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LEVOTHYROXINE USE IN THE ELDERLY IS ASSOCIATED WITH AN INCREASED RISK OF FRACTURES

Turner MR, Camacho X, Fischer HD, Austin PC, Anderson GM, Rochon RA, Lipscombe LL. **Levothyroxine dose and risk of fractures in older adults: nested case-control study.** BMJ 2011;342:d2238.

SUMMARY

BACKGROUND

Clinical hyperthyroidism is thought to increase the risk of fractures, especially in the elderly and postmenopausal women (1). Prior studies have shown that excessive thyroxine therapy resulting in subclinical hyperthyroidism (thyrotropin [TSH] suppressed below the reference range, with a free thyroxine level within the normal range) is associated with a lower bone density and bone quality (2). Previous studies have not definitively determined an increased risk of fractures in subclinical hyperthyroidism, in part, because of the inclusion of lower-risk, younger subjects and relatively small sample sizes. This report is unique in the large number of levothyroxine users (>200,000) with outcomes that can be quantitated by the national health system, which recorded new fractures at every emergency room visit and hospital admission in this population.

METHODS AND RESULTS

This study is a population-based, retrospective cohort study with a nested case–control design using a large population health database for Ontario, Canada. During the 5-year period ending March 31, 2007, a cohort of 213,511 adults older than 70 years who received at least one prescription for levothyroxine were followed for fractures until March 31, 2008. Subjects with a prior or current history of hyperthyroidism, thyroid cancer, hemodialysis, or palliative care were excluded. Case subjects were cohort members admitted to the hospital for any fracture, matched to five age- and sex-matched members of the cohort without fracture (controls). Fractures were excluded if they were associated with seizure, trauma, bone malignancy, or multiple myeloma. Members of the control group could become a "case" if fracture subsequently occurred. During the evaluation period, 22,236 (10.4%) of the subjects experienced a fracture; 88% of the subjects with fracture were women. Current users of levothyroxine had a higher risk of fracture (adjusted odds ratio [OR], 1.88; 95% confidence interval, 1.71 to 2.05) than those who had used levothyroxine in the past (>180 days before the index date). Among current levothyroxine users, high doses (>93 µg per day; OR, 3.45) and medium doses (44 to 93 µg per day; OR, 2.62) were associated with a significantly increased risk of fracture as compared with low-dose (<44 µg per day) levothyroxine therapy. There was a dose-related increased risk for

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all fractures, including hip fractures: low dose (OR, 1), medium dose (OR, 2.54; P<0.001), and high dose (OR, 3.39; P<0.001). Interestingly, there were fewer risk factors for fracture, including previous fractures, stroke, arrhythmia, dementia, and use of certain drugs in the high-dose group

CONCLUSIONS

This population-based study found a significant association between current levothyroxine use and increased risk of fractures in older adults (>70 years). There was a strong association with dose and with hip fracture in both sexes. Interpretation of this data is limited because thyroid function of the cohort was not able to be ascertained, but a recent reduction in levothyroxine dose was associated with a slight risk of fracture, which the authors speculate may indicate prior thyrotoxicosis in this group of patients.

COMMENTARY

Hypothyroidism is common with aging, with one study showing that 21% of elderly woman have TSH values above the reference range (3). This correlated with the estimate that over 20% of older women in North America are taking levothyroxine therapy (4). This study suggests that levothyroxine treatment may increase the risk of fractures in older people. The risk rises incrementally with the dose of levothyroxine typically used, >44 µg per day. Additional studies of large populations of adults younger than 70 years of age is needed to determine whether thyroid hormone with or without iatrogenic thyrotoxicosis is associated with unhealthy bones. Further, this study raises the speculation that the TSH target for older adults needs to be modified and lowered (5), as National Health and Nutrition Examination Survey studies suggest that 70% of older patients with TSH >4.5 mIU/L were within their age-specific reference range. Perhaps overreplacement with levothyroxine to achieve a TSH in a hypothyroid elderly patient within the reference range—that is, 0.4 to 4.5 mIU/L—may result in a relative thyroid hormone excess and abnormal bone metabolism.

— Stephanie L. Lee, MD, PhD

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SUBCLINICAL HYPOTHYROIDISM IS ASSOCIATED WITH INCREASED CORONARY HEART DISEASE AND ALL-CAUSE MORTALITY

McQuade C, Skugor M, Brennan DM, Hoar B, Stevenson C, Hoogwerf BJ. **Hypothyroidism and Moderate Subclinical Hypothyroidism Are Associated with Increased All-Cause Mortality Independent of Coronary Heart Disease Risk Factors: A PreCIS Database Study.** Thyroid 2011;21:837-43. Epub July 11, 2011.

SUMMARY

BACKGROUND

Hypothyroidism is associated with various coronary artery disease risk factors. The purpose of this study was to determine whether hypothyroidism and subclinical hypothyroidism (SCH) was associated with increased mortality among patients in a preventive cardiology clinic.

METHODS

The patient population consisted of 4765 euthyroid subjects (thyrotropin [TSH], 0.4 to 3.0 mU/L), 1218 with mild SCH (TSH, 3.1 to 6.0), 178 with moderate SCH (TSH, 6.1 to 10.0), and 79 who had hypothyroidism (TSH, >10) who enrolled at the Preventive Cardiology & Rehabilitation Program of the Cleveland Clinic between January 1995 and June 2008. The patients had an extensive evaluation for coronary heart disease (CHD) risk factors and were followed for up to 8 years. The time to death was defined as the difference between the patient's prevention clinic entry visit until the date of death.

RESULTS

Patients in the SCH and hypothyroid groups had greater risk for vascular disease as shown by a higher prevalence of baseline CHD ($P<0.001$) and higher Framingham risk scores ($P<0.001$). All-cause mortality was increased in the hypothyroid (25.7%) and the moderate SCH (18.0%) patient groups, as compared with the euthyroid group, but not in the mild SCH group. After adjusting for variables such as smoking, hypertension, cerebrovascular disease, body-mass index, triglycerides, glucose, and homocysteine, the hazard ratio for mortality was still significantly increased, to 1.61, in the moderate SCH group, and to 2.34 in the hypothyroid group.

