

# CLINICAL THYROIDOLOGY

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**Clinical Thyroidology**

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# CLINICAL THYROIDOLOGY

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## EDITOR'S COMMENTS

This issue of *Clinical Thyroidology* is dedicated to the memory of the late Dr. Robert D. Utiger. The tribute to Dr. Utiger written by P. Reed Larsen, M.D. that appears on the next page reminds us of Dr. Utiger's many accomplishments. It is because of him that *Clinical Thyroidology* enjoys such a firm foundation. We will all miss his guidance, friendship and keen sense of editorial fairness.

We learned two things about our first electronic issue of *Clinical Thyroidology* at the Chicago meeting of the American Thyroid Association. The good news was that our readers seemed to endorse the new format for the journal and especially liked the figures. In fact, several presentations at the meeting featured figures from the first issue of *Clinical Thyroidology*.

The bad news was that not everyone received the electronic notification of the journal, probably as a result of firewalls and antivirus fortifications. We believe we have corrected the problem; however, if you did not receive the August edition you may find it at Thyroid.org or by simply performing a Google search of *Clinical Thyroidology*. Both will provide the links to access the articles in PDF files.

**WHAT'S NEW** After consulting with the ATA Publication Committee and the ATA Board of Directors, we have decided to publish *Clinical Thyroidology* on a monthly basis beginning in January 2009. The plan is to provide about 5 to 10 articles each month, which we believe will increase our circulation and will provide very recently published articles.

Our thanks go to the people who have written commentaries and editorials for this issue, including Drs Martin Surks, Leonard Wartofsky, Kenneth Woeber and Reed Larsen.

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

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**Citations:** Several of our readers have asked that we provide the correct citation for Concise Reviews and Editorials written for *Clinical Thyroidology*. Beginning with this issue, an electronic citation will be appended at the end of each Concise Review and each Editorial. If our readers wish to cite commentaries at the end of each article, we can format the journal to do this as well.

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## IN MEMORIAM

### Dr. Robert David Utiger

This issue of *Clinical Thyroidology* is dedicated to the memory of the late Dr. Robert D. Utiger who served as the outstanding Editor-in-Chief of this journal from 2001 to 2007. Bob's death on June 29, 2008, leaves an enormous hole in the field of Endocrinology.

We were fortunate to have him as our colleague in the Thyroid Division at the Brigham and Women's Hospital in Boston for the last eight years and I have been asked by Dr. Mazzaferri to summarize his outstanding career.

Bob was born in Connecticut and graduated Phi Beta Kappa from Williams College and AOA from Washington University School of Medicine in St. Louis. He was on the house staff at Barnes Hospital, completing a Chief Residency in 1964 and he served as a fellow with William Daughaday (Wash. Univ.) and William Odell (NIH). His papers during this early phase of his training presaged the high quality of his subsequent work. His single-authored paper in the *Journal of Clinical Investigation* in 1965 described the radioimmunoassay of human TSH, a test which remains the most powerful screening tool for assessing a patient's thyroid status. He also contributed significantly to the first publication on clinical studies of thyrotropin-releasing hormone in man in a seminal article in *The New England Journal of Medicine* in 1971.

In 1969, he moved to the University of Pennsylvania, becoming Professor of Medicine and Chief of Endocrinology. There he developed a radioimmunoassay for T<sub>3</sub>, and used it in a remarkably productive period of clinical research on regulation of TSH secretion with fellows, including Drs. Peter Snyder and Charles Emerson. Later, he turned to the study of T<sub>4</sub> to T<sub>3</sub> conversion, working with Michael Kaplan, David Gardner, Tony Jennings, and Mansour Saberi, investigating the biochemistry of Type I deiodinase, the effect of fasting and illness on the pituitary-thyroid axis and on the inhibition of T<sub>4</sub> to T<sub>3</sub> conversion in response to that stress.

Bob moved to the University of North Carolina in 1979 and became Editor-in-Chief of *The Journal of Clinical Endocrinology and Metabolism (JCEM)* for a six-year period. He also continued an active role in the American Board of Internal Medicine, where he served in various capacities from 1973

to the time of his death.

In 1990, Bob came to Boston as Deputy Editor of *The New England Journal of Medicine* and Clinical Professor of Medicine at the BWH/Harvard Medical School. He served with Dr. Arnold Relman and Dr. Jerome Kassirer as Deputy Editor, focusing on endocrine studies. It is in this role at the *JCEM* and the *NEJM* that many of us were exposed to the depth of Bob's knowledge and his high standards for the written scientific word. The final hurdle for publication in these journals was responding to an often sentence-by-sentence, unbiased critique by Bob of what we naively thought of as a "final" manuscript. In my experience, the pages were covered by a sea of red ink. This could be disconcerting, but his comments invariably improved the clarity of the paper and educated us as well. Sadly, he is not here to correct this effort.

With his retirement from *The New England Journal* in 2000, he became a full-time member of the BWH Thyroid Division and continued his editorial activities with *Clinical Thyroidology*, as well as co-editing three editions of "The Thyroid: A Fundamental and Clinical Textbook" with Lew Braverman. It was in this venue that I saw firsthand his love of teaching and of patient care, as well as his encyclopedic knowledge of endocrinology. As far as we could tell, he had never forgotten any article he had ever read, and he had read virtually everything! As one might imagine, he was in great demand by the fellows as a clinical attending and gave of his time unstintingly to them and to students, residents, attendings, and, of course, to his patients. Bob received numerous honors, including the Van Meter Prize and the Distinguished Service Award of The American Thyroid Association, as well as the Sidney H. Ingbar Distinguished Service Award of The Endocrine Society. As a small gesture of our gratitude, the main conference room in our Endocrinology Division will be named in his honor. It was in this room at the weekly clinical Grand Rounds, the Journal Club and Research Conference that he taught us so much.

This brief summary of Bob's magnificent academic accomplishments unfortunately cannot capture his generous spirit, his wry sense of humor, and his thoughtfulness for colleagues, pupils and his patients. He was the epitome of the Academic Physician as well as great human being and is irreplaceable.

— P. Reed Larsen, MD

## CONCISE REVIEW

## TSH Reference Limits: Emerging concepts and implications for the prevalence of subclinical hypothyroidism

The diagnosis of hypothyroidism is based on negative feedback between serum thyroid hormones and serum thyrotropin (TSH). A raised TSH with decreased free thyroxine ( $T_4$ ) defines primary hypothyroidism, but when free  $T_4$  remains within reference limits, the diagnosis is subclinical hypothyroidism. Given the high prevalence of raised TSH, particularly among older patients with normal free  $T_4$ , designation of the upper reference limit is critical.

During the past 15 years, the reported upper limit has been considered to be about 4.0 to 5.5 mIU/L, and several national reference laboratories and manufacturers of TSH assay kits provide similar limits. Analysis of TSH distribution from the National Health and Nutrition Examination Survey III (NHANES III) (1) suggested an upper limit of 4.12 mIU/L for a large reference population that was free of thyroid disease and representative of the U.S. population. Also excluded from that group were subjects who were taking thyroid medications, or other medications that might affect thyroid measurements, as well as those who had antithyroid antibodies.

This Concise Review will address two issues: First, concerns regarding the proposal to lower the upper reference limit to 2.5 to 3.0 mIU/L; and second, new data that supports use of age- and ethnic-specific reference limits in evaluation of patients with thyroid dysfunction.

TSH reference limits are determined by analyzing TSH distribution after log transformation. Distribution curves generally show a skew toward higher TSH concentrations, which has been assumed to represent individuals with undetected autoimmune thyroid disease. The National Academy of Clinical Biochemistry suggested that the upper reference limit of rigorously screened individuals without thyroid disease would likely be 2.5 mIU/L (2), and some authorities and professional societies have recommended decreasing the upper limit from 4 mIU/L to 2.5 to 3.0 mIU/L (3) for a comparable population. This recommendation is not only controversial (4), but would have enormous public health consequences since TSH exceeds 2.5 mIU/L in 10 to 20% of individuals of all ages and 35% of people who are more than 70 years of age. Such individuals could be designated hypothyroid and possibly treated with levothyroxine, unnecessarily, for the duration of their life (4).

However, several recent studies of thyroid disease-free individuals found no significant change in the TSH upper limit when patients with antithyroid antibodies (5-7) or even abnormalities on thyroid ultrasound (5,6) were excluded.

Most recently, Hamilton et al. (6) studied a mainly white U.S. population (97.4%) without thyroid disease or antithyroid antibodies and found a similar 97.5th percentile whether or not those with thyroid ultrasound abnormalities were excluded. After correcting for changes in assay methods, the 97.5th percentile was 4.1 mIU/L, identical to the 97.5th percentile from NHANES III, 4.12 mIU/L (1). These findings in an iodine-sufficient North American population confirm similar observations from Europe that excluding people with antithyroid antibodies or ultrasound abnormalities did not significantly influence the 97.5 percentile (5). They provide additional evidence against an arbitrary decrease in the TSH upper limit.

The 97.5th percentile reported by Hamilton and colleagues (6) is for a population without thyroid disease. However, the 20-year follow-up of the Whickham study did show an increased rate of progression to overt hypothyroidism when TSH was  $>3.0$  mIU/L (8), suggesting that some in this group did have underlying thyroid disease. Further analysis of these data showed that progression to hypothyroidism occurred in less than 10% of 20- to 40-year-olds and in 5 to 15% of individuals 50 to 70 years of age who had TSH  $>3.0$  mIU/L (4). The prevalence increased further in those who had antithyroid antibodies. Since nearly 80% of subjects with TSH between 3.0 and 5.0 mIU/L do not have antithyroid antibodies (4), it is likely that the large majority of people with TSH in that range have little risk of hypothyroidism.

An explanation for the skew in TSH distribution curves toward higher serum TSH was recently reported (9). In all analyses thus far, TSH distribution curves were developed from TSH measurements from people of all ages, thus representing a composite curve across the spectrum of age. When the NHANES III database was reanalyzed by development of TSH distribution curves for specific age deciles, a progressive shift in the curves to higher TSH with age was observed, rather than a skew to higher values. These findings, confirmed by analysis of a more recent NHANES survey (1998–2002), suggested that TSH distribution and reference limits increase with age, and that TSH reference limits derived from curves that are composite for all ages could lead to significant misclassification of patients with thyroid disease. For example the upper age-specific limit for people older than 80 years of age was 7.5 mIU/L and it was estimated that about 70% of such people who had TSH  $>4.5$  mIU/L, previously considered to have raised values, were within their age-specific limits.

When an urban outpatient practice of medicine was similarly analyzed, the shift in TSH distribution and upper reference

limit with age was observed in the total population and in each major ethnic subgroup, blacks, whites, and Hispanics (10). Moreover, significant differences were observed in TSH distribution and reference limits between the individual ethnic subgroups, with blacks and Hispanics having a shift to lower TSH compared with whites. Significant misclassification of individuals with raised or decreased TSH occurred unless both ethnic- and age-specific limits were used.

## SUMMARY

Recent literature provides evidence against lowering the upper limit of the TSH reference range in the United States and emphasizes the importance of using both ethnic- and age-specific reference limits in order not to misclassify patients with thyroid disease.

**Martin I. Surks, MD, MACP**

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Surks, MI. TSH Reference Limits: Emerging concepts and implications for the prevalence of subclinical hypothyroidism. *Clinical Thyroidology* [serial online]. 2008;20(3):4-5. Available at: [http://thyroid.org/professionals/publications/clinthy/volume20/issue3/clinthy\\_v203\\_4\\_5.pdf](http://thyroid.org/professionals/publications/clinthy/volume20/issue3/clinthy_v203_4_5.pdf)  
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## HYPOTHYROIDISM

**EDITORIAL** **Levothyroxine therapy alone restores normal serum FT<sub>3</sub> levels after total thyroidectomy**

A small but significant proportion of patients placed on levothyroxine (L-T<sub>4</sub>) following thyroidectomy report not achieving their preoperative sense of well-being in spite of achievement of euthyroid reference range thyrotropin (TSH) values. While 80% of circulating serum triiodothyronine (T<sub>3</sub>) is derived from the peripheral monodeiodination of L-T<sub>4</sub>, thyroidectomy theoretically deprives the individual of the 20% contribution of direct T<sub>3</sub> secretion from the thyroid. That the nonspecific symptoms might be due to consequent relative T<sub>3</sub> insufficiency led to over a dozen studies in the past decade examining whether T<sub>4</sub>/T<sub>3</sub> combination therapy would result in an improved sense of well-being and cognitive function as compared with therapy with L-T<sub>4</sub> alone. Essentially all studies but one (1) found no significant difference in outcomes irrespective of the form of thyroid hormone replacement (2).

One key consideration in assessing outcomes is whether comparable levels of serum T<sub>3</sub> are achieved with L-T<sub>4</sub> therapy alone versus T<sub>4</sub>/T<sub>3</sub> combination therapy. When serum T<sub>3</sub> levels were compared in all of the studies published to date, the comparison was done in patients with hypothyroidism who were already taking L-T<sub>4</sub> who were either continued on L-T<sub>4</sub> therapy or switched to T<sub>4</sub>/T<sub>3</sub> combination therapy. Although the observations were paired, with the patients serving as their own controls, the comparison was of T<sub>3</sub> levels while taking L-T<sub>4</sub> alone as compared with taking L-T<sub>4</sub>/T<sub>3</sub>. Thus, there were no data on true baseline or preoperative serum T<sub>3</sub> levels—that is, either prior to development of hypothyroidism or prior to thyroidectomy. The rather simple study by Jonklaas et al. (3) fairly definitively addresses the issue of whether we can achieve levels of serum T<sub>3</sub> with L-T<sub>4</sub> replacement alone that are just as “normal” as a given patient’s preoperative serum T<sub>3</sub> levels. If the basis for reports of mood or motor dysfunction were due to T<sub>3</sub> insufficiency, patients achieving postoperative T<sub>3</sub> levels comparable to their baseline preoperative T<sub>3</sub> levels should feel no different once recovered from any perioperative symptoms unrelated to thyroid hormone replacement. In the study by Jonklaas et al., reference-range TSH levels were achieved in 94% of patients by the end of the study, although many patients had higher TSH levels shortly after surgery that required titration with an increased dosage of L-T<sub>4</sub>.

Because T<sub>4</sub> is converted to T<sub>3</sub>, it would follow that ultimately near-normal concentrations of serum T<sub>3</sub> could be restored by administering T<sub>4</sub> alone, providing enough L-T<sub>4</sub> is given. As had been seen in earlier published studies, attainment of T<sub>3</sub> levels in the normal range requires a dosage of L-

T<sub>4</sub> that is associated with free thyroxine (FT<sub>4</sub>) levels on replacement that are higher than preoperative basal FT<sub>4</sub> values. Nevertheless, the study provides proof of principle that sufficient levels of serum T<sub>3</sub>, statistically no different from patients’ preoperative basal T<sub>3</sub> levels, can be achieved during treatment with L-T<sub>4</sub> alone, and are associated as well with comparably normal TSH levels. Unfortunately, Jonklaas et al. did not assess patient satisfaction, mood, cognition, or responses to symptom questionnaires. It would have been of interest to determine whether restoration of serum T<sub>3</sub> levels to their original values was associated with a universal sense of well-being in all subjects or whether there was a subgroup who failed to achieve their baseline sense of well-being in spite of having comparable serum T<sub>3</sub> levels.

While there may be other, yet poorly understood, reasons why some patients continue to report reduced mood, memory, and psychomotor function while on replacement therapy with L-T<sub>4</sub> alone, this study confirms that such symptoms are not due to T<sub>3</sub> insufficiency, given an adequate L-T<sub>4</sub> dosage and normalization of TSH. In view of the controversy over what constitutes a “normal” TSH level (4) and because achievement of a TSH level within the population reference range may not be equivalent to achieving a patient’s individual “normal” range (5), perhaps we should be titrating L-T<sub>4</sub> dosages to achieve both the latter “personal best” TSH level and the preoperative or presurgical T<sub>3</sub> levels when known. Is it possible that the fraction of patients who report symptoms are those whom we have failed to truly restore to euthyroidism? Indeed, several studies have shown that 15 to 27% of patients treated by endocrinologists are undertreated (6,7). Moreover, these figures are based on TSH values at an upper limit of the reference range of 4.5 to 5.3 mIU/L, and the percentages of undertreated patients would be considerably higher given an upper limit of normal for TSH of 3 to 3.5 mIU/L. Conceivably, the number of patients with these persistent symptoms would be much reduced if patients were treated with sufficient L-T<sub>4</sub> to bring TSH levels to the range of 1.0 to 1.5 mIU/L.

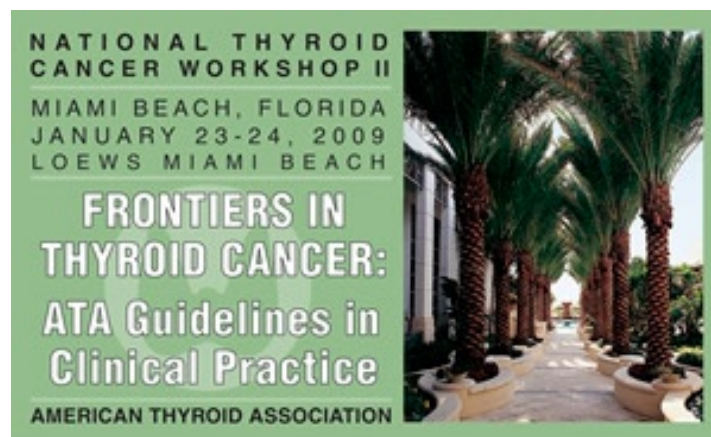
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# Levothyroxine therapy alone restores normal serum FT<sub>3</sub> levels after total thyroidectomy

Jonklaas J, Davidson B, Bhagat S, Soldin SJ. Triiodothyronine levels in athyreotic individuals during levothyroxine therapy. *JAMA* 2008;299:769-77.

## SUMMARY

**BACKGROUND** Clinical trials have demonstrated that adding liothyronine (T<sub>3</sub>) to levothyroxine (L-T<sub>4</sub>) confers no consistent benefit to patients being treated for hypothyroidism. However, there is no direct evidence that subtle T<sub>3</sub> deficiency is avoided by using L-T<sub>4</sub> alone. This study is designed to compare preoperative serum T<sub>3</sub> levels in patients with normally functioning thyroid glands with the T<sub>3</sub> levels in the same patients after they became surgically athyreotic and were being treated with L-T<sub>4</sub> alone.

