Clinical THYROIDOLOGY

NOVEMBER 2011
VOLUME 23 • ISSUE 11

AMERICAN THYROID ASSOCIATION
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VOLUME 23 • ISSUE 11 NOVEMBER 2011

APPROPRIATE DIETARY IODINE INTAKE DURING PREGNANCY IS IMPORTANT FOR MATERNAL AND FETAL THYROID FUNCTION

Fuse Y, Ohashi T, Yamaguchi S, Yamaguchi M, Shishiba Y, Irie M. **Iodine status of pregnant and postpartum Japanese women: Effect of iodine Intake on maternal and neonatal thyroid function in an iodine-sufficient area.** J Clin Endocrinol Metab. September 28, 2011 [Epub ahead of print].

SUMMARY

BACKGROUND

In early pregnancy, iodine requirements increase because of increased renal blood flow and glomerular filtration, which lead to increased iodine clearance and iodine loss in the urine. In later pregnancy, fetal demands for iodine increase, and iodine deprivation occurs because of the passage of iodine from the maternal circulation to the fetal–placental unit. In the postpartum period, additional iodine intake is needed to compensate for iodine loss into the breast milk. Recently, there have been increasing concerns about pregnant and lactating women, weaning infants, and older children who do not receive enough iodine in the countries that have been iodine-sufficient for several decades. In the United States and Canada, the American Thyroid Association and The Endocrine Society recommend iodine supplementation during pregnancy and lactation. The effect of dietary iodine intake during pregnancy on maternal and infantile thyroid function has not been well studied in iodine-sufficient areas, and there are few data on appropriate gestational age–specific reference ranges for urinary iodine (UI) excretion during pregnancy and lactation. The aim of this study was to examine the pattern of maternal UI excretion throughout gestation and to assess the influence of iodine status on maternal and neonatal thyroid function in an iodine-sufficient area.

METHODS

Between November 2005 and January 2007, healthy pregnant and postpartum women with no previous history of thyroid disease were consecutively recruited when they attended a routine antenatal clinic at Yamaguchi Hospital in Funabashi City, Chiba Prefecture, Japan. These women were prospectively studied during the three trimesters of pregnancy and the late puerperium at 5 to 6 weeks postpartum. Gestational dates were confirmed by ultrasound in the first trimester. Blood and random urine samples were taken from the

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participants once in each trimester and 1 month after birth; a heel-prick blood sample was taken between 72 and 120 hours after birth from all infants. The study group comprised 701 pregnant women, 545 postpartum women, and 722 newborn infants (365 boys and 350 girls). The mean (±SD) ages of the pregnant and postpartum women were 30.9±4.1 and 31.0±4.1 years, respectively. Serum thyrotropin (TSH), free thyroxine (T_4), and two thyroid autoantibodies (ThAb)—thyroperoxidase antibody (TPOAb) and thyroglobulin antibody (TgAb)—were measured in 729 serum samples obtained from 456 subjects in each trimester. Urine iodine concentration (IUC) was expressed relative to creatinine (Cr) excretion (UI/Cr; micrograms per gram of creatinine) or as a concentration in micrograms of iodine per 1000 ml of urine (micrograms per liter).

RESULTS

WHO/UNICEF/ICCIDD-recommended epidemiologic criteria based on a median UIC for assessing iodine intake in pregnant women are as follows: insufficient, <150 g/L; adequate, 150 to 249 g/L; more than adequate, 250 to 499 g/L; and excessive, ≥500 g/L. Criteria for lactating women and children less than 2 years of age are: insufficient, <100 g/L, and adequate, ≥100 g/L.

The overall median UIC during pregnancy was 219.0 µg/L, higher than that in postpartum women (135.0 µg/L). The prevalence of pregnant women with a low UIC (<100 µg/L) or a high UIC (>500 µg/L) was 16.1% and 22.2%, respectively. Urinary iodine excretion increased from 220.0 µg/L in the first trimester to 258.0 µg/L in the second trimester, decreased to 195.0 µg/L in the third trimester, and then remained at 137.0 µg/L postpartum. There were no significant direct correlations of UIC or UI/Cr with either serum TSH or free T_4 concentrations in any of the three trimesters. When the subjects were divided into two groups according to the serum TSH, with a cutoff value of 2.5 mU/L, the mean UIC and UI/Cr in the groups with a TSH of at least 2.5 mU/L had higher values as compared with the groups with <2.5 mU/L in each trimester. There was no significant difference in UIC between subjects with positive thyroid autoantibodies and those with negative antibodies. No significant correlation was found between neonatal TSH and maternal UIC or UI/Cr in each of the trimesters, gestational months, or postpartum period.

CONCLUSIONS

Iodine intake assessed by UIC in Japanese pregnant women is regarded as sufficient and not excessive according to World Health Organization criteria. Although the data are local, the authors' results provide additional information on the reference range for UIC throughout gestation in iodine-sufficient areas.

