplasm (FN/SFN), DC V = suspicious for malignancy, and DC VI = malignant (1). The purpose of the present report was to perform a meta-analysis of thyroid FNA studies in order to examine the validity of the system with regard to histologic outcomes and to assess the variability of the use of the six DCs between institutions.

Methods

The authors reviewed reports published between January 2008 and September 2011 that classified thyroid cytopathology according to the Bethesda System and included surgical histopathology. Incidentally detected lesions in the surgical specimens that were not the target of the thyroid FNA were excluded from the analysis.

Results

Eight published studies that included a total of 25,445 thyroid FNAs were selected for the meta-analysis. Surgery was performed in 6362 (25%; range, 12 to 45 among institutions) of the cases. The malignant category (DC VI) was assigned to 5.4% of the FNAs (range, 2 to 16); 74% had histologic follow-up and 98.6% were malignant. The suspicious for malignancy category (DC V) was assigned to 2.6% of the FNAs (range, 1 to 6); 74% had histologic follow-up and 75.2% were malignant. The FN/SFN (DC IV) category was assigned to 10.1% of the FNAs (range, 1 to 25); 70% had histologic follow-up and 26.1% were malignant. The AUS/FLUS category (DC III) was assigned to 9.6% of the FNAs (range, 3 to 27); 39% had histologic follow-up and 15.9% were malignant. The benign category (DC II) was assigned to 59% of the FNAs (range, 39 to 74); 10.4% had histologic follow-up and 3.7% were malignant. Lastly, the nondiagnostic category (DC I) was assigned to 13% of the FNAs (range, 2 to 24); 16% had histologic follow-up and 16.8% were malignant.

Conclusions

The BSRTC has proven to be an effective and robust thyroid FNA classification scheme to guide the clinical treatment of patients with thyroid nodules.

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ANALYSIS AND COMMENTARY

The data summarized in the current report show considerable variability among institutions with regard to the frequency of the various categories. This finding suggests that there may be a subjective element in categorizing a given FNA.

With regard to the possibility of malignancy for a given classification, the data corroborate the results anticipated when the classification was set up (1). In patients with benign FNA or inadequate specimens who undergo surgery, it is likely that clinical factors, such as a family history of thyroid cancer, the size of the nodule, compressive symptoms, or suspicious findings on ultrasonography are the basis for the decision to perform surgery.

The authors recommend that the FNA be repeated when the diagnosis is AUS/FLUS; this seems reasonable given that the alternative is to operate on all of these patients when the overall possibility of malignancy is 16% (about the same as the nondiagnostic category). Eventually, molecular markers may help to clarify which patients should be referred for surgery (2).

In patients in the suspicious for malignancy category, the data also show that there is a very high percentage of malignancy, 75%. Although the three categories of AUS/FLUS, FN/SFN, and suspicious for malignancy had previously been lumped together to comprise an "indeterminate" class (2), it is clear that when the FNA is in the suspicious for malignancy category (DC V), the patient should undergo thyroidectomy. It is reasonable to consider removing DC V, from the "indeterminate" classification. It should be noted that the authors do not use this term.

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Does TSH Directly Affect PCSK9, a Regulator of LDL Receptors, in Euthyroid Subjects?

Stephen W. Spaulding

Kwakernaak AJ, Lambert G, Kobold ACM, Dullaart RPF. Adiposity blunts the positive relationship of thyroid-stimulating hormone with proprotein convertase subtilisin-kexin type 9 levels in euthyroid subjects. Thyroid. October 29, 2012 [Epub ahead of print]. doi:10.1089/thy.2012.0434.

SUMMARY

Background

Patients with altered thyroid function may display a variety of lipid abnormalities, but the precise mechanisms involved are poorly understood. The protein PCSK9 (proprotein convertase subtilisin/kexin type 9) binds to low-density lipoprotein (LDL) receptors on the cell surface of hepatocytes, and targets them for lysosomal degradation, which raises the LDL cholesterol (LDL-C) level by impairing clearance. Recently, two monoclonal antibodies against PCSK9 were shown to acutely lower LDL-C levels in clinical studies (1,2). The current paper reports an initial exploration of possible relationships between the circulating level of PCSK9 and lipids, TSH, and FT_4.

