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Thyroid Health Supplements Contain Significant Amounts of Thyroid Hormones

Jerome M. Hershman

Kang G, Parks JR, Bader F, Chang A, Maged AR, Burch HB, Bernet V. Thyroxine and triiodothyronine content in commercially available thyroid health supplements. Thyroid. June 13, 2013 [Epub ahead of print].

SUMMARY

Background

Dietary supplements are widely used in the United States. The Dietary Supplement Health and Education Act of 1997 defined supplements as separate from drugs and made them exempt from FDA regulation. A number of dietary health supplements are marketed for "thyroid support." The purpose of this study was to determine the thyroid hormone content of some of these supplements.

Methods

Ten thyroid health supplements were purchased from stores or through the Internet. Five of them were herbal supplements with no indication on the label that they contained thyroid hormone; the labels of the other five stated that they contained raw thyroid tissue or powder from a bovine source.

The supplements were analyzed for their T_4 and T_3 content by dissolving them in a suitable solvent and measuring the T_4 and T_3 content by high-performance liquid chromatography.

Results

Nine of the ten products contained detectable amounts of T_3 ranging from 1.3 to 25.4 µg per tablet. Five products contained detectable amounts of T_4 ranging from <0.5 to 22.9 µg per tablet, and 4 of these 5 also contained T_3. Four of the five products containing bovine extract contained T_3, and two of them also contained T_4; one contained neither hormone. All of the herbal capsules contained T_3, and two also contained T_4. The herbal capsules contained 100 to 240 µg of iodine per capsule and 150 to 1000 mg of tyrosine per capsule. For

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one herbal product, the recommended dose of four capsules daily would provide 92 μg of T_4 and 17 μg of T_3, and for another, the recommended dose would provide 32 μg of T_3. One capsule daily of one product with the bovine extract would provide 9 μg of T_4 and 25 μg of T_3, whereas the others contained 0 to 9 μg of T_4 and 1 to 4 μg of T_3.

Conclusions

The majority of dietary thyroid supplements contained clinically significant amounts of T_3 and T_4. This could potentially expose patients to the risk of altering thyroid-function tests and could even cause thyrotoxicosis.

ANALYSIS AND COMMENTARY

This well-designed study is very relevant to the practice of endocrinology in the United States. Thyroid supplements are marketed to support thyroid function, improve energy, or promote weight loss. There have been a number of case reports and even small series of cases of thyrotoxicosis related to taking such products (1). Many years ago, my colleagues and I reported five patients with thyrotoxicosis caused by taking a weight loss product sold through the mail that contained 9 μg of T_3 and 84 μg of T_4 per capsule (2).

The high iodine content of herbal thyroid supplements could improve thyroid function in some patients with Graves' disease or, conversely, they could trigger hyperthyroidism in patients with multinodular goiter or cause hypothyroidism in euthyroid patients with Hashimoto's thyroiditis.

The authors of the study point out that a weakness in their study is the lack of measurements of thyroid function in patients taking these products. Of course, a sequel to this article could address that issue. The data in this article make it clear that it is important to ask our patients whether they are taking thyroid supplements, especially those patients with peculiar results on thyroid-function tests.

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There Is a High Rate of Incidental Thyroid Cancer in Surgical Series of Toxic and Nontoxic Multinodular Goiter

Cord Sturgeon

Smith JJ, Chen X, Schneider DF, Broome JT, Sippel RS, Chen H, Solórzano CC. Cancer after thyroidectomy: a multi-institutional experience with 1,523 patients. J Am Coll Surg 2013;216:571-9. Epub February 8, 2013.

SUMMARY

Background

The likelihood of malignancy in Graves' disease (GD), multinodular goiter (MNG), and toxic multinodular goiter (TMNG) has historically been thought to be quite low (5% to 10%) (1-3). Recent studies have suggested a much higher rate of malignancy within toxic and nontoxic MNG (10% to 22%) (4-6). The authors designed this multiinstitutional study to determine the prevalence of incidental cancer in patients undergoing thyroidectomy for presumed benign disease.

Methods

This retrospective study examined cases from prospectively collected databases at three institutions in the United States. Patients undergoing thyroidectomy for MNG, TMNG, or GD performed by members of the Departments of Surgery at Vanderbilt University, the University of Wisconsin, and the University of Miami were included in the study. Cases from 2000 to 2011 were included; the time spans were different at each institution. Patients with preoperative FNA results that were malignant or indeterminate were excluded. The total number of thyroidectomies was 1523. The incidental cancer rate was calculated and univariate and multivariate analyses were performed to identify predictors of malignancy.

Results

The overall cancer rate was 15.6%. There was no statistically significant difference in cancer rates among the three institutions in the study. The median age at surgery was 49 years, 18% of the cohort had lymphocytic thyroiditis, and 43% underwent preoperative FNA biopsy. The mean cancer size was 1.1 cm (range, 0.1 to 9.0). A total of 39% of cancers were larger than 1 cm. Younger age, male sex, and the presence of nodules were associated with a higher risk of thyroid cancer. Male patients represented 16% of the entire cohort, but 21% of cancers were in men. The risk of cancer was significantly higher in nodular goiter than diffuse goiter (odds ratio, 4.1). The highest rate of cancer was found in TMNG (18.3%) and the lowest was in GD (6.1%).

