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The Common Serum Antithyroid Antibodies: Measured Too Often?

The common serum antithyroid antibodies—antithyroid peroxidase and antithyroglobulin antibodies—are often measured in clinical practice to confirm a diagnosis of autoimmune thyroiditis. They also are often measured in observational studies to indicate the presence of autoimmune thyroiditis and whether it is associated with some other disorder. The two antibodies are measured by immunoassays using purified or recombinant thyroid peroxidase or thyroglobulin as a standard, and the results are expressed in units of the standard per milliliter or liter of serum. There are international reference preparations for both proteins with which the standards for individual assays should be compared. However, they are large glycosylated proteins, with multiple epitopes, and therefore both the standards and the antibodies may be heterogeneous. The consequences of this heterogeneity are wide variations in assay sensitivity and results in normal subjects (1).

An important practical problem concerns the lack of distinction between assay sensitivity and the normal range seen in some laboratory reports and papers. The lower end of the normal range is nearly always less than the sensitivity of the assay. The antibodies are therefore not detected in the serum of some normal people in many assays. However, the frequency of undetectable values is higher when the assay is more sensitive, indicating that the detection of antibodies in many less sensitive assays is probably a nonspecific effect of serum. Use of the terms "positive" or "negative" as code for a high, or undetectable or normal, serum antithyroid antibody concentration is not appropriate, and of course the particular antibody should be specified. (Nobody says that patients with hypothyroidism have negative serum thyroxine values or positive serum thyrotropin [TSH] values.)

For research, only very sensitive assays should be used, and both antibodies should be measured, because even patients with obvious autoimmune thyroiditis may have a high serum concentration of only one of the two antibodies. Many of the reported associations between high serum antithyroid antibody concentrations and other disorders, autoimmune or otherwise, are probably the result of use of nonspecific assays. Alternatively, the association exists, but it is really an association between thyroid dysfunction, which was not measured, and the other disorders. (Readers might consider the articles on pages 37–39 with these comments in mind.)

For clinical practice, these issues are less important because the value of measurements of these two serum antibodies is marginal (except for measurements of serum antithyroglobulin antibodies in patients in whom serum thyroglobulin is to be measured). Treatment is not different if serum antithyroid peroxidase or antithyroglobulin antibodies are undetectable or are falsely detected in patients with overt hypothyroidism. Patients who have subclinical hypothyroidism and a high serum antithyroid antibody concentration are more likely to have overt hypothyroidism in the future, as compared with those with subclinical hypothyroidism alone, but the risk of progression is still only a few percent per year (and is more dependent on the base-line serum TSH concentration) (2). This hardly warrants measurement of serum antithyroid antibodies in all patients with subclinical hypothyroidism. There are other situations in which the results of measurements of serum antithyroid antibodies may have prognostic value, for example, to predict miscarriage and postpartum thyroiditis in pregnant women, but since intervention is not possible now the result is academic.

The presence of a high serum concentration of one or both of these antibodies confirms the diagnosis of autoimmune thyroiditis. But nothing changes. We treat patients because they have thyroid dysfunction, not because they have autoimmune thyroiditis, at least not yet. When the day comes that we know what causes the disorder, and can measure that rather than a surrogate, then measuring something in addition to thyroid function may be useful.

Robert D. Utiger, M.D.

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Chronic musculoskeletal symptoms are inversely related to serum thyrotropin concentrations in women

Hagen K, Bjoro T, Zwart JA, Svebak S, Bovim G, Stovner LJ. Do high TSH values protect against chronic musculoskeletal complaints? The Nord-Trondelag Health Study (HUNT). Pain 2005;113:416-21.

SUMMARY

Background Both musculoskeletal symptoms and thyroid dysfunction are common, especially among women. The relationships between these two conditions were determined in this population-based study.

Methods The study subjects were 63,472 of the 94,197 adults (67 percent) living in a county of Norway who completed questionnaires about musculoskeletal symptoms and thyroid disease between 1995 and 1997. The 3631 people who reported any thyroid disease were excluded from the study. Serum thyrotropin (TSH) was measured in 30,693 of the remaining 59,841 people (51 percent) (normal range, 0.2 to 4.0 mU/L); they were a 5 percent random sample of those who were 20 to 40 years old, nearly all women >40 years old, and 50 percent of men >40 years old. Serum free thyroxine (T_4) (normal range, 0.6 to 1.6 ng/dl [8 to 20 pmol/L]) was measured in people who had abnormal serum TSH values.

Results Among the 30,693 people who completed the musculoskeletal questionnaire, had no self-reported thyroid disease, and had measurements of serum TSH, 16,260 (53 percent) reported chronic musculoskeletal symptoms, defined as continuous pain or stiffness of the muscles or joints of all of the following three regions (neck or shoulders; hips or back; and elbows, wrists or hands, knees, or ankles or feet), for at least three months.

In the women, but not men, the prevalence of chronic musculoskeletal symptoms was inversely related to the serum TSH concentration (Table 1). As compared with the women with normal serum TSH values, fewer of the women with serum TSH values ≥10 mU/L had chronic musculoskeletal symptoms at any site (odds ratio, 0.3 to 0.6).

Table 1. Chronic Musculoskeletal Symptoms as a Function of Serum TSH Concentrations in Women and Men with No Self-Reported Thyroid Disease.

	Women (n=20,114)		Men (n=10,579)	
Serum TSH (mU/L)	Total	No. with Symptoms*	Total	No. with Symptoms**
<0.2	164	100 (61%)	27	13 (48%)
0.2–4.0	18,823	10,549 (56%)	10,145	4832 (48%)
>4.0–<10	946	488 (52%)	369	179 (48%)
≥10	181	79 (44%)	39	20 (51%)

*P for trend=<0.01. **P for trend=0.71.

The results were similar when the women with abnormal serum TSH concentrations were subdivided according to their serum free T_4 concentrations. For example, 28 of the 45 women with overt hyperthyroidism (62 percent) had musculoskeletal symptoms, as compared with 68 of the 149 women with overt hypothyroidism (46 percent) (Table 2).

Table 2. Chronic Musculoskeletal Symptoms as a Function of Serum TSH and Free T_4 Concentrations in 20,107 Women.

Serum TSH (mU/L)	Serum Free T_4 (ng/dl)	Total	No. with Symptoms
<0.2 mU/L	>1.6 ng/dl	45	28 (62%)
<0.2 mU/L	0.6–1.6 ng/dl	113	69 (61%)
0.2–4.0 mU/L		18,823	10,549 (56%)
>4.0 mU/L	0.6–1.6 ng/dl	977	498 (51%)
>4.0 mU/L	<1.6 ng/dl	149	68 (46%)

To convert serum free T_4 values to pmol/L, multiply by 12.9.

Conclusion The frequency of chronic musculoskeletal symptoms is higher in women with hyperthyroidism, and lower in those with hypothyroidism, as compared with women with normal thyroid function.

COMMENTARY

Chronic musculoskeletal symptoms are common, but their frequency among these people seems high, given the requirement that they had to have had pain or stiffness in three or more regions continuously for three months within the past year. "Continuously" probably means intermittently, not daily, but is not precisely defined. These questions were part of a larger questionnaire, and therefore it is unlikely that people with musculoskeletal symptoms were preferentially enrolled in the study. On the other hand, perhaps those with no symptoms at all were more likely to decline enrollment. (The detailed data about thyroid function and disease in the cohort are in ref. 1)

These results seem at odds with what are usually considered the musculoskeletal manifestations of hyperthyroidism and hypothyroidism. They are muscle weakness among patients with hyperthyroidism and myalgia or arthralgia among those with hypothyroidism. Of course, patients may have independent musculoskeletal and thyroid disorders. The authors propose that patients with hypothyroidism are less sensitive to pain. In support of this proposal, they found a lower prevalence of headache in the women with serum TSH concentrations ≥10 mU/L in the same cohort (2).

Robert D. Utiger, M.D.

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Hypothyroidism and hyperthyroidism alter renal function

den Hollander JG, Wulkan RW, Mantel MJ, Berghout A. Correlation between severity of thyroid dysfunction and renal function. Clin Endocrinol (Oxf) 2005;62:423-7.

SUMMARY

Background Hypothyroidism and hyperthyroidism are associated with changes in renal function, but the extent and reversibility of the changes have not often been studied. In this study glomerular filtration rate and serum creatinine were measured in patients with hypothyroidism or hyperthyroidism before and after treatment.

Methods The study subjects were 37 patients (27 women, 10 men; mean age, 47 years) with hypothyroidism caused by chronic autoimmune thyroiditis, and 14 patients (13 women, 1 man; mean age, 38 years) with hyperthyroidism caused by Graves' disease. The patients were studied before treatment and again at least three months after initiation of either thyroxine (T_4) or antithyroid drug therapy.

Serum thyrotropin (TSH), free T_4, creatinine (normal range, 0.45 to 1.0 mg/dl [40 to 90 µmol/L]), urea nitrogen, and albumin were measured at both times. The glomerular filtration rate was calculated using the following formula: GFR (ml/min/1.73 m^2) = 170 × serum creatinine$^{-0.999}$ × age$^{-0.176}$ × 0.763 (if patient is female) × 1.18 (if patient is black) × serum urea nitrogen$^{-0.170}$ × serum albumin$^{+0.318}$.

Results Among the patients with hypothyroidism, the mean serum creatinine concentration was 1.0 mg/dl (90 µmol/L) before treatment and 0.9 mg/dl (77 µmol/L) after treatment (Table), and the glomerular filtration rates were 70 and 83 ml/min, respectively.

Table. Mean (±SD) Clinical and Biochemical Results in Patients with Hypothyroidism or Hyperthyroidism before and after Treatment.

	Hypothyroidism (n=37)		Hyperthyroidism (n=14)	
	Before Treatment	After Treatment	Before Treatment	After Treatment
Serum TSH (mU/L)	99.1±83.5	4.6±9.0*	<0.01	3.4±2.4*
Serum free T_4 (ng/dl)	0.5±0.2	1.2±0.3*	6.4±2.8	1.2±0.4*
Blood pressure (mm Hg)	131±20/ 81±13	128±15/ 75±12	140±27/ 76±9	134±22/ 79±8
Serum creatinine (mg/dl)	1.0±0.2	0.9±0.2*	0.6±0.1	0.8±0.2*
Glomerular filtration rate (ml/min)	70±17	83±24*	135±36	96±27*

To convert serum free T_4 to pmol/L, multiply by 12.9; and to convert serum creatinine to µmol/L, multiply by 88.4. *P<0.02

The mean pretreatment and postreatment serum creatinine concentrations in the patients with hyperthyroidism were 0.6 and 0.8 mg/dl (50 and 72 µmol/L), and the glomerular filtration rates were 135 and 96 ml/min, respectively.

There was a linear relationship between the $\log_{10}$ post-treatment serum free T_4/pretreatment serum free T_4 and the changes in serum creatinine concentration and in glomerular filtration rate.

Conclusion Renal function, as assessed by measurements of serum creatinine and glomerular filtration, is decreased in hypothyroidism and increased in hyperthyroidism.

COMMENTARY

The best-recognized effect of thyroid dysfunction on renal function is a decrease in glomerular filtration rate in patients with overt (but not subclinical) hypothyroidism. This decrease is largely a result of decreased renal blood flow, due to decreased cardiac output and increased systemic vascular resistance, and is largely reversible with T_4 therapy.

A more recently recognized change is the effect of hypothyroidism on the most common measure of renal function, the serum creatinine concentration. This had been thought to be unchanged in spite of the decrease in glomerular filtration, due to a decrease in the generation of creatinine. However, several studies have revealed increased serum creatinine concentrations in patients with overt hypothyroidism, leaving no doubt as to the effect (1,2). The concentrations often modestly exceed the normal range. The increases parallel the severity of hypothyroidism, can develop rapidly, are usually reversible, and are unaccompanied by evidence of intrinsic renal disease.

The decrease in glomerular filtration that occurs in patients with hypothyroidism is clinically important. It results in decreased iodide clearance, contributing to the slightly greater sensitivity of T_4-withdrawal-based, as compared with exogenous TSH-stimulation-based, radioiodine scans for the detection of recurrent or persistent tumor in patients with thyroid carcinoma. In these same patients, radioiodine therapy might be more effective when given after T_4 withdrawal than after exogenous TSH stimulation. Furthermore, that glomerular filtration may be decreased should be considered when administering renally excreted drugs to patients with thyroid disease, with possible reduced drug efficacy due to increased clearance in those with hyperthyroidism and increased efficacy, prolonged action, or increased toxicity due to decreased clearance in those with hypothyroidism. Rare patients with hypothyroidism may have acute renal failure due to altered drug metabolism or rhabdomyolysis.