COMMENTARY

There is increased concerned in developed, iodine-sufficient countries, about the dietary intake of women of child-bearing age during pregnancy and the postpartum period (1). This Japanese study in a country with a high dietary intake of iodine reported a median UIC in pregnant women of 219 µg/L, significantly higher than the UIC in postpartum women, which was 135 µg/L. The authors did not mention whether supplementation of iodine was prescribed during pregnancy and lactation. They concluded that iodine intake assessed by UIC is sufficient in their population and not excessive. Supporting their data, the authors previously reported that the median UIC of schoolchildren from the Tokyo and Hokkaido were 282 and 288 µg/L, respectively (2), somewhat higher than in their pregnancy study. Some epidemiologic studies in certain areas with adequate or high iodine intake suggest that the incidence of subclinical hypothyroidism and autoimmune thyroiditis increases (3), but this phenomenon is still controversial (4). In the present study, there were no differences in the

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prevalence of positive autoimmunity between the women with high iodine intake and those with normal intake. One important clinical note, confirmed in this study, is the lack of relevance in the interpretation of isolated urinary iodine determination in a given patient. For the above reasons, we should not be surprised by the wide range in the UIC results in spot urine samples, ranging from 6.0 µg/L to 16,300 µg/L; therefore 16.1% of pregnant women and 35.7% in the postpartum women had iodine excretion <100 µg/L, considered insufficient by WHO/UNICEF/ICCIDD-recommended epidemiologic criteria (5). At the other extreme, 22.2% of pregnant women and 14.1% of postpartum women excreted >500 µg/L, considered excessive. Only the epidemiologic criteria in study populations based on median UIC are accepted in assessing iodine intake. UIC values are affected by many factors, such as the time of urine collection (fasting or postprandial) and spot versus 24-hour urine samples. The decrease in UIC in the postpartum period should remind us to advise our patients not to discontinue supplemental iodine (mostly in the prenatal vitamins) after delivery and to continue it throughout lactation. In summary, this study reassured us of the adequacy of dietary iodine supply in pregnancy in areas with sufficient iodine intake and of its beneficial effect on maternal and neonatal thyroid function, Because of the decrease in urinary iodine following delivery it reminds us of the need to continue iodine supplementation in the postpartum period in lactating women.

— Jorge H. Mestman, MD

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HAVING A LOW CIRCULATING LEVEL OF ADIPONECTIN IS AN INDEPENDENT RISK FACTOR FOR PAPILLARY THYROID CANCER

Mitsiades M, Pazaitou-Panayiotou K, Aronis KN, Moon H-S, Chamberland JP, Liu X, Diakopoulos KN, Kyttaris V, Panagiotou V, Mylvaganam G, Tseleni-Balafouta S, Mantzoros CS. **Circulating adiponectin is inversely associated with risk of thyroid cancer: in vivo and in vitro studies.** J Clin Endocrinol Metab. September 21, 2011 [Epub ahead of print]. doi: 10.1210/jc.2010-1908.

SUMMARY

BACKGROUND

Although the mechanism is not clear, obesity increases the risk and worsens the prognosis of several cancers (1), and epidemiologic data suggest that this is also true for thyroid cancer. Adiponectin is the most abundant adipokine in the circulation, but its level is lower in obese patients, so they appear to receive less of its insulin-sensitizing, antiinflammatory, antiproliferative and vasoprotective effects. In contrast, the blood levels of cytokines such as interleukin-6 (IL-6), as well as leptin, insulin and insulin-like growth factor 1 (IGF-1), which can have mitogenic effects, are higher in obesity. In some disease models, increasing the adiponectin level can be protective, although the results may vary according to the particular form of adiponectin being studied. Low total adiponectin levels are associated with various clinical cancers: the current paper examined whether there was an association between adiponectin levels and thyroid cancer in patients from Northern Greece.

METHODS

Adiponectin (presumably the total level) was measured by radioimmunoassay (along with IGF-1, IGF binding protein 3, and leptin) in fasting sera from 175 patients with various thyroid cancers, and from 107 controls who had had thyroidectomies for Graves' disease, toxic or nontoxic multinodular goiter, or cold nodules but had no thyroid or other cancers. Ten percent of the cancer patients and 25% of controls were male ($P<0.01$). All subjects were on "appropriate" hormone replacement: the mean thyrotropin (TSH) level was significantly higher in the controls than in the cancer patients (1.39 vs. 0.56 mIU/L), as were the mean free triiodothyronine and free thyroxine levels ($P<0.01$ for each comparison). The protein levels of the two classical adiponectin receptors (adipoR1 and adipoR2) were assessed by immunohistochemistry on a commercial thyroid cancer tissue array. AdipoR1 and adipoR2 mRNAs were measured by real-time–polymerase-chain-reaction assay on a commercial panel that included 32 papillary thyroid cancer (PTC) samples plus 4 normal thyroid tissue samples, and also on two thyroid cancer cell lines. These cell lines were also treated with an active proteolytic fragment of adiponectin, and several growth responses were assayed.

