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THYROID DISEASE

Patients with Subclinical Thyroid Disease Have Few Clinical Abnormalities and Benefit Little from Treatment . . . 1

HYPERTHYROIDISM

Cardiac Failure in Pregnant Women with Hyperthyroidism Is Usually Precipitated by a Complication of Pregnancy 2

Children Who Accidentally Ingest Thyroid Hormone Have Few Symptoms and Signs of Hyperthyroidism Despite High Serum Thyroid Hormone Concentrations 3

The Efficacy of Radioiodine Therapy for Hyperthyroidism Is Not Reduced by Post-Radioiodine Methimazole Therapy 4

HYPOTHYROIDISM

Thyroxine and Triiodothyronine Are Not More Effective than Thyroxine Alone in Patients with Hypothyroidism Who Have Depressive Symptoms 5

Thyroxine and Triiodothyronine Are Not More Effective than Thyroxine Alone in Unselected Patients with Hypothyroidism 6

Triiodothyronine and Thyroxine Are Not More Effective than Thyroxine Alone in Ameliorating Hypothyroid Symptoms or Improving Cognitive Function 7

CONGENITAL HYPOTHYROIDISM

Mutations in a Cell-Membrane Thyroid Hormone-Transport Molecule Cause Neurologic and Thyroid Abnormalities 8

Thyroid Radioiodine Imaging Is Superior to Ultrasonography in Evaluating Infants with Congenital Hypothyroidism 9

Central Hypothyroidism Occurs in Infants of Mothers with Hyperthyroidism Due to Graves' Disease during Their Pregnancies 10

NODULAR GOITER

Thyroid Incidentalomas May Be Carcinomas 11

THYROID CANCER

Serum Calcitonin Should Be Measured in All Patients with Thyroid Nodules 12

Preoperative Ultrasonography Is Valuable for Detecting Lymph-Node Metastases and Local Recurrence in Patients with Thyroid Carcinoma 13

THYROID FUNCTION IN PREGNANCY

The Rise in Serum Thyroxine Binding during Pregnancy in Women with Hypothyroidism Only Partly Explains Their Increased Need for Thyroxine 14

THYROIDITIS

Painless Thyroiditis May Be Followed by Recurrence of Hyperthyroidism in Patients with Graves' Disease . . . 15

AUTOIMMUNE THYROID DISEASE

Seasonal Allergic Rhinitis May Be Followed by Recurrent Hyperthyroidism in Women with Graves' Disease . . . 16

Cerebrospinal Fluid Concentrations of Antithyroid Antibodies Are High in Hashimoto's Encephalopathy . . . 17

IODINE DEFICIENCY

Iodine Deficiency Continues to Be a Major Health Problem Worldwide 18

DRUG EFFECTS ON THYROID FUNCTION

Short-Term Ingestion of Kelp Has a Weak Antithyroid Effect in Normal Subjects 19

THYROID HORMONE SECRETION

Megalyn-Mediated Removal of Thyroid Hormone-Poor Thyroglobulin Facilitates Thyroid Hormone Secretion 20



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ATA News

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Patients with subclinical thyroid disease have few clinical abnormalities and benefit little from treatment

Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. Subclinical thyroid disease. Scientific review and guidelines for diagnosis and management. JAMA 2004;291:228-38.

SUMMARY

Background Subclinical hypothyroidism and subclinical hyperthyroidism are defined, respectively, by the presence of high or low serum thyrotropin (TSH) concentrations and normal serum free thyroxine (T₄) concentrations, independent of any symptoms or signs of thyroid dysfunction. Hypothyroidism and hyperthyroidism are considered overt only when the serum free T₄ concentration is low or high, respectively. The clinical effects of subclinical hypothyroidism and subclinical hyperthyroidism are uncertain, as are the benefits of treatment. This article describes the results of an analysis of these topics.

Methods The analysis was conducted by a panel of 13 experts in endocrinology, epidemiology, and preventive health services appointed by the American Thyroid Association, the American Association of Clinical Endocrinologists, and the Endocrine Society. Subclinical hypothyroidism and subclinical hyperthyroidism were defined as described above; for the purpose of this analysis, the normal range for serum TSH was considered to be 0.46 to 4.4 mU/L.

The panel reviewed and then rated the strength of the available information about the health effects and benefits of treatment of subclinical hypothyroidism and subclinical hyperthyroidism as good, fair, or insufficient. The panel then made recommendations regarding evaluation and treatment, with qualifications based on the perceived strength of the evidence.

Results The prevalence of subclinical hypothyroidism was estimated to range from 4 to 8.5 percent among adults in the United States, of whom about 75 percent have serum TSH concentrations of 4.5 to 10 mU/L. Table 1 shows the panel's summary of the health effects and benefits of treatment of subclinical hypothyroidism.

Table 1. Assessment of Evidence Regarding Effects of Subclinical Hypothyroidism and Benefits of Treatment.

	Strength of Evidence		Treatment Benefit	
	Serum TSH 4.5-10 mU/L	Serum TSH >10 mU/L	Serum TSH 4.5-10 mU/L	Serum TSH >10 mU/L
Progression to overt hypothyroidism	Good	Good	Yes	Yes
Symptoms of hypothyroidism	None	Insufficient	Insufficient	Insufficient
Cardiac dysfunction	Insufficient	Insufficient	Insufficient	Insufficient
Hypercholesterolemia	Insufficient	Fair	Insufficient	Insufficient

The prevalence of subclinical hyperthyroidism was estimated to be 3.2 percent, of whom about 75 percent have serum TSH concentrations of 0.1 to 0.45 mU/L. Table 2 shows the panel's summary of the findings regarding subclinical hyperthyroidism.

Table 2. Assessment of Evidence Regarding Effects of Subclinical Hyperthyroidism and Benefits of Treatment.

	Strength of Evidence		Treatment Benefit	
	Serum TSH 0.1-0.45 mU/L	Serum TSH <0.1 mU/L	Serum TSH 0.1-0.45 mU/L	Serum TSH <0.1 mU/L
Progression to overt hyperthyroidism	Insufficient	Good	Yes	Yes
Symptoms of hyperthyroidism	None	None	None	Insufficient
Cardiac dysfunction	Insufficient	Fair	Insufficient	Insufficient
Atrial fibrillation	Insufficient	Good	None	None
Osteopenia	None	Fair*	None	Fair

*In postmenopausal women.

The panel recommended against population-based screening for thyroid dysfunction.

Conclusion There is little evidence that patients with subclinical hypothyroidism or subclinical hyperthyroidism have clinical manifestations of their thyroid dysfunction or benefit from therapy.

COMMENTARY

In a similar analysis, Helfand (1) reached the same conclusions as to the lack of benefit of treatment of subclinical hypothyroidism and subclinical hyperthyroidism, and the U.S. Preventive Services Task Force has recommended against screening for thyroid dysfunction in adults.

Patients who seek medical care often have symptoms suggestive of thyroid dysfunction, and some of them have subclinical thyroid dysfunction. Given that

the changes in thyroid secretion in these patients are very small, even in the subgroups with the more abnormal serum TSH concentrations (Tables 1 and 2), and that the symptoms and other manifestations of thyroid hormone deficiency or excess are very nonspecific, it is not surprising that there is so little evidence of either disability or benefit of therapy. If nothing else, treatment should prevent progression to overt thyroid dysfunction. However, the rates of progression are low (<5 percent/year for both subclinical hypothyroidism and subclinical hyperthy-

roidism), and the rates of spontaneous normalization of serum TSH values are about the same.

Robert D. Utiger, M.D.

Reference

- Helfand M. Screening for subclinical thyroid dysfunction in nonpregnant adults: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2004;140:128-41.

Cardiac failure in pregnant women with hyperthyroidism is usually precipitated by a complication of pregnancy

Sheffield JS, Cunningham FG. Thyrotoxicosis and heart failure that complicate pregnancy. *Am J Obst Gynecol* 2004;190:211-7.

SUMMARY

Background There are similar changes in cardiovascular function in normal pregnant women and patients with hyperthyroidism. They include a decrease in peripheral vascular resistance, and an increase in blood volume, heart rate, cardiac contractility, and cardiac output. Compensation for the combined effects of the two conditions is usually adequate, but decompensation can occur. This study was done to determine the factors associated with cardiac failure in pregnant women with hyperthyroidism.

Methods and Results From 1974 through 2001, slightly more than 300,000 women delivered babies at the Parkland Hospital in Dallas, Texas. Among them 150 (<0.05 percent) had overt hyperthyroidism at some time during their pregnancy. Thirteen (9 percent) of the 150 women had cardiac failure, based on standard clinical criteria and confirmed by radiographic findings of cardiomegaly and pulmonary edema (and echocardiographic or other imaging evidence of depressed ventricular function in all five women tested). The women ranged in age from 17 to 34 years, and the duration of pregnancy ranged from 18 to 37 weeks. All the women had symptoms of hyperthyroidism, a diffuse goiter, and high serum total or free thyroxine concentrations at the time of hospitalization for cardiac failure.

Six women had cardiac failure before the time of fetal viability (23 weeks). Three also had an incomplete abortion, uterine hemorrhage, and sepsis, and two had pyelonephritis and septicemia; four of these women were anemic (hemat-

ocrit, <25 percent). Only one of the six women had no complicating problems. The extent of prenatal care, if any, in these women is not described.

Seven women had been pregnant for 29 or more weeks. Four were known to have hyperthyroidism, but had not been taking prescribed therapy, and three had received no prenatal care. Four of these women had severe preeclampsia or eclampsia, three were anemic, two had chorioamnionitis and sepsis, and one had no complicating problems.

Treatment for heart failure consisted of intravenous furosemide, and in some women digoxin or a β -adrenergic antagonist drug. Women with preeclampsia or eclampsia were treated with magnesium sulfate and hydralazine. All were treated with propylthiouracil, potassium iodide, and a glucocorticoid. Other treatments included antibiotics, blood transfusion, and uterine curettage. All the women improved rapidly, and cardiac evaluation was normal 5 weeks to 5 months later. The outcome of the pregnancies is not stated. Eleven of the women were last evaluated 2 to 25 years later, and all had a normal cardiac evaluation at that time. Three had been treated with iodine-131, one was taking propylthiouracil (3 years later), and seven were in remission (2 to 25 years later).

Conclusion Most pregnant women with hyperthyroidism who have cardiac failure also have sepsis, preeclampsia, or other complications of pregnancy.

COMMENTARY

Given the similarity of the changes in cardiovascular function in pregnant women and patients with hyperthyroidism, and the presumption that the cardiovascular effects of the two conditions are additive, it is perhaps surprising that cardiac failure is not more common in pregnant women with hyperthyroidism. Thyroid hormone excess probably has more direct chronotropic and inotropic effects on cardiac function than pregnancy, and less effect on blood volume, so perhaps the effects are less additive than might be expected.

These women were encountered over a period of many years, and relatively few had contemporary studies of cardiovascular function. In a study of six pregnant women with hyperthyroidism but not cardiac failure, cardiac output,

stroke volume, heart rate, and mean arterial pressure were higher, and peripheral resistance was lower, as compared with normal pregnant women at the same stage of gestation, and the values for all measurements were more normal during antithyroid drug therapy (1).

Cardiac failure may occur in patients with hyperthyroidism as a result of marked tachycardia, atrial fibrillation, or, rarely, cardiomyopathy. However, it is uncommon, certainly in women of child-bearing age. Hence, the presence of cardiac failure in 9 percent of pregnant women with hyperthyroidism is exceptional. This high frequency is probably explained by the high frequency of sepsis and disorders of pregnancy in these women. Preeclampsia, which seems to occur with increased frequency in women with hyperthyroidism, may increase afterload, and sepsis may increase preload,

beyond the capability of the heart to maintain adequate output; the consequence is cardiac failure.

Some of the complications of pregnancy may not be preventable, but severe hyperthyroidism is. Women known to have hyperthyroidism when they become pregnant should be followed with special care, and those caring for pregnant women should remember that hyperthyroidism can begin during pregnancy.

Robert D. Utiger, M.D.