Conclusions

There was a higher than expected rate of incidental cancer in TMNG (18.3%), MNG (17.5%), and GD (6.1%) across all three institutions. The risk factors for incidental thyroid cancer were male sex, thyroid nodules, and young age. Given this high rate of incidental cancer, a total thyroidectomy should be the preferred approach for patients undergoing surgery for bilateral nodular disease.

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ANALYSIS AND COMMENTARY

The rate of incidental thyroid cancer in this group of patients with presumably benign disease is alarmingly high. Nearly one in five patients with MNG or TMNG was found to have an incidental thyroid cancer. Despite the fact that these patients appear to have met the standard of care for preoperative thyroid assessment (all patients underwent a thyroid ultrasound and 43% had nodules interrogated by FNA), 15.6% of the overall group harbored an unsuspected malignancy, and 39% of the incidentally discovered cancers would be considered clinically significant (i.e., >1 cm). The strengths of this study are in its multiinstitutional nature and large number of patients. In support of these findings, previously published single-institution series have also demonstrated a nontrivial incidence of incidental thyroid cancer in patients undergoing thyroidectomy for presumably benign thyroid disease ranging from 12 to 16% (2-6). In light of these findings, total thyroidectomy by an experienced surgeon should be more strongly considered when managing nodular goiter, particularly in younger patients and males.

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Mutations of the RAS Oncogene Are Found in Follicular Variant Papillary Thyroid Carcinoma

Jerome M. Hershman

Gupta N, Dasyam AK, Carty SE, Nikiforova MN, Ohori NP, Armstrong M, Yip L, Lebeau SO, McCoy KL, Coyne C, Stang MT, Johnson J, Ferris RL, Seethala R, Nikiforov YE, Hodak SP. RAS mutations in thyroid FNA specimens are highly predictive of predominantly low-risk follicular-pattern cancers. J Clin Endocrinol Metab 2013;98:E914-22. Epub March 28, 2013; doi: 10.1210/jc.2012-3396.

SUMMARY

Background

Oncogenic mutations are found in more than half of differentiated thyroid cancers (DTCs). The most common mutation is BRAF V600E. The next most common mutation is in the RAS tyrosine kinase that is located upstream of RAF in the mitogen-activated protein kinase pathway. There are several RAS point mutations, subclassified as NRAS, HRAS, and KRAS. However, these mutations are also found in benign adenomas and less commonly in hyperplastic goiters. This article is a comprehensive clinical study of the largest series to date of tumors harboring RAS mutations that were detected prospectively in thyroid FNA biopsies.

Methods

All aspirated nodules were 1 cm or greater. The point mutations NRAS codon 61, HRAS codon 61, and KRAS codons 12 and 13 were detected using real-time PCR. The mutations were retested in resected specimens.

Results

Between April 2007 and April 2009, a total of 921 patients who underwent thyroid-nodule FNA were evaluated prospectively with a panel of molecular markers. RAS mutations were found in 68 aspirates from 66 patients (7.2%). The identified mutations were NRAS codon 61 in 49 (72%), HRAS codon 61 in 15 (22%), and KRAS codon 12 or 13 in 4 (6%) aspirates. Based on the Bethesda classification for thyroid FNA cytology, 63 of 68 RAS-positive aspirates (93%) had a diagnosis in the indeterminate categories, 3 (4%) were malignant, and 2 (3%) were negative for malignant cells. Of the 63 cytologically indeterminate aspirates, 32 (51%) were classified as follicular neoplasm/suspicious for follicular neoplasm, 22 (35%) as follicular lesion of undetermined significance, and 9 (14%) as suspicious for malignant cells.

Sixty-three nodules of RAS-positive patients were resected, and cancer was confirmed in 52 specimens (83%) from 50 patients. The RAS-positive cancers included 46 follicular variant PTC, 4 follicular thyroid carcinomas, 1 medullary thyroid carcinoma, and 1 anaplastic thyroid cancer. Microdissections of 4 DTCs with mutation analysis of three separate areas of each tumor showed the same mutation, indicating that they were clonal neoplasms.

Of the 63 RAS-positive aspirates, 11 nodules (17%) were found to be histologically benign; 7 of these nodules were follicular adenomas with microfollicular architecture and the other 4 were hyperplastic nodules.

Only one third of the RAS-positive malignant nodules had at least one ultrasonographic feature associated with cancer.

Conclusions

Most RAS-positive thyroid cancers have indeterminate cytology, lack suspicious ultrasound features, and are histologically low-grade follicular variant PTC.

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Mutations of the RAS Oncogene Are Found in Follicular Variant Papillary Thyroid Carcinoma

Jerome M. Hershman

ANALYSIS AND COMMENTARY

Although this study was relegated to the electronic (Web) pages of the Journal of Clinical Endocrinology and Metabolism, suggesting that it was of less clinical significance than papers in the print version, I believe that it has significant clinical importance. The study confirms that RAS mutations in FNA specimens are strongly indicative of thyroid cancer (1). The vast majority of the cancers were follicular variant PTC, a tumor that is difficult to diagnose accurately on FNA cytology. The finding of homogeneous distribution of the specific RAS mutation throughout the DTC indicates that these lesions are clonal neoplasms, suggesting that the RAS mutation is an early and crucial event in thyroid neoplasia. However, the fact that these mutations are also found in benign adenomas and hyperplasia diminishes their impact on being solely responsible for oncogenesis.