CONCLUSIONS

Hypothyroidism and moderate, but not mild, subclinical hypothyroidism are associated with increased prevalence of coronary heart disease and all-cause mortality.

COMMENTARY

As the authors note, this is a controversial area. Various meta-analyses have either supported or differed from their results. The population was by definition a high-risk population for coronary heart disease. The classification was based on a single TSH measurement at the entry visit. One fourth of the moderate SCH group and half of the hypothyroid group were on thyroid-replacement therapy but apparently not taking an optimal dose.

The findings confirm those in a population of Japanese men with subclinical hypothyroidism who had a 2-fold increase in all-cause mortality and coronary heart disease (1) and an Australian study that reported a 1.5-fold increased risk for coronary heart disease with subclinical hypothyroidism (2). In patients with known cardiac disease, an Italian study found more than a 2-fold increased risk in cardiovascular disease mortality in patients with subclinical hypothyroidism (3).

— Jerome M. Hershman, MD

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WOMEN OF CHILDBEARING AGE MAY BENEFIT FROM IODINE SUPPLEMENTATION SEVERAL MONTHS BEFORE CONCEPTION

Moleti M, Di Bella B, Giorgianni G, Mancuso A, De Vivo A, Alibrandi A, Trimarchi F, Vermiglio F. **Maternal thyroid function in different conditions of iodine nutrition in pregnant women exposed to mild-moderate iodine deficiency: an observational study.** Clin Endocrinol (Oxf) 2011;74:762-8.

SUMMARY

BACKGROUND

In a previous study by the same research group (in a mildly iodine-deficient area in Italy), thyroid function in pregnant women who had regularly used iodized salt for at least 2 years before becoming pregnant was compared with that of women who began using iodized salt upon becoming pregnant. That study showed that prolonged use of iodized salt was associated with a very low prevalence of maternal thyroid insufficiency during pregnancy. Therefore, it could be speculated that a high percentage of women of child-bearing age is likely to have iodine levels that are inadequate for the increased needs during pregnancy unless they are supplemented. The aim of the study was to examine the effect of different conditions of nutritional iodine intake on maternal thyroid function throughout gestation in a cohort of healthy, antithyroid peroxidase antibody (anti-TPOAb)–negative women from a mild-to-moderately iodine-deficient area.

METHODS

The study comprised 433 anti-TPOAb–negative women; excluded were those who were taking thyroid medications, those who had started iodine supplementation later than the first trimester, those who had used prenatal preparations whose iodine content was not at least 150 µg, or those who reported intermittent use of iodine supplements. The information on iodine intake was obtained from a patient questionnaire. Three study groups were obtained: The 150-µg-iodine (150-I) group comprised 168 women. They introduced iodized salt into their diets upon becoming pregnant or some time prior to pregnancy and received a daily iodine supplement of 150 µg per day from early pregnancy (range, 6 to 12 weeks; median, 9) to term.

The iodized-salt (I-salt) group included 105 women who had regularly used iodized salt for at least 2 years prior to becoming pregnant.

The no-iodine (no-I) group comprised 160 women who disregarded recommendations about iodine supplementation. Therefore, none of these women were taking prenatal preparations containing iodine or regularly using iodized salt.

In assessing maternal thyroid function, the authors considered both serum free thyroxine (T_4) and thyrotropin (TSH) internal trimester-specific reference intervals, previously calculated in a cohort of consecutive healthy and anti-TPOAb–negative pregnant women. TSH, free triiodothyronine, and free T_4 were measured at each sampling, whereas TPOAb were tested at the first sampling only. Urinary iodine excretion (UIE) was obtained from sporadic samples.

RESULTS

There was no difference in age and parity between the three groups. Conversely, median UIE was higher in the 150-I group than in either the I-salt ($P<0.001$) or no-I ($P<0.0001$) groups, and consistent with a more adequate, although still insufficient, dietary iodine intake for pregnancy (estimated iodine intake, 200 µg per day). UIE significantly increased from the early first (67.2 µg/L) to the late third (133.7 µg/L) trimester in the 150-I group only ($P<0.001$).

Serum free T_4 concentrations declined over the course of the observation period in all groups. Overall, the extent of this decline was roughly the same (approximately 20%) in all three groups, irrespective of iodine supplementation. Free T_4 concentrations were consistently higher in the I-salt group than those in both the 150-I and the no-I groups. No difference in

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free T_4 concentrations could be observed between the 150-I group and the no-I group at any time.

During the first half of gestation, changes in TSH concentrations were similar in the three groups. After a prompt, although not significant, decline between the early and late first trimesters, serum TSH levels increased in all three groups, peaking between weeks 14 and 19. However, this increase was statistically significance only in the 150-I group ($P<0.05$). Thereafter, TSH concentrations plateaued until the end of pregnancy in all three groups. The lowest TSH concentrations were consistently observed in the I-salt group.

Prevalence of raised TSH and decreased free T_4: Overall, in 44 of 168 (26.2%) of the 150-I group, 16 of 105 (15.2%) of the I-salt group, and 47 of 160 (29.4%) of the no-I group, TSH values were found to exceed the trimester-specific upper limit. A comparison of the three groups showed the prevalence of raised TSH throughout pregnancy to be slightly higher in the 150-I group than in the I-salt group ($P = 0.048$; odds ratio, 1.97; 95% confidence interval, 1.05 to 3.72), but not different from that found in the no-I group ($P = 0.51$). The prevalence of decreased free T_4 over the course of pregnancy was 8.3%, 9.5%, and 20% in the 150-I, I-salt, and no-I groups, respectively.

