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Designed By
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Metformin Prevents Goiter in Patients with Type 2 Diabetes

Jorge H. Mestman

Ittermann T, Markus MR, Schipf S, Derwahl M, Meisinger C, Völzke H. Metformin inhibits goitrogenous effects of type 2 diabetes. Eur J Endocrinol 2013;169:9-15.

SUMMARY

Background

The literature on the association between type 2 diabetes mellitus (T2DM) and thyroid volume is sparse. A recent experimental study demonstrated an inhibitory effect of metformin on the growth of human thyroid cells. According to the authors, no study on humans has investigated potentially modulating effects of metformin on the association between T2DM and thyroid volume. Their objective was to investigate these effects in a population-based cohort study.

Methods

The authors used data from the Study of Health in Pomerania (SHIP), a population-based cohort study conducted in West Pomerania, Germany. The population of the region had been iodine-deficient until the mid-1990s. Among older persons, the prevalence of goiter is still high. The study included 2570 individuals for cross-sectional and 1088 individuals for longitudinal analyses. T2DM was defined by physician-diagnosed self-report or by intake of antidiabetes medication. Age, sex, smoking status, drug intake, and T2DM were assessed by computer-assisted personal interviews. Initial examinations were performed between 1997 and 2001 and a follow up examination between 2002 and 2006 (1589 men and 1711 women, 83.5% of all eligible subjects). The median follow-up time was 5.0 years. Examinations at baseline and follow-up included anthropometry, thyroid ultrasonography, and laboratory measurements. For the longitudinal analyses, the authors considered sex, development of T2DM, and treatment with metformin or other antidiabetes drugs.

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Results

In the cross-sectional data, women with T2DM treated with antidiabetes medications other than metformin had a larger thyroid volume and a higher odds ratio (1.71) than women without T2DM. For men, no such association was detected. In women or men treated with metformin, T2DM was not associated with thyroid volume or goiter. In longitudinal analyses, incident T2DM not treated with metformin was significantly associated with a higher risk for incident goiter in the total population. Individuals with T2DM who changed from metformin to other antidiabetes agents during follow-up also had a higher risk for incident goiter than individuals without T2DM .

Conclusions

The authors demonstrate an inhibitory effect of metformin on prevalent and incident goiter and that the antigoitrogenic effect of metformin should be added to the general benefits of metformin treatment of T2DM.

ANALYSIS AND COMMENTARY

Patients diagnosed with T2DM and those with insulin resistance have been reported to have larger thyroid-gland volume as compared with control populations. In the present study, the authors followed a group of patients with T2DM and a control group, showing a significant decrease in the thyroid volume only in patients treated with metformin, versus those on diet alone or taking other antidiabetes agents; furthermore, in patients in the control group in whom diabetes developed, metformin prevented goiter. The relationship between metformin, thyroid function, and thyroid volume had been of interest to many investigators (1-4). A study by Cappelli et al. (4) (reviewed in Clinical Thyroidology [5]) confirmed the TSH-lowering effect of metformin in people with diabetes and hypothyroidism on L-T_4 treatment; in addition, the authors showed a significant reduction in serum TSH levels in euthyroid patients with higher baseline serum TSH levels independent of the presence of TPOAb. Metformin treatment was reported to reduce thyroid nodule size in a group of women diagnosed with the syndrome of insulin resistance (3). A recent study demonstrated an inhibitory effect of metformin on the growth of human thyroid cells, by activation of the adenosine monophosphate–activated protein kinase (AMPK)–mammalian target of rapamycin (mTOR) pathway and antagonism of the growth-stimulatory effect of insulin by inhibition of the mitogen-activated protein kinase (MAPK) pathway (6). A favorable metformin response to chemotherapy was reported in patients with breast cancer who had diabetes (7).

The above studies should be of clinical interest for practicing endocrinologists. Metformin is widely used in the management of prediabetes, metabolic syndrome, polycystic ovary syndrome, and T2DM. Recent studies of metformin's effect on thyroid function, beneficial action on thyroid volume, reduction in the size of thyroid nodules, and a possible potential effect on chemotherapeutic agents could bring exciting future alternative therapies for the benefit of our patients.

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Low Serum Cortisol After Surgery for Cushing's Syndrome Causes Hyperthyroidism Due to Inappropriate Secretion of TSH

Jerome M. Hershman

Tamada D, Onodera T, Kitamura T, Yamamoto Y, Hayashi Y, Murata Y, Otsuki M, Shimomura I. Hyperthyroidism due to thyroid stimulating hormone secretion after surgery for Cushing's syndrome: a novel cause of the syndrome of inappropriate secretion of thyroid stimulating hormone. J Clin Endocrinol Metab. May 13, 2013 [Epub ahead of print].