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Herbal medicines may cause hyperthyroidism

Ohye H, Fukata S, Kanoh M, Kubota S, Kuma K, Miyauchi A, Sugawara M. Thyrotoxicosis caused by weight-reducing herbal medicines. Arch Intern Med 2005;165:831-4.

SUMMARY

Background Hyperthyroidism can occur as a result of ingestion of not only pharmaceutical-grade thyroid hormone products, but also nonprescription products purported to promote loss of weight or adipose tissue or to boost energy that contain thyroid hormones or thyroid hormone analogs. This article describes patients who had hyperthyroidism caused by ingestion of herbal medicines that contained thyroid hormone.

Methods Twelve women, aged 23 to 68 years, had hyperthyroidism attributed to ingestion of either "Ever Youth" or "Dream Shape," products marketed for weight reduction in Japan. The former is said to contain Chinese matrimony vine, chrysanthemum, hawthorne, lotus leaf, radish, senna tea, and seaweeds, and the latter Chinese matrimony vine, chrysanthemum, hydrangea vine, maltose, saccharine, and seaweeds; both were thought to have been prepared in China. The diagnosis of hyperthyroidism was confirmed by measurements of serum thyrotropin (TSH), free thyroxine (T_4), and free triiodothyronine (T_3). Serum thyroglobulin and 24-hour thyroid radioiodine uptake were measured in some women. Serum TSH, free T_4, and free T_3 also were measured repeatedly for 24 hours after ingestion of a high dose of Ever Youth and Dream Shape in two other subjects, and T_4 and T_3 were measured in proteolytic digests of a capsule of each product.

Results Eight women were taking Ever Youth and four Dream Shape. One woman was taking 8 capsules of Ever Youth daily, and one 15 capsules of Dream Shape daily; the doses taken by the other women were not given. All 12 women had low serum TSH concentrations, and 8 had high serum free T_4 concentrations. The serum free T_3 concentration was high in 7 of the 9 women in whom it was measured. Serum thyroglobulin concentrations were high in 2 women, both of whom had a nodular goiter, and low normal in 6. Thyroid radioiodine uptake was low (0.3 to 4.2 percent) in the 6 women tested.

In a normal man who took 10 capsules of Ever Youth the serum free T_3 concentration increased gradually to a peak of approximately twice base line at 8 hours. In a normal woman who took 10 capsules of Dream Shape; the serum free T_3 concentration increased similarly, but the peak was at 4 hours. Serum free T_4 concentrations increased slightly and serum TSH concentrations decreased slightly in both subjects.

Ever Youth was found to contain 1.1 μg of T_3 and 4.5 μg of T_4 per capsule, and Dream Shape 0.97 μg of T_3 and 3.4 μg of T_4 per capsule. As a control, an acetaminophen tablet and two multivitamin capsules were similarly digested and assayed; no T_3 or T_4 was detected.

Conclusion Herbal medicines sold to promote weight loss may contain T_3 and T_4, presumably in the form of a crude thyroid extract, and therefore can cause hyperthyroidism.

COMMENTARY

If all the capsules of Ever Youth and Dream Shape contained the same amount of T_3 and T_4 present in those analyzed, even a small person would have to take more than 20 capsules daily to become hyperthyroid. The dose is given for only two women; the others may have been taking more. Also, some capsules may have contained considerably more thyroid extract than found in those analyzed. The nature of the thyroid hormone in the herbal concoctions (they can hardly be called medicines) is in doubt, because undigested capsules were not analyzed, but it is hard to believe that the manufacturers would add anything other than crude animal thyroid extract, and if there is some thyroid extract one wonders what other tissue extracts might be there as well.

These two products, as described in this paper, are not available in the United States, based on a search of the Internet. A search for "Ever Youth" revealed nothing. A search for "Dream Shape" revealed several sites marketing gamma-aminobutyric acid, advertised as stimulating growth hormone production and making fat disappear, but no thyroid-containing products. A search for "Thyroid Extract" revealed sites advertising multiple products. Some of these products clearly contained extracts of thyroid tissue, and often extracts of other tissues, including pituitary and adrenal tissue. Then there are the sites that sell dietary supplements that include synthetic, biologically active thyroid hormone analogs such as triiodothyroacetic acid (tiratricol) as "fat burners," an undisguised appeal to those wanting to lose weight (1).

These 12 cases are a reminder of the spectrum of exogenous hyperthyroidism. Some cases are iatrogenic, whether intended by a physician or not. Some are surreptitious; the patients, whether they have hypothyroidism or not, are taking high doses of thyroid hormone on the premise that if some is good more is better, but choose not to tell the physician. And some are neither, because the patient didn't know the product contained thyroid hormone. There may come a time when over-the-counter sale of products containing thyroid extracts or a thyroid hormone analog will be restricted in the United States, but it won't be soon.

Robert D. Utiger, M.D.

Reference

1. Bauer BA, Elkin PL, Erickson D, et al. Symptomatic hyperthyroidism in a patient taking the dietary supplement tiratricol. Mayo Clin Proc 2002;77:587-90.

Very long-term methimazole therapy is effective and safe in patients with hyperthyroidism caused by Graves' disease

Azizi F, Ataie L, Hedayati M, Mehrabi Y, Sheikholeslami F. Effect of long-term continuous methimazole treatment of hyperthyroidism: comparison with radioiodine. Eur J Endocrinol 2005;152:695-701.

SUMMARY

Background Some patients with hyperthyroidism caused by Graves' disease respond well to treatment with an antithyroid drug, but have recurrent hyperthyroidism after it is stopped. This study compared the effects of prolonged antithyroid drug and I-131 therapy in patients with recurrent hyperthyroidism.

Methods The study group initially consisted of 463 patients more than 40 years old with hyperthyroidism caused by Graves' disease who were treated with methimazole for 18 months. During the following year, 104 patients (22 percent) had recurrent hyperthyroidism, confirmed by high serum free thyroxine (T_4) and free triiodothyronine (T_3) concentrations and low serum thyrotropin (TSH) concentrations. These 104 patients were randomly assigned to receive long-term antithyroid drug or I-131 therapy, but 19 declined, leaving 85 patients, 34 in the methimazole group and 51 in the I-131 group.

The patients in the methimazole group were treated with 20 mg daily for one month, 10 mg daily for one month, and 2.5 to 10 mg daily thereafter. The patients in the I-131 group were treated with a mean dose of 7.9 mCi (292 MBq); 9 patients required two or more doses. All patients were evaluated monthly for three months, every three months for one year, and then every six months. The evaluations included measurements of serum free T_4, free T_3, and TSH; therapy in both groups was adjusted to maintain serum free T_4 and free T_3 concentrations in the mid-normal range. The number of visits at which the patients had normal, low, or high serum TSH concentrations was determined.

At the end of the study, the patients completed a quality-of-life questionnaire and had a physical examination. Serum free T_4, free T_3, TSH, and lipids were measured; and echocardiography and bone densitometry were performed.

Results The clinical and biochemical characteristics at the time of recurrent hyperthyroidism were similar in the 34 patients in the methimazole group and the 51 patients in the I-131 group. Sixty-seven patients completed the 10-year study, 26 (76 percent) in the methimazole group (mean dose, 4.9 mg) and 41 patients (80 percent) in the I-131 group. Some patients in the methimazole group had minor allergic reactions (number not given), but none had any serious adverse effect. Serum TSH was measured 627 times in the patients in the methimazole group; 48 values (8 percent) were low and 37 (6 percent) were high. Among 989 measurements in the patients in the I-131 group, 90 values (9 percent) were low and 127 (13 percent) were high.

At the end of the study, 16 of the 41 patients (39 percent) in the I-131 group were euthyroid, and 25 (61 percent) had hypothyroidism. At the same time, all 26 patients in the methimazole group were euthyroid. The mean age, scores on the quality-of-life questionnaire, body-mass index, blood pressure, and pulse rate in the two groups were similar, but more patients in the methimazole group had a goiter (50 vs. 25 percent). The mean serum TSH, free T_4, and free T_3 concentrations in the two groups were similar. The serum total and low-density lipoprotein cholesterol concentrations were higher in the I-131 group, but the values for other serum lipids were similar. The results of echocardiography and bone densitometry were similar in the two groups.

Conclusion Patients with recurrent hyperthyroidism caused by Graves' disease can be treated effectively and safely for 10 years with methimazole, as well as with I-131, and at that time their clinical and biochemical characteristics are similar.

COMMENTARY

Most patients with hyperthyroidism caused by Graves' disease who are treated with an antithyroid drug and have recurrent hyperthyroidism after the drug is stopped are treated with I-131. The rationale for this approach is that they are unlikely to have a long-term remission, but in fact there are few data on the likelihood of remission during a second course of antithyroid drug therapy. This study unfortunately does not directly address that point, because attempts to withdraw therapy are not described.

What the study does address is the efficacy and safety of long-term, low-dose methimazole therapy. That it was effective is not surprising, given that it was effective during the original 18-month treatment period. That it was safe may also be considered not surprising, given that it had been safe earlier, but safety for 10 years has not been well documented. In this regard, more should have been said about side effects.

I-131 therapy is often recommended on the grounds that follow-up, even if the patient has hypothyroidism, is simpler and less likely to be associated with variations in thyroid function than is antithyroid drug therapy. That was not the case in this study. There were 24 hormone measurements per patient in both groups at study end, and the frequency of abnormal serum TSH values was higher in the I-131 group.

Long-term methimazole therapy should gain wider acceptance. Had some patients treated with methimazole had a remission during the study, as seems likely, the results might have favored it even more.

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Long-acting octreotide is not an effective treatment for patients with Graves' ophthalmopathy

Wemeau JL, Caron P, Beckers A, Rohmer V, Orgiazzi J, Borson-Chazot F, Nocaudie M, Perimenis P, Bisot-Locard S, Bourdeix I, Dejager S. Octreotide (long-acting release formulation) treatment in patients with Graves' orbitopathy: clinical results of a four-month, randomized, placebo-controlled, double-blind study. J Clin Endocrinol Metab 2005;90:841-8.

SUMMARY

Background There is no safe, effective treatment for patients with ophthalmopathy caused by Graves' disease. Retroorbital tissue contains somatostatin receptors, and their expression is increased in orbital tissue from patients with Graves' ophthalmopathy. The efficacy of the long-acting somatostatin agonist analog octreotide-LAR in ameliorating Graves' ophthalmopathy was evaluated in this randomized, placebo-controlled study.

Methods The study subjects were 51 patients (41 women, 10 men; mean [±SD] age, 47±12 years) with Graves' ophthalmopathy, as defined by mild or moderate eyelid retraction, palpebral edema, proptosis, impaired ocular mobility, and retroorbital muscle enlargement, that was clinically active, as defined by a Clinical Activity Score ≥3 (eye pain, conjunctival or eyelid erythema or edema, scored as 0 to 10 points). The duration of ophthalmopathy was 21±27 months. Eighteen patients (35 percent) were current smokers. Forty-nine patients had a history of hyperthyroidism. At the time of the study, 31 (61 percent) were taking an antithyroid drug and 40 (78 percent) were taking thyroxine; these were continued, and all the patients had normal thyroid function throughout the study. Patients who had been treated with a glucocorticoid, other immunosuppressive drugs, or radiation in the preceding six months were excluded. Use of artificial tears and other topical products was permitted during the study.

The patients were randomly assigned (stratified by sex and smoking status) to treatment with octreotide-LAR, 30 mg, or placebo, given intramuscularly once monthly for four months. They were evaluated at base line, monthly during the four-month treatment period, and at six months. The primary end point was improvement in the severity of ophthalmopathy, combined with no change or a decrease in Clinical Activity Score (success/failure). Secondary end points were changes in the Clinical Activity Score, individual components of ophthalmopathy (proptosis), and quality of life, as measured using a general and an ophthalmopathy-specific questionnaire.

Results Twenty-six patients were assigned to the treatment group (1 withdrew after one dose) and 25 to the placebo group; 47 patients completed the study. The base-line characteristics of the patients in each group were similar.

There was no difference in the primary end point (success/failure) at the end of treatment or the end of the study (Table). The Clinical Activity Score decreased slightly in both groups. There was little overall change in proptosis; it decreased by ≥2 mm at the end of treatment in 1 patient in each group and at the end of the study in 4 patients in the octreotide-LAR group and 1 patient in the placebo group. There were no changes in quality of life in either group.