RESULTS

The mean adiponectin level was 13% higher in sera from controls than in that from patients with thyroid cancer ($P<0.001$). When the data from the patients with PTC and the controls were combined and divided into tertiles based on the adiponectin level, subjects in the highest tertile had significantly lower odds of being a patient with PTC, while the risk of PTC in the second and third tertiles was progressively greater, even after adjusting for confounders such as TSH, sex, age, body-mass index, diabetes, smoking and IGF-1 levels. Immunohistochemistry detected adipoR1 and adipoR2 in thyroid cancer samples, although the levels of adipoR1 and adipoR2 mRNA were significantly lower in PTC than in control thyroid samples, adjusted for age and gender. Incubating the thyroid cancer cell lines with globular adiponectin did not change their rates of proliferation or death.

CONCLUSIONS

A low circulating level of adiponectin is an independent risk factor for PTC. The absence of a direct effect of adiponectin on the growth or death of two thyroid cancer cell lines suggests that the negative association of adiponectin levels with PTC reflects decreased peripheral effect(s) of adiponectin.

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HAVING A LOW CIRCULATING LEVEL OF ADIPONECTIN IS AN INDEPENDENT RISK FACTOR FOR PAPILLARY THYROID CANCER

COMMENTARY

Adiponectin can affect cells (directly or indirectly) through pathways regulated by adenosine monophosphate–activated protein kinase (AMPK), p38, nuclear factor kB, jun N-terminal kinase (JNK), signal transducer and activator of transcription 3 (Stat3), Akt, ceramidase, peroxisome proliferator–activated receptors (PPARs), and/or insulin receptor substrate (IRS2) (1-3). Adiponectin can also directly bind to certain growth factors, inhibiting their ability to interact with receptors. Drugs like salsalate as well as some thiazolidinediones and angiotensin-receptor II blockers can raise adiponectin levels, but whether such agents might also affect cancer is not known. One should note that adiponectin levels can also be raised by extensive aerobic exercise or by a Mediterranean diet.

It is not clear why the results of the leptin assays performed in this study were not reported. Recent papers indicate that circulating leptin levels are not only increased in obesity, but are also associated with PTC; that leptin receptor levels are increased in PTCs; and that the levels of both leptin and its receptor are associated with more aggressive PTC behavior.

— Stephen W. Spaulding, MD

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ALL FORMS OF THYROID NODULE CALCIFICATION SEEN ON COMPUTED TOMOGRAPHY ARE ASSOCIATED WITH MALIGNANCY

Wu CW, Dionigi G, Lee KW, Hsiao PJ, Shin P, Tsai KB, Chiang FY. **Calcifications in thyroid nodules identified on preoperative computed tomography: Patterns and clinical significance.** Surgery 2011. September 10, 2011 [Epub ahead of print]. doi:10.1016/j.surg.2011.07.032.

SUMMARY

BACKGROUND

Several published studies show that a combination of sonographic features such as solid texture, hypoechogenicity, microcalcifications, macrocalcifications, and intranodular vascularity predict that a nodule is more likely to be malignant (1-3). This study examines the patterns and clinical importance of the calcification of thyroid nodules seen on preoperative computed tomography (CT).

METHODS

This was a retrospective review of all patients who had a thyroidectomy performed by a single head and neck surgeon at a tertiary referral center from January 2004 through May 2010. Most patients had the thyroidectomy because they had a large or substernal goiter or cytologic studies suggested malignancy. The CT scans were evaluated by two experienced head and neck surgeons and a radiologist who had no knowledge of the original CT interpretation or histopathological diagnosis.

The thyroid calcifications were put into one of four categories: (1) peripheral calcifications (coarse curvilinear eggshell-like pattern); (2) coarse calcification (large, amorphous calcifications >2 mm); (3) single punctate calcification (intranodular single microcalcification <2 mm); or (4) multiple punctate calcifications (multiple intranodular microcalcifications <2 mm). If a lesion had punctate calcifications and another pattern, the nodule was classified as just punctate microcalcifications. The calcification type on CT was compared with the histopathological findings.

RESULTS

During the study period, 488 patients underwent thyroidectomy, and 383 (78.5%) had a preoperative CT scan available for review. The average age was 49.3 years, with a male-to-female ratio of 1 to 2.54. A total of 114 (29.8%) of patients were found on histopathology to have thyroid cancer. Intrathyroidal calcifications were noted in 125 (35%) of patients. Most of the benign lesions with calcifications were associated with nodular goiter (65 of 70; 93%) and most of the malignant calcified lesions were papillary thyroid carcinoma (59 of 65; 91%). Calcifications were noted in 57% (65 of 114) of the malignant nodules and 26% (70 of 269) of the benign nodules. When calcification was seen in a clinically solitary thyroid nodule, the nodule was malignant in 35 of 42 patients (83%).