SUMMARY

Background

The syndrome of inappropriate secretion of TSH in the presence of high levels of thyroid hormones (SITSH) is rare and usually due to a TSH-secreting pituitary tumor or resistance to thyroid hormone. In the present report, the authors describe several cases of patients in whom SITSH developed after treatment of Cushing's syndrome when on low glucocorticoid replacement, a new finding.

Case Reports

Case 1 was a 45-year-old woman who had typical features of Cushing's syndrome that progressed during a 4-year period. She had high serum cortisol and urinary free cortisol and undetectable plasma ACTH. CT of the abdomen showed a 3-cm adrenal tumor that was removed laparoscopically. She was treated with 30 mg of hydrocortisone, and on postoperative day 18, the dose was reduced to 15 mg. After this, she experienced palpitation, fatigue, and weight loss. On day 40, she had an elevated free T_4 of 2.1 ng/dl, with TSH of 2.5, indicating SITSH. Further evaluation showed no pituitary tumor or findings of autoimmune thyroid disease. When the dose of hydrocortisone was increased to 30 mg/day, her symptoms and thyroid hormone levels improved promptly. When the dose of hydrocortisone was reduced progressively to 10 mg/day, her serum TSH increased and free T_3 increased in association with her symptoms of hyperthyroidism. Again, 30 mg of hydrocortisone normalized thyroid function.

Case 2 was a 37-year-old man with ACTH-dependent Cushing's disease caused by a 6-mm pituitary adenoma. After successful removal of the adenoma, SITSH developed, with elevated free T_3 when his replacement hydrocortisone dose was reduced to 20 mg/day. He was restarted on 30 mg followed by dose reduction of 10 mg every 4 days. On 10 mg of hydrocortisone per day, TSH increased and free T_3 rose above normal. He was discharged on 20 mg/day and remained euthyroid.

Seven additional patients with Cushing's syndrome had evaluation of thyroid function after surgery, and 4 of them had SITSH. All of those with SITSH had serum cortisol that was suppressed to <1.0 mcg/dl 5 days after surgery.

Conclusions

Insufficient replacement of hydrocortisone after surgery for Cushing's syndrome causes hyperthyroidism due to inappropriate secretion of TSH.

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ANALYSIS AND COMMENTARY

The authors have made a unique observation, probably catalyzed by the symptoms of hyperthyroidism in case 1. The degree of hyperthyroidism, based on free T_4 and T_3 levels, is very mild, but TSH is clearly inappropriately normal in this situation. This paper should stimulate evaluation of patients for this post-Cushing's SITSH.

What is the pathogenesis of this condition? Cortisol is known to attenuate TSH secretion (1). Elevated serum TSH has been reported in Addison's disease; it has been attributed to autoimmune thyroid disease and has not been associated with increased levels of thyroid hormones. Cortisol increases type 2 deiodinase (D2), which could result in increased T_3 in the hypothalamus and pituitary, in turn suppressing serum TSH (2). A lack of cortisol could attenuate D2, thereby increasing the secretion of TSH. This mechanism could explain the syndrome of SITSH when glucocorticoid deficiency is present, especially after the persistent stimulation of D2 is withdrawn.

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Patients with Thyroid Cancer Are at Higher Risk of Bankruptcy than Patients with Other Types of Cancer, or Those Without Cancer

Cord Sturgeon

Ramsey S, Blough D, Kirchhoff A, Kreizenbeck K, Fedorenko C, Snell K, Newcomb P, Hollingworth W, Overstreet K. Washington state cancer patients found to be at greater risk for bankruptcy than people without a cancer diagnosis. Health Aff (Millwood) 2013;32:1143-52. Epub May 15, 2013.

SUMMARY

Background

It is well understood that medical expenses contribute to personal financial insolvency; however, the relationship between specific cancer diagnoses and the risk of bankruptcy has not been well described. This study was performed to determine the incidence and time course of bankruptcy among patients with a new diagnosis of cancer.

Methods

The study evaluated persons 21 to 90 years of age from the Western District of Washington State between the years 1995 and 2009. A retrospective cohort analysis was performed using data from Surveillance, Epidemiology, and End Results (SEER) linked with LexisNexis. Matched cancer and control cohorts were identified, and these cohorts were both linked with records from the U.S. Bankruptcy Court for the Western District of Washington State. Probabilistic algorithms were used to link the SEER and LexisNexis records to the bankruptcy records. Kaplan–Meier analysis was used to determine the incidence of Chapter 7 and Chapter 13 bankruptcy filings in the two cohorts. Multivariate Cox regression was used to calculate hazard ratios for filing for bankruptcy, and the data were stratified by cancer diagnosis.