Reference

1. Easterling TR, Schmucker BC, Carlson KL, et al. Maternal hemodynamics in pregnancies complicated by hyperthyroidism. *Obstet Gynecol* 1991;78:348-52.

Children who accidentally ingest thyroid hormone have few symptoms and signs of hyperthyroidism despite high serum thyroid hormone concentrations

Willgerodt H, Keller E, Sorger D, Hoepffner W. Acute ingestion of thyroxine and triiodothyronine in young children. *Eur J Pediatr* 2003;162:639-41.

SUMMARY

Background Thyroxine (T₄) and other thyroid hormone products are widely prescribed, and therefore are likely to be accidentally ingested by young children. This study describes the findings in a group of young children who ingested large amounts of thyroid hormone.

Methods The study subjects were 30 children seen in one hospital between 1983 and 2000. The inclusion criteria were age ≤5 years, a history of accidental ingestion of thyroid hormone, and the availability of results of measurements of serum T₄ and triiodothyronine (T₃). Information concerning numbers of tablets ingested and timing of the ingestion was obtained from the parents. The children were treated by gastric lavage, followed by administration of activated charcoal and sodium sulfate (0.25 g/kg). Until 1988, all children were hospitalized, but thereafter they were hospitalized only if they were ill or were thought to have ingested >500 µg of T₄. Blood samples for hormone assay were usually obtained two to six hours after ingestion, and multiple samples were obtained from a few children.

Results The median age of the 30 children was 2.4 years (range, 1.6 to 4.8 years). Seven had ingested T₄, in amounts ranging from 300 to 9500 µg, one had ingested T₃ (600 µg), and 16 had ingested both, in amounts ranging from 80 µg of

T₄ and 20 µg of T₃ to 2500 µg of T₄ and 630 µg of T₃; the median doses were 760 µg of T₄ and 150 µg of T₃; no information on amount ingested was available for six children. Seven children were followed as outpatients and 23 were hospitalized. Only eight children (27 percent) had any signs of hyperthyroidism (usually tachycardia), and none had seizures or other central nervous system abnormalities.

The initial serum T₄ concentrations ranged from 7.1 to 94.5 µg/dl (91 to 1219 nmol/L; median, 13.1 µg/dl [169 nmol/L]), and the initial serum T₃ concentrations ranged from 169 to 3195 ng/dl (2.6 to 49.2 nmol/L; median, 532 ng/dl [8.2 nmol/L]). In four children, serum T₄ and T₃ were measured repeatedly for up to 120 hours after the ingestion. Their serum T₄ concentrations were highest at 4 to 8 hours; in two the value had fallen by 50 percent at 48 hours and in one by 72 hours. In three of these four children the peak serum T₃ concentration was at 6 hours and in the fourth it was at 24 hours. There was no correlation between the initial serum T₄ and T₃ concentrations and clinical manifestations of hyperthyroidism.

Conclusion Children who accidentally ingest large amounts of T₄ and T₃ have few or no clinical manifestations of hyperthyroidism despite high serum T₄ and T₃ concentrations.

COMMENTARY

Clinical manifestations of hyperthyroidism were rare not only in these 30 children, but also in larger studies of this problem (1,2). In the largest study, of 92 children <6 years of age, only 8 (9 percent) had any clinical manifestations of hyperthyroidism (2). Standard therapy consists of gastric lavage and administration of charcoal and a cathartic. The efficacy of these treatments is not known.

In these studies virtually all children who had any symptoms or signs of hyperthyroidism had ingested >5 mg of T₄, although other children tolerated these doses well (1,2). These findings have led to the recommendation that gastrointestinal decontamination procedures need not be undertaken if the T₄ dose is ≤5 mg (1). There are multiple reasons why children tolerate single high doses of T₄ well. Fractional absorption is probably lower than for therapeutic

doses of T₄. The rate of T₄ clearance is higher in children than adults, and clearance of T₄ when its serum concentration is very high is more rapid than when its concentration is normal. Also, conversion to T₃ is relatively slow, so that serum T₃ concentrations tend to rise and fall slowly.

In 2002, 4730 children <6 years of age ingested a "thyroid preparation," according to data accumulated by the 64 centers that constitute the Toxic Exposure Surveillance System of the American Association of Poison Control Centers (3). For all ages the total was 9438, of which 8418 (89 percent) were unintentional, 1899 (20 percent) were treated in a health care facility, and 5 died (age not given). Given these statistics, it seems likely that most of the children who ingested some thyroid preparation were evaluated only by telephone and were not treated, presumably because the dose was low. T₄ and other thyroid

preparations are present in many homes, and care should be taken to keep them out of the hands of children.

Robert D. Utiger, M.D.

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1. Litovitz TL, White JD. Levothyroxine ingestions in children: an analysis of 78 cases. *Am J Emerg Med* 1985;3:297-300.
2. Tunget CL, Clark RF, Turchen SG, Manoguerra, AS. Raising the decontamination level for thyroid hormone ingestions. *Am J Emerg Med* 1995;13:9-13.
3. Watson WA, Litovitz TL, Rodgers GC Jr, et al. 2002 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 2003;21:353-421.

The efficacy of radioiodine therapy for hyperthyroidism is not reduced by post-radioiodine methimazole therapy

Bonnema SJ, Bennedbaek FN, Gram J, Veje A, Marving J, Hegedus L. Resumption of methimazole after ¹³¹I therapy of hyperthyroid diseases: effect on thyroid function and volume evaluated by a randomized clinical trial. *Eur J Endocrinol* 2003;149:485-92.

SUMMARY

Background Some patients with hyperthyroidism who are treated with iodine-131 (I-131) are given an antithyroid drug before or after I-131, or at both times, but there has been concern that the antithyroid drug may reduce the efficacy of I-131. In this study the effects of methimazole or no drug therapy given after I-131 on thyroid function and size were compared in patients with hyperthyroidism.

Methods The study subjects were 149 patients (124 women, 25 men; median age, 59 years) with hyperthyroidism caused by a toxic multinodular goiter in 81 (54 percent), Graves' disease in 46 (31 percent), and a thyroid adenoma in 22 (15 percent). All the patients had been treated with methimazole, and were euthyroid, as determined by normal serum free thyroxine (T₄) and free triiodothyronine (T₃) index values, for at least three months. Then, methimazole was stopped, and four days later I-131 was given. The I-131 dose was based on thyroid volume, as determined by ultrasonography; the mean (±SD) dose was 10.8±4.2 mCi (400±154 MBq). Seven days later, the patients were randomly assigned to resume the same dose of methimazole or to receive no drug therapy.

Thyroid function was assessed periodically for one year after I-131 therapy. The methimazole was discontinued after one or more months if the patient was euthyroid. Patients in the no-drug-therapy group were given methimazole if they had hyperthyroidism six or more weeks after I-131 was given. Patients in either group in whom methimazole could not be stopped were given a second dose of I-131 nine or more months after the first dose.

Results At the time of I-131 therapy, the patients in the two groups were similar in age, causes of hyperthyroidism, thyroid volume, serum free T₄ and free T₃ index values, and 24-hour thyroid I-131 uptake values.

At the end of the one year follow-up period, 84 patients (56 percent) were euthyroid, 29 (20 percent) had hypothyroidism, and 36 (24 percent) had persistent hyperthyroidism. The patients with a toxic multinodular goiter were more likely to be euthyroid (74 percent), than those with Graves' disease (33 percent). There were no differences in outcome in the methimazole and no-drug-therapy groups. For example, among the patients with Graves' disease in the methimazole group, 24 percent were euthyroid, 35 percent had hypothyroidism, and 41 percent had persistent hyperthyroidism, as compared with 38 percent, 31 percent, and 31 percent, respectively, in the no-drug-therapy group.

The mean serum free T₄ and free T₃ index values increased by approximately 30 percent three and six weeks after I-131 therapy in the no-drug-therapy group, whereas both values declined slightly in the methimazole group. Among the patients who became euthyroid, thyroid volume decreased by 43 percent (39 percent in the methimazole group and 48 percent in the no-drug-therapy group; P<0.05).

Conclusion Among patients with hyperthyroidism previously treated with methimazole, resumption of methimazole after I-131 therapy does not alter the actions of I-131, except to reduce slightly its effect on thyroid volume.

COMMENTARY

The rationales for administration of an antithyroid drug before or after I-131 therapy, or at both times, are that the drug may ameliorate hyperthyroidism sooner and reduce the likelihood of an exacerbation of hyperthyroidism as a result of radiation-induced thyroiditis, as compared with I-131 given alone. On the other hand, antithyroid drug therapy may reduce the efficacy of I-131 therapy.

In any assessment of the available data, the differences in the timing of antithyroid drug therapy in relation to I-131 therapy—before, after, or both—must be kept in mind. Among

patients pretreated with methimazole, there is little evidence that the overall duration of hyperthyroidism is shorter than in those given I-131 alone, and it does not diminish the long-term effect of I-131 (1). In this new study, in which all patients received methimazole before and methimazole or no drug after I-131 therapy, there was no difference in the efficacy of I-131 therapy. Comparable data are not available for propylthiouracil.

It is good to know that treatment with methimazole does not alter the long-term efficacy of I-131. It would be even better to have stronger evidence that it has overall benefit when given before or after I-131, or at both times, as

compared with I-131 alone. Otherwise, it complicates therapy and exposes patients to drug side effects unnecessarily.

Robert D. Utiger, M.D.

Reference

1. Andrade VA, Gross JL, Maia AL. The effect of methimazole pretreatment on the efficacy of radioactive iodine therapy in Graves' hyperthyroidism: one-year follow-up of a prospective, randomized study. *J Clin Endocrinol Metab* 2001; 86:3488-93.

Thyroxine and triiodothyronine are not more effective than thyroxine alone in patients with hypothyroidism who have depressive symptoms

Sawka AM, Gerstein HC, Marriott MJ, MacQueen GM, Joffe RT. Does a combination regimen of thyroxine (T₄) and 3,5,3'-triiodothyronine improve depressive symptoms better than T₄ alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled trial. *J Clin Endocrinol Metab* 2003;88:4551-5.

SUMMARY

Background Most patients with hypothyroidism are treated with thyroxine (T₄), but despite restoration of normal serum T₄ and thyrotropin (TSH) concentrations many continue to have some symptoms, particularly psychological symptoms, suggestive of hypothyroidism. Treatment with T₄ plus triiodothyronine (T₃) may ameliorate these symptoms. In this study the effects of T₄ alone and T₄ plus T₃ were compared in patients with hypothyroidism receiving chronic T₄ therapy who had symptoms of depression.

Methods Forty patients (36 women and 4 men; mean age, 47 years) with primary hypothyroidism (mean duration, 9 years) were studied. Specific inclusion criteria were treatment with a constant dose of T₄ for at least six months, symptoms of depression (score >5 on the General Health Questionnaire, which is designed to identify psychiatric dysfunction), and a normal serum TSH concentration. Patients with a history of hyperthyroidism, thyroid carcinoma, or any thyroid surgery were excluded. The mean daily prestudy dose of T₄ was 120 µg in the T₄ group and 132 µg in the T₄-plus-T₃ group.

The study patients were randomly assigned to receive their usual dose of T₄ once daily plus a placebo twice daily, or half their usual dose of T₄ plus T₃, 12.5 µg twice daily, for 15 weeks. The dose of T₃ was adjusted by an independent investigator to maintain normal serum TSH concentrations. The patients were evaluated using the Symptom Check-List-90 (SCL-90) and the Comprehensive Epidemiological Screens for Depression (CES-D), and serum TSH, free T₄, and free T₃ were measured, at base line and at 2, 4, 6, 9, 12, and 15 weeks. The patients were evaluated using the Short Form 36 at base line and at 6 and 15 weeks. The first two questionnaires focus on psychological symptoms. The Short Form 36 focuses on general physical and mental health and well-being; it has eight subscales and two summary scores. Neither the patients nor the examiners were aware of treatment-group assignment.

