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Radioiodine Ablation Does Not Increase Survival in Patients with Low-Risk Differentiated Thyroid Cancer

Schvartz C, Bonnetain F, Dabakuyo S, Gauthier M, Cueff A, Fieffé S, Pochart JM, Cochet I, Crevisy E, Dalac A, Papathanassiou D, Toubeau. Impact on overall survival of radioactive iodine in low-risk differentiated thyroid cancer patients. J Clin Endocrinol Metab. February 16, 2012 [Epub ahead of print].

SUMMARY

Background

In recent years, the clinical efficacy of ^{131}I ablation of possible remnants after surgery for low-risk differentiated thyroid cancer (DTC) has been questioned. Radioiodine ablation (RAI) is not recommended now for low-risk patients with papillary cancers smaller than 1 cm confined to the thyroid. The current paper reports an analysis of recurrence and survival of patients with differentiated cancers up to 4 cm with no other risk factors who had RAI, as compared with a group who did not undergo RAI.

Methods

The study included 1298 low-risk patients from two French centers, Reims and Dijon, who were treated between 1975 and 2005. The low-risk patients who were included had complete tumor resection, single tumors 1 to 4 cm with negative lymph nodes or without lymph-node dissection (Nx) corresponding to stage 1 for patients under 45 years old and stages 1 and 2 for patients over 45 years old by the TNM classification. They excluded patients with tumors smaller than 1 cm and those with positive lymph nodes or known metastatic disease. Patients were treated by thyroidectomy or lobectomy. In Dijon, all patients received RAI and had a post-therapy scan, whereas in Reims, patients received RAI based on risk factors (age >45, tumor >3 cm). Eighty-eight percent of the patients received 100 mCi and 12% received only 20 mCi. Patients were followed by conventional means, including clinical examination, serum thyroglobulin (Tg), anti-Tg, and neck ultrasound. Overall survival (OS) was defined as the time from diagnosis to death, and disease-free survival (DFS) was defined as the time from diagnosis to recurrence, second cancer, or all-cause death. A high Tg or anti-Tg was not considered as relapse without evidence of recurrent disease. Univariate and multivariate analyses were carried out, and based on the multivariate analysis, the likelihood of having been given RAI, a "propensity score," was determined for each patient.

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Results

The mean age was 47 and 83% of the 1298 patients in the cohort were female; 72% had papillary cancer and 28% had follicular cancer. Thyroidectomy was performed in 81% and lymph-node dissection in 55%. Seventy percent received RAI and 30% did not. The mean follow-up was 10.3 years. Both disease-free and overall survival were slightly but significantly higher in those who were not given RAI. The10-year DFS rates were 88.7% (95% CI, 85.96 to 90.97) for patients treated with RAI and 93.1% (95% CI, 89.68 to 95.47) for patients not treated with RAI (P<0.0013). Recurrences were found in 1.6% of those who received RAI and 1.0% of those who did not receive RAI. Survival did not differ between those who received 100 mCi or 20 mCi RAI.

In the multivariate Cox analysis, age and sex were the only two independent prognostic factors associated with DFS and OS. Survival was worse in those over age 45 and in men. The clinical characteristics significantly associated with RAI treatment were age greater than 45 years, male sex, diagnosis before 1998, total thyroidectomy, lymph-node dissection, papillary histology, and pT2 (tumors 2 to 4 cm). Survival curves based on propensity score (i.e., adjusting for factors that predisposed to the use of RAI) did not differ between the RAI and no RAI groups.

Conclusions

The study failed to prove any survival benefit of RAI after surgery in a large cohort of patients with low-risk DTC.

ANALYSIS AND COMMENTARY

Like all retrospective studies of this type, regional factors and current modes of practice probably entered into the decisions for RAI ablation therapy. In Dijon, the use of RAI was based on clinical factors such as age, size of the tumor, and perhaps other factors such as sex and whether it was papillary or follicular. Despite the authors sophisticated statistical calculation indicating that the propensity score for using RAI showed that there was no difference in these factors between those who received RAI and those who did not, I suspect that when low-dose RAI was chosen there were considerations, such as an apparently good prognosis and rules requiring hospitalization, that influenced the decision about whether to choose 100 mCi or 20 mCi. The only way to settle the efficacy or lack of benefit of RAI ablation would be a randomized, controlled study that could now perhaps be extended to T2 tumors and possibly follicular carcinomas. However, the authors offer a caveat of possible misclassification of follicular variants of papillary thyroid cancer being diagnosed as follicular cancers in that bygone era. Since true follicular cancers have a worse prognosis than papillary carcinomas, unless they are minimally invasive into the capsule and show no vascular invasion, many endocrinologists would currently recommend RAI ablation for follicular cancers.

Nevertheless, this study supports the skepticism regarding RAI for low-risk papillary cancers with negative nodes reported from the Mayo Clinic (1). In a review, Sawka et al. concluded that the benefit of RAI in low risk patients with DTC was unclear (2). In a review of the Surveillance, Epidemiology, and End Results American database, Podnos et al. did not find any significant effect of RAI in overall survival with papillary thyroid carcinoma (3). Lastly, Sacks et al., in an extensive recent review of the literature, reported that the majority of studies did not find a statistically significant improvement in mortality or disease-specific survival in patients with low-risk DTC treated with RAI, but improved survival was confirmed for high-risk patients (4).

— Jerome M. Hershman, MD

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Stimulated Thyroglobulin 5 Years after Initial Treatment Detects Recurrence in 5.4% of Patients Despite a Thyroglobulin on T_4 <1 ng/ml

Rosario PW, Furtado MS, Fiho AF, Lacerda RX, Calsolari MR. Value of repeat stimulated thyroglobulin testing in patients with differentiated thyroid carcinoma considered to be free of disease in the first year after ablation. Thyroid. December 16, 2011 [Epub ahead of print]. doi: 10.1089/thy.2011.0214.