**METHODS** The study subjects were 50 euthyroid patients aged 18 to 65 years who were scheduled for total thyroidectomy for suspected or known thyroid cancer, goiter, or benign nodular thyroid disease. Thyroid hormone levels were measured before thyroidectomy in individuals not receiving thyroid hormone therapy, and again after surgery when they were being treated with L-T<sub>4</sub> alone. Postoperatively, patients with benign thyroid disease were given L-T<sub>4</sub> (1.7 µg/kg daily) replacement therapy aimed at keeping the serum TSH levels in the normal range, and others were given L-T<sub>4</sub> (2.2 µg/kg daily) to maintain the serum TSH level below normal for the treatment of thyroid cancer. The L-T<sub>4</sub> doses were adjusted during the two postoperative (third and fourth) thyroid profiles to achieve the treatment goals. Patients underwent a complete history and physical examination and had two separate thyroid profiles before and two after thyroidectomy when they were taking L-T<sub>4</sub> and had achieved stable serum thyrotropin (TSH) levels. At the end of the study, the medication history and physical examination were repeated.

**RESULTS** Of the 50 subjects who completed the study, 37 (74%) were female, 19 (51%) of whom were premenopausal and 18 (49%) menopausal. The mean age of the subjects was 49 years. Thyroidectomy was performed for benign disease in 33 patients (66%) and for thyroid cancer in 17 others (34%). In all, 34 (68%) required an alteration of their L-T<sub>4</sub> dose in the third time point to maintain the target TSH level, which was achieved by the fourth time point. The serum TSH levels were significantly higher than the prethyroidectomy values at time point 3 but not at time point 4 (Figure 1). The serum free T<sub>4</sub> (FT<sub>4</sub>) levels increased significantly at postthyroidectomy time points 3 and 4 as compared with prethyroidectomy FT<sub>4</sub> levels at the first and second time points; however, the serum FT<sub>4</sub> levels did not differ between time points 3 and 4 (Figure 2). As

would be expected the serum TSH levels were significantly lower and the serum FT<sub>4</sub> levels were significantly higher in patients with thyroid cancer as compared with preoperative values (Figures 1 and 2). By the end of the study, there were no significant decreases in serum T<sub>3</sub> levels in patients receiving L-T<sub>4</sub> therapy as compared with their prethyroidectomy

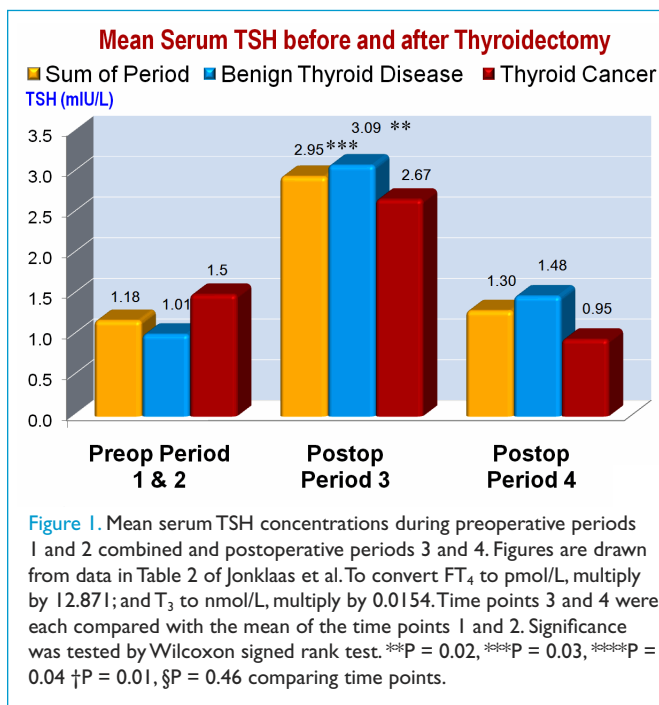


Figure 1. Mean serum TSH concentrations during preoperative periods 1 and 2 combined and postoperative periods 3 and 4. Figures are drawn from data in Table 2 of Jonklaas et al. To convert FT<sub>4</sub> to pmol/L, multiply by 12.871; and T<sub>3</sub> to nmol/L, multiply by 0.0154. Time points 3 and 4 were each compared with the mean of the time points 1 and 2. Significance was tested by Wilcoxon signed rank test. \*\*P = 0.02, \*\*\*P = 0.03, \*\*\*\*P = 0.04 †P = 0.01, §P = 0.46 comparing time points.

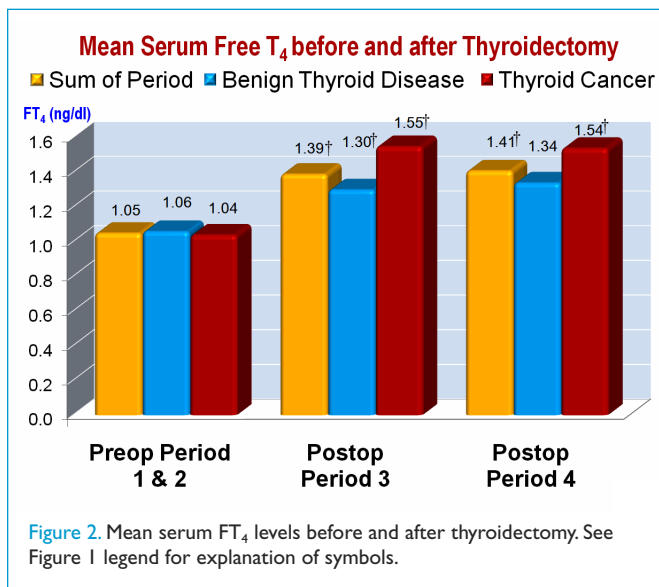
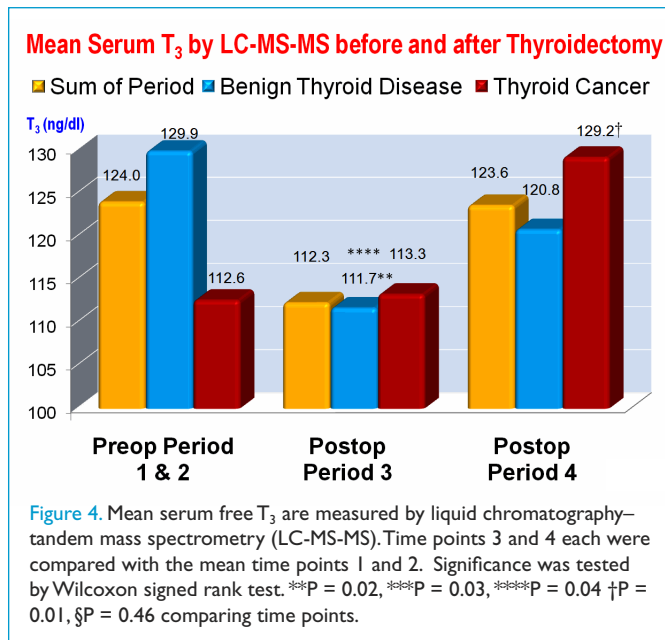
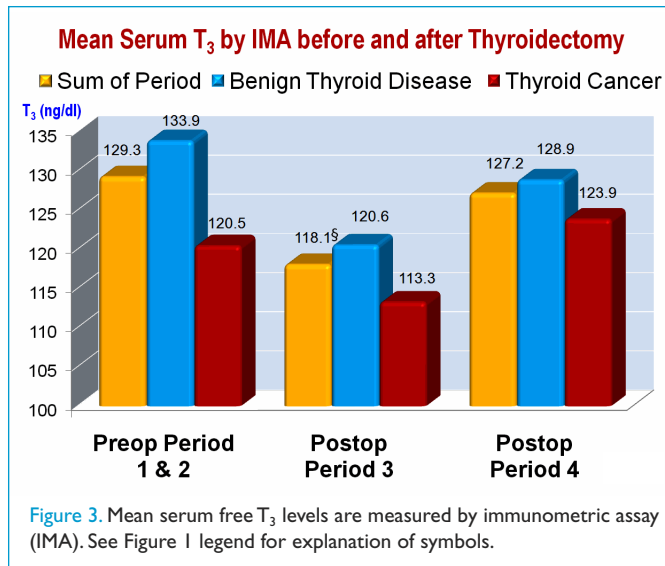


Figure 2. Mean serum FT<sub>4</sub> levels before and after thyroidectomy. See Figure 1 legend for explanation of symbols.



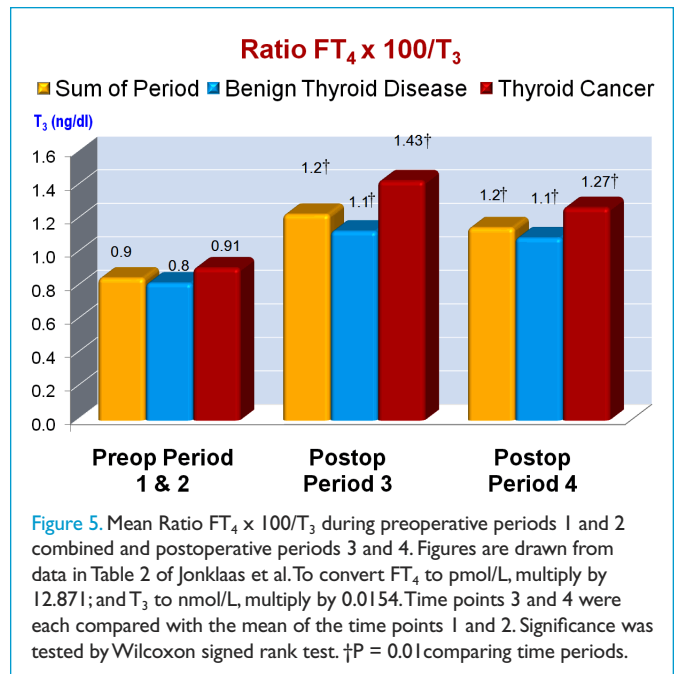
T<sub>3</sub> levels (mean, 127.2 vs. 129.3 ng/dl) as measured by T<sub>3</sub> immunometric assay or by liquid chromatography tandem mass spectrometry (Figures 3 and 4).

**CONCLUSION** Levothyroxine therapy alone restores normal serum FT<sub>3</sub> levels after total thyroidectomy.



**Reference**

1. Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ, Jr: Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. *N Engl J Med* 1999;340:424-9.



**COMMENTARY**

The treatment of hypothyroidism has been the subject of controversy for some time, mainly because a small group of patients with hypothyroidism do not feel entirely well with levothyroxine replacement therapy. As a consequence, some have suggested that thyroid hormone replacement with T<sub>4</sub> therapy alone may not precisely duplicate the normal thyroid hormone environment comprising both thyroxine (T<sub>4</sub>) and triiodothyronine (T<sub>3</sub>), causing the symptoms that some patients experience. Still, T<sub>3</sub> is normally converted from T<sub>4</sub> and nearly every published study has failed to find that the addition of T<sub>3</sub> to T<sub>4</sub> is beneficial, save for the study by Bunevicius et al. (1), which found that among patients with hypothyroidism, partial substitution of T<sub>3</sub> for T<sub>4</sub> may improve mood and neuropsychological function, suggesting a specific effect of the T<sub>3</sub> normally secreted by the thyroid gland. Despite the many studies exploring this question, none have measured serum T<sub>3</sub> levels before and after therapy in the same patients taking levothyroxine for various forms of hypothyroidism. This relatively simple approach, which was taken by Jonklaas et al., leaves little doubt that T<sub>3</sub> deprivation does not explain why some patients do not feel well when treated with levothyroxine.

Dr. Wartofsky explores this problem in the current issue of *Clinical Thyroidology*.

Ernest L. Mazzaferri, MD, MACP

# The diagnosis of subclinical hypothyroidism is severely limited by a single set of thyroid function tests and the biologic variation in thyroid testing from visit to visit

Karmisholt J, Andersen S, Laurberg P. Interval between tests and thyroxine estimation method influence outcome of monitoring of subclinical hypothyroidism. *J Clin Endocrinol Metab* 2008;93:1634-40.

**SUMMARY**

**BACKGROUND** Although subclinical hypothyroidism is a common diagnosis, there is no consensus concerning when treatment should be initiated and how untreated patients should be monitored. This prospective study evaluates the reliability of the information obtained from sequential clinical observations and monthly thyroid-function tests measured over a 13 month period.

**METHODS** The study subjects were selected from 34 individuals who fulfilled the following criteria: no previous history of thyroid disease, not pregnant within the past 2 months, no change in medicine in the past 3 months, serum thyrotropin (TSH) levels of 5 to 12 mIU/L (detection limit, 0.005; reference range, 0.27 to 4.2 mIU/L), total thyroxine (T<sub>4</sub>) within the laboratory reference range (0.4 detection limit; range, 4.7 to 10.8 ng/dl L),\* free thyroxine (FT<sub>4</sub>) within the laboratory reference range (detection limit, 0.02; reference range, 0.9 to 1.7 ng/dl),\* and stable thyroid-function tests on repeated testing after 3 months. At each visit serum was obtained to measure T<sub>4</sub>, FT<sub>4</sub>, and T<sub>4</sub>/T<sub>4</sub> (thyroid-binding globulin). Hypothyroid signs and symptoms were evaluated as described by Zulewski et al(1). The study participants were evaluated monthly for 13 months. Blood samples were obtained at 9 to 10 a.m., and were determined immediately, and again at the end of the study in serum samples separated and frozen at -20°C. Three patients were taking stable doses of oral contraceptives or estrogen.

\*Total T<sub>4</sub> ng/dl × 12.9 = nmol/L

\*Free T<sub>4</sub> ng/dl × 12.9 = pmol/L

**RESULTS** The study entrance criteria were met by 21 patients, 19 (90%) of whom were women. The mean (±SD) patient age was 57±12.2 years, and lean mean body mass index was 28.4±4.9 kg/m<sup>2</sup>. Serum antithyroid peroxidase antibodies (TPOAb) were detected in 18 patients (86%). During a period of 13 months, the mean serum TSH was 7.59±2.3 mIU/L (range, 3.3 to 14.7) and the mean FT<sub>4</sub> was 1.03±0.12 ng/dl (range, 0.81 to 1.6). After meeting the entrance criteria, one patient had normal thyroid-function tests throughout 13 months of study, and another had overt hypothyroidism after four visits. During the 13-month study period, the criteria for subclinical hypothyroidism were satisfied in 15% to 100% of the patients at various times, and in 29% of the patients during all the visits; the diagnoses were variable 67% of the

time. Overall, the hypothyroid score did not differ between patients with overt or subclinical hypothyroidism.

The number of patients fulfilling the criteria for subclinical or overt hypothyroidism, or for euthyroidism at each of the 13 visits is shown in Figure 1. Overall, subclinical hypothyroidism would have been diagnosed during 74% of the visits, overt hypothyroidism in 22%, and euthyroidism in 4%. This and subsequent figures are drawn from the data of Karmisholt et al.

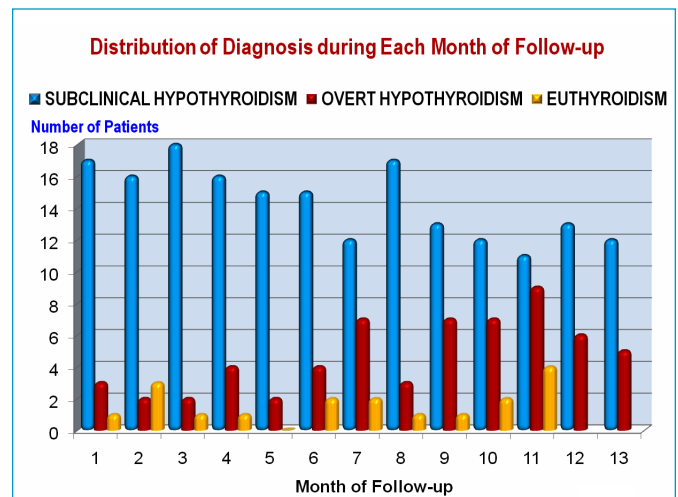


Figure 1. The number of patients fulfilling the criteria for subclinical or overt hypothyroidism, or for euthyroidism at each of the 13 visits is shown. Overall, subclinical hypothyroidism would have been diagnosed during 74% of the visits, overt hypothyroidism in 22%, and euthyroidism in 4%. This and subsequent figures are drawn from the data of Karmisholt et al.

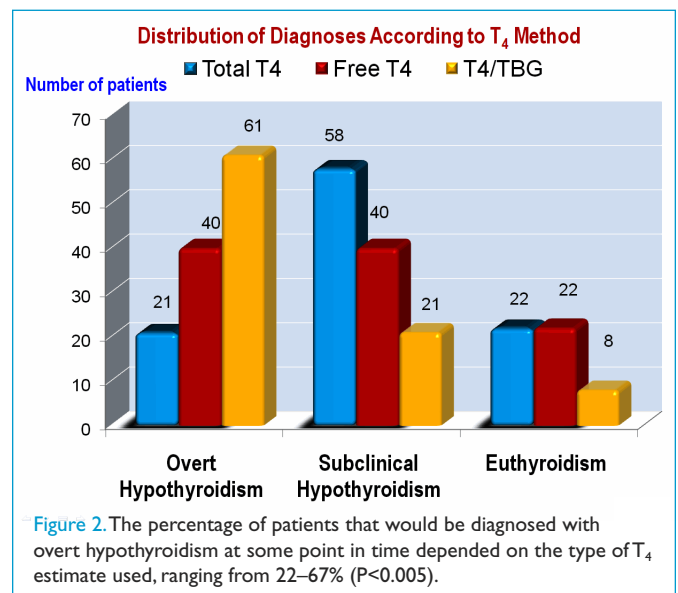
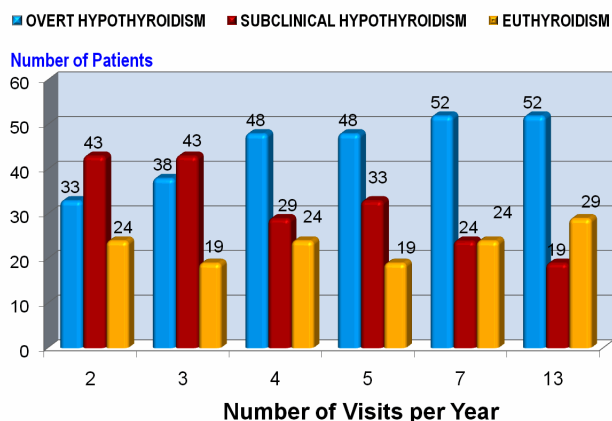


Figure 2. The percentage of patients that would be diagnosed with overt hypothyroidism at some point in time depended on the type of T<sub>4</sub> estimate used, ranging from 22–67% (P<0.005).