Methods

The subjects were recruited by advertising in Groningen newspapers. Any candidate who was pregnant, smoked, consumed more than three drinks per day, took any medication other than oral contraceptives, had a history of thyroid disease or had thyroid abnormality on physical examination was excluded, as was anyone with a history of diabetes, hypertension, clinically manifest cardiovascular disease, or substantial liver or renal abnormalities. The paper reports results on fasting samples from 74 subjects, of whom 10 were obese (body-mass index [BMI, the weight in kilograms divided by the square of the height in meters], 30.2 to 35.2) and 31 were women. Four subjects (all non-obese) had positive anti-TPO or anti-Tg antibody levels. Insulin sensitivity, measured by the Homeostasis Model Assessment (HOMA), was calculated based on insulin and glucose levels. Apolipoprotein B (ApoB), total cholesterol, and high-density lipoprotein cholesterol (HDL-C) and triglyceride levels were measured, and non-HDL-C and LDL-C levels were calculated. PCSK9 levels were measured by sandwich enzyme-linked immunoabsorption. Most of the data are provided only as medians and interquartile values. Between-group differences were assessed using chi-squared or nonparametric Mann–Whitney U tests; Spearman's rank correlation coefficient was used to assess univariate differences between obese and non-obese subjects; and multiple linear regression was used to assess the contributions and interactions between multiple variables.

Results

The obese and non-obese groups did not differ in their TSH, FT_4, PCSK9, non-HDL-C, LDL-C, or ApoB levels. In the non-obese group, the PCSK9 level displayed a moderate linear correlation with the TSH level ($r = 0.285$, $P = 0.023$) When the data from both obese and non-obese groups were combined to assess univariate relationships, the PCSK9 level correlated with insulin, total cholesterol, non-HDL-C, LDL-C, ApoB, and triglyceride levels. When the non-obese group was analyzed separately, the same correlations were found, except that the correlation with insulin was no longer significant. In contrast, in the obese subjects, PCSK9 levels correlated only with insulin and HOMA levels. Interestingly, however, TSH levels in the obese subjects did correlate significantly with BMI. If obesity was expressed simply as a dichotomous variable (BMI either < or >30), multiple regression analysis on the data from all 74 subjects indicated a significant interaction between TSH and BMI, after accounting for the direct effects of age, sex, FT_4, TSH, and obesity.

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Remarkably, none of the lipid parameters showed any correlation with the FT_4 level.

Conclusions

In euthyroid non-obese subjects, the circulating level of PCSK9 correlated linearly with the TSH level. In the entire group of 74 subjects, the PCSK9 level showed univariate correlations with total cholesterol, non-HDL-C, LDL-C, ApoB, and triglyceride levels. In the obese euthyroid subjects, the TSH level was positively associated with the BMI.

ANALYSIS AND COMMENTARY

The modest association observed between PCSK9 and TSH levels in this selected group of 64 non-obese subjects was not found in the small group of 10 obese subjects. Larger studies that include the assessment of other factors known to affect the variables studied, and that include more overweight and obese individuals, will be required in order to better evaluate associations of PCKS9 with TSH. (It is unfortunate that T_3 levels were not measured and that only a single measurement of FT_4 and TSH was made). Even so, it seems that PCSK9 will need to be added to the growing list of genes thought to link lipid and thyroid metabolism. Clinical studies show that the circulating level of PCSK9 responds promptly to fasting and to cholesterol depletion. One important factor that regulates PCSK9 is SREBP-2 (sterol regulatory element binding protein 2), a transcription factor that integrates signals from many pathways, including thyroid hormone. (I also note in passing that the PCSK9 gene contains a potential thyroid hormone receptor binding site [AGTGGAGGTAGGTGA] upstream of the transcription start site]). Despite such theoretical connections of PCSK9 with thyroid hormone levels, we must face the fact that this study reports that the PCSK9 level is associated with TSH, and not with FT_4. It is clear that functional TSH receptors are expressed in many tissues in addition to the thyroid and that some clinical studies on euthyroid subjects have found direct associations between TSH and cholesterol LDL-C and non-HDL-C levels (3). Several clinical papers suggesting a direct action of TSH on hepatic hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase were recently reviewed in Clinical Thyroidology (4). What is more, a direct association of BMI with TSH—but not with FT_4—was recently reported in a study of the National Health and Nutrition Examination Survey (NHANES) database (5). I look forward to further studies that assess how overt thyroid dysfunction affects PCSK9, and I hope that a specific mechanism that connects the level of TSH with that of PCSK9 will be uncovered.