Table. Effects of Octreotide-LAR Therapy in Patients with Graves' Ophthalmopathy.

	Octreotide-LAR	Placebo
Success at end of treatment	7/25 (28%)	11/25 (44%)
Success at end of study	9/24 (38%)	11/24 (46%)
Clinical Activity Score		
Base line	4±2	4±2
End of treatment	3±2	3±2
End of study	2±1	3±2
Proptosis (mean mm for both eyes)		
Base line	21±2	20±2
End of treatment	21±2	20±2
End of study	20±2	20±2

Conclusion Octreotide-LAR therapy, given for four months, was not more effective than placebo in patients with mild or moderate ophthalmopathy caused by Graves' disease.

COMMENTARY

This is the second randomized trial of long-acting octreotide therapy in patients with Graves' ophthalmopathy. As in the first trial (1), there was no benefit. The patients enrolled in both trials had rather long-standing ophthalmopathy that was considered moderately active, and many had previously received some treatment for it as well as for hyperthyroidism. The size of the trials was similar, as were the dose and duration of octreotide-LAR therapy and the methods used to evaluate the effects of therapy. It is possible that this therapy might be more effective if given much sooner after the onset of ophthalmopathy, but how soon? The course is sufficiently variable and difficult to predict that establishing criteria for early intervention with an experimental therapy would be difficult. Until direct evidence that activation of somatostatin receptors reduces inflammation in retroorbital tissue is forthcoming, consideration should be given to reducing inflammation by inhibiting the production of tumor-necrosis factor or other cytokines.

Robert D. Utiger, M.D.

Reference

1. Dickinson AJ, Vaidya B, Miller M, et al. Double-blind, placebo-controlled trial of octreotide long-acting repeatable (LAR) in thyroid-associated ophthalmopathy. J Clin Endocrinol Metab 2004; 89:5910-5 [Clinical Thyroidology 2005; 17:5.]

Subclinical hypothyroidism in women with type 2 diabetes rarely worsens and is not a risk factor for cardiovascular disease

Chubb SA, Davis WA, Inman Z, Davis TM. Prevalence and progression of subclinical hypothyroidism in women with type 2 diabetes: the Fremantle Diabetes Study. Clin Endocrinol (Oxf) 2005;62:480-6.

SUMMARY

Background Subclinical hypothyroidism may be more common in patients with diabetes mellitus than in otherwise normal subjects. This study was done to determine the frequency of subclinical hypothyroidism, the likelihood of its progression, and its relationship to cardiovascular disease in women with type 2 diabetes.

Methods The study subjects were 420 women (89 percent white) with type 2 diabetes who were participants in the Fremantle (Australia) Diabetes Study, a prospective, community-based observational study. Type 2 diabetes was defined as diabetes controlled by diet or oral hypoglycemic drugs, age ≥60 years and any treatment, or age 40 to 59 years and either first treatment not insulin or body-mass index >30 kg/m^2.

The women were evaluated annually for up to 5 years. Serum thyrotropin (TSH), free thyroxine (T_4), antithyroid peroxidase (TPO) antibodies, glucose, and lipids were measured at base line and at 5 years. Subclinical hypothyroidism was defined as a high serum TSH concentration (>5.1 mU/L) and a normal serum free T_4 concentration in a woman with no thyroid disorder (no history of thyroid hormone, antithyroid, lithium, or amiodarone therapy, or self-reported thyroid disease). Coronary heart disease was defined as a self-reported history of myocardial infarction, angina, coronary artery surgery or angioplasty, or definite electrocardiographic evidence of past myocardial infarction, and by review of hospital databases.

Results At base line, the mean (±SD) age of the 420 women was 64±13 years, the mean duration of diabetes was 4 years (range, 1 to 9), and the mean body-mass index was 30±6 kg/m^2; 38 (9 percent) had some thyroid disorder. Among the 382 women with no thyroid disorder, serum TSH concentrations were high in 33 (9 percent) and low in 7 (2 percent); all had normal serum free T_4 concentrations. Serum anti-TPO antibody concentrations were high in 12 (36 percent) and 0, respectively, and in 29 of the 342 women (8 percent) with normal serum TSH concentrations. Serum concentrations of cholesterol and its fractions and triglycerides were similar in the women in the three serum TSH groups, as was the proportion taking a statin.

There was no association between subclinical hypothyroidism at base line and blood pressure, coronary heart disease, cardiac failure, body-mass index, or metformin or insulin therapy at base line or follow-up.

At 5 years, 111 of the 382 women (29 percent) returned for reevaluation; their characteristics were similar to those of the women not reevaluated. The number of women with a high serum TSH concentration was similar to that at base line (Table). Their serum TSH values ranged from 5.3 to 7.9 mU/L at base line and from 5.2 to 8.4 mU/L at 5 years; the values were high at both times in 3 women, high only at base line in 4 women, and high only at 5 years in 6 women. Serum anti-TPO antibody concentrations were high in 9 women at base line and 10 women at 5 years, all but 1 of whom had normal serum TSH concentrations.

Table. Serum TSH Concentrations in 111 Women with Type 2 Diabetes at Base Line and 5 Years Later.

	Serum TSH (mU/L)		
	<0.34	0.34–5.1	>5.1
Base line	2 (2%)	102 (92%)	7 (6%)
5 years	0 (0%)	102 (92%)	9 (8%)

Conclusion Some women with type 2 diabetes have subclinical hypothyroidism, but it is not a risk factor for hyperlipidemia, hypertension, coronary heart disease, or cardiac failure, and progression to overt hypothyroidism is rare.

COMMENTARY

The frequency of subclinical hypothyroidism in nondiabetic women of similar race/ethnicity and age living in the same community is not known, but based on surveys elsewhere is not likely to be much different. There is no known autoimmune component of type 2 diabetes, and thus no obvious link between its pathogenesis and that of subclinical hypothyroidism, which is usually caused by chronic autoimmune thyroiditis. (Six percent of the women in this study had a positive test for serum antiglutamic acid decarboxylase antibodies, a hallmark of type 1 diabetes, and there was a very weak [P<0.20] association between a positive test for these antibodies and subclinical hypothyroidism).

The most important results of this study were the low rate of progression to overt hypothyroidism and the lack of increased risk of cardiovascular disease in the women with subclinical hypothyroidism at base line. The results thus confirm in a small way the 20-year follow-up results of the Whickham, United Kingdom, study of subjects with subclinical hypothyroidism (1). However reassuring these new results, they are compromised by the fact that less than one third of the women returned for the follow-up studies.

Robert D. Utiger, M.D.

Reference

1. Vanderpump MP, Tunbridge WM, French JM, et al. The development of ischemic heart disease in relation to autoimmune thyroid disease in a 20-year follow-up study of an English community. Thyroid 1996;6:155-160.

Hypothyroidism can occur after thyroid lobectomy

Piper HG, Bugis SP, Wilkins GE, Walker BA, Wiseman S, Baliski CR. Detecting and defining hypothyroidism after hemithyroidectomy. Am J Surg 2005;189:587-91.

SUMMARY

Background Patients with a thyroid nodule are often treated by thyroid lobectomy, which does not usually result in hypothyroidism unless the functional reserve of the remaining thyroid lobe is subnormal. In this retrospective study thyroid function was assessed in patients who had undergone thyroid lobectomy, and the results were correlated with the severity of lymphocytic infiltration of the resected thyroid lobe.

Methods The records of all 88 patients who underwent thyroid lobectomy by one of three surgeons during a 24-month period were reviewed. Among them, 22 patients were excluded; 9 had thyroid carcinoma, 11 were treated with thyroxine (T_4) before or soon after surgery, 1 had hyperthyroidism after surgery, and 1 was lost to follow-up.

The remaining 66 patients formed the study group. All had normal serum thyrotropin (TSH) concentrations before surgery. Serum TSH was measured within 3 months after surgery in 46 patients (70 percent), between 4 and 6 months in 8 (12 percent), between 7 and 12 months in 8 (12 percent), and later in 4 (6 percent). At the time of the study, serum TSH was measured if it had not been measured in the preceding six months. The records of patients with high serum TSH values (>5.5 mU/L) were reviewed, or their primary care physicians were contacted; those with no symptoms of hypothyroidism were considered to have biochemical hypothyroidism, and those with symptoms clinical hypothyroidism. Serum T_4 was not measured. The histologic sections of each patient's resected thyroid were reviewed by one pathologist who was unaware of the patients' postoperative thyroid status. The extent of lymphocytic infiltration was graded from 0 (none) to 4+ (diffuse, with lymphoid germinal centers).

Results The 66 study patients included 46 women and 20 men (mean age, 46 years; range, 22 to 81). The pathologic diagnoses were goiter, not otherwise specified, but presumably meaning one or more hyperplastic nodules (32 patients), follicular adenoma (21 patients), cyst (6 patients), Hurthle-cell adenoma (4 patients), and Hashimoto's thyroiditis (3 patients).

Twelve patients (18 percent) had hypothyroidism. Nine had been evaluated within 3 months after surgery; four had high serum TSH values then. Eight had high serum TSH values by 6 months, and in four the high values were detected between 9 and 18 months. Three patients had clinical hypothyroidism, and were treated with T_4. Five patients had biochemical hypothyroidism, of whom three were treated with T_4. The serum TSH values in these eight patients ranged from 5.6 to 78 mU/L 3 to 17 months after surgery. The four other patients had transient hypothyroidism (first high serum TSH value 1 to 19 months after surgery, and normal serum TSH values 5 to 28 months after surgery).

The review of the histology of the operative specimens revealed 3+ or 4+ lymphocytic infiltration in 14 patients (21 percent). They included 4 of the 12 patients (33 percent) with hypothyroidism, and 10 of the 54 patients (18 percent) who did not have hypothyroidism. None of the patients with transient hypothyroidism had the same degree of lymphocytic infiltration.

Conclusion Patients with a benign thyroid nodule who undergo thyroid lobectomy may have hypothyroidism, especially those in whom there is marked lymphocytic infiltration of the resected thyroid tissue.

COMMENTARY

In a study in which patients with a follicular adenoma were evaluated at regular intervals for 90 days after thyroid lobectomy, serum T_4 concentrations decreased slightly within the normal range and serum TSH concentrations increased slightly, to just above normal in a few patients; all had normal thyroid function 36 months after surgery (1). This new study was much less systematic, the definitions of types of hypothyroidism were unusual, and the criteria for initiation of T_4 therapy were not described. Had the approach been more rigorous, more of the patients with hypothyroidism would probably have regained normal thyroid function.

If there was extensive lymphocytic infiltration in the lobe that was removed, the contralateral lobe would probably be similarly infiltrated, and, therefore, there would be some risk of permanent hypothyroidism. That is not to say that any patient who undergoes lobectomy and in whom histologic study of the resected lobe reveals marked lymphocytic infiltration should be given T_4, but perhaps follow-up should be closer.

The presence of lymphocytic infiltration, probably in the extranodular portion of the resected lobe (though this is not stated), indicates the presence of chronic autoimmune thyroiditis. Does it affect abnormal thyroid tissue, for example, a hyperplastic nodule or a follicular adenoma, to the same extent that it affects normal thyroid tissue, or less or not at all? The answer might provide some insight into the susceptibility of different types of thyroid tissue to autoimmune thyroiditis.

Robert D. Utiger, M.D.

Reference

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Clinical manifestations and results of treatment of craniopharyngioma are similar in children and adults

Karavitaki N, Brufani C, Warner JT, Adams CB, Richards P, Ansorge O, Shine B, Turner HE, Wass JA. Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. Clin Endocrinol (Oxf) 2005;62:397-409.

SUMMARY

Background Craniopharyngiomas are benign tumors of remnants of Rathke's pouch that originate within or above the sella turcica. They occur in both children and adults, and have both endocrine and neurologic effects. In this retrospective study the clinical manifestations and effects of treatment were analyzed in patients with a craniopharyngioma, with special attention to the differences in clinical manifestations and outcome in children and adults.

Methods From 1994 to 2003, 121 patients with craniopharyngioma were seen at the Radcliffe Infirmary, Oxford, United Kingdom. Among them, 42 (19 girls, 23 boys) were <16 years old (median, 10), and 79 (37 women, 42 men) were ≥16 years old (median, 43). The diagnosis was based on histologic findings in 117 patients and analysis of cyst fluid in 4 patients. Radiologic and endocrine studies were done at base line and periodically during follow-up, as deemed clinically important. Endocrine function was assessed by measurements of serum hormones basally or after stimulation.