CONCLUSION

There was a strong association between CT-detected calcifications and thyroid malignancy, especially with single or multiple punctate calcifications (52 of 54; 70%) or patients in whom calcifications were noted within a solitary nodule. Nearly all of the microcalcifications were associated with papillary carcinoma (49 of 52; 94%). Peripheral or egg-shell calcifications were associated with malignancy in 22% (2 of 9) cases. Of the cases with coarse dystrophic intranodular calcifications, 21% (11 of 52) were associated with a malignant nodule. Although CT imaging is not commonly obtained and not recommended by the 2009 revised ATA guidelines for the evaluation of a thyroid nodule (4), these findings provide additional information to help guide the selection of nodules for biopsy and/or extent of surgery.

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COMMENTARY

In the past few years, several guidelines (4,5), including the 2009 ATA guideline do not recommend preoperative cross-sectional anatomic imaging with CT scanning or magnetic resonance imaging. There are clinical scenarios to obtain preoperative cross-sectional imaging to fully assess: (1) the extent of substernal goiter, (2) tracheal narrowing, and (3) nodal involvement, especially deeper than the tracheal esophageal groove, in the anterior mediastinum, or high in level 2 (under the mandible). This report provides the CT equivalent of what we already know about the increased risk of malignancy with sonographic evidence of microcalcifications and macrocalcifications of thyroid nodules. This report supports that most of the malignant calcified lesions were papillary carcinoma (91%) but that calcification is also associated with follicular carcinoma (3 of 5; 60%) but less commonly in follicular adenoma (3 of 26;12%). Of the 31 follicular neoplasms on cytology, 6 of these nodules had calcifications and half had cancer. Thus, this CT study confirms sonographic evidence that microcalcifications are highly associated with papillary thyroid carcinoma and either egg-shell or dystrophic calcifications are also associated with thyroid malignancy, but with less frequency. Thus, when a preoperative CT scan of a large goiter or a substernal goiter shows thyroid nodules with calcifications, especially punctate single or multiple microcalcifications, these nodules should be biopsied to help guide the extent of surgery.

— Stephanie L. Lee, MD, PhD

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TELOMERE LENGTH AND TELOMERASE EXPRESSION ARE SIMILAR IN FAMILIAL AND SPORADIC PAPILLARY THYROID CANCER

Jendrzejewski J, Tomsic J, Lozanski G, Labanowska J, He H, Liyanarachchi S, Nagy R, Ringel MD, Kloos RT, Heerema NA, de la Chapelle A. **Telomere length and telomerase reverse transcriptase gene copy number in patients with papillary thyroid carcinoma.** J Clin Endocrinol Metab. September 7, 2011 [Epub ahead of print].

SUMMARY

BACKGROUND

Papillary thyroid cancer (PTC) is familial in 5% to 10% of cases, but the basis for the inheritance is unknown. One group reported that patients with familial PTC had a shorter-length telomere and that there was increased telomerase activity in patients with familial PTC as compared with those who had sporadic PTC (1). Telomeres are the unique DNA caps on the ends of chromosomes that protect them from degradation. Telomerase is a reverse transcriptase enzyme that is necessary for synthesis of the telomere. The discovery of the telomere and telomerase was the basis for the Nobel Prize in Medicine in 2009. Genetic integrity is lost as telomeres shorten, and this is thought to play a role in aging.

The current study attempted to confirm the findings of the Italian group (1) in patients with familial PTC in the United States.

METHODS

The investigators studied 42 patients with familial PTC from separate families; the proband had to have at least two first- or second-degree relatives with PTC. The results were compared with 65 sporadic cases. The female/male ratio and ages were similar in the two groups. Using white cells, they measured telomere length and telomerase gene copy number by a quantitative real-time polymerase chain reaction assay. In a subset of patients from both groups and in normal controls, telomere length was measured by fluorescence in situ hybridization (FISH) and telomerase mRNA was measured.

RESULTS

The mean telomere length and telomerase gene copy number were nearly identical in both the patients with familial and those with sporadic PTC. When telomere length was measured by FISH, there was also no significant difference between the two groups of patients. In addition, the telomerase mRNA did not differ among the patients with PTC and the controls.

CONCLUSIONS

The results showed no difference between familial and sporadic PTC with regard to telomere length, telomerase copy number, or expression in this cohort, and therefore do not confirm the previous study.

COMMENTARY

It is possible that the differences between the Italian and U.S. studies are due to the selection of patients in each study. Since there is considerable discrepancy between the results of the two studies, it would be desirable to have additional studies of telomere length in familial PTC to clarify this point. From a hypothetical point of view, longer telomeres may prevent cells from degradation. However, it is also possible that increased telomerase activity is a compensatory mechanism to prevent further shortening of the telomere in some cancer cells. Increased telomerase activity has been found in more aggressive thyroid cancers (2).

Based on the current article, it is likely that the genetic basis for familial PTC is still unknown. From a clinical point of view, the only marker is the family history.

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In a recent encounter with a patient who had several first-degree relatives with PTC, I used this history as the basis for my recommendation for thyroidectomy when fine-needle aspiration biopsy of her nodule was inconclusive. In such an instance, a molecular marker could play a decisive role.