SUMMARY

Background

It is not clear when or if TSH-stimulated thyroglobulin (Tg) testing should be repeated in patients with differentiated thyroid carcinoma who are thought to be disease-free after the initial therapy. This study evaluated the utility of repeat TSH-stimulated Tg testing in patients considered to be free of disease 6 to 12 months after the initial thyroid ablation who also had a Tg <1 ng/ml while on TSH-suppressing doses of levothyroxine.

Methods and Results

Medical records were reviewed for 307 subjects with differentiated thyroid cancer who had evidence of complete resection of tumor after total thyroidectomy and ablation with 1.1 to 5.5 GBq (~30 to ~150 mCi) ^{131}I (RAI) with a posttherapy whole-body scan (WBS) showing no distant metastases. This group was considered to be disease-free 6 to 12 months after ablation when they had a TSH-stimulated Tg <2 ng/ml (negative thyroglobulin antibody [TgAb] level) and a negative diagnostic RAI WBS. Patients were excluded if they had evidence of distant metastases, TSH-stimulated Tg >2 ng/ml at 6 to 12 months after ablation, positive TgAb, or apparent disease (n = 58). At this institution, after an initial treatment with total thyroidectomy and RAI ablation all patients routinely had TSH-stimulated Tg for confirmation of the absence of disease (Tg <2 ng/ml).This cohort of patients continued to have an annual exam with neck ultrasonography, Tg and TgAb measurements. If the TSH-stimulated Tg was >2 ng/ml, neck ultrasonography; CT scans of the neck, chest, and mediastinum; and a 99mTc-methoxyisobutyl isonitrile (MIBI) scan were obtained. If the TSH-stimulated Tg was >10 ng/ml in a patient with apparent disease, then an empirical dose of 3.7 GBq (100 mCi) ^{131}I was administered and a posttherapy scan was performed.

There were 203 patients who met the inclusion criterion of being disease-free (Tg on T_4 <1 ng/ml, negative TgAb, and no clinical evidence of tumor recurrence) 5 years after initial therapy. Ten patients were excluded because of a Tg on T_4 >1 ng/ml, positive TgAb, or clinical tumor recurrence. Evaluation 54 to 64 months after initial therapy showed that 192 patients (94.6%) had hypothyroid-stimulated Tg <2 ng/ml and 188 of these patients had a stimulated Tg <1 ng/ml. During the subsequent follow-up, for a mean of 102 months, there were no new cases of tumor recurrence in this subgroup. Eleven (5.4%) of the 203 patients had a stimulated Tg >2 ng/ml. Of these patients 3 had nodal metastases found on neck ultrasound, 5 had metastases (2 neck nodes,1 mediastinal node, and 2 pulmonary metastases) found on other imaging methods (CT scan, 99mTc-MIBI, or posttherapy RAI WBS). In the remaining 3 patients, no metastases were found, and stimulated Tg continued to be mildly elevated, at >2 ng/ml (2.3, 3.5, and 5 ng/ml).

Conclusions

There were 11 (5.4%) patients initially considered to be disease-free in whom a stimulated Tg >2 ng/ml had developed when they were evaluated between 54 and 64 months after initial treatment. The entire cohort was followed for a mean of 102 months. Metastases were located in 8 of these 11 patients. This recurrent disease was not associated with sex, age, or original AJCC staging of the tumor. All the patients had identical initial treatment with total thyroidectomy and RAI ablation. None of the patients with a low stimulated Tg level at 54 to 64 months had tumor recurrence over a mean of 102 months of follow-up.

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ANALYSIS AND COMMENTARY

The 2009 American Thyroid Association Guideline for Thyroid Nodules and Cancer suggests using both the TNM AJCC/UICC staging plus risk factors to completely assess risk for death and persistence/recurrence of the tumor (1). In addition, there has been the suggestion that patients should be "restaged" periodically, taking into account absence or progression of disease (2). The advantages of this study are that the patients had identical initial treatment with total thyroidectomy and RAI ablation and were carefully evaluated for recurrence over a long time (mean, 8.5 years). This careful follow-up likely resulted in a higher detection of recurrence (5.4%) as compared with the literature (3). In this cohort who initially at 6 to 2 months were considered to be free of disease (negative neck ultrasound, stimulated Tg <2 ng/ml, and negative RAI WBS), half of the recurrences were found clinically and half were found only after hypothyroid-stimulated Tg testing. This study supports repeat TSH-stimulated Tg testing 5 years after ablation in patients thought to be disease-free 6 to 12 months after treatment despite a Tg on T_4 <1 ng/ml and negative TgAb tests. Other investigators have suggested, with a negative predictive value of 100%, a second negative stimulated Tg in patients initially believed to be disease-free (4). It is an important result that a negative predictive value of 100% was achieved for patients followed for a mean of 102 months when a negative stimulated Tg was found at 5 years. This result suggests that no further stimulated Tg tests are necessary. My conclusion is that it is reasonable to repeat a stimulated Tg at 5 years even if the patient is considered to be disease-free. If the Tg is >2 ng/ml, this would allow for early detection of recurrences and/or intensified follow-up for these patients while reducing or stopping follow-up of patients with a low stimulated Tg.