Results Thirty-three of the 40 patients (82 percent) completed the study. At the end of the study, the mean daily T₄ dose was 118 µg in the T₄ group and 67 µg in the T₄-plus-T₃ group, and the mean T₃ dose in the latter group was 19 µg. The mean base-line serum TSH, free T₄, and free T₃ concentrations were similar in the two groups. During and at the end of the study the mean serum TSH concentrations in the two groups were similar, whereas the mean serum free T₄ concentration was lower and the mean serum free T₃ concentration was higher in the T₄-plus-T₃ group at all times (Table).

In both groups, the scores for the subtests (depression, anxiety, global severity index, positive symptom total, and positive symptom distress index) of the SCL-90 test and the score for the CES-D test were similar at base line. The scores improved during the study, but there were no differences between the groups at any time. The scores for all the subscales and the summary scores of the Short Form 36 also were similar at base line, and changed little in either group (Table).

Table. Mean Serum TSH and Free T₄ Concentrations and Results of Scores for Selected Subscales of the Short Form 36 in the T₄ and T₄-plus-T₃ Groups at Base Line and after Treatment for 15 Weeks.

	T ₄ Group		T ₄ -plus-T ₃ Group	
	Base Line	15 Weeks	Base Line	15 Weeks
Serum TSH (mU/L)	2.2	1.7	1.8	1.8
Serum free T ₄ (ng/dl)*	1.3	1.4	1.2	0.8
Short Form 36**				
Physical functioning	77	77	75	79
General health	63	69	58	59
Vitality	35	51	32	51
Social functioning	70	73	55	76
Mental health	63	70	56	63

*To convert to pmol/L, multiply by 12.9.

**Scored on a scale of 0 (poorest health) to 100 (optimal health).

Conclusion In patients with hypothyroidism who have depressive symptoms despite adequate T₄ therapy, the combination of T₄ plus T₃ is no more effective than T₄ alone in ameliorating these symptoms and improving overall health and well-being.

COMMENTARY

These three studies provide strong evidence against the suggestion, first made many years ago and resurrected several years ago (1), that patients with hypothyroidism feel better when treated with T₃ and T₄ than when treated with T₄ alone.

This suggestion was based on several facts. One is that the thyroid produces and secretes both T₄ and T₃, and therefore in patients with hypothyroidism T₄ alone is inadequate replacement. This is true, even if the thyroidal component of daily T₃ production is relatively small (approximately 20 to 25 percent). To restore serum T₃ concentrations fully to

normal, one then must give enough T₄ to raise serum T₄ concentrations to the upper part of the normal range. Since little is known about tissue penetration of T₄ and T₃ and the intracellular conversion of T₄ to T₃ in different tissues, notably the brain, it is not hard to envision that T₄ alone might not restore normality. In other words, the small amount

continued on page 6

Thyroxine and triiodothyronine are not more effective than thyroxine alone in unselected patients with hypothyroidism

Walsh JP, Shiels L, Lim EM, Bhagat CI, Ward LC, Stuckey BG, Dhaliwal SS, Chew GT, Bhagat MC, Cussons AJ. Combined thyroxine/liothyronine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone: a randomized controlled trial in patients with primary hypothyroidism. *J Clin Endocrinol Metab* 2003;88:4543-50.

SUMMARY

Background In many patients with hypothyroidism thyroxine (T₄) therapy does not fully restore normal health and well-being. This study was done to determine if substitution of triiodothyronine (T₃) for some T₄ resulted in symptomatic changes in both unsatisfied and satisfied patients with hypothyroidism being treated with T₄.

Methods The study subjects were 110 patients (101 women, 9 men; mean age 48 years) with primary hypothyroidism who had been taking at least 100 µg of T₄ daily (mean dose, 136 µg) for at least two months. Based on clinical history at base line, 49 patients (45 percent) felt well and were satisfied with their treatment and 61 patients (55 percent) were dissatisfied, because of persistent symptoms such as impaired well-being, tiredness, and weight gain; all had a normal serum thyrotropin (TSH) concentration at that time. The mean duration of hypothyroidism was 8 years; 94 patients (85 percent) had chronic autoimmune thyroiditis, 12 (11 percent) had undergone thyroidectomy, and 4 (4 percent) had received iodine-131 therapy (patients with thyroid carcinoma were excluded).

The patients were randomly assigned to receive their usual T₄ dose or a 50-µg lower dose of T₄ plus 10 µg of T₃ (prepared in identical capsules) once daily for 10 weeks. This was followed by a four-week period during which the patients took their usual T₄ dose. The patients then took the opposite treatment for 10 weeks. At base line and the end of each 10-week treatment period, the patients were examined and completed three questionnaires, and serum TSH, free T₄, and free T₃ were measured. The questionnaires were the Short Form 36 (see page 5), the General Health Questionnaire (GHQ), which measures psychological dysfunction, and the Thyroid Symptom Questionnaire (TSQ), which assesses symptoms commonly present in patients taking T₄. The GHQ and TSQ are scored on a scale of 0 (symptom absent) to 3 (symptom severe). Subjective satisfaction with treatment was also assessed using a similar scale

(0, very satisfied; 3, very dissatisfied). The patients also completed 10 visual analog scales about their well-being, anxiety, and related symptoms (0 mm, bad or present; 100 mm, good or absent). Cognitive function was tested using the Symbol Digital Modalities Test, the Trail-Making Test, and the Digit Span Test. The patients and examiners were unaware of treatment-group assignment.

Results One hundred one of the 110 patients (92 percent) completed the 24-week crossover study. There were no differences in weight, blood pressure, or ankle-reflex relaxation time at any time. The mean serum TSH concentration was higher and the mean serum free T₄ concentration was lower after T₄-plus-T₃ treatment. (Table). There were no differences in the scores for the Short Form 36, GHQ, TSQ, and visual analog scales, the satisfaction scale, or the results of the cognitive function tests at the end of the two treatment periods (Table).

	T ₄ Therapy	T ₄ -plus-T ₃ Therapy
Serum TSH (mU/L)	1.5	3.1
Serum free T ₄ (ng/dl)*	1.2	0.9
Short Form 36**		
Physical functioning	48	47
General health	66	67
Vitality	53	50
Social functioning	79	80
Mental health	75	74

*To convert to pmol/L, multiply by 12.9.
**Scored on a scale of 0 (poorest health) to 100 (optimal health).

The results were similar in subgroups based on serum TSH values, satisfaction with therapy, or scores on the questionnaires or subscales of the questionnaires and tests at base line; the few differences were small and could be ascribed to multiple statistical tests.

Conclusion Combined T₄ and T₃ therapy is not more effective than T₄ alone in relieving symptoms and improving quality of life in patients with hypothyroidism.

continued from page 5

of T₃ contributed by the thyroid might be important.

The second fact is that many patients with hypothyroidism thought to be adequately treated with T₄, mostly as determined by a normal serum TSH concentration, do not feel well. The information on this point is largely but not

completely anecdotal (2); on the other hand it is clear that the frequency of symptoms suggestive of hypothyroidism differs little between people with high serum TSH concentrations and normal subjects (3). Then there are the questions of what is a patient's normal serum TSH concentration, and is there a difference

in well-being when a patient's serum TSH concentration is 0.8 or 2.8 mU/L? And is there too much reliance on serum TSH values anyhow, if only because they are easy to measure?

Whatever the merits of the above comments, Sawka, Walsh, and Clyde and their colleagues found that replacing

continued on page 7

Triiodothyronine and thyroxine are not more effective than thyroxine alone in ameliorating hypothyroid symptoms or improving cognitive function

Clyde PW, Harari AE, Getka EJ, Shakir KM. Combined levothyroxine plus liothyronine compared with levothyroxine alone in primary hypothyroidism; a randomized controlled trial. *JAMA* 2003;290:2952-8.

SUMMARY

Background This study, like those described on the preceding two pages, compared the effect of combined thyroxine (T₄) and triiodothyronine (T₃) therapy with T₄ therapy alone for four months in unselected patients with hypothyroidism.

Methods The study subjects were 44 patients (36 women, 8 men; mean age, 44 years) with primary hypothyroidism. The patients were recruited by advertisements inviting them to participate in a study of treatment of hypothyroidism. The inclusion criteria included treatment for at least six months, with no change in dose within the last three months. The mean duration of T₄ therapy was 90 months and the mean daily dose of T₄ was 128 µg. The causes of hyperthyroidism were chronic autoimmune thyroiditis (31 patients [70 percent]), iodine-131 therapy for hyperthyroidism or goiter (10 patients [23 percent]), and therapy for thyroid carcinoma, external radiation therapy, and thyroidectomy for goiter (1 patient each [7 percent]).

The patients were randomly assigned to receive their usual dose of T₄, less 50 µg, once daily and a capsule containing 25 µg of T₄ twice daily (T₄ group), or their usual dose of T₄, less 50 µg, once daily and a capsule containing 7.5 µg of T₃ twice daily, for four months. The patients were evaluated using a health-related quality of life (HRQL) questionnaire for hypothyroidism, which contains 27 questions about symptoms that may be present in hypothyroid patients and is scored on a 5-point scale (1, symptom absent; 5, symptom constantly present; mean score in 20 normal subjects, 49); standardized tests of cognitive function (attention, learning, working memory, visual coordination, manual dexterity, and word fluency); and the Beck Depression Inventory. Both the patients and examiners

were unaware of treatment-group assignment. These tests and serum thyrotropin (TSH) and free T₄ were measured at base line and at the end of treatment period. Serum TSH also was measured after 5 weeks of treatment; and the T₄ dose was adjusted by a separate physician to maintain a normal serum TSH concentration.

Results During the four-month treatment period, there were no changes in weight, heart rate, blood pressure, or serum TSH, lipid, or sex hormone-binding globulin concentrations in either group, but the serum free T₄ concentration decreased in the T₄-plus-T₃ group (Table). The hypothyroid HRQL scores decreased in both groups, but the decreases were similar in magnitude in both groups. There were no differences in the scores on the cognitive tests or the Beck Depression inventory in the two groups either at base line or at the end of the study.

Table. Mean Serum TSH and Free T₄ Concentrations, Hypothyroid HRQL Scores, and Selected Cognitive Test Results in the T₄ and T₄-plus-T₃ Groups before and after Treatment for Four Months.

	T ₄ Group		T ₄ -plus-T ₃ Group	
	Base Line	Four Months	Base Line	Four Months
Serum TSH (mU/L)	2.2	2.1	2.6	2.1
Serum free T ₄ (ng/dl)*	1.2	1.2	1.3	0.8
HRQL Score				
Logical Memory I**	45	51	44	48
Visual Reproduction I**	89	89	88	92
Word Fluency**	18	21	16	18

*To convert to pmol/L, multiply by 12.9.

**Ranges of possible scores not given. Higher scores indicate superior performances.

Conclusion In patients with hypothyroidism, treatment with T₄ plus T₃, as compared with T₄ alone, for four months has no beneficial effects on symptoms of hypothyroidism and tests of cognitive function or depression.

continued from page 6

some T₄ with some T₃ had no beneficial effects. Altogether, they studied nearly 200 patients with hypothyroidism of varying causes and duration. The patients were recruited in different ways; some apparently were asymptomatic and content with their existing treatment and some were neither. The treatment regimens and durations varied, but the patients remained euthyroid, as defined by serum TSH values. The methods of assessment of well-being, psychological and mental status, and cognitive function varied considerably (and rarely are scores for normal subjects given, a point rele-

vant to the preceding paragraph). The many variations make it difficult to compare the three studies closely, but on the other hand they make for a very strong overall conclusion—among patients with hypothyroidism replacing some T₄ with some T₃ has no beneficial effects.

Robert D. Utiger, M.D.

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Mutations in a cell-membrane thyroid hormone-transport molecule cause neurologic and thyroid abnormalities

Dumitrescu AM, Liao XH, Best TB, Brockmann K, Refetoff S. A novel syndrome combining thyroid and neurological abnormalities is associated with mutations in a monocarboxylate transporter gene. *Am J Hum Genet* 2004;74:168-75.