— Jerome M. Hershman, MD

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PAX8-PPARG REARRANGEMENT OCCURS IN ONLY 1.9% OF FOLLICULAR ADENOMAS AND IS LIKELY TO BE AN ONCOGENE MARKER FOR FOLLICULAR CARCINOMA

Klemke M, Drieschner N, Laabs A, Rippe V, Belge G, Bullerdiek J, Sendt W. **On the prevalence of the PAX8-PPARG fusion resulting from the chromosomal translocation t(2;3)(q13;p25) in adenomas of the thyroid.** Cancer Genet 2011;204:334-9.

SUMMARY

BACKGROUND

Distinguishing follicular adenomas from follicular carcinomas in thyroid fine-needle aspiration biopsies (FNAB) is a major diagnostic challenge. Molecular markers may help to achieve this distinction. The chromosomal rearrangement t(2;3)(q13;p25) is a recurrent cytogenetic aberration in follicular neoplasias of the thyroid leading to a fusion of the genes encoding the thyroid-specific transcription factor PAX8 and the peroxisome proliferator–activated receptor gamma (PPARγ). When first described the PAX8-PPARG rearrangement was considered to be a marker of follicular carcinoma (1). However, it was also found in follicular adenomas with a prevalence that ranged from 0 to 54.5% in different reports (summarized in the paper being reviewed here). The purpose of this study was to determine the prevalence of the PAX8-PPARG rearrangement in a large series of follicular adenomas using frozen tissue samples.

METHODS AND RESULTS

Tissue samples were snap frozen at surgery. The PAX8-PPARG rearrangement was detected by two methods: fluorescence in situ hybridization (FISH, a cytogenetic method) and by reverse-transcription polymerase chain reaction (RT-PCR).

Of 192 follicular adenomas, the authors identified only two tumors that were positive for the PAX8-PPARG rearrangement. In a review of 16 reports in which the rearrangement was detected by RT-PCR, it was found in 35.9% of 245 follicular carcinomas and in 8.2 % of 281 follicular adenomas. However, when the data in the literature using the cytogenetic FISH method for detection is combined with that of the authors, only 5 of 265 (1.9%) were positive for the PAX8-PPARG rearrangement.

CONCLUSIONS

The results indicate that the chromosomal t(2;3)(q13;p25) rearrangement and the resulting fusion of PAX8 and PPARG is rare in follicular adenomas. Its prevalence is overestimated in studies using RT-PCR.

COMMENTARY

Because molecular studies will be increasingly used in the evaluation of thyroid biopsy material, the results of this brief report are very important. In recent studies of FNAB material, the PAX8-PPARG rearrangement has been studied. It was found in 1 of 84 biopsies in one study with the pathology showing a follicular carcinoma (2), but it was not was found in any of 235 samples in another biopsy study (3). These studies were all done by RT-PCR, the method that could lead to false positives according to the current report. However, because of the rarity of the PAX8-PPARG rearrangement, only 8.2% when detected by RT-PCR, it is probably appropriate to send patients who have this molecular marker to surgery, although the data from this study suggest that false positives are lower than previously reported, even by RT-PCR. Some believe that large follicular adenomas are precursors to follicular carcinoma. The presence of the PAX8-PPARG rearrangement provides some evidence for this concept. Nevertheless, the RT-PCR may result in a fourfold increase of false positive diagnosis of follicular carcinoma when the pathologic diagnosis is follicular adenoma.

— Jerome M. Hershman, MD

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INEXPERIENCE, CYSTIC NODULES, AND MACROCALCIFICATIONS OFTEN RESULT IN INADEQUATE THYROID BIOPSY SPECIMENS

Choi SH, Han KH, Yoon JH, Moon HJ, Son EJ, Youk JH, Kim EK, Kwak JY. **Factors affecting inadequate sampling of ultrasound-guided fine-needle aspiration biopsy of thyroid nodules.** Clin Endocrinol (Oxf) 2011;74:776-82. doi: 10.1111/j.1365-2265.2011.04011.x.

SUMMARY

BACKGROUND

Inadequate samples are reported in 1% to 20% of thyroid fine-needle aspiration biopsies (FNAB). The purpose of this study was to evaluate the ultrasound features and clinical factors that contribute to inadequate sampling.

METHODS

FNAB was performed using a 23-gauge needle; usually two punctures were made in the nodule of interest. An adequate specimen was classified as having a minimum of six groups of cells with more than 10 cells per group. Malignant ultrasound features were marked hypoechogenicity, irregular margins, microcalcifications, and a taller than wider shape; a positive ultrasound had at least one of these features.