CONCLUSIONS

The regular use of iodine-containing supplements proved effective in reducing the risk of inappropriately low free T_4 levels during pregnancy. The observed TSH increase in the 150-I group may be due to a transient stunning effect on the thyroid gland, occurring as a result of the abrupt increase in daily iodine intake. While the importance of gestational iodine supplementation is undisputed, the authors believed that in mild-to-moderately iodine-deficient areas, women considering conception should be advised to take iodine supplementation for several months prior to becoming pregnant. Given the large number of unplanned pregnancies, such a strategy would reasonably guarantee the adequate replenishment of maternal intrathyroidal iodine stores and prevent any possible adverse effect on the mother and fetus.

COMMENTARY

In euthyroid adults, the average daily iodine requirement is estimated to be about 95 µg per day, and the corresponding recommended nutrient intake for men and nonpregnant or lactating women is 150 µg per day (1). During pregnancy, the demand for iodine increases because of increased maternal TSH production, which occurs very early in gestation; the transfer of T_4 and iodide from the mother to the fetus; and a presumed increased loss of iodide through the kidney (2). Overall, these factors cause an estimated rise in the daily iodine requirement of at least 50% to 70%, with the recommended daily iodine intake for pregnant women of 250 µg per day. In a recent issue of *Clinical Thyroidology*, Elizabeth Pierce (3) commented on the 2005–2006 and 2007–2008 National Health and Nutrition Examination Survey studies on iodine status in the U.S. population and stated "the fact that pregnant women in the samples from these two surveys were mildly iodine-deficient is quite worrisome." Dr. Pierce concluded that until new studies identify particular U.S. women at risk for iodine deficiency, "all pregnant women are best advised to take a prenatal multivitamin containing 150 µg of iodine daily."

The study by Moleti et al. indicates that iodine supplementation should be started months, perhaps even 2 years before conception, to ensure a euthyroid state throughout pregnancy, avoiding potential relative mild hypothyroidism in women who start iodine supplementation after conception. The

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incidence of hypothyroidism in pregnancy is estimated to be around 4%, with most of the women having subclinical disease; the women who were detected were newly diagnosed or those with iodine deficiency (the incidence is very low in the United States), or about 40% of women who were on levothyroxine therapy at the time of the first obstetrical visit (4). It was shown that women on levothyroxine ($L\text{-}T_4$) therapy with a preconception serum TSH <1.3 mIU/L (5), attained a normal serum TSH (<2.5 mIU/L) at the first obstetrical visit. Therefore, it appears reasonable, until further studies confirm the work of Moleti et al., to advise all women in the United States who are of reproductive age to add an extra 150 µg of iodine daily to their regular diet, and in addition to advise those on $L\text{-}T_4$ therapy to maintain their serum TSH levels at not more than 1.3 mIU/L. The exception is women who have undergone thyroidectomy for thyroid cancer, who usually require a lower serum TSH level. As we all know very well, unplanned pregnancy is not a rare event in our daily practice.

— Jorge H. Mestman, MD

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TREATMENT OF GOITER AND NODULES IS SUCCESSFUL WITH NON-TSH-SUPPRESSING DOSES OF THYROXINE PLUS IODINE

Grussendorf M, Reiners C, Paschke R, Wegscheider K, on behalf of the LISA investigators. **Reduction of thyroid nodule volume by levothyroxine and iodine alone and in combination: a randomized, placebo-controlled trial.** J Clin Endocrinol Metab. June 29, 2011 [Epub ahead of print]. doi: 10.1210/jc.2011-0356.

SUMMARY

INTRODUCTION

Thyroid nodules and multinodular or diffuse goiters are frequent clinical findings, particularly since ultrasound examinations have become routine. In some European countries with moderate iodine deficiency, goiters and or thyroid nodules can be found in one third of the elderly adult population. For many decades the standard nonsurgical treatment for both conditions was to administer thyroxine at doses high enough to suppress serum thyrotropin (TSH) to <0.2 or <0.1 mU/L. With this approach, volume reduction of nodules was not only unpredictable and highly variable, but side effects were frequent, in particular atrial fibrillation and a tendency toward osteopenia in postmenopausal women. With progress in ultrasound examination, more precise studies could be undertaken, and some studies have indicated that even a partial inhibition of thyroid function, with serum TSH levels remaining above 0.2 mU/L, was still able to reduce thyroid or nodule volume to some extent, but only in some patients. Therefore, there was never any agreement as to whether this method deserved widespread clinical application. Some authors have recommended the addition of iodide for reduction of thyroid volume. In the present German multicenter study, carried out in a modestly iodine-deficient population, three treatment groups were compared and evaluated against placebo. One group of patients received thyroxine only (approximately 75 μg per day), another 150 μg of iodide only, and the third thyroxine plus 150 μg of iodide.

METHODS AND RESULTS

In more than 60 centers, a total of 1013 patients were investigated. The observation period was 12 months. Warm nodules and pretreated patients were excluded. Since the quality and precision of the ultrasound evaluation was crucial for the study, two test phantoms with six different nodules had to be evaluated by each center. The coefficient of variation of the different estimations was quite high, 10% to 11%. For TSH suppression, the target was 0.2 to 0.8 mU/L. This was obtained with an average dose of 75 μg of thyroxine per day. There was no difference in the decrease of serum TSH if thyroxine alone or thyroxine plus iodide was given. In the first 3 months, the serum TSH decreased to 0.2 mU/L and increased thereafter to 0.6 mU/L, possibly because of minor adjustments of treatment. As expected in Germany, iodide excretion before treatment was rather low, approximately 60 μg/L in all groups (World Health Organization recommendation, >100 μg/L).

Reduction of the total thyroid volume was significant as compared with the placebo group, but even in the best-responding group (the one treated with thyroxine plus iodide) it did not exceed 10%. For thyroid nodules, the results of volume changes were more interesting. All treated groups showed significant reductions in volume. The highest success rate—a 17% reduction of nodular volume—was obtained with the combined treatment of thyroxine plus iodide. With thyroxine alone or with iodide alone, the nodular volume reductions were not significant (–7% and –4%). The volume of the nodules in patients treated with thyroxine plus iodide seemed to decrease continuously over the 12 months, whereas for the other two groups, the volume reduction was seen only in the first 3 months. Yet, even though the thyroid nodules treated with thyroxine plus iodide decreased in volume, the response of the individual cases was quite variable. Surprisingly, in 26% of these cases the volume increased even under treatment.