Results

A total of 197,840 patients with newly diagnosed cancer met inclusion criteria and comprised the experimental group; 197,840 matched controls were identified. During the study period, 2.2% (n = 4408) of the patients with cancer filed for bankruptcy as compared with 1.1% (n = 2291) of the controls; 0.52% of the overall cancer cohort filed for bankruptcy within 1 year of the cancer diagnosis and 1.7% within 5 years. The incidence rates for bankruptcy in the first year following cancer diagnosis were calculated based on cancer type and described as incidence per 1000 person-years. The cancer diagnosis with the highest incidence of bankruptcy was thyroid cancer, at 9.3 per 1000 person-years. Other cancer types with a high incidence of bankruptcy were lung (9.1), uterine (6.8), leukemia/lymphoma (6.2), colorectal (6.2), melanoma (5.7), breast (5.7), and prostate (3.7). Patients with cancer had a significantly higher risk of bankruptcy (hazard ratio, 2.65) than persons without cancer. Patients with thyroid cancer had a hazard ratio of 3.46. Patients with cancer who were younger, were unmarried, and had thyroid cancer or lung cancer had the highest rates of bankruptcy.

Conclusions

Bankruptcy rates were higher for those persons <65 years old; 62% of the bankruptcy filings were from patients with cancer who were 40 to 64. The youngest age groups had up to 10 times the rate of bankruptcy as that of the older age groups, a finding that may be due to higher debt-to-income ratios in the younger group. Furthermore, younger patients may have health care insurance that is linked to employment status, and cancer treatment may lead to inability to work. In contrast, the income

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of older patients is less likely to be linked to their ability to work (e.g., they may be receiving social security benefits) and they are more likely to have insurance coverage that is also not linked to employment status (i.e., Medicare). The authors surmise that patients with thyroid cancer might have lower rates of employment, lower wages, lower household income, and less access to health insurance.

ANALYSIS AND COMMENTARY

This is a sobering study that examines the personal financial burden of cancer by comparing rate of bankruptcy in a group of nearly 200,000 patients with cancer with that in a control group matched for age, sex, and ZIP Code of residence. It is well known that a cancer diagnosis can place a ponderous financial burden on the patient and furthermore that health care costs are major contributors to personal bankruptcy (1-3). The specific medical diagnoses most associated with the risk of bankruptcy, however, have not been well described. The authors of this study found that patients diagnosed with cancer are more than twice as likely to file for bankruptcy as are persons without cancer (2.2% vs 1.1%). In addition, they found that most patients who file for bankruptcy do so in the first year following the cancer diagnosis. In 2006, The USA Today/Kaiser Family Foundation/ Harvard School of Public Health National Survey of Households Affected by Cancer found a similar rate of bankruptcy of 3% for patients with cancer (1). A surprising finding from the current study was that thyroid cancer appears to place patients at an even higher risk of bankruptcy; nearly 3.5 times higher than that for persons without cancer. This association might be partially explained by the fact that patients with thyroid cancer are at risk for lost wages because they may not be able to work during the postoperative period or during the time surrounding radioiodine ablation. Furthermore, because of the young average age for patients with thyroid cancer, these patients are more likely to have a high debt-to-income ratio, are less likely to have access to high-quality health insurance, and do not qualify for Medicare and social security benefits.

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Serum Tg Before Radioiodine Ablation Is an Effective Predictor of Recurrence in High Risk Differentiated Thyroid Cancer Patients

Jerome M. Hershman

Piccardo A, Arecco F, Puntoni M, Foppiani L, Cabria M, Corvisieri S, Arlandini A, Altrinetti V, Bandelloni R, Orlandi F. Focus on high-risk DTC patients: high postoperative serum thyroglobulin level is a strong predictor of disease persistence and is associated to progression-free survival and overall survival. Clin Nucl Med 2013;38:18-24. doi: 10.1097/RLU.0b013e318266d4d8.

SUMMARY

Background

Patients with differentiated thyroid cancer (DTC) classified as high risk by staging systems are more likely to have recurrent disease after their initial therapy, but the factors that stratify risk have not been quantified. The staging systems, such as TNM or MACIS, were developed to predict the risk of death rather than the recurrence of disease. The current study evaluates the positive predictive value (PPV) of serum thyroglobulin at the time of ablation (ablation Tg) for predicting recurrent or persistent thyroid cancer.