The encapsulated follicular variant of PTC with the RAS mutations that predominated in this series tends to have a much better prognosis than classical PTC, especially those that harbor the BRAF mutation (2). Because only 7.2% of the nodules had RAS mutations, one can argue that it may not be cost-effective to screen for it, even though it is much more prevalent than the BRAF mutation (1). The argument for screening for the BRAF mutation is that it has an ominous prognosis; finding it can be a basis for more aggressive therapy. However, BRAF is found in the classical PTC that can be diagnosed frequently by positive ultrasound findings, such as microcalcifications. Because ultrasonography is usually not suggestive of malignancy in nodules with the RAS mutations, as found in this series, screening for the mutation can be very helpful to indicate whether thyroidectomy is justified.

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Interstitial Laser Photocoagulation Provides Effective Therapy for Thyroid Cysts

Jerome M. Hershman

Døssing H, Bennedbæk FN, Hegedüs L. Interstitial laser photocoagulation (ILP) of benign cystic thyroid nodules—a prospective randomized trial. J Clin Endocrinol Metab 2013;98:E1213-7 [Epub June 18, 2013].

SUMMARY

Background

Thyroid cysts are common. Although a cyst may harbor a papillary thyroid cancer in its wall, this is relatively rare. The main problems that cysts cause are a feeling of pressure in the neck and cosmetic symptoms. Aspiration of cysts is usually successful in reducing their size and relieving acute symptoms, but there is frequent recurrence to the original size. Eventually, surgical removal of the cyst, often accompanied by lobectomy, is required, even though the cyst is benign. The current study compares treatment of cysts by aspiration alone versus interstitial laser photocoagulation (ILP).

Methods

Forty-four euthyroid patients (30 women and 14 men, median age, 49 years) had palpable, symptomatic, cystic thyroid nodules that were cytologically classified as benign. The patients were randomly assigned to one of the two treatment groups. They were studied at baseline and 1, 3, and 6 months after the treatment by ultrasonographic measurements of cyst volume as well as of the solid part of the nodule, and by patients' self-report of symptoms.

Under lidocaine anesthesia, the cyst was aspirated through an 18-gauge needle containing a 0.4-mm laser fiber. Then the laser fiber was positioned in order to induce necrosis and destroy the cyst membrane and the solid part of the nodule using a power of 2 to 3 watts.

Results

Pure cysts were found in 8 of the 22 patients in the aspiration group and in 9 of the 22 in the ILP group. The other patients had mixed cystic and solid lesions, but the cysts were the dominant portion of the nodules. The median total nodule volume was 10.0 ml in the aspiration group and 11.8 ml in the ILP group. In the ILP group, remission of the cystic part (<1 ml remaining) occurred in 15 of 22 patients (68%), as compared with 4 of 22 (18%) treated with aspiration alone ($P<0.002$), at the 6-month evaluation. The reduction of the cystic component was 94% in the ILP group and 32% in the aspiration group ($P<0.007$). There was a reduction in the solid component in 54% of the ILP group (2.5 ml reduced to 1.0 ml), but no reduction in the aspiration group (2.6 ml increased to 3.0 ml).

The duration of the ILP treatment was 600 seconds. As a consequence of the procedure, 11 patients in the ILP group reported slight to moderate pain that lasted about 2 days, necessitating mild analgesics in 8 patients. There were no laryngeal-nerve injuries. At the 6-month evaluation, there was relief of symptoms in the ILP group but not in the aspiration group.

A total of 10 patients in the aspiration group who had recurrence of their cyst were subsequently cured by ILP. Eventually, 9 patients with persistent cysts had thyroid surgery and were found to have benign histology.

Conclusions

Interstitial laser photocoagulation significantly reduces the recurrence rate of thyroid cysts and the volume of the solid nodule component; it also relieves pressure symptoms. This procedure constitutes an important alternative to surgery.

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Interstitial Laser Photocoagulation Provides Effective Therapy for Thyroid Cysts

Jerome M. Hershman

ANALYSIS AND COMMENTARY

The current study is a randomized, controlled trial of this innovative procedure previously reported by this outstanding Danish group (1). They also reported that ILP could be used to treat benign solid nodules (2), and others showed that it was effective therapy for cervical nodal recurrence of papillary thyroid cancer (3), reviewed recently in Clinical Thyroidology (4). The authors have reported similar results with the treatment of thyroid cysts by ethanol (5), but prefer the ILP procedure because seepage of ethanol outside the capsule may cause pronounced pain or more serious side effects, such as paresis of the vocal cords or extraglandular fibrosis.

The main disadvantage of ILP is that it requires a highly trained and skillful operator. The procedure is beyond the expertise of clinical endocrinologists in the United States.

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Minimal Alcohol Consumption Reduces the Risk of Graves' Disease

Albert G. Burger

Carlé A, Bülow Pedersen I, Knudsen N, Perrild H, Ovesen L, Rasmussen LB, Jørgensen T, Laurberg P. Graves' hyperthyroidism and moderate alcohol consumption: evidence for disease prevention. Clin Endocrinol 2013;79:111-119. Epub April 19, 2013.

SUMMARY

Background

Alcohol consumption is known to provide some protection not only from cardiovascular diseases but also from autoimmune disorders. Moderate consumption of alcohol, it is claimed, prevents hypothyroidism. As far as a possible link between alcohol consumption and hyperthyroidism is concerned, there is considerable controversy. The present results, obtained from the Danish iodination program, which included 2 million person-years, are relevant to this debate.