— Stephanie L. Lee, MD, PhD

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Measurement of Four MicroRNAs Accurately Differentiates Malignant from Benign Indeterminate Thyroid Lesions

Keutgen XM, Filicori F, Crowley MJ, Wang Y, Scognamiglio T, Hoda R, Buitrago D, Cooper D, Zeiger MA, Zarnegar R, Elemento O, Fahey TJ 3rd. A panel of four microRNAs accurately differentiates malignant from benign indeterminate thyroid lesions on fine needle aspiration. Clin Cancer Res. February 20, 2012 [Epub ahead of print].

SUMMARY

Background

A plethora of papers has recently appeared on the use of microRNAs for the diagnosis of thyroid cancer. As discussed in the article by Stephen Spaulding in the December 2011 issue of Clinical Thyroidology (pp 14–15), miRNAs are single-stranded noncoding small RNA segments, 19 to 23 nucleotides in length, that bind to multiple mRNAs by sequence-specific interaction with the 3' untranslated region of the mRNA targets. They cause suppression of translation and increased degradation of the specific mRNA. In cancers, a number of miRNAs have been shown to be tumor suppressors and are often down-regulated.

The current paper is a study of specific miRNAs in lesions cytologically classified to be indeterminate. Such lesions have a possibility of approximately 25% of being malignant.

Methods

A "derivation" group, classified by FNA as indeterminate lesions, consisted of 15 benign and 14 malignant specimens from which RNA was obtained at FNA biopsy. Based on an extensive search of the literature on miRNAs that were differentially expressed in thyroid cancer versus benign tissue, the authors decided to measure the levels of six miRNAs: mir-328, mir-222, mir-197, mir-181a, mir-146b, and mir-21. Measurements were performed on carefully prepared miRNAs using quantitative RT-PCR and 45 cycles of amplification; results were compared in terms of cycle number with the housekeeping gene RNU6B. They evaluated several methods for building statistical models that can predict benign versus malignant status based on expression profiles of the six miRNAs. After developing the model, they applied it to a validation group of 72 consecutive FNA specimens that were classified as indeterminate and in which all the patients had agreed to have surgery.

Results

Using nonparametric analysis in the derivation group of 29 specimens, they found that four miRNAs were differentially expressed between malignant and benign lesions; these included miR-222 ($P<0.005$), miR-21 ($P<0.03$), miR-181a ($P<0.04$), and miR-146b ($P<0.03$). MicroRNA expression of mir-197 ($P = 0.3$) and mir-328 ($P = 0.6$) was not significantly different. By highly sophisticated statistical analysis, they developed a model that gave 85% sensitivity and 85% specificity for a diagnosis of malignancy using the four miRNAs. The model was then applied to the validation samples.

There were 50 benign lesions and 22 malignant lesions in the validation group based on final histopathology. The model that used the four miRNAs correctly classified 65 of the 72 FNA samples. The sensitivity was 100% and the specificity 86% for the diagnosis of cancer. Five of the seven lesions that the model predicted incorrectly to be malignant were Hürthle-cell neoplasms on FNA and hyperplastic nodules or adenomas on final pathology.

Conclusions

This study shows that that the expression of miR-222, miR-328, miR-197, and miR-21 combined in a predictive model is reasonably accurate for differentiating malignant from benign indeterminate thyroid lesions on FNA.

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ANALYSIS AND COMMENTARY

This field of measuring miRNA in FNA specimens is moving rapidly and competes with the measurement of oncogenes (1) or the measurement of an array of proteins (2) for diagnosis of thyroid cancer in the specimens. It may have great utility when applied to specimens classified as indeterminate or even those deemed to be inadequate based on cytology. Unfortunately, there has not been uniformity in the choice of which miRNAs are most useful to measure. In contrast with this paper, another recent paper reported measurements of miR-7, miR-126, miR-374a, and let-7g and found that miRNA-7 was most useful for the diagnosis of cancer in inconclusive FNA specimens (3). Yet another report found that miRNA-138 was the most useful for the diagnosis of cancer in a series of 125 FNA biopsies that had been classified as indeterminate (4). Still another recent report in Thyroid focused on miRNA analysis of FNA specimens classified as atypia of undetermined significance (5). The results showed that a panel of miR-146b, -221, -187, and -30d had good accuracy for identification of papillary thyroid cancers but not follicular cancers. Although each of these four reports of miRNA measurements resulted in a choice of the best miRNA for the diagnosis of cancer, it is worth emphasizing that each report concluded that a different panel of miRNA was the most useful.

It is important to note that a single miRNA may modify the expression of several genes. In the paper studied here, the authors point out that the four miRNAs they used for the predictive model were all involved in control of the cell cycle or in cell proliferation.

— Jerome M. Hershman, MD

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Measuring a Three-Gene Panel May Distinguish Malignant from Benign FNA Samples

Prasad NB, Kowalski J, Tsai HL, Talbot K, Somervell H, Kouniavsky G, Wang Y, Dackiw AP, Westra WH, Clark DP, Libutti SK, Umbricht CB, Zeiger MA. Three-gene molecular diagnostic model for thyroid cancer. Thyroid. 2012;22:275-84. Epub January 26, 2012.

SUMMARY

Background

Fine-needle aspiration (FNA) biopsy of thyroid nodules results in an indeterminate or suspicious diagnosis in one fourth of biopsies. This often leads to surgical thyroidectomy in patients who have benign nodules. To improve the diagnosis of thyroid cancer, one approach has been to measure molecular markers that are highly expressed in thyroid cancers in comparison with benign nodules. By microarray analysis of benign and malignant thyroid tumors, these authors had previously identified 75 genes that were differentially expressed. This study determined that measurement of three unique genes resulted in good diagnostic discrimination of benign from malignant nodules.

