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Clinical Thyroidology

EDITORS' COMMENTS

This is the eleventh 2010 issue of *Clinical Thyroidology*.

EDITORS' CHOICE ARTICLES are particularly important studies that we recommend you read in their entirety.

SEARCH FOR PREVIOUS ISSUES OF *Clinical Thyroidology* Many of our readers have asked for a quick way to find articles published in this journal over the past years. Now you can access previous issues using key words, author names, and categories such as Hyperthyroidism, Thyroid cancer, or other terms pertaining to thyroidology. You will find this by simply clicking the following URL: http://thyroid.org/professionals/publications/clinthy/index.html.

FIGURES The articles in *Clinical Thyroidology* contain figures with the ATA logo and a CT citation with the volume and issue numbers. We encourage you to continue using these figures in your lectures, which we hope will be useful to you and your students.

WHATS NEW On the last page of the journal, in addition to the section HOT ARTICLES AND REVIEWS, we have added CURRENT GUIDELINES that have relevance to thyroidologists, endocrinologists, surgeons, oncologists, students, and others who read this journal. We hope you will find this useful.

We welcome your feedback and suggestions.

Ernest L. Mazzaferri, MD, MACP
Jennifer A. Sipos, MD

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Over half (55%) of the pregnant women with clear abnormalities suggestive of autoimmune thyroiditis with or without thyroid insufficiency would be missed if only the high-risk criteria are examined.

Horacek J, Spitalnikova S, Dlabalova B, Malirova E, Vizda J, Svilias I, Cepkova J, Mc Grath C, Maly J. Universal screening detects two-times more thyroid disorders in early pregnancy than targeted high-risk case finding. Eur J Endocrinol 2010;163:645-50. EJE-10-0516 [pii];10.1530/EJE-10-0516 [doi]

SUMMARY

BACKGROUND

Chronic autoimmune thyroiditis is often manifested by thyroid peroxidase antibodies (TPOAb) with or without thyroglobulin antibodies (TgAb), which is associated with a twofold to fourfold increase in the miscarriage rate and premature deliveries. Moreover, there is a 30 to 50% chance of postpartum thyroiditis (PPTD) developing in a pregnant woman with positive TPOAb. Even in regions of sufficient iodine intake, chronic autoimmune thyroiditis is still the most common cause of hypothyroidism, which often is at subclinical levels, and may further aggravate the increased requirement for thyroid hormones during pregnancy. The lack of thyroid hormone is associated not only with an increased risk for obstetrical complications, but also with impaired neuropsychological development early in the development of the child.

As levothyroxine replacement therapy can easily reduce the risk for obstetrical complications, even in euthyroid women with positive TPOAb levels, active screening for thyroid disease in pregnancy seems reasonable and cost-effective; yet screening pregnant women or those of childbearing age remains controversial. The Endocrine Society Clinical Practice Guideline recommends targeted case finding by measuring serum thyrotropin (TSH) in women with a specified high risk for thyroid disease. Studies that directly compared the outcome of universal screening with that of case findings based on a similar set of risk factors found that this approach would miss about a third of pregnant women with hypothyroidism. In addition, they focused on hypothyroidism, but also found women with positive TPOAb in 8% of their population, which is a similar fraction as that found in other studies, with most of them (73%) being euthyroid. As positive TPOAb confers risks of obstetric complications and PPTD independent of hypothyroidism, this variable seems worth including in the screening panel.

The yield and cost-effectiveness of screening are dependent not only on the range of the screened population, but also on the variables used and on assay cutoffs. Moreover, the reference range provided by the manufacturer is not suitable for women in early pregnancy, and the cutoffs should be adjusted. This is a pilot study of screening non-selected pregnant women for autoimmune thyroiditis with or without hypothyroidism using TSH, TPOAb, and free thyroxine (FT_4), demonstrating that fewer than half of the women screened would have been identified if only those fulfilling the recommended criteria for targeted case finding were examined.

SUBJECTS AND METHODS

This is a study from University in Hradec Kralove, Charles University in Prague, Sokolska, Hradec Kralove, Czech Republic.

Study Physicians

Regional gynecologists were offered the addition of three thyroid-related variables into the prenatal screening panel in the 9th to 11th week of pregnancy that is offered to all pregnant women in this study. They explained the reasons for thyroid testing to the pregnant women and the possible participation of an endocrinologist in the follow-up and received written informed consent from the pregnant women. Funding was sufficient to recruit 400 women.

Laboratory Studies

Serum samples were sent to the same laboratory responsible for the standard prenatal screening and were assayed for TSH, FT_4, and TPOAb. The TSH reference range of 0.15 to 5.0 mIU/L was measured by immunoradiometric assay, the FT_4 reference range of 11 to 23 pmol/L , and the TPOAb reference range of <12 IU/ml were all performed by national laboratories such as Immunotech, Beckman Coulter. The interassay coefficient of variation was 5.5% for TSH, 8.4% for FT_4, and 7.5% for TPOAb. The recommended cutoff values for screening in pregnancy have

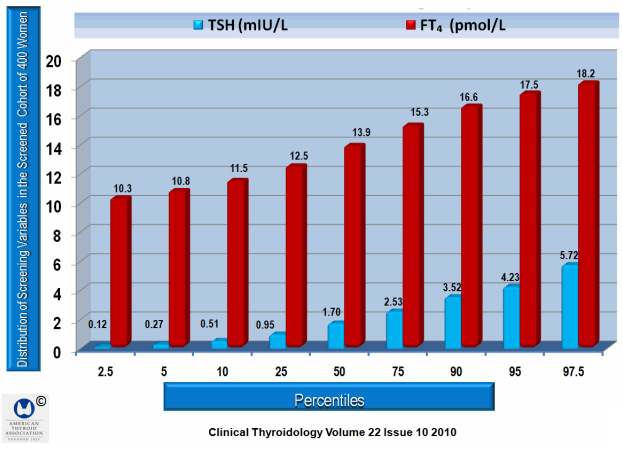

Figure 1. This figure shows the distribution of screening variables in the screened sample of 400 women in the 9th to 11th week of pregnancy. FT_4 = free thyroxine; TPOAb = thyroid peroxidase antibodies. The data for this figure are derived from Table 1 of Horacek et al.