Results The duration of symptoms before diagnosis ranged from 0.5 months to 20 years (median, 12). Among the children, ≥20 percent had one or more of the following (in decreasing frequency): headaches, nausea or vomiting, visual-field defects or decreased visual acuity, growth failure, other cranial nerve palsies, papilledema, poor energy, or anorexia or weight loss. Among the adults, ≥20 percent had headaches, visual-field defects or decreased visual acuity, poor energy, impaired sexual function, nausea or vomiting, or lethargy; 57 percent of the women had menstrual disorders and 8 percent had galactorrhea.

At the time of diagnosis, major visual-field defects were present in 54 percent of the children and 63 percent of the adults. The frequency of hormonal deficiencies was high (Table), and 55 percent of the adults had hyperprolactinemia.

Table. Hormonal Deficiencies in Patients with Craniopharyngioma before Treatment and 5 and 10 Years Later.

Hormone	Before Treatment	5 Years	10 Years
Growth hormone	95%	86%	88%
Gonadotropins	74%	83%	90%
Corticotropin	62%	85%	86%
Thyrotropin	36%	75%	80%
Vasopressin	18%	62%	65%

The number of patients tested for each deficiency at the three times varied from 22 to 118.

Nearly all patients were treated by total or partial tumor resection, followed by radiation (median dose, 5000 cGy). Among the patients who underwent resection, the tumor was intrasellar in 6 percent, extrasellar in 41 percent, and both in 53 percent. The tumor was mostly cystic in 46 percent, solid in 18 percent, and both in 36 percent.

The median duration of follow-up was 103 months (range, 0.3 to 468). The 5- and 10-year recurrence-free survival rates were 100 percent in patients who underwent total tumor resection, with or without radiation therapy; 82 and 77 percent, respectively, in patients who underwent partial resection and were treated with radiation; and 47 and 38 percent, respectively, in those who underwent partial resection and did not receive radiation. The rates were similar in children and adults.

No patient with a hormonal deficiency at the time of diagnosis had normal function after treatment. The cumulative 5- and 10- year rates of hormonal deficiencies were high (Table); there were no differences between children and adults. At 10 years, 48 percent of the patients had major visual-field defects, 39 percent had hyperphagia or obesity, and 12 percent had seizures.

Conclusion Among both children and adults with a craniopharyngioma, surgery and radiation together are the most effective treatment, but endocrine and nonendocrine sequelae are common.

COMMENTARY

The key hormonally related abnormalities that should raise the suspicion of craniopharyngioma are short stature in children, oligomenorrhea or amenorrhea in women, and diabetes insipidus in both children and adults. Given the high frequency of individual hormonal deficiencies before and especially after treatment, most patients must have had multiple deficiencies. Their causes include loss of the capacity to produce hypothalamic hormones, interruption of the hypothalamic–pituitary portal system, and loss of the capacity to produce pituitary hormones. Note that hypothyroidism was the least common of the anterior pituitary hormone deficiencies. This could have been due, at least in part, to the reliance on basal measurements of serum thyrotropin (normal or low) and free thyroxine (low) for diagnosis. In contrast, the diagnoses of growth hormone and corticotropin deficiency were based on the results of provocative testing, with the result that some patients with normal basal secretion of these hormones might be classified as having a deficiency. Alternatively, normal growth hormone and corticotropin secretion may be more dependent on their respective hypothalamic-releasing hormones than is thyrotropin secretion dependent on thyrotropin-releasing hormone.

Robert D. Utiger, M.D.

Therapy with thyroxine and triiodothyronine is not more effective than thyroxine alone in patients with hypothyroidism (I)

Appelhof B, Fliers E, Wekking EM, Schene AH, Huyser J, Tijssen JG, Endert E, van Weert HC, Wiersinga WM. Combined therapy with levothyroxine and liothyronine in two ratios, compared with levothyroxine monotherapy in primary hypothyroidism: a double-blind, randomized, controlled clinical trial. J Clin Endocrinol Metab 2005;90:2666-74.

SUMMARY

Background Patients with hypothyroidism who are treated with thyroxine (T_4) and have normal serum T_4 and thyrotropin (TSH) concentrations may not feel well. Their serum triiodothyronine (T_3) concentrations are not quite normal, because the thyroidal contribution to serum T_3 is lacking. This study evaluated the effect of T_4 alone and two combinations of T_4 and T_3 in hypothyroid patients.

Methods The study subjects were 141 patients (120 women, 21 men; mean age, 48 years) with hypothyroidism caused by autoimmune thyroid disease. All had been taking T_4 (mean group dose at base line, 1.5 to 1.7 µg/kg per day) for at least six months and had normal serum TSH concentrations. They were randomly assigned to receive T_4 alone, T_4 and T_3 in a ratio of 5:1, and T_4 and T_3 in a ratio of 10:1. In the 5:1 and 10:1 groups, the daily T_4 dose was reduced by 25 µg and T_3 was added in a dose that was 20 percent or 10 percent, respectively, of the remaining T_4 (a patient taking 100 µg of T_4 received 75 µg of T_4 and 15 µg of T_3 if assigned to the 5:1 group and 75 µg of T_4 and 7.5 µg of T_3 if assigned to the 10:1 group). After five weeks, serum TSH was measured, and the T_4 component adjusted by 12.5 or 25 µg daily, depending the degree of serum TSH abnormality (the T_3 component was adjusted to maintain the 5:1 or 10:1 ratio); adjustments were needed in 33 to 59 percent of the patients in the three groups.

The patients were evaluated at base line and at 5, 10, and 15 weeks. Neither the patients nor the investigators were aware of treatment group assignment. The primary outcome was the patient's subjective assessment of therapy at 15 weeks, graded on a five-point scale (much better to no different to much worse), as compared with their previous T_4 regimen. The patients also completed standard questionnaires about mood (Profile of Mood States), fatigue (Multidimensional Fatigue Inventory), quality of life (Short Form-36), psychopathology (Symptom Checklist-90), cognitive function and memory (Wechsler Adult Intelligence Scale), and verbal learning (California Verbal Learning Test), and serum TSH (normal range, 0.11 to 4.0 mU/L), free T_4, and other substances were measured after an overnight fast.

Results The base-line clinical and biochemical characteristics of the patients in each group were similar (group mean serum TSH concentrations, 1.0 to 1.1 mU/L). Some outcome data were available for 140 patients, and 130 patients (92 percent) completed the 15-week study.

The preference for study therapy increased with increasing T_3 content of the regimen. As compared with the previous T_4 regimen, the study regimen was preferred by 14 of 48 patients (29 percent) in the T_4 group, 19 of 46 patients (41 percent) in the 10:1 T_4–T_3 group, and 24 of 46 patients (52 percent) in the 5:1 T_4–T_3 group (P for trend=0.02). The scores for nearly all tests of mood, fatigue, quality of life, and psychopathology improved during treatment in all three groups, but there were no between-group differences in the degree of improvement. The scores for the tests of cognitive function, memory, and learning also improved, with few between-group differences.

The patients in the T_4 group gained 0.1 kg, those in the 10:1 T_4–T_3 group lost 0.5 kg, and those in the 5:1 T_4–T_3 group lost 1.8 kg (P=0.01). Heart rate increased more in the latter group, as did serum sex hormone–binding globulin and osteocalcin concentrations. The changes in serum TSH and free T_4 are shown in the Table. The median final serum TSH concentrations were 0.64, 0.35, and 0.07 mU/L, respectively.

Table. Median Changes in Serum TSH, and Free T_4 Concentrations from Base Line during the 15-Week Treatment Period in Patients with Hypothyroidism.

	T_4 Group	10:1 T_4–T_3 Group	5:1 T_4–T_3 Group	P for Trend
Serum TSH (mU/L)	−0.36	−0.75	−0.93	<0.01
Serum free T_4 (ng/dl)	0.03	−0.13	−0.18	<0.01

To convert free T_4 to pmol/L, multiply by 12.9.

Conclusion Patients with hypothyroidism preferred combined T_4 and T_3 therapy, especially when given in a ratio of 5:1 T_4–T_3, as compared with T_4 alone. This was associated with weight loss and the lowest serum TSH concentrations, but not with greater improvement in the scores on mood, quality-of-life, and other questionnaires.

COMMENTARY

These studies provide no support for the hypothesis that a combination of T_4 and T_3 is more effective than T_4 alone, when given in doses intended not to alter serum TSH concentrations much, in alleviating symptoms and improving well-being in patients with hypothyroidism, confirming the results of at least four other studies (1). The design of these new studies differed, but they had in common the fact that many end points—somatic and psychologic symptoms, cognitive function, and biochemical and physiologic measures—were assessed. There was not only little benefit of combined therapy with respect to particular symptoms of hypothyroidism, but also little evidence of a preferential action of the added T_3 on the central

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Therapy with thyroxine and triiodothyronine is not more effective than thyroxine alone in patients with hypothyroidism (II)

Escobar-Morreale HF, Botella-Carretero JI, Gomez-Bueno M, Galan JM, Barrios V, Sancho J. Thyroid hormone replacement therapy in primary hypothyroidism: a randomized trial comparing L-thyroxine plus liothyronine with L-thyroxine alone. Ann Intern Med 2005;142:412-24.

SUMMARY

Background This crossover study provides more information on the question of whether patients with hypothyroidism benefit from combined thyroxine (T_4) and triiodothyronine (T_3) therapy, as compared with T_4 alone.

Methods The subjects in this study were 28 women (mean [±SD] age, 48±11 years; body-mass index, 26±7 kg/m^2) with overt hypothyroidism who had been taking 100 µg of T_4 and had normal serum thyrotropin (TSH) concentrations for at least one year. Twenty-three women had chronic lymphocytic thyroiditis and five had been treated with radioiodine for Graves' hyperthyroidism or a toxic multinodular goiter.

The women were randomly assigned to take 100 µg of T_4 alone or 75 µg of T_4 plus 5 µg of T_3 for eight weeks, and then the other regimen for eight weeks. Thereafter, all women were given 87.5 µg of T_4 plus 7.5 µg of T_3 for eight weeks. The 75 µg T_4:5 µg T_3 regimen was chosen on the basis of the T_4:T_3 ratio in thyroid venous blood and the differences in intestinal absorption of the two hormones.

The women were studied at the end of the three treatment periods. The primary outcomes were the woman's preference, as reported at the end of the study (how it was assessed is not stated), and the results of questionnaires about mood (Profile of Mood States), cognition (Digit Symbol Substitution Test, Digit Span Test, Visual Scanning Test) and measurements of serum TSH and free T_4 at the end of each treatment period. Other outcomes were the results of quality-of-life and symptom questionnaires (Short Form-36, Nottingham Health Profile, a hypothyroid symptom scale, Visual Analog Mental Scales), echocardiography, visual and auditory evoked potentials, and thyroid-related biochemical tests.

Results Twenty-six women completed the study. At the end of the study, 12 women (46 percent) preferred the regimen of 75 µg T_4 plus 5 µg T_3, 6 (23 percent) the regimen of 87.5 µg T_4 plus 7.5 µg T_3, and 2 (8 percent) the T_4 regimen; 6 (23 percent) had no preference (P=0.015). The Profiles of Mood States scores, cognitive performance scores, quality-of-life and hypothyroid symptom scores, and Visual Analog Mental Scale scores were similar at the end of each treatment period, with only a few exceptions. For example, the scores for several components of the Digit Span Test were better after 75 µg T_4 plus 7.5 µg T_3, as compared with the other two treatments; and the scores for the copies subtest of the Digit Symbol Substitution Test and hypothyroid symptom score were better after 87.5 µg T_4 plus 7.5 µg T_3, as compared with T_4 alone.

The values for body-mass index were similar at the end of each treatment period, as were the results of nearly all other tests. The mean serum low-density lipoprotein cholesterol concentration was slightly higher after therapy with 75 µg T_4 plus 5 µg T_3. Urinary markers of bone resorption, but not serum sex hormone–binding globulin concentrations, were slightly higher after therapy with 87.5 µg T_4 plus 7.5 µg T_3. The serum TSH and free T_4 values at the end of each regimen are shown in the Table.

Table. Mean Serum TSH, Free T_4, and Free T_3 Concentrations at the End of Each 8-Week Treatment Period in Women with Hypothyroidism.

	T_4 Alone	75 µg T_4 plus 5 µg T_3	87.5 µg T_4 plus 7.5 µg T_3
Serum TSH (mU/L)	1.95	2.56	1.09
Serum free T_4 (ng/dl)	1.6	1.3	1.3

To convert free T_4 to pmol/L, multiply by 12.9.