Methods

A set of 95 intraoperative FNA specimens was collected for molecular analysis and the results were correlated with the permanent histology. RNA was extracted from the samples and subjected to quantitative RT-PCR for analysis of 10 genes that previous work had shown to be promising candidates. Of the 95 samples, 27 had corresponding indeterminate or suspicious preoperative cytology. Each marker was examined separately and in combination by univariate and multivariable analysis to determine odds ratios and 95% confidence intervals of various models. The proteins expressed by these same genes were examined by immunohistochemistry in separate studies on material obtained from paraffin blocks.

Results

The FNA samples were obtained from the following histologic lesions: 50 adenomatoid nodules, 10 follicular adenomas, 5 Hürthle-cell adenomas, 23 papillary thyroid carcinomas, 5 follicular variant of papillary thyroid carcinomas, 1 lymphocytic thyroiditis nodule, and 1 Graves' disease.

In the FNA samples, all 10 genes showed significantly higher odds of being associated with malignancy as compared with benign lesions; the gene, MRC2 (mannose receptor, C type 2) showed the highest discriminating ability. The combination of 3 genes—MRC2+HMGA2 (high mobility group AT-hook 2)+SFN (stratifin)—had a sensitivity of 71%, specificity of 84%, positive predictive value (PPV) of 65%, and negative predictive value (NPV) of 88%. Of the 27 samples that had suspicious or indeterminate FNA results preoperatively, the 3-gene model was 96% specific and 60% sensitive in the prediction of malignancy (PPV, 75%; NPV, 91%). The results of the immunohistochemistry were similar to the PCR data for these 3 genes.

Conclusions

The results suggest that a 3-gene model for the molecular diagnosis of indeterminate thyroid nodules is feasible and promising and that implementation of this as an adjunct to thyroid cytology may significantly impact the clinical management of patients with suspicious or indeterminate thyroid FNA nodules.

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ANALYSIS AND COMMENTARY

Although a great deal of work went into this study by a very prolific group, the results must still be regarded as preliminary. There were no follicular carcinomas in the FNA group, although there were some follicular and Hürthle-cell carcinomas in the immunohistochemistry group. Since there were no follicular cancers in the FNA samples, the three-gene classifier (MRC2+HMGA2+SFN) is not established for distinguishing follicular adenoma from carcinoma. As the authors state, the method must now be validated by applying it to a test set of samples. A different three-gene biomarker panel was thought to be useful for diagnosis of thyroid cancer, but its diagnostic accuracy was low in a subsequent study (1).

The efficacy of this study must be compared with that of the miRNA studies described in the previous article in this issue (2) and with the use of the more established thyroid cancer biomarkers, BRAF, RET/PTC, RAS, and PAX8/PPARg (3). These biomarkers represent mutations that are understood well with regard to activating pathways of growth. In contrast, the genes up-regulated in the current study do not have well-established roles in oncogenesis, but certainly have potential for contributing to neoplastic growth.

MRC2 is a recycling endocytic receptor that functions in cell motility and remodeling of the extracellular matrix by promoting cell migration and uptake of collagens for intracellular degradation. HMG proteins function as architectural factors and are essential components of the enhancesome. The protein contains structural DNA-binding domains and may act as a transcriptional regulating factor. SFN is an adapter protein that binds to a large number of partners implicated in the regulation of a large spectrum of both general and specialized signaling pathways. I look forward to reading the study that validates these genes as accurate biomarkers for thyroid cancer when applied to FNA in the clinical setting.

— Jerome M. Hershman, MD

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Ultrasound Characteristics Predict BRAF V600E Mutational Status

Kabaker AS, Tublin ME, Nikiforov YE, Armstrong MJ, Hoak SP, Stang MT, McCoy KL, Carty SE, Yip L. Suspicious ultrasound characteristics predict BRAF V600E-poisitive papillary thyroid carcinoma. Thyroid. February 23, 2012 [Epub ahead of print]. doi:10.1089/thy.2011-0274.

SUMMARY

Background

The ATA guideline (1) and recent Society of Radiologists in Ultrasound consensus statement (2) recommend ultrasound (US) assessment of all thyroid nodules with biopsy of those that are larger 1 cm with worrisome sonographic features. The BRAF V600E mutation has been associated with an increased risk of extrathyroidal extension (ETE) and nodal metastases with a higher risk of persistent disease (3) but may not indicate a worse prognosis (4). This study investigated whether specific US characteristics can reliably detect papillary thyroid carcinoma (PTC) with a BRAF V600E mutation.

Methods and Results

This was a blinded retrospective study of a cohort of 106 patients with a histologic diagnosis of PTC ≥1 cm who had a cervical US, initial thyroid surgery, and molecular testing for BRAF V600E on the fine-needle aspiration prior to surgery or histologic sections after surgery. There were 55 patients who had BRAF-positive PTC and 51 patients had BRAF-negative PTC. Preoperative US images were evaluated by a single radiologist who was unaware of BRAF status for nodule size and suspicious sonographic features (taller-than-wide shape, ill-defined margins, hypoechogenicity, calcifications, noncystic composition. and absence of halo). The BRAF V600E mutation was associated with suspicious US findings, including taller-than-wide shape (47% vs. 7%, P<0.001), ill-defined margins (42% vs. 9%, P<0.001), hypoechogenicity (83% v. 36%, P<0.001), microcalcifications/macrocalcifications (87% vs. 24%, P<0.001), and absent halo (85% vs. 27%, P<0.001). BRAF mutation was not associated with solid composition. BRAF-positivity was predicted with a positive predictive value of 82% when ≥3 suspicious US features were present. The absence of suspicious US features together with negative BRAF testing predicted PTC without extrathyroidal extension or lymph-node metastasis (negative predictive value [NPV], 88%).