been a matter of controversy, but it is generally accepted that TSH levels in the first trimester are lower. A recent study from the Czech Republic suggested TSH 3.67 mIU/L as the upper limit of normal in this population, and patients with a TSH >3.5 mIU/L were invited to visit the Endocrine Clinic. In women with TSH below the reference range of 0.15 mIU/L, only those with increased FT_4 or clinical symptoms of hyperthyroidism were considered for endocrine consultation, but no women were found to have this problem. Women with FT_4 values <10 pmol/L were invited for consultation. The authors suggest that the selected value for positivity of TPOAb is method-dependent, and the manufacturer's cutoff values may not have been appropriate; the authors accordingly decided on the basis of their previous experience with the laboratory method to invite women with TPOAb >50 IU/ml.

Endocrine Consultation

The endocrine consultation included taking a detailed personal and family history and performing a physical examination with attention to the risk factors defined by the consensus guidelines of the Endocrine Society. In addition, patients had thyroid ultrasonography with power Doppler imaging, which estimated the thyroid-gland volume, and the gland was assessed for homogeneity, echogenicity, and vascularity, especially in women in whom chronic autoimmune thyroiditis was suspected, and were stratified on a modified semiquantitative scale: 1 = normal, 2 = borderline, 3 = suspect and 4 = typical thyroiditis. In the case of borderline screening values, the tests were repeated with further assays. Levothyroxine treatment (50 µg/day) was initiated in all women with a clearly positive TPOAb (>50 IU/ml) and suspect or typical sonographic pattern together strongly suggested chronic autoimmune thyroiditis. Treatment was targeted in women with TSH levels < 2.5 mIU/L, and if necessary the dose of levothyroxine was adjusted on a subsequent visit 4 weeks later. In addition, treatment was initiated in women without a clear indication of chronic autoimmune thyroiditis but with a TSH that was consistently >2.5 mIU/L.

RESULTS

The Distribution of Screening Variables (Figure 1)

The distribution of the three screening variables is shown in Figure 1. Among the 400 pregnant women, TSH >3.5 mIU/L was found in 41 (10.3%), FT_4 <10 pmol/L in 8 (2%), and TPOAb >50 IU/ml in 33 (8.3%). A total of 65 women(16.3%) had at least one abnormality. Excluded from the analysis were 5 women already being treated who were receiving follow-up by their endocrinologist for autoimmune thyroiditis. The remaining women were offered endocrine consultation *(Figure 1)*.

Levothyroxine Therapy for Autoimmune Thyroiditis (Figure 2)

Fifty-one women were examined and had follow-up in the authors' clinic, 42 of whom (82%) had chronic autoimmune thyroiditis confirmed by ultrasonography and measurement of antibodies. Of this group, 27 (64%) also had TSH levels >2.5 mIU/L, suggesting thyroid insufficiency. Seven other women had consistently higher serum TSH levels without a typical pattern of autoimmune thyroiditis. Levothyroxine therapy was initiated in all of the 49 women (96%) with consistent abnormalities. A dose of 50 µg/day of levothyroxine was enough to maintain the TSH levels in 41 (84%) of the women at <2.4 mIU/L without an overdose of TSH to <0.15 mIU/L during follow-up. The women were also evaluated according to 10 accepted high-risk criteria, as shown in *Figure 2*.

Risk Factors in Women in Women Treated with Levothyroxine (Figure 3)

Of the 49 women who screened positively for levothyroxine therapy, there were no risk factors in 27 (55%; 95% confidence interval [CI], 40 to 69). Moreover, in a well-defined subgroup of

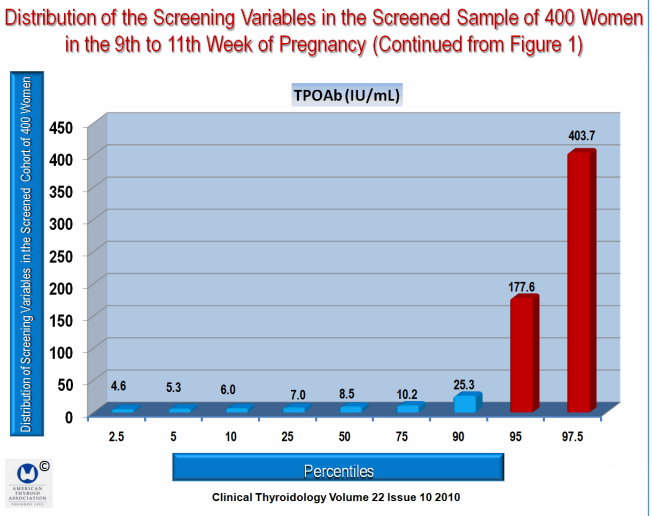

Figure 2. This figure shows the prevalence of consensus Endocrine Society guideline risk factors among positively screened and levothyroxine-treated pregnant women (n = 49).The percentages show the frequency with which risk factors were identified in the women who were screened and required levothyroxine therapy. The data in this figure and Figure 3 are derived from Table 2 of Horacek et al.

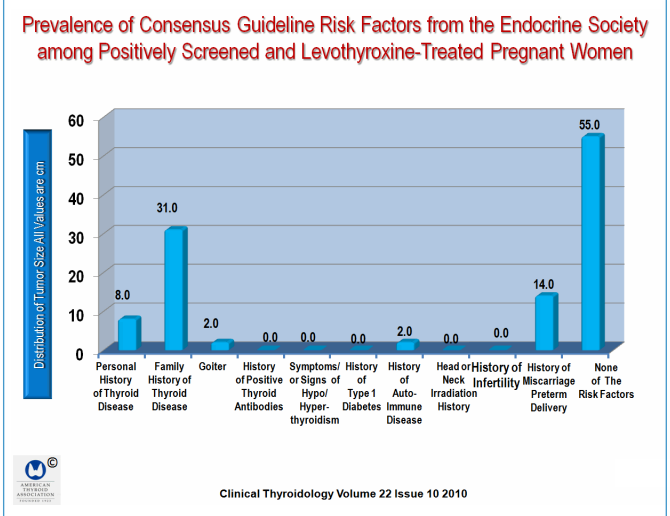

Figure 3. This figure is continued from Figure 2. The percentages are the frequency of risk-factor occurrence.