Conclusion In a crossover trial of T_4 and two regimens of T_4 plus T_3 in women with hypothyroidism, the regimen of 75 µg T_4 plus 5 µg T_3 was preferred by nearly 50 percent, but there were few subjective, biochemical, or other differences at the end of the three treatment periods.

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nervous system, arguing against the hypothesis that it is more dependent on serum T_3 than on T_3 produced locally by deiodination of T_4 than are other organs. No one has compared T_3 alone and T_4 alone in studies like these.

The T_4:T_3 ratios in the combination therapy regimens varied from 15:1 to 5:1. The T_3 was given once daily, which results in a discernible rise in serum T_3 concentrations to a peak in about four hours, even when the dose is low (2). As a result, once-daily measurements of serum T_3 during combination therapy are more or less worthless. A sustained release T_3 preparation that minimizes, but does not entirely prevent, the post-T_3 ingestion rise in serum T_3 concentrations has been developed (2). It has not been tested in studies like these, but it is hard to believe it will be effective when standard T_3 was not.

The 5:1 ratio studied by Appelhof et al. caused subclinical hyperthyroidism in many patients and probably overt hyperthyroidism in some (median serum TSH concentration, 0.07 mU/L; 95 percent confidence interval, 0.02 to 1.06). A higher percentage of patients preferred this regimen, as compared with their prestudy T_4 regimen, than did the patients in the 10:1 T_4–T_3 group. The patients in the former group lost more weight and had

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Therapy with thyroxine and triiodothyronine is not more effective than thyroxine alone in patients with hypothyroidism (III)

Saravanan P, Simmons DJ, Greenwood R, Peters TJ, Dayan CM. Partial substitution of thyroxine (T_4) with triiodothyronine in patients on T_4 replacement therapy: results of a large community-based randomized controlled trial. J Clin Endocrinol Metab 2005;90:805-12.

SUMMARY

Background This large study, like the studies described on the preceding two pages, compared the effects of thyroxine (T_4) and triiodothyronine (T_3) and T_4 alone in patients with hypothyroidism receiving a stable dose of T_4.

Methods The study subjects, who were recruited from 28 family practices in the United Kingdom, were 697 patients with hypothyroidism who were 18 to 75 years old, had taken ≥100 µg of T_4 for at least three months, and had normal serum thyrotropin (TSH) concentrations.

The patients were randomly assigned to take their usual dose of T_4 or that dose minus 50 µg plus 10 µg of T_3 once daily. They were evaluated at base line and after 3 and 12 months. The evaluations included the General Health Questionnaire-12 (scored by visual analog and threshold methods); a hypothyroid symptom score; the Hospital Anxiety and Depression Scale; 23 visual analog scales of mood, cognition, and physical symptoms; a well-being questionnaire; assessment of neuromuscular symptoms; and physical examination. The primary end point was the General Health Questionnaire-12 score at three months. Serum TSH, free T_4, free T_3, and thyroid-related substances were measured at each evaluation.

Results The base-line characteristics of the 344 patients assigned to the T_4-plus-T_3 group and the 353 patients assigned to the T_4 group were similar (mean age, 57 vs. 58 years; women, 83 vs. 84 percent; duration of T_4 therapy, 12 vs. 11 years; daily dose of T_4, 125 vs. 123 µg; base-line serum TSH concentration, 1.4 vs. 1.5 mU/L). At 3 and 12 months, 616 patients (88 percent) and 573 patients (82 percent), respectively, were taking their assigned therapy.

At three months, the General Health Questionnaire-12 score improved in both groups, with slightly greater improvement in the T_4-plus-T_3 group. The hypothyroid symptom, anxiety, and depression scores also improved in both groups, with a slightly greater improvement in the anxiety score in the T_4-plus-T_3 group. Well-being increased in 26 percent of the patients in the T_4-plus-T_3 group and 29 percent of those in the T_4 group (P=0.89). The percentage of patients with no neuromuscular symptoms increased from approximately 27 percent to 35 percent in both groups. Body weight did not change. Serum TSH, free T_4, and free T_3 values are shown in the Table. There were no changes in serum sex hormone–binding globulin, cholesterol, or creatine kinase in either group.

Table. Mean Serum TSH and Free T_4 Concentrations at Base Line and after Treatment with T_4 plus T_3 or T_4 Alone for 3 and 12 Months.

	T_4-plus-T_3 Group			T_4 Group		
	Base Line	3 Months	12 Months	Base Line	3 Months	12 Months
Serum TSH (mU/L)	0.85	1.21	1.25	0.87	0.78	0.79
Serum free T_4 (ng/dl)	1.6	1.1	1.1	1.6	1.5	1.6

To convert free T_4 to pmol/L, multiply by 12.9.

At 12 months, the initial differences favoring therapy with T_4 plus T_3 were no longer present. All other questionnaire results, body weight, and thyroid-related biochemical values were similar to those at three months, and not different between the two groups.

Conclusion Among patients with hypothyroidism, combined T_4-plus-T_3 therapy was slightly more effective than T_4 alone, in terms of ameliorating some symptoms, but the benefit was not sustained.

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some other manifestations of thyroid excess, but their scores on the questionnaires did not improve more. Asking patients to compare recent therapy with therapy 15 weeks earlier is subject to bias, but the possibility arises that the multiple questionnaires used in this and the other studies do not get at what really bothers patients with hypothyroidism. Escobar-Morreale et al. also studied two T_4-plus-T_3 regimens. The difference in the ratio of T_4 to T_3 was small (15:1 and 11.7:1), and the regimen with the smallest amount of T_3 was preferred.

It seems clear that combination therapy that does not result in more than minimal changes in serum TSH concentrations is no more effective than T_4 alone. What is not clear is what is optimal therapy, and whether the right questions are being asked to determine that.

Robert D. Utiger, M.D.

References

1. For references (and commentary), see Clinical Thyroidology 2004;16:5-7, and 2004;16:29.

2. Hennemann G, Docter R, Visser TJ, et al. Thyroxine plus low-dose, slow-release triiodothyronine replacement in hypothyroidism. Thyroid 2004;14:271-5.[(Clinical Thyroidology 2004:16:30).]

Laser thermocoagulation reduces the volume of benign thyroid nodules

Dossing H, Bennedbaek FN, Hegedus L. Effect of ultrasound-guided interstitial laser photocoagulation on benign solitary cold thyroid nodules—a randomised study. Eur J Endocrinol 2005;152:341-5.

SUMMARY

Background Laser-induced thermocoagulation of benign poorly functioning or nonfunctioning thyroid nodules was recently demonstrated to be feasible (Clinical Thyroidology 2003;15:11). The effect of this therapy was compared with observation alone in this randomized trial.

Methods The study subjects were 30 women with a solitary, solid, benign, nonfunctioning thyroid nodule, as determined by ultrasonography, biopsy, and radionuclide imaging. The nodules had been detected by clinical examination, the women were clinically euthyroid, and their serum thyrotropin (TSH) and calcitonin concentrations were normal. All had concerns about the appearance of their neck or symptoms of compression, but had declined surgery.

The women were randomly assigned to one laser-thermocoagulation procedure or no treatment, and were followed for six months. Under local anesthesia and with ultrasound guidance, a 0.4-mm laser fiber was inserted into the nodule through an 18-gauge needle, after which the needle was withdrawn. Treatment was delivered with an output power of 2.5 to 3.6 W; this resulted in formation of vapor seen as an irregular enlarging echogenic area. The treatment was repeated two or three times in different areas of the nodule. The median total energy delivered was 2007 J.

The women rated the cosmetic and pressure symptoms on 10-cm visual analog scales, and serum TSH was measured at base line and 6 months. Nodule volume was measured by ultrasonography at base line and at 1 and 6 months. The women in the laser-treatment group underwent indirect laryngoscopy at base line and at 6 months, and they were asked to rate the pain of the procedure and their willingness to undergo it again immediately after it was done.

Results At base line, the age of the women, the interval between nodule diagnosis and treatment, the frequency of pressure and cosmetic symptoms, and nodule volume were similar in the laser-treatment and observation groups.

In the laser-treatment group, the median nodule volume decreased from 8.2 to 6.1 ml at one month and to 4.8 ml at six months (median decrease, 44 percent) (Table), whereas it increased from 7.5 to 9.0 ml at six months (median increase, 9 percent) in the observation group.

Table. Change in Nodule Volume and Nodule-Related Symptoms in the Laser-Treatment and Observation Groups.

	Laser Treatment		Observation	
	Base Line	6 Months	Base Line	6 Months
Median nodule volume (ml)	8.2	4.8	7.5	9.0
Mean score for pressure symptoms*	3	1	4	4
Mean score for cosmetic symptoms*	1	0.2	0.5	0.5

*Scored on a 10-cm visual analog scale (0, no symptoms; 10, severe symptoms) (values extrapolated from a figure).

Seven women in the laser-treatment group had mild to moderate neck pain or tenderness for up to seven days after treatment; all said they would consent to another treatment. None had vocal cord paralysis, local infection, or other serious complication. Thirteen women in the laser-treatment group had some pressure symptoms at base line, and 10 had marked relief at six months; cosmetic symptoms also decreased. Neither type of symptom changed in the observation group.

Conclusion In women with a solid thyroid nodule, ultrasound-guided laser thermocoagulation decreases nodule-related symptoms and nodule volume and is well tolerated.

COMMENTARY

Laser thermocoagulation seems to be a reasonably simple and safe way to reduce the size of thyroid nodules and the symptoms caused by them. It is probably difficult to destroy a nodule completely; the echogenic area of injury is often irregular, due to differences in cell density and structure and amount of interstitial tissue, and therefore penetration of the heat varies. And care needs to be taken to ensure that the area of injury does not extend into the thyroid tissue outside the nodule or, more important, to adjacent vessels or nerves. But in fact there is rarely, if ever, any need to destroy the nodule completely; even a moderate decrease in volume results in substantial amelioration of symptoms and improvement in cosmetic appearance. The procedure has also been used to treat hyperfunctioning adenomas and even an anaplastic carcinoma (1).

The other treatment options for patients with a bothersome thyroid nodule are surgery, percutaneous ethanol injection, and, possibly, thyroxine. Surgery is swift and effective, but not risk-free. Percutaneous ethanol injections are about as effective as laser thermocoagulation, but repeated injections are needed and they are painful. Thyroxine is little more effective than placebo (2). Given the alternatives, laser therapy looks attractive when something needs to be done.

Robert D. Utiger, M.D.

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Radioactive iodine therapy often results in hypothyroidism in patients with hyperfunctioning thyroid adenomas

Ceccarelli C, Bencivelli W, Vitti P, Grasso L, Pinchera A. Outcome of radioiodine-131 therapy in hyperfunctioning thyroid nodules: a 20 years' retrospective study. Clin Endocrinol (Oxf) 2005;62:331-5.

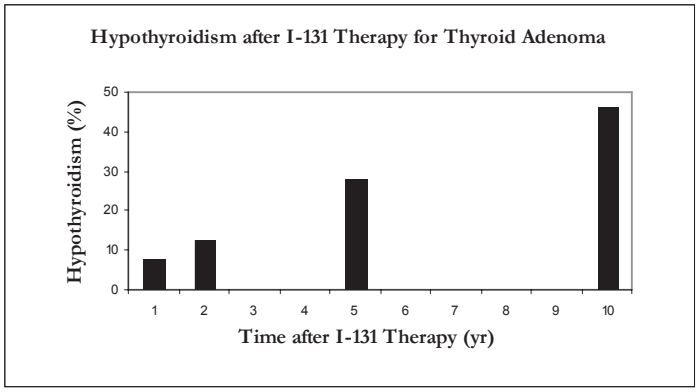
SUMMARY

Background Patients with a hyperfunctioning adenoma of the thyroid gland are often treated with radioactive iodine (I-131). It is effective, and is generally thought to be less likely to cause hypothyroidism in these patients than in patients with hyperthyroidism caused by Graves' disease. This study was done to determine the long-term effects of I-131 therapy in patients with a hyperfunctioning adenoma.

Methods The study subjects were 346 patients with a hyperfunctioning thyroid adenoma treated with I-131 and followed for up to 20 years. The diagnosis was based on the presence of I-131 accumulation in a palpable nodule; nodule size was measured as the largest diameter of the nodule as seen on a thyroid I-131 scan. The patients were categorized as having hyperthyroidism or not according to clinical findings and the results of measurements of serum free triiodothyronine (T_3); serum thyrotropin (TSH) values, if measured then, are not reported. The dose of I-131 was calculated using the formula: estimated nodule weight (g) × 200 μCi (7.4 MBq) ÷ 24-hour thyroid I-131 uptake. The patients were followed until they had hypothyroidism, defined as a serum TSH concentration ≥3.7 mU/L, or their last evaluation.