Methods

From 1997 to 2000 the populations of two districts of Denmark were enrolled in a study of iodine deficiency. In this group of subjects, newly diagnosed cases of hyperthyroidism were studied. For a diagnosis of Graves' disease, a positive TSH receptor antibody titer and/or thyroid scintigraphy were required. A total of 484 cases of Graves' disease were identified in 1682 patients with overt hyperthyroidism. These subjects were required to fill out a questionnaire aimed at gathering information on alcohol consumption and the presence of comorbidities. The staff of this case–control study investigated 272 cases of newly diagnosed Graves' disease and 1018 individually matched control subjects from the same population. Alcohol consumption was expressed in units consumed per week, with one unit corresponding to 12 g of alcohol. Alcohol consumption was scored during the year before the diagnosis and at the maximum during any calendar year of the subjects' lives.

Results

The age of the patients ranged from 20 to 79 years. Patients with Graves' disease had a 30% prevalence of cardiovascular comorbidity.

Abstainers were more frequent in the group of patients with Graves' disease than in the control group. The difference was considerable—28% of patients with Graves' disease were abstainers, versus 12% in the control group. This difference was even observed in the group with the lowest alcohol consumption. The patients in this group consumed approximately 12 g of alcohol per week at the time they were diagnosed. With higher alcohol consumption (up to 120 g), the protective effect steadily increased. Twelve grams of alcohol corresponds to one 0.33-liter bottle of beer or one 120-ml glass of wine, clearly a moderate consumption. There was no detectable difference between types of alcohol consumption—beer, wine or spirits.

Conclusions

Even a minimal amount of weekly alcohol consumption (one bottle of beer or one glass of wine) appears to reduce the risk of Graves' disease. This finding was independent of age, sex, smoking, and comorbidities. This effect of alcohol was higher with moderate alcohol consumption, such as 1 to 2 glasses of wine or a similar amount of any other kind of alcohol per day.

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Minimal Alcohol Consumption Reduces the Risk of Graves' Disease

Albert G. Burger

ANALYSIS AND COMMENTARY

Even a small alcohol intake may have some preventive effect on the mechanisms that produce Graves' disease. This conclusion appears to apply independently of cofactors such as age, sex, and smoking. The present extensive study strongly supports earlier work, so that one can now add Graves' disease to the list of autoimmune diseases—such as lupus erythematosus, rheumatoid arthritis, and autoimmune diabetes—known to be prevented by the effect of alcohol. The odds ratio between abstainers and minimal alcohol consumers for Graves' disease developing was 1.7. This rather convincing difference remained stable regardless of whether the data of current or earlier alcohol consumption was taken into account. Several mechanisms for the protective effect of alcohol are proposed, such as loss of natural killer cell activity and alterations in both T helper cell 1 (Th1)- and Th2-mediated immunity. In many studies, mostly done in animals, the impact of large quantities of alcohol on the immune system were tested. These results may not be relevant to the present observation. Alcohol consumers will not be bothered about the lack of explanation but will probably appreciate the message.

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Smoking in Pregnancy Increases Subsequent Maternal Hyperthyroidism Risk but Protects Against Subsequent Hypothyroidism

Elizabeth N. Pearce

Andersen SL, Olsen J, Wu CS, Laurberg P. Smoking reduces the risk of hypothyroidism and increases the risk of hyperthyroidism: evidence from 450,842 mothers giving birth in Denmark. Clin Endocrinol (Oxf). July 1, 2013 [Epub ahead of print].

SUMMARY

Background

It has previously been shown that smoking increases the risk for Graves' disease and for Graves' ophthalmopathy (1,2). However, relationships between smoking and hypothyroidism have been inconsistent across studies. Smoking cessation was recently observed to be associated with a transiently increased risk for autoimmune hypothyroidism (3). The goal of this study was to determine associations between maternal smoking in pregnancy and the subsequent risk for thyroid dysfunction in a large population sample.

Methods

This retrospective study was performed using data from linked Danish registries. All children born in Denmark between 1996 and 2008 were identified using a national birth registry. Maternal thyroid dysfunction and smoking status were ascertained using the Danish National Hospital Register, which includes inpatient and outpatient diagnosis codes. The Danish National Prescription register was used to obtain information about prescriptions for thyroid hormone and antithyroid drugs dispensed between 2005 and 2008. Hyperthyroidism was defined as a first-time hospital diagnosis of hyperthyroidism with prescription of an antithyroid medication or at least two dispensed prescriptions of antithyroid medication. Similarly, hypothyroidism was defined as a first-time hospital diagnosis of hypothyroidism with at least one thyroid hormone prescription or at least two prescriptions of thyroid hormone without any antithyroid medications. Sociodemographic information was obtained from Statistic Denmark. Area of residence was used as a proxy for dietary iodine status. Cox proportional-hazards models were used to determine the risk of incident hyperthyroidism and hypothyroidism in smoking versus nonsmoking mothers, stratified by age, amount of smoking, and area of residence.