42 women with autoimmune thyroiditis, 21 (50%; 95% CI, 34 to 66) had no risk factors. A clustering of risk factors was even less common, as only 6 women had two risk factors and none had three or more risk factors.

The most accurate risk factors were a positive family history of miscarriage (present in 31%) or preterm delivery (14%) and a positive personal history (8%). A history of other autoimmune disorders and a history or presence of goiter was not diagnostically helpful. Overall, the presence of goiter was rare, as the largest sonographically measured thyroid volume was 21 ml. None of the other risk factors was observed in this group. Of the other items of personal history that were not included in the consensus guideline criteria were a history of allergy that seemed to show some positive prognostic value, being positive in 14 of 49 women (29%), a proportion similar to the best of the consensus risk factors.

CONCLUSION

Over half (55%) of the pregnant women with clear abnormalities suggestive of autoimmune thyroiditis with or without thyroid insufficiency would have been missed if only the high-risk criteria were examined.

COMMENTARY

This is an important study, the main finding of which is that over half the patients with autoimmune thyroiditis would have been missed if only the current high-risk criteria were examined. The proportion of missed diagnoses was even higher in a study by Vaidya et al. (1), who noted that recent consensus guidelines do not advocate universal thyroid-function screening during pregnancy but instead recommend testing high-risk pregnant women with a personal history of thyroid or other autoimmune disorders or with a family history of thyroid disorders.

The objective of the study by Vaidya et al. was to evaluate the efficacy of a targeted high-risk case-finding approach to identify women with thyroid dysfunction during early pregnancy. This was a single-center cohort study in which the authors prospectively analyzed TSH, FT_4, and free triiodothyronine in 1560 consecutive pregnant women during their first antenatal visit (median gestation, 9 weeks). TPOAb were tested in 1327 women(85%), and 413 (26.5%) who had a personal history of thyroid or other autoimmune disorders or a family history of thyroid were classified as a high-risk group. The study examined whether testing only such a high-risk group would pick up most pregnant women with thyroid dysfunction. The study found that 40 women (2.6%) had an elevated serum TSH (>4.2 mIU/L). The prevalence of which was greater in the high-risk group (6.8%, vs. 1.0% in the low-risk group); the relative risk (RR) was 6.5 (95% CI, 3.3 to 12.6; P<0.0001). The authors found that a personal history of thyroid disease (RR, 12.2; 95% CI, 6.8 to 22; P<0.0001) or other autoimmune disorders (RR, 4.8; 95% CI, 1.3 to 18.2; P = 0.016), TPOAb (RR, 8.4; 95% CI, 4.6 to 15.3; P<0.0001), and family history of thyroid disorders (RR, 3.4; 95% CI, 1.8 to 6.2; P<0.0001) all significantly increased the risk of an elevated serum TSH. However, 12 of 40 women with raised serum TSH levels (30%) were in the low-risk group based on the current guidelines. The authors concluded that targeted thyroid-function testing of only the high-risk group would miss about one third of pregnant women with overt or subclinical hypothyroidism.

The Horacek study was focused on early detection of autoimmune thyroiditis, because of a higher risk for obstetrical complications as well as PPTD and hypothyroidism and the fact that these complications can be treated with levothyroxine (2-4). Ultrasonography played an important role in identifying women with thyroid disease in the Horacek study, and is gaining more use for this problem (5).

This is a complex and controversial issue that will require further study. Still, the fact that thyroid testing in early pregnancy misses a significant number of pregnant women with thyroid disease raises serious questions about the current approach to this problem, and the notion that more extensive screening will identify a significantly larger number of patients must be taken under consideration.

— Ernest L. Mazzaferri, MD, MACP

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FDG PET positivity in papillary thyroid microcarcinomas is a useful way to identify lymph-node metastases and extracapsular tumor extension

Yun M, Noh TW, Cho A, Choi YJ, Hong SW, Park CS, Lee JD, Kim CK. visually discernible [18F]fluorodeoxyglucose uptake in papillary thyroid microcarcinoma: a potential new risk factor. J Clin Endocrinol Metab 2010;95:3182-8. jc.2009-2091 [pii];10.1210/jc.2009-2091 [doi]

SUMMARY

BACKGROUND

Papillary thyroid microcarcinomas (PTMCs), which are generally indolent tumors ≤1 cm, comprise almost half of all thyroid cancers. Although these tumors generally have an excellent prognosis, a subset has more aggressive behavior, with lymph-node metastases and extrathyroidal tumor capsular invasion that can be associated with about a 5% tumor recurrence rate and occasional cancer-specific mortality of approximately 2%. The problem is that preoperative neck ultrasonography commonly does not identify lymph-node metastases in the central neck compartment and fails to identify tumor invasion. This is a retrospective study aimed at assessing the value of 18F-fluorodeoxyglucose (18F-FDG) uptake in PTMC as a potential risk factor for preoperative risk stratification.

PATIENTS AND METHODS

Study Subjects

The medical records of 4615 patients who had total thyroidectomy with central lymph-node dissection from 2005 through 2008 revealed 2311 patients (50%) with PTMC (the study group). Of this group of 2311 patients with PTMC, 145 (6.3%) had an 18F-FDG–positron-emission tomographic (PET) scan 3 months before surgery. Ten of the 145 patients had 18F-FDG–PET for screening of cancer that eventually led to a diagnosis of PTMC, whereas 18F-FDG–PET was performed after the diagnosis of PTMC in 134 patients; however, the latter 10 patients were excluded because they represent a different group that would introduce bias into the data.