### Distribution of Diagnoses at 1 Year According to the Length of Follow-up



**Figure 3.** Using thyroid-function tests performed every 2nd, 3rd, 4th, 6th or 12th month, resulted in a steady fall in the diagnosis of overt hypothyroidism and a rise in the diagnosis of subclinical hypothyroidism, which varied from 19% with monthly testing to 43% after testing every 6th or 12th month.

overt hypothyroidism in 22%, and euthyroidism in 4%. The diagnoses varied according to the three different estimates of  $T_4$  (Figure 2). It also varied according to the extent of follow-up (Figure 3). In a theoretical scenario, patients who fulfilled

the criteria for overt hypothyroidism were permanently treated with levothyroxine and those meeting the laboratory criteria for euthyroidism no longer underwent follow-up, while the patients with subclinical hypothyroidism continued to undergo follow-up. Using thyroid-function tests performed every 2nd, 3rd, 4th, 6th or 12th month, resulted in a steady fall in the diagnosis of overt hypothyroidism and a rise in the diagnosis of subclinical hypothyroidism, which varied from 19% with monthly testing to 43% after testing every 6th or 12th month. The number of patients still classified as subclinical hypothyroidism after 1 yr was highly dependent on the number of testings. It varied from 19% with monthly testing to 43% after testing every 6th or 12th month. The percentage of patients diagnosed with overt hypothyroidism was 58% higher with monthly testing compared with testing every 12th month ( $P < 0.016$ ) (Figure 3). The rate of euthyroidism remained relatively steady during the 13 months of follow-up.

**CONCLUSION** The diagnosis of subclinical hypothyroidism is severely limited by a single set of thyroid-function tests and their variation from visit to visit. As a result, a relatively large number of euthyroid patients might be assigned to permanent levothyroxine therapy.

### COMMENTARY

This study shows that relatively small differences in the monitoring paradigms for patients with subclinical hypothyroidism have considerable influence on the stability of the diagnosis and that systematic assessment of symptoms and signs of hypothyroidism do not differ between patients with overt hypothyroidism and those with subclinical hypothyroidism. The authors of this study recently reported (2) that serum TSH concentrations varied more in normal controls than it did in the same set of patients with subclinical hypothyroidism in the present study; however, the percent variation in TSH was lower in patients with subclinical hypothyroidism than in euthyroid controls, but increased with higher mean serum TSH levels. In that study they found that the number of tests required for a diagnosis of subclinical hypothyroidism was high, and that two tests in the same patient must vary by 40% for TSH and by 15% for  $FT_4$  and

$FT_3$  to be truly different. In a previous 12-month longitudinal study of 16 healthy men, the same group of investigators (3) found that each individual had unique thyroid function, with individual and reference ranges for TSH and  $T_4$  within a narrow range as compared with group reference ranges used to develop laboratory reference ranges. In yet another study, Andersen et al. (4) found that even TSH within the reference range may be associated with slightly abnormal thyroid function. As shown in Figure 3, the number of patients classified as having subclinical hypothyroidism after 1 year is highly dependent on the number of tests performed. The main message of these studies is that a long period of follow-up without therapy is necessary to establish the correct diagnosis of subclinical hypothyroidism.

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# Radioiodine therapy for women with thyroid cancer does not adversely affect subsequent pregnancies and those offspring over a 10-year follow-up period

Garsi JP, Schlumberger M, Rubino C, Ricard M, Labbe M, Ceccarelli C, Schwartz C, Henri-Amar M, Bardet S, De Vathaire F. Therapeutic administration of <sup>131</sup>I for differentiated thyroid cancer: radiation dose to ovaries and outcome of pregnancies. J Nucl Med 2008;49:845-52.

**SUMMARY**

**BACKGROUND** Ten years ago this group reported that radioiodine (<sup>131</sup>I) therapy had no effects on the outcome of subsequent pregnancies and offspring in women treated for thyroid cancer, with the exception of miscarriages in a small number of women that occurred during the first year after <sup>131</sup>I therapy. The current study has twice the number of pregnancies, and updates these earlier findings.

**METHODS** From 1994 to 2004 the entire cohort of women treated for thyroid cancer at the Institut Gustave-Roussy and the Institut Jean Godinot in France and at the Institute of Endocrinology in Pisa were routinely interviewed by trained data managers, who collected information regarding the following features of each pregnancy: induced abortion, miscarriage, stillbirth, prematurity, birth weight below the 10th percentile for gestational age, congenital abnormalities, and death during the child's first year of life and the development of thyroid disease in children, including tumors at other sites.

**RESULTS** Study subjects were 1126 women with differentiated thyroid cancer who had a total of 2078 pregnancies, of which 112 (5%) occurred before patients had undergone surgery alone for thyroid cancer and 483 (23%) after <sup>131</sup>I therapy. In the latter group, 212 (44%) were given 3700 MBq or more of <sup>131</sup>I (≥ 100 mCi) in 1 to 2 treatments that were administered a mean of 35 months (range, 0 to 243) before conception.

A total of 341 therapeutic and elective abortions were done, 221 (65%) before any treatment, 26 (8%) after thyroid cancer surgery alone, and 94 (28%) after both surgery and <sup>131</sup>I therapy. Abortions were more frequent after surgical therapy, both with and without <sup>131</sup>I therapy, than before any treatment had been done (odds ratio [OR] = 2.14, Figure 1), Higher cumulative activities of <sup>131</sup>I (370 to 3700 MBq [10 to 100 mCi]) before pregnancy were not associated with a greater probability of an induced abortion (OR = 0.83, Figure 1). Yet both the cumulative <sup>131</sup>I received during the year preceding pregnancy (P < 0.001 for trend) and smoking during pregnancy (OR = 2.15) significantly increased the probability of an induced abortion. A total of 18 induced abortions of 34 pregnancies (53%) occurred in women who had received ≥370 MBq (≥ 100 mCi) <sup>131</sup>I during the year before conception, which was a greater proportion of abortions than occurred in pregnancies preceded by smaller amounts of <sup>131</sup>I (16 to 25%, P < 0.001). Abortions were significantly more frequent in women older

than 45 years and in women who continued using alcohol or tobacco during pregnancy (OR = 3.3, P < 0.001).

Miscarriages were observed in 193 of 1857 pregnancies (10%) before any thyroid cancer treatment was administered, and were more frequent (21%) in pregnancies that occurred after surgery alone, but were about the same before

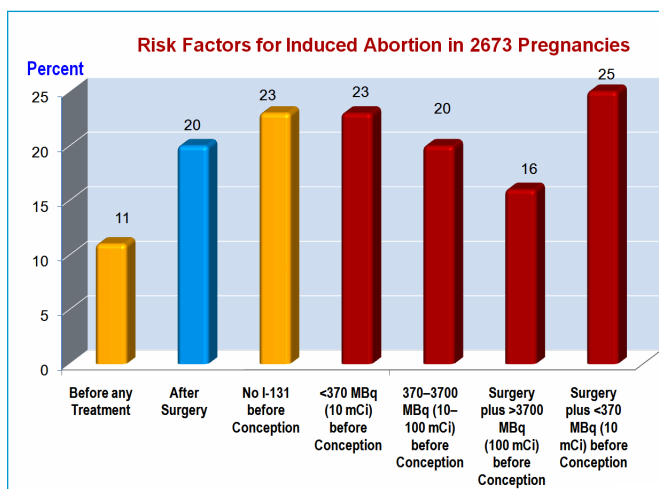


Figure 1. Risk factors for therapeutic and elective abortions are shown according to the cumulative amount of <sup>131</sup>I given to the mother before conception (rounded to nearest integer). This figure is drawn from the data in Table 1 of Garsi et al.

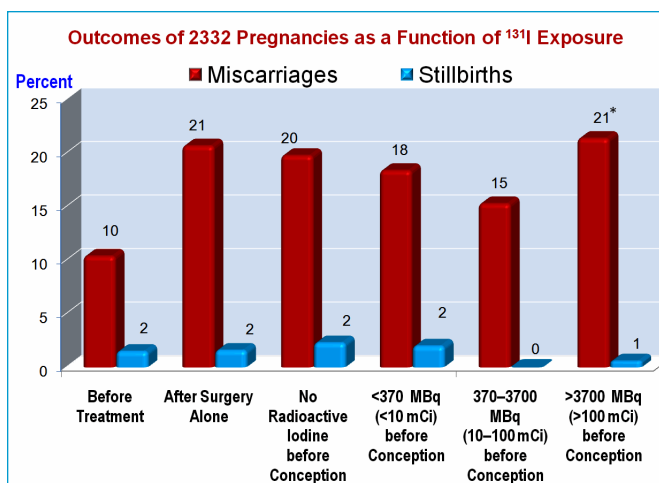
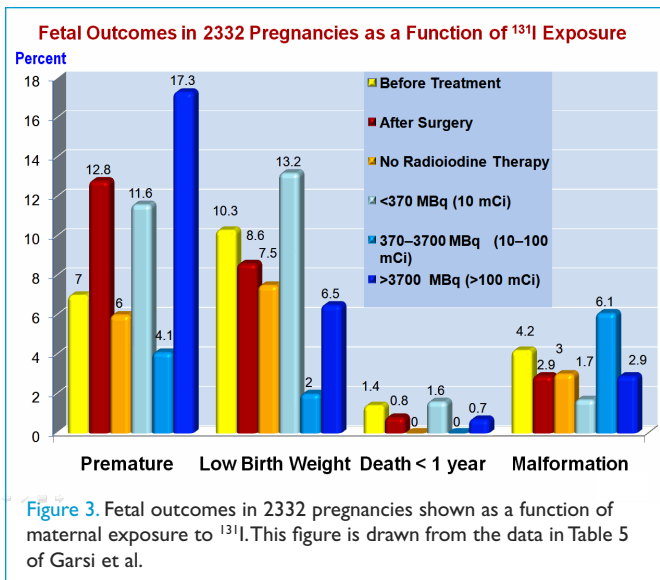


Figure 2. The risk factors for miscarriage and stillbirth in 2332 pregnancies are shown according to maternal exposure to <sup>131</sup>I prior to conception. \*P = 0.05, as determined by  $\chi^2$  test for heterogeneity. This figure is drawn from the data in Table 3 of Garsi et al.



(20%) and after (19%) <sup>131</sup>I therapy (Figure 2). There was no correlation between the cumulative <sup>131</sup>I activity and the occurrence of miscarriage. The only significant factors that predicted miscarriage, with and without <sup>131</sup>I therapy, were pregnancy after a diagnosis thyroid cancer (OR = 1.59),

### COMMENTARY

This is the largest study of the outcomes of pregnancy in women treated with <sup>131</sup>I. In a 1996 study (1) of 2113 pregnancies in women previously exposed to <sup>131</sup>I for the treatment of thyroid cancer; Schlumberger et al. reported that miscarriages were more frequent (40%) in 10 women who were treated with <sup>131</sup>I (mean dose, 3.8 MBq [108 mCi]) during the year preceding conception. However, with the exception of this finding, there was no evidence that maternal exposure to <sup>131</sup>I affected the outcome of subsequent pregnancies and offspring. The current study confirms all of the results in the previous study, with the major exception that the risk of miscarriage is not elevated by increasing <sup>131</sup>I activity.

The authors were able to document the reason for abortion in only a few (45 of 341) abortions, which were for therapeutic purposes such as concern regarding <sup>131</sup>I exposure, ongoing treatment, and suspicion of fetal malformation. Still, the greatest problem in this group of patients is the high rate of induced abortions, regardless of the reason.

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the mother's age >35 years at the time of pregnancy (OR = 2.12) and low birth weight, which was more common in the low-socioeconomic-status group (P<0.05). Women who took medications during pregnancy had a slightly increased risk of miscarriage (10% vs. 12%, OR = 1.04, P = 0.06), and their babies had a significantly greater risk of prematurity (10.4% vs. 5.5%, OR = 2.10).

Among the 2009 live births, none of the following appeared to be modified by mother's previous surgery or <sup>131</sup>I exposure: prematurity, low birth weight, death before 1 year, malformation, thyroid disease, and cancers. In all, 25 of 1633 children (1.3%) died less than 37 weeks after birth, 22 (1.4%) before mothers were given treatment, and 3 (0.8%) after the mother's surgery for thyroid cancer (Figure 3).

**CONCLUSION** The rates of therapeutic or elective abortions and miscarriages are increased in women before any treatment of thyroid cancer has been done, and are even higher after surgery but are the same before and after <sup>131</sup>I therapy. However, the risk of spontaneous miscarriage is not elevated by <sup>131</sup>I and children of mothers treated with <sup>131</sup>I have no measureable adverse effects.

Although <sup>131</sup>I therapy for thyroid cancer causes transient alterations in ovarian function, even in younger women after a mean activity of 4.2 MBq (115 mCi) (2), the risk of permanent ovarian damage after <sup>131</sup>I appears to be low (3,4). However, one of the major uncertainties is the amount of radiation necessary to induce ovarian damage. Based on an assumption that the doubling dose is 1 Gy—the amount of radiation required to produce genetic damage equal to the spontaneous mutation rate—the authors of this study found that only a few women had received an ovarian dose of sufficient magnitude to produce damage and that 139 women had received more than 140 mGy (mean dose, 305 mGy) As a result, they concluded that the study was not sufficiently powered to answer this question.

It is likely that subtle birth malformations will not be detected without large population studies. Still, this study provides strong support for the notion that maternal exposure to <sup>131</sup>I is not likely to cause significant problems during subsequent pregnancies.

Ernest L. Mazzaferri, MD, MACP

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# Patients with hyperthyroidism treated with radioiodine may be at increased risk of long-term morbidity and hospitalization for arrhythmias and cardiovascular disease

Metso S, Auvinen A, Salmi J, Huhtala H, Jaatinen P. Increased long-term cardiovascular morbidity among patients treated with radioactive iodine for hyperthyroidism. *Clin Endocrinol (Oxf)* 2008;68:450-7.

**SUMMARY**

**BACKGROUND** Some long-term studies find an increase in cardiovascular disease (CVD) mortality in patients with hyperthyroidism treated with radioactive iodine (<sup>131</sup>I). However, hyperthyroidism itself may account for the increase in CVD mortality. The aim of this study was to compare the rate and causes of hospitalization in patients with hyperthyroidism that were treated with <sup>131</sup>I with the general population.

**METHODS** This population-based case-control study comprised 2611 patients with hyperthyroidism treated with radioiodine (<sup>131</sup>I); 430 were men (16.5%) and 2181 were women (83.5%). Age and gender-matched controls were selected from a population registry. The causes and dates of hospitalization for each individual were obtained from a nationwide Finnish registry. The cause of hospitalization was classified into 13 general groups, which included infectious disease, gastrointestinal disease, and fracture, and CVD which was further subclassified as hypertension, coronary artery disease, pulmonary circulation disorders, arrhythmias, heart failure, cerebrovascular diseases, and diseases of other arteries and cerebrovascular diseases.

**RESULTS** The median age of study subjects and controls was 62 years (range, 49 to 72) and the median follow-up period was 9.0 years for the patient group and 9.1 years for the control group. For both groups, CVD was the most frequent cause of hospitalization. Still, the rate of hospitalization was higher in the patient group as compared with the control group (637.1 vs. 476.4 per 10,000 patient years, RR 1.12). The risk remained elevated for as long as 35 years after <sup>131</sup>I therapy.

Among the causes of CVD, hospitalization was more common in the patient group than the control group for arrhythmia (RR, 1.22), atrial fibrillation (RR, 1.35), cerebrovascular disease (RR, 1.31), other artery and vein disease (RR, 1.22), hypertension (RR, 1.20), and heart failure (RR, 1.48 (Figure 1). Although coronary artery disease was the second most common cause of hospitalization, the rates were not significantly different between patients and controls. The third highest rate of hospitalization was for cerebrovascular disease, with rates of 160.2 in patients and 122.8 in controls per 10,000 person years (RR P<0.001, Fig. 1). Sixty percent

of the patients with CVD had Graves' disease and 40% had toxic multinodular goiter or toxic adenoma. Patients with nodular thyroid disease had higher hospitalization rates for CVD than controls (650.9 vs. 568 hospitalizations per 10,000 person-years) but the rates in patients with Graves' disease were not statistically significant.

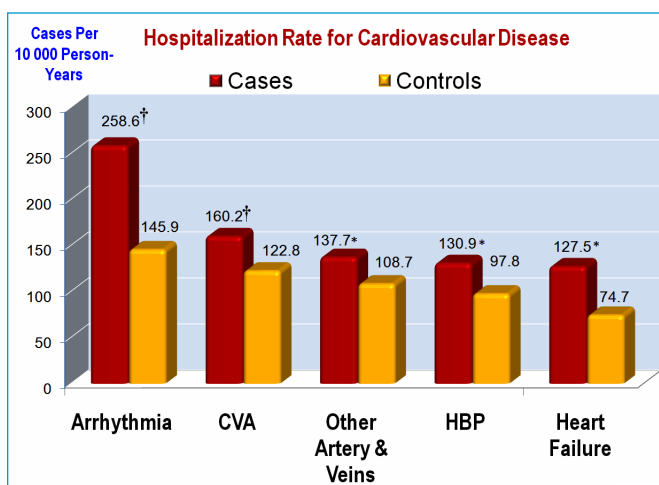


Figure 1. The rate of hospitalization for patients and controls with cardiovascular diseases. CVA denotes cerebrovascular accident, and HBP hypertension. †P = 0.001, and \*P<0.05 comparing cases and controls. This figure is drawn from the data in Table 2 of Metso et al.

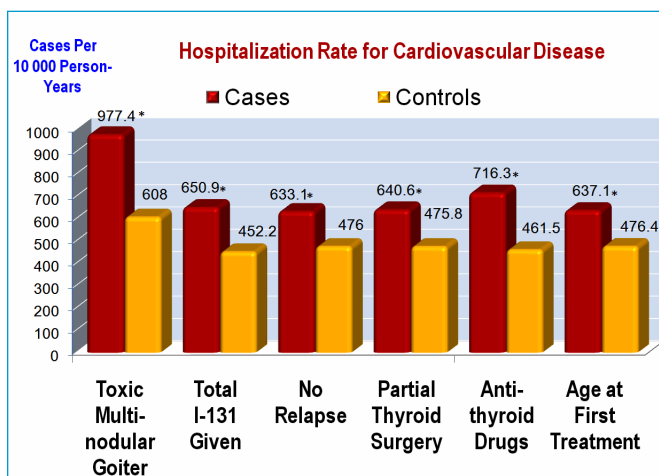


Figure 2. The hospitalization rates for cardiovascular diseases are shown in cases and controls. \*P<0.05 comparing cases and controls. This figure is drawn from data in the text and Table 3 of Metso et al.