Methods

Of 1894 patients with DTC treated from 1992 to 2010, a total of 243 were classified as high risk. Treatment included total thyroidectomy, remnant ablation with 100 mCi ^{131}I, and L-T_4 suppression therapy. Study exclusions were distant metastases at time of diagnosis, unknown lymph-node status (Nx), and positive Tg antibodies. Ablation Tg was measured before RAI ablation when serum TSH was >30 mU/L 4 to 6 weeks after surgery without replacement thyroid hormone therapy.

Patients were divided into four groups based on outcome: (A) complete remission after initial therapy (n = 149); (B) persistent disease after initial therapy and complete remission after further adequate treatment (surgery and/or ^{131}I administration) (n = 64); (C) persistent disease after initial therapy and progression or stable disease after further adequate treatment (surgery and/or ^{131}I administration) (n = 19); and (D) persistent disease after initial therapy and fatal progression of disease after further adequate treatment (surgery and/or ^{131}I and/or radiotherapy (n = 11).

Results

Median follow-up was 4 to 5 years (55 months) in the four groups. Ablation Tg increased significantly from group A to group D. Ablation Tg of 50 ng/ml or greater gave the highest PPV for recurrence, 0.97, of any clinical parameter, including tumor size, grade, lymph-node status, and MACIS score. The multivariate logistic model showed that only three parameters (ablation Tg, tumor dimension, and nodal status) were independently and significantly associated with disease persistence. Ablation Tg levels were the most important predictive and prognostic factor in terms of risk estimates, especially when comparing patients who had ablation Tg levels of 50 ng/ml or higher with patients in the lowest-level category (ablation Tg, <2 ng/ml). A total of 58 of 60 patients with ablation Tg of 50 ng/ml or greater had persistent disease; in contrast 126 of 136 patients who had ablation Tg <10 ng/ml had complete remission after initial therapy. The prognostic value of ablation Tg was also confirmed in Kaplan–Meier survival curves.

Conclusions

Ablation Tg levels of 50 ng/ml or greater are a valuable initial predictor of disease persistence or recurrence in patients at high risk for DTC.

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ANALYSIS AND COMMENTARY

The current study provides a valuable, easily measured indicator of disease recurrence in high-risk subjects, namely the serum Tg at the time of ablation when it is stimulated by TSH. Although the authors measured ablation Tg 4 to 6 weeks after surgery (without substitution therapy), which gives a more sustained elevation of serum TSH levels than recombinant TSH, the likelihood is that ablation Tg after recombinant TSH will be similarly useful.

The study confirmed that ablation Tg <10 ng/ml has a high negative predictive value (93%) for disease recurrence in high-risk patients, as this group had reported previously for low-risk patients (1).

The study has some limitations, including the retrospective nature of the evaluation and the relatively short follow-up of 4 to 5 years for DTC. However, in the high-risk patients, this may be sufficient for evaluating recurrence.

This study will alter my practice by adding the measurement of ablation Tg to my routine management of patients with DTC in order to predict disease recurrence.

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Percutaneous Laser Ablation Is Effective Therapy for Cervical Nodal Recurrence of Papillary Thyroid Cancer

Jerome M. Hershman

Mauri G, Cova L, Tondolo T, Ierace T, Baroli A, Di Mauro E, Pacella CM, Goldberg SN, Solbiati L. Percutaneous laser ablation of metastatic lymph nodes in the neck from papillary thyroid carcinoma: preliminary results. J Clin Endocrinol Metab. May 10, 2013 [Epub ahead of print].

SUMMARY

Background

Papillary thyroid carcinoma (PTC) frequently metastasizes to cervical lymph nodes. The recurrence can be identified by ultrasonography and FNA of the abnormal nodes. At present, the therapy for this recurrence is either ^{131}I or surgical resection. This study describes percutaneous laser ablation (PLA) of metastatic cervical nodes, a new therapy.

Methods

Fifteen patients were included in the study, and all had at least 6 months of follow-up after PLA. The procedure was applied to 24 newly identified lymph-node recurrences in patients who had undergone thyroidectomy and radioiodine ablation. At the time of recurrence, the patients had uptake of FDG in the node on PET/CT but had a negative radioiodine scan.

Each lymph node was identified by ultrasound and by contrast-enhanced ultrasound (CEUS). The ablation procedure was performed using a commercially available ultrasound system with an integrated laser source under local anesthesia. Introducer needles were placed in the lymph node, an optic fiber was advanced to the needle tip, and laser power was administered to cover several millimeters more than the volume of the nodule. At the end of the procedure, the effect of the treatment was confirmed by showing a lack of enhancement by CEUS, indicating destruction of the node. Patients were followed by ultrasonography, serum thyroglobulin (Tg), and PET/CT at 6 and 12 months after the procedure.

