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Meta-analysis of Studies of Thyroidectomy Specimens Shows a Positive Correlation between Papillary Thyroid Carcinoma and Hashimoto's Thyroiditis

Karen T. Le, Bojana Jankovic, and Jerome M. Hershman

Lee JH, Kim Y, Choi JW, Kim YS. The association between papillary thyroid carcinoma and histologically-proven Hashimoto's thyroiditis: a meta-analysis. Eur J Endocrinol. December 4, 2012 [Epub ahead of print].

SUMMARY

Background

Hashimoto's thyroiditis (HT) is found in a high proportion of resected thyroid specimens. There has been considerable controversy as to whether having HT predisposes a patient to papillary thyroid cancer (PTC). This study is a meta-analysis designed to clarify the relationship between PTC and histologically demonstrated HT and to investigate the clinical and pathologic features of PTC with coexistent HT.

Methods

The authors performed an extensive literature search for articles that had primary data showing an association of PTC and "classical HT" based on histopathologic examination of thyroid specimens. Articles lacking pathologic data were excluded. On the basis of these criteria, 38 studies were selected for the meta-analysis.

Odds ratios (OR) with 95% confidence intervals (CI) were calculated and combined using a random-effects model.

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Results

The 38 studies consisted of 37 case–control studies and one cohort study. The number of patients in each study ranged from 6 to1788, with a total of 10,648 PTC cases. Only 11 studies compared the frequency of HT in cases of PTC and benign thyroid disease. HT was found in 938 of 2317 (40.5%) of PTC cases and in 634 of 3019 (21%) of benign cases (OR, 2.77;95% CI, 1.95 to 3.93; P<0.001) for the coexistence of HT with PTC, but there was significant statistical heterogeneity among the studies.

In 16 studies comparing the prevalence of HT in PTC and in other thyroid cancers (follicular and medullary), HT was found in 17% of patients with PTC and in only 8% of patients with the other thyroid cancers (OR, 2.43 for the comparison; 95% CI, 1.61 to 3.66; P<0.001). HT with PTC was found in 23% of female patients and in 11% of male patients (OR, 2.678; 95% CI, 1.755 to 4.087; P<0.001). HT in PTC was not associated with the age of the patient or with the size of the tumor. Recurrence-free survival outcomes were provided in four studies including 616 patients who had PTC with HT and 4241 patients who had PTC without HT; HT in PTC was significantly associated with a longer duration of recurrence-free survival (hazard ratio, 0.576; 95% CI, 0.421 to 0.790; P = 0.001).

Conclusions

The meta-analysis showed that papillary thyroid cancer is significantly associated with pathologically confirmed Hashimoto's thyroiditis.

ANALYSIS AND COMMENTARY

The relationship between Hashimoto's thyroiditis and PTC has been a subject of considerable controversy for many decades. The authors of this meta-analysis suggest that PTC is significantly associated with pathologically confirmed HT. Although the incidence of HT is increased in patients with PTC, there has been no evidence suggesting a cause–effect relationship between the two entities. Paradoxically, patients with PTC and concurrent HT have significantly favorable outcomes. Could the immune reaction have a tumor-retarding effect on the PTC instead of being a predisposing factor?

The present study, though comprehensive, has a few shortcomings. It analyzed patients with already diagnosed PTC and calculated the frequency of HT in these cases. It does not explore the risk of PTC developing in patients with HT. Thus, the design of the study creates a considerable bias due to patient selection. The study population consisted of only cases of thyroidectomy, which is not reflective of the general outpatient population.

A retrospective study found that of 10,508 patients referred to an outpatient service for FNA, there was no statistically significant difference in the frequency of observed PTC in patients who had HT versus those who did not have HT (1.9% vs. 2.7%) (1). A prospective study of FNA specimens reported no significant difference between the incidence of PTC in patients who had HT versus those who did not have HT (2). Of 191 nodules from 164 patients with histologically diagnosed HT, only 1% were malignant, similar to the 2.7% malignancy rate in 713 nodules in 551 patients without HT (P = 0.279) (2). We conducted a recent literature review and found that the prevalence of PTC in HT is significantly higher among thyroidectomy specimens than among FNA specimens (3). The average prevalence rate of PTC in patients with HT was 1.2% (range, 0 to 2.95) in FNA studies of 18,023 specimens and 27.6% (range, 9.5 to 36.60) in archival thyroidectomy studies of 9884 specimens (3). It appears to us that the FNA studies are more applicable to the population of patients with HT.

Another limitation is the statistically significant heterogeneity between the studies in this meta-analysis

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based on the Q values provided. The authors of the present study sought to examine the clinical behavior of PTC with coexisting HT by investigating sex, age, tumor size, tumor extension, lymph-node metastasis, multifocality, and survival analysis. Among seven clinicopathologic characteristics, survival analysis and tumor extension were the only two that did not have significant heterogeneity, allowing valid conclusions to be reached.