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CONCLUSIONS

In a moderately iodine-deficient area, 12 months of treatment with thyroxine plus iodide significantly reduced thyroid nodule size. The decrease in volume seemed to be a continuous process until the end of the observation period. However, 26% of the cases were not only nonresponders, but the size of the nodule increased with thyroxine plus iodide treatment.

These results were obtained with only partial TSH suppression. Indeed, serum TSH levels in the second half of the treatment period were 0.6 mU/L, a level certainly not associated with any side effects. The volume reduction of the nodules with thyroxine treatment alone or iodide alone did achieve a small but nonsignificant volume reduction. The effects on total thyroid volume have to be considered marginal.

COMMENTARY

This is a large multicenter study performed in a country with moderate iodine deficiency. Under these circumstances, the treatment with a moderate dose of thyroxine combined with 150 μg of iodide for thyroid nodules is clearly superior to a treatment with thyroxine or iodide alone. The effect of the combined treatment was surprising, because the results were obtained with an average serum TSH of 0.6 mU/L, which is likely to be well tolerated. The volume decrease was 17%, as compared with the placebo group. This reduction is significant but not remarkable. There was, in addition, a large variability of individual responses. In some cases, the volume reduction exceeded 50%, while in 26% of cases the volume of the nodule even increased. This is not unexpected, since in benign nodules growth is not necessarily dependent on TSH-mediated mechanisms. For instance, a recent study showed that benign nodules bearing RET/PTC rearrangements and mutations were particularly prone to rapid growth (1); 15% of all investigated nodules were positive for these gene alterations. This number is about the same order of magnitude as that seen in the study under discussion for nodules increasing under treatment.

An important question remains unanswered. In areas of sufficient iodine supply, is this combined treatment of thyroxine plus iodide superior to thyroxine alone? In these areas, most endocrinologists do not advise suppressive treatment with thyroxine and rely on the growth rate of the nodule for choosing clinical follow-up alone or surgery. Still, since the effect of the combined treatment with thyroxine plus iodide was possibly not simply an additive effect of the two components, it is possible that this treatment could show some beneficial results in a subgroup of thyroid nodules, even in the presence of adequate iodine intake. The heterogeneity of clinically relevant responses favors the hypothesis that a successful treatment would be limited to possible subgroups of thyroid nodules. Therefore, careful ultrasound follow-up under treatment is certainly indicated.

— Albert G. Burger, MD

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SMALL THYROID BED MASSES FOUND AFTER INITIAL TREATMENT OF DIFFERENTIATED THYROID CANCER HAVE A BENIGN OUTCOME

Rondeau G, Fish S, Hann LE, Fagin JA, Tuttle RM. **Ultrasonographically detected small thyroid bed nodules identified after total thyroidectomy for differentiated thyroid cancer seldom show clinically significant structural progression.** Thyroid 2011;21:845-53.

SUMMARY

BACKGROUND

High-resolution ultrasound neck surveys have become an accepted routine method of detecting recurrence of differentiated thyroid cancer after the initial treatment of thyroidectomy with or without radioactive iodine ablation (1). Masses in the thyroid bed include metastatic nodes and tumor recurrence, but they also may be a result of postoperative fibrosis or suture granulomas (2). Although the revised ATA guidelines for thyroid cancer allow for observation without biopsy of small suspicious cervical nodes found on sonography, there are no recommendations for nodules in the thyroid bed. Masses in the thyroid bed may be benign or malignant. The management of malignant masses in the thyroid bed presents a dilemma because invasion may result in recurrent laryngeal-nerve damage or tracheal invasion and surgical removal may also result in morbidity from recurrent nerve dysfunction or hypoparathyroidism. This study was designed to determine the likelihood, magnitude, and rate of growth of small masses found in the thyroid bed (level VI) after initial therapy.

METHODS AND RESULTS

This is a retrospective review of 1531 patients with differentiated thyroid cancer who had two or more cervical sonographic studies between August 1998 and June 2009. Thyroid-bed nodules were present in 521 (34%) of the patients, but only 191 had masses <11 mm and had at least two additional follow-up exams. The patients all had a total thyroidectomy for a differentiated thyroid cancer with central-neck dissection, and 84% subsequently received radioactive iodine (RAI) remnant ablation (median activity, 146 mCi) and were followed for a mean of 7 years (median, 5 years). Patients had at least one small thyroid-bed nodule (range, 1 to 6) and 35% of these patients had at least one new additional thyroid-bed nodule (range, 1 to 9) on a follow-up exam. The median size of the thyroid-bed nodules was 5 mm (range, 2 to 11). Suspicious sonographic features (microcalcifications, hypoechogenicity or increased peripheral or intranodular vascularity) were seen in 63% of the patients. RAI uptake in the thyroid bed occurred in 23% of the patients and fluorodeoxyglucose uptake in 24%. Patients were excluded if the thyroid-bed mass was >11 mm or if they did not have enough follow-up exams. Patients receiving additional RAI therapies or who had other abnormal nodes in the central or lateral compartments were included. Only 17 of the 191 (9%) of the patients had an increase in size (≥3 mm in the largest dimension) of the thyroid-bed nodule during a mean follow-up of 7 years and a median follow up of 5 years. The 3-mm cutoff was selected because it was thought that this is the minimal size change that can be reproducibly determined by high-resolution ultrasound (3, 4). Only 3 of these 17 patients had a fine-needle aspiration biopsy, and all masses were confirmed as papillary thyroid carcinoma. The remaining 14 patients continued to be followed without biopsy or treatment with either radioactive iodine or surgery. Most thyroid-bed nodules showed only minor growth over several years, often showing a waxing and waning growth pattern. The median rate of growth of the nodules that grew was 1.3 mm per year (range, 0.4 to 3.7). Only 1 patient had significant growth from 9 mm on the first exam to 16 mm 40 months later and then 27 mm approximately 48 months later. There were no specific clinical or sonographic features that reliably determined which nodules were likely to grow. Negative predictive values (NPVs) with an absence of suspicious features on ultrasound (NPV, 0.97), absence of abnormal cervical nodes (NPV, 0.94), and absence of rising serum thyroglobulin (NPV, 0.93) provide reassurance that a mass is unlikely to grow.