Results

A total of 450,842 mothers (mean age, 29 years) were included in the analyses, of whom 19.7% smoked during the first pregnancy within the study period. Overall, 2.9% of women had thyroid dysfunction during the study period. Following pregnancy, hyperthyroidism developed in 1.03% of smokers and 0.68% of nonsmokers (P<0.001) over a mean follow-up of 4.2 years. After pregnancy, hypothyroidism developed in 1.27% of nonsmokers and 1.03% of smokers (P<0.001). The protective effects of smoking on hypothyroidism risk were most marked within the 2 years following delivery; (hypothyroidism developed in 0.35% of nonsmokers and 0.18% of smokers within 2 years; P<0.001) and in younger mothers (hazard ratio [HR], 0.54 [95% CI, 0.43 to 0.68] in women under age 30 and 0.78 in women older than 30 [95% CI, 0.70 to 0.86]). The risk of hyperthyroidism was increased in older mothers who smoked (HR, 1.26 [95% CI, 1.13 to 1.40] for women under age 30; and HR, 1.51 [95% CI, 1.35 to 1.69] for women 30 years or older). Smoking increased the risk for both Graves' disease (HR, 1.44; 95% CI, 1.28 to 1.62) and toxic nodular goiter (HR, 1.60; 95% CI, 1.16 to 2.21). Iodine status did not alter any of these associations.

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Smoking in Pregnancy Increases Subsequent Maternal Hyperthyroidism Risk but Protects Against Subsequent Hypothyroidism

Elizabeth N. Pearce

Conclusions

Smoking among pregnant women increases the risk for the subsequent development of hyperthyroidism, but it appears to protect against the subsequent development of hypothyroidism.

ANALYSIS AND COMMENTARY

A major strength of this study is the very large sample size. Future studies are needed to determine whether effects of smoking on the risk for thyroid dysfunction are durable over a longer follow-up period and how changes in smoking behavior affect thyroid risk. This study did not address any effects of maternal smoking on fetal or neonatal thyroid function.

These results are in accordance with previous data demonstrating that smoking is a risk factor for the exacerbation of Graves' hyperthyroidism. The mechanisms for this remain unknown. Thiocyanate, a metabolite of cigarette smoke, is an inhibitor of the sodium iodide symporter. Therefore, smoking might have been expected to increase the risk for hypothyroidism, especially in iodine-deficient women. Surprisingly, smoking appeared to protect against the development of hypothyroidism in this cohort. Although antithyroid antibodies were not assessed in this study, smoking has previously been associated with a decreased risk for thyroid autoantibody positivity (4), which may be the reason for the protective effect against hypothyroidism.

How should these data alter clinical practice? Although the proportion of U.S. women who smoke during pregnancy has decreased substantially over the past two decades, in 2005, a total of 10.7% of U.S. pregnant women were still smokers (5). There are many reasons to counsel against smoking during pregnancy apart from the increased risk for hyperthyroidism, including increased risks for low-birthweight infants, preterm delivery, and infant death (6). Providers should be particularly alert to signs and symptoms of hyperthyroidism among women who smoke during pregnancy, especially within the first 2 years after delivery.

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Prepregnancy Care and Patient Education Are Essential in Women with Thyroid Disease in Order to Prevent Pregnancy Complications

Jorge H. Mestman

Männistö T, Mendola P, Grewal J, Xie Y, Chen Z , Laughon SK. Thyroid diseases and adverse pregnancy outcomes in a contemporary US cohort. J Clin Endocrinol Metab 2013;98:2725-33. Epub June 6, 2013.

SUMMARY

Background

Thyroid diseases are inconsistently reported to increase the risk for pregnancy complications. The objective of these authors was to study pregnancy complications associated with common and uncommon thyroid diseases.

Methods

Thyroid disease diagnosis (history of thyroid disease) and outcomes were derived from both electronic medical records and discharge summaries. Medication and laboratory data were not available. The authors analyzed singleton pregnancies (n = 223,512) from a retrospective U.S. cohort, the Consortium on Safe Labor (2002–2008). Multivariable logistic regression with generalized estimating equations estimated adjusted odds ratios (ORs) with 99% CIs. Main outcome measures included hypertensive diseases, diabetes, preterm birth, cesarean sections, inductions, and intensive care unit (ICU) admissions.

Results

Controls were pregnant women with no thyroid disease (n = 216,901). Primary hypothyroidism (n = 3183, 1.5% of pregnancies) was associated with increased odds of preeclampsia (OR, 1.47), superimposed preeclampsia (OR, 2.25), gestational diabetes (OR, 1.57), preterm birth (OR, 1.34), induction of labor (OR, 1.15), cesarean section (prelabor, OR, 1.31; after spontaneous labor, OR, 1.38), and ICU admission (OR, 2.08). Iatrogenic hypothyroidism due to thyroid surgery or ablation (n = 178, 0.1% of pregnancies) was associated with increased odds of placental abruption (OR, 2.89), breech presentation (OR, 2.09), and cesarean section after spontaneous labor (OR, 2.05). Hyperthyroidism (n = 417, 0.2% of pregnancies) was associated with increased odds of preeclampsia (OR, 1.78), superimposed preeclampsia (OR, 3.64), preterm birth (OR, 1.81), induction of labor (OR, 1.40), and ICU admission (OR, 3.70).

Conclusions

Thyroid diseases were associated with obstetrical, labor, and delivery complications. Although the authors lacked information on treatment during pregnancy, these nationwide data suggest either that there is a need for better thyroid disease management during pregnancy or that there may be an intrinsic aspect of thyroid disease that leads to poor pregnancy outcomes.