There were two study results that appear to be inconsistent with the conclusions presented by the authors: the results pertaining to tumor extension and lymph-node metastasis. HT was found in 17.5% of 4128 PTCs without extrathyroidal extension and in 17.2% of 2897 PTCs with extrathyroidal extension. The authors concluded that the coexistence of HT in PTCs was associated with no extrathyroidal involvement. However, the equal prevalence of HT in PTC with and without extrathyroidal extension suggests no relationship. Similarly, HT was present in 17.8% of 4185 PTCs without lymph-node metastasis and in 17.9% of 3462 PTCs with lymph-node metastasis, suggesting no relationship. However, the authors concluded that there was a positive relationship between the coexistence of HT and PTC and the absence of lymph-node metastasis.

This is the second largest meta-analysis to evaluate the association between PTC and HT. It provides a detailed review of the literature about the ongoing debate. However, studies of archival thyroidectomy specimens should be interpreted with caution. Although they provide valuable information about the correlation between the two entities, a significant positive association appears to be observed only in this high-risk population of patients whose disease state leads to a thyroidectomy. We suggest that this association in archived thyroidectomy specimens should not be used in making a decision about management of a thyroid nodule in a patient with Hashimoto's thyroiditis. Instead the decision should be based, as usual, on the result of the FNA cytopathology.

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Generic and Branded Levothyroxine Preparations Are Not Bioequivalent in Children with Congenital Hypothyroidism

Elizabeth N. Pearce

Carswell JM, Gordon JH, Popovsky E, Hale A, Brown RS. Generic and brand-name L-thyroxine are not bioequivalent for children with severe congenital hypothyroidism. J Clin Endocrinol Metab. December 21, 2012 [Epub ahead of print].

SUMMARY

Background

Generic substitution of levothyroxine (L-T_4) products determined to be bioequivalent by the Food and Drug Administration (FDA) is allowed in the United States. Bioequivalence is determined based on short-term pharmacokinetic studies of serum T_4 levels—and no assessment of chronic TSH responses—in healthy adult volunteers, a method that may not be adequately sensitive (1). It is known that in infants with severe congenital hypothyroidism, even small decrements in thyroid hormone may be associated with adverse developmental outcomes (2). Few clinical studies have been performed to date to determine whether generic and branded L-T_4 are truly bioequivalent in patients with hypothyroidism.

Methods

This was a prospective, unblinded, randomized, crossover trial. Study participants included 31 children and adolescents 3 to 18 years of age with known overt hypothyroidism (serum TSH concentration at diagnosis, >100 mIU/L). Twenty of the children had congenital hypothyroidism, while the rest had Hashimoto's thyroiditis with positive antithyroid antibodies. At baseline, all participants had maintained a normal serum TSH for at least 4 weeks on their usual L-T_4 formulation. Patients with gastrointestinal disease that could affect L-T_4 absorption or who were taking medications that could interfere with L-T_4 absorption or metabolism were excluded. One patient was excluded for failure to come to clinic visits. Participants were assigned to receive their usual L-T_4 dose as Synthroid (Abbott Laboratories) for 8 weeks and as the AB-rated generic (Sandoz) L-T_4 for 8 weeks; the sequence of the two treatments was randomly determined. Serum TSH, free T_4, and total T_3 at the end of each 8-week treatment period were compared for each subject. An intention-to-treat analysis was used.

Results

The serum TSH was significantly lower (0.7 mIU/L vs. 1.8 mIU/L, P = 0.002) after 8 weeks of Synthroid than after 8 weeks of the generic L-T_4; this difference remained significant after adjustment for age. Subgroup analyses determined that this difference was seen only in children with congenital hypothyroidism. In the children with Hashimoto's disease, TSH did not differ between branded and generic L-T_4. Results did not differ depending on whether generic or branded L-T_4 was administered first. There were no differences in free T_4 or total T_3 following each treatment period. Results did not differ when two patients who had been noncompliant with therapy were excluded from analyses.

Conclusions

This study demonstrates that Synthroid and generic Sandoz L-T_4 were not bioequivalent in children with congenital hypothyroidism, despite being deemed by the FDA to be interchangeable. The children with congenital hypothyroidism, at least 15 of whom had thyroid dysgenesis, may have been less able to compensate for a slight reduction in L-T_4 because of limited thyroid reserve.

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ANALYSIS AND COMMENTARY

A major strength of the study was its prospective, randomized, interventional design. Study participants served as their own controls, which minimizes concerns about confounding. A limitation is the relatively small sample size; only 20 children with congenital hypothyroidism were studied.

Further research is needed to confirm these results and to determine whether they apply to other vulnerable populations, such as patients with athyreotic thyroid cancer. However, in light of these findings it would seem prudent to avoid substitution of L-T_4 products, especially in young children with severe congenital hypothyroidism and in other patients with hypothyroidism in whom alterations of the thyroid hormone level could have particularly deleterious effects. These data lend fresh support to the positions of the American Thyroid Association, The Endocrine Society, and the American Association of Clinical Endocrinologists that different L-T_4 formulations deemed interchangeable by the FDA may not be truly bioequivalent and that thyroid-function testing for dose titration is essential if formulations are changed (3).

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Is Serum TSH Not the Gold Standard for Thyroxine Treatment?

