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ATA News

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13th International Thyroid Congress
October 30 to November 4, 2005
Buenos Aires, Argentina

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Multinodular goiter is the most common cause of subclinical, but not overt, hyperthyroidism in elderly patients

Diez JJ. Hyperthyroidism in patients older than 55 years: an analysis of the etiology and management. Gerontology 2003:49:316-23.

SUMMARY

Background Several thyroid disorders cause hyperthyroidism, and their frequency varies according to patient age and type of hyperthyroidism. This study evaluated the cause of hyperthyroidism in patients aged ≥55 years.

Methods The study subjects were 313 consecutive patients (246 women, 67 men; age, ≥55 years) with overt or subclinical hyperthyroidism seen at a single clinic in Madrid, Spain. Overt hyperthyroidism was defined as a serum thyrotropin (TSH) concentration <0.4 mU/L and a serum free thyroxine (T_4) concentration >2 ng/dl (26 pmol/L), and subclinical hyperthyroidism as a serum TSH concentration <0.4 mU/L and a serum free T_4 concentration of 0.75 to 2.0 ng/dl (10 to 26 pmol/L). The cause of hyperthyroidism was determined, based on the results of clinical, serologic, thyroid radionuclide uptake and imaging studies, and thyroid ultrasonography at the time of diagnosis.

Results There were 263 patients with spontaneously occurring hyperthyroidism, of whom 165 were previously diagnosed and 98 were newly diagnosed, and 50 patients with iatrogenic hyperthyroidism. At the time of diagnosis, 167 patients had overt hyperthyroidism and 146 patients had subclinical hyperthyroidism. Multinodular goiter was the most common cause of subclinical hyperthyroidism, whereas Graves' disease was the most common cause of overt hyperthyroidism (Table 1).

There were substantial differences in the characteristics of the patients with the three most common causes of hyperthyroidism, particularly with respect to whether the patient had overt or subclinical hyperthyroidism (Table 2).

Table 1. Causes of Hyperthyroidism in 313 Patients ≥55 Years Old.

	Hyperthyroidism (n=313)
Multinodular goiter	135 (43%)
Graves' disease	67 (21%)
Thyroid adenoma	37 (12%)
Iatrogenic hyperthyroidism	50 (16%)
Iodine-induced hyperthyroidism	5 (1%)
Subacute thyroiditis	3 (1%)
Painless thyroiditis	1 (0.3%)
Factitious hyperthyroidism	1 (0.3%)
TSH-secreting pituitary adenoma	2 (1%)
Unknown	12 (4%)

Table 2. Characteristics of Patients with Nodular Goiter, Graves' Disease, and Thyroid Adenoma.

	Age (yr)		Sex		Hyperthyroidism	
	55-64	≥65	Women	Men	Overt	Subclinical
Multinodular goiter (n=135)	46 (34%)	89 (66%)	116 (86%)	19 (14%)	58 (43%)	77 (57%)
Graves' disease (n=67)	35 (52%)	32 (48%)	43 (64%)	24 (36%)	63 (94%)	4 (6%)
Thyroid adenoma (n=37)	17 (46%)	20 (54%)	27 (73%)	10 (27%)	32 (86%)	5 (14%)

Among the patients with previously diagnosed hyperthyroidism, all 93 patients with overt hyperthyroidism had been treated. Most of those with Graves' disease were treated with an antithyroid drug, whereas most of those with a multinodular goiter or thyroid adenoma were treated with iodine-131. Among the 72 patients with previously diagnosed subclinical hyperthyroidism, most of whom had a multinodular goiter, 67 had not been treated. How the newly diagnosed patients were treated is not stated.

Conclusion Among elderly patients seen in a thyroid clinic, multinodular goiter is the most common cause of subclinical hyperthyroidism, and almost as common as Graves' disease as a cause of overt hyperthyroidism.

COMMENTARY

The principal finding of this study of hyperthyroidism in older people was the high frequency of multinodular goiter among the patients with subclinical hyperthyroidism. This can probably be attributed to marginal iodine intake. Given that this was a six-year study, and that most of the patients with subclinical hyperthyroidism were not treated, it is unfortunate that nothing is said about the evolution of subclinical to overt hyperthyroidism. At present, little is known about the frequency of this evolution. In the same vein, one wonders about the occurrence of cardiac rhythm and other cardiac disturbances in the untreated patients with subclinical hyperthyroidism during follow-up. Treatment is sometimes advised to prevent these disturbances, as well as progression to overt hyperthyroidism, but the long-term value of treatment for preventing either these disturbances or progression is not known.

One important clinical finding was the low frequency of goiter (36 percent), as detected by palpation, in patients with Graves' disease. Though not a new finding (1), it reinforces the importance of basing evaluation for hyperthyroidism on the presence of symptoms and signs of thyroid hormone excess, not on the presence (or absence) of thyroid enlargement. On the other hand, palpable thyroid enlargement was noted in 90 percent of patients with multinodular goiter and 81 percent of those with a thyroid adenoma, and it could well have been 100 percent.

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Reference

1. Trivalle C, Doucet J, Chassagne P, et al. Differences in the signs and symptoms of hyperthyroidism in older and younger patients. J Am Geriatr Soc 1996;44:50-3.

Ingestion of ground beef patties prepared by gullet trimming can cause hyperthyroidism

Parmar MS, Sturge C. Recurrent hamburger thyrotoxicosis. CMAJ 2003;169:415-7.

SUMMARY

Background Ingestion of high doses of thyroid hormone is a well known cause of hyperthyroidism. Less known is that hyperthyroidism can be caused by ingestion of meat that includes thyroid tissue. This case report describes a woman who had recurrent hyperthyroidism caused by ingestion of such meat.