ANALYSIS AND COMMENTARY

Thyroid diseases are not uncommon in women of reproductive age, with an estimation of 5% to 15% of women being affected, depending on geographic area, method of detection, and other, unknown, factors. Euthyroid chronic thyroiditis is the most common thyroid condition, frequently suspected in the presence of a concomitant autoimmune disease,

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Prepregnancy Care and Patient Education Are Essential in Women with Thyroid Disease in Order to Prevent Pregnancy Complications

Jorge H. Mestman

a family history of thyroid disease, or palpation of a goiter and confirmed by the presence of serum TPOAb or TgAb. About 3% to 5% of patients with thyroiditis suffer from thyroid dysfunction, mainly subclinical hypothyroidism. In the majority of cases, this is detected during pregnancy if thyroid tests are ordered routinely. Universal screening for thyroid disease in pregnancy is controversial, but thyroid studies are strongly recommended at the time of the first obstetrical visit for women diagnosed with thyroid dysfunction before pregnancy, those on thyroid replacement therapy, and women with risk factors such as a family history of thyroid disease, autoimmune diseases, presence of goiter, and others (1,2). In the past two decades, numerous publications reported maternal, fetal, and neonatal complications and long-term neuropsychological deficits in children of mothers not properly diagnosed and treated during pregnancy. More alarming is the fact that 50% of women on thyroid replacement therapy have a serum TSH in the hypothyroid reference range when tested during pregnancy (3). The increase in demand for thyroid hormone in pregnancy is very well known, and due mainly to the stimulation of thyroid function by human chorionic gonadotropin (4). A recent paper showed that 80% of women with hypothyroidism who are on levothyroxine therapy before conception achieved a serum TSH within the reference range for gestational age, if the serum TSH within 6 months of conception was less than 1.2 mIU/L, as compared with women with a serum TSH above 1.2 mIU/L (5). Encouraging reports recently published appeared to indicate that correction of maternal hypothyroidism in the second half of pregnancy achieved normal cognitive outcome in the offspring (6,7). The authors of the present study collected data limited to pregnancy outcome in a large multicenter study in women with a history of thyroid disease; however, no information on thyroid status was available at either conception or delivery. As recognized by the authors, the strengths of the study are its large size and comprehensive data collection from the hospital medical records from the intrapartum admission, allowing for the evaluation and adjustment for important confounding factors. In spite of the limitation in diagnostic and treatment data, the incidence and type of complications are similar to the ones reported in the literature.

Several studies in pregnant women with clinical hyperthyroidism and hypothyroidism showed that normalization of thyroid dysfunction has an impact in decreasing maternal and fetal complications. In this regard, the importance of prepregnancy education in our patients with thyroid disease is imperative; the endocrine community has educated women with prepregnancy diabetes about the importance of planning their pregnancies and achieving the best hemoglobin A1c values possible before conception, with a very successful result in reducing congenital malformations and other pregnancy complications. It is my opinion that the same approach should be used for women with thyroid disease, even if they are not contemplating pregnancy, keeping in mind that over 50% of pregnancies are unplanned. This educational approach should include women: (a) with active hyperthyroidism (contraception until euthyroidism is achieved); (b) on levothyroxine therapy, to achieve a serum TSH target close to 1 mIU/L before conception; (c) with euthyroid chronic thyroiditis, considering levothyroxine therapy if the preconception serum TSH is >1.5 mIU/Lml; and (d) with risk factors for thyroid disease, offering a determination of thyroid tests (including both, TSH and TPOAb). In addition, these women should have thyroid-function tests at the time of pregnancy diagnosis and regularly throughout pregnancy and postpartum as clinically indicated. This approach should reduce pregnancy complications and prevent late offspring neurocognitive dysfunction.

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Is Osteopontin a Good Marker for Graves' Disease?

Stephen W. Spaulding

Qi Y, Li X, Ma X, Xu L, Zhang X, Jiang X, Hong J, Cui B, Ning G, Wang S. The role of osteopontin in the induction of the CD40 ligand in Graves' disease. Clin Endocrinol (Oxf). April 26, 2013 [Epub ahead of print]. doi:10.1111/cen.12229.

SUMMARY

Background

CD40 is a receptor expressed on various antigen-presenting cells, such as the B cell. If a B cell presents an antigen recognized by an activated CD4+ T cell, the ligand for CD40 (CD40L) that becomes expressed on the T-cell stimulates the B cell to multiply and form plasma cells that produce copious amounts of antibody against the target antigen (for example, the TSH receptor). CD40L can be expressed on the surface of many cell types and also can be partly cleaved by proteases and released into the circulation. Both the surface-bound and the soluble forms of CD40 ligand have biologic activity. CD40, a member of the tumor necrosis factor (TNF)–receptor family, also has been detected on thyrocytes, and a single-nucleotide polymorphism in the CD40 gene may increase the risk of Graves' disease. Thus, understanding how CD40/CD40L interactions are regulated may help in understanding the pathophysiology of Graves' disease.

Osteopontin (not to be confused with osteocalcin) is a cytokine associated with many autoimmune and chronic inflammatory diseases. It can bind to cells via several surface receptors, including beta integrins on T cells, and it promotes the migration of lymphocytes and their production of cytokines. The authors of the current article previously showed that the level of osteopontin was elevated in Graves' disease and was closely associated with Graves' disease activity, prompting them to suggest that it could be a biomarker for active Graves' disease (1). In the present article, they examined the effects of plasma from patients with Graves' disease—and the effects of synthetic osteopontin—on the expression of CD40L in plasma and on CD4+ T cells, and on the production of immunoglobulins by peripheral-blood mononuclear cells (PBMCs).