Conclusions

This study demonstrates that a combination of suspicious sonographic features is associated with an increased risk of a BRAF mutation, and the lack of suspicious US features and negative BRAF testing have a good NPV (88%) for ETE and metastatic nodes. This information may assist in the planning of the initial surgical management and risk stratification of patients with PTC.

ANALYSIS AND COMMENTARY

The 2009 American Thyroid Association Guideline for Thyroid Nodules and Cancer (1) suggests using both the TMN AJCC/UICC staging plus risk factors to completely assess risk for death and persistence/recurrence of the tumor. These risk categories state that microscopic ETE (stage 3 in patients >45 years old) and metastatic nodes (stage 3 or 4a if >45 years) place patients at increased risk of recurrence and death. Classic PTC histology, ETE, and metastatic nodes are associated with the BRAF V600E mutation. Although the ATA guidelines suggest consideration of using molecular markers, including BRAF V600E, in the management of thyroid nodules with an indeterminate FNA biopsy, it is not yet in the current 2009 guidelines as a risk factor to alter therapy of a

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patient with PTC. It is clear that three or more suspicious features greatly increase the risk of PTC (2) in a nodule. This study suggests that three or more features increase the risk of the BRAF V600E mutation, ETE, and metastatic nodes. At this point, I would not use the US appearance to infer BRAF V600E status. If multiple suspicious sonographic features are seen in a nodule, I would consider testing for the mutation on the FNA biopsy and performing a careful sonographic evaluation for metastatic neck nodes and extension of the tumor outside the thyroid. Although some investigators (3,4) have suggested using the presence of BRAF V600E mutation to direct surgery (level VI node dissection, total vs. lobectomy), this has not yet been tested and shown to impact patient outcomes. A future large multi-institution study showing the utility of using preoperative BRAF V600E status to direct surgery will be needed before current guidelines for the management of thyroid cancer are altered.

— Stephanie L. Lee, MD, PhD

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Thyroidal Secretion Is Increased in Cold-Exposed Populations

Andersen S, Kleinschmidt K, Hvingel B, Laurberg P. Thyroid hyperactivity with high thyroglobulin in serum despite sufficient iodine intake in chronic cold adaptation in an Arctic Inuit hunter population. Eur J Endocrinol 2012;166:433-40. Epub December 14, 2011.

SUMMARY

Background

It has recently been demonstrated that brown adipose tissue (BAT) can be activated by cold exposure (1, 2). The activation of this tissue depends on the sympathetic innervation as well as on the saturation of its nuclear T_3 receptors. BAT deiodinase type II activity plays a crucial part in this process by generating high local T_3 concentrations under sympathetic stimulation (3). Studies on U.S. Army personnel stationed in the Antarctic had previously indicated that in people exposed to a cold environment T_3 turnover and T_3 production are considerably enhanced, approximately 40%, and that serum thyroglobulin levels increase during their stay in the Antarctic. These findings point to an overall increase of thyroid activity (4, 5). The study reported here comes from Greenland where thyroid parameters of a local population exposed to a very cold climate were studied.

Methods and Results

The researchers studied a population of Inuits residing in eastern Greenland in remote settlements without modern comforts. These Inuits had been living in isolation until recently, and a large proportion of the them still earn their living by hunting at sea all year round. These subjects were compared with a population living in the capital in western Greenland, where many Danes live. The subjects were selected using the national civil registration system for the district of Ammassalik. The clinical examination of the subjects was performed by the authors. The selected individuals were between 50 and 69 years old. Thyroid hormones and thyroglobulin were measured in the serum, and iodine excretion was assessed in the urine. Besides finding increased thyroglobulin levels, the authors confirm a slightly lower FT_3, with no change in serum TSH in hunters and settlement dwellers. In this group of subjects, the iodine excretion was, if anything, slightly higher than in the residents of the capital, and it was considered to be largely sufficient. Therefore, iodine deficiency was not the cause of the increased thyroglobulin levels found in the residents of eastern Greenland. Other parameters, such as alcohol consumption and tobacco use, could also be excluded as critical factors in explaining the increased thyroglobulin levels. The increase was not large, but it was still highly significant. For Inuit hunters, the mean was 20.3 µg/L, for Inuit- nonhunters 17.2 µg /L, and for Caucasian men 13.9 µg/L. In the same samples, the differences in serum TSH were not significant, even though TSH was slightly lower in Inuit hunters.

Conclusions

The eastern Greenland population, which is largely of Inuit origin with all-year hunting as a traditional occupational activity, has slightly but significantly higher thyroglobulin levels than the more westernized population in the capital. There was no obvious explanation for this difference. Most importantly, insufficient iodine intake was excluded. Despite the absence of any significant change in serum TSH, there was a slight decrease of FT_3. However, this is not synonymous with a decreased T_3 production (see below). The authors conclude that the increased thyroglobulin levels are an indication of increased thyroid gland activity, consistent with an increased thyroid activity in the cold.