Patients who had a diagnosis of PTMC before PET agreed to undergo PET imaging studies. Thus, 134 patients represented a randomly selected population. Of these 134 patients, three additional groups were excluded to avoid bias, and 8 patients were excluded because of a history of head and neck malignancies. Also excluded were 30 patients with multifocal carcinomas because it was not possible to determine which of the multiple nodules was responsible for lymph-node metastases if they were present, and if the degree of 18F-FDG uptake varied among these multiple nodules, the relationship between the 18F-FDG uptake and lymph-node metastases could not be determined. Finally excluded were 10 patients with diffuse 18F-FDG uptake by thyroid carcinomas, which might not be accurately measured. The final study group thus comprised 87 patients with pathologically confirmed unifocal PTMC, 70 (80.5%) of which were women and 17 (19.5%) men, with a mean age of 51.2 years (range, 29 to 74).

Image Interpretation

The nuclear medicine specialists who were unaware of the patients' clinical, statistical, and pathology reports performed semiquantitative analysis on the tumor nodules. 18F-FDG uptake in PTMCs was visually categorized as positive if there was visibly higher 18F-FDG uptake and as negative if there was no visibly higher 18F-FDG uptake than in surrounding thyroid tissue. A region of interest was drawn around these microcarcinomas, and the peak standard uptake value (SUV) was recorded. When a nodule was not visually discernible on PET, a region of interest was drawn according to the location of the nodule based on other anatomical images. Any central lymph node with discernible 18F-FDG uptake was regarded as being positive for metastases. Lymph nodes in level VI were considered to be positive for metastases, according to the American Head and Neck Society.

RESULTS

Comparison of Results of Independent Variables with Extrathyroidal Extension (Figure 1)

The clinical and histopathologic characteristics of the 87 patients with PTMC are shown in Figure 1. Of the 87 PTMCs, 44 (51%) were confirmed by pathology specimens to have extrathyroidal extension of tumor.

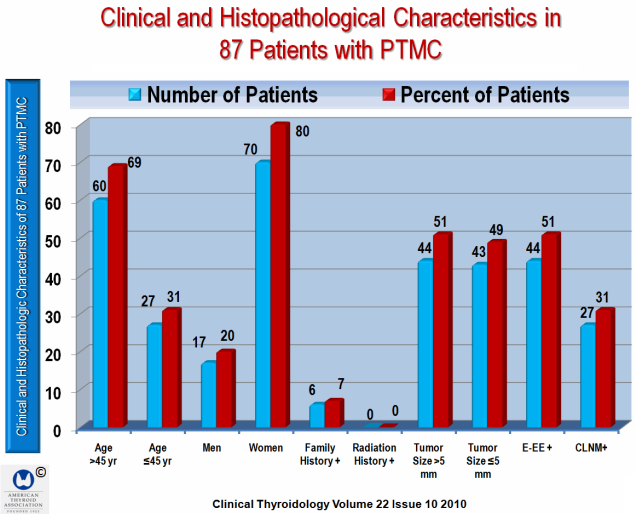

Figure 1. This figure shows the number and percent of clinical and histopathologic characteristics of 87 patients with PTMC. + = positive; CLNM = central lymph-node metastases; EE = extrathyroidal extension of tumor. This figure is derived from data in Table 1 of Yun et al.

Correlation of Independent Variables with Extrathyroidal Extension (EE) in Patients with PTMC (Figure 2)

Figure 2 shows the results of various analyses of the dichotomized variables with or without continuous independent variables with extrathyroidal extension. Patient age and sex were not significant independent variables. Also, there was no difference in the age of 44 patients with and 43 without extrathyroidal expression (mean [±SD] age, 50.8±9.3 and 51.6±11.9 years, respectively; P = 0.74).

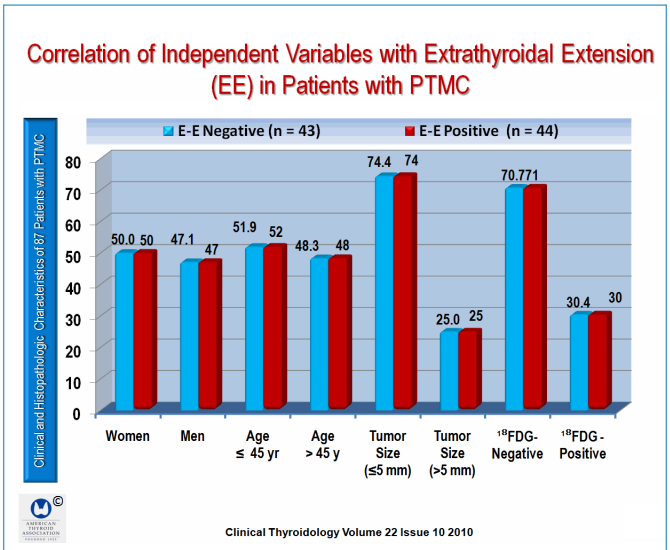

Figure 2. This figure shows the correlation of independent variables with EE in patients with PTMC. Sex and age were not significantly independent variables. Also, there was no difference in age among 44 patients with and 43 patients without EE. Mean (±SD) age was 50±9.3 and 51.6±11.9 years respectively. These data for this figure were derived from Table 2 of Yun et al.

The size of PTMC tumors ranged from 2 to 10 mm, with a mean of 5 mm; and 43 tumors were ≤5 mm (75% vs. 26%; P = 0.0005). The tumor size was significantly larger in patients with extrathyroidal extension (6.8±2.0 vs. 4.3±2.2 cm; P<0.001) *(Figure 2)*.