SUMMARY

Background Thyroxine (T₄) and triiodothyronine (T₃) must enter cells to regulate gene expression, their major if not sole action. Their entry is facilitated by transporter molecules located in the plasma membrane of the cells. One such molecule is a member of a group of monocarboxylic acid transporters (MCT), MCT8. This study describes the results of clinical and molecular studies of two families with mutations of the *MCT8* gene.

Family 1 The proband was an 8-year-old boy whose parents were normal and who was born after a normal pregnancy. He had onset of dystonia, irritability, and poor feeding within days after birth, and his subsequent development was markedly delayed. At age 2 years he could not sit, crawl, or speak, and had dystonia. He later became quadriplegic. At age 17 months, his serum TSH concentration was 4.1 mU/L, and at age 2 years it was 8.6 mU/L; he was treated with T₄, with no benefit. When studied at age 8 years and thereafter, he repeatedly had low serum total T₄ and free T₄ index, low reverse T₃, high total and free T₃, and high normal or slightly high TSH values (Table). His mother had similar but more normal values. His father, only sibling (a boy), and other maternal relatives were normal.

Family 2 The proband was a 3-year-old boy who was the product of a normal pregnancy. Neonatal screening revealed low blood-spot T₄ and normal TSH values, confirmed by serum assays on day 12. He was thought to have central hypothyroidism, and was treated with T₄. At age 3 months, he had feeding problems, disconjugate gaze, and hypertonia, and then quadriplegia. Later thyroid hormone values (while taking a low dose of T₄) were similar to those

in the proband of family 1 (Table). His mother, a maternal aunt, the maternal grandmother had similar, but more normal values; a maternal uncle had died at age 10 years with cerebral palsy and severe developmental delay.

Serum	Family 1			Family 2		
	Patient	Mother	Father	Patient	Mother	Father
T ₄ (µg/dl)	4.7	5.9	6.5	4.6	6.5	7.1
Free T ₄ index	4.8	5.7	7.5	5.7	5.5	8.0
T ₃ (ng/dl)	251	174	116	263	169	136
Reverse T ₃ (ng/dl)	7	12	20	8	12	25
TSH (mU/L)	3.9	1.6	1.2	4.8	2.9	1.1

Normal values: T₄, 5-12; free T₄ index, 6-10.5; T₃, 90-180; reverse T₃, 14-30; and TSH, 0.4-3.6. To convert serum T₄ values to nmol/L, multiply by 12.9; to convert serum T₃ and reverse T₃ values to nmol/L, multiply by 0.015.

Molecular Studies Analysis of the *MCT8* gene, which is located on the X chromosome, revealed different mutations, each likely to cause loss of function in the transporter, in the probands and their mothers in both families. In family 1, the mutant allele may have come from the maternal grandfather (who had died), or occurred very early in development of the mother. In family 2, the mutant allele was found not only in the mother, but also in a maternal aunt, the maternal uncle who had died, and the maternal grandmother.

Conclusion Mutations in the X-linked *MCT8* gene, which can transport T₄ and T₃ into cells, results in severe developmental delay and neurologic abnormalities and unusual abnormalities in thyroid function in hemizygous males and only very mild abnormalities in thyroid function in heterozygous females.

COMMENTARY

Most, if not all, cells have cell-membrane molecules that can transport carboxylic acids and amino acids, including T₄ and T₃ into the cells. There are several groups of these transporters; their distribution among tissues varies, as does their affinity for different carboxylic and amino acids. MCT8 is one of a group of 14 monocarboxylate transporters; among them it is probably the most specific transporter of T₄ and T₃. It must be expressed in neural tissue, given the clinical abnormalities in the two boys. However, these abnormalities were not those of hypothyroidism (and there was

little systemic evidence of it), suggesting that the primary role of MCT8 is to transport some other carboxylic acid(s).

What is the explanation for the abnormalities in serum thyroid hormone values in the two boys? TSH secretion might be increased as a result of decreased entry of T₄ into the thyrotroph cells of the pituitary, not compensated by the increase in type 2 deiodinase activity that results from T₄ deficiency in these cells. The excess serum T₃ could be coming from larger tissues rich in deiodinase, such as muscle, into which T₄ is carried by transporters other than MCT8, and the thyroid, as a result of TSH stimulation of deiodinase activity there. Some

other carboxylic acid normally transported by MCT8 may preferentially block T₃ transport by another transporter. Possible causes of the slightly low serum T₄ concentrations include decreased thyroidal secretion, and preferential transport of T₄ by other transporters into tissues that actively convert it to T₃ and export the T₃, which probably requires still other transporters.

Robert D. Utiger, M.D.

Thyroid radioiodine imaging is superior to ultrasonography in evaluating infants with congenital hypothyroidism

Bubuteishvili L, Garel C, Czernichow P, Leger J. Thyroid abnormalities by ultrasonography in neonates with congenital hypothyroidism. *J Pediatr* 2003;143:759-64.

SUMMARY

Background Most infants with congenital hypothyroidism have developmental abnormalities of the thyroid gland. They include thyroid agenesis, hypoplasia, and ectopic thyroid tissue, disorders collectively referred to as thyroid dysgenesis. The remaining infants have a normal or increased mass of normally located thyroid tissue that has little thyroid biosynthetic activity; these disorders are collectively referred to as thyroid dyshormonogenesis. Thyroid dysgenesis and dyshormonogenesis are customarily distinguished by radionuclide imaging. This study was done to evaluate the value of thyroid ultrasonography in distinguishing among the causes of congenital hypothyroidism.

Methods The study subjects were 66 infants with congenital hypothyroidism identified by newborn screening and confirmed by clinical examination and measurements of serum thyrotropin and free thyroxine (T_4) at age 12 ± 6 (mean \pm SD) days after birth at a single hospital in France. Thyroid imaging 30 minutes after intravenous injection of iodine-123 and thyroid ultrasonography were done at that time or soon thereafter.

Results As determined by radioiodine imaging, 42 infants (64 percent) had ectopic thyroid tissue, 12 (18 percent) had thyroid agenesis, and 12 (18 percent) had normally located thyroid tissue.

Among the 42 infants in the ectopic thyroid group, ultrasonography revealed ectopic thyroid tissue high in the neck in 9 (21 percent) and no thyroid tissue in the other 33 (79 percent). The mean serum free T_4 concentration was higher in these 9 infants than in the infants in whom no thyroid

tissue was detected by ultrasonography. Among the 12 infants who had thyroid agenesis, as determined by radioiodine imaging, ultrasonography revealed a normally located enlarged thyroid gland in one and a normally located hypoplastic thyroid gland in one.

Based on both tests, 42 infants (64 percent) had ectopic thyroid tissue, 10 (15 percent) had thyroid agenesis, and 14 (21 percent) had normally located thyroid tissue. Seven of the latter had an enlarged thyroid gland, 2 had a normal-sized thyroid gland, and 5 had an abnormal thyroid gland (hypoplasia, 1 infant; hemiagenesis of the left lobe, 2 infants; hypoplasia of the left lobe, 1 infant; and marked asymmetry of the lobes, 1 infant). In these 5 infants, ultrasonography was more informative than radioiodine imaging in defining the thyroid. All 14 infants in the group with some normally located thyroid tissue had permanent hypothyroidism, as determined by recurrence when T_4 therapy was stopped temporarily at some later time.

In all the infants with thyroid agenesis or ectopic thyroid tissue, ultrasonography revealed approximately 5×5 mm structures in the thyroid area that were isoechoic with respect to fat and hyperechoic with respect to muscle or normal thyroid tissue. Six infants in the ectopic thyroid group had cysts in the thyroid area, and four infants had tissue with the appearance of thymus in the thyroid area.

Conclusion Radioiodine imaging is more informative than thyroid ultrasonography in determining the cause of congenital hypothyroidism. However, ultrasonography reveals additional abnormalities in infants with thyroid dysgenesis that may provide insight into the causes of congenital hypothyroidism.

COMMENTARY

There has been renewed interest in the contribution of ultrasonography to the etiologic diagnosis of congenital hypothyroidism. There is general agreement that, even with the newest equipment and with the most skilled operators, ultrasonography is less sensitive than radionuclide imaging for the detection of ectopic thyroid tissue, which results fundamentally from arrested migration of the thyroid anlage into the lower neck and is the most common cause of congenital hypothyroidism.

The contribution of this and similar recent studies (1) using ultrasonography is of a more theoretical nature. The presence of structures resembling thymic

tissue in the usual location of thyroid tissue in four infants is consistent with the finding that *Hoxa-3*^{-/-} mice have abnormalities in both thyroid and thymic development (2), although pathologic confirmation of the presence of thymic tissue in this location in these infants is lacking. By contrast, the cystic structures detected in six infants probably correspond to the cystic remnants of the ultimobranchial bodies seen on histologic studies of the thyroid bed in some patients with a lingual thyroid (3).

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Central hypothyroidism occurs in infants of mothers with hyperthyroidism due to Graves' disease during their pregnancies

Kempers MJ, van Tijn DA, van Trotsenburg AS, de Vijlder JJ, Wiedijk BM, Vulsma T. Central congenital hypothyroidism due to gestational hyperthyroidism: detection where prevention failed. *J Clin Endocrinol Metab* 2003;88:5851-7.

SUMMARY

Background Congenital hypothyroidism is usually caused by thyroid dysgenesis or dysfunction, but in a few infants it is caused by hypothalamic or pituitary dysfunction. One cause of the latter is ongoing suppression of fetal hypothalamic-pituitary function by hyperthyroidism in fetuses of mothers with hyperthyroidism caused by Graves' disease. This study was done to define the clinical and biochemical abnormalities and course of infants with this type of congenital central hypothyroidism.

Methods The study subjects were 18 infants with central congenital hypothyroidism born to mothers with hyperthyroidism caused by Graves' disease. The mothers were either not treated or were inadequately treated during their pregnancies. The infants were identified through the newborn screening program in the Netherlands because they had low or normal blood-spot thyroxine (T_4) and low thyrotropin (TSH) values 4 to 14 days after birth. At recall, the diagnosis of central hypothyroidism in these infants was based on a plasma free T_4 concentration <0.9 ng/dl (12 pmol/L), a plasma TSH concentration <20 mU/L, and the presence of Graves' hyperthyroidism in the mother. Twelve of the 14 mothers (86 percent) had high plasma TSH-receptor antibody values (measured by receptor assay), as did 6 of the 11 infants (54 percent).

Results There were 12 girls and 6 boys; their gestational ages ranged from 34.6 to 40.9 weeks, and their birth weight ranged from 1840 to 3660 g. Their screening blood-spot T_4 and TSH concentrations ranged from 1.9 to 16.9 μ g/dl

(24 to 218 nmol/L) and from <1 to 5 mU/L, respectively.

The mothers and infants were divided into three groups. Nine mothers were found to have hyperthyroidism during the first weeks after delivery, usually after the infants were diagnosed as having central hypothyroidism. Thyroid function had not been assessed during pregnancy in any of these mothers. At recall all of these infants had low plasma free T_4 and normal or low plasma TSH concentrations. Four mothers were found to have hyperthyroidism during the second or third trimester of pregnancy. All had been treated with an antithyroid drug and propranolol, and three had normal plasma free T_4 concentrations at the time of delivery. At recall these infants had low plasma free T_4 and normal or low plasma TSH concentrations. Four mothers (one had a twin pregnancy) had hyperthyroidism and had been treated with an antithyroid drug before pregnancy, but only one was treated throughout pregnancy, and all had plasma free T_4 concentrations >1.7 ng/dl (22 pmol/L) during their pregnancies. At recall or later these infants had low plasma free T_4 and normal or low plasma TSH concentrations.

Seventeen infants were treated with T_4 , which was later stopped without recurrence of hypothyroidism in one infant and with recurrence in another infant. One infant became euthyroid during evaluation and was not treated.

Conclusion Infants of mothers with hyperthyroidism caused by Graves' disease may have central hypothyroidism in the neonatal period, presumably as a result of hyperthyroidism in utero.