Results There were 277 women (80 percent) and 69 men (20 percent); their mean (±SD) age was 56±11 years. The nodule was <4 cm in 223 patients (64 percent) and ≥4 cm in 123 (36 percent). There was some extranodular uptake of I-131 in 163 patients (47 percent), but none ("complete parenchymal suppression") in 183 patients (53 percent). Based on clinical findings, 237 patients (68 percent) had hyperthyroidism, and 109 (32 percent) were euthyroid. Serum free T_3, measured in 295 patients, was high in 219 (74 percent). Factors associated with hyperthyroidism were older age and larger nodule size.

Administration of a single dose of 14±4 mCi (513±158 MBq) of I-131 resulted in a decrease in thyroid function to normal or below in 325 patients (94 percent); the remaining patients required additional doses, for a total of 27±8 mCi (999±300 MBq). The mean duration of followup was 46 months (range, 1 to 243). The incidence of hypothyroidism increased progressively from 8 percent at 1 year to 46 percent at 10 years (Figure), and it was 60 percent at last follow-up. Factors associated with hypothyroidism were older age and higher 24-hour I-131 uptake.



Conclusion Among patients with a hyperfunctioning thyroid adenoma who are treated with I-131, there is a progressive increase in the incidence of hypothyroidism.

COMMENTARY

The incidence of hypothyroidism in this study was high, but there have been few studies in which so many patients with thyroid adenomas were followed for so long. I-131 therapy can cause hypothyroidism in these patients in two ways. One is by destruction of extranodular tissue by I-131 taken up by the nodule. The second is uptake of I-131 by the extranodular tissue. Hypothyroidism would be expected to occur less often in patients in whom a diagnostic I-131 (or I-123) scan revealed no extranodular uptake of I-131 (complete suppression), as compared with patients in whom the scan revealed some extranodular uptake (partial suppression). However, in this study the cumulative risk of hypothyroidism in the two groups was similar, although precise results are not given. Perhaps scans done after administration of the therapeutic dose of I-131 would have revealed some I-131 uptake in the extranodular tissue in the complete-suppression group. The appearance of new cases of hypothyroidism with time suggests a radiation effect on cell replication, as has been postulated to explain the occurrence of hypothyroidism years after I-131 therapy in patients with Graves' hyperthyroidism.

These patients should be followed indefinitely, not just until their hyperthyroidism, if present, disappears, and their nodule has decreased in size (not recorded in this study). In general, thyroid function declines more rapidly than nodule volume, but occasional patients need a second dose of I-131. There is also the rare occurrence of Graves' hyperthyroidism in patients with thyroid adenoma treated with I-131 (there were two cases of Graves' ophthalmopathy, but none of Graves' hyperthyroidism, during follow-up in this study).

Robert D. Utiger, M.D.

The risk of tumor recurrence is low in patients with thyroid carcinoma who have low serum thyroglobulin concentrations after surgery

Kim TY, Kim WB, Kim ES, Ryu JS, Yeo JS, Kim SC, Hong SJ, Shong YK. Serum thyroglobulin levels at the time of ^{131}I remnant ablation just after thyroidectomy are useful for early prediction of clinical recurrence in low-risk patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 2005;90:1440-5.

SUMMARY

Background Measurements of serum thyroglobulin are of great value as a marker of persistent or recurrent tumor in patients with papillary or follicular carcinoma of the thyroid. This study was done to determine the value of measurements of serum thyroglobulin at the time of initial iodine-131 (I-131) therapy for predicting recurrence in patients with these tumors.

Methods The study subjects were 268 patients (228 women, 40 men; mean age, 44 years), with thyroid carcinoma, of whom 254 had papillary carcinoma, 11 follicular carcinoma, and 3 Hurthle-cell carcinoma. The tumor was >4 cm in 24 patients (9 percent), multifocal in 43 (16 percent), and involved lymph nodes in 155 (58 percent). Patients with extracervical tumor or high serum antithyroglobulin antibody concentrations at the time of initial surgery and I-131 therapy were excluded. All the patients were operated on by a single surgeon, who left no visible thyroid tissue.

Five to six weeks after surgery, during which thyroid hormone had been withheld (serum thyrotropin [TSH] concentrations >30 mU/L), serum thyroglobulin was measured (assay sensitivity, 1 ng/ml), and the patients were given 100 to 150 mCi (3.7 to 5.55 GBq) of I-131 to destroy any remaining thyroid tissue. Thyroid hormone therapy was then given. Six to twelve months later, therapy was stopped, serum thyroglobulin was measured, and a diagnostic whole-body scan was done. Patients who had any I-131 uptake in the thyroid bed were given a second dose of I-131. Thyroid hormone therapy was resumed. Thereafter, serum thyroglobulin was measured and diagnostic whole-body I-131 scans and other imaging tests were done after cessation of thyroid hormone therapy at 1- to 2-year intervals.

Results The first follow-up diagnostic whole-body I-131 scan revealed no thyroid remnants in 266 patients (99 percent), and the second dose of I-131 destroyed the remnants in the remaining 2 patients.

During a mean (±SD) follow-up period of 5.7±1.4 years, 35 patients (13 percent) had a recurrence, nearly all of which were in cervical lymph nodes. Among these 35 patients, the serum thyroglobulin value at the time of remnant ablation was >10 ng/ml in 27 (77 percent), >2 to 10 ng/ml in 6 (17 percent), and ≥1 to 2 ng/ml in 2 (6 percent). Seventy-three patients (27 percent) had detectable (≥1 ng/ml) serum thyroglobulin values on one or more occasions after cessation of thyroid hormone therapy, but no other evidence of recurrence. The remaining 160 patients (60 percent) had a complete remission, as defined by serum thyroglobulin values <1 ng/ml and negative diagnostic whole-body I-131 scans and negative neck ultrasonography during follow-up.

At the time of remnant ablation, 64 patients had a serum thyroglobulin concentration >10 ng/ml, of whom 27 (42 percent) had a recurrence (Table). The remaining 8 patients who had a recurrence had serum thyroglobulin values ranging from 1.6 to 6.6 ng/ml at that time.

Table. Outcome as a Function of Serum Thyroglobulin Concentration at the Time of Remnant Ablation.

Serum thyroglobulin at remnant ablation	No.	Recurrent Tumor	No Recurrence Follow-up Serum Thyroglobulin ≥1 ng/ml	No Recurrence Follow-up Serum Thyroglobulin <1ng/ml
>10 ng/ml	64	27 (42%)	28 (44%)	9 (14%)
>2–10 ng/ml	79	6 (8%)	24 (30%)	49 (62%)
≤2 ng/ml	125	2 (2%)	21 (17%)	102 (81%)

The positive predictive value for tumor recurrence in patients with serum thyroglobulin values >2 ng/ml at the time of remnant ablation was 23 percent (33 of 143 patients). The negative predictive value for recurrence in patients with serum thyroglobulin values ≤2 ng/ml was 98 percent (123 of 125 patients).

Conclusion Patients with thyroid carcinoma who have low serum thyroglobulin concentrations when hypothyroid at the time of remnant ablation after surgery are unlikely to have a recurrence of their tumor.

COMMENTARY

Most studies of serum thyroglobulin in patients with thyroid carcinoma have been done after both surgery and remnant ablation, and there is considerable evidence that patients with low basal and especially those with low stimulated values (whether stimulated by endogenous or exogenous TSH) at this time are unlikely to have a recurrence.

Measurements after surgery alone have been thought to be much less reliable, because the results may be confounded by thyroglobulin produced by thyroid remnants. The results of this study suggest that it does not matter very much; the measurements of serum thyroglobulin during hypothyroidism at a time when there was some remaining thyroid tissue had considerable predictive value with respect to tumor recurrence, and they correlated well with measurements done during hypothyroidism 6 or 12 months after remnant ablation. Thus, the finding of an undetectable or very low serum thyroglobulin value during hypothyroidism at the time of remnant ablation should allow simplification of follow-up.

Robert D. Utiger, M.D.

Combined surgical and radiation therapy may improve prognosis in patients with anaplastic thyroid carcinoma

Kebebew E, Greenspan FS, Clark OH, Woeber KA, McMillan A. Anaplastic thyroid carcinoma: treatment outcome and prognostic factors. Cancer 2005;103:1330-5.

SUMMARY

Background Anaplastic thyroid carcinomas grow rapidly, and few patients survive for more than a year. This study was done to describe the clinical manifestations and outcome in a large cohort of patients with this tumor.

Methods The study subjects were patients with anaplastic thyroid carcinoma seen between 1973 and 2000 at hospitals in the five states and seven metropolitan regions of the United States that constitute the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute. The data submitted to the program from the participating states and metropolitan areas included demographic information and data on tumor size and stage at the time of diagnosis, treatment, and outcome. The diagnosis was confirmed by pathologic examination of the tumor in all patients, but patients whose tumors were diagnosed only at autopsy were excluded.

Results During the 27-year period 516 patients with anaplastic carcinoma were reported to the program. There were 345 women (67 percent) and 171 men (33 percent). Their mean (±SD) age was 71±13 years. The mean tumor size was 6±3 cm (range, 1 to 15). The tumor was confined to the thyroid gland in 39 patients (7 percent), was locally invasive or involved cervical lymph nodes in 194 (38 percent), and was distantly metastatic in 222 (43 percent); the stage was not reported for 61 patients (12 percent). Some type of thyroidectomy was done in 253 patients (49 percent), and 326 (63 percent) received radiation therapy. The radiation was given after surgery in 147 patients (28 percent) or in the absence of surgery in 143 patients (27 percent). No information about chemotherapy was available.

The cancer-related mortality rate was 69 percent at 6 months and 81 percent at 12 months. The median and mean cancer-specific mortality rates were 3 and 12 months, respectively. On univariate analysis, younger age, smaller tumor size, lesser extent of disease, surgical therapy, external radiation therapy, and combined surgical and external radiation therapy were statistically significant prognostic factors (Table). On multivariate analysis, younger age, lesser extent of disease, and combined surgical and external radiation therapy were the only significant prognostic factors.

Table. Prognostic Factors for Anaplastic Thyroid Carcinoma.

	Univariate Factor (P value)	Multivariate Hazard Ratio (95% confidence interval)
Age (<60 years)	<0.01	0.48 (0.27–0.87)
Size of tumor (≥5 cm)	0.02	1.24 (0.85–1.82)
Stage	<0.01	
Local		0.57 (0.37–0.89)
Regional		0.83 (0.61–1.13)
Distant		1.49 (1.11–2.00)
Surgical resection	<0.01	0.78 (0.31–1.95)
External radiation therapy	<0.01	0.53 (0.15–1.94)
Resection and radiation	<0.01	0.72 (0.59–0.89)

Conclusion Among patients with anaplastic thyroid carcinoma, younger age, limited extent of tumor, and combined surgical and external radiation therapy are associated with a better prognosis.

COMMENTARY

This is the largest series of patients with anaplastic thyroid carcinoma yet reported, and as such it offers insights into the factors that affect the outcome in patients who have this uncommon tumor. Specifically, it confirms that less than 20% of patients survive for 1 year, and that long-term survival is rare. While the number of patients was large, they were seen and treated at multiple hospitals, and therefore there were probably variations not only in diagnosis but also in treatment, even within the categories described by the authors. For example, tumor histology was not centrally reviewed; some patients may not have had an anaplastic carcinoma, but rather a nonanaplastic, albeit poorly differentiated, thyroid carcinoma or thyroid metastasis of another primary tumor. While multivariate analysis revealed several characteristics predicting longer survival, it would be interesting to know the characteristics and causes of death of the few patients who survived at least one year. Was their survival due to earlier diagnosis, better selection of treatment, or more effective treatment, and was their quality of life improved and their death less likely to be due to local invasion and suffocation?

While the combination of surgery and radiation therapy was beneficial in this cohort, there are no data on chemotherapy, which is undoubtedly the key to better outcomes. In a study of 30 patients, the combination of surgery, hyperfractionated radiation therapy, and chemotherapy (cisplatin and doxorubicin) resulted in a median survival of 10 months, and an overall 3-year survival rate of 27 percent (1). Whether this more favorable outcome was due to the effect of hyperfractionated radiation therapy, the drugs, or patient selection, with more patients being treated at an earlier stage, is not clear, but at least the outlook is not invariably bleak.