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Management of Aggressive Metastatic Papillary Thyroid Cancer Involves Multiple Treatment Methods

Wendy Sacks

CASE PRESENTATION

The patient is a 37-year-old man who found a painless lump in his neck in March 2010. An ultrasound revealed a 4-cm right-sided thyroid nodule with microcalcifications; fine-needle aspiration results were suspicious for papillary thyroid cancer (PTC). He underwent thyroidectomy in April and was found to have a multifocal, bilateral, midline PTC with a dominant right-sided nodule measuring 5.8 cm. There was lymphovascular invasion, extrathyroidal extension of the tumor and extension of the tumor into the soft tissue through the lymph nodes. The tumor involved five of six left jugular lymph nodes, with extranodal extension. Metastatic carcinoma involved six of seven regional pretracheal lymph nodes. The pathological diagnosis was pT3b, pN1b, pMX. Postoperatively, a serum thyroglobulin (Tg) was >3000 ng/ml. The patient was begun on levothyroxine for TSH suppression. Postoperatively, he had a CT scan of the neck and chest with the inadvertent administration of contrast material, which demonstrated bilateral diffuse metastatic disease throughout both lung fields as well as mediastinal and supraclavicular lymphadenopathy consistent with metastatic disease.

He presented to our institution for a second opinion regarding ongoing management of his thyroid cancer. He had palpable lymphadenopathy and an ultrasound performed in the office revealed diffuse malignant lymphadenopathy involving levels II, III, and IV in the right jugular chain and levels II to IV in the left jugular chain. Because he had been given iodine contrast for the CT scan, radioactive iodine (RAI) treatment was postponed. Bilateral central and lateral neck dissections were recommended, and these were performed at another institution. A total of 22 of 54 lymph nodes were found to have metastatic PTC. Five months later, he received 155 mCi of 131I. An RAI whole-body scan (WBS) performed 9 days later showed diffuse uptake in the pulmonary parenchyma as well as in both sides of the neck, anterior mediastinum, and right supraclavicular area. In March 2011, the Tg was 134 ng/ml, TgAb <0.4 U/ml, and TSH 0.11 mIU/L.

The patient returned to our institution the following year. To further assess the extent of disease involvement, he underwent a high-resolution neck ultrasound and repeat thyroglobulin testing. The ultrasound of the neck showed a mass overlying the trachea measuring 2 cm and biopsy confirmed metastatic PTC. There were two small (<1 cm) lymph nodes in the right lateral neck. His Tg level was 88 ng/ml, TgAb <0.4 U/ml, and TSH <0.01 mU/L.

The patient's clinical data was reviewed by our multidisciplinary institutional Thyroid Cancer Tumor Board, which is composed of endocrinologists, surgeons, nuclear medicine specialists, oncologists, radiation oncologists, and pathologists. On the basis of their consensual recommendation, the patient underwent resection of the mass overlying the trachea, which showed a metastatic lesion measuring 2.5 cm by 1.0 cm by 1 cm consisting of one lymph node and soft tissue. The surgery was followed by a second dose of RAI (209 mCi) after recombinant human TSH stimulation. The 7-day post-RAI WBS demonstrated uptake in the right thyroid bed and diffuse uptake in the lungs. An FDG–PET scan showed moderate

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activity in the right paratracheal region measuring 4 mm, corresponding to a 1.5-cm lymph node on simultaneous CT scanning. Because of persistent macroscopic metastatic disease in the neck, some of which had dedifferentiated based on PET positivity, external-beam radiation therapy (EBRT) was recommended. He received 5940 cGy to his thyroid using intensity-modulated radiation therapy (IMRT).

One year later, his Tg was 126 ng/ml and TgAb <0.4 U/ml. FDG–PET imaging showed decreased metabolic activity at the site of the prior abnormality in the right neck corresponding to a decrease in size of the lymph node on CT scanning. Lung imaging showed relatively stable micronodules in both lungs, with the largest nodule decreased in size from 7 mm to 3 mm. A 123I scan showed persistent uptake in the lungs, and he was treated with another dose of 250 mCi of RAI, which resulted in a cumulative dose of 614 mCi of 131I. The lungs and two areas in the right neck took up iodine on the 7-day posttreatment WBS.

ANALYSIS AND COMMENTARY

This young man initially presented with biologically aggressive but histologically differentiated thyroid cancer metastatic to central compartment and lateral neck lymph nodes, cervical soft tissue, and lungs. He had persistent disease in his neck despite extensive resection of lymph-node metastases and one treatment with RAI. Although the Tg level decreased with postoperative thyroid hormone suppression, its elevated level was consistent with distant metastatic disease. The primary goals for ongoing treatment were to decrease morbidity from potential invasive metastatic disease to the major vessels in the neck and trachea and to improve overall survival despite pulmonary metastatic disease.