COMMENTARY

The incidence of permanent congenital hypothyroidism in The Netherlands is approximately 1 in 20,000 infants, and most have multiple pituitary hormone deficiencies. Central congenital hypothyroidism due to inadequately treated gestational Graves' disease is estimated to occur in 1 in 35,000 newborn infants. Looked at from the perspective of Graves' hyperthyroidism in the mother, the authors estimated that 1 in 70 affected women (1.4 percent) will give birth to a child with congenital central hypothyroidism. This incidence is similar to the that of neonatal hyperthyroidism due to maternal Graves' hyperthyroidism.

Whatever the exact figures, pediatricians need to be aware of and test for

not only neonatal Graves' hyperthyroidism but also central hypothyroidism in infants of mothers with Graves' hyperthyroidism. The cause of the former is fetal and neonatal stimulation caused by transplacental passage of TSH receptor-stimulating antibodies. The cause of the latter is prolonged inhibition of thyrotropin-releasing hormone and TSH secretion by preceding hyperthyroidism, and there is no reason to doubt that it could occur in an infant who had hyperthyroidism at birth and during the first days or even weeks thereafter as well as in utero.

Infants with congenital central hypothyroidism caused by hyperthyroidism in utero and soon after birth are probably at risk for adverse neurological outcomes, like infants with congenital

thyroidal hypothyroidism. The hypothyroidism may not be permanent, but even if it lasts only a few weeks it may have a deleterious effect on neurodevelopment.

Nine of the 17 mothers (53 percent) of these 18 infants had not been diagnosed with hyperthyroidism during their pregnancies, and in others the hyperthyroidism had been poorly treated. Detecting and treating infants with congenital central hypothyroidism in the newborn period is laudable, but detecting and treating hyperthyroidism in pregnant women will lead to the best infant outcome.

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Thyroid incidentalomas may be carcinomas

Nam-Goong IS, Kim HY, Gong G, Lee HK, Hong SJ, Kim WB, Shong YK. Ultrasonography-guided fine-needle aspiration of thyroid incidentaloma: correlation with pathological findings. *Clin Endocrinol (Oxf)* 2004;60:21-8.

SUMMARY

Background Many thyroid nodules are detected incidentally, by ultrasonography or other imaging procedures done to evaluate nonthyroid problems. There has been debate as to the importance of these incidentalomas and the extent to which patients found to have them should be evaluated. This study was done to define the frequency of thyroid carcinoma and its extent in patients with incidentalomas.

Methods The study subjects were 267 patients (209 women and 58 men; mean age, 51 years [range, 26 to 75]) referred for evaluation of thyroid nodules detected by ultrasonography. None of the nodules was palpable. Nodules ≥ 0.5 cm in diameter (and some smaller nodules) were biopsied using a 21-gauge needle with ultrasound guidance. The biopsies were categorized as benign, indeterminate, suspicious for follicular tumor, suspicious for or consistent with papillary carcinoma, or inadequate. Biopsies categorized as indeterminate were those in which the cellularity was too little and the amount of colloid too large to warrant the diagnosis of suspicious for follicular tumor.

Results Three hundred seventeen nodules were biopsied in the 267 patients. These nodules ranged from 0.2 to 1.5 cm (mean \pm SD, 0.9 ± 0.3) in diameter. Twenty-five nodules were < 0.5 cm, of which 13 were ≥ 0.5 cm at the initial ultrasound study and 12 were newly detected at the time of biopsy in a patient who had a larger nodule. Overall, 130 patients (49 percent) had a solitary nodule and 137 (51 percent) had multiple nodules. The cytologic findings are shown in the Table.

Among the 29 indeterminate nodules and the 101 nodules for which the biopsy was inadequate, 22 were biopsied again; 9 biopsies revealed benign cells, 6 were indeterminate, and 7 were inadequate.

Table. Results of Ultrasound-Guided Fine-Needle Biopsies in 267 Patients with 317 Thyroid Incidentalomas.

	Nodule Diameter		
	< 0.5 (n=25)	0.5 to 0.9 cm (n=153)	≥ 1.0 to 1.5 cm (n=139)
Benign	11 (44%)	62 (40%)	66 (48%)
Indeterminate	3 (12%)	17 (11%)	9 (7%)
Papillary carcinoma	2 (8%)	22 (15%)	18 (13%)
Follicular tumor		2 (1%)	2 (1%)
Other malignant tumor*		2 (1%)	
Inadequate	9 (36%)	50 (33%)	42 (30%)

*Anaplastic carcinoma (1), lymphangioma (1).

The biopsy diagnosis was papillary carcinoma or other malignant tumor in 8 percent of the < 0.5 -cm nodules, 15 percent of the 0.5- to 1.0-cm nodules, and 14 percent in the > 1.0 - to 1.5-cm nodules. Forty of the 48 patients who had a biopsy diagnosis of papillary carcinoma or other malignancy or follicular tumor underwent surgery. All of the 35 patients with a biopsy diagnosis of papillary carcinoma had a histologic diagnosis of papillary carcinoma. Among the 3 patients with a biopsy diagnosis of follicular tumor, 1 had a follicular carcinoma, 1 medullary carcinoma, and 1 follicular adenoma. One of the other 2 patients had an anaplastic carcinoma and the other a lymphangioma.

At surgery, 16 of the 36 patients (44 percent) with papillary or follicular carcinoma had extrathyroidal extension, 18 (50 percent) had regional lymph-node metastases, and 14 (39 percent) had multifocal tumors. The frequency of these findings was similar in the patients with nodules < 1 cm and those with nodules ≥ 1 cm.

Conclusion Among patients with thyroid incidentalomas who had biopsy findings indicative of thyroid carcinoma and who underwent surgery, 12 percent had a papillary carcinoma or other malignant tumor.

COMMENTARY

Thyroid incidentalomas are, by definition, not palpable, but are identified by ultrasonography or other imaging procedures. Most are < 1 or 1.5 cm in diameter, but even larger nodules may not be palpable if the nodule is embedded within the thyroid or behind or below it.

It is standard practice to biopsy only incidental thyroid nodules ≥ 1 cm, necessarily with ultrasound guidance. This practice is based on several premises. One is that it is harder to get adequate samples from small nodules. The second

is that the proportion that are carcinomas is lower than if the nodule is bigger. Last, even if the nodule is a carcinoma, there is no penalty for delayed diagnosis. In this and other biopsy studies of incidentalomas (1), size was not a determinant of the success of biopsy, and the proportion of nodules that were carcinomas did not vary as a function of size. As for the possibility of penalty, there probably is none, notwithstanding the substantial frequency of extrathyroidal extension and regional node metastases.

Given the high frequency of thyroid incidentalomas in the population (30 to

60 percent), and the very low likelihood that those that are carcinomas will ever cause trouble, it seems wise to continue the above biopsy policy.

Robert D. Utiger, M.D.

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Serum calcitonin should be measured in all patients with thyroid nodules

Elisei R, Bottici V, Luchetti F, Di Coscio G, Romei C, Grasso L, Miccoli P, Iacconi P, Basolo F, Pinchera A, Pacini F. Impact of routine measurement of serum calcitonin on the diagnosis and outcome of medullary thyroid carcinoma: experience in 10,864 patients with nodular thyroid disorders. *J Clin Endocrinol Metab* 2004;89:163-8.

SUMMARY

Background Medullary thyroid carcinoma is rare among patients with thyroid nodules, and therefore serum calcitonin is not measured routinely in the evaluation of these patients. This study was done to determine the value of routine measurements of serum calcitonin in patients with thyroid nodules.

Methods Serum calcitonin was measured in 10,864 patients (8692 women, 2172 men; mean age, 49 years) with thyroid nodular disease seen in a single center between 1991 and 1998. The patients also underwent thyroid ultrasonography, radionuclide imaging, assessment of thyroid function, and fine-needle aspiration biopsy. In patients with a serum calcitonin concentration ≥ 20 pg/ml (assay sensitivity, 14 pg/ml; upper limit of the normal reference range, 20 pg/ml), the measurement was repeated. If the value was again high, pentagastrin (0.5 $\mu\text{g}/\text{kg}$, intravenously) was given, and serum calcitonin was measured 2, 5, 15, and 30 minutes later; a serum calcitonin concentration >60 pg/ml was considered abnormal. Thyroid surgery was recommended in patients with high basal serum calcitonin values, confirmed by a supranormal serum calcitonin response to pentagastrin, and those in whom fine-needle aspiration biopsy was suspicious for any type of thyroid carcinoma.

The results of follow-up in the patients in this group who had medullary carcinoma were compared with the results in 45 patients with medullary carcinoma diagnosed between 1970 and 1990, before serum calcitonin screening.

Results Among the 10,864 patients, basal serum calcitonin concentrations were high (20 to 6200 pg/ml) in 47 (0.4 percent). Two patients with high values had chronic

renal failure; biopsies of their thyroid nodules revealed benign thyroid cells. One patient (serum calcitonin, 30 pg/ml) refused further testing. The peak post-pentagastrin serum calcitonin concentrations in the remaining 44 patients ranged from 118 to 72,000 pg/ml.

The clinical diagnosis in 27 of these 44 patients was multinodular goiter. The biopsy diagnosis was medullary carcinoma in 13, other thyroid carcinoma in 5, and benign thyroid cells in 7; the biopsy was inadequate in 2. The clinical diagnosis in the other 17 patients was uninodular goiter. Among them, the biopsy diagnosis was medullary carcinoma in 7, other carcinoma in 4, and benign thyroid cells in 4; the biopsy was inadequate in 2. These 44 patients underwent total thyroidectomy and resection of lymph nodes in the central compartment of the neck. All but one proved to have medullary carcinoma in the nodule that was biopsied (in that patient the medullary carcinoma was in a smaller adjacent nodule). Genetic screening in 40 of the 44 patients revealed *ret* proto-oncogene mutations in 8 (20 percent).

In comparison with the 45 patients with medullary carcinoma in the 1970 to 1990 group, in whom the diagnosis was made by biopsy (2 patients) or at surgery (43 patients), the TNM tumor stage was lower in the 1991–1998 group (stage I and II, 68 vs. 44 percent). The proportion of patients with undetectable serum calcitonin concentrations three months after surgery in the 1991–1998 group was higher (66 vs. 3 percent), and the mortality was lower (by 6 years after surgery the mortality rate was 4 percent in the 1991–1998 group and 33 percent in the 1970–1990 group).

Conclusion Routine measurement of serum calcitonin should be included in the routine evaluation of patients with thyroid nodules.

COMMENTARY

It is clear from this and other studies that routine measurement of serum calcitonin in patients with thyroid nodules identifies some sporadic medullary carcinomas that might otherwise be missed, either because of biopsy misdiagnosis or because the carcinoma is elsewhere in the thyroid gland. This doesn't happen often, because these tumors are rare and most can be identified by biopsy.

According to surveys of members of the European Thyroid Association and the American Thyroid Association, 43 percent of the former but only 5 percent of the latter order measurements of serum calcitonin in patients with thyroid

nodules (1,2). Why the difference (assuming that physicians do what they say they do)? Some possibilities are that physicians in the United States are more conservative in ordering tests (true for patients with thyroid nodules), unaware of this value of serum calcitonin measurements (maybe, because virtually all the surveys have been done in Europe), unable to confirm a high basal serum calcitonin value because pentagastrin is not available (unlikely), or satisfied with biopsy (maybe). Whatever the explanation, it may be time to reconsider.

Robert D. Utiger, M.D.

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Preoperative ultrasonography is valuable for detecting lymph-node metastases and local recurrence in patients with thyroid carcinoma

Kouvaraki MA, Shapiro SE, Fornage BD, Edeiken-Monro BS, Sherman SI, Vassilopoulou-Sellin R, Lee JE, Evans DB. Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. *Surgery* 2003;134:946-55.

SUMMARY

Background Many patients with differentiated thyroid carcinoma have involvement of cervical lymph nodes, either at diagnosis or later. Later recurrences may be minimized by better detection of nodal involvement and resection of involved nodes. This study compared the value of physical examination and ultrasonography for the detection of local and regional metastases in patients with differentiated thyroid carcinoma and medullary thyroid carcinoma.