Visual Analysis of PET Scans

Visual analysis of PET scans showed discernible 18F-FDG uptake in 46 (53%) of the 87 PTMCs, and 41 did not have visible uptake. Extrathyroidal tumor extension was found in 32 of 46 (70%) of the 18F-FDG-positive group as compared with 12 of 41 (29%) of the 18F-FDG-negative group (P<0.0001). The SUVs in all 87 PTMCs ranged from 0.7 to 15.0, with a median of 2.1. The median SUV was 2.8 in 44 patients with extrathyroidal extension as compared with 1.8 in 43 patients without extension (P<0.0021).

Univariate and Multivariate Logistic-Regression Analysis (Figures 3 and 4)

Multivariate logistic-regression analysis revealed that tumor size and visual 18F-FDG positivity were significant independent variables that correlated with extrathyroidal extension as compared with 1 of 9 patients without tumor extension (P = 0.013). Ten of 12 patients with tumors >5 mm were associated with extrathyroidal extension, as compared with 3 of 8 patients with tumors ≤5 mm (P = 0.013). The diagnostic accuracy of 18F-FDG positivity was 73% for sensitivity, 67% for specificity, 70% for the positive predictive value, and 71% for the negative predictive value *(Figure 5)*.

Pathologically confirmed central lymph-node metastases occurred in 27 patients (31%). Figure 4 shows the results from univariate and multivariate analyses. Among the independent variables, visual 18F-FDG positivity in PTMCs and tumor size were the only significant variables in the multivariate analysis.

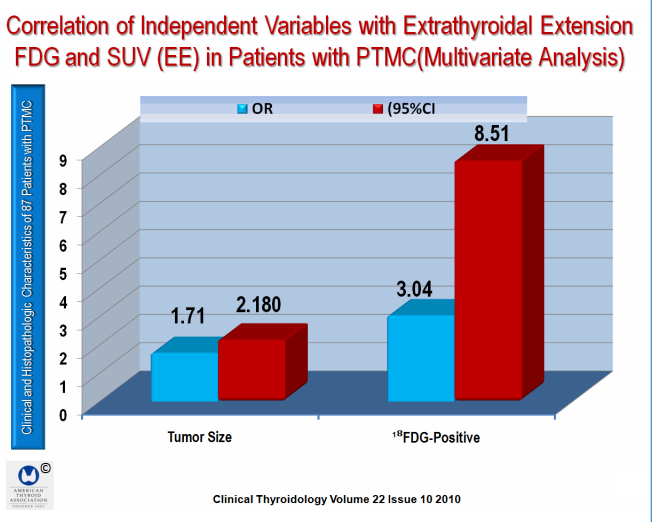

Figure 3. This figure shows the correlation of independent variables with extrathyroidal EE in patients with PTMC. Multivariate analysis logistic regression EE extension was present in 70% of the 18F-FDG-positive group as compared with 29% in the 18F-FDG-negative group. Tumor size ≤5 mm and > 5 mm is and FDG SUVs are significant independent variables. + = positive; CI = confidence interval; OR = odds ratio. The data for this figure were derived from table 2 of Yun et al.

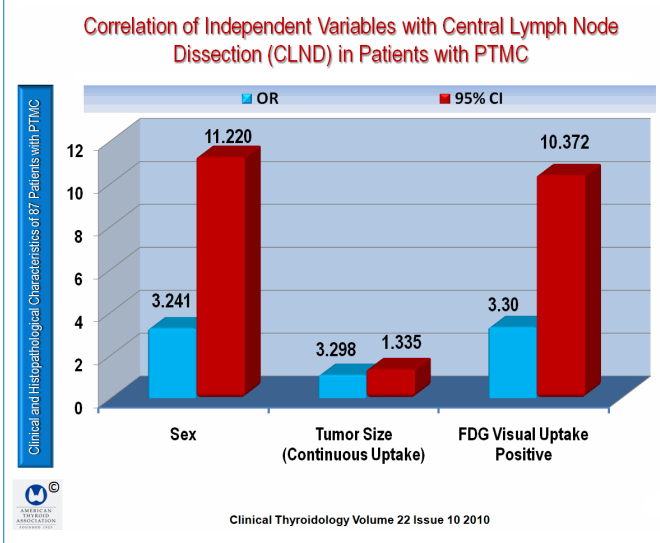

Figure 4. This figure shows the correlation of independent variables with central lymph-node dissections. CI = confidence interval; OR = odds ratio. The data for this figure are derived from Table 3 of Sun et al.

The frequency of central lymph-node metastases in the 18F-FDG-positive group was 19 of 46 (41%) as compared with 8 of 41 (20%) in the FDG-negative group (P = 0.037). The sensitivity, specificity, positive predictive value, and negative predictive value of 18F-FDG uptake for the diagnosis of central lymph-node metastases were 70, 55, 41, and 80%, respectively. Tumor size as a continuous variable almost approached statistical significance by univariate analysis (P = 0.063) but was found to be completely insignificant by the subsequent multivariate analysis (P = 0.534)

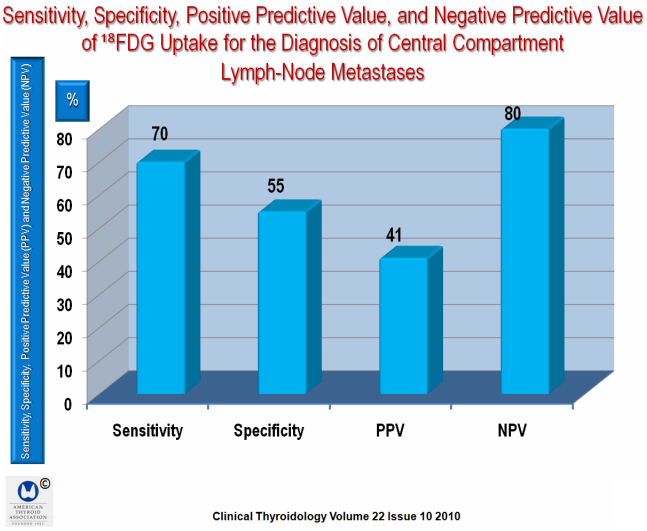

Figure 5. This figure shows the sensitivity, specificity, PPV (positive predictive value), and NPV (negative predictive value of 18F-FDG).