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Premature delivery is increased in pregnant women with subclinical hypothyroidism

Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, Cunningham FG. Subclinical hypothyroidism and pregnancy outcomes. Obstet Gynecol 2005;105:239-45.

SUMMARY

Background Hypothyroidism in pregnant women is associated with complications of pregnancy and abnormal fetal development. In this study, pregnant women were screened for hypothyroidism, and the outcome of the pregnancy was compared in women with subclinical hypothyroidism and normal women.

Methods Serum thyrotropin (TSH) was measured in 17,298 women who were ≤20 weeks pregnant and who later delivered a singleton infant at the same hospital. Serum free thyroxine (T_4) was measured in those women who had a serum TSH concentration >3.0 mU/L. Women who had a high serum TSH and a low free T_4 concentration were referred for further evaluation and were excluded. Women with a serum TSH concentration greater than the 97.5th percentile for gestational age (which ranged from 5.1 mU/L at 6 weeks to 2.7 mU/L at 16 weeks) and a serum free T_4 concentration >0.68 ng/dl (8.8 pmol/L) were considered to have subclinical hypothyroidism. Their pregnancy outcomes were compared with those in the women with serum TSH values between the 5th and 95th percentiles.

The outcomes evaluated included gestational hypertension, defined as a blood pressure ≥140/90 mm Hg or higher; severe preeclampsia, defined as a blood pressure >160/90 mm Hg, serum creatinine >1.0 mg/dl (88.4 μmol/L), thrombocytopenia, or proteinuria; and placental abruption. Preterm birth was defined as gestational age ≤34 weeks at the time of delivery.

Results Among the 17,298 women, 32 (0.2 percent) had overt hypothyroidism, 404 (2.3 percent) had subclinical hypothyroidism, and 15,689 had normal serum TSH values (5th to 95th percentile). The serum TSH concentrations in the 404 women with subclinical hypothyroidism ranged from 2.7 to >75 mU/L; 50 (12 percent) had values >10 mU/L. These women were slightly older than the normal women, but parity, body-mass index, and duration of pregnancy at the time of screening were similar in the two groups.

The frequency of gestational hypertension and severe preeclampsia was similar in the two groups, but placental abruption was more frequent in the women with subclinical hypothyroidism (P=0.03) (Table). The mean gestational age at delivery was 39 weeks in the two groups, but delivery at or before 34 weeks was more common in the subclinical-hypothyroidism group (P=0.01).

Table. Pregnancy and Infant Outcomes in Women with Subclinical Hypothyroidism and Normal Women.

	Subclinical Hypothyroidism (n=404)	Normal Serum TSH (n=15,689)
Gestational hypertension	41 (11%)	1400 (9%)
Severe preeclampsia	23 (6%)	842 (5%)
Placental abruption	4 (1%)	52 (0.3 %)
Gestational age (weeks)	39	39
Gestational age ≤34 weeks	18 (4%)	385 (2%)
Birth weight (g)	3317	3367
Admission to intensive care	16 (4%)	347 (2%)
Respiratory distress syndrome	11 (3%)	235 (1%)
Fetal and neonatal deaths	4 (1%)	115 (1%)

The mean birth weight of the infants in the two groups was similar, as was the frequency of birth weight <2500 g and <1500 g, but more of the infants in the subclinical-hypothyroidism group were admitted to the intensive-care unit and had the respiratory distress syndrome (P=0.05). There were no differences in major malformations, fetal deaths, or neonatal deaths.

Conclusion The risk of delivery at or before 34 weeks of gestation is increased in pregnant women who have subclinical hypothyroidism at or before 20 weeks of gestation.

COMMENTARY

Should pregnant women be screened for thyroid disease, in particular hypothyroidism? Among those with overt hypothyroidism who are not treated or are poorly treated, the frequency of preeclampsia and other complications of pregnancy, low birth weight, and perinatal morbidity and mortality is high.

The frequency of these events is much lower in women with subclinical hypothyroidism, but nonetheless may be higher than in normal women. In this study, the increase was in preterm birth and its complications.

In another study, of 9403 women who were 15 to 18 weeks pregnant (1), 209 (2.2 percent) had serum TSH concentrations ≥6 mU/L. There was no increase in the complications of pregnancy, gestational age at delivery, birth weight, and neonatal death, but fetal mortality was higher in the women with high serum TSH values (0.9 vs. 3.8 percent).

The similar frequency of subclinical hypothyroidism in the two studies, one of mostly Hispanic women in Texas and the other of mostly white women in Maine, suggests the results of screening would be similar throughout the United States.

The inconsistent outcome results, and the lack of evidence that T_4 therapy would alter any of the outcomes, argue against implementation of screening at this time.

Robert D. Utiger, M.D.

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Serum antithyroid antibodies are detected most often in people with high serum thyrotropin concentrations and thyroid enlargement

Bulow Pedersen I, Laurberg P, Knudsen N, Jorgensen T, Perrild H, Ovesen L, Rasmussen LB. A population study of the association between thyroid autoantibodies in serum and abnormalities in thyroid function and structure. Clin Endocrinol (Oxf) 2005;62:713-20.

SUMMARY

Background The hallmark of chronic autoimmune thyroiditis is a high serum concentration of antithyroid peroxidase (TPO) or antithyroglobulin (Tg) antibodies. Thyroid function may be normal or low, and the thyroid gland may be enlarged, normal-sized, or small. In this study the relationships between thyroid autoimmunity, size, and function were assessed in large cohort of people in Denmark.

Methods The cohort was recruited from specific groups of people living in two regions of the country (median urinary iodide concentrations, 53 and 68 μg/L), excluding those with known thyroid disease and women who had been pregnant within the preceding year. The groups were women aged 18 to 22 years, 25 to 30 years, 40 to 45 years, and 60 to 65 years, and men aged 60 to 65 years; there were approximately 850 subjects per group.

Thyroid volume was measured by ultrasonography (normal, 6.6 to 14.9 ml). Serum thyrotropin (TSH) (normal, 0.4 to 3.6 mU/L), anti-TPO antibodies (detection limit, 30 U/L), and anti-Tg antibodies (detection limit, 20 U/L) were measured by immunoassays.

Results The thyroid gland was small in 196 subjects (5 percent), normal in 2518 (60 percent), and large in 1454 (35 percent) (Table). Serum TSH concentrations were <0.4 mU/L in 194 subjects (5 percent), 0.4 to 3.6 mU/L in 3794 (91 percent), and >3.6 mU/L in 180 (4 percent).

Overall, serum anti-TPO, anti-Tg antibodies, or both, were detected in 784 subjects (19 percent). One or both antibodies were detected in 18 percent of the subjects with low serum TSH concentrations, 17 percent of those with normal concentrations, and 65 percent of those with high concentrations. Serum TSH concentrations were high in 40 percent of the subjects in whom both serum antibodies were detected, and in only 2 percent of those in whom neither antibody was detected.

Table. Serum TSH and Antithyroid Antibody (Ab) Concentrations and Thyroid Size in Healthy Subjects.

	Serum TSH Concentration (mU/L)			
Thyroid volume	<0.4	0.4-3.6	>3.6	Total
Small				
Total	1	168	27	196
Serum Ab present*	1 (100%)*	14 (8%)	12 (44%)	27 (14%)
Normal				
Total	48	2352	118	2518
Serum Ab present	8 (17%)	393 (17%)	73 (62%)	474 (19%)
Large				
Total	145	1274	35	1454
Serum Ab present	25 (17%)	226 (18%)	32 (91%)	283 (19%)
Total	194	3794	180	4168
Serum Ab present	34 (18%)	633 (17%)	117 (65%)	784 (19%)

*Percentage of subjects with detectable serum anti-TPO or anti-Tg antibodies in that serum TSH and thyroid-volume subgroup.

Among the subjects with serum TSH concentrations >3.6 mU/L, serum anti-TPO or anti-Tg antibodies were detected in nearly all (91 percent) who had a large thyroid, 62 percent of those with a normal-sized thyroid, and 44 percent of those with a small thyroid (Table). In contrast, among the subjects with serum TSH concentrations ≤3.6 mU/L, there was no relationship between serum anti-TPO or anti-Tg antibodies and thyroid volume.

Conclusion Among healthy subjects, the presence of serum anti-TPO or anti-Tg antibodies is associated with increasing serum TSH concentrations, and with a large thyroid in those with high serum TSH concentrations.

COMMENTARY

Spontaneously occurring overt hypothyroidism is most often caused by chronic autoimmune thyroiditis, which classically occurs in two forms—a goitrous form (Hashimoto's disease) and a nongoitrous (atrophic) form. The anatomic difference is due to differences in lymphocytic infiltration, fibrosis, and thyroid follicular-cell hyperplasia. There may be immunologic differences as well, not in terms of differences in serum anti-TPO and anti-Tg antibody concentrations, but in the presence of cytotoxic antibodies or TSH receptor-blocking antibodies in patients with atrophic thyroiditis and their absence in those with goitrous thyroiditis.

These generalizations apparently do not apply to subjects with subclinical hypothyroidism (serum free thyroxine results were not given, but in surveys like this the values are normal in most if not all subjects with high serum TSH values). Among the subjects with high serum TSH concentrations, more of those with a large thyroid had detectable serum anti-TPO or anti-Tg antibodies, as compared with those with a normal-sized or small thyroid. The authors suggest that the rate of progression of atrophic thyroiditis is more rapid than is that of goitrous thyroiditis, so that fewer patients with subclinical hypothyroidism caused by the former will be detected at any one time. This would to some extent fit with the histology of thyroid follicular-cell destruction in atrophic thyroiditis and some follicular-cell hyperplasia—preventing a marked fall in thyroid hormone production—in goitrous thyroiditis. The lower frequency of detection of serum antithyroid antibodies in the absence of thyroid enlargement could also indicate that there are other causes of nongoitrous hypothyroidism in addition to chronic autoimmune thyroiditis.

Robert D. Utiger, M.D.

High serum antithyroid antibody concentrations are not associated with infection with *Helicobacter pylori*

Tomasi PA, Dore MP, Fanciulli G, Sanciu F, Realdi G, Delitala G. Is there anything to the reported association between *Helicobacter pylori* infection and autoimmune thyroiditis? Dig Dis Sci 2005;50:385-8.

SUMMARY

Background Some studies have found high rates of infection with *Helicobacter pylori* in patients with autoimmune thyroiditis, which has raised the possibility that the response to infection with this organism may be important in the pathogenesis of the thyroid disorder. In this study serum antithyroid antibodies were measured in patients with dyspepsia with and without *H. pylori* infection.

Methods The study subjects were consecutive patients with dyspeptic symptoms (epigastric pain or discomfort, heartburn, early satiety, regurgitation, and nausea and vomiting) for at least three months who were referred for upper gastrointestinal endoscopy (which presumably did not reveal a peptic ulcer). Patients who had been treated with bismuth, antisecretory drugs, or antibiotics within the preceding three months were excluded, as were patients who had been treated specifically for *H. pylori* infection, were taking nonsteroidal antiinflammatory drugs, or had undergone gastrointestinal surgery.

The patients were evaluated for *H. pylori* infection with the C-13 urea breath test, and for thyroid disorders by measurements of serum thyrotropin (TSH), antithyroid peroxidase (TPO) antibodies, and antithyroglobulin (Tg) antibodies. *H. pylori* infection was defined as a positive C-13 urea test. Hyperthyroidism and hypothyroidism were defined as a low (<0.46 mU/L) and a high (>4.7 mU/L) serum TSH concentration, respectively; serum free thyroxine and free triiodothyronine also were measured, but no results are given. Autoimmune thyroiditis was defined as a high (>10 U/ml) serum anti-TPO or a high (>100 U/ml) anti-Tg antibody concentration.

Results A total of 302 patients with dyspepsia were evaluated; 181 (60 percent) were women and 121 (40 percent) were men. Their mean (±SD) age was 51±16 years. Among them, 111 (37 percent) had *H. pylori* infection, and 191 (63 percent) did not.

The frequency of hypothyroidism, hyperthyroidism, and high serum antithyroid antibody concentrations was similar in the patients with and without *H. pylori* infection (Table).

Table. Thyroid Function and Serum Antithyroid Antibody Concentrations in Patients with Dyspepsia with and without *H. pylori* Infection.

	H. pylori Infection (n=111)	No *H. pylori* Infection (n=191)
Hypothyroidism (serum TSH >4.7 mU/L)	5 (4.7%)	10 (5.5%)
Hyperthyroidism (serum TSH <0.46 mU/L)	6 (5.8%)	10 (5.5%)
High serum anti-TPO antibodies (>10 U/ml)	24 (21.6%)	36 (18.8%)
High serum anti-Tg antibodies (>100 U/ml)	6 (5.4%)	7 (3.6%)
Both serum anti-TPO and anti-Tg antibodies high	8 (7.2%)	14 (7.3%)

There were no differences in hormonal values in the patients with and without *H. pylori* infection.