CONCLUSION

This study demonstrates the benign behavior of thyroid-bed masses found after the initial therapy

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(thyroidectomy, level VI dissection, and RAI ablation). Small thyroid-bed nodules were found in 34% of patients after initial therapy and only 9% increased in size over a median follow-up period of 5 years.

COMMENTARY

The risk of locoregional recurrence of papillary thyroid carcinoma in the cervical lymph nodes of the thyroid bed ranges from 15% to 25% (5). Careful structural evaluation by high-resolution ultrasound with measurement of basal or thyrotropin-stimulated thyroglobulin has the highest sensitivity for detecting thyroid cancer recurrence. According to the revised ATA thyroid cancer guidelines, cervical ultrasound to evaluate the neck should be performed 6 to 12 months after initial surgery then periodically thereafter depending on the risk for recurrence (3). This article demonstrates that small nodules in the thyroid bed were detected in 34% of their patients who had aggressive initial therapy including total thyroidectomy, central-neck dissection, and RAI remnant ablation in 84%. This study did not indicate whether the patients without RAI ablation had a higher risk of a mass in the thyroid bed consistent with a normal thyroid remnant. Thus, without biopsy it is not known what fraction of these masses represent normal remnant, nodal metastases, or invasive residual disease. The authors did not report any complications such as tracheal or recurrent nerve invasion during the follow-up period. The benign behavior confirms that the growth of persistent/recurrent thyroid carcinoma is indolent. This article will change my practice, as my surgical experts worry that thyroid-bed masses after thyroidectomy, central-neck dissection, and RAI ablation represent a more aggressive, invasive residual tumor that places the patient at risk for recurrent nerve damage or tracheal invasion and should be removed. In fact, this study suggests that the presence of small masses in the thyroid bed, whether thyroid remnant or metastatic disease, grow slowly, with no evidence of invasive behavior. These patients with thyroid-bed masses can be under watchful waiting rather than be exposed to the risks of additional RAI therapy or difficult reoperation with a higher risk of hypoparathyroidism and recurrent laryngeal-nerve damage. The absence of suspicious sonographic features, abnormal cervical nodes, and rising thyroglobulin levels strongly predicts a quiescent behavior of the mass. This watchful observation with serial ultrasound evaluation is consistent with the revised ATA guideline recommendations regarding the observation without biopsy of small abnormal cervical lymph nodes in patients with differentiated thyroid carcinoma (3).

— Stephanie L. Lee, MD, PhD

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ARE LOBECTOMY AND THYROIDECTOMY WITHOUT RADIOACTIVE IODINE REMNANT ABLATION A SAFE PROCEDURE IN SELECTED THYROID CANCER PATIENTS?

Vaisman F, Shaha A, Fish S, Tuttle R. **Initial therapy with either thyroid lobectomy or total thyroidectomy without radioactive iodine remnant ablation is associated with very low rates of structural disease recurrence in properly selected patients with differentiated thyroid cancer.** Clin Endocrinol (Oxf). February 8, 2011 [Epub ahead of print]. doi: 10.1111/j.1365-2265.2011.04002.x.

SUMMARY

BACKGROUND

In the past 20 years there has been a marked evolution in the treatment of well-differentiated intrathyroidal papillary and follicular carcinomas. Treatment has become less aggressive and, particularly, the indications for complementary treatment with radioactive iodine (radioactive iodine remnant ablation [RAA]) have been restricted. The general attitude is described in the guidelines published by the American and European Thyroid Associations (1, 2). Because of the slow progression of most of these cancers, it is difficult to foresee their natural course and to appreciate the true beneficial value of any of the proposed therapeutic approaches. Many of the recommendations are based on expert opinion rather than on facts. The therapeutic approaches for intermediate-risk thyroid cancers, defined as those having a diameter of <4 cm and the absence of microscopic extrathyroidal or intrathyroidal invasion and cervical lymph-node metastases, are particularly subject to personal opinion and experience. The authors of this article have adopted, during the past 40 years, a particularly conservative approach, consisting, in appropriate cases, of thyroidectomy alone or even lobectomy (more precisely, lobectomy and isthectomy) not followed by RAA.

METHODS AND RESULTS

Lobectomy was performed for tumors of <4 cm with no lymph-node involvement and with a normal contralateral thyroid lobe. Total thyroidectomy without RAA was performed in selected tumors of <4 cm with minimal or no clinically apparent lymph nodes and/or microscopic intrathyroidal or extrathyroidal extension and with thyroglobulin serum levels of <10 mg/L. The presence of lymph nodes was evaluated preoperatively by ultrasound. During the operation no systematic central-neck dissection was performed. Follow-up examinations were performed after 6 months and yearly thereafter. Evidence for recurrent disease was evaluated by ultrasound and in cases of a suspicious finding on cytologic study of lymph nodes, by radioactive scans and 18fluorodeoxyglucose–positron-emission tomographic (FDG-PET) scans.

Of 289 consecutive patients, 217 (75%) had total thyroidectomy and 72 (25%) had lobectomy. In 55% of cases, the primary tumor was >1 cm in diameter; microscopic extrathyroidal extension was found in 10% and microscopic intrathyroidal extension in 6%. For both groups of interventions, the status of the lymph nodes was 68% N0, 7% N1a, and 2% N1b. In 23 cases, the lymph-node status could not be identified (Nx).

As expected, thyroglobulin levels were low after thyroidectomy and not interpretable after lobectomy.

With regard to tumor size, only 13.5% of the cases were stage T3; the rest were smaller. Nevertheless, 26% of all cases were considered intermediate-risk cases, of which 79% underwent total thyroidectomy and 21% lobectomy.