Miscellaneous Findings (Figure 4)

PET–computed tomography (CT) revealed foci of increased 18F-FDG uptake, suggesting central lymph-node metastases in only 2 of the 27 patients with confirmed lymph-node disease. Of the remaining 60 patients without central lymph-node metastases, PET–CT was false positive in 1 patient and true negative in 59 patients. In addition, PET–CT revealed no abnormalities outside the cervical region in all 87 patients. There was a moderate dependency of SUV on tumor size (P<0.001). Still, the tumor SUVs varied even among nodules of similar sizes. Moreover, the tumor SUV and size were found to be independent variables for the extrathyroidal extension by multivariate analysis *(Figure 4)*.

CONCLUSION

Visually apparent 18F-FDG uptake was observed in approximately half of the unifocal PTMCs and is associated with a significantly higher prevalence of extrathyroidal extension and central lymph-node metastases as compared with the 18F-FDG-negative group. The authors conclude that 18F-FDG positivity is a potential new risk factor that may be useful for predictive risk stratification.

COMMENTARY

Papillary microcarcinoma is being diagnosed with increasing frequency (1). Although it carries a low risk for cancer-specific mortality, the risk is not nil. The 10-year cancer-specific mortality rate in a study of 52,173 patients with papillary thyroid cancer found a 2% 10-year cancer-specific mortality rate for PTMC (2). Moreover, recurrent disease after total or near-total thyroidectomy is surprisingly common, with a 10-year recurrence rate of 5% for PTMC.

Not surprisingly, the management of PTMC continues to provoke substantial debate (3-5). Recommendation 26 of the 2009 American Thyroid Association Guidelines suggest that thyroid lobectomy alone may be sufficient treatment for small (<1 cm), low-risk, unifocal, intrathyroidal papillary carcinomas in the absence of prior head and neck irradiation or with radiologically or clinically involved cervical lymph-node metastases. Recommendation rating: A.

There is a significantly different opinion concerning the extent of surgery and the use of radioiodine in the management of these small tumors (3;4). A recent study has classified microcarcinomas into two categories: low-risk and very-low risk PTMC (6), with the latter comprising unifocal tumors with no lymph-node metastases or extrathyroidal tumor invasion, whereas low-risk PTMCs may have extrathyroidal tumors or other features that portend a less favorable outcome, such as lymph-node metastases, extrathyroidal tumor extension, and tumor multifocality. For example an editorial by Pearce and Braverman(7) concerning the study by Pellegriti et al. (8) suggested that routine total or near-total thyroidectomy and postoperative radioactive iodine thyroid remnant ablation was suggested in patients with one or more of the following: tumor multicentricity, positive lymph nodes, or capsular or vessel invasion, which may improve recurrence rates and facilitate the use of serum thyroglobulin concentrations for postoperative risk assessment. They also argue for near-total or total thyroidectomy in patients with multinodular goiter or dominant benign nodules, given the relatively high rate of incidentally discovered PTMC, which prompts reoperation for completion thyroidectomy and recurrent contralateral benign nodular disease.

The study by Yun et al. found that visually discernible 18F-FDG uptake was apparent in approximately half of the unifocal PTMCs, and was associated with a significantly higher prevalence of extrathyroidal extension and central lymph-node metastases as compared with the 18F-FDG-negative group. The authors' conclusion that FDG can be useful for preoperative risk stratification is a reasonable conclusion, and the caveat that prospective studies are warranted to assess the long-term benefit and cost-effectiveness of preoperative 18F-FDG–PET is warranted.

— Ernest L. Mazzaferri, MD, MACP

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Weight loss that occurs during levothyroxine treatment of hypothyroidism is predominantly due to loss of excess body water accumulated during the development of myxedema

Karmisholt J, Andersen S, Laurberg P. Weight Loss after Therapy of Hypothyroidism Is Mainly Caused by Excretion of Excess Body Water Associated with Myxoedema. J Clin Endocrinol Metab 2010. jc.2010-1521 [pii];10.1210/jc.2010-1521[doi]

SUMMARY

BACKGROUND

Patients with hypothyroidism generally experience alterations in body weight that are either due to energy intake or expenditure, leading to a loss or accumulation of body fat or a change in body water content resulting from second diseases or medical therapy. The basal metabolic rate is the sum of the total daily energy expenditure that is generally in the range of 60%, which includes the energy required for physical activity (approximately 10 to 30% or more), or from the thermogenic effect of food that includes another 10% or more. As thyroid hormones are major determinants of the basal metabolic rate, it is the likely cause of the correlation between biochemical thyroid function and the body mass index. Still, there is another possibility for the weight increase with hypothyroidism, which is a decreasing level of daily spontaneous activity. The authors of this study suggest that changes in body water content might be involved in the weight changes that occur in hypothyroidism. To evaluate this notion, body composition, resting energy expenditure (REE) and physical activity levels in patients with overt hypothyroidism were studied before and after 12 months of levothyroxine (L-T_4) replacement therapy.

PATIENTS AND METHODS

The Study Subjects

The study subjects were patients with newly diagnosed autoimmune overt hypothyroidism who were referred to the authors' clinic. Excluded from this study were patients with previous thyroid disease, hypothyroidism treated for more than 1 wk, use of medication that might interfere with thyroid function tests, a psychiatric diagnosis, physical incapacity, and pregnancy within 12 months, or age less than 18 or above 80 years.

The 12 patients who comprised the study group had a physical examination, measurement of body composition, REE (resting energy expenditure), and evaluation of physical activity. The patient's general practitioner monitored thyroid function and adjusted the L-T_4 treatment as necessary. Blood samples were obtained at baseline and after 1 year of L-T_4 therapy. The patients were studied after 1,2,3, and 6 months with pedometers and a physical activity questionnaire, and were studied after an overnight fast.

Body Composition

A Dual-energy x-ray analysis was performed with participants in light clothing, without shoes and after voiding.