Methods The medical records of all patients with differentiated or medullary carcinoma who underwent ultrasonography of the neck before surgery between 1991 and 2003 were reviewed. The patients were divided into three groups according to whether their surgery was for initial therapy (group 1), persistent disease, defined as reoperation within six months after initial surgery (group 2), or recurrent disease, defined as reoperation more than six months after initial surgery (group 3).

Lymph nodes seen at ultrasonography were considered benign if they were oval or elongated, had a smooth cortex, and a central fatty hilum. They were considered malignant if they were round or if the central hilum was absent or truncated. Lymph node size was not a criterion of malignancy.

Results There were 212 patients (145 women and 67 men; median age at the time of diagnosis, 43 years [range, 5 to 86]), of whom 130 (61 percent) had papillary carcinoma, 21 (10 percent) follicular (including Hurthle-cell) carcinoma, and 61 (29 percent) medullary carcinoma. Among the 151 patients with differentiated carcinoma, 85 (56 percent) were in group 1, 18 (12 percent) in group 2, and 48 (32 percent) in group 3. Among the 81 patients with medullary carcinoma, 22 (36 percent) were in group 1, 10 (16 percent) in group 2, and 29 (48 percent) were in group 3.

Ultrasonography revealed lymph-node metastases or soft-tissue recurrence in 113 of the 212 patients (53 percent). Biopsy was done in 69 of these 113 patients (61 percent); 64 biopsies were positive for tumor. Ultrasonography revealed lymph-node metastases or local recurrence not detected by physical examination in 52 of the 151 patients (34 percent) with differentiated carcinoma and 30 of the 61 patients (49 percent) with medullary carcinoma; the discrepancy was most marked in the patients in group 3.

Lymph nodes containing tumor or tumor involving soft tissue were removed from 183 of the 212 patients (86 percent); the other 29 patients did not undergo surgery because of lack of evidence of tumor on both physical examination and ultrasonography. Tumor was found at these sites in 50 of 83 patients (60 percent) in group 1, all of 24 patients (100 percent) in group 2, and all of 76 patients (100 percent) in group 3. The sensitivity and specificity of ultrasonography for detecting tumor in lymph nodes in the central, ipsilateral, and contralateral lymph-node compartments ranged from 52 to 79 percent and 93 to 96 percent, respectively. The results of ultrasonography were falsely negative in 74 patients (35 percent)—47 of the 151 patients (31 percent) with differentiated carcinoma and 27 of the 61 patients (44 percent) with medullary carcinoma. The surgical procedure was altered by the results of ultrasonography in 82 of the 212 patients (39 percent).

During a median follow-up period of 36 months (range, 1 to 140 months), 16 of the 207 patients (8 percent) for whom data were available had recurrence of tumor in the neck.

Conclusion In patients with thyroid carcinoma, ultrasonography of the neck often reveals lymph-node metastases and recurrences in soft tissue not detectable by physical examination, and therefore leads to more extensive tumor removal.

COMMENTARY

It is no surprise that ultrasonography, whether done before initial surgery or before reoperation, reveals lymph node metastases and other deposits of tumor that cannot be palpated in patients with thyroid carcinoma. In this study, it led to more extensive surgery fairly often, implying that surgeons do not look closely at all three node-bearing locations in

the neck (the central compartment and the two lateral compartments) in many patients. This is perhaps understandable in patients with stage I or II tumors undergoing their first operation (74 patients in this study), but is less so in those patients with higher-stage tumors or those undergoing reoperation. Whether survival is altered by a more extensive operation, no matter why it is done, is of course not known, but the

need for additional operations for later recurrences in the neck should be reduced, and surely that is to patients' advantage.

Robert D. Utiger, M.D.

The rise in serum thyroxine binding during pregnancy in women with hypothyroidism only partly explains their increased need for thyroxine

Zigman JM, Cohen SE, Garber JR. Impact of thyroxine-binding globulin on thyroid hormone economy during pregnancy. *Thyroid* 2003;12:1169-75.

SUMMARY

Background Thyroid secretion increases during pregnancy in normal women, and many women with hypothyroidism who are being treated with thyroxine (T₄) need higher doses to maintain normal serum thyrotropin (TSH) concentrations when they are pregnant. One postulated mechanism for the increased need for T₄ during pregnancy is that serum thyroxine-binding globulin (TBG) concentrations increase, reducing serum free T₄ concentrations, and therefore more T₄ is needed to restore serum free T₄ concentrations to normal. This case report describes a woman with hypothyroidism and familial TBG deficiency who needed an increase in T₄ dose during pregnancy.

Case Report The patient was a 42-year-old woman who was found to have hypothyroidism (serum TSH concentration, 86 mU/L; serum total T₄ concentration, 2.2 µg/dl [28 nmol/L]) in 1991. In 1993, while taking 0.125 mg of T₄ daily, her serum TSH concentration was low (0.03 mU/L) and her serum total T₄ concentration was normal (7.1 µg/dl [92 nmol/L]). T₄ therapy was stopped, with recurrence of mild hypothyroidism; at the same time she had a triiodothyronine (T₃)-resin uptake value of 44 percent (normal, 24 to 37) and her serum TBG concentration was <1.0 mg/dl (normal, 1.2 to 3.0). T₄ therapy was resumed. The patient's parents and a sister were said to have hypothyroidism, and a nephew to have congenital hypothyroidism that later resolved; TBG deficiency was suspected but not documented in any of them.

In 1999, the patient had a normal term pregnancy. At two-months' gestation, while taking 0.112 mg of T₄ daily, her serum TSH concentration was 4.1 mU/L. The dose was raised to 0.112 mg nine times per week, after which her serum TSH concentrations were normal, her serum total T₄

concentrations were normal (for nonpregnant women), and her serum free T₄ index values were normal. Her serum TBG concentration near term was 1.3 mg/dl (normal, 1.7 to 3.6). At term, she delivered a normal baby girl. Two months postpartum, her serum TBG concentration was 0.5 mg/dl.

She had another pregnancy in 2002. Her serum hormonal values and doses of T₄ during and after this pregnancy are shown in the Table. This child was a boy, who had an undetectable serum TBG concentration and a normal serum TSH concentration, documenting the presence of X-linked TBG deficiency in this family.

Table. Serum TSH, Free T₄ Index, and TBG Values and T₄ Doses during and after Pregnancy in a Woman with Partial TBG Deficiency.

	Month of Pregnancy					Postpartum
	1	3	5	7	9	Month 4
Serum TSH (mU/L)	3.2	1.5	4.7	2.2	2.8	0.08
Serum free T ₄ index	2.8	2.2	2.4	1.8	2.1	2.3
Serum TBG (mg/dl)	0.1	0.9	1.5	1.4	1.7	0.5
Dose of T ₄ (mg/day)		0.1	0.1	0.114*	0.114*	0.1

Normal serum values: TSH, 0.35 to 5.5 mU/L; free T₄ index, 1.8 to 3.8; and TBG, 1.7 to 3.6 mg/dl.
*0.1 mg eight times/week.

The patient's serum TBG concentrations ranged from 0.3 to 0.7 mg/dl when she was not pregnant and from 0.9 to 1.7 mg/dl when she was pregnant, the mean increase was 1.0 mg/dl (mean increase in normal women, 2.0 mg/dl). In contrast, her need for 15 to 30 percent more T₄ during her pregnancies approximated that of other women with spontaneously occurring hypothyroidism.

Conclusion The need for higher doses of T₄ during pregnancy in women who have hypothyroidism is not caused solely by the pregnancy-induced increase in serum TBG concentrations.

COMMENTARY

Many, but not all, women with hypothyroidism being treated with T₄ need higher doses during pregnancy (1). The likelihood of a need for more T₄ depends on multiple variables. One is the severity of hypothyroidism. Others include the prepregnancy level of replacement, how the women are assessed and what results lead to changes in therapy, and possible changes in absorption of T₄ (pregnant women are often given iron and calcium supplements that can reduce T₄ absorption).

Still others are the extent of the rise in serum TBG concentrations, loss of T₄ to the fetus, and extent of placental 5-deiodination of T₄ to reverse T₃ and of T₃ to 3,3'-diiodothyronine.

This woman needed a substantial increase in T₄ dose during her pregnancies. The conclusion that she needed more T₄ than would be expected simply from the increase in serum TBG concentrations can be questioned, but is plausible. It is supported by the infrequent and very small changes indicative of hypothyroidism that occur when women with hypothyroidism being treated with T₄ are

given estrogen and have an increase in their serum TBG concentrations (2).

Robert D. Utiger, M.D.

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Painless thyroiditis may be followed by recurrence of hyperthyroidism in patients with Graves' disease

Iitaka M, Morgenthaler NG, Momotani N, Nagata A, Ishikawa N, Ito K, Katayama S, Ito K. Stimulation of thyroid-stimulating hormone (TSH) receptor antibody production following painless thyroiditis. *Clin Endocrinol (Oxf)* 2004;60:49-53.

SUMMARY

Background Thyroid inflammation may not only be caused by autoimmune thyroid disease, but may also induce or exacerbate it. In this study patients with painless thyroiditis were followed to determine if the inflammatory process led to the onset or recurrence of hyperthyroidism caused by Graves' disease.

Methods The study subjects were 92 patients with painless thyroiditis, as defined by transient hyperthyroidism and a painless diffuse goiter; 24-hour radioiodine uptake, measured in 88 patients, was low. Among them, 40 patients (39 women and 1 man; mean [\pm SD] age, 33 ± 11 years) had a history of Graves' hyperthyroidism. Nineteen were in remission after prolonged antithyroid drug therapy; they had onset of painless thyroiditis 33 ± 22 months (range, 13 to 122) after the therapy was stopped (in 10 the onset of thyroiditis was postpartum). The other 21 patients with a history of Graves' hyperthyroidism had stopped antithyroid drug therapy during a pregnancy; they had the onset of painless thyroiditis 8 ± 2 months (range, 4 to 12) after therapy was stopped. Fifty-two patients (43 women, 9 men; mean age, 40 ± 14 years) with painless thyroiditis had no history of Graves' disease.

All the patients were followed for at least six months after the onset of painless thyroiditis. Serum thyrotropin (TSH), free thyroxine (T_4), free triiodothyronine (T_3), and TSH receptor antibodies were measured on several occasions. The antibodies were measured as TSH binding-inhibitory immunoglobulins (TBII) using recombinant human TSH receptors (normal, ≤ 10.4 percent inhibition of TSH binding to the receptors). Recurrent hyperthyroidism after the episode of painless thyroiditis was confirmed by a high

24-hour radioiodine uptake or a rise in serum thyroid hormone and TBII values.

Results At the time of diagnosis of painless thyroiditis, the mean serum free T_4 and free T_3 concentrations were similar in the patients with and those with no history of Graves' hyperthyroidism.

The serum TBII values in the patients with a history of Graves' hyperthyroidism, measured 2 to 12 months before the onset of painless thyroiditis, were normal. At the onset of painless thyroiditis, their mean serum TBII value was 7.7 ± 9.8 percent, and the value in the patients with no history of Graves' hyperthyroidism was 1.4 ± 5.4 percent ($P=0.001$). Twelve of the 40 patients (30 percent) with a history of Graves' hyperthyroidism had high serum TBII values, as compared with 3 of the 52 patients (6 percent) with no history of Graves' hyperthyroidism.

Seven of the 40 patients (18 percent) who had a history of Graves' hyperthyroidism had recurrent hyperthyroidism 8 to 10 weeks after the onset of painless thyroiditis (two in the long-term remission group and five in the group that stopped therapy during pregnancy). At the onset of painless thyroiditis, the mean serum TBII value in the 7 patients who had recurrent hyperthyroidism was 17.0 ± 11.8 percent, as compared with 5.6 ± 8.0 percent in the 33 patients who did not have recurrent hyperthyroidism. No patient in the group with no history of Graves' hyperthyroidism developed hyperthyroidism during follow up.

Conclusion Patients with Graves' hyperthyroidism who are in remission may have a recurrence of Graves' hyperthyroidism after an episode of painless thyroiditis.