Results

The procedure was technically successful in all patients. In 2 patients, CEUS showed residual enhancement of the treated lymph node after the first ablation, so a second PLA was performed in the same session. The 6-month follow-up showed that local control was achieved in 11 of the 15 patients. Imaging showed that 20 of 24 nodes were negative on PET and CEUS. There were no immediate or late major complications.

One patient had extensive progression of lung and lymph-node recurrence and was excluded from further follow-up. At the 12-month follow-up, 16 of 20 treated nodes were negative on imaging. Local control was achieved in 10 of the 14 patients, but lung metastasis developed in 1. In 3 other patients with apparent local control, Tg was elevated.

Conclusions

Percutaneous laser ablation is a feasible, safe, and effective treatment for cervical nodal recurrence of PTC.

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ANALYSIS AND COMMENTARY

This small series shows the potential efficacy of this new procedure. It is technically demanding and requires that the interventionist possess skills in ultrasonography and laser therapy. The results of this study were similar to another recent series that included only five patients (1).

In patients with aggressive PTC, the usual first-line therapy for cervical recurrence is extensive neck dissection, but this is successful in only about three-fourths of patients. For patients with radioiodine uptake in nodes, ^{131}I may eradicate the recurrence, but it is certainly not uniformly successful; apparently, none of the patients in this series had radioiodine uptake in their nodes. Fortunately, the armamentarium for treatment of cervical recurrences is rapidly increasing and now includes alcohol injection, radiofrequency, microwaves, and cryoablation in addition to PLA (2,3). Each technique requires special expertise. As experience accrues with PLA and these other methods, it will be worthwhile to compare the results of these methods to each other and to those achieved with surgical therapy.

I hope to hear from our readership with regard to your use of these new techniques for treatment of recurrent cervical nodes.

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The Relationship between Serum TSH and Free T_4 Is Not Log-Linear and Varies by Age and Sex

Elizabeth N. Pearce

Hadlow NC, Rothacker KM, Wardrop R, Brown SJ, Lim EM, Walsh JP. The relationship between TSH and free T_4 in a large population is complex, non-linear and differs by age and gender. J Clin Endocrinol Metab. May 13, 2013 [Epub ahead of print].

SUMMARY

Background

In older studies, the relationship between serum TSH and free T_4 appeared to be log-linear (1,2). However, in a more recent study, a complex and nonlinear relationship was seen (3). This had not previously been assessed in a very large population sample. In addition, there have been conflicting reports regarding the effects of age and sex on the relationship between TSH and free T_4 (4-6).

Methods

This cross-sectional study assessed relationships between TSH and free T_4 values using thyroid-function tests measured during 2000 and 2011 at a single statewide private laboratory in Western Australia. Individuals with concurrent TSH and free T_4 measurements were included. Individuals who were hospitalized, pregnant, less than 1 year of age, being treated by endocrinologists, with unknown sample-collection times, with unknown ages, or with samples collected outside of usual office hours were excluded. In addition, patients with a history of thyrotoxicosis, thyroid cancer, thyroidectomy, or hypopituitarism and those treated with radioactive iodine or with drugs that might affect thyroid function were also excluded. In all, 15% of the records initially identified were excluded from analyses. Individuals taking levothyroxine (L-T_4) were included, but were analyzed separately.

The median value for every TSH concentration associated with a given integer free T_4 value was calculated, with upper and lower quartiles. Because they were nonnormally distributed, serum TSH values were log-transformed. Nonlinear quantile regression models were used to assess relationships between serum TSH and free T_4 values, with age and sex as covariates.

Results

A total of 445,994 TSH–free T_4 pairs from 152,261 individual subjects were analyzed. Most study subjects (75%) were women, and 21% were taking L-T_4. Among individuals not taking L-T_4, median log TSH and free T_4 values were inversely related. The relationship was not linear, but rather was best described by two negative sigmoid curves. Among patients taking L-T_4, the relationship was similar. Median serum TSH values were higher for males than for females (3.8 mIU/L vs. 3.3 mIU/L; $P<0.001$) and serum free T_4 values were slightly higher in males (14.0 vs. 13.7 pmol/L; $P<0.001$). Median TSH was higher in men than in women at almost every free T_4 value, with more extreme differences in the upper part of the reference range. Among those with normal serum free T_4 values who were not treated with L-T_4, median TSH increased with age. Among the 4403 patients with untreated overt hypothyroidism (elevated TSH and free T_4 <10 pmol/L), median TSH was lower in older than in younger adults.