Case Report A 61-year-old woman was seen in 2001 because of a three-week history of weight loss (4 kg), palpitations, and increased perspiration. Physical examination revealed tachycardia and tremor, but no thyroid enlargement or ophthalmopathy. Her serum free thyroxine (T_4) concentration was high (3.6 ng/dl [46 pmol/L]) and her serum thyrotropin (TSH) concentration was low (0.02 mU/L). She had a normal erythrocyte sedimentation rate, normal serum antithyroid antibody (type not specified) and TSH-binding inhibitory immunoglobulin concentrations, and a low serum thyroglobulin concentration. She improved spontaneously, and eight weeks later her serum free T_4 concentration was normal (0.9 ng/dl [12 pmol/L]).

Review of her history revealed that this was the woman's fifth episode of hyperthyroidism in the preceding 10 years. These episodes had occurred at approximately two-year intervals, and each was characterized by symptoms of hyperthyroidism that lasted 8 to 12 weeks. She had low radioiodine uptake values and normal serum antithyroid antibody concentrations during the first and several subsequent episodes, and her serum thyroglobulin concentration was low during the episode in 1998. She had low normal serum free T_4 concentrations and high normal or slightly high serum TSH concentrations after hyperthyroidism during several of the episodes.

Based on the above findings, a source of exogenous thyroid hormone ingestion was sought. The patient and her husband lived on a farm in Ontario, and their main source of meat was beef from a cow that they slaughtered every two or three years. The butcher prepared ground meat from the muscles of the larynx (gullet trimmings), unaware that gullet trimming had been prohibited. The patient, but not her husband, usually ate patties prepared from this ground meat within a few months after the butcher prepared it, and none was available for analysis.

Conclusion Periodic ingestion of meat products contaminated with thyroid tissue can cause recurrent hyperthyroidism mimicking silent thyroiditis.

COMMENTARY

The initial episode of hyperthyroidism in this woman was attributed to silent (painless) thyroiditis. That was quite reasonable; her hyperthyroidism was mild, she probably had no goiter (at least she did not during the fifth episode), her thyroid radioiodine uptake was low, and the hyperthyroidism subsided in a few weeks. Attributing subsequent episodes to silent thyroiditis is more problematic; repeated recurrences of this disorder are rare except in women with postpartum thyroiditis, in whom the likelihood of recurrence after a subsequent pregnancy is high.

The key clue that this patient's recurrent hyperthyroidism was not caused by thyroiditis was a low serum thyroglobulin value during the 1998 and 2001 episodes. Measurements of serum thyroglobulin are rarely indicated in patients who do not have thyroid carcinoma. Among adults the only exception is to distinguish between exogenous hyperthyroidism, in which the concentrations are low (as in this woman), and endogenous hyperthyroidism, in which the concentrations are always high (whatever the cause). Among infants with congenital hypothyroidism, these measurements help to distinguish between thyroid agenesis and dysgenesis as causes of hypothyroidism.

There have been two small epidemics of meat (hamburger)-induced hyperthyroidism, both many years ago (1,2). The explanation for both proved to be the same as described here, the inclusion of thyroid tissue in neck muscle in ground meat patties. Analysis of several samples of the ground meat implicated in one of the epidemics revealed a mean T_4 concentration of 11 μg/g and a triiodothyronine concentration of 0.7 μg/g (1); a quarter-pound hamburger (114 g) would contain 1254 μg T_4 and 80 μg T_3. Given these values, a person eating one or more of these hamburgers daily or every other day for a week or so might well have symptomatic hyperthyroidism.

This case serves as a reminder that thyroid hormone can be obtained from unexpected sources. In addition to ground meat, they include nutritional supplements, herbal products, and so-called fat burners.

Robert D. Utiger, M.D.

References

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2. Kinney JS, Hurwitz ES, Fishbein DB, et al. Community outbreak of thyrotoxicosis: epidemiology, immunogenetic characteristics, and long-term outcome. Am J Med 1988;84:10-8.

Prolonged low-dose antithyroid drug therapy is associated with a high remission rate in patients with hyperthyroidism caused by Graves' disease

Kashiwai T, Hidaka Y, Takano T, Tatsumi K, Izumi Y, Shimaoka Y, Tada H, Takeoka K, Amino N. Practical treatment with minimum maintenance dose of anti-thyroid drugs for prediction of remission in Graves' disease. Endocr J 2003;50:45-9.

SUMMARY

Background Many patients with hyperthyroidism caused by Graves' disease are treated with an antithyroid drug, in anticipation that the disease will remit (disappear), so that the patient remains euthyroid after therapy is stopped. However, there is no simple, reliable way to determine if a remission has occurred. This study was designed to determine the likelihood of sustained remission in patients who remained euthyroid during treatment with a low dose of an antithyroid drug for a prolonged period (six months).

Methods The study subjects were 57 patients (44 women, 13 men; mean age, 48 years) with hyperthyroidism caused by Graves' disease. All were treated initially with 30 mg of methimazole or 300 mg of propylthiouracil daily. The dose was reduced to 20 or 200 mg daily, respectively, after the patients' serum free T_4 and triiodothyronine (T_3) concentrations fell to within their respective normal ranges. The dose was further reduced to 5 mg of methimazole or 50 mg of propylthiouracil every other day over an interval of three to six months if the serum free T_4 values remained normal and serum TSH values were normal or high. This every-other-day regimen was given for at least six months, and then stopped if the patient had normal serum free T_4 and TSH concentrations during this interval. The patients were followed for two years therafter.