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ANALYSIS AND COMMENTARY

It is interesting to compare the studies performed at the Antarctic base McMurdo, where American soldiers lived during the austral winter under highly protected camp conditions. Their exposure to extreme cold was not more than half an hour per day and was limited to the face. In Greenland, the climate is less cold but cold exposure was clearly more sustained. Both studies report increased serum thyroglobulin levels. In the Antarctic, kinetic studies were performed in addition. They indicated an increased volume of distribution and turnover of T_3, pointing to an increased T_3 production, despite a slight decrease of circulating FT_3 (6). These findings are also known as "polar T_3 syndrome." The kinetic data can be explained, for instance, by an increased production and turnover of T_3 in one or several organs. Since we now know that even in adult humans BAT and its deiodinase type II activity can be activated by cold exposure, it is tempting to speculate that this tissue may contribute to the observed changes in thyroid function. Thyroid hormones may also play a role in nonshivering thermogenesis of skeletal muscle. A caveat: So far it has been shown by positron-emission tomography (PET) scan that the activity of BAT disappears in western societies with age. Thus, in the age group studied in Greenland, the presence of BAT would have to be demonstrated (7). The clinical relevance is becoming evident if one realizes that BAT, at least in animals, can also be activated by excessive feeding of a favorite food (8). It could, therefore, play a role in obesity and insulin resistance. The future will show whether thyroid hormones are significant contributors to BAT activity.

— Albert G. Burger, MD

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Clinical THYROIDOLOGY
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Diagnosis of Subclinical Hypothyroidism Early in Pregnancy Is a Risk Factor for the Development of Severe Preeclampsia

Wilson KL, Casey BM, McIntire DD, Halvorson LM, Cunningham FG. Subclinical thyroid disease and the incidence of hypertension in pregnancy. Obstet Gynecol 2012;119:315-20.

SUMMARY

Background

Thyroid hormones have a number of actions on cardiovascular physiology and blood-pressure regulation, which are mediated by genomic mechanisms that cause ventricular remodeling or by direct effects. In most cases, cardiovascular aberrations follow long-term exposure to excessive or decreased hormone levels. Some evidence shows that subclinical hypothyroidism in some, usually older, patients can cause hypertension, heart failure, and atherosclerotic vascular disease; subclinical hypothyroidism has been proved to cause endothelial-cell dysfunction characterized by diminished nitric oxide production with impaired vasorelaxation. Pregnant women with untreated overt hypothyroidism are at risk for the development of preeclampsia, placental abruption, and heart failure. The objective of the authors was to investigate the relationship between hypertensive disorders and subclinical thyroid dysfunction in a large cohort of women who presented for prenatal care before 20 weeks of gestation.

Methods

This is a secondary analysis of a prospectively collected database initially designed to estimate normative values for thyroid hormone analyses in a large population of pregnant women at Parkland Hospital, University of Texas Southwestern Medical Center in Dallas. Serum TSH and FT_4 were obtained before 20 weeks of gestation. Women identified as having both abnormal serum TSH and FT_4 values were excluded from the study . Normal values were considered to be those that comprised the range from the 2.5th to the 97.5th percentile for the entire cohort and were calculated to be a TSH of 0.03 to 4.13 mU/L and an FT_4 of 0.9 to 2.0 ng/dl. Pregnancy outcomes were retrieved from the computerized perinatal database. Three groups of women were included for the study: euthyroid, subclinical hyperthyroid and subclinical hypothyroid. Hypertensive disorders were compared for the three cohorts described. Hypertensive disorders were defined and classified as followed: (1) gestational hypertension: persistent blood pressures of 140/90 mm Hg or more, occurring after 20 weeks of gestation, without evidence of proteinuria; (2) mild preeclampsia: women with hypertension who also had proteinuria, as determined by urine dipstick analysis from a catheterized specimen; and (3) severe preeclampsia: women with hypertension who had at least two of the following: proteinuria determined by dipstick analysis from a catheterized urine sample, blood pressure higher than 160/110 mm Hg, persistent headache, visual disturbances, right upper quadrant or epigastric pain, serum creatinine 1.2 mg/ml or more, serum aspartate transaminase levels more than twice the upper limit of normal, or thrombocytopenia less than 100,000/ml. Multivariable analyses were included to adjust for the effect modifiers of maternal age and weight as continuous measures, and categorical effects of race and parity.

Results

During the 30-month study, a total of 24,883 women who delivered singleton neonates weighing more than 500 g were included in this study. Of these, 23,771 (95.5%) had TSH values within the normal range and were considered to be euthyroid; 528 (2.1%) had TSH levels more than 4.13 mU/L with normal FT_4 levels (subclinical hypothyroidism). The remaining 584 (2.3%) had TSH levels less than 0.03 mU/L along with normal FT_4 levels (subclinical hyperthyroidism). Parity was the same in the three

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groups. Almost 80% of women were classified as Hispanic. The incidences of pregnancy-associated hypertensive disorders as well as mild and severe preeclampsia were compared between the three study cohorts. In general, as the serum TSH level increased in the entire population, the incidence of hypertensive disorders increased concomitantly (P for trend, 0.004). Women with subclinical hyperthyroidism who had the lowest TSH levels had an incidence of hypertensive disorders of 6.2%, as compared with 8.5% of euthyroid women and 10.9% of subclinical hypothyroid women. These differences when unadjusted were significant (P = 0.016); when adjusted for maternal age, race, parity, and weight using logistic regression, the only remaining significant association was in the cohort of women with subclinical hypothyroidism who were at increased risk for severe preeclampsia (adjusted odds ratio, 1.6; 95% confidence interval, 1.1 to 2.4; P = 0.031).

Conclusions

Women with subclinical hypothyroidism identified during pregnancy have an increased risk for severe preeclampsia as compared with euthyroid women. The authors are of the opinion that their findings are more biologically significant than clinically relevant and that their observations add to accruing data that subclinical hypothyroidism, a relatively common finding in women of childbearing age, may be associated with some adverse perinatal outcomes. Nonetheless, the authors remain convinced that routine prenatal screening for thyroid disorders should not be implemented until clear benefit is established.