In 2.3% of thyroidectomized patients, recurrence of the disease was found during the relatively short follow-up period of 4 to 6 years. After lobectomy, reintervention was performed more frequently (9%), but recurrence was confirmed in only 4.1%. Recurrent disease was treated by operation and RAA.

CONCLUSIONS

This article adds interesting information concerning patients with intermediate-risk thyroid cancers. According to the guidelines, in 55% of the patients

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who had a thyroidectomy, RAA would have been considered by most thyroidologists. With only 2.1% of thyroidectomized patients having recurrence or persistence of the disease, the results can be considered excellent. After lobectomy, the reinterventions were relatively high (9%) but tumor was found in only 4.1%. The intermediate-risk group of both thyroidectomized and lobectomized patients represented 53% of all patients, many of whom would have been treated elsewhere with RAA after the primary intervention. In both surgical groups, only one patient was not cured after the secondary intervention and there was no mortality.

COMMENTARY

The results for low-risk patients are in accordance with the current opinion on this subject. More interesting are the results in the intermediate-risk patients, for whom the guidelines leave treatment to the discretion of the physician, with agreement by the patient. It is likely that intermediate-risk patients with tumors >2 cm in diameter and perhaps microscopic intrathyroidal or even extrathyroidal extension would have been treated with RAA in other centers because this facilitates the follow-up through the use of ultrasound evaluation and thyroglobulin levels. Also a 9% reoperation rate in patients with lobectomy cannot be disregarded, even though tumor was found in only 4%. There is no way to know if the two patients who were not cured after the second intervention would have benefited from an initial more aggressive attitude.

The patients with successful lobectomy will, however, be grateful since they avoided not only RAA but also lifelong treatment with thyroid hormone substitution. In addition, some publications suggest that in patients treated with radioactive iodine there is an increased incidence of secondary tumors, particularly of the lymphatic and colorectal systems (3, 4). These observations were obtained with much higher doses of radioactive iodine than are currently used. Doubt persists, however. The physician must therefore balance the potential benefit of treating such patients with completely resected thyroid plus RAA versus lobectomy or thyroidectomy without RAA. The decision is an individual one, and the patient needs to be fully informed.

— Albert G Burger, MD

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THE DOUBLING TIME OF SERUM THYROGLOBULIN IS A VERY STRONG PREDICTOR OF PROGNOSIS IN PATIENTS WITH PAPILLARY THYROID CARCINOMA

Miyauchi A, Kudo T, Miya A, Kobayashi K, Ito Y, Takamura Y, Higashiyama T, Fukushima M, Kihara M, Inoue H, Tomoda C, Yabuta T, Masuoka H. **Prognostic impact of serum thyroglobulin doubling-time under thyrotropin suppression in patients with papillary thyroid carcinoma who underwent total thyroidectomy.** Thyroid 2011;21:707-16. Epub June 7, 2011.

SUMMARY

BACKGROUND

Measureable thyroglobulin (Tg) levels in patients with papillary thyroid carcinoma after initial therapy are suggestive of persistent or recurrent disease. The purpose of this study was to examine the serum Tg kinetics in patients with papillary thyroid carcinoma and to correlate the Tg doubling time (Tg-DT) with the prognosis.

METHODS AND RESULTS

From January 1998 through December 2004, a total of 426 patients had a total thyroidectomy for papillary thyroid carcinoma and had at least four measurements of Tg with negative Tg antibody and a suppressed thyrotropin level (<0.1 mIU/L). This group of patients was composed of 349 women and 77 men, between 14 and 81 years of age (mean, 51.5). The tumor status in tumor–node–metastasis (TMN) staging was T1 (in 43 patients), T2 (in 129), T3 (in 119), and T4 (in 135). Radioiodine was given to 167 patients. In this retrospective study, the Tg-DT was calculated based on Tg tests obtained during routine follow-up. For the majority of the patients, Tg levels were measured 1 and 3 months after surgery and two times per year thereafter. The Tg measurements were more frequent in the high-risk patients and once a year in the very-low-risk patients. Neck sonography was performed annually with chest x-ray examination or computed tomography scanning, if indicated. Patients were followed for a mean of 88.1 months and a median of 86.7 months. During the study period, 6 patients died of the disease, 58 had locoregional recurrences, and 25 had distant metastases. A total of 137 of the 426 patients had detectable Tg levels. Patients were placed into four groups based on their calculated Tg-DT of <1 year (17 patients), 1 to 3 years (21), ≥3 years (30), and a negative Tg-DT due to decreasing Tg levels (69). A total of 88 patients were excluded from analysis because they had fewer than four Tg measurements and 201 had Tg levels that were always below the level of detection. The cause-specific survival correlated with the Tg-DT. Fast Tg-DT (<1 year) had a 10-year cause-specific survival of 50% ,while a Tg-DT of 1 to 3 years had 95% survival. Groups with a Tg-DT of >3 years, a Tg-DT with a negative slope (Tg level decreasing with time), or a Tg level always lower than the detection limit had a cause-specific 10-year survival of 100%. The Tg-DT calculated using only the first four data points or all data points was the only independent predictor of survival, distant metastases, and locoregional recurrence on multivariate analysis.

CONCLUSION

Tg-DT is a very strong predictor of prognosis in patients with papillary thyroid carcinoma.

COMMENTARY

Other investigators, including Baudin et al. (1), have noted that a rising Tg was associated with detection of recurrent disease while a stable or falling Tg, especially if <10 ng/ml, was an indication of quiescent disease with a low positive predictive value of detecting recurrence. Similarly, serum calcitonin doubling time is a strong prognostic factor for recurrence and death from medullary thyroid carcinoma (2). This study demonstrates that the Tg-DT can be determined by the first four measurements, and the shorter time is associated with lower cause-specific survival and increased risk for distant metastases and locoregional recurrence. The Tg-DT derived from

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the first four data points was a significant prognostic factor in univariate and multivariate analysis. In this study, thyroid cancer–specific deaths occurred only in stage IV disease. But only 6 of 189 (3.2%) of patients in stage IV died of the disease, giving a 10-year cause-specific survival rate of 94.6%. Using the Tg-DT, 5 of 17 patients with a Tg-DT of <1 year and 1 of 21 of patients with Tg-DT of 1 to 3 years died of thyroid cancer, while none of the patients in the other groups died. Thus, the Tg-DT was better than TMN staging at predicting the risk of death. This investigation has put a quantitative number on what we are already knew clinically, namely that patients with rising Tg levels are at high risk for recurrence and death. We should use the Tg-DT in the same way we use calcitonin doubling time to predict which patients with medullary thyroid cancer are at high risk for recurrence and death.