Serum free T_4, free T_3, and TSH were measured once or twice monthly for the first six months after therapy was stopped, and then every three to four months for 18 months. Serum thyroid-binding inhibitory immunoglobulins (TBII) and thyroid-stimulating antibodies (TSAb) were measured by radioreceptor assay and bioassay, respectively, when therapy was stopped. Patients who had high serum free T_4 or T_3 concentrations or low serum TSH concentrations during the six-month minimal-dose treatment period were given a higher dose of drug, and the protocol for every-other-day low-dose therapy was resumed. Recurrent hyperthyroidism after therapy was stopped was defined as high serum free T_4 and T_3 concentrations and low serum TSH concentrations.

Results Among the 57 patients who completed this antithyroid drug regimen, 46 (81 percent) remained euthyroid and 11 (19 percent) had recurrent hyperthyroidism during the two-year follow-up period (Table). The recurrence was within eight months in 9 of the 11 patients (82 percent). The serum free T_4, free T_3, and TSH concentrations were similar in the groups at the time therapy was stopped.

Table. Clinical and Biochemical Data at the Time Antithyroid Drug Therapy Was Stopped in 57 Patients with Graves' Hyperthyroidism.

	Remission (n=46)	Recurrence (n=11)
Age-yr	49±10	45±10
Women/men	34/12	10/1
Serum free T_4-ng/dl	1.2±0.2	1.2±0.2
Serum free T_3-ng/dl	0.4±0.1	0.4±0.05
Serum TSH-mU/L	2.1±1.1	1.5±0.8
Total duration of therapy-mo	74±39	60±3

Values are means (±SD). To convert serum free T_4 and free T_3 values to pmol/L, multiply by 12.9 and 15.4, respectively.

When therapy was stopped, serum TBII values were high in 4 of the 46 patients (9 percent) who remained euthyroid and 6 of the 11 patients (54 percent) who had recurrent hyperthyroidism. At the same time, the serum TSAb values were high in 23 of the patients who remained euthyroid (50 percent) and 9 of the patients who had recurrent hyperthyroidism (82 percent).

Conclusion Prolonged low-dose antithyroid therapy is associated with a high remission rate in patients with hyperthyroidism caused by Graves' disease.

COMMENTARY

The two-year remission rate of 81 percent in these patients is impressively high, but it applies only to the 57 patients who successfully completed the planned course of therapy, and a long course at that. What patients want to know, of course, is the overall probability of remission before any therapy is given, not the probability of remission after they have been treated for months or years.

From a practical perspective, it is prudent to treat patients with a low dose of antithyroid drug for several months before stopping therapy, documenting that they have not only normal serum thyroid hormone concentrations but also normal serum TSH concentrations. This demonstrates that their thyroid secretion is no longer TSH-independent, whatever the results of measurements of serum TSH-receptor antibodies. With respect to the latter, this study demonstrates once again that these measurements have little value for predicting whether a patient is likely to have recurrent hyperthyroidism or remain well after therapy is stopped (1).

Robert D. Utiger, M.D.

Reference

1. Feldt-Rasmussen U, Schleusener H, Carayon P. Meta-analysis evaluation of the impact of thyrotropin receptor antibodies on long term remission after medical therapy of Graves' disease. J Clin Endocrinol Metab 1994;78:98-102.

Persistent production of thyrotropin receptor-stimulating antibodies may inhibit thyrotropin secretion during antithyroid drug therapy in patients with Graves' hyperthyroidism

Brokken LJ, Wiersinga WM, Prummel MF. Thyrotropin receptor autoantibodies are associated with continued thyrotropin suppression in treated euthyroid Graves' disease patients. J Clin Endocrinol Metab 2003;88:4135-8.

SUMMARY

Background Thyrotropin (TSH) secretion is inhibited in nearly all patients with hyperthyroidism, and the inhibition may persist for weeks or even months after thyroid secretion is reduced to normal or below normal by antithyroid therapy. In patients with hyperthyroidism caused by Graves' disease, TSH receptor-stimulating antibodies may contribute to this inhibition. These investigators have presented evidence that folliculostellate cells in the pituitary have TSH receptors, and they hypothesize that TSH-receptor-stimulating antibodies may inhibit TSH secretion by activating these receptors, causing the cells to signal the thyrotrophs of the pituitary to inhibit TSH secretion. This study was designed to test this hypothesis by relating TSH secretion to the serum concentrations of free thyroxine (T_4), triiodothyronine (T_3), and TSH receptor-stimulating antibodies in patients with Graves' hyperthyroidism during antithyroid drug therapy.

Methods The study subjects were 45 patients with hyperthyroidism caused by Graves' disease, as defined by high serum free T_4 and T_3 concentrations, low serum TSH concentrations, diffuse thyroid radionuclide uptake, and high serum concentrations of TSH receptor-stimulating antibodies, measured as TSH-binding inhibitory immunoglobulins (TBII) (normal, ≤12 U/L). The patients were treated with an antithyroid drug (mostly methimazole), and subsequently T_4 was added, with the goal of normal serum free T_4 and T_3 concentrations and serum TSH concentrations ≤4 mU/L. Serum TBII were measured again after the patients had been euthyroid for at least three months while receiving combined therapy, and the values were correlated with the serum free T_4, T_3, and TSH values at that time.

Results All patients were clinically and biochemically euthyroid when restudied after treatment for 7±4 months. At that time, serum TBII values were normal in 25 patients (mean, 5 U/L) and high (mean, 30 U/L in 20 patients (Table). At base line, the serum thyroid hormone and TSH values were similar in these two groups, but the serum TBII values were higher in the latter group (mean, 52 vs. 14 U/L).