Albert G. Burger

Hoermann R, Midgley JE, Larisch R, Dietrich JW. Is pituitary thyrotropin an adequate measure of thyroid hormone-controlled homeostasis during thyroxine treatment? Eur J Endocrinol. November 26, 2012 [Epub ahead of print].

SUMMARY

Background

This article is complementary to several recent articles, one from the authors of the current article and one recently reviewed by me in Clinical Thyroidology (1-3). The authors raise the question of whether the current approach, monitoring thyroxine treatment with the serum TSH alone, is adequate. To answer this question, they studied serum FT_4 and FT_3 levels in thyroxine-treated patients and compared them with those of untreated subjects.

Methods

The study was done between October 2006 and January 2007. The first blood samples of 1994 patients seen in a thyroid clinic were studied. The median age of the patients (predominantly women) was 61 years. Thyroid antibodies were not measured routinely. A total of 1059 patients were untreated—they did not receive any thyroid hormone or other drug treatment; 50 patients were given iodine supplementation alone (100 to 200 µg per day). Of the 190 patients with hypothyroidism, only 53 (28%) had autoimmune disease; in the rest of the group, hypothyroidism was due to surgery and radioactive iodine treatment.

The patients were treated with 50 to 200 µg of levothyroxine daily. Subclinical hyperthyroidism was defined by a serum TSH below the reference range (<0.2 mU/L) and FT_4 and FT_3 in the reference range. A complex mathematical model postulated interference of various factors, among which the deiodinases were prominent.

Results

The authors confirmed their earlier work and the remarkable work of Ito et al. (1). In T_4-substituted subjects, serum FT_3 levels are low as compared with those of untreated patients with an equal serum TSH value. They used complex mathematical correlations that showed that for a given serum TSH, FT_3 values were clearly lower than those in control subjects. Obviously, serum FT_4 levels were higher in control subjects than in levothyroxine-treated subjects for a similar TSH. Based on their mathematical program, these authors postulated that the deiodinases (types 1 and 2) in the pituitary are still functioning, with high T_4 levels resulting in an inhibited serum TSH. According to the authors, under thyroxine treatment the peripheral deiodinases are less active, resulting in lower FT_3 levels as compared with the serum TSH in normal subjects.

Conclusions

In a group of levothyroxine-treated patients with serum TSH from 0.2 to 4 mU/L, the levels of serum FT_3 are below the normal reference range of healthy subjects. The authors conclude that in patients undergoing thyroxine substitution, TSH cannot be considered to be the gold standard of adequate substitution. Based on the mathematical program, they postulate that deiodinases type 1 and 2 are more effective in the pituitary than in the periphery.

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ANALYSIS AND COMMENTARY

This article is highly based on mathematical considerations. Most clinicians, including myself, are not capable of understanding the mathematical part of the article. Nevertheless, the present work is confirmatory of many earlier reports, some dating back 15 years.

It is well established that in normal subjects, 15% to 20% of the circulating T_3 is directly secreted from the thyroid. In hyperthyroidism, this percentage is even higher. Thyroxine treatment lacks this contribution to the circulating T_3. This is so well recognized that approximately 20 years ago a patent was granted for a slow release T_3 that would have overcome the problem of the relatively short half-life of triiodothyronine (Cytomel). Yet the compound was never developed. One could argue that with a combined thyroxine and slow-release T_3 treatment, patients with hypothyroidism could be monitored not only according to their serum TSH but also according to their FT_3 and FT_4 values. This would be particularly adequate in patients who were euthyroid before thyroidectomy, whose own serum values could be used as an individual reference range. However, this argument falls short by not taking into consideration the normal fluctuations of serum T_3 values due to many nonthyroidal factors, such as fasting, disease, iodine supply, and depression. At present, there are no objective criteria comparing the true value of the two treatments, since we have no objective tests measuring clinically subtle but potentially relevant differences.

From their mathematical program, the authors infer differences between peripheral and pituitary deiodinases. This is not well documented. It is much more likely that the lack of thyroidal secretion of T_3 explains the difference. Also, all mathematical programs can produce results only from the data that were put into them. TSH control cannot be explained by deiodinases. Leptin, transporters of T_4 and T_3, and such are only some examples of other possible factors affecting the regulation of serum TSH.

As stated in my recent review (3), I believe that for practical reasons thyroxine treatment alone of patients in need of thyroid hormone replacement is adequate. I do not exclude the occasional use of a combination of thyroxine and triiodothyronine in an exceptional patient.

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A Survey of Management of Uncomplicated Graves' Disease Shows that Use of Methimazole Is Increasing and Use of Radioactive Iodine Is Decreasing

Jerome M. Hershman

Burch HB, Burman KD, Cooper DS. A 2011 survey of clinical practice patterns in the management of Graves' disease. J Clin Endocrinol Metab 2012;97:4549-58. Epub October 5, 2012; doi: 10.1210/jc.2012-2802.

SUMMARY

Background

In 2011, the authors performed a survey of the management of Graves' disease by members of various endocrine societies here and abroad. The results were compared with those of a similar survey published in 1990 (1).