Conclusions

The relationship between serum T_4 and serum TSH was not log-linear. Among euthyroid individuals, TSH was higher in men and increased with advancing age. The rise in TSH with overt hypothyroidism is attenuated in older adults.

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ANALYSIS AND COMMENTARY

Strengths of this study include the very large sample size, which allowed the investigators ample power to study sex and age subgroups and both treated and untreated hypothyroidism. Information about some potentially important covariates, such as race/ethnicity, body-mass index, and smoking status, was not ascertained. Importantly, it is possible that the lack of a log-linear relationship between TSH and free T_4 was merely an artifact due to inadequacies of the free T_4 assay used. Future studies could conduct similar analyses using different free T_4 assay methods, in particular the gold standard methods of equilibrium dialysis or isotope-dilution liquid chromatography with tandem mass spectroscopy.

What relevance do these results have for clinical practice? These data suggest that TSH reference ranges are not one-size-fits-all, and the use of a single TSH range for all subpopulations might result in misclassification of thyroid status in some cases, in particular the inappropriate diagnosis of subclinical hypothyroidism. The age-associated increase in serum TSH among euthyroid individuals seen in this and previous studies (4) argues against routine treatment of mild TSH elevations in elderly patients. Age- and sex-specific TSH reference ranges might be used to more accurately classify thyroid status (5). Although race and ethnicity were not examined by Hadlow and colleagues, racial and ethnic variability in serum TSH values have been described previously (5) and racial/ethnic subpopulation-specific TSH values might also be helpful in some regions.

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The Diluted TSHR Antibody Titer in Untreated Graves' Disease May Predict Who Will Respond to Six Month's Treatment with Methimazole, and Mc4-Expressing CHO Cells Can Detect Both Blocking and Stimulating TSHR Antibodies

Stephen W. Spaulding

Background

Antibodies that bind to the TSH receptor (TSHR) can cause hyperthyroidism or, more rarely, hypothyroidism. However most commercially available TSHR antibody measurements are not very useful for making a pretreatment prediction about the efficacy of antithyroid drug treatment. Furthermore, the absolute values of antibody determinations often do not correlate between assays, despite the use of an "international standard." Nonetheless, several third-generation assays are sufficiently sensitive and specific to use as affirmation of one's clinical diagnosis in the bulk of patients with Graves' disease. (The tests do require some technical proficiency, but their cost is only 5% to 10% of a thyroid scan and uptake.) Here, I review two recent papers that use CHO cells expressing Mc4, a TSHR/luteinizing hormone (LH)/chorionic gonadotropin receptor (CGR) chimera. One study assesses the prognostic value of measurements of TSHR-stimulating activity in serial dilutions of serum samples, while the other assesses their use for measuring TSHR-blocking antibodies.

STUDY 1

Leschik JJ, Diana T, Olivo PD, König J, Krahn U, Li Y, Kanitz M, Kahaly GJ. Analytical performance and clinical utility of a bioassay for thyroid-stimulating immunoglobulins. Am J Clin Pathol 2013;139:192-200.

Methods

First, two third-generation assays were compared for detection, quantitation and cutoff limits, as well as for half-maximal effective concentrations in response to stimulation with the human monoclonal M22 TSHR antibody. The results from the Thyretain bioassay, which uses cryopreserved Chinese hamster ovary (CHO) cells that stably express the Mc4 chimera plus a cAMP-induced luciferase reporter gene, were compared to the results from the Roche Elecsys assay, which measures antibody binding to wells coated with the porcine TSHR, followed by ruthenium-labeled M22 that binds to the unoccupied sites remaining on the porcine TSHR, and is detected by electrochemiluminescence.Second, a small clinical study compared the Thyretain and Roche assays prospectively on 40 German patients with thyrotoxic Graves' disease to determine whether pretreatment and intratreatment anti-TSHR titers were of use in predicting the likelihood that a patient would be in remission after 6 months of treatment with MMI. Sera were obtained before and during a 24-week course of MMI and after 12 weeks of follow-up; 20 of the 40 remained in remission at 36 weeks. Undiluted sera and threefold dilution up to at least 1:81 were assayed, and the number of samples becoming undetectable at each dilution were determined. The Thyretain assay was positive on more samples ($P<0.0001$) (e.g., at the 1:9 dilution, two thirds of samples remained positive in

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the Thyretain assay, while only one fourth remained positive in the Elecsys assay). The dilution at which a sample that first fell below the cutoff threshold was called the "dilution titer."