Table. Serum TBII and TSH Values in Patients with Graves' Hyperthyroidism, According to the Serum TBII Values When Euthyroid during Therapy.

	Normal Serum TBII (n=25)	High Serum TBII (n=20)	P Value
Serum TBII value at base line-mean (range)	14 U/L (5-114)	52 U/L (19-400)	<0.001
Serum TSH value at base line-mean (range)	<0.01 mU/L (<0.01-0.04)	<0.01 mU/L (<0.01-0.19)	0.28
Serum TBII during therapy-mean (range)	5 U/L (3-12)	30 U/L (17-278)	<0.001
Serum TSH during therapy-median (range)	0.8 mU/L (0.01-4.2)	0.09 mU/L (<0.01-4.3)	0.02

At the seventh-month study, the mean serum free T_4 and T_3 values and doses of T_4 were similar in the two groups, but the serum TSH values were significantly higher in the group with normal serum TBII values than in the group with high serum TBII values (lower line, Table). The serum TSH and TBII values in all patients were negatively correlated at this time (P=0.004).

Conclusion In patients with Graves' hyperthyroidism serum TSH concentrations may remain low despite restoration of euthyroidism because of persistent production of TSH receptor-stimulating antibodies.

COMMENTARY

Though not its purpose, this study demonstrates once again that antithyroid drug therapy is associated with a decrease in TSH receptor-stimulating antibodies, whether caused by amelioration of hyperthyroidism, an immunosuppressive action of antithyroid drugs, or simply passage of time.

The results of the study suggest that TSH receptor-stimulating antibodies inhibit TSH secretion, perhaps by the paracrine mechanism outlined above (1). They provide one explanation for why serum TSH concentrations may remain low in patients with Graves' hyperthyroidism after they become euthyroid during antithyroid drug therapy. Another explanation is that thyroid secretion, even though within the normal range, has not fallen below the set point for TSH secretion in that patient. Finally, the severity and duration of hyperthyroidism, and therefore the extent and duration of inhibition of TSH secretion, vary, and both are likely to play a role in determining the rate of recovery of TSH secretion.

A paracrine pathway for inhibition of TSH secretion activated by TSH receptor-stimulating antibodies could also potentially slow the onset of hyperthyroidism in patients with Graves' disease, by speeding inhibition of TSH secretion. But when activated by TSH it would slow the rise in TSH secretion in patients with hypothyroidism, thereby reducing the thyrotropic effect of TSH and speeding the onset of hypothyroidism. So activation of this pathway, if is exists, must be easily overridden by the effects of thyroid hormone excess or deficiency on the hypothalamus and pituitary.

Robert D. Utiger, M.D.

Reference

1. Prummel MF, Brokken LJ, Meduri G, et al. Expression of the thyroid-stimulating hormone receptor in the folliculostellate cells of the human anterior pituitary. J Clin Endocrinol Metab 2000;85: 4347-53.

Thyroid dysfunction can be detected by umbilical cord blood sampling in fetuses of mothers with Graves' disease

Nachum Z, Rakover Y, Weiner E, Shalev E. Graves' disease in pregnancy: prospective evaluation of a selective invasive treatment protocol. Am J Obstet Gynecol 2003;189:159-65.

SUMMARY

Background In pregnant women, Graves' disease can result in fetal hyperthyroidism or hypothyroidism. The former is caused by transplacental passage of thyrotropin (TSH) receptor-stimulating antibodies (TSHR-SAb), and the latter by transplacental passage of antithyroid drugs. This study evaluated the efficacy of a protocol designed to maintain normal thyroid function in fetuses of mothers with Graves' disease.

Methods All pregnant women with Graves' disease cared for at a single center from 1991 through 2002 were followed prospectively. The follow-up included serial measurements of maternal serum TSH, free thyroxine (T_4) and TSHR-SAb, and monthly ultrasound studies to determine fetal heart rate, growth, and goiter. Umbilical cord blood sampling was recommended if the maternal serum TSHR-SAb concentration was >10 U/L, or if the fetus had tachycardia, goiter, growth retardation, or hydrops; TSH and free T_4 were measured in the fetal serum samples.

If fetal hyperthyroidism was present, the mother was given more antithyroid drug or treatment was started. If fetal hypothyroidism was present, the mother was given less antithyroid drug. If this was ineffective, T_4 was injected into the amniotic fluid at a dose of 500 μg biweekly. Umbilical cord blood sampling was repeated two to four weeks later, and treatment modified as appropriate. It was not repeated if the fetus was euthyroid and ultrasonography was normal. At delivery, the infant was examined and cord blood was collected for measurements of serum TSH and free T_4.

Results During the study period there were 40,000 deliveries at this center. Twenty-four of the deliveries (26 infants) were from 18 women with Graves' disease (1:1700, or 0.06 percent). There were two twin pregnancies, two women had two pregnancies, and one woman had four pregnancies. Sixteen women took propylthiouracil during part or all of their pregnancies, and 13 took T_4, having previously been treated with iodine-131 (I-131). Maternal serum TSHR-SAb concentrations were high during 13 pregnancies in eight women.