ANALYSIS AND COMMENTARY

In their initial 2005 analysis of pregnancy outcome in women with subclinical hypothyroidism, these authors found that hypertensive disorders were not recognized as a complication. As in many other studies since then, the potential role of autoimmunity was not routinely considered; in the majority of studies, only one thyroid determination was obtained in each patient, status of iodine sufficiency was not mentioned, serum TSH and FT_4 reference ranges differ between studies, and other factors such as body-mass index, age, and ethnicity were not always included in the final analysis. Therefore, it is understandable that there is no consensus on the significance of subclinical thyroid disease and the obstetric, medical, and neonatal complications, which brings more fire to the heated argument among physicians and medical societies concerning universal versus selective screening in the obstetric population. Several issues are of clinical significance in the Wilson et al. study. The definition and diagnosis of subclinical hyperthyroidism is complicated by the fact that undetectable serum TSH values are found in some normal pregnant women in the first half of pregnancy; the majority of them do not have thyroid pathology and their serum TSH normalizes with the progression of pregnancy. Many of them may suffer from mild morning sickness or more severe hyperemesis gravidarum, known to be associated with dehydration and low blood pressure. Severe preeclampsia as a complication of hypothyroidism was reported in early publications by their group and others (2, 3), including some women with subclinical disease. The authors' conclusion that their "findings are of more biological significance than clinically relevant" is arguable. The authors discussed some of the published studies implicating subclinical hypothyroidism with cardiovascular effects and "causing endothelial cell dysfunction" (4) . They did not discuss the beneficial effect of thyroid hormone therapy in the management of subclinical hypothyroidism in relation to the course of gestational hypertension; in one study published almost 20 years ago (3), normalization of serum TSH at delivery significantly decreased the development of gestational hypertension. Therefore, it appears that their findings have clinical significance and that treatment of women with subclinical hypothyroidism is clinically indicated as recommended by the recent guidelines of the ATA (5) and the Endocrine Society (6)

— Jorge H. Mestman, MD

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Clinical THYROIDOLOGY
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Could Low-Molecular-Weight TSH Receptor Antagonists Become a Therapy for Graves' Orbitopathy?

van Zeijl CJ, van Koppen CJ, Surovtseva OV, de Gooyer ME, Plate R, Conti P, Karstens WJ, Timmers M, Saeed P, Wiersinga WM, Miltenburg AM, Fliers E, Boelen A. Complete inhibition of rhTSH-, Graves' disease IgG-, and M22-induced cAMP production in differentiated orbital fibroblasts by a low-molecular-weight TSHR antagonist. J Clin Endocrinl Metab 2012, March 14, 2012 [Epub ahead of print]. doi: 10.1210/jc.2011-2931.

SUMMARY

Background

Although some G-protein–coupled receptors are activated when their ligands bind at sites in crevices within their seven membrane-spanning domains, the TSH receptor is activated when TSH or TSH receptor (TSHR)–stimulating immunoglobulins bind to its extracellular domain. Small-molecule agonists/antagonists for several glycoprotein hormone receptors, including the TSHR, have now been reported that appear to act within the receptors' membrane-spanning domains and do not compete for TSH binding (1, 2). These compounds are proving useful for understanding how hormones act, but they also present the exciting prospect of a new approach for treating some endocrine diseases.

The small polycyclic compound Org-274179-0 was recently shown to act in FRTL-5 thyrocytes as a potent antagonist of the cyclic AMP responses to TSH and also to M22, a TSHR-binding human monoclonal antibody (1). Furthermore, in CHO cells expressing the human TSHR, Org-274179-0 blocked the cyclic AMP and also the phospholipase C responses to TSH and M22. It also blocked these responses in CHO cells expressing constitutively active human TSHR mutants (2). M22 did not stimulate CHO cells expressing LH or FSH receptors. In the current article, Org-274179-0 was tested for its effects on the release of cyclic AMP from adipocytes that were prepared from fibroblasts obtained from retroorbital fat removed from patients undergoing decompressive surgery for Graves' orbitopathy.

Methods

Cultures of Graves' orbital fibroblasts obtained from eight patients with active disease who had recently received large doses of corticosteroids and from six patients with inactive disease that had required no treatment for the previous 6 months were treated with factors that promote the fibroblasts' differentiation into adipocytes that express the TSHR. After three to seven passages, the adipocytes were grown to near-confluence, then preincubated with the phosphodiesterase inhibitor 3-isobutyl-1-methylxanthine for 30 minutes, then with Org-274179-0 (presumably dissolved in 6% DMSO) for 5 minutes, and finally they were exposed for 6 hours to: (1) recombinant human TSH; (2) IgG from a patient with high TSHR-antibody–binding activity or IgG from a control patient; or (3) M22 or to a control monoclonal IgG. Data on the mean (±SEM) levels of cyclic AMP in the culture medium were provided, but the number of wells of adipocytes from each patient assayed with each agent was not clear. Cyclic AMP levels were measured in the culture medium (which may not parallel cyclic AMP levels in intracellular compartments).

Results

Adipocytes from five patients were incubated with human TSH (hTSH; 10 mU/ml) plus increasing concentrations of Org-274179-0: the cyclic AMP response was reduced by 50% at about 2.5 nM, and complete inhibition was obtained at about 1 μM. Org-274179-0 had no effect on cyclic AMP released from cells incubated with vehicle alone. Adipocytes from three patients were incubated with IgG (1 mg/ml) from a

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patient with high TSHR-antibody–binding activity. Org-274179-0 reduced the cyclic AMP response by 50% at about 1 nM, but even at 1 μM, cyclic AMP levels remained somewhat elevated, probably reflecting the fact that the normal control IgG also increased cyclic AMP levels, both in the absence of inhibitor and also at the highest two concentrations of inhibitor. Adipocytes from a single patient were incubated with monoclonal M22 (500 ng/ml). Org-274179-0 reduced the cyclic AMP response by 50% at about 0.5 nM, but even at 1 μM, the cyclic AMP level remained somewhat elevated, probably reflecting the fact that the normal control human monoclonal antibody also increased cyclic AMP levels, both in the absence of inhibitor and at the highest concentrations of inhibitor. The inhibitor did not block the ability of forskolin to directly activate adenylate cyclase. It is not clear why samples from more patients were tested with hTSH than with M22 and IgG, nor is it clear which cultures came from patients with active versus inactive Graves' orbitopathy.