COMMENTARY

These results indicate that painless thyroiditis, whether postpartum or otherwise, can reactivate production of TSH receptor-stimulating antibodies, and therefore be followed by recurrent hyperthyroidism in patients with Graves' hyperthyroidism who are in remission, but it does not cause production of these antibodies or Graves' hyperthyroidism de novo. At the onset of painless thyroiditis, the patients with a history of Graves' hyperthyroidism—although euthyroid—presumably had less tolerance to thyroid antigens. Therefore, antigen release

induced by thyroid inflammation evoked an increase in production of TSH receptor-stimulating antibodies, and in some of them recurrence of Graves' hyperthyroidism. The relatively low frequency of recurrent hyperthyroidism in this group may have been due to variations in the completeness of remission at the onset of thyroiditis, variations in the severity or duration of painless thyroiditis, continued thyroid injury that limited thyroid responsiveness to TSH receptor-stimulating antibodies, or production of TSH receptor-blocking rather than TSH receptor-stimulating antibodies.

Thyroid injury can occasionally cause Graves' hyperthyroidism, for example, in patients with Hodgkin's disease treated with external radiation and in patients with a nontoxic nodular goiter treated with radioiodine. Painless thyroiditis alone does not seem to do so, as exemplified by this study and by the limited long-term studies of women who had postpartum thyroiditis. So it would seem that the susceptibility of the host is more important than the nature of any thyroid injury in evoking Graves' hyperthyroidism.

Robert D. Utiger, M.D.

Seasonal allergic rhinitis may be followed by recurrent hyperthyroidism in women with Graves' disease

Takeoka K, Hidaka Y, Hanada H, Nomura T, Tanaka S, Takano T, Amino N. Increase in serum levels of autoantibodies after attack of seasonal allergic rhinitis in patients with Graves' disease. *Int Arch Allergy Immunol* 2003;132:268-76.

SUMMARY

Background Allergic rhinitis induced by Japanese cedar pollen is a seasonal disorder that has been associated with high serum immunoglobulin (Ig) E concentrations, as has Graves' disease. This study was undertaken to determine the effect of seasonal allergic rhinitis on the clinical course and serum concentrations of antithyroid antibodies in patients with hyperthyroidism caused by Graves' disease. In Japan, cedar pollens are disseminated in February and March.

Methods The study subjects were 10 women aged 19 to 58 years with Graves' hyperthyroidism in the past; six were in remission and four were euthyroid while taking a low dose of methimazole. Five of the women had a history of seasonal allergic rhinitis caused by Japanese cedar pollen. The women were evaluated clinically and biochemically at 2- to 4-month intervals from August 1999 (or 2000) to December 2000 (or 2001). The evaluations included measurements of peripheral blood eosinophil counts and serum cedar-pollen-specific IgE (normal, ≤ 0.34 U/ml); thyrotropin (TSH)-receptor antibodies (measured by receptor assay; normal, ≤ 1 U/L); and antithyroid peroxidase, antithyroglobulin, and antistreptolysin O antibodies.

Results At base line, all five women with allergic rhinitis, but not the other five women, had high serum cedar-pollen-specific IgE concentrations. All of the women in the former group, but none in the latter group, had an episode of allergic rhinitis the following March. This episode was followed by increases in eosinophil counts and serum concentrations

of cedar-pollen-specific IgE and, slightly later, anti TSH-receptor antibodies (Table), and, even later, antithyroid peroxidase and antithyroglobulin antibodies. Serum antistreptolysin O concentrations did not change in either group.

Table. Peripheral Blood Eosinophil Counts and Serum Antibody Concentrations during Follow-up.

	Eosinophil Count (cells/mm ³)		Cedar-Pollen IgE (U/ml)		TSH-Receptor Antibody (U/L)	
	Nov-Jan	Apr-May	Nov-Jan	May-June	Nov-Jan	Jun-Oct
Allergic rhinitis	174	396	15.6	25.1	1.1	13.1
No allergic rhinitis	166	151	<0.34	<0.34	1.5	1.7

Values are means of two or three measurements in each patient during each time interval. Undetectable values assigned the lowest detectable value for each assay.

Among the five women who had allergic rhinitis, three had substantial increases in serum TSH-receptor antibody concentrations (all values were undetectable in the other two women). The first woman developed subclinical hyperthyroidism, and she ultimately resumed methimazole therapy. The second woman also had subclinical hyperthyroidism, which resolved coincident with a fall in the serum antibody concentration. The third woman had overt hyperthyroidism, and she also resumed therapy. None of the women who did not have allergic rhinitis had as much as a twofold rise in serum TSH-receptor antibody concentrations or recurrent hyperthyroidism during the study period.

Conclusion Seasonal allergic rhinitis induced by cedar pollen may be followed by an increase in serum concentrations of TSH-receptor and other antithyroid antibodies and recurrent hyperthyroidism in women with Graves' disease.

COMMENTARY

Is there a specific relationship between seasonal allergic rhinitis, or more specifically, seasonal allergic rhinitis induced by cedar pollen, and Graves' hyperthyroidism, or was the increase in serum TSH-receptor and other antithyroid antibody concentrations in these women simply a nonspecific anamnestic response initiated by the allergic reaction? The answer is not known. Thyroid injury can initiate and also reactivate production of these antibodies and lead to hyperthyroidism (see p. 15). There is no evidence for thyroid injury during the course of allergic rhinitis, but onset of Graves' hyperthyroidism after an episode of allergic rhinitis has been reported (1). No other allergic disorders have been linked to Graves' hyperthyroidism, but has

anyone looked carefully?

There are some other relevant data. High serum IgE concentrations were found in 41 of 107 Japanese patients (38 percent) with Graves' hyperthyroidism. Among those with high baseline serum IgE values, methimazole therapy was less effective in inducing remission, and it resulted in long-term remission less often, than in those with normal values (1). And in a study of Japanese patients with Graves' hyperthyroidism in remission after antithyroid drug therapy, recurrences were clustered from March through August (3).

It is time to look closely for a relationship between allergic disorders, not just allergic rhinitis, and Graves' disease, and not only in Japan.

Robert D. Utiger, M.D.

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Cerebrospinal fluid concentrations of antithyroid antibodies are high in Hashimoto's encephalopathy

Ferracci F, Bertiato G, Moretto G. Hashimoto's encephalopathy: epidemiologic data and pathogenetic considerations. *J Neurol Sci* 2004;217:165-8.

SUMMARY

Background Hashimoto's encephalopathy is usually defined as the presence of encephalopathy in a patient who has a high serum concentration of antithyroid peroxidase or antithyroglobulin antibodies. This study was done to determine the frequency of high cerebrospinal fluid (CSF) concentrations of these antibodies in patients with neurologic disorders.

Methods From January, 2000, to October, 2002, 1978 patients with an acute confusional state, progressive cognitive impairment, stroke, or seizures were evaluated at a single hospital in Italy. Serum samples were obtained from those patients with unexplained encephalopathy or myelopathy for measurements of antithyroid peroxidase and antithyroglobulin antibodies. In those patients with high serum concentrations of one or both antibodies, the antibodies were measured in CSF. The antibodies were also measured in the serum and CSF of 26 patients with other neurologic disorders (8 patients with multiple sclerosis, and lesser numbers of patients with headache, suspected meningoencephalitis, peripheral neuropathy, hemichorea, Hashimoto's thyroiditis and headache (1 patient), and Hashimoto's thyroiditis and ptosis (1 patient)).

The diagnosis of Hashimoto's encephalopathy was based on the presence of neurologic abnormalities and a high CSF concentration of one or both antithyroid antibodies. The diagnosis of Hashimoto's thyroiditis was based on a high serum antithyroid antibody concentration and the results of

thyroid ultrasonography and biopsy.

Results Among the 1978 patients, 143 had the findings that warranted measurements of serum antithyroid antibodies. Twelve of these 143 patients (8 percent) had a high serum concentration of one or both antithyroid antibodies. Nine of the 12 patients had high CSF concentrations of one or both antithyroid antibodies, and therefore were considered to have Hashimoto's encephalopathy. There were 8 women and 1 man, ranging in age from 17 to 77 years. Six had Hashimoto's thyroiditis, 1 a goiter, and 1 a history of hypothyroidism; all had normal thyroid function.

The symptoms in the nine patients considered to have Hashimoto's encephalopathy were: confusion, 5; impaired consciousness, 3; paresthesias, 3; memory loss, 2; ataxia, 2; sensory deficit, 2; paraparesis, 1; and hemiparesis, 1. The serum to CSF ratio of antithyroid peroxidase antibodies ranged from 1 to 109, and ratio for antithyroglobulin antibodies ranged from 1 to 44. Four patients were treated with glucocorticoids, two of whom improved, as did four of the five patients who were not treated.

Three of the patients in the control group, including the two patients with Hashimoto's thyroiditis, had high serum antithyroid antibody concentrations, but no antithyroid antibodies were detected in their CSF.

Conclusion Hashimoto's encephalopathy should be diagnosed only in patients with high CSF concentrations of antithyroid antibodies.

COMMENTARY

Brain et al., in the conclusion of their 1966 paper describing the first patient with encephalopathy and high serum antithyroid antibody concentrations, concluded that "Antibody studies in future cases of unexplained encephalopathy should show whether we have described a syndrome or a coincidence" (1). Since then, several hundred patients with these two findings, and often other neurologic abnormalities as well (seizures, focal deficits, myoclonus, and so on), have been reported under the rubric Hashimoto's encephalopathy. A 2003 review in which the case definition was rather rigid—clouding of consciousness (with or without other symptoms), no evidence of CSF infection, and a high

serum concentration of any antithyroid antibody—yielded 83 cases (2).

Ferracci et al. propose a new, less exclusive, definition—neurologic abnormalities and a high CSF concentration of an antithyroid antibody. Excluding a requirement for encephalopathy (four of the patients did not have clouding of consciousness or even confusion), no matter what other neurologic abnormalities are present, will not make it easier to clarify the disorder. Furthermore, no one has determined the specificity of a high CSF antithyroid antibody concentration as an indicator of any neurologic disorder.

High serum and perhaps CSF antithyroid antibody concentrations seem to be a marker for some type of encephalopathy, but what the fundamen-

tal problem might be is not known. Whether the antibodies define a syndrome or are a coincidence remains unanswered.

Robert D. Utiger, M.D.

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Iodine deficiency continues to be a major health problem worldwide

De Benoist B, Andersson MA, Takkouche B, Egli I. Prevalence of iodine deficiency worldwide. *Lancet* 2003;362:1859-60.

SUMMARY

Background Iodine deficiency is the most common cause of preventable mental deficiency in the world, despite efforts to increase iodine intake in many countries. This study summarizes the results of surveys of iodine nutrition conducted by the World Health Organization (WHO) in the past decade in many countries.

Methods Data were collected on urinary iodine excretion, measured in spot urine samples, in many countries from 1993 to 2003. The country-wide prevalence of iodine deficiency, defined as urinary iodine excretion <100 µg/L, was then estimated. These estimates were based on the extent of sampling within the country (local, regional, or national) and the people who were studied (children, adults, pregnant women). The data and the details of this analysis can be seen at <http://www3.who.int/whosis/micronutrient/> (accessed March 15, 2004 [ed]).

Results Data on urinary iodine excretion were available from 192 WHO member states, representing 92 percent of the world's population. Worldwide, based on population

estimates for 2002, more than 1.9 billion people were iodine-deficient (Table). They included 285 million school-age children (6 to 12 years), representing 36 percent of all school-age children.

	All Ages (×10 ⁶)	School-Age Children (×10 ⁶)
Africa	260 (43%)	49 (42%)
Americas	75 (10%)	10 (10%)
Eastern Mediterranean	228 (54%)	40 (55%)
Europe	435 (57%)	42 (60%)
Southeast Asia	624 (40%)	96 (40%)
Western Pacific	365 (24%)	47 (26%)
Total	1,989 (35%)	284 (36%)

There was considerable regional variation in the prevalence of iodine deficiency. The prevalence was lowest in the Americas and highest in Europe. These prevalence rates correlate with estimates of the proportions of households in which iodized salt is consumed, which are 90 percent in the Americas and 27 percent in Europe.