None of the criteria for umbilical cord blood sampling was met in 12 fetuses, and at delivery all the infants were normal. For 14 fetuses, one or more criteria were met, most commonly a high maternal serum TSHR-SAb concentration, plus tachycardia or goiter in four fetuses. Nine mothers gave consent for the sampling (done first at 20 to 33 weeks' gestation). There were no complications. The results were normal in four fetuses. Two fetuses had hyperthyroidism; their cord serum free T_4 concentrations were 4.1 and 2.3 ng/dl (53 and 30 pmol/L, respectively, extrapolated from Figure 1). Both mothers had been treated with I-131 and were taking T_4; propylthiouracil was then given, with improvement of the fetuses. One of these infants had neonatal hyperthyroidism, and was treated with propylthiouracil for three weeks after delivery. Three fetuses had hypothyroidism; their cord serum TSH concentrations were 100, 14, and 10 mU/L. All three mothers were taking propylthiouracil; it was reduced or stopped, and intraamniotic T_4 was later given to one of these infants. All three infants were normal at birth. The fetuses of the mothers who declined umbilical cord sampling grew normally and were normal at birth.

All the children, followed for up to nine years, developed normally.

Conclusion Measurements of TSH and free T_4 in serum collected by umbilical cord blood sampling are helpful for recognizing thyroid dysfunction in fetuses whose mothers have Graves' disease.

COMMENTARY

The statement above that "Graves' disease can result in fetal hyperthyroidism or hypothyroidism" is an oversimplification, because it is not only the disease but also the treatment for hyperthyroidism that affects the fetus. The mother must have Graves' disease, and she must be producing thyroid-stimulating antibodies. She has to have had hyperthyroidism at some time. That time could be now, in which case she may be taking an antithyroid drug, or she may have hypothyroidism and be taking T_4, having been treated with I-131 or thyroidectomy in the past. Since both the antibodies and antithyroid drugs cross the placenta, the fetus may have either hyperthyroidism or hypothyroidism. Neither cross the placenta readily, however, so many fetuses are not affected.

The finding of thyroid dysfunction in five of the nine fetuses who underwent umbilical cord blood sampling is offered as evidence that the procedure, and the therapy that was based on it, were beneficial. But it is an invasive procedure that is not needed to justify therapy, which in any event is best avoided unless there is compelling evidence of fetal harm. Fetal hyperthyroidism can be suspected, as noted by the authors, on the basis of a high maternal serum TSHR-SAb antibody concentration, fetal tachycardia, and certain ultrasound abnormalities, and some fetuses have been treated on the basis of these findings alone. Fetal hypothyroidism may be suspected if ultrasonography reveals fetal goiter and poor growth and the mother is taking an antithyroid drug, and it can be treated by reducing or stopping the drug. The keys are very conservative treatment of the mother and careful observation of the fetus.

Robert D. Utiger, M.D

Complete thyroid ablation reduces the activity of Graves' ophthalmopathy

Moleti M, Mattina F, Salamone I, Violi MA, Nucera C, Baldari S, Lo Schiavo MG, Regalbuto C, Trimarchi F, Vermiglio F. Effects of thyroidectomy alone or followed by radioiodine ablation of thyroid remnants on the outcome of Graves' ophthalmopathy. Thyroid 2003;13:653-8.

SUMMARY

Background Ophthalmopathy is an integral component of Graves' disease, although it is less common than hyperthyroidism, and its occurrence may depend on the presence of thyroid tissue if not thyroid dysfunction. This study was done to evaluate the effect of thyroid ablation in patients with Graves' ophthalmopathy.

Methods The study subjects were 55 patients (44 women, 11 men; age range, 23 to 78 years) with hyperthyroidism caused by Graves' disease and mild or moderate ophthalmopathy, as defined by mild-to-moderate periorbital swelling, intermittent diplopia, proptosis <24 mm, and a limited decrease in visual acuity. After treatment of hyperthyroidism with methimazole, they underwent total or near-total thyroidectomy; the indications for surgery were a large goiter, recurrent hyperthyroidism, or a thyroid nodule with biopsy suspicious for carcinoma. Sixteen patients in whom differentiated carcinoma was seen in the resected thyroid tissue received iodine-131 (I-131) after surgery. All were treated with thyroxine (T_4); the goal of treatment was a serum thyrotropin (TSH) concentration of 0.5 to 1.5 mU/L in those without and 0.1 mU/L in those with carcinoma.

For the purpose of this study, the patients were divided into those with active ophthalmopathy and those with inactive ophthalmopathy, on the basis of their Clinical Activity Score. This score ranges from 0 to 7 points, one point being given for each of the following; eyelid swelling, chemosis, swollen caruncle, conjunctival hyperemia, eyelid hyperemia, deep eye pain, and pain on upward or downward gaze. Active ophthalmopathy was defined as a score of 3 points or more. The score was determined at the time of surgery (base line) when the patients were euthyroid, and at 6, 12, and 24 months after surgery.

Results At base line, 31 patients had active eye disease (mean [±SD] score, 4.2±0.8), and 24 had inactive eye disease (mean score, 1.7±0.4). The mean age (about 50 years), percentage of smokers (about 25 percent), duration of ophthalmopathy (about 12 months), and duration of methimazole therapy before surgery (about 12 months) were similar in both groups.

In the 31 patients with active eye disease, the Clinical Activity Score decreased from 4.2±0.8 to 2.5±1.6 at 6 months ($P<0.01$), 2.3±1.8 at 12 months, and 2.1±2.0 at 24 months. At 6 months, 19 patients (61 percent) had inactive eye disease (score, <3 points). At 24 months, 22 patients (71 percent) had inactive eye disease. In the 24 patients with inactive eye disease, the Clinical Activity Score increased slightly, from 1.7±0.4 at base line to 1.9±2.1 at 24 months. In 9 patients (38 percent), the eye disease became active during the 24-month follow-up period.