— Stephanie L. Lee, MD, PhD

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MEDULLARY THYROID MICROCARCINOMAS HAVE SIGNIFICANT RATES OF POOR PROGNOSTIC FEATURES AND REQUIRE APPROPRIATE SURGICAL MANAGEMENT

Kazaure HS, Roman SA, Sosa JA. **Medullary thyroid microcarcinoma: a population-level analysis of 310 patients. Cancer.** June 29, 2011 [Epub ahead of print]. doi: 10.1002/cncr.26283.

SUMMARY

BACKGROUND

Medullary thyroid cancer (MTC) makes up about 5% of thyroid cancers but causes 13% of thyroid cancer deaths. The treatment is thyroidectomy with at least central-neck lymph-node dissection. Medullary thyroid microcarcinoma (microMTC) is defined as MTC <1 cm. The prevalence of microMTC in autopsy series is 0.14% (1). There is debate about the surgical management of microMTC with regard to whether the surgery should be as aggressive as that in MTC >1 cm. The purposes of the current study were to describe the incidence and the demographic, clinical, and pathologic characteristics of microMTCs and to determine the likelihood of lymph-node metastases.

METHODS

The data source for this study was the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database; the regions used were those with the most complete data sets for this study. Multiple demographic, clinical, and pathologic variables were analyzed. Disease stage was categorized as localized if the tumor was confined to the thyroid without lymph node metastasis, regional if the tumor extended beyond the thyroid into surrounding tissues or metastasized to regional lymph nodes, and distant if metastases to extracervical lymph nodes or organs was present.

RESULTS

A final sample of 310 patients was analyzed. Pediatric patients made up only 8% of the group. The incidence rate of microMTC was 4.2 per 10 million population in 1997, about one fifth of all MTC, and the annual increment was 4.2%. Mean (±SD) tumor size was 5.7±0.2 mm; 92% of tumors were intrathyroidal and 31% were multifocal.

Lobectomy alone was performed in 11% of patients. Lymph nodes were removed in 57%. Approximately 37% of patients whose lymph nodes were examined had metastases; almost 12% had more than10 positive lymph nodes. More than 5% of patients with microMTC had distant metastases at the time of diagnosis. The overall 10-year survival rate was 91.6%. The cause-specific mortality rate was 3.5%. Survival decreased with higher disease stages. The 10-year survival rates for patients with localized, regional, and distant disease were 96%, 87%, and 50%, respectively (P<0.001). Tumor size and extrathyroidal extension were the only factors associated with lymph-node metastases. A 5-mm microMTC was associated with at least a 23% risk of lymph-node metastases, independently of other risk factors, and this increased with tumor size to 37% for a 10-mm tumor.

CONCLUSIONS

The results indicate that microMTCs have significant rates of poor prognostic features that can reduce survival. They require appropriate surgical management.

COMMENTARY

This is a unique retrospective study based on the SEER database. Unfortunately, the database does not provide the method of diagnosis of the microMTC. Since only 8% were pediatric cases, the diagnosis of small tumors is probably not related mainly to family screening. In fact, there are no data about family history, about fine-needle aspiration of small nodules, or about calcitonin levels. Nevertheless, the results indicate that microMTC constitutes a dangerous disorder that is similar in its spread and potential lethality to that of ordinary MTC.

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The study raises the question of screening small nodules by measuring serum calcitonin in order to detect MTC at an early stage. This is a debatable topic because elevated serum calcitonin detected a 0.5 to 1.5% incidence of microMTC in several large European series of patients who were going to have surgery for nodular goiter, but not for small nodules. The data are summarized well in an editorial by Hodak and Burman, who concluded that calcitonin screening without evidence of a family history of MTC yielded too many false positives associated with thyroiditis (1). In a review by Valle and Kloos of 24 autopsy series published from 21 countries, the average prevalence of occult microMTC was 0.14% (2). Finally, the current ATA guidelines "cannot recommend either for or against the routine measurement of serum calcitonin" for evaluation of thyroid nodules (3).

— Jerome M. Hershman, MD

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WHEN IS A POSITIVE ANTI-TG, ANTI-TPO OR ANTI-TSH-RECEPTOR TITER CLINICALLY USEFUL?

Hutfless S, Matos P, Talor MV, Caturegli P, Rose NR. **Significance of prediagnostic thyroid antibodies in women with autoimmune thyroid disease.** J Clin Endocrinol Metab. June 29, 2011 [Epub ahead of print]. doi:10.1210/jc.2011-0228.

SUMMARY

BACKGROUND

Antithyroid antibodies are often present in the serum by the time a patient is diagnosed with either Graves' disease or Hashimoto's thyroiditis. The authors measured antithyroid peroxidase (TPO), anti-thyroglobulin (Tg) and anti-TSH receptor (TSH-R) levels in serum samples drawn years earlier from women now 23 to 50 years of age in whom Graves' or Hashimoto's disease developed in an attempt to find out when the antibodies first began to appear.

METHODS

Between 1998 and 2007, 1684 (of more than 540,000) female active-duty U.S. military personnel who were seen in a rheumatology, family medicine, obstetrics–gynecology, internal medicine, or endocrine clinic were given a new diagnosis of Hashimoto's thyroiditis or Graves' disease. A blood sample drawn within 6 months before or after the diagnoses, plus three earlier serum samples had to be available. The four samples from each randomly selected patient with Hashimoto's thyroiditis or Graves' disease (87 each), and from 348 age-matched controls were assayed for anti-TPO and anti-Tg (both by enzyme-linked immunosorbent assay [ELISA]). TSH-R antibody levels were assayed (by ELISA) in all the patients with Graves' disease and in some controls.