Methods

The survey was administered by a Web-based commercial survey management service. The target groups were members of the American Thyroid Association (ATA), The Endocrine Society (TES), and the American Association of Clinical Endocrinologists (AACE). The index case was the same as the patient used in the 1990 survey (1): A 42-year-old woman presents with moderate symptoms of hyperthyroidism of 2 months' duration. She is otherwise healthy, takes no medications, has two children, and does not plan on becoming pregnant again. This is her first episode of hyperthyroidism. She has a diffuse goiter, approximately two to three times normal size, a pulse rate of 105, and a normal eye examination. Thyroid hormone levels are found to be twice the upper limit of normal with an undetectable TSH level. The questions focused on management with regard to both diagnosis and therapy. A variation of the case included a patient with concurrent ophthalmopathy; another variation was a 22-year-old woman with hyperthyroidism who planned to become pregnant in 6 to 12 months.

Results

There were 730 respondents, including 162 members of ATA, 648 of TES, and 333 of AACE, many having dual membership in the societies. Sixty-one percent of the respondents were from North America. Ninety-two percent ran adult endocrinology practices. With regard to additional diagnostic tests, 58% would measure TSH-receptor antibodies, 47% would measure RAI uptake, and 27% would obtain thyroid ultrasound scans.

A beta-adrenergic blocker was used by 92%. For primary therapy, 54% preferred antithyroid drugs (ATDs), 45% preferred RAI, and only 1% preferred thyroidectomy. In North America, 59% would choose RAI, as compared with 69% in 1990. In Europe, Latin America, and Asia-Oceania, 86%, 74%, and 71%, respectively, opted for ATDs. With regard to the choice of ATDs, 83.5% would use methimazole, 13.8% carbimazole, and only 2.7% propylthiouracil (PTU), whereas in 1990, 73% selected PTU. With regard to the duration of ATD therapy, 19.3% would treat for 24 months, 35.4% for 18 months, 30.2% for 12 months, and 13.9% for less than 1 year.

With regard to pretreatment of patients with ATD before RAI, 49% used this only in selected patients, 13% never did this, and 38% did this routinely.

In the presence of Graves' ophthalmopathy, 63% would use prolonged therapy with ATDs, 18% selected thyroidectomy, 17% selected RAI with prophylactic corticosteroids, and only 2% used RAI alone.

For the primary treatment of the 22-year-old woman with hyperthyroidism who planned to become pregnant in 6 to 12 months, 50% preferred prolonged

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ATD therapy, 30% would use RAI, and 20% would use thyroidectomy. Of those recommending ATD, 54% would use PTU and 46% would use methimazole and switch to PTU when pregnancy was confirmed.

Conclusions

During the past two decades, there has been a shift away from RAI and toward ATDs for treatment of patients with uncomplicated Graves' disease.

ANALYSIS AND COMMENTARY

Although the authors noted that only a small proportion of the members of the various societies participated in the survey, 730 is a substantial number of responses from clinical endocrinologists, and these clinicians probably have a strong interest in the management of Graves' disease. I am one of them.

The changes in practice during the past 20 years are substantial and based on several influential studies noted below. There has been a shift away from RAI and toward ATDs for therapy of uncomplicated Graves' disease, although most U.S. endocrinologists still prefer RAI, which is in contrast to the strong preference for ATDs by their European, Latin American, and Asian colleagues. The dramatic avoidance of PTU is based on the report of Rivkees and Szarfman showing that PTU, but not methimazole, has been associated with severe hepatic injury in young patients (2). However, methimazole causes congenital defects and PTU does not (3), thus leading to the preferential use of PTU in pregnancy.

The near-uniform avoidance of using RAI in patients with Graves' ophthalmopathy is striking and attributable mainly to the Italian studies showing that RAI worsens ophthalmopathy and that this can be prevented by corticosteroids (4,5).

It is difficult to predict how patients with Graves' disease will be treated 20 years from now, but I hope that we will have some rational therapy that is directed at the autoimmune origin and that makes our entire current armamentarium obsolete.

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How Important Are Preexisting Comorbidities and Genetic Proclivities in Explaining the Increased Risk of Mortality in Hyperthyroidism?

Stephen W. Spaulding

Brandt F, Almind D, Christensen K, Green A, Brix TH, Hegedüs L. Excess mortality in hyperthyroidism: the influence of preexisting comorbidity and genetic confounding: a Danish nationwide register-based cohort study of twins and singletons. J Clin Endocrinol Metab 2012;97:4123-9. Epub August 28, 2012; doi: 10.1210/jc.2012-2268.

SUMMARY

Background

Patients with hyperthyroidism have an increased risk of mortality. Clearly the associated atrial fibrillation, coagulopathies, and thromboembolism can increase mortality, but the importance of preexisting diseases and of different genetic backgrounds remain to be established. The authors report a retrospective population-based study, using a variety of Danish databases, to begin to address some of these issues.