RESULTS

Of 4077 FNAB performed between April 2008 and December 2008, a total of 654 (16.1%) were categorized as inadequate. With regard to nodule size, the rate of inadequate samples was 21.2% for nodules <5 mm, 15.3% for those 5 to 9.9 mm, 14.2% for those 10 to 19.9 mm, and 18.0% for those >20 mm. The rate of inadequate sampling was 23.6% of nodules with dominant cysts as compared with 15.6% for solid nodules. With regard to calcifications, nodules with macrocalcification showed a significantly higher rate of inadequate sampling (21.3%) than those in the microcalcification group (11.9%) or those without calcification (15.6%). Hypoechogenicity, irregular margins, and taller-than-wide shape were not associated with the rate of inadequate sampling.

Experienced doctors were those performing >300 FNAB/year and inexperienced did fewer than that. The rate of inadequate sampling was significantly higher for those less experienced 25.8% (51 of 198) than for the more experienced, 15.6% (603 of 3879). Cyst dominance and macrocalcification were independent factors that predisposed to inadequate samples for experienced physicians in multivariate analysis, but none of the ultrasonographic factors was significant in the inexperienced group.

CONCLUSIONS

Cyst dominance and macrocalcifications in thyroid nodules and inexperience of the performing doctor were factors associated with high rates of inadequate samples of FNAB in thyroid nodules.

COMMENTARY

Getting a report that the FNAB was inadequate is frustrating for both the patient and the physician who does the biopsy. Unfortunately, this happens more in teaching hospitals, where trainees perform some of the procedures, than may be the case when a physician with considerable experience does it without a trainee. The ATA guideline recommends that a repeat FNAB be performed when the result is inadequate (1). In the current study, the result was considered inadequate even when there was abundant colloid. In such an instance, the Bethesda conference suggested that this result should be considered benign even without six groups of follicular cells (2). This would have reduced the number in the inadequate category in this Korean study. In my experience there are some stubborn nodules that just do not yield sufficient material for diagnosis, even with a third FNAB. Also, as noted in this study, nodules <5 mm are more likely to give an inadequate result. Most of these small

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nodules can be watched, unless there are a variety of criteria indicating that they are malignant.

As noted in a Clinical Thyroidology article in August 2011, a possible maneuver to avoid unnecessary surgery in such an instance is to perform a positron-emission tomography–computed tomography (PET/CT) scan, provided the nodule is >1.5 cm (3). If the PET/CT scan is negative, the possibility of malignancy is very small. If it is positive, the possibility of malignancy rises to 62%. As one letter writer noted, this is a very expensive diagnostic test, but it is still cheaper than surgery.

— Jerome M. Hershman, MD

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Clinical THYROIDOLOGY
AMERICAN THYROID ASSOCIATION FOUNDED 1923

IS TRANSESOPHAGEAL ECHOGRAPHY USEFUL TO PREDICT THROMBOEMBOLIC COMPLICATIONS IN HYPERTHYROID PATIENTS WITH LONG-STANDING ATRIAL FIBRILLATION?

De Souza MV, Duarte MM, Coeli CM, Vaisman M. **Atrial fibrillation & hyperthyroidism: relation between transesophageal markers of a thrombogenic milieu and clinical risk factors for thromboembolism.** Clin Endocrinol. September 26, 2011 [Epub ahead of print].
doi: 10.1111/j.1365-2265.2011.04232.x.

SUMMARY

BACKGROUND

Atrial fibrillation is a feared complication of hyperthyroidism. It occurs mostly in severe forms of hyperthyroidism and can be a source of thromboembolic events. Patients with atrial fibrillation usually undergo anticoagulation with warfarin or even heparin, regardless of the recommendation that patients younger than 55 years of age should undergo anticoagulation only if they are at particular risk. Transesophageal echography allows visualization of the cardiac atria, including the left arterial appendage, and can reliably recognize the presence of thrombi. It may also provide information about low velocities of blood flow in atrial appendages that favor thrombi formation. A better appreciation of the need for anticoagulation can therefore be given with this technique and the information may be correlated with clinical risk factors for embolism.

METHODS AND RESULTS

The investigators studied 31 patients with severe hyperthyroidism, most of whom had Graves' disease; the ages range from 18 to 65 years. Most of the patients were pretreated with antithyroid drugs. One third were men, a higher percentage than regularly seen in hyperthyroidism. In nearly half of the patients, atrial fibrillation (29 cases with persistent atrial fibrillation) was present for 6 months or more, and 23% of the patients had had fibrillation for only the past month. Hyperthyroidism was diagnosed a median time of 24 months before investigation. It was severe, since median free thyroxine was 68 pmol/L and serum total triiodothyronine was 6.6 nmol/L. A history of hypertension was present in 68% of the patients and 58% had a history of congestive heart failure.