Among the 39 patients treated by thyroidectomy alone, the base-line Clinical Activity Score was 3.0±1.4, and 20 patients (51 percent) had active eye disease. At 24 months, the disease was still active in 18 of these patients (46 percent). Among the 16 patients treated with surgery and I-131, the baseline Clinical Activity Score was 3.3±1.5, and 11 patients (69 percent) had active eye disease. At six months, only two patients (12 percent) had active eye disease, and at 24 months no patient in this group had active eye disease.

Conclusion In patients with Graves' ophthalmopathy, the eye disease becomes inactive more often in patients treated with thyroidectomy and I-131 than in those treated with thyroidectomy alone.

COMMENTARY

Does thyroidectomy (and I-131 therapy) have an effect on ophthalmopathy? Put another way, does the presence of thyroid tissue have an effect on ophthalmopathy? Ophthalmopathy does not appear or worsen more often after subtotal thyroidectomy than during antithyroid drug therapy (1), but might it appear or worsen less often after more complete thyroid destruction? In this study, near- total thyroidectomy alone was followed by a decrease in activity score in those patients with active eye disease, but activity increased in a few patients with inactive eye disease at base line. All these patients probably had some remaining thyroid tissue, and the changes in activity of eye disease might well have occurred in patients whose hyperthyroidism was treated in another way.

The patients with active eye disease who were treated with surgery and I-131 probably had complete thyroid ablation. They had a decrease in activity in 6 months, and all had inactive eye disease at 24 months. They improved despite the fact that they all had hypothyroidism for several weeks before the administration of I-131. Among patients given I-131 as treatment for hyperthyroidism, the onset or worsening of ophthalmopathy has been attributed to transient hypothyroidism after I-131 therapy, rather than I-131 therapy itself. The decrease in activity in this group argues against an effect of either hypothyroidism or I-131 itself to worsen ophthalmopathy. It does argue for the hypothesis that complete elimination of thyroid tissue somehow ameliorates ophthalmopathy—whether by eliminating most TSH receptors or many thyroid-sensitized T lymphocytes.

Robert D. Utiger, M.D.

Reference

1. Tallstedt L, Lundell G, Torring O, et al. Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. N Engl J Med 1992;326:1733-8.

The prevalence of hypothyroidism may be increased among outpatients with HIV infection

Beltran S, Lescure FX, Desailloud R, Douadi Y, Smail A, El Esper I, Arlot S, Schmit JL, and the Thyroid and VIH Group. Increased prevalence of hypothyroidism among human immunodeficiency virus-infected patients: a need for screening. Clin Infect Dis 2003;37:579-83.

SUMMARY

Background Several types of thyroid dysfunction have been found in patients with human immunodeficiency virus (HIV) infection, the type depending at least in part on the severity of the infection and its clinical consequences. This study was a survey of the prevalence of thyroid dysfunction in a cohort of patients with HIV infection receiving antiretroviral drug therapy. Then, the characteristics of the patients with hypothyroidism and those with normal thyroid function were compared in a case–control study.

Methods The study subjects were 350 patients with HIV infection seen in seven outpatient clinics in France between May and December 2001. Thyroid function was assessed by measurements of serum thyrotropin (TSH), free thyroxine (T_4), and free triiodothyronine (T_3). The patients were categorized as having overt hypothyroidism, subclinical hypothyroidism, overt hyperthyroidism, subclinical hyperthyroidism, and low serum free T_4 (low serum free T_4 and normal TSH concentrations). The clinical characteristics of the patients with hypothyroidism and those with low serum free T_4 were then compared with those of the patients with normal thyroid function.

Results The 350 patients included 114 women and 236 men (mean [±SD] age, 41±10 years). Among them, 287 (82 percent) had normal thyroid function and 56 (16 percent) had hypothyroidism. The hypothyroid group included 9 patients (3 percent) with overt hypothyroidism, 23 (6 percent) with subclinical hypothyroidism, and 24 (7 percent) with low serum free T_4 values. The prevalence of subclinical hypothyroidism was higher in men than in women (19 men [8 percent) vs. 4 women [4 percent]). One patient had a low serum free T_3 value, three had a high serum free T_3 value, two had subclinical hyperthyroidism, and one had high serum free T_3 and TSH values; these seven patients were excluded from the case–control study.

The ratio of women to men and the mean age, body mass index and plasma HIV level were similar in the 287 patients with normal thyroid function and the 56 patients with hypothyroidism. The patients with hypothyroidism had been infected longer (9.4 vs. 7.7 years), and their CD4 cell count was lower (384 vs. 488 cells/mm^3). There were differences between these groups in the type of antiretroviral drug therapy (Table), but the cumulative doses were similar. In multivariate analysis, treatment with stavudine and a low CD4 cell count were associated with hypothyroidism.

Table. Risk Factors for Hypothyroidism among Outpatients with HIV Infection.

	Hypothyroidism (n=56)	Normal Thyroid Function (n=287)	Odds Ratio (95%CI)
CD4 cell count ≤200/mm^3	18 (32%)	43 (13%)	2.5 (1.4-4.4)
Highly active anti-HIV therapy	51 (91%)	227 (79%)	2.7 (1.0-7.1)
Stavudine	41 (73%)	149 (52%)	2.5 (1.3-4.6)
Didanosine	37 (66%)	143 (50%)	1.9 (1.0-3.5)
Efavirenz	27 (48%)	95 (33%)	1.9 (1.0-3.3)
Ritonavir	21 (38%)	69 (24%)	1.9 (1.0-3.5)
Loprinavir	7 (13%)	6 (2%)	6.7 (2.2-20.8)
Amprenavir	5 (9%)	6 (2%)	4.6 (1.4-15.7)

Conclusion Thyroid dysfunction, mainly hypothyroidism, may be present in outpatients with HIV infection, and to some extent are related to severity of illness and treatment.