The majority of patients under 45 years of age who have differentiated thyroid cancer confined to the thyroid with lymph-node involvement have an excellent prognosis. The presence of distant metastases to the lungs at the time of initial diagnosis is not common and is reported to be between 3% and 15%. While there are many different staging systems, the American Thyroid Association guidelines recommend use of the UICC/AJCC TNM staging system for differentiated thyroid carcinoma (1,2). Patients younger than 45 years who have distant metastasis are classified as stage II with a 100% 5-year disease-specific survival (DSS), while those patients over age 45 with distant metastases are stage IV, which confers a 51% 5-year DSS. Good prognostic factors in patients with pulmonary metastases include young age (<45 years), micronodular pulmonary metastases, complete local control, and RAI-sensitive disease. Clinicopathological features that confer a poor prognosis include age over 70 years, distant metastases not confined to the lungs, macronodular lung metastases (>2 cm), lymph-node metastases >3 cm, follicular histology, and a poorly differentiated component in the primary thyroid neoplasm. Multiple institutional reviews report the 10-year DSS to be significantly better for younger patients with pulmonary metastases versus older patients, ranging from 94% to 100% and 36% to 46%, respectively (3-8).

A recent retrospective review from the Memorial Sloan-Kettering Cancer Center identified 52 patients of 1810 (2.9%) treated from 1985 to 2006 with distant metastases at the time of initial diagnosis with a male:female predominance of 3:2. Similar to our patient, the majority of their subjects with pulmonary metastases had pT3 or higher disease (77%) and lymph-node involvement, primarily in the lateral compartment (75%). Treatment included total thyroidectomy with lymph-node resection followed by RAI. The 5-year overall and disease-specific survival of the whole cohort (including pulmonary and extrapulmonary metastases) were 65% and 62%, respectively.

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Of the patients under age 45 years with pulmonary metastases, none died from thyroid cancer after a median follow-up of 80 months (range, 18 to 188), for a 100% 5-year DSS, whereas patients over age 45 years had a 56% 5-year DSS. As expected, patients with iodine-avid pulmonary metastases had a better 5-year DSS as compared with those with non–iodine-avid metastases (85% and 62%, respectively). Higher numbers of patients under age 45 had iodine-avid pulmonary metastases as compared with those over age 45 (P = 0.049) (9).

EBRT is used to improve local control and prevent relapse, especially in patients with gross extrathyroidal extension, or local failure despite adequate surgery and appropriate RAI. It is also considered in patients with poorly differentiated or insular thyroid carcinoma with minimal extrathyroidal extension or even in those with no extrathyroidal extension and close margins, where no further surgery is possible. EBRT has significant morbidity and is usually reserved for patients at high risk for tumor recurrence and those with gross residual disease. Acute (0 to 6 months) EBRT side effects include esophagitis, dysphagia, erythema, and a need for tracheostomy, while late complications (6 months to 2 years) include xerostomia, esophageal stenosis, tracheal constriction, carotid stenosis, and brachial plexopathy. IMRT offers dose intensification while reducing side effects of treatment by avoiding or reducing exposure to normal tissue and critical structures such as the esophagus (10,11). Because of a lack of prospective, randomized clinical trials, the benefit of EBRT, particularly in patients under 45 years of age, is uncertain. Nevertheless, as was done in our patient, EBRT should be considered in those with significant local progression after RAI therapy.

Our patient is nearing the maximum dose of RAI beyond which the risk for leukemia and other secondary malignancies increases, such that the risks may outweigh the benefits. Other options, such as targeted therapy using tyrosine kinase inhibitors (TKIs), must be considered. Clinical trials using TKIs for thyroid carcinoma have shown stabilization of disease in 50% to 70% of patients, but the response tends to be limited to 2 to 3 years, after which disease progresses (12-14). Because of this short-lived response, it is often difficult to decide when to initiate TKI therapy. We would consider a TKI in our patient when the doubling time of the lung nodules is less than 1 year.

Conclusions

While the majority of patients with differentiated thyroid cancer may be cured, the biologic behavior of the cancer varies substantially. We present an uncommon case of a young man with aggressive PTC with extensive lymph-node involvement and lung metastases. Despite advanced disease, he has a fairly good prognosis since he is young and the tumor is iodine-avid.