Methods

All twins born in Denmark since 1954 have been entered in a twin registry, and the vital status and cause of death for everyone in Denmark has been recorded since 1968. Since 1977, all hospital discharge International Classification of Diseases, 8th (ICD8) or 10th (ICD10) Revision diagnoses—and since 1995, the ICD diagnoses for all outpatient hospital clinic visits and all purchases of antithyroid drugs—have also been recorded. The authors randomly selected 5% (339,481) of all patient records, and then excluded about 60,000 patients who were under 18 years of age or had died before 1977. From the remainder, all who had been given one of the ICD codes for hyperthyroidism and/or who had purchased antithyroid drugs at least twice since 1995 were identified, and the cause of death (or survival up to the end of 2008) was determined. Hyperthyroidism was found in 4850 patients who had been single births. From the twin registry, hyperthyroidism was identified in 926 same-sex twins, and 625 had a twin pair who did not have hyperthyroidism up to 2008. Four controls, matched for age and sex, were obtained for each singleton with hyperthyroidism, while for each twin with hyperthyroidism, four nonrelated non-control twins who did not have hyperthyroidism, matched for age, sex, and zygosity, were obtained. The Charlson comorbidity index—a weighted sum for 19 common medical conditions, which predicts 1-year mortality—was calculated for each patient and control, based on ICD codes. Pearson chi-square tests were used to compare group frequencies, t-tests to test group means, Mann–Whitney tests for group medians, and paired t-tests for paired comparisons.

Results

Each group with hyperthyroidism had more comorbidity than its control group. The risk for mortality in the 4850 singleton patients with hyperthyroidism was increased by 37% (hazard ratio [HR], 1.37; 95% confidence interval [CI], 1.30 to 1.46), as compared with their controls over a mean of 10 years of follow-up. After adjusting for sex and comorbidity, essentially the same results were obtained. The 2065 singleton patients with hyperthyroidism who had no documented comorbidity before their hyperthyroidism had been diagnosed still had an increased risk for mortality (HR, 1.28; 95% CI, 1.21 to 1.36), suggesting the hyperthyroidism was directly associated with the increased mortality.

In the 625 twin pairs discordant for hyperthyroidism, the HR for mortality was 1.43 (95% CI, 1.09 to 1.88),

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as compared with the euthyroid sibling, over a mean follow-up period of 10.5 years. A similar increase was found when the twin with hyperthyroidism was compared with its four control twins. In the 418 same-sex dizygous twin pairs, the HR was 1.80 (95% CI, 1.27 to 2.55), as compared with the euthyroid sibling. In marked contrast, when the 201 monozygous twin pairs were compared, the mortality in the sibling with hyperthyroidism was not significantly different from that of the unaffected sibling. When the 413 twins who had had no comorbidity prior to the diagnosis of hyperthyroidism were studied, again the dizygous twins with hyperthyroidism still had increased mortality, yet the monozygous twins with hyperthyroidism did not.

Conclusions

In singletons with hyperthyroidism as well as in same-sex dizygous twin pairs discordant for hyperthyroidism, the risk of mortality is increased, independent of any medical conditions documented before the diagnosis of hyperthyroidism was made. In contrast, mortality in same-sex monozygous twins discordant for hyperthyroidism may be more influenced by genetic factors.

ANALYSIS AND COMMENTARY

One might question the validity of lumping twins with Graves' disease together with twins with toxic nodular goiter, because of the well-recognized genetic component of Graves' disease. It therefore is worth noting that Swedish patients hospitalized with toxic nodular goiter were found to have twice the risk of having a sibling who also had toxic nodular goiter, versus the risk of patients hospitalized with Graves' having a sibling with Graves' disease, although the number with toxic nodular goiter was much smaller than the number with Graves' disease (1). Over the 31 years that the Danish data were being recorded, methods of testing, diagnostic criteria, and therapies for many diseases improved, and some of the death codes used and the individuals who performed the coding underwent changes. Furthermore, the relative frequency of different causes of hyperthyroidism in Denmark also changed, since dietary iodine levels and the relative incidence of Graves' disease versus toxic nodules underwent major shifts during the period of the study. In addition, subacute hyperthyroidism and transient hyperthyroidism due to thyroiditis became better recognized. Another issue is the possibility that hyperthyroidism was induced in patients with preexisting cardiovascular conditions when iodine-containing drugs or contrast agents were administered. The assessment of comorbidities may also be incomplete, since some diseases known to be associated with hyperthyroidism, as well as some complications known to be produced by therapies for hyperthyroidism, might not have been noted in the Charlson score, as it is based on only 19 common diseases.

Information concerning thyroid-function tests, therapies used, the period between diagnosis and restoration of euthyroidism, recurrences, and so forth was not available. It might have been instructive to show the survival curves after hyperthyroidism was diagnosed, in view of earlier studies showing that the excess mortality after treatment with radioiodine occurred mostly in the first year (2), and also to look for possible time trends in the causes of mortality.

Notwithstanding these caveats, such studies are very difficult to do, and are important if we are to eventually understand why (and when) patients with hyperthyroidism are at increased risk of mortality.