COMMENTARY

As in many surveys of this type, thyroid function was assessed only once, the actual hormonal values are not given, and no information regarding the presence of clinically apparent thyroid disease is provided. A more serious problem is the absence of data from normal subjects, so that no definite statement about increased prevalence of hypothyroidism, as defined in this study, is warranted. That said, the prevalence of overt and subclinical hypothyroidism probably was slightly increased in these relatively young patients, especially the men.

Included among the 56 patients considered to have hypothyroidism were 24 with low serum free T_4 and normal serum TSH concentrations. These results are found in some patients with nonthyroidal illness, and also in some patients with hypothalamic–pituitary disease (central hypothyroidism). The former explanation seems unlikely, because the patients were not in the hospital and their weight was similar to that of the patients with normal thyroid function. The latter explanation also seems unlikely; among groups of patients with central hypothyroidism some have low serum TSH and low free T_4 values, a combination not found in any of these 350 patients. And central hypothyroidism, or indeed any hypothalamic–pituitary disease, is not a recognized feature of HIV infection. Serum free T_3 values are not given, but would be unlikely to distinguish between these two causes of low serum free T_4 values. One is left to wonder if one or a combination of antiretroviral drugs might occasionally alter T_4 production or metabolism, and perhaps the TSH response to such alterations, in such a way as to cause these findings.

Robert D. Utiger, M.D.

High serum thyrotropin concentrations are associated with poor in vitro fertilization of oocytes retrieved from infertile women

Cramer DW, Sluss PM, Powers RD, McShane P, Ginsburg ES, Hornstein MD, Vitonis AF, Barbieri RL. Serum prolactin and TSH in an in vitro fertilization population: is there a link between fertilization and thyroid function? J Assist Reprod Genet 2003;20:210-5.

SUMMARY

Background The extent to which thyroid dysfunction affects fertility is not well-defined. In this study, serum thyrotropin (TSH) was measured in a large group of women with infertility who underwent assisted reproduction.

Methods The study subjects were 509 women with infertility (duration not stated) who underwent at least one cycle of assisted reproduction at three in vitro fertilization centers from 1994 to 2001 and in whom serum TSH and prolactin were measured before any treatment was given.

After initial evaluation to determine the cause of infertility, the women underwent one or more cycles of administration of a gonadotropin-releasing hormone agonist and gonadotropins for controlled ovarian stimulation, oocyte retrieval, in vitro fertilization, and embryo transfer. Only the results of the first cycle were evaluated. The main outcomes were the rates of oocyte retrieval, fertilization, implantation, clinical pregnancy, spontaneous abortion, and live birth.

Results Most of the women were aged 30 to 39 years and had a normal body-mass index. The primary diagnosis was tubal infertility in 118 women (23 percent), male factor infertility in 92 women (18 percent), endometriosis in 74 women (14 percent), ovulatory dysfunction in 54 women (11 percent), and other or unexplained in 171 women (34 percent). The mean (±SD) serum TSH concentration in the women in the male factor group was 3.0±5.8 mU/L, significantly higher (P<0.01) than the mean values (1.8 to 2.0 mU/L) in the other four groups. Serum prolactin concentrations were similar in all groups.

Serum TSH concentrations were similar in the women who achieved a clinical pregnancy and those who did not during the first cycle (or later cycles) of in vitro fertilization (Table). Serum TSH concentrations were higher in the women whose oocytes were not fertilized, as compared with the other outcomes listed, and six of these women (27 percent) had high values. The association between serum TSH and fertilization failure remained after adjustment for age, cause of infertility, and number of oocytes retrieved.

Table. Mean (±SD) Serum TSH Concentrations and Outcomes of a First Cycle of in vitro Fertilization in 509 Infertile Women.

	No.	Serum TSH (mU/L)
Clinical Pregnancy		
Yes	151 (30%)	2.2±2.2
No	358 (70%)	2.1±3.1
Other outcomes		
Failure of retrieval	50 (10%)	1.8±1.2
Failure of fertilization	22 (4%)	5.1±11.6*
Failure of implantation	285 (56%)	1.9±1.2
Spontaneous abortion	22 (4%)	2.7±3.0
Live birth	126 (25%)	2.1±2.1
Fertilization rate		
<50%	141 (32%)	2.5±4.7**
≥50%	305 (68%)	2.0±1.7

*P<0.01, **P=0.05.

Ten women (2 percent) had serum TSH concentrations >5 mU/L (highest, 55 mU/L). Their in vitro fertilization results are not given.

Conclusion Among infertile women who attempt pregnancy by in vitro fertilization and embryo transfer, serum TSH concentrations are associated with decreased oocyte fertilization in vitro.

COMMENTARY

These 509 women were part of a larger cohort of women treated at the same centers; in the others, serum TSH was not measured before treatment or the outcome of treatment was not known. However, the frequency of high serum TSH concentrations in these women was low, similar to that in a study in which serum TSH was measured in all women seeking treatment for infertility (1), and certainly similar to what would be expected in normal women of the same age (2). Serum thyroxine was not measured, although it is likely that the most of the handful of women with high serum TSH values had subclinical hypothyroidism. Nothing is said about low serum TSH concentrations.