A total of 2106 patients (80.7%) were given a single <sup>131</sup>I treatment, 397 (15.2%) were given two treatments, and 71 (2.7%) received three treatments. A mean of 304 MBq (8.2 mCi) of <sup>131</sup>I was administered (range, 55 to 2664 MBq [1.5 to 72 mCi]). Hospitalization rates for CVD were elevated only among patients treated with a cumulative of 259 to 369 MBq of <sup>131</sup>I (7 to 10 mCi), and were 650.9 in patients and 452.2 per 10,000 person-years in controls, (RR, 1.20; Figure 2). The risk of hospitalization due to CVD was lower in patients who did not undergo subtotal thyroidectomy or did not develop hypothyroidism or recurrence after <sup>131</sup>I therapy. Patients treated with antithyroid drugs for less than 3 months or for more than 2 years were at increased risk of hospitalization due to CVD as compared with controls (Figure 2). Age at the time of first treatment predicted an increased risk of hospitalization in patients compared with controls (6.37 vs.

476.5 per 10,000 patient-years) and was greatest in patients aged 60 to 98 years.

The clinical factors predicting hospitalization for CVD were toxic multinodular goiter, older age at first <sup>131</sup>I treatment, cumulative <sup>131</sup>I dose, and duration of antithyroid drug therapy. Treatment with <sup>131</sup>I was associated with an increased risk of hospitalization for infectious disease (RR, 1.23), gastrointestinal disease (RR, 1.23), and fracture (RR, 1.18), which was more common in women aged 50 years of age or older or in women younger than 50 or in men.

**CONCLUSION** The rate of hospitalization for cardiovascular diseases, especially cerebrovascular disease and arrhythmia, may be increased in patients with hyperthyroidism treated with radioiodine

## COMMENTARY

Patients treated with <sup>131</sup>I for hyperthyroidism have been reported to be at increased risk for death, but it is not clear whether this is due to hyperthyroidism itself or to the effect of <sup>131</sup>I therapy. A similar study by Metso et al. (1) of 2793 patients treated with <sup>131</sup>I for hyperthyroidism showed, after a median follow-up of 9 years, that all-cause mortality was increased in patients as compared with controls (453 vs. 406 deaths per 10,000 person-years; RR, 1.12). Cerebrovascular diseases accounted for most of the increased mortality (RR, 1.40), although mortality from cancer increased as well (RR, 1.29). As in the current study, mortality increased with the cumulative amount of administered <sup>131</sup>I and with multinodular goiter, but did not increase in patients with Graves' disease. Also similar to the current study, mortality increased by <sup>131</sup>I treatment of hyperthyroidism (RR, 1.56) and age (RR, 1.10) at the time of treatment; however, the development of hypothyroidism reduced mortality significantly. Based on these findings the authors conclude that hyperthyroidism itself probably accounted for the increased cerebrovascular mortality after <sup>131</sup>I treatment.

The most striking finding of the current study by Metso et al. is the increased rate of CVD morbidity that persisted for as long as 35 years after <sup>131</sup>I therapy. As a practical matter, this suggests that patients should undergo careful long-term follow-up with the usual surveillance for CVD. Also, the findings that gastrointestinal disease and fractures are increased in older women suggest that primary care physicians should perform the usual surveillance for loss of bone density in older women and be aware that occult gastrointestinal disease, especially gastric cancer, is a possibility in these patients (2). In an editorial on this article, Burman (3) opined that there are several deficits in the two Metso studies, including ascertainment bias resulting from the fact that only hospitalized patients were studied and that the multiple conclusions in the studies are difficult to apply to clinical practice, and that it is particularly difficult to understand how <sup>131</sup>I therapy would increase the infectious disease rates. I agree with this opinion and find it difficult to understand how this risk might last as long as 35 years. Nonetheless, patients should be made aware of these findings and should also know the potential weaknesses of the observations.

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# Patients with subclinical thyrotoxicosis experience significant improvements in mood and motor learning but have minor declines in self-perceived general and physical health status

Samuels MH, Schuff KG, Carlson NE, Carello P, Janowsky JS. Health status, mood, and cognition in experimentally induced subclinical thyrotoxicosis. *J Clin Endocrinol Metab* 2008;93:1730-6.

## SUMMARY

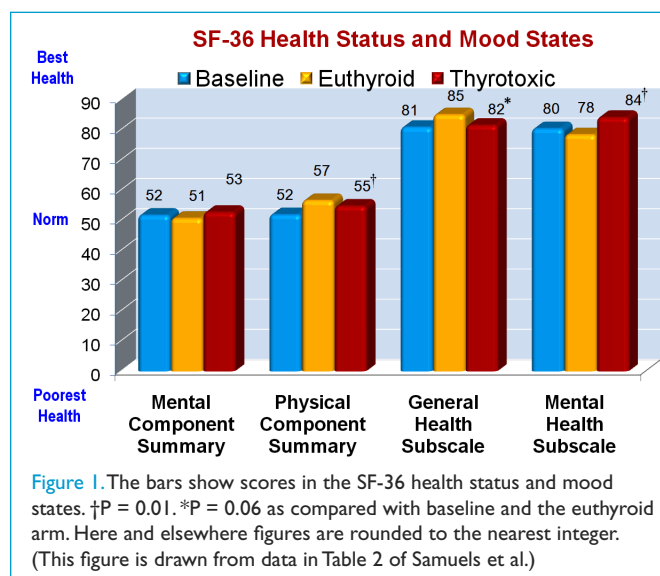
**BACKGROUND** The authors suggest that subclinical thyrotoxicosis, defined as an abnormally suppressed serum thyrotropin (TSH) level with normal serum free T<sub>4</sub> (FT<sub>4</sub>) and free T<sub>3</sub> (FT<sub>3</sub>) levels may adversely affect mood and cognition. They recently reported that subclinical hypothyroidism leads to decrements in health status, mood, and working memory. The aim of this double-blind, randomized, crossover study was to establish whether subclinical thyrotoxicosis also alters health status, mood, and cognitive function.

**METHODS** The study subjects were 33 volunteers with adult-onset hypothyroidism, which in 2 cases was caused by radioiodine therapy for Graves' disease and in 31 others by autoimmune hypothyroidism. Subjects were randomly assigned to receive either their usual doses of levothyroxine (L-T<sub>4</sub>) (euthyroid arm) or higher doses of L-T<sub>4</sub> aimed at achieving a serum TSH level of 0.01 to 0.4 mU/L (subclinical thyrotoxicosis arm). Six weeks later, L-T<sub>4</sub> compliance was assessed and dose adjustments were made as needed. Twelve weeks after the baseline visit, subjects returned for an extended visit, at which they underwent evaluations of health status, mood, and cognition with Short Form 36 (SF-36) and Profile of Mood States (POMS) and evaluations for thyrotoxicosis symptoms using the Hyperthyroid Symptom Scale. The subjects then crossed over to the second arm of the study, and their new doses of L-T<sub>4</sub> were dispensed. At the end of the study, subjects were asked to identify the high-dose study arm and which arm they preferred.

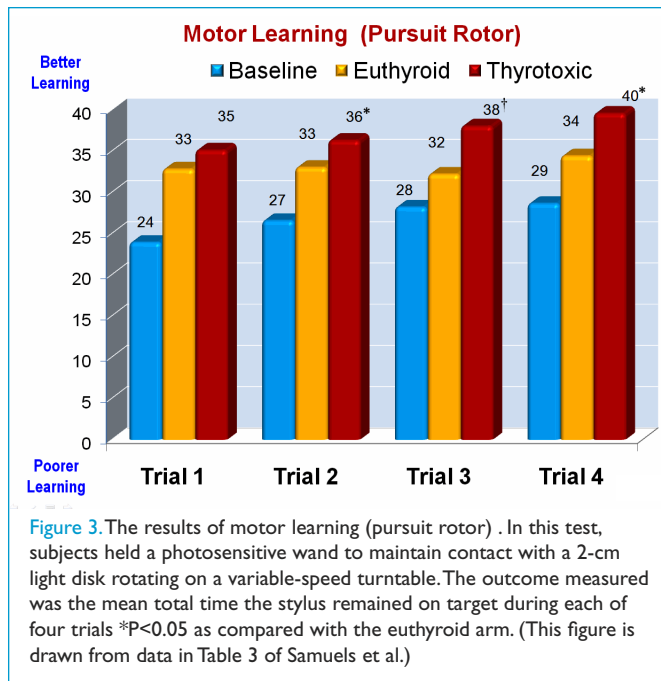
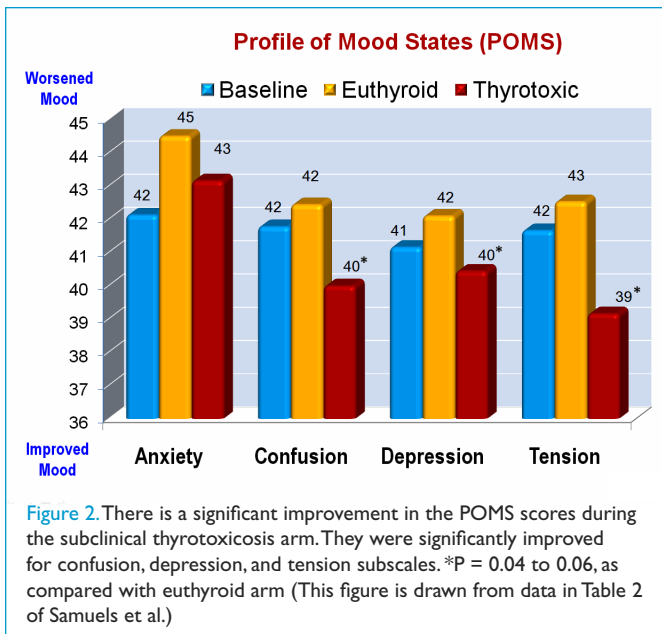
The SF-36 is a multipurpose health survey with 36 questions that yield an 8-scale profile of functional health and well-being scores as well as a psychometrically based health utility index. Higher scores on SF-36 reflect better health status and well-being. The POMS is a measure of six dimensions of affect or mood, including tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. Respondents rate 65 adjectives on a 5-point intensity scale, in terms of how they have been feeling in the past week (0 = not at all and 4 = extremely). Except for vigor-activity, the higher the score, the greater the mood disturbance or the more distress. Also a battery of cognitive tests for different forms of memory was administered to assess different cognition areas of the brain.

**RESULTS** The mean (±SEM) baseline, euthyroid arm, and thyrotoxic arm serum TSH levels were 2.58±0.27, 2.15±0.31, and 0.17±0.06 mIU/L, respectively; the serum FT<sub>4</sub> levels were 1.33±0.04, 1.40±0.04, and 1.70±0.06 ng/dl; and the FT<sub>3</sub> levels were 262.7±6.3, 259.3±6.2, 320.2±11.4 pg/dl (P<0.001 for all thyroid tests). Study subjects were unable to reliably predict which arm was the subclinical thyrotoxicosis arm. Fifteen of 33 (45.5%) guessed correctly, 10 (30%) guessed incorrectly, and 8 (24%) had no opinion. Sixteen (48.5%) preferred the L-T<sub>4</sub> dose that they perceived was the higher dose, 5 (15%) preferred the dose they perceived was the euthyroid dose, and 12 (36%) had no preference (P not significant)

At the end of the subclinical thyrotoxicosis arm the SF-36 physical health status was slightly worse (P = 0.01), the mental component summary scale was slightly but not significantly better (P = 0.15) and the mental health subscale was significantly improved (P = 0.01, Figure 1). The POMS confusion, depression, and tension subscales were significantly improved during the subclinical thyrotoxicosis arm (P = 0.04 to 0.06, Figure 2). There were no other significant effects on the SF-36 or POMS subscales. Changes in the mental component summary and the general health subscale scores of SF-36 were directly related to changes in the serum FT<sub>3</sub> levels between the two study arms; changes in the mental component summary were also related to serum FT<sub>4</sub>. The other significant finding was that changes in motor learning, a basal ganglia, and cerebellar function, were observed (Figure 3).







**CONCLUSION** Patients with subclinical thyrotoxicosis experience improvements in mood and motor learning but have small declines in self-evaluated general and physical health status, suggesting that patients with hypothyroidism should not be treated with suppressive doses of L-T<sub>4</sub>.

**COMMENTARY**

In a similarly designed study with the same outcome measures, Samuels et al. (1) found that subclinical hypothyroidism was associated with decrements in working memory but not in motor learning, as compared with improved motor learning without changes in working memory in the subclinical thyrotoxicosis study. This suggests that different parts of the brain were affected. The authors opine that taken together these studies suggest that there is a “window” of thyroid function of overall health, as defined by the SF-36 physical-component summary and the general health subscale, but that mental health and mood may improve, as defined by the SF-36 mental-component summary and POMS.

One of the interesting findings of the Samuels study is that more than half the subjects were unable to accurately

identify when they were in the thyrotoxic arm of the study. This is similar to findings by Walsh et al. (2), who performed a double-blinded, randomized clinical trial of 56 subjects with hypothyroidism who were taking 100 µg or more of L-T<sub>4</sub> daily that was altered by 25-µg increments to stratify patients into low, middle, and high L-T<sub>4</sub> treatment groups. There were no significant treatment effects identified by any of the instruments, such as SF-36, the Thyroid Symptom Questionnaire, and tests assessing well-being, and in quality of life or cognitive function, and there was no significant treatment preference. Small changes in L-T<sub>4</sub> dosage did not produce measurable changes in symptoms of hypothyroidism, well-being or quality of life, despite the changes in serum TSH and other markers of thyroid hormone action.

Ernest L. Mazzaferri, MD, MACP

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## Subclinical thyrotoxicosis progresses to overt hyperthyroidism more often in Graves' disease than with toxic nodular goiter

Rosario PW. The natural history of subclinical hyperthyroidism in patients below the age of 65 years. *Clin Endocrinol (Oxf)* 2008;68:491-2.

### SUMMARY

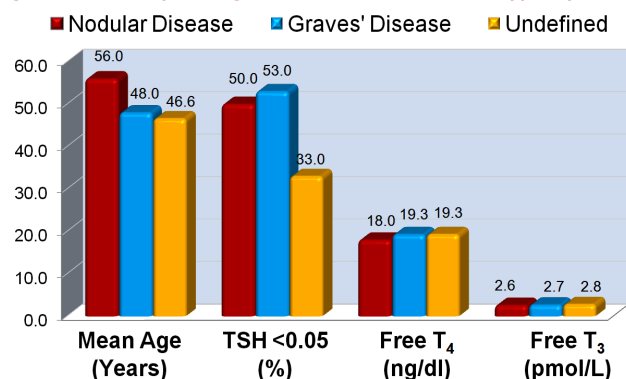
**BACKGROUND** Subclinical hyperthyroidism (SCH) is characterized by persistently reduced serum thyrotropin (TSH) levels in the range of 0.01 to 0.4 mIU/L, and normal serum thyroxine (T<sub>4</sub>) and triiodothyronine (T<sub>3</sub>) concentrations. Although it usually does not progress to overt hyperthyroidism, it is more common with serum TSH levels <0.1 mIU/L. It has been suggested that the course of SCH is influenced by its etiology, with a higher rate of spontaneous cessation in Graves' disease, but most such studies have been conducted on individuals over 60 years of age. This is a study in a younger patient cohort.

**METHODS** Sixty women younger than 65 years old were enrolled in the study if their serum TSH was <0.1 mIU/L and they had no elevations of serum FT<sub>4</sub> or T<sub>3</sub>, or a history of thyroid disease. Also excluded were those who were pregnant and those who were taking medication, or had conditions known to affect serum TSH levels, or had resting tachycardia, or an unintentional weight loss greater than 5%. Six to 8 weeks after enrollment, serum TSH, FT<sub>4</sub>, and T<sub>3</sub> concentrations were remeasured and four patients with elevations in serum FT<sub>4</sub> or T<sub>3</sub> or both, and eight with a TSH >0.1 mIU/L (0.22 to 1.9 mIU/L) were excluded from the study. The remaining 48 patients who continued to have a serum TSH <0.1 mIU/L with normal serum FT<sub>4</sub> and T<sub>3</sub> levels underwent follow-up for 2 years without therapeutic intervention. Clinical and laboratory follow-up (TSH, FT<sub>4</sub>, and T<sub>3</sub>) was performed, respectively, at 3- and 6-month intervals.

**RESULTS** Fifteen of 48 patients (31%) had Graves' disease verified by diffuse uptake on scans and ophthalmopathy, with or without positive TSH-receptor antibodies (TRAb), and 24 (50%) had toxic multinodular goiter or a single toxic nodule without TRAb, and the cause was uncertain in 3 (6%). The average age was 56 years in those with nodular disease, 48 in those with Graves' disease, and 47 in those with SCH of undefined cause (Figure 1). The serum TSH was <0.05 mIU/L in 24 (50%) of the patients with nodular disease and 8 (53%) with Graves' disease, and serum FT<sub>4</sub> and T<sub>3</sub> levels were within the upper limit of normal ( $\geq 14.16$  ng/dl and  $\geq 2.16$  pmol/L). Two patients were lost to follow-up after 9 and 12 months and a 59-year-old patient with a toxic thyroid nodule and persistent SCH had atrial fibrillation. Overt hyperthyroidism developed in 6 of 30 patients (20%) with toxic nodular disease and in 6 of 15 (40%) with Graves' disease (Figure 2). Serum TSH spontaneously returned to normal in 6 of 30 (20%) patients with

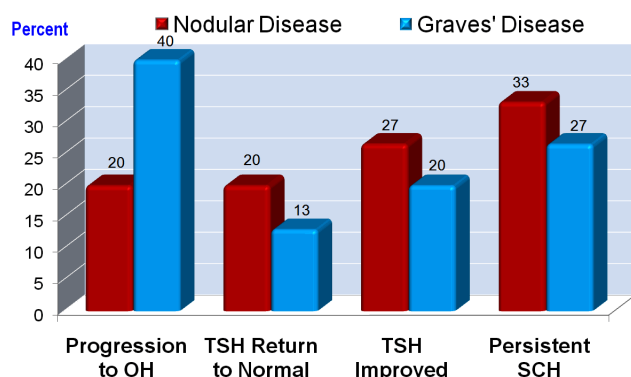
nodular disease and in 2 of 15 (13%) with Graves' disease, and TSH improved (0.14 to 0.3 mIU/L) in 8 of 30 (26.6%) patients with nodular disease and 3 of 15 (20%) with Graves' disease. Subclinical hyperthyroidism persisted in 10 of 30 (33.3%) with nodular disease and 4 of 15 (26.6%) with Graves' disease (Figure 2). Among 8 patients (33%) with serum TSH <0.05 mIU/L, 4 of 15 (26.2%) with nodular disease and 4 of 8 (50%) with Graves' disease progressed to overt hyperthyroidism (Figure 3). In comparison, overt hyperthyroidism developed in 4 patients with TSH levels ranging from 0.05 to 0.1 mIU/L—2 of 15 (13.3%) who had nodular goiter and 2 of 7 (28%) with Graves' disease (Figure 3).