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Serum FT_4 Values in the Upper Normal Range in the First Trimester of Pregnancy Are Associated with Lower Birth Weight

Jorge H. Mestman

Medici M, Timmermans S, Visser W, de Muinck Keizer-Schrama SM, Jaddoe VW, Hofman A, Hooijkaas H, de Rijke YB, Tiemeier H, Bongers-Schokking JJ, Visser TJ, Peeters RP, Steegers EA. Maternal thyroid hormone parameters during early pregnancy and birth weight: the Generation R Study. J Clin Endocrinol Metab 2013;98:59-66. Epub November 12, 2012; doi: 10.1210/jc.2012-2420.

SUMMARY

Background

Maternal hyperthyroidism during pregnancy is associated with an increased risk of low birth weight, resulting in a predisposition to neonatal morbidity and mortality. The objective of the authors was to study the effects on birth weight of early pregnancy maternal serum thyroid parameters within the normal range, as well as the relation between umbilical-cord thyroid parameters and birth weight.

Methods

In early pregnancy, serum TSH, FT_4, and thyroid peroxidase antibody levels were determined in 4464 pregnant women. Cord serum TSH and FT_4 levels were determined in 2724 newborns. Small size for gestational age at birth (SGA) was defined as a gestational age–adjusted birth weight below the 2.5th percentile. The associations between normal-range maternal and cord thyroid parameters, birth weight, and SGA were studied using regression analyses.

Results

In mothers with normal-range FT_4 and TSH levels, higher maternal FT_4 levels were associated with lower birth weight (P = 1.6x10–5), as well as with a slightly increased risk of SGA newborns (odds ratio, 1.09; 95% confidence interval, 1.01 to 1.17; P = 0.03). Birth weight was positively associated with both cord TSH (P = 0.007) and cord FT_4 levels (P = 9.2x10–13).

Conclusions

The authors showed that maternal high-normal FT_4 levels in early pregnancy are associated with lower birth weight and an increased risk for the delivery of SGA newborns. In addition, birth weight is positively associated with cord TSH and FT_4 levels. The authors postulated that even mild variation in thyroid function within the normal range can have important consequences for the fetus.

ANALYSIS AND COMMENTARY

In the past two decades, several population studies reported an association between euthyroid autoimmune disease, mild thyroid dysfunction (including isolated maternal hypothyroxinemia), and abnormal pregnancy outcome (mainly, but not limited to miscarriages, prematurity, and impaired neurodevelopment in the offspring). Not all the studies are consistent, with the same type and frequency of complications. Several major factors may have contributed to this, among them, iodine status in a given population, lack of thyroid-test trimester-specific reference intervals for each population, and exclusion of complications intrinsic to pregnancy, such as gestational diabetes

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and pregnancy-induced hypertension. Therefore, it may be hypothesized that screening for thyroid disease before pregnancy, or very early in pregnancy, and proper maternal treatment might prevent such abnormal outcomes. Unfortunately, this is a controversial topic among clinicians caring for these patients, with no definite answers in spite of recent guidelines published by The Endocrine Society and the American Thyroid Association (1,2). The provocative findings of the current study may result in more discussion and confusion about interpretation and significance of high "normal" FT_4 values in the first trimester of pregnancy. The current publication is part of the Generation R Study, a population-based cohort from early fetal life onward in Rotterdam, the Netherlands (3). For the study, serum TSH, FT_4, and TPOAb were obtained in the first trimester of pregnancy in 4464 women who delivered between April 2002 and January 2006, after exclusion of women with known comorbidities. Based on the 2.5th and 97.5th percentiles, maternal reference ranges were 0.03 to 4.04 mU/L for TSH and 10.4 to 22.0 pmol/L for FT_4. Fetal growth was estimated by ultrasound measurements in midpregnancy (gestational age, 20 weeks) and late pregnancy (gestational age, 30 weeks). Cord serum TSH and FT_4 levels were available in 2724 of their newborns. Outcome information on birth weight was obtained from medical records completed by community midwives and obstetricians. Accepted definitions for small-for-gestational-age (SGA), premature, and low-birth-weight (LBW) infants were used.

Serum FT_4 concentrations in the upper quintile of normal (between 17.01 and 22.00 pmol/L) were associated with reduced growth (SGA) in the fetus (116 g lower birth weight) and a 2.8-fold increased odds for infants weighing less than 2500 g (LBW) as compared with FT_4 concentrations in the lowest quintile (between 10.38 and 12.80 pmol/L). An interesting finding based on fetal ultrasonography was the lower birth weight detected only in late pregnancy, pointing, perhaps, to a specific complication of pregnancy such as pregnancy-induced hypertension as the reason for this finding.

One potential factor that was not discussed by the authors is the relation between initial TSH and FT_4 values, although they stated, "Trends toward lower maternal TSH levels and lower birth weight and estimated fetal weights were observed but did not reach statistical significance." One unexplained finding was the absence of complications in the mothers with euthyroid chronic thyroiditis, 5.5% of their population. As discussed by Mannisto in the accompanying editorial (4), we are not yet ready to redefine normal levels for FT_4 in pregnancy or to measure FT_4 levels in all pregnant women. "Although an association between both early and late pregnancy high-normal free T_4 and lower birth size has been demonstrated, we are far from showing causality or a strength of association that merits action."