Results

The Thyretain assay responded to M22 over a range of 0.012 to 0.4 ng/ml, whereas the Elecsys assay responded between 20 and120 ng/ml. The Elecsys assay limits of detection and of quantitation were about 250 times less, and cutoff and half-maximal effective concentration were about 800 times less when M22 was used, but this difference in sensitivity was much less dramatic when patient sera were used. Twenty of the 40 patients remained in remission for at least 3 months after MMI was discontinued. Assays on the undiluted pre-MMI samples did not distinguish between those who went on to relapse from those who remained in remission. However, when the samples were diluted with normal serum, the Thyretain assay on the pretreatment samples of the 20 nonresponders was 4.0±0.39, whereas it was only 2.9±0.25 (mean ±SD) in the 20 who remained in remission (P = 0.018), and after 12 weeks of MMI, the difference between mean dilution titers increased twofold (P<0.00012). Using the Elecsys assay, the mean dilution titer in the baseline samples was 2.65±0.29 for the nonresponders versus 1.65±0.16 for the responders (P = 0.003), and after 24 weeks on MMI, the difference between the mean titers was 1.85 (P<0.0001). Thus, with either assay, patients whose dilution titer was lower at baseline—and those in whom the titer decreased after 12 weeks of MMI—achieved normal thyroid hormone levels by 24 weeks and remained euthyroid clinically and biochemically for at least 12 more weeks off MMI.

Conclusions

The Thyretain bioassay is much more sensitive to M22 and slightly more sensitive to low-but-positive concentrations of TSHR-stimulating antibodies, as compared with the Roche Elecsys automated TSHR binding assay. However, both assays had similar abilities to predict at least a 12-week remission on pretreatment samples and on samples drawn after 12 weeks of MMI treatment, but only if the titer of TSHR-stimulating activity was measured on serial dilutions.

STUDY 2

Li Y, Kim J, Diana T, Klasen R, Olivo PD, Kahaly GJ. A novel bioassay for anti-TSH receptor autoantibodies detects both thyroid-blocking and stimulating activity. Clin Exp Immunol. May 7, 2013 [Epub ahead of print].

Methods

Serum antibodies that block the binding of TSH to the TSHR or that block the stimulation of cAMP production have been detected in patients with a variety of autoimmune thyroid diseases. Mc4-expressing CHO cells, as well as CHO cells expressing wild-type TSHR, were incubated with bovine TSH (bTSH) for 3 hours along with increasing concentrations of K1-70, a potent TSHR-blocking monoclonal antibody, to compare the percent inhibition of the cAMP response in the two cell types. After determining the assay cutoff level for blocking activity, sera from 300 euthyroid subjects were used to establish the mean percent inhibition produced by normal serum. Assay reproducibility was assessed on sera known to contain low, medium, and high levels of blocking antibodies. Samples from 171 patients with Graves' disease were then assayed for both stimulatory and blocking activity in the two CHO-cell assays. The two CHO-cell assays were tested on 50 normal sera and on sera from 50 patients with various autoimmune thyroid disorders.

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The Diluted TSHR Antibody Titer in Untreated Graves' Disease May Predict Who Will Respond to Six Month's Treatment with Methimazole, and Mc4-Expressing CHO Cells Can Detect Both Blocking and Stimulating TSHR Antibodies

Results

CHO cells expressing wild-type TSHR were more sensitive to bTSH and recombinant human TSH (rhTSH), but Mc4-expressing CHO cells were 5 times more sensitive to inhibition by K1-70 when stimulated with 100 mIU/L of bTSH. The cAMP responses to TSH or M22 were inhibited by 50% using similar levels of K1-70. The CHO-Mc4 bioassay was estimated to be about 20 times more sensitive to the inhibitory action of K1-70 than the Kronus TRAb ELISA. Sera from 300 euthyroid controls produced a mean percent inhibition of –4% with a standard deviation of 21%, so the 2 SD cutoff limit for inhibition was about 40%, while for negative inhibition it was 46%. Sera with low, medium, and high levels of blocking antibody produced about 45%, 65%, and 95% inhibition, with coefficients of variation of about 4%, 9%, and 25%, respectively. Sera with high titers of blocking antibody could be diluted as much as 700-fold before they fell below the cutoff level. Sera from 50 tightly selected healthy euthyroid controls had blocking activity ranging from –16% to +37% inhibition. Sera from 50 patients with various autoimmune diseases had blocking activity ranging from –157% to +108% inhibition. Sera from 15 of the 50 patients displayed significant blocking activity: 2 were from patients with Graves' disease and 13 from patients with Hashimoto's thyroiditis (7 had hypothyroidism, including 2 with TSH >100). The Roche Elecsys assay detected activity in 10 of these 15 samples, which could have been interpreted as a TSHR-stimulating antibody. The assay of sera from 171 patients with Graves' disease revealed that the stimulatory activity in the CHO-Mc4 bioassay correlated closely with negative inhibition in the blocking assay, although sera with low but detectable stimulatory activity did not display significant negative blocking activity.