**Age and Laboratory Findings in Patients with Subclinical Hyperthyroidism**

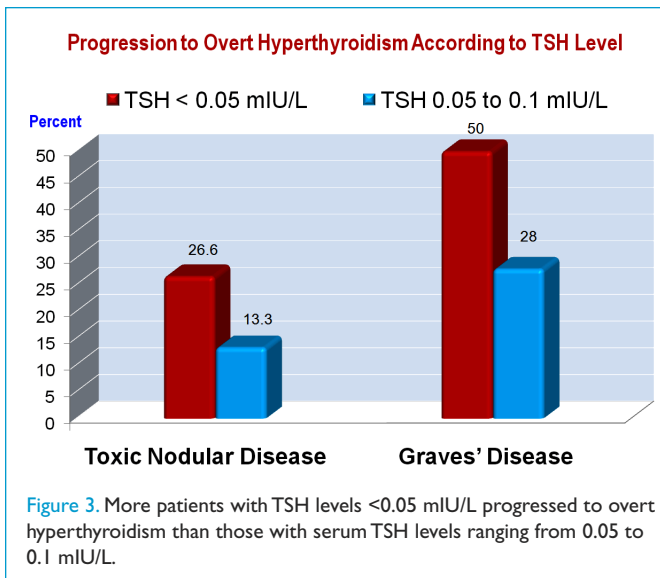


**Figure 1.** The initial clinical and laboratory findings are summarized according to cause of thyrotoxicosis in 48 patients. All figures are drawn from the data of Rosario et al. None of the differences are statistically significant.

**Change in Clinical Status during Follow-up**



**Figure 2.** During follow-up, more patients with Graves' disease had progression to overt hyperthyroidism (OH) and fewer had TSH levels that returned to normal as compared with patients with toxic nodular disease.



**CONCLUSION** Patients younger than 65 years of age who have subclinical hyperthyroidism have a somewhat different outcome than older patients, depending on the cause of the disease. After a 2-year follow-up, the progression rate to overt hyperthyroidism was about 10% per year for toxic nodular disease and about 20% for Graves' disease. Serum TSH levels spontaneously returned to normal in more patients with toxic nodular disease than it did in patients with Graves' disease.

### COMMENTARY

The natural history of SCH is uncertain, and the influence thereon of the cause of subclinical hyperthyroidism is even more uncertain. Earlier studies that have addressed this question involved elderly patients of whom most had subclinical hyperthyroidism associated with multinodular goiter. These studies collectively indicated that a subnormal serum TSH is more likely to persist in patients with goiter or when the initial serum TSH value is <0.1 mIU/L and that only a minority of patients progress to overt hyperthyroidism (1–3). A more recent retrospective analysis examined the natural history of subclinical hyperthyroidism in 7 patients with Graves' disease and 9 patients with multinodular goiter (4). In the patients with Graves' disease, serum TSH returned to normal in 5 patients (71%) within 3 to 19 months and persisted in 2 patients, 1 of whom had overt hyperthyroidism at 36 months. By contrast, in the patients with multinodular goiter, subnormal serum TSH persisted without progression

to overt hyperthyroidism during a cumulative follow-up period of 11 to 36 months.

The study by Rosario represents a significant contribution to our understanding of the natural history of subclinical hyperthyroidism. It provides convincing evidence that progression to overt hyperthyroidism is more common in patients with Graves' disease than in patients with nodular goiter, while persistence of subclinical hyperthyroidism appears to be more common in nodular goiter. The cardinal difference from the small retrospective study lies in the finding of a greater likelihood of spontaneous remission in nodular disease than in Graves' disease, a difference that can be resolved only by additional study.

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# Widely metastatic follicular thyroid cancer may cause T<sub>3</sub> thyrotoxicosis from increased tumor deiodinase activity identifiable only by serum T<sub>3</sub> levels and stopping levothyroxine therapy

Miyauchi A, Takamura Y, Ito Y, Miya A, Kobayashi K, Matsuzuka F, Amino N, Toyoda N, Nomura E, Nishikawa M. 3,5,3'-Triiodothyronine thyrotoxicosis due to increased conversion of administered levothyroxine in patients with massive metastatic follicular thyroid carcinoma. *J Clin Endocrinol Metab* 2008;93:2239-42.

## SUMMARY

**BACKGROUND** Patients with widely metastatic thyroid cancer may have triiodothyronine (T<sub>3</sub>) thyrotoxicosis due to increased deiodinase-1 and deiodinase-2 (D-1 and D-2) activity that converts thyroxine (T<sub>4</sub>) to T<sub>3</sub> in amounts sufficient to cause thyrotoxicosis, but the prevalence, diagnosis, and treatment of this problem have not been fully elucidated. This retrospective study describes the prevalence and cause of T<sub>3</sub> thyrotoxicosis in this setting and describes the clues to its diagnosis.

**METHODS** The study subjects were 58 patients with metastatic thyroid cancer measuring 2 cm or larger in diameter; 31 (54%) had papillary cancer, 20 (35%) had follicular cancer, and 7 (12%) had medullary thyroid cancer. In all, there were 79 metastatic sites, 42 (53%) in the lung, 23 (29%) in bone (29%), 4 (5%) in the liver; and 10 (13%) in other sites. Study controls were 17 patients with papillary thyroid cancer who had no sign of tumor recurrence after total thyroidectomy. Sera from all patients were obtained for measurements of thyrotropin (TSH), free T<sub>4</sub> (FT<sub>4</sub>), free T<sub>3</sub> (FT<sub>3</sub>), and thyroglobulin (Tg). Frozen stored sera remaining from past measurements were used to measure FT<sub>3</sub> to clarify the course of change in these patients. Three stored frozen tumors, two primary tumors and one metastatic subcutaneous tumor from two patients were studied for measurement of D-1 and D-2 activity.

**RESULTS** Four of 20 (20%) patients had T<sub>3</sub> thyrotoxicosis; their mean (±SD) age was 59.5±16.1 years. There were no statistical differences in the mean age, in levels of TSH and FT<sub>4</sub> among the four study groups with papillary, follicular, and medullary thyroid cancer; and in the control patients with papillary cancer (Figure 1). Patients with papillary or follicular thyroid cancer were taking significantly larger doses of levothyroxine (L-T<sub>4</sub>) than the other groups (P<0.05; Figure 1). The four patients with T<sub>3</sub> thyrotoxicosis and follicular cancer had abnormally high serum FT<sub>3</sub> levels and a serum FT<sub>3</sub>/FT<sub>4</sub> ratio greater than 3.5 (Figure 2). Two patients with T<sub>3</sub> thyrotoxicosis had palpitations, tachycardia, and weight loss, while the others had only mild tachycardia. Withdrawal of L-T<sub>4</sub> in the four patients with thyrotoxicosis for 1 week resulted in a decrease of serum FT<sub>4</sub> and FT<sub>3</sub> levels in all four patients, indicating that the high T<sub>3</sub> levels were not produced by

functioning metastases but instead originated from increased conversion of T<sub>4</sub> to T<sub>3</sub> in tumor tissue.

Normal thyroid tissue D-1 and D-2 activities, respectively, were 140±112 pmol/mg of tumor protein /hr; and 8.6±8.6

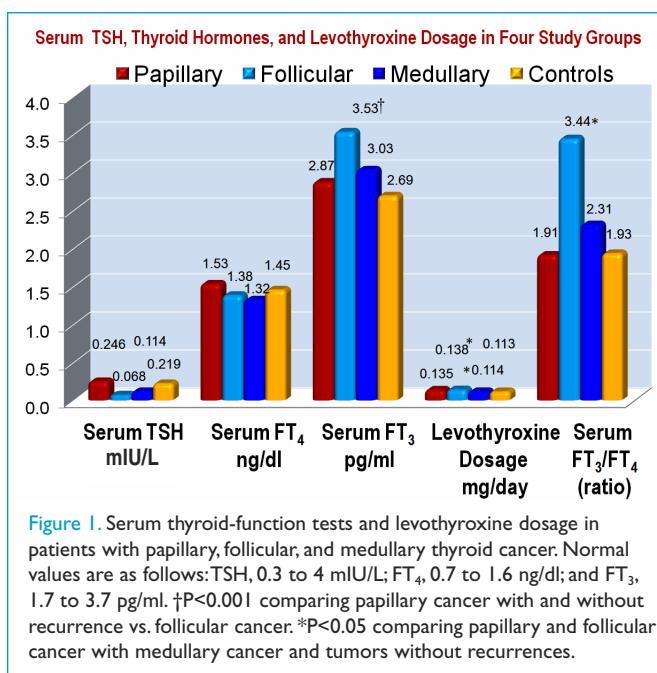


Figure 1. Serum thyroid-function tests and levothyroxine dosage in patients with papillary, follicular, and medullary thyroid cancer. Normal values are as follows: TSH, 0.3 to 4 mIU/L; FT<sub>4</sub>, 0.7 to 1.6 ng/dl; and FT<sub>3</sub>, 1.7 to 3.7 pg/ml. †P<0.001 comparing papillary cancer with and without recurrence vs. follicular cancer. \*P<0.05 comparing papillary and follicular cancer with medullary cancer and tumors without recurrences.

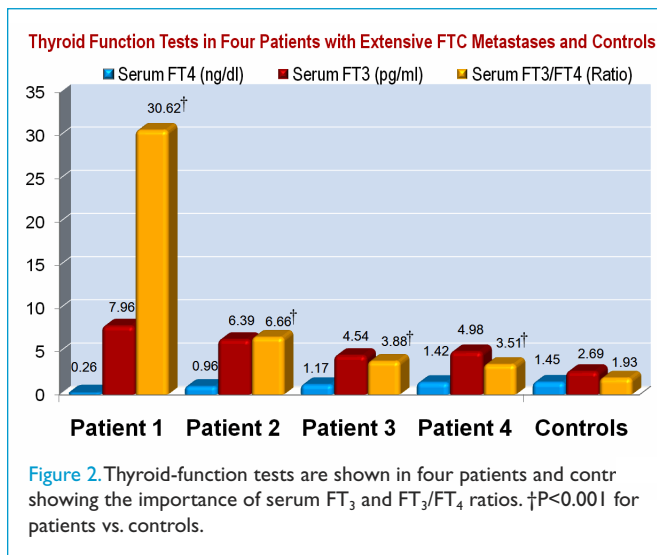


Figure 2. Thyroid-function tests are shown in four patients and controls showing the importance of serum FT<sub>3</sub> and FT<sub>3</sub>/FT<sub>4</sub> ratios. †P<0.001 for patients vs. controls.

fmol/mg of tumor protein/hr. In contrast, tumor tissues from patients with  $T_3$  thyrotoxicosis had D-1 and D-2 activities that were, respectively, about 8-fold and 250-fold those in normal thyroid tissues.

Analyses of stored sera from two patients with  $T_3$  thyrotoxicosis revealed that  $FT_3$  levels had started to increase about 2 to 4 years earlier while  $FT_4$  levels gradually declined

but remained in the normal range. Also, in one patient both  $FT_4$  and  $FT_3$  declined to undetectable levels during a 1-month period in which L- $T_4$  was stopped to facilitate  $^{131}I$  therapy.

**CONCLUSION** One in five patients with widely metastatic follicular thyroid cancer has  $T_3$  thyrotoxicosis from increased tumor deiodinase activity that can be identified by measuring serum  $T_3$  levels and stopping levothyroxine therapy.

## COMMENTARY

Approximately 80% of serum  $T_3$  is formed by outer-ring deiodination of  $T_4$  removing either iodine atom from the outer ring (designated as 5' deiodination), which occurs in various tissues. This deiodination is catalyzed by iodothyronine D-1 mainly expressed in the liver, kidney, and thyroid gland and D-2, mainly expressed in the brain, pituitary, cardiac and skeletal muscle, and placenta. Thus, converting it to 3,5,3'  $T_3$ . Deiodinase-3 (D-3), which is found in the brain, skin, and placenta catalyzes the removal of one iodine atom in the inner ring of  $T_4$  or  $T_3$  to form 3,3,5' triiodothyronine, reverse  $T_3$ , thus inactivating both hormones. Studies have shown that D2 expression in human thyroid gland is regulated at the transcriptional level through the TSH receptor and is elevated in patients with Graves' disease and in hyperfunctioning thyroid adenoma (1).

Routine surveillance of patients with differentiated thyroid cancer usually includes measurements of serum TSH,  $T_4$  or  $FT_4$  and serum thyroglobulin levels; however, serum  $T_3$  measurements are not performed routinely. The only obvious reason to do this is the appearance of thyrotoxicosis without an elevation of serum  $FT_4$ .

Kim et al. (2) first identified three patients with large or widely metastatic follicular thyroid cancer who had persistently increased  $T_3/T_4$  ratios in the absence of  $T_3$  production by the tumor. They assayed D-1 and D-2 activity in a large follicular thyroid cancer resected from one of these patients and found that D-2 was 8-fold higher than in normal human thyroid tissue and resection of the tumor, leaving the left thyroid lobe intact, normalized the serum  $T_3/T_4$  ratio. They concluded that this had probably come about by the increase in D-2 activity.

The study by Miyauchi et al. adds important information concerning  $T_3$  thyrotoxicosis in patients with follicular thyroid cancer. Miyauchi and colleagues (3) previously studied two cases of follicular thyroid cancer with distant metastases that showed high levels of  $FT_3$  with  $FT_4$  levels in the low normal range. They found that both D-1 and D-2 were expressed in the primary tumor and lung metastases at the same level as in normal thyroid tissue, and they suggested that  $T_3$  toxicosis was caused by  $T_4$  hyperconversion of administered L- $T_4$ .

The present study adds more weight to these observations. Three of the four patients with high  $FT_3$  levels had normal  $FT_4$  levels, while one had clearly low  $FT_4$  levels. Retrospective measurements of  $FT_3$  in the previously stored frozen sera samples indicated that an increase in serum  $FT_3$  levels above the upper normal range had occurred well before the present study. The authors point out that low serum  $T_4$  levels in patients being treated with a fixed dose of levothyroxine can be a clue to the early diagnosis of this problem. Moreover, withdrawal of levothyroxine for 1 week resulting in a fall in serum  $FT_4$  and  $FT_3$  is an easy way to rule out the possibility of  $T_3$  production by a functioning tumor. Of considerable importance, only two patients had mild symptoms of thyrotoxicosis such as palpitations and weight loss; these were common symptoms in patients with advanced cancer and the clinical signs were even vaguer.

It is important to recognize this syndrome by measuring serum  $T_3$  levels to avoid unnecessarily increasing the L- $T_4$  dosage that might promote severe thyrotoxicosis.

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# Levothyroxine absorption is not impaired in normal subjects treated short-term with gastric acid inhibitors famotidine or esomeprazole, or with ezetimibe

Ananthakrishnan S, Braverman LE, Levin RM, Magnani B, Pearce EN. The effect of famotidine, esomeprazole, and ezetimibe on levothyroxine absorption. *Thyroid* 2008;18:493-8.

## SUMMARY

**BACKGROUND** Gastric acid suppression is inconsistently reported to interfere with levothyroxine (L-T<sub>4</sub>) absorption. This is a prospective study of the absorption of L-T<sub>4</sub> in normal volunteers taking famotidine, a histamine H-2 antagonist, esomeprazole, a proton-pump inhibitor, and ezetimibe, a lipid-lowering drug that inhibits intestinal absorption of cholesterol and related phytosterols. Ezetimibe was included in this study because the authors had preliminary information suggesting that the drug might interfere with L-T<sub>4</sub> absorption.

**METHODS** During the initial screening, 39 subjects with normal serum thyrotropin (TSH), thyroxine (T<sub>4</sub>), triiodothyronine (T<sub>3</sub>), free T<sub>4</sub>, and free T<sub>4</sub> index levels were selected. Eligible subjects also had normal liver- and renal-function tests, a normal fasting gastrin level, negative *Helicobacter pylori* antibody titers, and normal hemoglobin; the women had a negative pregnancy test. Excluded were individuals with a history of thyroid disease, peptic ulcer disease, gastroesophageal reflux, erosive esophagitis, and erosive gastritis, or the current use of any drugs known to cause L-T<sub>4</sub> malabsorption. Nine subjects were excluded for various reasons. The 30 remaining study subjects were healthy, euthyroid volunteers who were assigned to one of three independent study groups, famotidine, esomeprazole, and ezetimibe (n = 10 in each group). In the three study groups, the mean (±SD) age was 28.1±3.1, 26.1±4.7 and 27.0±3.4 years, respectively, and the mean body weight was 139.9±8, 182.2±24.2 and 160.9±32.1 lb. Eleven were men and 19 were women, and the number of men and women in the three groups was 2/8, 4/6, and 5/5, respectively. At baseline, L-T<sub>4</sub> absorption was tested, followed by a 6-week washout period, after which a serum TSH was remeasured to reconfirm the subject's euthyroid state. The final L-T<sub>4</sub> absorption test was performed approximately 1 week after the subjects were assigned to drug administration and immediately before the third and final L-T<sub>4</sub> absorption test. The study was performed as follows in the three study groups: 1 week of 20 mg famotidine (Pepcid) twice daily with meals, or 1 week of 40 mg esomeprazole (Nexium) daily with breakfast, or a single 10-mg dose of ezetimibe (Zetia). A 1-week administration of the gastric acid suppressive medications was selected to achieve a gastric pH >4 (range, 12 to 19). After an overnight fast, the L-T<sub>4</sub> absorption test was carried out with the administration of 600 µg of L-T<sub>4</sub> (Synthroid). Blood samples were obtained prior to and at 2,

4, 6, and 8 hours after L-T<sub>4</sub> administration. Mean and peak L-T<sub>4</sub> levels and calculated areas under the curve (AUCs) were obtained during absorption testing before and after study drug administration. In a secondary analysis, AUCs were compared using a subtraction model to correct for the baseline contribution of endogenous T<sub>4</sub> values from time zero before L-T<sub>4</sub> was administered. In another secondary analysis repeated-measures analysis of variance (ANOVA) testing was used to compare mean differences in hormone levels before and after administration of each study drug.