Clinical risk evaluation was based on the CHADS2 (history of congestive heart failure, hypertension, age >75 years, diabetes mellitus, previous strokes) score (1). Using this stratification, groups of low-, moderate-, and high-risk patients were formed: 23% belonged to the low-risk, 19% to the moderate-risk, and 58% to the high-risk group. Transesophageal echocardiography (TEE) findings were compared with the CHADS2 classification. TEE revealed that 23% of patients had impaired systolic function with the median left atrial diameter slightly increased. Spontaneous echo contrast (signaling turbulence) was visualized in 55% and thrombi in 32% of the patients, suggesting that left atrial function was moderately reduced in 70% of the patients. Using strict criteria for the presence of an increased risk of thromboembolic events (called thrombogenic milieu), 45% of the patients needed warfarin treatment. Interestingly there was no correlation between the presence of a thromboembolic milieu and traditional risk factors such as hypertension and diabetes. The commonly recommended age limit of 55 years for warfarin treatment was not relevant. As expected, thromboembolic milieu was more prevalent with a longer history of atrial fibrillation, while the duration of thyroid disease did not affect the thromboembolic milieu.

CONCLUSIONS

The group of patients was characterized by severe and long-standing hyperthyroidism and atrial fibrillation. Significant thromboembolic risk by TEE was documented in 45% of the patients, who thus needed warfarin therapy. The results of TEE did not correspond to the evaluation by CHADS2 score for atrial fibrillation–related stroke risk. Interestingly, there was no correlation between the presence of thrombogenic features and age, diabetes, hypertension, or heart failure. As expected there was a strong correlation with the duration of atrial fibrillation.

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COMMENTARY

This group of patients is unusual for its severe and long-standing hyperthyroidism and high percentage of comorbidities favoring high thromboembolic risk. In the opinion of the authors, TEE allowed restricting warfarin treatment to a subgroup of 45% of the patients. This might be an important finding, particularly in an area in which the clinical follow-up of patients on anticoagulation therapy is not easy. Should we now conclude that TEE is a highly desirable procedure in most or even all patients with hyperthyroidism complicated by atrial fibrillation? For a rational answer, several aspects have to be considered. One is to balance the morbidity of TEE and its cost—both of which are not negligible—with the inherent risk of warfarin treatment. This certainly depends on the local availability of an excellent medical follow-up. Moreover, should cardioconversion be considered at a later time, TEE will need to be repeated. Finally, even a normal TEE result does not exclude the occurrence of thrombi at any later time. Therefore, I believe, that in real life, most patients with atrial fibrillation—whether they have hyperthyroidism or not—should undergo anticoagulation therapy. Thus, in my personal opinion, TEE for defining those patients to be treated by warfarin is justified in only a few circumstances.

— Albert G. Burger, MD

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WHAT IS THE ROLE OF DEIODINASE TYPE 2 POLYMORPHISM FOR THE REGULATION OF THE SET POINT BETWEEN SERUM TSH AND FT_4?

Hoftijzer HC, Heemstra KA, Visser TJ, le Cessie S, Peeters RP, Corssmit EP, Smit JW. **The type 2 deiodinase ORFa-Gly3Asp polymorphism (rs12885300) influences the set point of the hypothalamus-pituitary-thyroid axis in patients treated for differentiated thyroid carcinoma.** J Clin Endocrinol Metab 2011;96:E1527-E1533. Epub June 29, 2011.

SUMMARY

BACKGROUND

It is believed that each individual has a specific set point that controls thyroid function and that the genetic background underlying this setting is of crucial importance. Even before the genetic era, evidence emerged that a human being has a much narrower range of free thyroxine (T_4) and thyrotropin (TSH) variations than defined by the reference range, indicating a remarkable stability of thyroid function in a healthy individual (1,2). Some known factors are race and obesity. The activating and inactivating metabolism of thyroxine is certainly another possible factor. As for the deiodinases, several polymorphisms have been described with the possibility for differences in their activities, a question raised by several research groups. For instance, in young and healthy subjects (but not in elderly ones) with the polymorphic variant D2-ORFa-Asp (rs12885300), lower free T_4 levels despite normal TSH values have been described (3). Since thyroid function can be affected by many environmental situations in normal subjects, it is difficult to isolate the effect of genetic differences in the deiodinase structure from such confounding effects. In the present study, this problem was avoided by studying patients who had undergone thyroidectomy and radioactive iodine ablation.

METHODS AND RESULTS

The investigators studied 151 consecutive thyroid cancer patients. Only cured patients were included; patients taking interfering drugs (e.g., dopamine and derivatives, amiodarone, and steroids) were excluded. The observation period lasted from 1992 to 2007, yielding a large number of serum TSH and thyroxine levels. For each individual a mean of 12 measurements was evaluated (with a large range, from 4 to 32). The average (±SD) therapeutic dose of thyroxine was 2.18±0.97 μg/kg, a rather high dose. For comparison of the set point of the hypothalamic–pituitary–thyroid axis, the correlation between the natural logarithm of TSH and free T_4 was calculated. Genotyping was performed in 2007. Four polymorphisms were studied, three of which did not show any significant difference for serum free T_4 and TSH as compared with the wild-type values. For the polymorphism of interest, D2-rs12885300 (D2-ORFa-Gly3Asp), 70 patients with wild-type (Gly/Gly), 64 heterozygotes (Gly/Asp), and 13 homozygotes (Asp/Asp) were studied. Interestingly, there were significant differences between homozygotes and the wild-type and heterozygote groups. Expressed in clinical terms, for a free T_4 level of 10 pmol/L, serum wild-type TSH would be 5.64 mU/L, while the homozygote TSH would be 13.46 mU/L. For a free T_4 of 20 pmol/L, the difference in the corresponding values is less pronounced, 0.225 and 0.42 mU/L.