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Clinical THYROIDOLOGY
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Subacute Thyroiditis Is Treated Effectively by a Low Dose of Prednisolone

Jerome M. Hershman

Kubota S, Nishihara E, Kudo T, Ito M, Amino N, Miyauchi A. Initial treatment with 15 mg of prednisolone daily is sufficient for most patients with subacute thyroiditis in Japan. Thyroid. December 10, 2012 [Epub ahead of print].

SUMMARY

Background

Subacute (granulomatous, DeQuervain's) thyroiditis is an uncommon condition that has been treated with either nonsteroidal antiinflammatory drugs (NSAIDs) or corticosteroids for many years. The response to steroids is often more dramatic and quicker than the response to NSAIDs, but physicians are reluctant to use corticosteroids for this usually self-limited disorder because of their well-known side effects. The usual initial dose is 40 mg of prednisone. The basis for this dose has not been established by prospective studies. The current report is an evaluation of the efficacy of a prednisolone dose of 15 mg per day for 2 weeks, with reduction of the dosage by 5 mg every 2 weeks, as patients are carefully followed.

Methods

Subacute thyroiditis was diagnosed based on the criteria of swelling, pain, and tenderness within the thyroid gland associated with increased FT_4, decreased TSH, increased C-reactive protein (CRP), and a hypoechoic area in the thyroid ultrasonogram corresponding to the tender area. Patients were treated with 15 mg of prednisolone per day for 2 weeks with reduction of the dose by 5 mg every 2 weeks for 6 weeks. If pain continued or the CRP remained high, prednisolone treatment was extended and then tapered over 12 weeks. All patients received "anti-ulcer" drugs.

Results

From February 2005 through December 2008, the diagnosis of subacute thyroiditis was made in 384 patients; 54 were not treated with medication, 33 were treated with NSAIDs, 9 dropped out of the treatment protocol, 69 violated the protocol, and 219 followed the protocol and are the subjects of this report. Patients were followed every 2 weeks.

The mean age of the patients was 49 years, 88% were women, and the mean weight was 55 kg. The mean FT_4 was 2.5 ng/dl (normal range, 0.7 to 1.6) and the mean FT_3 was 7.15 pg/ml (normal range, 1.70 to 3.70); FT_4 was elevated in 80% of the patients.

Thyroiditis improved in 6 weeks and did not recur in 113 patients (51.6%); 106 patients took prednisolone for 7 weeks or longer and 27 of them took prednisolone for more than 12 weeks. Seven patients required >15 mg per day; 2 of these patients were treated with 30 mg per day and 5 with 20 mg per day. About 20% took more than 8 weeks to recover. There was a significant negative correlation between the FT_4 and the duration of therapy and between the FT_3 and the duration of therapy.

Transient hypothyroidism occurred in 31% of patients, and permanent hypothyroidism was found in only 3.6% of patients.

Conclusions

Subacute thyroiditis can be treated effectively with a daily dose of 15 mg of prednisolone for 2 weeks and subsequently tapering by 5 mg per day every 2 weeks.

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ANALYSIS AND COMMENTARY

This study is a valuable clinical contribution to thyroidology because it is the first study that analyzed the response to corticosteroid therapy in a large population of patients with subacute thyroiditis. Treatment with about half of the usually recommended steroid dose was effective in ameliorating the disorder in 80% of patients within 8 weeks. Because the mean weight of these Japanese patients, mainly women, was only 55 kg, the 15-mg dose (0.27 mg per kilogram) would probably be equivalent to at least 20 mg of prednisone in a Western population.

The late Robert Volpé was an expert in this disorder and wrote an excellent review of its management (1). Volpé advocated a dose of 40 mg of prednisone, tapering it over 6 weeks. He noted that about 20% of patients will have a recurrence, necessitating the restoration of a higher dose, similar to the findings of the current report. Volpé expressed a preference for early initiation of steroid therapy, which is also the preferred therapy of the authors of this paper rather than initiating therapy with NSAIDs, as recommended by the guideline 96 of the ATA, before using prednisone therapy (2). The 6-week duration of corticosteroid therapy in this study is somewhat longer than that reported with empirical therapy of 49 patients in Minnesota with tapering of 40 mg of prednisone in 7 days and continuation of the reduced dose for only 30 days (3). However, two thirds of the group also received other therapy, probably NSAIDs.

It is interesting that the patients with higher thyroid hormone levels had faster restoration of normal levels with the glucocorticoid therapy and were more likely to be in the short-term medication group (6 weeks). The explanation suggested by the authors is that these patients had more destruction of their thyroid glands as compared with those who required a longer duration of therapy for resolution of the disorder. Presumably, the destruction reversed more quickly because the maximum destruction occurred at an earlier time—a unique hypothesis.

It is interesting that the authors followed the guidelines of the Japan Thyroid Association (www.japan-thyroid.jp/doctor/guideline/english.html#akyuu) and did not perform a radioactive iodine–uptake test to confirm the diagnosis. This is another instance in which ultrasonography is replacing the use of radioisotopes in clinical diagnosis.