RESULTS

Anti-TPO, anti-Tg, or both were positive in 50 of the controls. In the pre-Hashimoto's samples, the percent that were positive did not change over 5 to 7 years: 66% had positive anti-TPO titers and 50% had positive anti-Tg titers at 5 to 7, 3 to 5, and 0.5 to 2 years before, as well as at the time of diagnosis. No TSH-R antibodies were found in 17 pre-Hashimoto's serum samples drawn 5 to 7 years before the diagnosis was made. In the pre-Graves' samples, the mean anti-Tg and anti-TPO levels were not significantly different from controls at any individual time point before the diagnosis, although the rate of increase was significantly higher than in controls. TSH-R antibodies were detected in only 2% of samples drawn 5 to 7 years before the diagnosis was made, in 7% of samples at 3 to 5 years, in 20% of samples at 6 to 24 months before diagnosis, and in 55% at the time of diagnosis ±6 months.

CONCLUSIONS

The authors conclude that thyroid antibodies in apparently healthy individuals should not be neglected and may serve as a useful tool to screen for autoimmune thyroid diseases before clinical diagnosis.

COMMENTARY

In general, the most sensitive test of thyroid hormone status is the TSH level, recognizing that after treatment of either Hashimoto's thyroiditis or Graves' disease, the TSH level can lag behind the normalization of thyroxine (T_4) and triiodothyronine (T_3) levels (TSH values were not provided in the present study). Antibodies to TPO and TG are not uncommon in euthyroid individuals. When the thyroids of such individuals have been examined, foci of lymphocytic infiltration have been found. Such foci are also found in thyroids of patients with Graves' disease as well as in or near benign and malignant thyroid tumors, but generally are more extensive in Hashimoto's thyroiditis. The epitopes on TPO and TG that are recognized by antibodies can change with time, and the balance between antibodies that stimulate and those that block the TSH receptor can shift, influencing thyroid size or nodularity as well as hormone levels.

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Hashimoto's thyroiditis often presents as a goiter in adolescents and young adults, and these patients often remain euthyroid, whereas some whose TSH was initially above normal or who were overtly hypothyroid subsequently return to euthyroidism, and yet others continue to or subsequently have hypothyroidism (1). Adult patients with Hashimoto's thyroiditis often do not have a goiter (clinical information about the patients was not provided in the present study). A common diagnostic and clinical problem is the patient who has symptoms that might indicate hypothyroidism but who has no positive physical findings. When tests for T_4/free T_4, T_3, and TSH are ordered, they turn out to be normal. However, if antithyroid antibodies are also ordered and they turn out to be positive, what should the physician do? Most will follow the patient's TSH level closely. However, if you simply assume that the diagnosis is Hashimoto's thyroiditis and put the patient on levothyroxine therapy, then even if the patient's symptoms improve, you have not established that your diagnosis is correct. On the other hand, a euthyroid woman with positive antibodies and a TSH that is within the normal range but >2.5 mU/L is more than four times as likely to have hypothyroidism over the next 13 years than if her TSH is ≤2.5 mU/L (2).

Only 55% of the patients with Graves' disease had positive anti-TSH-R antibodies in this study, perhaps because samples could be drawn 6 months after the diagnosis was made, and antithyroid therapy can reduce mean anti-TSHR-stimulating antibody levels by more than half (and anti-TPO titers by two-thirds) in adults within 6 months (3). Anti-TSH-R assays can be useful in evaluating pregnant women who currently have or previously had Graves' disease; in newborns with possible neonatal hyperthyroidism or who may be transiently hypothyroid because of blocking antibodies; in patients in whom euthyroid Graves' ophthalmopathy is suspected; in confirming Graves' disease in hyperthyroid patients in whom a radioiodine uptake and scan should not or cannot be performed; and possibly in determining the likelihood of a recurrence of Graves' disease before discontinuing antithyroid drug therapy.

— Stephen W. Spaulding, MD

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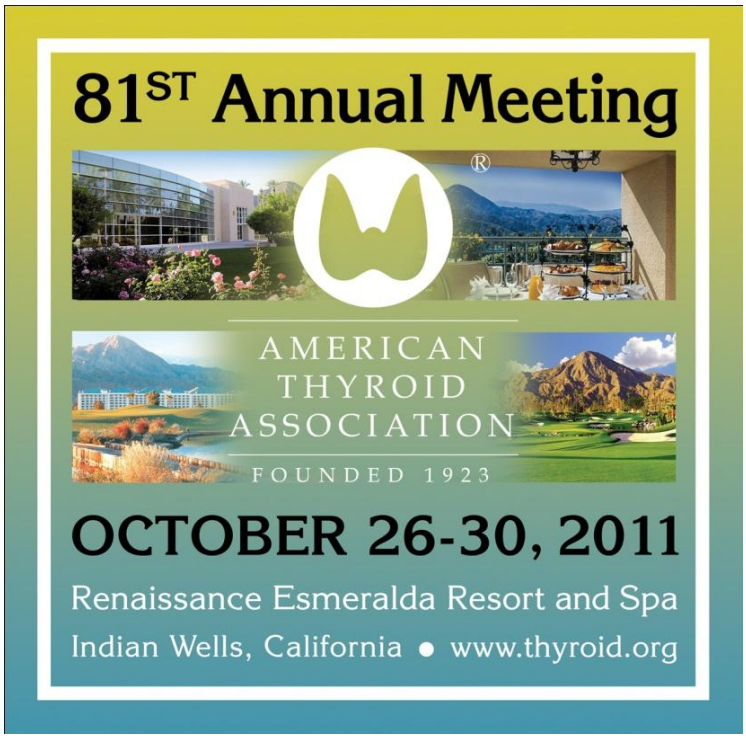

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