Conclusion Iodine deficiency continues to be common in most regions of the world.

COMMENTARY

This useful summary agrees generally with other information on global iodine nutrition, for example, that collected by the International Council for the Control of Iodine Deficiency Disorders (1). All such information is fragmentary, because national surveys of iodine nutrition are not conducted in many countries. For example, people living in remote rural areas are often not surveyed, or are underrepresented in the surveys that are done, and therefore substantial iodine deficiency in these areas may be overlooked. Also, staying current is a major challenge: governmental policies regarding iodine supplementation and monitoring and agricultural and animal husbandry practices that involve some use of iodine may change. Therefore information that is only a few years old may be out of date.

Iodine intake is best supplemented by iodization of salt, and salt iodization should be mandated wherever adequate iodine nutrition is not being met from other sources. And regular monitoring of iodine nutrition is essential, because

change can occur quietly and unpredictably, like the approximately 50 percent decrease in iodine intake in the United States between 1971-4 and 1988-94 (2).

The best available measure of iodine nutrition in a population is the median urinary iodine concentration, measured in spot urine samples. These measurements are often done in schoolchildren, certainly an important group, but they should also be done on a more widespread basis, particularly in pregnant women. This is when iodine deficiency has its most damaging effects, and therefore when the need for an adequate iodine intake is the greatest. Iodine nutrition is also monitored by collection of data on production of iodized salt and surveys of household use of iodized salt. These measures help to document implementation of iodine supplementation, but do not address iodine nutrition per se.

Recent progress to improve iodine nutrition in many countries has been substantial, but nonetheless many people in many countries are still iodine-deficient. This short article by de Benoist et al. helps by highlighting the remarkable durability of a condition that has devas-

tating, but entirely preventable, effects on both individual people and societies.

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Short-term ingestion of kelp has a weak antithyroid effect in normal subjects

Clark CD, Bassett B, Burge MR. Effects of kelp supplementation on thyroid function in euthyroid subjects. *Endocr Pract* 2003;9:363-9.

SUMMARY

Background High doses of iodine have a weak antithyroid action in normal subjects, and can cause either hypothyroidism or hyperthyroidism in patients with thyroid disease. Kelp is a type of seaweed that contains large amounts of both inorganic and organic iodine. It is eaten as food or consumed in encapsulated form as a nutritional supplement. Given its iodine content, it has the potential to cause thyroid dysfunction. In this study the effects of kelp on thyroid function were determined in normal subjects.

Methods Thirty-six normal subjects (18 women, 18 men; mean age, 33 years) were randomly assigned to take four capsules of kelp (high-dose kelp group), two capsules of alfalfa and two capsules of kelp (low-dose kelp group), and four capsules of alfalfa (control group) daily for four weeks. The iodide content of the kelp capsules was 330 µg. Serum thyrotropin (TSH), free thyroxine (T₄), and triiodothyronine (T₃) were measured at base line and four weeks, and two weeks after cessation of kelp ingestion. At base line and four weeks, serum TSH was measured 30 minutes after the intravenous injection of thyrotropin-releasing hormone (TRH); urinary iodide and creatinine excretion and basal metabolic rate were also measured at these two times.

Results The characteristics of the subjects in the three groups were similar. In the kelp groups, the mean serum TSH concentration increased and the mean serum free T₄

concentrations did not change. The mean serum T₃ concentration decreased slightly in the high-dose kelp group (by 13 ng/dl [0.2 nmol/L]; P=0.04). The serum TSH response to TRH increased only in the high-dose kelp group. Urinary iodide excretion increased substantially in both kelp groups. In the alfalfa group, the mean serum TSH and T₃ concentrations did not change (Table), but the mean serum free T₄ concentration decreased slightly, from 1.2±0.1 to 1.0±0.2 ng/dl (15±1 to 13±2 pmol/L, P=0.01). There was no change in basal metabolic rate in any group.

Table. Mean (±SD) Serum TSH Concentrations and Urinary Iodide Excretion in the High- and Low-Dose Kelp and Alfalfa Groups.

		High-Dose Kelp Group	Low-Dose Kelp Group	Alfalfa Group
Serum TSH (mU/L)	Base line	1.8±1.1	1.5±0.5	1.4±0.6
	4 weeks	2.5±1.3	2.1±0.4*	1.7±1.0*
Serum TSH response to TRH (mU/L)	Base line	15.8±7.8	11.8±4.9	12.5±5.4
	4 weeks	20.1±9.0	15.0±8.9	12.5±5.1*
Urinary iodide (µg/g creatinine)	Base line	190±89	223±98	229±140
	4 weeks	982±224	545±77*	233±170*

*P≤0.04, as compared with the high-dose kelp group.

Two weeks after kelp ingestion was stopped, serum TSH, free T₄, and T₃ concentrations were similar to those at base line, except that the serum TSH concentration was lower in the high-dose kelp group (1.3±0.8 vs. 1.8±1.1 mU/L at base line; P<0.05).

Conclusion Ingestion of kelp for four weeks has a weak antithyroid action, manifested by a small increase in TSH secretion, in normal subjects.

COMMENTARY

The very weak antithyroid effect of kelp taken daily for four weeks by these normal subjects is similar to that of comparable and higher doses of inorganic iodine given for several weeks or months (1-3). Therefore, it is unlikely that any other constituents of kelp contributed to the changes.

Might these few capsules of kelp, taken chronically as a nutritional supplement, cause clinically important thyroid dysfunction? Possibly. Patients with some thyroid disorders, notably patients with chronic autoimmune thyroiditis or radiation-damaged thyroid glands, are more sensitive to the antithyroid actions of iodine than are normal subjects, and they may develop overt hypothyroidism when given inorganic or organic iodine. These antithyroid actions are inhibition of T₄

and T₃ synthesis and inhibition of thyroglobulin proteolysis, and hence release of T₄ and T₃ from the thyroid gland. Conversely, patients with poorly functioning thyroid adenomas and multinodular goiters are at risk for iodine-induced hyperthyroidism. This prothyroid action of iodine is due to the diffusion of iodine, when extracellular iodine concentrations are high, into thyroid cells that have little iodine transport capacity.

The iodine doses associated with both iodine-induced hypothyroidism and iodine-induced hyperthyroidism have usually been large, e.g. many milligrams per dose or per day, and the minimum dose that has either antithyroid or prothyroid actions in patients with thyroid dysfunction is not known (but is probably low).

Robert D. Utiger, M.D.

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Megalyn-mediated removal of thyroid hormone-poor thyroglobulin facilitates thyroid hormone secretion

Lisi S, Pinchera A, McCluskey RT, Willnow TE, Refetoff S, Marcocci C, Vitti P, Menconi F, Grasso L, Luchetti F, Collins AB, Marino M. Preferential megalin-mediated transcytosis of low-hormonogenic thyroglobulin: a control mechanism for thyroid hormone release. *Proc Natl Acad Sci USA* 2003;100:14858-63.

SUMMARY

Background Thyroglobulin, located in the lumen of thyroid follicles, is both the site of synthesis and the site of storage of thyroxine (T_4) and triiodothyronine (T_3). It subsequently re-enters thyroid follicular cells in one of two ways. One is by fluid-phase endocytosis, with formation of colloid droplets that then fuse with lysosomes, after which it undergoes proteolysis and its constituent T_4 and T_3 are released into the extracellular space and ultimately reach the circulation. The other is by receptor-mediated uptake. The receptor is megalin, a thyrotropin (TSH)-dependent transmembrane protein located in the apical membrane of thyroid follicular cells. Thyroglobulin binds to megalin, and the megalin–thyroglobulin complex is then internalized and carried across the cell to the basolateral membrane (transcytosis), where the thyroglobulin, bound to a fragment of megalin, is released into the extracellular space. This may be the major pathway by which thyroglobulin reaches the circulation. This study was done to determine whether the hormonal content of thyroglobulin affects its megalin-mediated uptake and transcytosis.

Methods and Results Rat thyroglobulin (Tg) containing no T_4 and T_3 (hormone-poor Tg) was taken up by and passed through confluent rat thyroid (FRTL-5) cells grown on a filter to a lower chamber to a greater extent than was Tg containing T_4 and T_3 (hormone-rich Tg), and the increase was blocked when anti-megalyn antibodies were added. Hormone-poor Tg reduced the transcytosis of hormone-rich Tg to a greater extent than hormone-rich Tg reduced the transcytosis of hormone-poor Tg.

Addition of hormone-rich Tg to the cells resulted in the appearance of some T_3 in the lower chamber, indicative of proteolysis of Tg. Co-addition of anti-megalyn antibodies, but not control antibodies, increased the content of T_3 in the lower chamber, indicating more proteolysis of hormone-rich Tg despite inhibition of megalin-mediated uptake and transcytosis of Tg. Co-addition of hormone-

poor Tg, however, did not increase the T_3 content in the lower chamber, indicating that it was less effective than anti-megalyn antibodies in diverting hormone-rich Tg into the proteolytic pathway.

In mice lacking both alleles of the gene for megalyn, serum TSH concentrations were higher and serum Tg concentrations were lower than in heterozygous mice (which are normal), whereas their serum free T_4 concentrations were similar (n=3 in each group).

In rats given aminotriazole to inhibit thyroid peroxidase and T_4 to prevent TSH hypersecretion, the thyroidal content and distribution of megalyn, as determined by immunofluorescence, was similar to that in control rats. Serum TSH and T_3 concentrations were similar in the two groups, but serum Tg concentrations were higher in the treated rats. Serum Tg in both groups was immunoprecipitated by anti-Tg antibodies, but only in the serum of the treated rats was the Tg immunoprecipitated by anti-megalyn antibodies, presumably because more of the Tg had reached the circulation via transcytosis.

In thyroid tissue from patients with Graves' hyperthyroidism, megalyn immunostaining was more intense than in normal thyroid tissue. In 13 patients who had been treated with methimazole for three months and were euthyroid and had normal serum TSH concentrations, serum TSH receptor antibody concentrations were lower (but still high) and serum Tg concentrations were the same as before treatment (approximately 200 ng/ml). The proportion of serum Tg that was bound to megalyn, as determined by the reduction in serum Tg concentrations after adsorption with anti-megalyn antibodies, increased after treatment.

Conclusion The megalyn pathway of thyroglobulin metabolism in the thyroid gland may serve to eliminate hormone-poor thyroglobulin from the gland, and therefore increase proteolysis of hormone-rich thyroglobulin.

COMMENTARY

The megalyn pathway of Tg metabolism in thyroid follicular cells seems to facilitate the transfer of Tg from the follicular lumen to the circulation. However, it seems unlikely that the pathway exists simply for this purpose. Circulating Tg has no biologic actions, and even if hormone-rich, the amounts of T_4 and T_3 in it are so small that complete extrathy-

roidal proteolysis of the Tg would add negligibly to the serum pools of T_4 and T_3 . What seems more likely is that the megalyn pathway serves to divert hormone-poor Tg and perhaps Tg that is abnormal in other ways away from the Tg proteolytic pathway that provides the free T_4 and T_3 that are secreted. This assumes that the capacity of the proteolytic pathway to break down Tg is limited, or that the amounts of abnormal Tg are large, so

that a pathway for shunting these forms of Tg away from the proteolytic pathway is needed to keep the latter open for hormone-rich Tg.

The role of megalyn is just beginning to unfold, but it already seems clear that it is more than just a way to carry normal, hormone-rich Tg out of the thyroid.

Robert D. Utiger, M.D.

Thyroid Review Articles

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Corrections

The carpal tunnel syndrome is a feature of hypothyroidism, but several other musculoskeletal disorders are not associated with thyroid dysfunction (November 2003:49). The last line in the Table should have read "Overt hypothyroidism", and not "Overt hyperthyroidism".

Low maternal serum free thyroxine concentrations are a risk factor for delayed infant neurodevelopment (November 2003:58). Lines 2 and 3 of the Conclusion should read "...low serum free T₄ concentrations at 12 weeks of gestation, ...", not "10 weeks".

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