Conclusions

Assaying sera for blocking activity with CHO-Mc4 cells is about 20 times more sensitive than a commercial TSHR-binding assay that does not discriminate between stimulatory and blocking activity. The CHO-Mc4 blocking assay not only detects blocking antibodies, but it also indicates the presence of stimulatory antibodies, reporting them by their negative blocking activity, although it is not as sensitive as the regular CHO-Mc4 stimulatory assay.

ANALYSIS AND COMMENTARY

It is currently believed that patients with Graves' disease who are treated with antithyroid drugs are more likely to have a remission if their thyroid-stimulating antibody levels fall smoothly during treatment (1). Presumably, patients whose MMI dose needed to be adjusted downward had a better prognosis, although this is not mentioned in the article by Leschik et al. The new finding in their article is that pretreatment sera can be used to predict whether a patient will have a remission after 6 month's treatment with MMI, based on the serial dilution titer. Assuming the findings are confirmed in larger series of patients—and in laboratories not involving the assay's developers—serial dilution seems to be a promising way to predict which patients with Graves' disease will have a remission (which one would hope would last for more than 3 months). Serial dilution produced very similar results when the Roche Elecsys assay was used.

Li et al. report that CHO-Mc4 cells can be used to detect TSHR-blocking activity, while at the same time detecting TSHR-stimulating activity as negative

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inhibition. There is some irony to this report, since the TSHR/LH/CGR chimera was initially believed to be insensitive to TSHR-blocking antibodies, based on cAMP release from Cos-7 cells incubated with purified IgGs in the presence of isobutylmethylxanthine (2). The availability of the potent monoclonal antibodies M22 and K1-70 now provide a solid starting point for developing better TSHR antibody assays, but the pathophysiology of Graves' disease still seems to involve multiple binding sites and multiple antibodies. Indeed, studies using batteries of monoclonal antibodies directed at limited targets seem to indicate that the hinge–transmembrane region in the native LH receptor may have a more open structure than the native TSH receptor (3), which could be one reason the Mc4 chimeric receptor seems to be more responsive to some TSHR-stimulating antibodies when compared to the responsiveness of the wild-type TSH receptor. The likelihood that a patient with Graves' disease will have both blocking and stimulating antibodies is unknown, although in the 50 patients with autoimmune thyroid diseases, 2 such patients were found. One clinical situation that begs to be addressed with the blocking assay is the patient with Graves' disease who goes into remission after a course of antithyroid drug treatment, but then relapses. How commonly does this reflect a blocking antibody appearing during the "remission," which then disappears, while the stimulating antibody does not?

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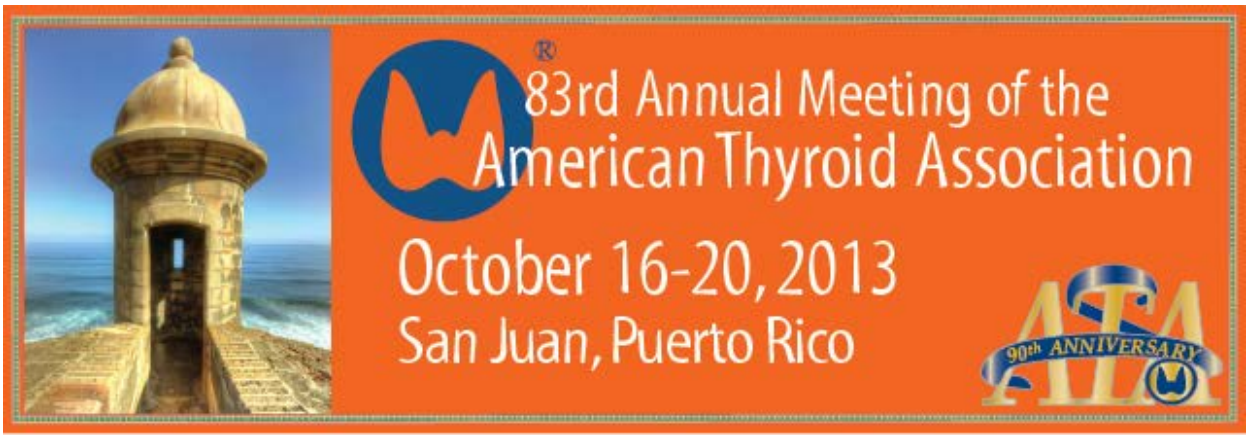

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