Methods

Blood from 40 patients with active Graves' disease, 21 patients with Graves' disease in remission after 6 months of MMI treatment, and 27 healthy subjects was drawn into EDTA-containing tubes on ice and immediately centrifuged to obtain platelet-free plasma. The level of CD40L expressed on the surface of CD4+ T cells (prepared from PBMCs) was measured using flow cytometry. The levels of soluble CD40L and osteopontin were measured by ELISA and were correlated with laboratory measures of Graves' activity. PMBCs were incubated for a day with normal plasma, with plasma from patients with untreated Graves' disease (final dilutions, 1:4), or with recombinant human osteopontin, and also with anti-osteopontin or control antibody. The surface expression of CD40L on CD4+ T cells was then assessed by flow cytometry on the PBMCs. Other PBMCs were incubated with the same agents for 12 hours, and the level of CD40L mRNA was measured by RT-PCR on CD4+ T cells obtained by flow cytometry. Still other PBMCs were incubated with osteopontin with or without anti-CD40L monoclonal antibody, and after 10 days' culture, the incubation media were analyzed for IgG and IgM levels.

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Results

The levels of both soluble and membrane-bound CD40L were 3 times as high in patients with active Graves' disease as in patients in remission or in normal controls. The plasma level of osteopontin correlated closely with the level of soluble CD40L. Both the plasma level of CD40L and that of osteopontin correlated positively with free T_4, free T_3, anti-TPO, anti-Tg, and anti-TSH-receptor levels and correlated negatively with TSH levels. For membrane-bound CD40L, the correlations were similar, except that those with anti-TPO and anti-Tg were not significant and the correlation with osteopontin was not as tight. The mean basal expression of membrane-bound CD40L on CD4+ T cells from patients with active Graves' disease was about twice that in controls (5 in each group). Treating these CD4+ T cells with osteopontin or with plasma from patients with active Graves' increased the surface expression of CD40L, whereas adding a monoclonal antibody against osteopontin blocked the responses. The levels of mRNA encoding CD40L responded similarly to these combinations of agents. The secretion of IgG was about 50% greater in the medium from unstimulated Graves' PBMCs as compared with control cells. Stimulation with osteopontin increased IgG levels by about 70% in the medium from Graves' PBMCs and about 60% in controls. Baseline IgM levels were about twice as high in Graves' cell media than in controls. Osteopontin stimulated IgM levels 7-fold in medium from Graves' PBMCs and 2.5-fold in controls. Adding anti-CD40L antibody blocked the IgG and IgM responses to osteopontin.

Conclusions

Plasma osteopontin levels correlate positively with anti-TSH-receptor antibody levels and negatively with TSH levels in patients with Graves' disease. Adding osteopontin or plasma from patients with active Graves' disease to CD4+ T cells increases both the membrane expression and the mRNA for CD40L, whereas adding anti-osteopontin monoclonal blocks these responses. Osteopontin induces a rise in CD40L that in turn increases the production of immunoglobulins from PBMCs.

ANALYSIS AND COMMENTARY

The plasma level of osteopontin may not be a very selective biomarker for Graves' disease, because in addition to its connection with bone turnover, it can also be regulated by hypoxia, transforming growth factor β, TNF-α, interleukin-1β, angiotensin II, nitric oxide, and hyperglycemia. Furthermore, a recent study found serum osteopontin levels to be increased in hyperthyroidism but to be decreased in hypothyroidism (2), and experimental studies indicate that osteopontin levels rise and fall together with the thyroid hormone level, so the current findings probably reflect the altered thyroid hormone levels rather than Graves' disease per se. In view of the fact that multiple isoforms of osteopontin (and CD40L) exist, their roles probably deserve further exploration. Nonetheless, the increased level of osteopontin could well be connected with some of the effects of Graves' disease on the skeletal, adipose, and cardiovascular systems.

The same research group also recently reported that the plasma level of the cytokine CCL20 is increased in Graves' disease (3). The CCL20 level correlated with plasma osteopontin levels, and recombinant osteopontin increased expression of CCL20 mRNA in CD4+ T cells. Adding plasma from patients with untreated Graves' disease increased the CCL20 expression 3-fold as compared with normal plasma, and this response was blocked by antibodies to osteopontin as well as to β3 integrin (a receptor for osteopontin) and also by inhibitors of the nuclear factor κB and mitogen-activated protein kinase pathways. The authors again suggest that CCL20 could be a biomarker for Graves' disease. In passing, one might note that both osteopontin and CCL20 have been reported to be overexpressed in RET/PTC papillary thyroid cancer, suggesting a possible connection with the recently discussed report of increased aggressiveness of cancers associated with Graves' disease (4).

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BOOK REVIEW: The 10th Edition of Werner & Ingbar's Thyroid Is Outstanding

Malika Chowdhry

Book Review of: Braverman LE, Cooper D, eds. *Werner & Ingbar's The Thyroid: A Fundamental and Clinical Text, 10th ed.* Philadelphia: Lippincott Williams and Wilkins, 2013.

Werner & Ingbar's The Thyroid: A Fundamental and Clinical Text is a well-known reference book and can probably be seen on the shelves of most endocrinologists today. In the new 10th edition, the authors and editors have continued the tradition of putting together a comprehensive book with a fresh new look.

The book is divided into two general sections. The first section discusses the thyroid anatomy and development, thyroid hormone synthesis and function, and the thyrotropin receptor and its regulation. This section explores topics in basic science but also incorporates clinical medicine to keep the reader engaged. The next section details the various thyroid diseases in depth, along with the management of these diseases. The book also dedicates a large section to the various aspects of thyroid cancer, including epidemiology, genetics, staging, prognosis, and medical management. This textbook even provides details about thyroid disease during pregnancy and in infants and children.