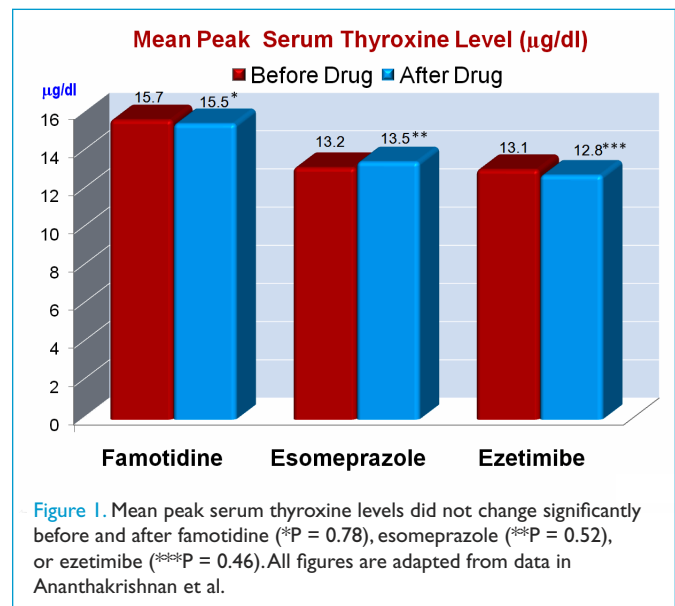


Figure 1. Mean peak serum thyroxine levels did not change significantly before and after famotidine (\*P = 0.78), esomeprazole (\*\*P = 0.52), or ezetimibe (\*\*\*P = 0.46). All figures are adapted from data in Ananthakrishnan et al.

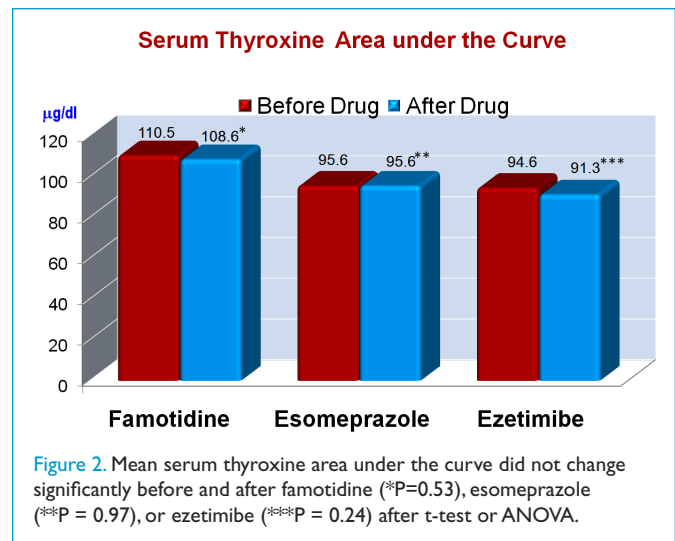
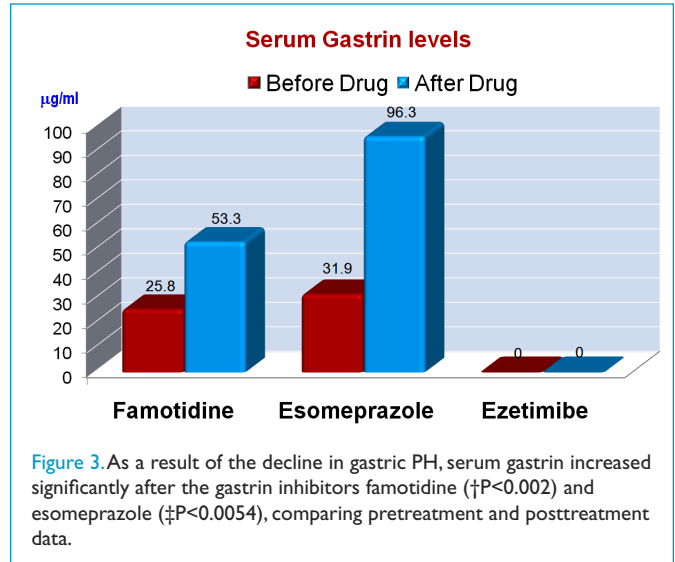


Figure 2. Mean serum thyroxine area under the curve did not change significantly before and after famotidine (\*P=0.53), esomeprazole (\*\*P = 0.97), or ezetimibe (\*\*\*P = 0.24) after t-test or ANOVA.

**RESULTS** Peak mean hormone levels and AUCs of T<sub>4</sub>, T<sub>3</sub>, and free T<sub>4</sub> (FT<sub>4</sub>) and free T<sub>4</sub> index during the absorption testing before and after each of the three study medications did not differ significantly by paired t-test and ANOVA (Figures 1 and 2). Even when using the subtractive correction method of AUC, there were no significant differences before and after the administration of study medication (Figure 2). L-T<sub>4</sub> absorption did not change after a simultaneous dose of ezetimibe (Figure 1). After treatments with famotidine and esomeprazole, serum fasting gastrin levels were significantly higher than baseline levels as a result of gastric pH elevations (Figure 3), indicating compliance with the study medications.

**CONCLUSION** Short-term treatment with the gastric acid inhibitors famotidine and esomeprazole, and with ezetimibe, which inhibits intestinal absorption of cholesterol, does not affect L-T<sub>4</sub> absorption in healthy volunteers.



**COMMENTARY**

Approximately 62% to 82% of the oral dose of levothyroxine is absorbed by the intestinal mucosa, principally at the level of the upper jejunum and ileum (1), within the first and third hours (2) of ingestion. The rate of absorption can be estimated by the ingestion of radioactive iodine-labeled L-T<sub>4</sub> (3) or simply with large oral doses of L-T<sub>4</sub>, in the range of 600 µg (4, 5). These observations have led to the discovery of a number of conditions that can lead to malabsorption of L-T<sub>4</sub>, ranging from intestinal disease, timing of L-T<sub>4</sub> ingestion with meals, and the simultaneous use of drugs that inhibit L-T<sub>4</sub> absorption. In some ways, this study is a breath of fresh air because it found no impairment of L-T<sub>4</sub> absorption in healthy euthyroid subjects treated for 1 week with gastric acid inhibitors. Previous studies have shown that patients with impaired gastric acid secretion require an increased dose of L-T<sub>4</sub>, suggesting that normal gastric acid secretion is necessary for effective absorption of oral L-T<sub>4</sub>. Centanni et al. found that patients with impaired gastric acid secretion require an increased dose of levothyroxine, suggesting that normal gastric acid secretion is necessary for effective

absorption of oral L-T<sub>4</sub> (6). Checchi et al. (7) recently reported that patients with hypothyroidism and autoimmune gastritis require larger than usual doses of L-T<sub>4</sub> to maintain the serum TSH in a normal range, which may be due to gastric mucosal atrophy. Still, this does not fully explain why L-T<sub>4</sub> absorption is impaired by gastric mucosal impairment, since most L-T<sub>4</sub> absorption occurs in the jejunum. The other drug studied by Ananthakrishnan et al. was ezetimibe, which targets the enterocytes at the small intestine brush border, blocking the absorption of biliary and dietary cholesterol from the small intestine by up to 50% or more, without blocking fat-soluble vitamins, bile acids, or triglycerides. The authors encountered a patient with primary hypothyroidism who was taking ezetimibe and required unusually large doses of L-T<sub>4</sub> to maintain the serum TSH in the normal range. However, this study shows that the drug did not impair L-T<sub>4</sub> absorption in normal subjects. Thus, all three drugs studied by Ananthakrishnan et al. did not impair L-T<sub>4</sub> absorption when given for a 1-week period.

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## Coffee interferes with the intestinal absorption of levothyroxine

Benvenga S, Bartolone L, Pappalardo MA, Russo A, Lapa D, Giorgianni G, Saraceno G, Trimarchi F. Altered intestinal absorption of L-thyroxine caused by coffee. *Thyroid* 2008; 18:293-301.

### SUMMARY

**BACKGROUND** Many things interfere with levothyroxine (L-T<sub>4</sub>) absorption, such as iron, bile acid-binding resins, cholestyramine and colestipol, over-the-counter drugs containing iron and calcium, gastric conditions such as achlorhydria, and food ingestion around the time L-T<sub>4</sub> is taken. The authors of this study have previously reported cases of delayed intestinal absorption of L-T<sub>4</sub> and have thus been more than usually attentive to this problem, eliciting detailed histories from their patients about the use of other drugs and the dietary habits patients follow when taking L-T<sub>4</sub>. Primary physicians referred patients who were taking L-T<sub>4</sub> for replacement therapy or to suppress serum thyrotropin (TSH) that failed to produce the expected results. The authors found that several patients were consistently drinking coffee or espresso to facilitate swallowing their L-T<sub>4</sub> pills or were taking L-T<sub>4</sub> with water followed shortly by drinking coffee or espresso, suggesting that this might be the cause of the problem.

**METHODS** The study subjects were eight patients, all of whom were women. Their mean (±SD) age was 45±11.38 years (range, 31 to 62) and their serum TSH levels were 2.7±20 mIU/L (range, 2.9 to 55). Ten healthy volunteers, four men and six women aged 24 to 52 years, were also studied. Patients and volunteers underwent in vitro studies of intestinal L-T<sub>4</sub> absorption using an oral dose of L-T<sub>4</sub> in lieu of radioisotopic techniques. Instead of using ≥600 µg of L-T<sub>4</sub> for the test, which is the usual dose for this purpose, patients and volunteers were given two 100-µg L-T<sub>4</sub> tablets with approximately 200 ml of water to facilitate swallowing, which was the baseline study. A second test substituted espresso (25–30 ml) for water while ingesting L-T<sub>4</sub>, and a third test used water alone to facilitate L-T<sub>4</sub> swallowing followed 1 hour later by espresso. The studies were repeated 4 to 6 weeks later and again after another 4 to 6 weeks, although in the last tests the sequence of water and espresso was random. To further test the in vivo effects of known inhibitors of L-T<sub>4</sub> intestinal absorption, two patients and two volunteers each ingested two packets of bran dissolved in 200 ml of water when they took L-T<sub>4</sub> or 20 ml of aluminum hydroxide plus magnesium hydrochloride (Maalox) 5 minutes after swallowing 200 µg of L-T<sub>4</sub>. The in vitro experiments were done by combining a solution with 10 µg/dL of L-T<sub>4</sub> with either 200 or 400 µL of Maalox, or with sucralfate, or dietary fibers of bran.

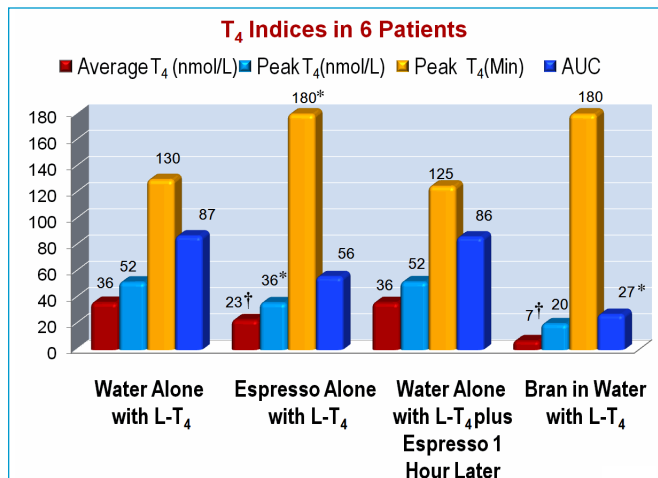


Figure 1. T<sub>4</sub> absorption in the acute loading test of 200 µg of oral T<sub>4</sub> in four different methods of ingestion. Bran was ingested by only two patients. AUC is area under the curve for T<sub>4</sub>. \*P<0.05 comparing patients with controls drinking water alone with L-T<sub>4</sub>. †P<0.001 compared with controls drinking water.

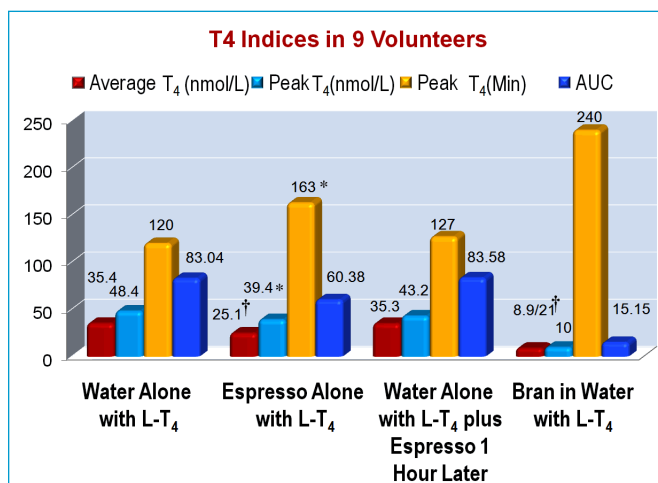


Figure 2. Data for 9 volunteers. See Figure 1 explanation. \*P<0.05 and †P<0.001 for result vs. water alone.

**RESULTS** The main in vivo findings of intestinal T<sub>4</sub> absorption are shown in Figures 1 to 3. Taking 200 µg of L-T<sub>4</sub> while drinking espresso significantly lowered the average serum T<sub>4</sub> (P<0.001) and the peak serum T<sub>4</sub> concentrations (P<0.05) compared with taking L-T<sub>4</sub> with water alone. It also lowered the T<sub>4</sub> area under the curve, but this was not significantly different from that found in the control observations. Drinking



espresso 1 hour after taking L-T<sub>4</sub> had no significant effect on L-T<sub>4</sub> intestinal absorption. However, the decrease in L-T<sub>4</sub> absorption with simultaneous L-T<sub>4</sub> and espresso ingestion was not as great as with L-T<sub>4</sub> and bran (Figures 1 and 2) or L-T<sub>4</sub> with Maalox (Figure 3). These effects were seen in both patients and volunteers (Figures 1 to 3). The in vitro studies that tested the recovery of T<sub>4</sub> from a solution containing a known concentration of T<sub>4</sub> found that espresso was 1.8-fold to 2.5-fold weaker than bran and 1.7- to 2.7-fold weaker than Maalox in lowering the T<sub>4</sub> concentration in the solution.

**CONCLUSION** Drinking coffee or espresso at the time L-T<sub>4</sub> is taken interferes with the intestinal absorption of L-T<sub>4</sub>.

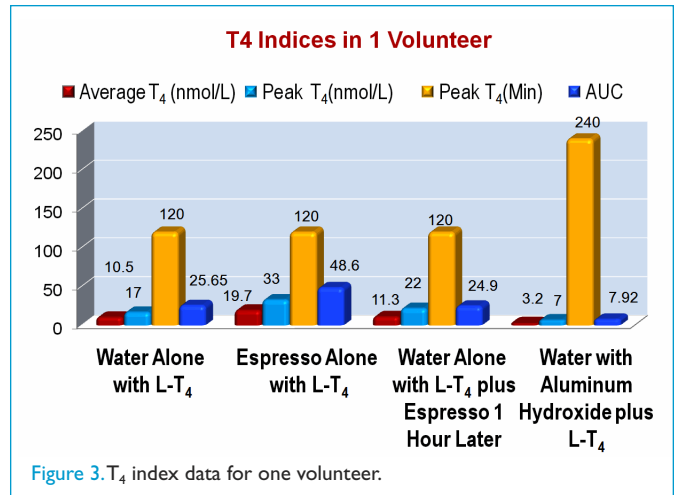


Figure 3. T<sub>4</sub> index data for one volunteer.

### COMMENTARY

This study clearly shows that drinking espresso or coffee may interfere with intestinal absorption of L-T<sub>4</sub> if one drinks it with or shortly after levothyroxine is taken. This pattern of taking espresso or coffee with L-T<sub>4</sub> was highly consistent among the eight study patients. The effect was significant, but is not as severe as that produced by Maalox or by bran ingested at the time L-T<sub>4</sub> is taken. The effect of espresso was obviated by drinking it 60 minutes after taking L-T<sub>4</sub>. The study also shows that espresso sequesters L-T<sub>4</sub> in vitro, although one of the volunteers had an increase in the absorption of L-T<sub>4</sub> with coffee ingestion. The mechanism by which espresso decreases L-T<sub>4</sub> absorption is uncertain, but the authors opine that it acts by sequestering L-T<sub>4</sub>, rendering the hormone less available for uptake by intestinal epithelium. Also, all the in vivo studies were done with espresso and not coffee per se, raising some concerns that these findings might not apply

to regular coffee. For instance, the effects of coffee on the gastric epithelial cells differ according to different roasting methods and different coffees and may vary in their effect on the intestinal mucosa (1, 2). Still, all eight patients had TSH levels in the therapeutic range, after being instructed to refrain from drinking coffee and to abstain from eating for 60 minutes after taking L-T<sub>4</sub>. Coffee does not change the gastric pH, nor does it impair gastric emptying and intestinal transit in normal volunteers. Because the Benvenaga study is retrospective, it relied on the recollections of patients rather than a systematic recording of the timing of meals and coffee ingestion. Still, the observations are strong enough, and the recommendations are simple enough to merely warn patients about this problem and to add coffee to the list of things to be avoided at the time that L-T<sub>4</sub> is taken.

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# Men with hyperthyroidism or hypothyroidism commonly have erectile dysfunction that often spontaneously improves after restoration to euthyroidism

Krassas GE, Tziomalos K, Papadopoulou F, Pontikides N, Perros P. Erectile dysfunction in patients with hyper- and hypothyroidism: how common and should we treat? J Clin Endocrinol Metab 2008;93:1815-9.