Resting Energy Expenditure

REE was measured with indirect calorimetry on an open-circuit system using a Delatatrack II metabolic monitor (Datex, Helsinki, Finland). Flow and gas concentration measurements were performed at every minute for 30 minutes and the last 20 recordings were used for the calculation of REE, expressed as kilocalories per 24 hours.

Physical Activity

Step counting and two different questionnaires were the three methods used to study physical activity. Step-counting was performed with sealed waistband pedometers. The patients were asked to ambulate as usual and to wear the pedometer during all waking hours, which was thus performed during all waking hours in the day, except for weekends and holidays. Fewer than 1000 step counts were considered as measurement failures and were accordingly discarded. A mean of 3 days of pedometer measurements were used for the calculations.

Physical activity was also measured in the physical activity questionnaire, which recorded the number of hours per day during which study participants were engaged in nine different levels of physical activity. This yielded a total physical activity score that reflected physical activity during an average working day during the previous month.

The physical component summary from the general quality-of-life questionnaire Short Form 36 (SF36) version 1 in Danish was used for this study. A higher score is better in both questionnaires.

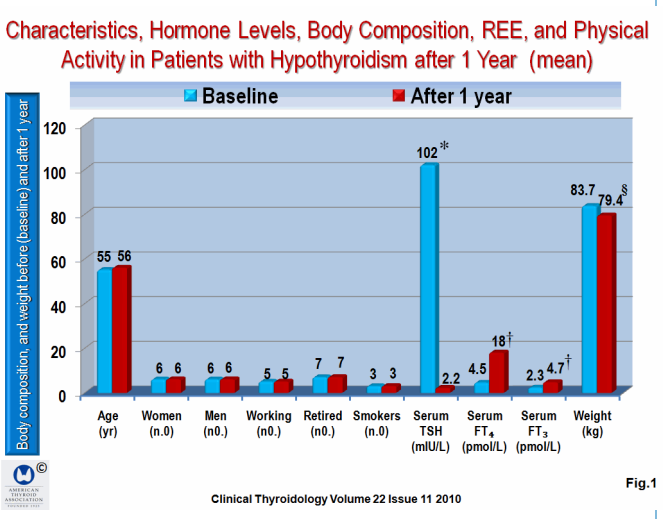

Figure 1. This figure shows the characteristics, hormone levels, body composition, and weight before (baseline) and after 1 year REE = Resting Energy Expenditure. *P=0.004 for serum TSH. Here and elsewhere the comparisons are baseline vs. after 1 year. *P= 0.004; †P< 0.001, for serum FT_4, and FT_3, and §P = 0.002 for weight. The data for this figure and figures 2 and 3 are derived from Table 1 of Karmisholtet.al.

Evaluation of the Consistency of Measurements

A control group was included to validate the consistency of the measurement methods. Also included were 10 patients treated with radioactive iodine for euthyroid goiter more than 1 year previously. All participants were euthyroid throughout the study, although two had thyroid peroxidase autoantibodies, and none received L-T_4 therapy or antithyroid drugs at any time. Except for a minimal increase in TSH, no significant changes were observed in any of the variables in the control patients after 1 year.

RESULTS

Body Composition and REE (Figures 1 and 2)

The characteristics of the study patients and thyroid function tests and after 12 months are shown in Figure 1. Body weight decreased an average of 4.3 kg after 1 year of L-T_4 therapy, which was caused by a significant decrease of 3.8 kg in lean body mass sub compartment *(Figure 2)*. An insignificantly small decrease was observed in the fat mass sub compartment, and bone mass was equal between the two measurements. *(Figure 2)*

On entry of the study, patients were asked about their weight 6 months earlier. This recalled weight was 82.1 kg, with an estimated increase in weight during the 6 months before inclusion of 2.8 kg. This was significantly different from the weight at inclusion (P = 0.03) but not after 12 months (P = 0.37).

After 1 year of treatment, unadjusted REE and REE/lean mass increased significantly to 11.6 and 21.8%, respectively. *(Figure 1)* FT_4 predicted body weight changes during L-T_4 therapy, because baseline FT_4 hormone levels correlated to the decrease in body weight during the year (Spearmans p = 0.64; P = 0.035). This correlation was also significant for changes in lean mass sub compartment (Spearmans P = 0.66; P = 0.029) but not for fat or bone mass changes during the year. *(Figure 2)*

Physical Activity Level

The step counts varied widely from day to day in all of the participants. No significant trend (P = 0.99) or change occurred in the number of daily steps during the year, (P = 0.55). The physical activity score (PAS) increased during the year (Friedman, P = 0.018) and after 1 year (P = 0.025). Also, after 1 year, the physical component summary (PCS score) evaluated by the SF-36 was increased. *(Figure 3)*

CONCLUSION

Body weight decreased on average 4.3 kg after 1 yr of L-T_4 therapy, which was caused by a significant decrease of 3.8 kg in the lean mass sub-compartment

Therapy of hypothyroidism was followed by a moderate decrease in body weight. Although the loss in body weight might have been caused by an increase in energy expenditure, the average increase in REE after 1 year of therapy was 215kcal/24 h. If the increase in REE was effective during 6 months of the treatment period, this transforms to combustion of 4.4 kg of fat tissue. This theoretical estimate is in contrast with the virtual absence of change in the observed body fat.

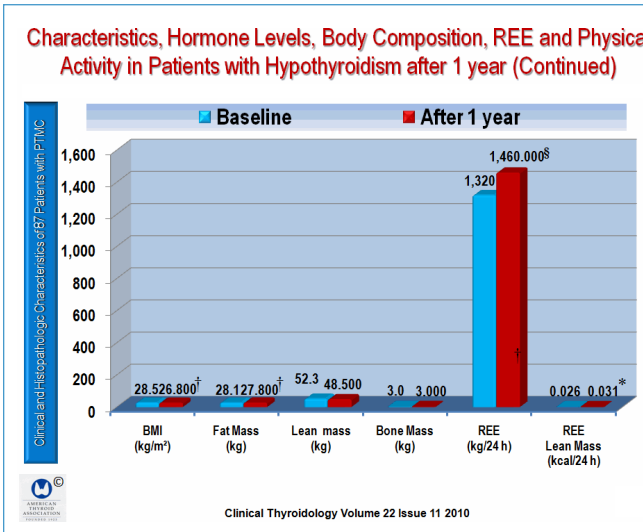

Figure 2. This is a continuation of Figure 1. The figure shows the BMI, fat mass, lean mass and bone mass, REE (kg/24 h) and REE Lean Mass (kcal/24 h). †P <0.001 for BMI; §P0.023 for REE; *P<0.004 for lean mass.