CONCLUSIONS

In completely athyroid yet otherwise healthy patients, the homozygote variant of D2-rs12885300 changes the set point of the hypothalamic–pituitary–thyroid axis, suggesting a reduced negative feedback of T_4 in these subjects. No deductions on possible alterations of thyroid hormone metabolism could be made, since only a few serum triiodothyronine (T_3) and reverse T_3 values were available.

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COMMENTARY

It is remarkable that in this particular clinical setting such differences in the set point of the hypothalamic–pituitary–thyroid axis could be identified. The results clearly indicate a crucial role of deiodinases in the central control of TSH. The clinical consequences are not to be neglected, as exemplified above for serum TSH concentrations corresponding to free T_4 levels of either 10 or 20 pmol/L. These results are comforting for the clinician who often finds considerable differences in the amount of thyroxine needed to suppress serum TSH. Nevertheless, they do not explain the large interindividual differences seen in normal subjects, for whom many additional parameters can influence the ratio between serum TSH and free T_4. This fact is well documented in earlier works (1). To what extent, the genetic background really affects the clinical data in normal subjects remains uncertain.

— Albert G. Burger, MD

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AMERICAN THYROID ASSOCIATION
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Call for Proposals – American Thyroid Association (ATA) Research Grants -- Deadline: January 31, 2012

Electronic Submission: Proposals must be submitted electronically through the research grant application feature on the ATA website, www.thyroid.org.

The American Thyroid Association (ATA) is pleased to announce the availability of funds to support new investigator initiated research projects in the area of thyroid function and disease. Topics may include, but are not limited to, Thyroid Autoimmunity, Iodine Uptake and Metabolism, Thyroid Cancer, Medullary Thyroid Cancer, Clinical Disorders of Thyroid Function, Thyroid Hormone Action and Metabolism, Thyroid Imaging, Thyroid Nodules and Goiter, Thyroid Development and the Brain. Research awards are intended to assist new investigators in obtaining preliminary data for submission of a more substantial application (i.e., to the NIH). Research grants, up to $25,000 annually, will be awarded for two year terms based on receipt and review of a satisfactory progress report from funded investigators in the fourth quarter of the first year of funding.

Guidelines for All Research Grant Proposals: As mentioned above, research awards are targeted for funding of new investigators to obtain preliminary data for submission of a more substantial application (i.e., to the NIH). Interested investigators should submit a brief description of the proposed research by January 31, 2012.

Eligibility of Applicant and Use of Funds Guidelines:

a. New investigators are individuals who are less than 6 years from completion of their post-doctoral fellowship and have never been a PI on an NIH RO1 or equivalent grant (recipients of NIH R29, R21 and KO8 awards are eligible).
b. Faculty members (MD and PhD) are eligible; however, those investigators who have reached the rank of associate professor or higher are not eligible.
c. Postdoctoral fellows are eligible if their department provides written confirmation that at the time of the award the applicant will have a junior faculty position.
d. Students working towards an MD or a PhD are not eligible.
e. Investigators and individuals who have previously received ATA, ThyCa or THANC awards are not eligible.
f. Applications are limited to one per individual researcher.
g. The funds can be used for direct costs associated with the proposal, including technician's salary, supplies or equipment but not for PI's salary.
h. Recipients of ATA grants must be ATA members (submit application online if not already a member). For new members, membership dues for the first year will be waived.

Proposal Requirements (please submit the following documents online):

1. Demographic information: Name /affiliation of applicant, complete work/home contact information – submitted into online system (do not include in grant proposal).
2. Grant Proposal (A **s**hort proposal that should be no longer than 900 words (including selected references) and no more than three double-spaced pages in 12 point type with 1" margins. These space requirements are absolute and nonconformance will preclude review. Do not include letterhead, name, address, institution, etc. This short proposal should include:
   - Title of proposed study
   - Background to the project
   - Hypothesis and/or outline of proposed studies
   - Outline of methodology
   - Anticipated results and implications
   - A short statement of how the grant will aid the applicant
   - Selected References (e.g. Uchino S, et al. World J Surg 2002;26:897-902)

   a. CV (NIH-style CV – up to 4 pages) - including evidence that the applicant is a new investigator with date of completion of postdoctoral training and current grant support (if any). In the case of postdoctoral fellows, written confirmation from the department chair must be provided that the applicant will have a junior faculty position at the time of the award. **Note: Without a suitable CV, applications will not be considered.**
3. Cover letter

Grant Review: The ATA Research Committee will rank proposals according to their scientific merit. Authors of selected proposals will be notified in March 2012 and invited to submit a complete grant application.

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

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

As a Friend of the ATA we will send you:

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

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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.

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

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

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