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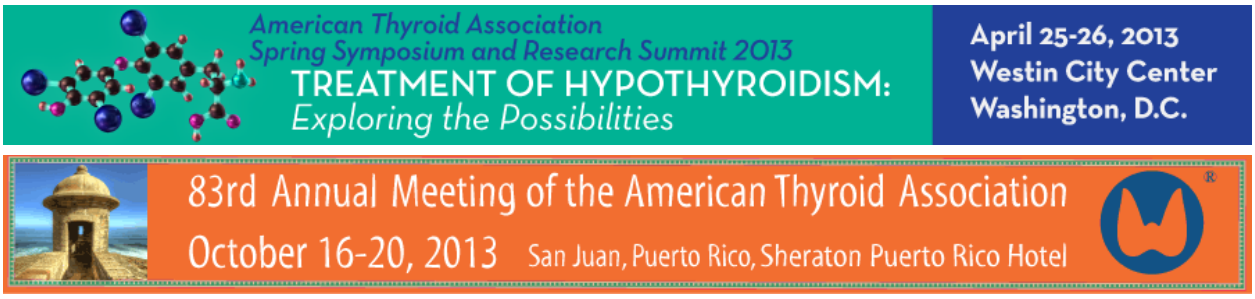

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7. The funds can be used for direct costs associated with the proposal, including technician's salary, supplies or equipment but not for PI's salary.
8. Applicants of ATA grants must be ATA members (submit application online if not already a member at www.thyroid.org). For new members, membership dues for the first year (January 2013-December 2013) will be waived.

Proposal Requirements (please submit the following documents online at http://mc.manuscriptcentral.com/ata2013grants):

1. Demographic information: Name /affiliation of applicant, complete work/home contact information – submitted into online system (do not include in grant proposal).
2. Grant Proposal (A short proposal that should be no longer than 900 words (including selected references) and no more than three double-spaced pages in 12 point type with 1" margins. These space requirements are absolute and nonconformance will preclude review. Do not include letterhead, name, address, institution, etc. This short proposal should include:
   - Title of proposed study
   - Background to the project
   - Hypothesis and/or outline of proposed studies
   - Outline of methodology
   - Anticipated results and implications
   - A short statement of how the grant will aid the applicant
   - Selected References (e.g. Uchino S, et al. World J Surg 2002;26:897-902)
3. CV (NIH-style CV – up to 4 pages) - including evidence that the applicant is a new investigator with date of completion of postdoctoral training and current grant support (if any). In the case of postdoctoral fellows, written confirmation that the applicant will have a junior faculty position at the time of the award, must be provided from the department chair. **Note: Without a suitable CV, applications will not be considered.**
4. Cover letter

Grant Review: The ATA Research Committee will rank proposals according to their scientific merit. Authors of selected proposals will be notified in March 2013 and invited to submit a complete grant application.

Stay Informed About Thyroid Disease — Become a Friend of the ATA

Let your patients know that they can become Friends of the ATA by signing up to get the latest thyroid health information and to be among the first to know the latest cutting-edge thyroid research of importance to patients, their families and the public.

As a Friend of the ATA we will send you:

- *Clinical Thyroidology for Patients* -- This publication is a collection of summaries of recently published articles from the medical literature covering the broad spectrum of thyroid disorders.
- The Calendar of Events highlights educational forums and support groups that are organized by members of the Alliance for Thyroid Patient Education. The Alliance member groups consist of: the *American Thyroid Association,* the *Graves' Disease Foundation,* the *Light of Life Foundation* and *ThyCa: Thyroid Cancer Survivors' Association, Inc*.
- *Friends of the ATA e-news*, providing up-to-date information on thyroid issues, answers to thyroid questions from leading thyroid experts, and invitations to upcoming patient events.
- Updates on the latest patient resources through the ATA website and elsewhere on the World Wide Web.
- Special e-mail alerts about thyroid topics of special interest for patients and the public.

AMERICAN THYROID ASSOCIATION® FOUNDED 1923

The American Thyroid Association (ATA) is a nonprofit medical society composed of physicians and scientists who specialize in the research and treatment of thyroid diseases. Dedicated to improving the lives of the millions of Americans of all ages living with thyroid problems, we are strongly committed to serving as a resource for these patients and the public and to promoting the prevention, treatment, and cure of thyroid-related diseases.

With extensive online resources for thyroid patients, families, and the general public at *www.thyroid.org*, each year we reach thousands of people who have come to rely on us for health information they can trust.

- Answers to frequently asked questions, or FAQs;
- Brochures on specific thyroid diseases;
- A database of ATA members called "Find a Thyroid Specialist";
- A toll-free telephone number with referrals to patient education materials and support groups; and
- Links to the ATA Alliance for Patient Education: organizations that provide support for understanding and coping with thyroid disease and its treatments.

Visit *www.thyroid.org* and become a *Friend of the ATA*.