The figures, graphs, and tables complement the text well and aid the reader in understanding the contents of the chapters. The chapter on thyroid disorders during pregnancy is quite comprehensive and has an excellent summary of the text in tables, which make it easy to use as a reference at a later time. In the chapter about the effects of drugs on TSH secretion, the figure that accompanies the text breaks down the effects of different drugs on TSH inhibition, T_4 absorption, synthesis, secretion, transport, and metabolic abnormalities. This not only provides a summary of the drugs but also gives the reader a visual aid to better understand the mechanisms at different levels of the thyroid axis.

The chapter on the molecular genetics of tumors of the thyroid follicular cells is very detailed but is divided well into subsections. The reader who chooses to read only a certain section will be thoroughly educated on that topic without having to read the rest of the chapter, as each section is self-contained. The chapter describes basic oncogenic pathophysiology and ties it in with thyroid cancer, which makes it easy to understand the basic pathophysiology of thyroid cancer.

The thyroid pathology and cytopathology chapter is particularly well written, with excellent descriptions of the various thyroid diseases. However, some of the images fail to complement the description in the text because they are not in color. Color images would better elucidate the descriptions in the text.

Each book is only as good as its authors and the references used by them. The editors have done an outstanding job of recruiting national and international experts in special areas of thyroidology as authors, resulting in content that is extremely thorough. The authors have used a combination of old and new references to ensure that the information in the book is up to date and yet does not overlook seminal articles. The new references incorporate changes in the field

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of thyroidology over the past few years. Even though the writing styles are different from one chapter to the next, the overall flow of the book is still consistent throughout. The new edition has many new authors. Some of them wrote entirely new chapters and others updated various other chapters. New chapters include surgical management of thyroid cancer and thyroid hormone analogs.

The true test of a reference or book is its utility in answering a query when a clinical question arises. While I was on inpatient medicine, I received a consult about a patient in the ICU with thyroid-function test abnormalities. I was able to go to the nonthyroidal illness chapter in the book and use it as a resource to answer my question. The text was accompanied by very descriptive figures, for visual learners, which made it easy to understand the concepts written in the text. In another instance, I was asked about the causes of congenital hypothyroidism, and I was able to quickly look through the chapter on this topic to answer the question.

As a second year endocrinology fellow, I belong to a generation that grew up reading online journals and articles to obtain most of my medical information. In an era in which online texts and journals are the source of most of our learning and references, books seem a thing of the past. However, it is nice to have a book that is easy to read, yet comprehensive, and can serve as a reliable reference. The text comes with access to the complete contents online and is fully and effectively searchable this way. In most chapters, the text is reiterated in the form of tables or charts that which make the material much easier to recall and reference.

This book is aimed at a large audience, including internists, clinical endocrinologists, and endocrinology fellows. However, I believe it will be most useful to practicing endocrinologists as well as those in training. It is a great resource for endocrinology fellows who are trying to learn about molecular genetics, cytology, and pathophysiology of thyroid diseases along with the management of most thyroid diseases.

Overall, this book is comprehensive without being overbearing or hard to read. As this is an all-inclusive book about the thyroid, there are a few sections that are burdensome to read, but that is true of any book that contains as much detail as this book does. Nonetheless, it provides information that would be useful for every reader, from a general practitioner to a seasoned endocrinologist. It is a well-balanced book that does not focus on either pathophysiology or medical management but has a good balance of both. I highly recommend this new edition for endocrinologists, especially endocrinology fellows, because even though there are many endocrinology texts available to us, no other thyroid book is as comprehensive as *Werner & Ingbar's The Thyroid*.

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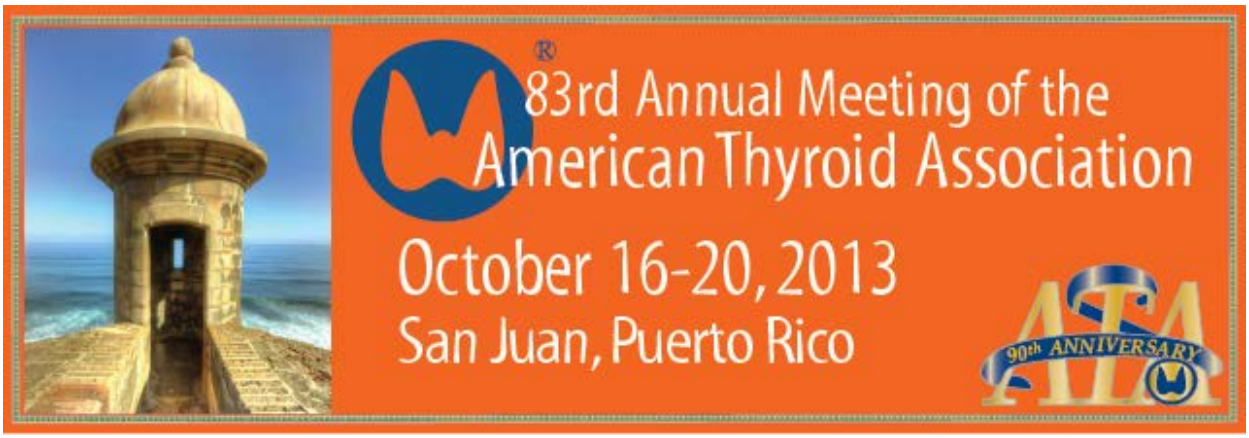

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