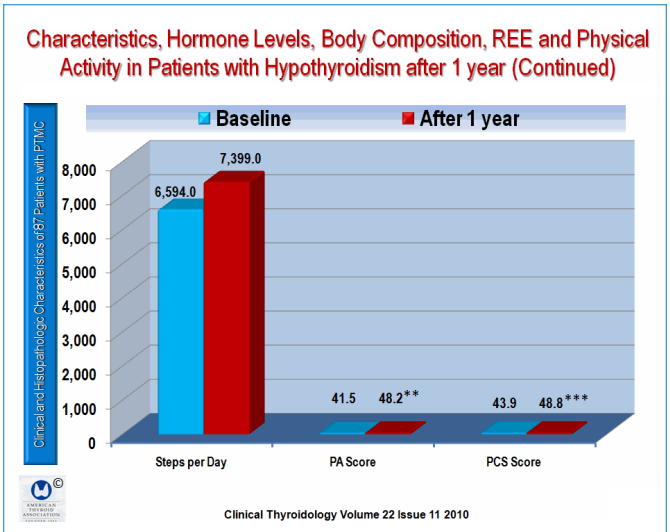

Figure 3. This figure shows the physical activity in patients with hypothyroidism before and after 1 year of L-T_4 therapy. PA score-=physical activity score, **P<0.025; for REE kcal/24 h; *P<0.004 for PCS score.PCS score = physical component summary, which is from SF-36 questionnaire. **P= 0.55 for steps/day;

COMMENTARY

Changes in Physical Activity during Treatment of Hypothyroidism

During treatment, physical activity increased as evaluated with questionnaires, but not as evaluation of daily steps. The coefficient of variation during the year was 27% in the physical activity questionnaire, as compared with 42% for the pedometer measurements. The large variation in the pedometer measurements is a shortcoming, which was reflected by the fact that no significant changes in the step count were observed during the year. The authors suggest that the difference in step counts may have been caused by the everyday life-style habits of individuals, or may be largely unaffected by the fact that the patients had hypothyroidism.

Possible Mechanisms 0f Weight Loss during Treatment of Hypothyroidism

The only significant predictor of the 5% decrease in body weight during L-T_4 therapy was the baseline FT_4 level. The authors suggest that weight change was caused by an alteration in lean body mass, as fat mass was largely unaltered. As hypothyroid patients have reduced capacity of free-water excretion(1), the authors suggested that increased antidiuretic hormone level, and increased amounts of tissue glycosaminoglycans, which have a large water-binding capacity, account for the edema (2). The high water content of the skin, observed in severe hypothyroidism was originated from the term myxedema, shortly after which it was noted that an increased urine output occurred shortly after the administration of thyroid hormone therapy.

Regained weight was significantly different from the weight found at inclusion (P= 0.03) but not after 12 months of therapy. (P = 0.37). One year after L-T_4 therapy of hypothyroidism is associated with decreased body weight attributable to decrease in lean body mass because total fat mass was largely unchanged.

Unadjusted resting energy expenditure (REE) as well as REE lean body mass increased significantly, 11.6 and 21.8% kg respectively, after 1 year of L-T_4 therapy *(Figures 1 and 2)*. FT_4 predicted body weight changes during L-T_4 therapy, mainly because the FT_4 levels were correlated to the decrease in body weight over the year of L-T_4 therapy. This was also correlated to lean body mass sub compartment but not to bone mass.

The authors suggest that the strength of their study is the spontaneous level of physical activity using three different methods and the addition of a measurement control group. On the other hand, they suggest that the limitations of the study are the lack of registration of energy intake and of measurement of the thermogenic effect of food.

Nonetheless, this is an innovative study that provides insight into the mechanisms involved in body weight changes associated with hypothyroidism.

— Ernest L. Mazzaferri, MD, MACP

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DISCLOSURE

Dr. Mazzaferri is a consultant to Genzyme.

Dr. Sipos Lectures for Abbott Pharmaceutical and Genzyme.

Call for Proposals – American Thyroid Association (ATA) Research Grants
Deadline: January 31, 2011

Electronic Submission: Proposals should 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, clinical thyroidology, thyroid autoimmunity, thyroid and the brain, thyroid hormone action and metabolism, and thyroid cell biology. 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).

Eligibility of Applicant and Use of Funds Guidelines:

1. 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).
2. Faculty members (MD and PhD) are eligible.
3. 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.
4. Students working towards an MD or a PhD are not eligible.
5. Investigators and individuals who have previously received ATA, ThyCa or THANC awards are not eligible. In general, investigators who have achieved the rank of associate professor or higher are not eligible.
6. Applications are limited to one per individual researcher.
7. 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.
8. 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: Interested investigators should submit a brief description of the proposed research by January 31, 2011. Each proposal must include the following:

1. Name and affiliation of applicant with complete work and home contact information
2. Title of proposed study
3. Short proposal that should be no longer than 900 words or three double-spaced pages in 12 point type. These space requirements are absolute and nonconformance will preclude review. This short proposal should include:
   - 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
   - References (selected)
4. An NIH-style CV (no longer than four pages) including evidence that the applicant is a new investigator (see above), namely 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.**

Grant Review: The ATA Research Committee will rank proposals according to their scientific merit. Authors of selected proposals will be notified in March 2011 and invited to submit a complete grant application.

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