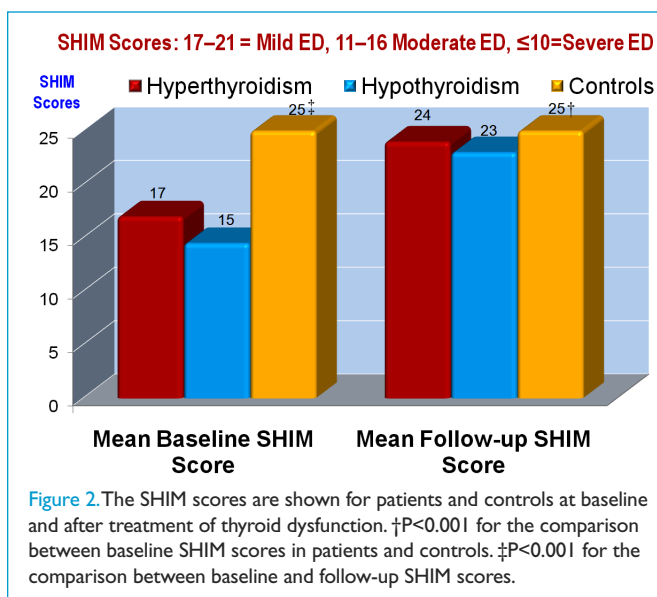
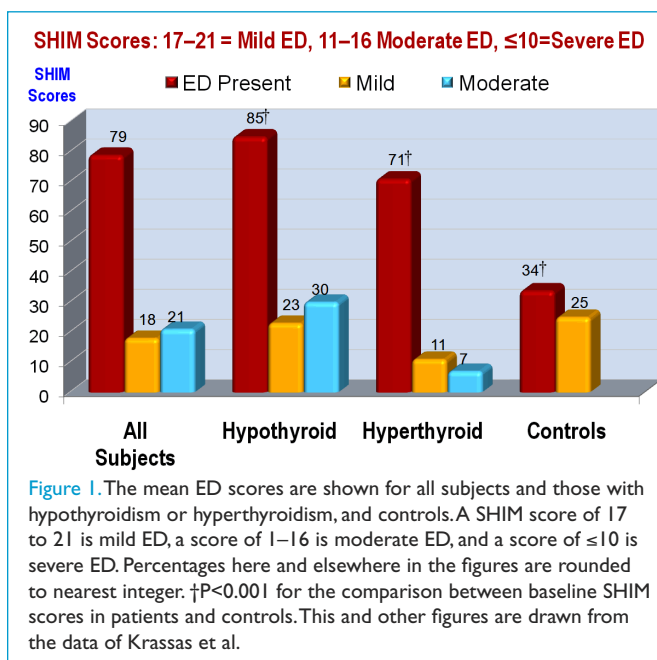
## SUMMARY

**BACKGROUND** Erectile dysfunction (ED) is a common disability associated with aging and numerous diseases. Symptoms of ED for 3 months are usually required to establish the diagnosis. The aim of this study was to investigate the impact of hyperthyroidism and hypothyroidism on the health of male sexual function and dysfunction by using the Sexual Health Inventory for Males (SHIM) instrument (5), which is a validated and widely used five-item questionnaire concerning a man's ability to attain and maintain an erection.

**METHODS** The SHIM questionnaire was administered to 76 consecutive men with hyperthyroidism or hypothyroidism seen in the thyroid clinic in Panagia General Hospital in Thessaloniki, Greece. Five patients did not wish to participate, leaving 71 study subjects to complete the questionnaire. Controls were age-matched healthy normal men. Individuals who had diabetes mellitus or cardiovascular or urologic disease were excluded. None of the patients were taking thyroid hormone or antithyroid drugs at the time the questionnaire was administered, but about one third of the patients and controls were taking other medications, mainly  $\beta$ -blockers, statins, diuretics, hypertensive agents, and mild sedatives. The diagnosis of hyperthyroidism was based on elevated serum free thyroxine ( $FT_4$ ) and suppressed serum thyrotropin (TSH) levels, and the diagnosis of hypothyroidism was based on increased serum TSH and decreased  $FT_4$  levels. Also measured were prolactin, antithyroid peroxidase antibodies (TPOAbs), antithyroglobulin antibodies (TgAbs), and free testosterone. ED was judged as mild if the responses to SHIM questions 1 to 5 added to a score between 17 and 21, as moderate if the score was between 11 and 16, and as severe if it was 10 or less. After the questionnaire was completed, patients were treated with either antithyroid drugs or levothyroxine ( $L-T_4$ ).

**RESULTS** The study included 71 subjects, 27 with hyperthyroidism and 44 with hypothyroidism, and 71 euthyroid controls. The mean ( $\pm$ SD) age was  $52.6 \pm 13.7$  years for the hyperthyroid group,  $55.9 \pm 15.3$  for the hypothyroid group, and  $54 \pm 15.2$  for the control group. Fifty-six (79%) men with thyroid dysfunction had a SHIM score  $\leq 21$ , indicating some degree of ED, 37 (52.1%) with hypothyroidism and 19 (26.8%) with hyperthyroidism, compared with 24 controls (33.8%) with a similar ED score ( $P < 0.0001$ ) (Figure 1). Severe

ED (SHIM  $\leq 10$ ) was found in 21 patients (37.5%), 13 (29.5%) with hypothyroidism and 8 (29.6%) with hyperthyroidism, as compared with 6 controls (25%) (Figure 1). ED was found in a significantly larger number of patients with hyperthyroidism (71%) and hypothyroidism (85%) as compared with controls (25%) ( $P < 0.001$  for both) (Figure 1). SHIM scores in the



patients with hypothyroidism correlated positively with FT<sub>4</sub> (P = 0.05) and negatively with TSH levels (P<0.001) but this was not found in patients with hyperthyroidism. After treatment of thyroid dysfunction, SHIM scores increased significantly in patients with hypothyroidism and those with hyperthyroidism (P<0.001 for both) (Figures 2 and 3). After follow-up for 1 year there was no difference in SHIM scores in patients treated for thyroid dysfunction (Figures 2 and 3).

**CONCLUSION** Men with thyroid dysfunction commonly have ED that is reversible with restoration of the euthyroid state. Although screening for ED is recommended for these men, specific treatment should be postponed for at least 6 months after restoring euthyroidism because it may take this long for ED to spontaneously resolve.

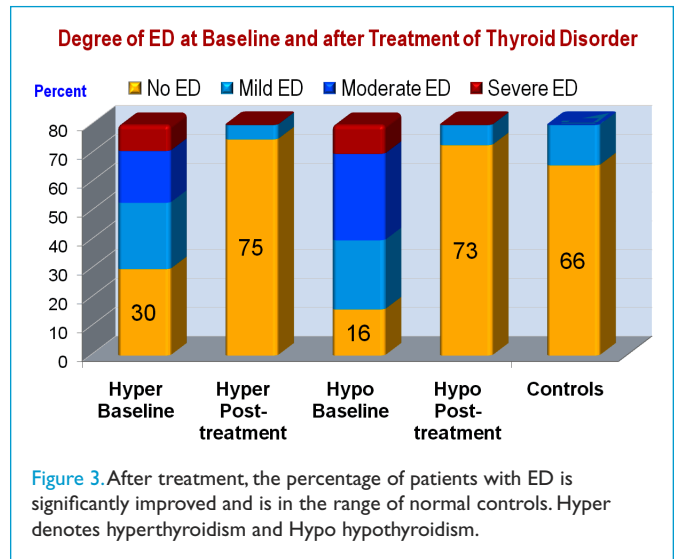


Figure 3. After treatment, the percentage of patients with ED is significantly improved and is in the range of normal controls. Hyper denotes hyperthyroidism and Hypo hypothyroidism.

### COMMENTARY

As assessed by the international SHIM instrument, approximately 80% of the patients in this study had ED, as compared with 37.5% of the controls. After euthyroidism was restored, 30% of the patients had ED, a rate similar to that in controls. This study hinges on the test used to assess ED. What is the SHIM test, and how accurate is it? The test is a simple five-step questionnaire that has been widely used as an instrument to evaluate male erectile function (1–3). The self-administered test asks questions about a man's ability to achieve and maintain an erection and satisfaction with attempted intercourse, scoring the response on a Likert scale of 1 (strongly agree) to 5 (strongly disagree). A SHIM score of 21 or less suggests that a man has ED. This and similar tests have been widely used since medications to treat ED became available (1–3). A 2008 review by Derogatis (4) points out that the recent recognition of the high prevalence of sexual dysfunctions and disorders in our society, along with the development of drugs to treat ED, has resulted in a significant expansion in the development of valid and reliable

measures of sexual function/dysfunction. He explains that the instruments generally are brief self-report inventories, typically requiring 10 to 20 minutes of patient time for completion. All of these instruments, which must adhere to recently prescribed rigorous guidelines set forth by the Food and Drug Administration, have been demonstrated to be valid and reliable indicators of the status and quality of sexual functioning in both men and women. Moreover, these self-reported questionnaires are generally used alone in assessing erectile function without using confirmatory objective tests of erectile function. This study makes it clear that men with thyroid dysfunction should be considered for ED evaluation (5). It also must be appreciated that therapy for thyroid dysfunction alone may be enough to treat the ED, and that more aggressive diagnostic testing and therapy should be postponed for at least 6 months after restoring euthyroidism because ED may resolve spontaneously over time.

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## Patients with thyrotoxicosis, especially those with Graves' disease, gain weight for up to 9 months after becoming euthyroid with antithyroid drug therapy

Rathi MS, Miles JN, Jennings PE. Weight gain during the treatment of thyrotoxicosis using conventional thyrostatic treatment. *J Endocrinol Invest* 2008;31:505-8.

### SUMMARY:

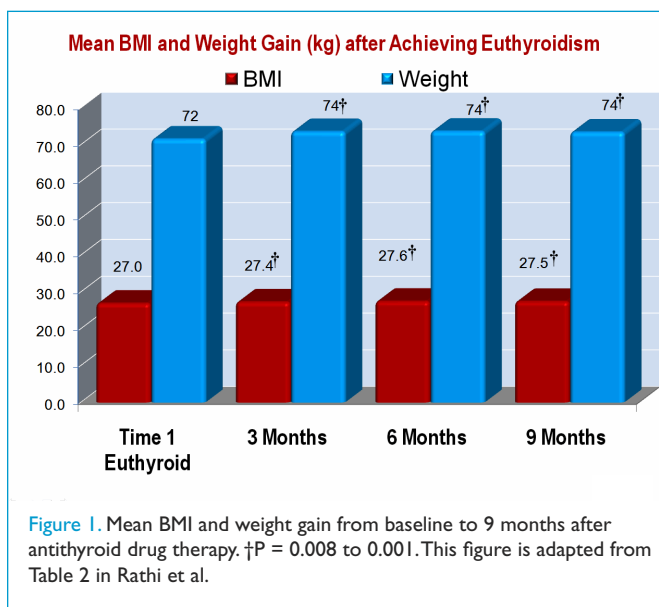
**BACKGROUND** A common presenting symptom of hyperthyroidism is weight loss. Perhaps even more common is the weight gain that often occurs with reversal of the hyperthyroidism, which may be as great as 26 lb (12 kg). This is generally attributed to the change in body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) that occurs when a patient becomes hypothyroid as a result of treatment. Previous studies of weight gain have included patients treated with radioiodine and surgery. The aim of this study was to determine whether patients with thyrotoxic Graves' disease continue to gain weight after becoming euthyroid in response to treatment with antithyroid drugs. The other aims of the study were to determine the length of time that patients could expect to continue gaining weight and to identify the patients at risk for weight gain.

**METHODS** This is a retrospective study of 60 consecutive euthyroid patients with Graves' disease or toxic nodular goiter who were rendered euthyroid with antithyroid drugs for at least six months. Body weight, which was determined at the study site, was calibrated to the nearest 0.4 lb (0.2 kg). The following data were taken from the patient's chart: age at the time of diagnosis, gender, weight, height, and the amount of weight loss, smoking history, antithyrotropin (thyroid-stimulating hormone [TSH]) antibody status, and the presence or absence of goiter, Grave's ophthalmopathy, medication, and serum concentrations of free triiodothyronine (FT<sub>3</sub>), free thyroxine (FT<sub>4</sub>), and serum TSH. Patients were divided into two groups. One comprised patients with Graves' disease based on the presence of a diffuse goiter, Graves' ophthalmopathy, and a significant thyroid peroxidase antibody titer (>1100 IU/L). The other group comprised those with toxic nodular goiter based on the finding of a nodular goiter on physical exam or ultrasonography and absence of signs of Graves' disease. Patients on a block and replacement regimen (antithyroid drug therapy and replacement with thyroid hormone), those in whom transient hypothyroidism developed on treatment, or those who experienced other problems causing weight gain were excluded.

**RESULTS** The mean age of the study group was 46.13 years (range, 21 to 73) and the male:female ratio was 5:55. In all, 36 patients (60%) had Graves' disease and 24 (40%) had nodular goiter. The mean time to normalization of thyroid function was 6.7 months. At the time of diagnosis, the mean ( $\pm$ SEM)

body weight was 149.1 $\pm$ 4.6 lb (range, 101.2 to 275) (67.75 $\pm$ 2.1 kg [range, 46 to 125]) and the mean BMI was 25.8. It took an average of 6.7 months for the patients to become euthyroid, at which time mean body weight was 157.5 lb (range, 101 to 275) (71.61 kg [range, 46 to 125]). Even after becoming euthyroid, patients continued to gain weight at 3, 6, and 9 months. Regardless of prior weight loss, patients gained weight from the time of initial diagnosis until achieving euthyroidism, after which they continued to gain weight for as long as 9 months (Figure 1). Nearly 50% of the patients were overweight or obese at the time of diagnosis (mean BMI, 25.81) and this increased to 61% after patients became euthyroid, but after 9 months only 57.5% were overweight. Multivariate analysis found the following: (1) patients with Graves' disease were more likely to gain weight than those with other causes of hyperthyroidism (BMI, 1.11 and 2.18, respectively); (2) nonsmokers gained significantly more weight than smokers ( $P < 0.01$ ); (3) weight gain was not related to age ( $P = 0.94$ ) or gender ( $P = 0.78$ ); and (4) serum FT<sub>3</sub> and FT<sub>4</sub> levels at presentation were not predictive of weight gain ( $P = 0.104$ ). Prior history of weight loss and initial BMI did not predict weight gain. The amount of time required to achieve euthyroidism was not related to weight gain.

**CONCLUSION** Patients with thyrotoxicosis, especially those with Graves' disease, gain weight for as long as 9 months after becoming euthyroid with antithyroid drug therapy.



## COMMENTARY

This is the first study to examine the effects of antithyroid drug therapy alone on the weight gain that occurs when patients with thyrotoxicosis become euthyroid. Previous studies found that treatment of thyrotoxicosis with surgery, radioiodine, and antithyroid drugs all result in weight gain (1); however, some describe a greater risk of weight gain with surgery as compared with the other two forms of treatment (2). Although the mechanism responsible for a change in BMI is not clear, some have proposed that euthyroid patients are simply gaining the weight they lost as a result of hyperthyroidism.

However, Rathi et al. found no correlation between prior weight losses from hyperthyroidism and the subsequent weight gain observed after patients became euthyroid. Others (1) propose that treatment of hyperthyroidism

slows the metabolic rate, after which patients continue to eat in the same manner as when they were thyrotoxic, and the subsequent slowing of their metabolic rate itself leads to the weight gain. A study by de la Rosa et al. (4) that examined the body composition of patients after treatment of thyrotoxicosis, found that weight gain was the result of an increase in lean body mass, not body fat and mineral content, which also increased, albeit not significantly.

Whatever the mechanism, patients, especially those with Graves' disease, are clearly at risk for weight gain after treatment of hyperthyroidism and should be counseled regarding dietary changes and initiation of an exercise regimen prior to restoration of euthyroidism.

Jennifer Sipos, M.D.

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# The success rate of thyroid remnant ablation in low risk patients is greater using a fixed amount of <sup>131</sup>I determined by tumor stage than selecting it according to a 24-hr <sup>131</sup>I uptake

Verkooijen RB, Verburg FA, Van Isselt JW, Lips CJ, Smit JW, Stokkel MP. The success rate of I-131 ablation in differentiated thyroid cancer: comparison of uptake-related and fixed-dose strategies. *Eur J Endocrinol* 2008;159:301-7.

**SUMMARY**

**BACKGROUND** Remnant ablation with <sup>131</sup>I has for decades been an integral part of the management of differentiated thyroid cancer; yet the optimal protocol remains uncertain. The aim of this retrospective study was to compare the success rate of remnant ablation performed according to a fixed amount of <sup>131</sup>I based upon tumor stage compared with an <sup>131</sup>I activity determined by an uptake-based protocol.

**METHODS** The study subjects are 359 patients treated with total or near-total thyroidectomy for differentiated thyroid carcinoma without distant metastases that subsequently had <sup>131</sup>I remnant ablation in one of two academic hospitals in the Netherlands. A total of 153 patients (43%) were treated at the Leiden University Medical Center according to a <sup>131</sup>I-uptake protocol and 206 others (57%) were treated at the University Medical Center Utrecht according to a fixed-dose protocol.

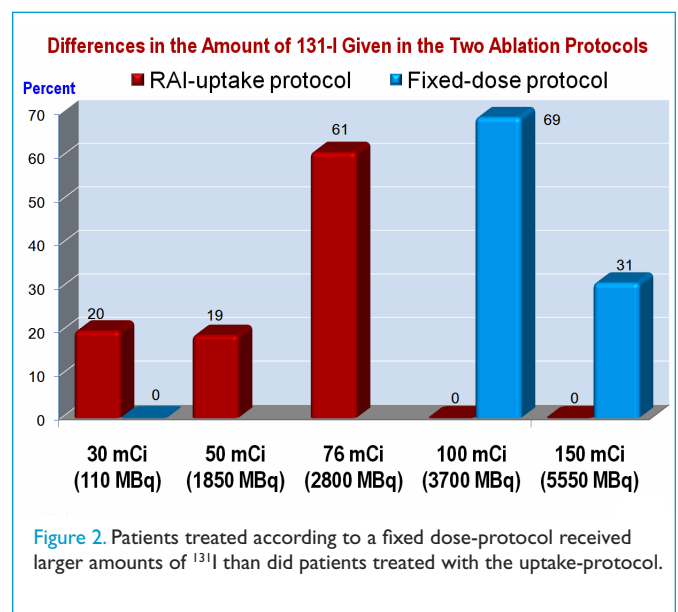
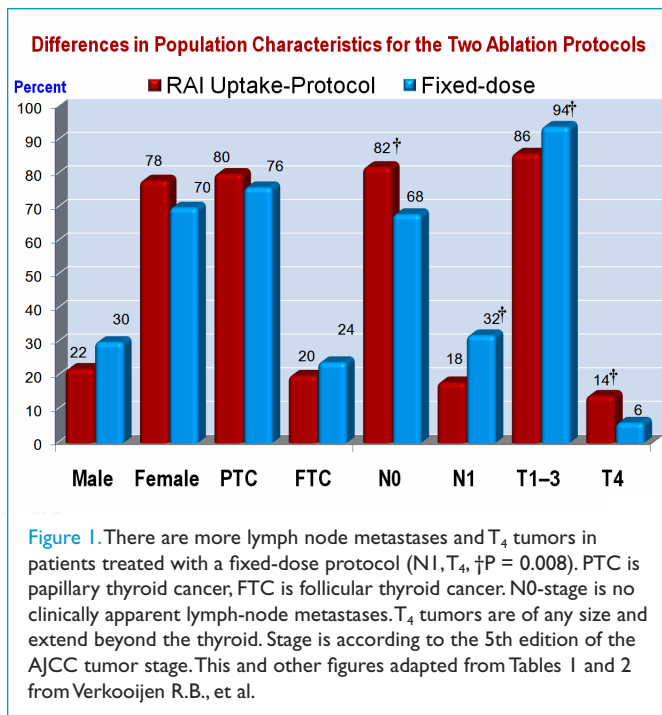
For the uptake protocol, the 24-hour neck uptake of 1 mCi of <sup>131</sup>I (40 MBq) was stratified into 3 levels: >10, 5 to 10, or <5%, which was followed by 30, 50, or 75 mCi of <sup>131</sup>I (2800, 1850, or 1110 MBq), respectively.