Conclusions

Nanomolar concentrations of Org-274179-0 inhibit the ability of TSHR to generate cyclic AMP in response to TSH, M22, or thyroid-stimulating IgG when added to adipocytes differentiated from Graves' retroorbital fibroblasts.

ANALYSIS AND COMMENTARY

Administration of small-molecule antagonists could become a clinically important form of therapy for Graves' disease if they are specific for the human TSHR in vivo and if they do not have major side effects at doses that are clinically effective. Blocking the actions of thyroid-stimulating immunoglobulins on orbital fibroblasts could also have a role in treating Graves' orbitopathy. However, orbitopathy does not develop in patients whose serum TSH levels are chronically elevated unless they also have Graves' disease, so it is clear that factors in addition to the prolonged stimulation of TSHR by immunoglobulins are at work. In this regard, the higher levels of hyaluronic acid (HA) that are known to be present in Graves' orbital fat and connective tissue are of interest. The authors previously reported that Graves' IgGs stimulate HA release from a much higher percentage of adipocytes from patients with Graves' disease than the percentage of these adipocytes that respond to hTSH (3). A recent report indicates that when Graves' adipocytes are exposed to M22 for 48 hours—in the absence of a phosphodiesterase inhibitor—the release of HA is mediated by phosphoinositide-3-kinase rather than by cyclic AMP–dependent protein kinase activity (4). It will therefore be important to learn how Org-274179-0 affects the HA and phospholipase C responses in adipocytes incubated under the conditions described in the current article. In passing, we note that incubation with Org-274179-0 (1 μM for four hours) slightly reduced the release of labeled TSH previously bound to membranes from TSHR-expressing CHO cells (2), which might indicate that high levels of the agent can affect the association of TSHR with membrane proteins, or the formation of TSHR multimers. Data in the current article indicated that a high concentration of Org-274179-0 increased cyclic AMP production in response to the single control IgG and monoclonal antibody used, yet it did not alter the response to M22 (or TSH) in the absence of the control IgG and monoclonal antibody. Perhaps this simply reflects a fluke in both of the controls, but it would be interesting to know whether similar effects are produced by other control IgGs, such as were used in the authors' previous study (3). Furthermore, high levels of Org-274179-0 actually increased expression of a cyclic AMP reporter in CHO cells that stably express the LH receptor as well (2). It will be fascinating to learn the results of studies of these agents, in both in vivo and additional in vitro models.

— Stephen W. Spaulding, MD

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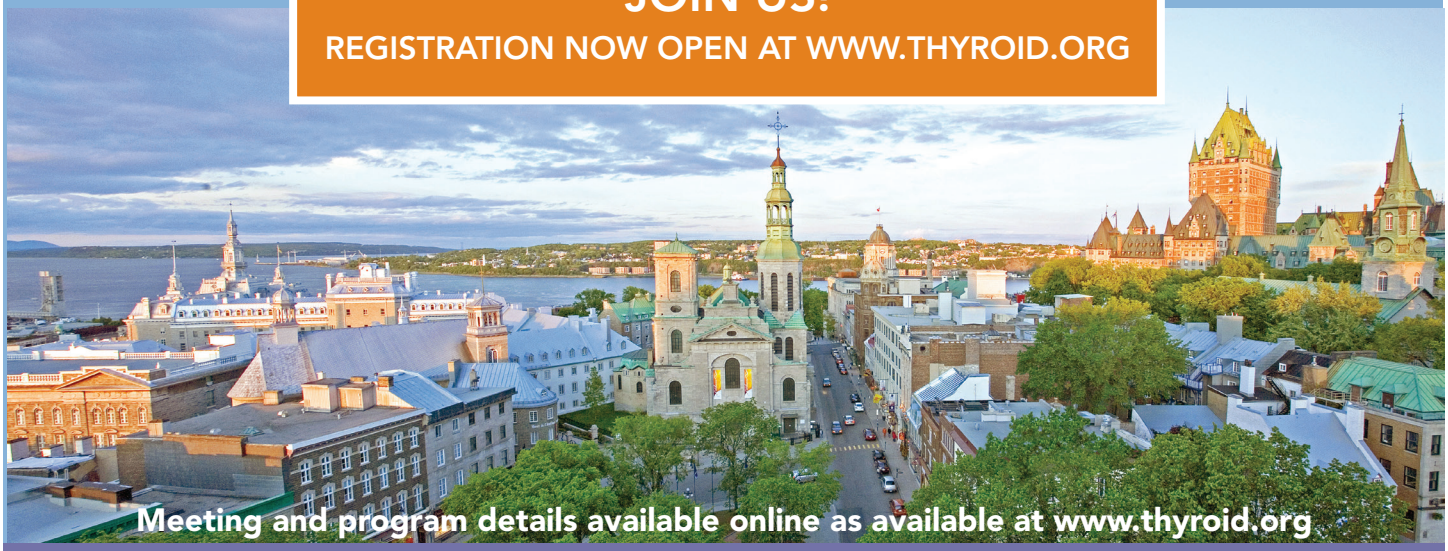

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