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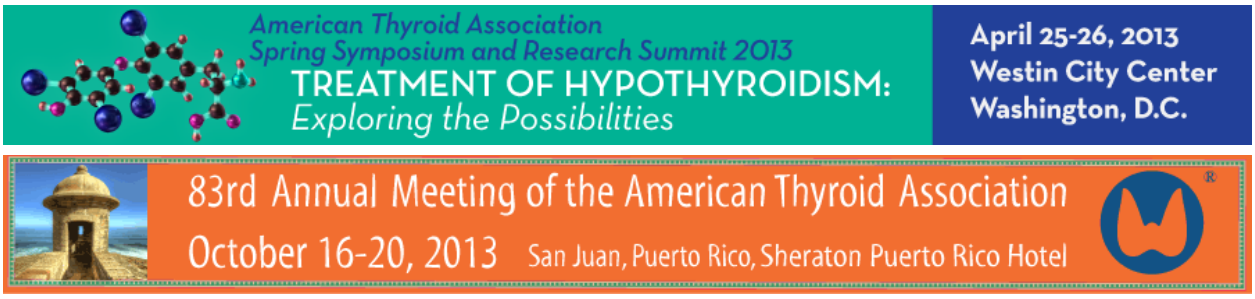

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Call for Nominations for 2013
American Thyroid Association
Board of Directors

In accordance with the Bylaws of the American Thyroid Association, the Nominating Committee is soliciting nominations from the membership for candidates for the offices of President and Directors (2) to serve on the ATA Board of Directors. Candidates will be selected by the Nominating Committee and submitted to the ATA Board for final approval.

A ballot will be sent to the membership electronically in August 2013. Newly elected Board members will be announced at the Annual Business Meeting on Thursday, October 17, 2013.

ATA President
The **President** will serve a one-year term as President-Elect (2013-2014), followed by one year as President (2014-2015), and another year as a Past-President (2015-2016). See job description in Policies and Procedures under "Members Only" at www.thyroid.org. *Election of the President will be competitive.*

Nominee: _____

ATA Board Director
Two **Directors** will each serve a four-year term (2013-2017). See job description in Policies and Procedures under "Members Only" at www.thyroid.org. *Election of directors will be competitive.*

Nominee: _____

Nominee: _____

Nominated by (please print or type): _____

Signature: Date:

All nominations must be submitted to the Executive Director, Bobbi Smith, by letter, fax, or e-mail bsmith@thyroid.org by March 31, 2013.

American Thyroid Association
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Call for Nominations for the 2013 Awards
American Thyroid Association

▪ Distinguished Service Award ▪ Sidney H. Ingbar Distinguished Lectureship ▪
▪ Van Meter Lecture ▪ Paul Starr Lecture •
• Lewis E. Braverman Lectureship • John B. Stanbury Thyroid Pathophysiology Medal ▪

The Van Meter Award Lecture established in 1930, recognizes outstanding contributions to research on the thyroid gland or related subjects. The award is given each year to an investigator who is not older than the age of 45 in the year of the award. The Van Meter award winner is kept secret until the time of the award lecture during the annual meeting. An honorarium and expenses are awarded to the Van Meter recipient. This award receives support from Mary Ann Liebert, Inc., Publishers.

Nominee: Date of Birth

The Sidney H. Ingbar Distinguished Lectureship Award, endowed by contributions to honor the memory of Sidney H. Ingbar, recognizes outstanding academic achievements in thyroidology, in keeping with the innovation and vision that epitomized Dr. Ingbar's brilliant investigative career. The Ingbar award is conferred upon an established investigator who has made major contributions to thyroid-related research over many years. An honorarium will be presented to the recipient.

Nominee:

The Paul Starr Award Lecture recognizes an outstanding contributor to clinical thyroidology. An honorarium will be presented to the recipient. This award receives support from Dr. Boris Catz.

Nominee:

The Lewis E. Braverman Lectureship Award recognizes an individual who has demonstrated excellence and passion for mentoring fellows, students and junior faculty; has a long history of productive thyroid research; and is devoted to the ATA. The award is endowed by contributions to honor Dr. Lewis E. Braverman. An honorarium will be presented to the recipient.

Nominee:

The Distinguished Service Award (DSA) honors a member who has made important and continuing contributions to the American Thyroid Association (ATA). The DSA award certificate is presented at the ATA Annual Banquet.

Nominee:

The John B. Stanbury Thyroid Pathophysiology Medal recognizes outstanding research contributions, either conceptual or technical, to the understanding of thyroid physiology or the pathophysiology of thyroid disease, as evidenced by having a major impact on research or clinical practice related to thyroid diseases. A medal, funded by Dr. John Stanbury, is conferred at the Annual Banquet.

Nominee:

Nominated by: (print or type) *Signature:* *Date:*

Nominators must submit all of the following electronically to thyroid@thyroid.org to complete the nomination by the deadline of March 31, 2013:

1. Completed and signed Nomination Form – candidates must be re-nominated every 3 years.
2. CV and brief nomination letter, emphasizing major accomplishments.
3. List of 2 to 4 most significant publications with PDF or URL to provide access to these papers.

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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.

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