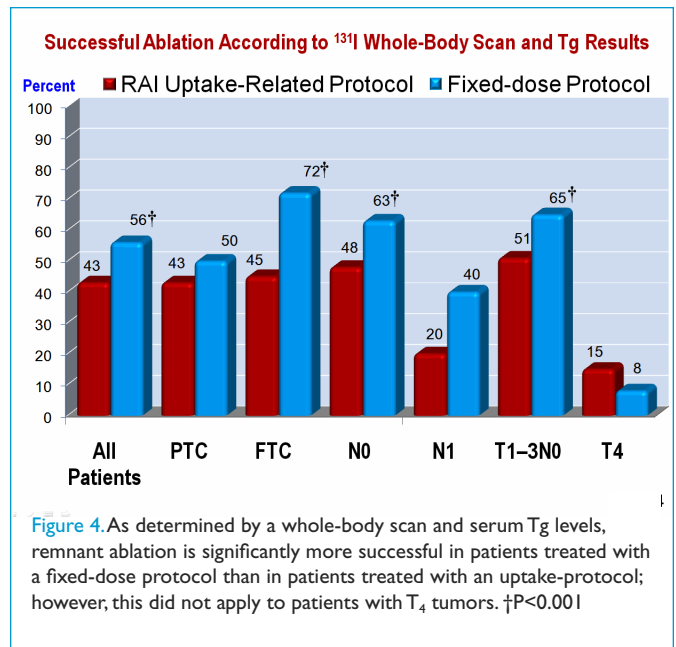
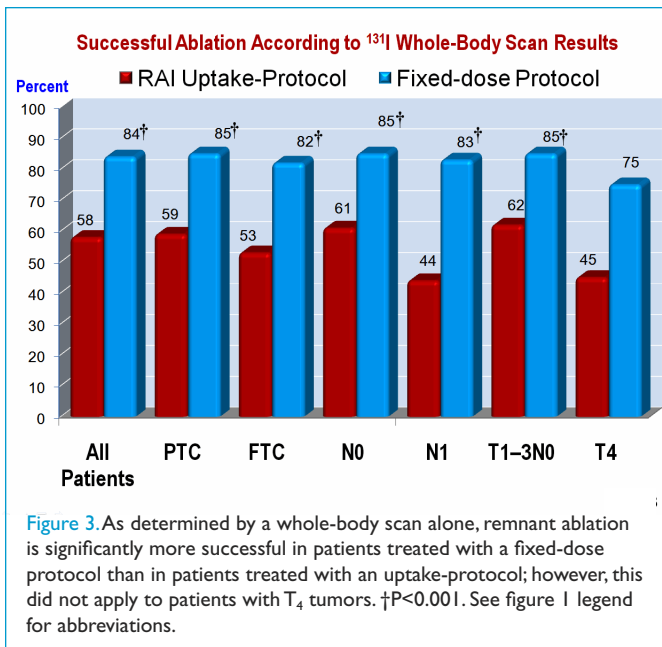
For the fixed-dose protocol, 100 or 150 mCi of <sup>131</sup>I (3700 to 5550 MBq) was administered depending upon the tumor stage.\* Using this protocol, most patients were treated with 100 mCi for T<sub>1</sub> to T<sub>3</sub> tumors, which are 1 to 4 cm and limited to the thyroid gland without lymph-node metastases. Those treated with 150 mCi had T<sub>4</sub> tumors, which are tumors of any size extending beyond the thyroid capsule with or without lymph-node metastases.

Follow-up was performed 6 and 12 months after <sup>131</sup>I ablation when patients were evaluated by serum thyroglobulin (Tg) after levothyroxine withdrawal and <sup>131</sup>I whole body diagnostic scans performed 24 hours after 1 mCi (40 MBq), although a few were performed with recombinant human thyrotropin (rhTSH). Successful ablation was defined as a Tg-off below the functional sensitivity of the assay and negative diagnostic whole body scans.

\* Tumor stage (T=tumor stage, N=lymph-node stage and M=distant metastasis) was determined according to the 5th edition of the American Joint Committee on Cancer (AJCC), [www.cancerstaging.org](http://www.cancerstaging.org).

**RESULTS** The mean patient ages in the uptake and fixed dose-protocol groups were, respectively, 42.6 (range 15 to 87) and 43.1 years (range 19 to 82, P = 0.68). There were





no statistically significant differences in the gender ratio or tumor histology among the two groups ( $P = 0.07$ , Figure 1). However, lymph-node metastases were found in 27 patients (18%) in the uptake-protocol group and 66 patients (32%) in the fixed-dose group ( $P = 0.008$ , Figure 1). Larger <sup>131</sup>I activities were given to patients treated with the fixed-dose protocol than those given to the uptake protocol group (Figure 2). With the uptake protocol, 60 of 139 patients (43%) had successful <sup>131</sup>I ablation compared with 111 of 199 (56%) patients who were treated with a fixed-dose protocol ( $P =$

0.022); however, successful ablation depended upon whether it was defined by whole body scans alone or with serum Tg measurements. Moreover, patients with T<sub>4</sub> tumors had similar ablation rates with the two protocols (Figures 3 and 4).

**CONCLUSION** The success rate of thyroid remnant ablation is greater following a fixed amount of <sup>131</sup>I than is treatment based upon a 24-hr <sup>131</sup>I uptake in patients with non-metastatic tumors measuring 1 to 4 cm confined to the thyroid gland.

### COMMENTARY

The main conclusion of this study by Verkooijen et al. is that empirically selecting <sup>131</sup>I activity based upon tumor stage is more effective than is uptake-selected <sup>131</sup>I activity. In effect, this conclusion compares the efficacy of low and high <sup>131</sup>I activities in the range of 30 to 75 mCi with amounts in the range of 100 to 150 mCi. Thus the essential conclusion is that larger fixed amounts of <sup>131</sup>I are therapeutically more effective than are the smaller <sup>131</sup>I activities that usually result from an uptake-determined protocol. Still, successful remnant ablation was achieved in only 56% of those treated with the fixed-dose protocol and was a mere 43% in those treated according to the uptake-related protocol—both very low ablation rates.

For example, the large randomized study by Pacini et al. (1) found that successful ablation was achieved at 8 months in 100% of the patients prepared by either thyroid hormone withdrawal or rhTSH-stimulation. Successful ablation was rigorously defined by no visible <sup>131</sup>I uptake 48 hours after a 4 mCi diagnostic whole body scan or, if visible uptake was found,

an uptake of <0.1%. Moreover, an rhTSH-stimulated Tg < 1 ng/ml as the criterion for successful ablation found that 96% had a successful outcome. Other prospective randomized studies also report successful remnant ablation in about 80% of patients treated with 30 to 50 mCi of <sup>131</sup>I. (2;3)

Why is there a discrepancy among these studies? The most obvious answer is that almost 10% of the patients in the Verkooijen study had T<sub>4</sub> tumors, which are tumors of any size extending beyond the thyroid capsule, some of which had lymph-node metastases. The authors point out that neither protocol failed to show a significant advantage in patients with T<sub>4</sub> tumors. The authors also found a low sensitivity of <sup>131</sup>I diagnostic whole body scans, an observation also reported by others (4), which means that tumor was missed by this test. There are other important features of this study that bear mention. First, different Tg assays were used in the two hospitals and long-term recurrence rates are not available. I agree with the authors' conclusion that follow-up studies are necessary to judge whether the difference between the

two methods of selecting  $^{131}\text{I}$  activity results in long term differences in outcome.

For now, the weight of evidence suggests that remnant ablation can be successfully performed in patients treated with 30 to 50 mCi (1110 to 1850 MBq) provided the patient

has low-risk tumors confined to the thyroid gland, which is the majority of patients with papillary thyroid cancer.

**Ernest L. Mazzaferri, MD, MACP**

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# PET/MRI fusion studies provide important information that may change decisions regarding surgical therapy for patients with thyroid cancer

Seiboth L, Van Nostrand D, Wartofsky L, Ousman Y, Jonklaas J, Butler C, Atkins F, Burman K. Utility of PET/neck MRI digital fusion images in the management of recurrent or persistent thyroid cancer. *Thyroid* 2008;18:103-11,

## SUMMARY

**BACKGROUND** Serum thyroglobulin levels and neck ultrasound examinations comprise the mainstay of diagnostic follow-up studies in low risk patients who clinically appear free of disease. However, patients with more serious disease usually require a variety of imaging studies to identify the site and extent of metastatic tumor. Positron-emission tomography (PET) scanning is one such study that is being increasingly used with computed tomography (CT) or magnetic resonance imaging (MRI) to produce images that provide both anatomic and metabolic information. This study assesses the clinical utility of coregistered (fused) images of PET and MRI in patients with thyroid cancer.

**METHODS** The study subjects comprised 34 patients with thyroid cancer who had undergone PET and MRI imaging for thyroid cancer at some point during their follow-up. Of this group, 31 (91%) had papillary thyroid cancer and one had medullary thyroid cancer, all of which were initially treated with total or near-total thyroidectomy. During follow-up, patients routinely had serum thyrotropin (TSH), free thyroxine (FT<sub>4</sub>), and serum thyroglobulin (Tg) measurements, except for the patient with medullary thyroid cancer, who had serum calcitonin measurements. In addition to neck ultrasound exams, each patient routinely had <sup>18</sup>fluorodeoxyglucose (FDG)-PET and gadolinium MRI scans that were subsequently digitally fused. The individual PET scanning and MRI were usually performed on the same day or not more than 5 months apart, but most were performed within 2 weeks of each other. A radiologist and nuclear medicine physician first independently reviewed each patient's MRI and PET scan, and after the PET/MRI fusion studies were generated, they were collaboratively interpreted. As part of the study, and prior to the PET/MRI coregistration, four endocrinologists who were unaware of the results of the fusion studies each retrospectively and individually reviewed the patient charts to make a clinical assessment and theoretical treatment plan. After this was accomplished, each endocrinologist was individually provided the results of the PET/MRI studies. With these new images, each endocrinologist made a revised clinical assessment and treatment plan and then categorized the PET/MRI information into three groups: (1) new information that altered the treatment plan, (2) new information that confirmed the initial proposed treatment plan, or (3) no new information. Two statistical analyses were done. The first combined the two

positive responses into a single score and compared it with a response that did not provide new information. The second statistical test determined the extent of agreement among the four endocrinologists.

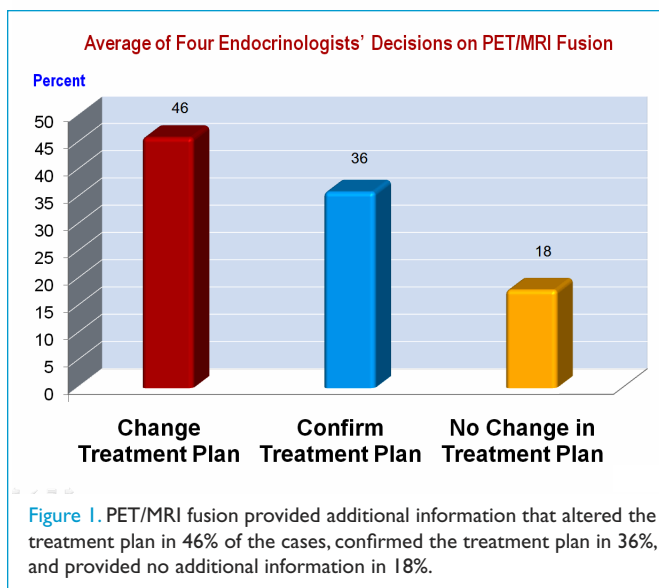


Figure 1. PET/MRI fusion provided additional information that altered the treatment plan in 46% of the cases, confirmed the treatment plan in 36%, and provided no additional information in 18%.

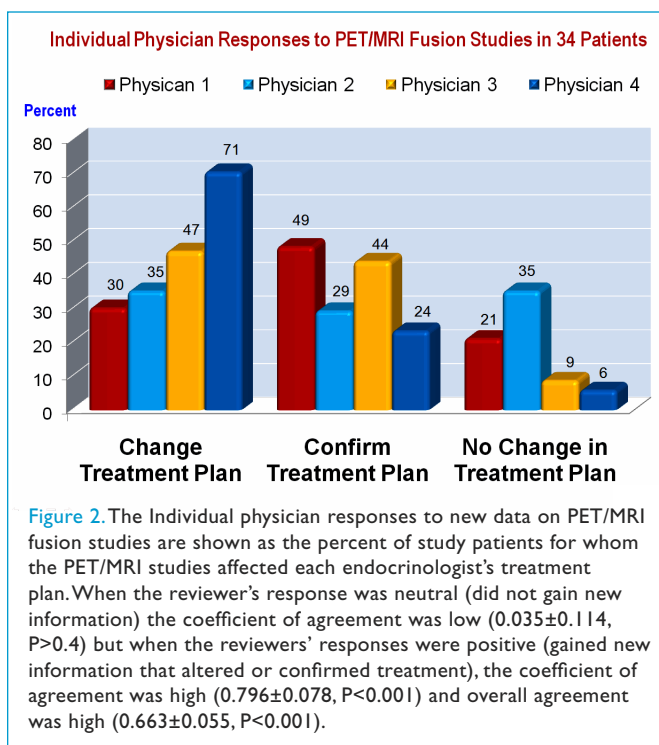


Figure 2. The Individual physician responses to new data on PET/MRI fusion studies are shown as the percent of study patients for whom the PET/MRI studies affected each endocrinologist's treatment plan. When the reviewer's response was neutral (did not gain new information) the coefficient of agreement was low (0.035±0.114, P>0.4) but when the reviewers' responses were positive (gained new information that altered or confirmed treatment), the coefficient of agreement was high (0.796±0.078, P<0.001) and overall agreement was high (0.663±0.055, P<0.001).

**RESULTS** Of the 34 study subjects, 23 (68%) were female and the mean age ( $\pm$  SD) was  $43.8 \pm 12.5$  years (range, 15 to 65). The patients had had a mean of  $1.7 \pm 0.6$  past surgeries, and 29 (85%) had received at least one radioiodine ( $^{131}\text{I}$ ) treatment 6 months to 24 years prior to this study, receiving an average of  $331.8 \pm 320.2$  mCi (range, 129 to 1046) of  $^{131}\text{I}$ . In addition, 18 (58%) patients had positive neck ultrasound examinations, 13 (38%) had positive CT scans, 26 (82%) had positive MRIs, and 30 (85%) had detectable serum Tg levels that averaged  $95.2 \pm 439.5$  ng/ml (range,  $<0.5$  to  $>2500$ ). The PET/MRI fusion studies provided additional information that altered the treatment plan in 16 patients (46%) and confirmed

the proposed treatment plan in 12 (36%) and provided no additional information in 6 (18%). The endocrinologists agreed more often than they disagreed about the impact of the new PET/MRI information (Figure 1). The first statistical analysis was inconclusive for a neutral response by the reviewers concerning the PET/MRI information; however, there was strong overall agreement between the reviewers for a positive response (Figure 2).

**CONCLUSION** PET/MRI studies provide structural and functional information that may change the surgery plan in patients with persistent thyroid cancer.

### COMMENTARY

This preliminary study suggests that  $^{18}\text{F}$ FDG-PET/MRI fusion studies may have a useful place in the management of thyroid carcinoma. This is not surprising, since it is widely held that  $^{18}\text{F}$ FDG-PET/CT plays a major role in the management of differentiated thyroid carcinoma, providing important restaging information by identifying the location and magnitude of occult tumor metastases (1) while providing a powerful means of estimating prognosis in patients with extensive disease (2). Several studies now suggest that  $^{124}\text{I}$ -PET/CT may be superior to  $^{18}\text{F}$ FDG-PET/CT in tumor restaging (3). The study by Seiboth et al. suggests that  $^{18}\text{F}$ FDG-PET/MRI fusion studies are superior to  $^{18}\text{F}$ FDG-PET or CT alone and to neck ultrasonography, and is potentially capable of changing

the treatment plans for patients with aggressive disease. It is not yet clear which of the perturbations of PET fusion will eventually become the most widely used, or whether there will be unique indications for these different tests. Still, fusing PET with MRI offers some interesting advantages, such as reducing total-body radiation and finding tumor in locations that typically are best identified by MRI such as brain and spinal metastases. The next level of studies should compare PET/CT with PET/MRI. The Seiboth study underscores the major clinical advantage gained by fusing PET and MR images that potentially can provide important information. This study is likely to spark further studies of PET/MRI in patients with thyroid cancer.

Ernest L. Mazzaferri, MD, MACP

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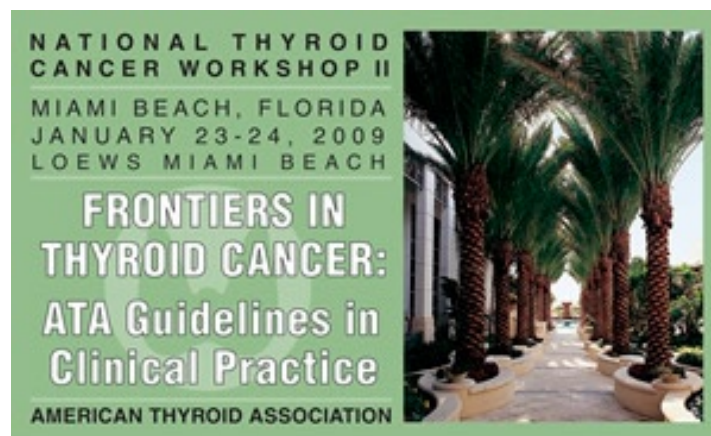
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## Disclosure

Dr. Mazzaferri receives honoraria from Genzyme for providing lectures.

Dr. Sipos receives honoraria from Abbott for providing lectures.



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