Conclusion High serum antithyroid antibody concentrations and thyroid dysfunction are not more frequent in patients with dyspepsia who have *H. pylori* infection, as compared with patients with dyspepsia who do not have the infection.

COMMENTARY

There have been two studies in which the frequency of asymptomatic *H. pylori* infection was increased in patients with autoimmune thyroiditis, as compared with normal subjects (1) or patients with a nontoxic multinodular goiter (2). In the only study in which the effect of antibiotic treatment of the infection was evaluated, done in five apparently asymptomatic women with high serum anti-TPO and anti-Tg antibody concentrations, the concentrations declined slowly, but not in five similar women who declined treatment (3).

This new study provides no support for a relationship between *H. pylori* infection, as manifested clinically by dyspepsia, and autoimmune thyroiditis. Whether *H. pylori* infection causes dyspepsia is still debated, but if there is a relationship between the infection and autoimmune thyroiditis it should not matter whether the infection is asymptomatic or has caused dyspepsia or peptic ulcer.

While the meager available evidence is contradictory, the possibility of a relationship between *H. pylori* infection and autoimmune thyroiditis should not be dismissed. If there is a relationship, it is likely that *H. pylori* infection plays a role in the pathogenesis of autoimmune thyroiditis, not the reverse. So little is known about the risk factors for autoimmune thyroiditis that pursuing the possible role of *H. pylori* infection is warranted. Lest one say this is nonsense, recall the skepticism that greeted the demonstration that infection with *H. pylori* caused peptic ulcer disease.

Robert D. Utiger, M.D.

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Thyroxine therapy does not improve the outcome of assisted reproduction in women with chronic autoimmune thyroiditis

Negro R, Mangieri T, Coppola L, Presicce G, Casavola EC, Gismondi R, Locorotondo G, Caroli P, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in thyroid peroxidase antibody-positive women undergoing assisted reproduction technologies: a prospective study. Hum Reprod 2005;20:1529-33.

SUMMARY

Background Chronic autoimmune thyroiditis, as manifested by high serum antithyroid antibody concentrations, has been associated with both infertility and miscarriage. In this study, the pregnancy, miscarriage, and delivery rates were determined in infertile women with high serum antithyroid peroxidase (TPO) concentrations who were treated with thyroxine (T_4) or placebo and then underwent assisted reproduction. Infertile women who did not have high serum anti-TPO antibody concentrations were also studied.

Methods The study subjects were 484 infertile women (mean age, 30 years; range, 20 to 45) scheduled to undergo a first assisted reproduction cycle. The causes of infertility were ovarian dysfunction (36 percent), tubal factors (28 percent), endometriosis (17 percent), and idiopathic (19 percent). Serum anti-TPO antibodies (normal, ≤100 U/L), thyrotropin (TSH), and free T_4 were measured. Women with overt thyroid dysfunction were excluded.

Among the 484 women, 72 (15 percent) had a high serum anti-TPO antibody concentration. They were randomly assigned to receive T_4, 1.0 μg/kg per day, or placebo. One month later, assisted reproduction was begun. T_4 therapy was continued throughout any pregnancy.

The assisted reproduction regimen consisted of administration of a gonadotropin-releasing hormone antagonist and follicle-stimulating hormone, starting on day 2 of the menstrual cycle, until at least three 17-mm follicles were seen on ultrasonography. Chorionic gonadotropin was then given to induce ovulation, and the oocytes were retrieved and fertilized in vitro. One to three embryos, depending on morphological quality, were transferred to the woman's uterus. Pregnancy was confirmed by increasing serum chorionic gonadotropin concentrations on two occasions ≥10 days after transfer. Clinical pregnancy was diagnosed by ultrasonography five weeks after transfer. The end points were pregnancy rates, miscarriage rates, including early pregnancy loss (biochemical pregnancy), and delivery rates.

Results The mean age, reproductive history, causes of infertility, and serum TSH and free T_4 concentrations were similar in the two groups of women with high serum anti-TPO antibody concentrations (T_4-treatment and placebo) and the other 412 women. Among the women given T_4, the mean serum TSH concentration decreased from 1.9 to 1.1 mU/L and the mean serum free T_4 concentration increased from 1.1 to 1.4 ng/dl (14 to 18 pmol/L) in one month. In all three groups, the mean number of oocytes retrieved was 6 and the mean number of embryos transferred was 2.5.

The pregnancy rate was similar in the three groups (Table). Among the women who became pregnant, the miscarriage rate was 25 percent in the women with normal serum anti-TPO antibody concentrations, and 40 and 47 percent in those with high serum anti-TPO concentrations treated with T_4 and not treated, respectively.

Table. Outcome of First Assisted Reproduction Cycle in Infertile Women with and without a High Serum Anti-TPO Antibody Concentration.*

	No.	Pregnancy	Miscarriage	Delivery
High serum anti-TPO antibodies				
T_4 treatment	36	20 (56%)	8 (40%)	12 (60%)
No T_4 treatment	36	19 (53%)	9 (47%)	10 (53%)
Normal serum anti-TPO antibodies	412	224 (54%)	56 (25%)	168 (75%)

*The outcome results in the published paper are incorrect. The correct results, supplied by the first author, are given here.

Conclusion The rate of pregnancy in women undergoing assisted reproduction is similar in women with and without high serum anti-TPO antibody concentrations. The rate of miscarriage is higher in the former, and among them it is not altered by T_4 treatment.

COMMENTARY

Several aspects of reproductive function seem to be impaired in women who have high serum antithyroid antibody concentrations. Their fertility may be decreased. The rate of miscarriage is increased in those found to have high serum antithyroid antibody concentrations before or during pregnancy and in those who undergo successful assisted reproduction, as in this study.

These changes may be due to concomitant subclinical hypothyroidism or a direct effect of the antithyroid antibodies; alternatively, the high serum antithyroid antibody concentrations are simply an indicator of the women's susceptibility to loss of tolerance to other self-antigens. Among antithyroid antibodies a likely candidate might be anti-TSH receptor antibodies, acting on gonadotropin receptors. Chorionic gonadotropin binds to TSH receptors, so might not antibodies that bind to TSH receptors also bind to the receptors normally activated by gonadotropins of pituitary or chorionic origin, thereby blocking the action of the gonadotropins, with deleterious effects on fertility or a pregnancy?

Robert D. Utiger, M.D.

Thyrotropin secretion is correlated with body mass in obese women with normal thyroid function

Iacobellis G, Ribaudo MC, Zappaterreno A, Iannucci CV, Leonetti F. Relationship of thyroid function with body mass index, leptin, insulin sensitivity and adiponectin in euthyroid obese women. Clin Endocrinol (Oxf) 2005;62:487-91.

SUMMARY

Background Thyroid dysfunction is associated with changes in adipose tissue metabolism and the production of several hormones primarily of adipose tissue origin (adipokines). This cross-sectional study was done to determine the relationships between thyroid function, body weight, insulin sensitivity, and adipokine secretion in obese, euthyroid women.

Methods The study subjects were 87 women with obesity (body-mass index [BMI], >30 kg/m^2) that was long-standing (mean duration, 15 years). Their mean (±SD) age was 35±9 years, and their mean BMI was 40±7 kg/m^2. All had a normal physical examination, normal thyroid function and serum antithyroid antibody concentrations, normal glucose tolerance, and normal serum lipid concentrations.

The following were measured in all women: fat mass and fat-free mass (by bioimpedance); resting energy expenditure (by indirect calorimetry); serum thyrotropin (TSH), free thyroxine (T_4), and free triiodothyronine (T_3) (by immunoassay); serum insulin, adiponectin, and leptin (by immunoassay); and insulin sensitivity, measured by the homeostatic model assessment for insulin resistance (HOMA-IR, calculated as fasting serum glucose [mmol/L] × fasting serum insulin [μU/ml] ÷ 22.5) and the euglycemic hyperinsulinemic clamp method.

Results The BMI was <40 kg/m^2 in 47 women (54 percent) and ≥40 kg/m^2 in 40 (46 percent). The age of the women in the two groups was similar, as was their blood pressure and serum lipid concentrations. Serum glucose concentrations, after both an overnight fast and oral glucose administration, were similar in both groups, but fasting serum insulin concentrations were higher and insulin resistance was greater in the women with a BMI ≥40 kg/m^2 (Table).

Table. Metabolic and Hormonal Characteristics of Two Groups of Obese Women.

	BMI <40 kg/m^2 (n=47)	BMI ≥40 kg/m^2 (n=40)
Fat-free mass (kg)	49.5	52.5
Resting energy expenditure (kcal/24 hr)	1586	1995*
Fasting serum insulin (μU/ml)	12.7	17.8*
HOMA-IR (mmol/L per uU/ml)	3.3	4.6*
Glucose utilization (mg/kg fat-free mass/min)	9.6	7.4*
Serum leptin (ng/ml)	30	48*
Serum adiponectin (μg/ml)	42	28*
Serum TSH (mU/L)	1.5	2.3*
Serum free T_4 (ng/dl)	1.4	1.3
Serum free T_3 (ng/dl)	0.4	0.4

*P<0.05. To convert free T_4 and free T_3 to pmol/L, multiply by 12.9 and 15.4, respectively.

Serum TSH concentrations were correlated with BMI (r=0.44, P<0.01) and also with serum leptin (r=0.41, P<0.01) and serum leptin/BMI (r=0.33, P=0.03), and negatively correlated with serum adiponectin (r=-0.25, P=0.05), but serum free T_4 and free T_3 concentrations were not correlated with any of these measures.

Conclusion Among healthy obese women with normal thyroid function, serum TSH concentrations, but not serum free T_4 and free T_3 concentrations, are correlated with body mass and serum leptin concentrations, suggesting a role for leptin in the regulation of TSH secretion.

COMMENTARY

The higher serum TSH concentrations in the more obese women in this study were not associated with lower serum free T_4 and T_3 concentrations, arguing against a possible antithyroid effect of obesity. On the other hand, their serum free T_4 and free T_3 concentrations were not higher than those in the less obese women, as might be expected if the primary abnormality was an increase in secretion of biologically active TSH. These findings suggest that the biologic activity of TSH declines as BMI increases. Another possibility is that the circadian pattern of 24-hour secretion is altered, such that daytime TSH pulse frequency or amplitude is increased, but 24-hour TSH secretion, and therefore thyroid secretion, is normal.

The correlation between serum TSH concentrations and BMI in these obese women could be a reflection of their higher serum leptin concentrations. The strongest determinant of leptin secretion is obesity, and leptin, acting via the hypothalamus, may increase TSH secretion, via an increase in thyrotropin-releasing hormone. Conversely, leptin secretion falls during fasting, as does TSH secretion. And TSH secretion tends to be low in the rare patients with congenital leptin deficiency or resistance. These findings, taken together, suggest that leptin contributes to the regulation of TSH secretion. On the other hand, changes in thyroid secretions do not have consistent effects on serum leptin concentrations.

Robert D. Utiger, M.D.

Review Articles

Castro MR, Gharib H. Continuing controversies in the management of thyroid nodules. Ann Intern Med 2005;142:926-31.

Cooper DS. Antithyroid drugs. N Engl J Med 2005;352:905-17.

Krohn K, Fuhrer D, Bayer Y, Eszlinger M, Brauer V, Neumann S, Paschke R. Molecular pathogenesis of euthyroid and toxic multinodular goiter. Endocr Rev 2005;26:504-24.

Papi G, Pearce EN, Braverman LE, Betterle C, Roti E. A clinical and therapeutic approach to thyrotoxicosis with thyroid-stimulating hormone suppression only. Am J Med 2005;118:349-61.

Park SM, Chatterjee VK. Genetics of congenital hypothyroidism. J Med Genet 2005;42:379-89.

Corrections

Octreotide is not an effective therapy for patients with Graves' ophthalmopathy (March 2005;17:5). Octreotide was incorrectly identified as a somatostatin antagonist. It is a somatostatin agonist.

Basal but not stimulated serum thyroglobulin values vary according to number and site of metastases in patients with thyroid carcinoma (March 2005;17:13). The page numbers in the citation for the original article (J Clin Endocrinol Metab 2004;89:6016-16) are wrong. The correct page numbers are 6010-6.

CLINICAL THYROIDOLOGY

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