There is no obvious explanation for the finding of higher serum TSH concentrations in the women in the male factor group. As far as the results of assisted reproduction are concerned, hypothyroidism, however mild, seems not to alter oocyte development in response to gonadotropin stimulation, but instead to impair the final steps of oocyte maturation or the process of fertilization itself. Whatever the details of the impairment, and given the complexity, cost, and substantial rate of failure of assisted reproduction overall, these results provide an impetus to measure serum TSH in all women seeking treatment for infertility, and to treat those with high values for several months before initiating treatment for infertility.

Robert D. Utiger, M.D.

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The carpal tunnel syndrome is a feature of hypothyroidism, but several other musculoskeletal disorders are not associated with thyroid dysfunction

Cakir M, Samanci N, Balci N, Balci MK. Musculoskeletal manifestations in patients with thyroid disease. Clin Endocrinol 2003;59:162-7.

SUMMARY

Background Patients with either hyperthyroidism or hypothyroidism may have symptoms and signs of muscle and joint dysfunction, but there has been no recent systematic study of muscle and joint function in these patients. This study was undertaken to determine the frequency and extent of several musculoskeletal disorders in patients with overt and subclinical hyperthyroidism and hypothyroidism.

Methods The study subjects were 137 patients (111 women, 26 men; mean [±SD] age, 46±12 years) with thyroid disease seen in an endocrinology clinic. They included 42 patients (31 percent) with overt hyperthyroidism, 23 (17 percent) with subclinical hyperthyroidism, 39 (28 percent) with normal thyroid function, 10 (7 percent) with subclinical hypothyroidism, and 23 (17 percent) with overt hypothyroidism. The patients with overt thyroid dysfunction were symptomatic, but those with subclinical thyroid dysfunction were not. There were 38 patients (28 percent) with toxic nodular goiter, 32 (23 percent) with Graves' disease, 40 (29 percent) with diffuse or nodular goiter who were euthyroid, and 27 (20 percent) with Hashimoto's disease. These diagnoses were based on the results of clinical examination, thyroid ultrasonography, and measurements of serum thyroid hormones, thyrotropin, and antithyroid antibodies. Patients with other illnesses were excluded.

The patients completed a questionnaire that included questions about sensory symptoms, muscle weakness, joint mobility, and musculoskeletal pain. They then underwent a detailed musculoskeletal and neurologic examination, with special attention directed to signs of adhesive capsulitis of the shoulder (frozen shoulder), carpal tunnel syndrome, limited hand mobility, Dupuytren's contracture, and fibromyalgia.

Results Overall, adhesive capsulitis of the shoulders was the most common musculoskeletal disorder, occurring in 15 patients (11 percent). Thirteen patients (10 percent) had the carpal tunnel syndrome, 12 (9 percent) had Dupuytren's contracture, 10 (7 percent) had fibromyalgia, and 6 (4 percent) had limited hand mobility.

The frequency of these disorders in the patients with the different types of thyroid dysfunction is shown in the Table. The only musculoskeletal disorder that was significantly more common in any thyroid-dysfunction group, as compared with the euthyroid group, was the carpal tunnel syndrome (P=0.004).

Table. Frequency of Musculoskeletal Disorders in Patients with Thyroid Diseases.

	Adhesive Capsulitis	Carpal Tunnel Syndrome	Dupuytren's Contracture	Fibromyalgia	Limited Hand Mobility
Overt hyperthyroidism (n=42)	3 (7%)	3 (7%)	4 (10%)	2 (5%)	1 (2%)
Subclinical hyperthyroidism (n=23)	4 (17%)	—	1 (4%)	1 (4%)	1 (4%)
Euthyroid (n=39)	5 (13%)	3 (8%)	2 (5%)	3 (8%)	2 (5%)
Subclinical hypothyroidism (n=10)	—	—	—	2 (20%)	—
Overt hyperthyroidism (n=23)	3 (13%)	7 (30%)	5 (20%)	2 (9%)	2 (9%)

Conclusion The frequency of several musculoskeletal disorders is not increased in patients with overt or subclinical thyroid disease, except for an increase in the frequency of the carpal tunnel syndrome in patients who have overt hypothyroidism.

COMMENTARY

This study is of interest for two reasons. One, the patients were examined systematically, and undoubtedly symptoms were elicited and abnormalities were detected that would be overlooked or missed in the course of usual clinical practice. Two, patients with subclinical hyper- and hypothyroidism were included, so that the question of whether they have any musculoskeletal abnormalities could be addressed. The limitations of the study are that there was no true control group (all the patients had thyroid disease), and the more common musculoskeletal abnormalities associated with thyroid dysfunction, such as muscle weakness and myalgia, were not evaluated.

The authors cite studies indicating that the frequency of the musculoskeletal disorders sought in this study was higher than would be expected in otherwise healthy people. That seems unlikely, given the similar results in the different study groups (except for the relationship between the carpal tunnel syndrome and overt hypothyroidism).

In clinical practice, it would not be prudent to tell patients with thyroid dysfunction who had one or more of these musculoskeletal disorders, even including the carpal tunnel syndrome, that thyroid hormone or antithyroid therapy will relieve their symptoms. But a "maybe" would probably be OK!

Robert D. Utiger, M.D.

Raloxifene induced malabsorption of thyroxine in a patient with hypothyroidism

Siraj ES, Gupta MK, Reddy SS. Raloxifene causing malabsorption of levothyroxine. Arch Intern Med 2003;163:1367-70.

SUMMARY

Background The efficacy of thyroxine (T_4) therapy in patients with hypothyroidism may be reduced by drugs and other substances and gastrointestinal disorders that decrease the absorption of T_4, increases in serum thyroxine-binding globulin concentrations, and drugs and disorders that increase the clearance of T_4. This case report describes a patient in whom raloxifene, a selective estrogen-receptor modulator, caused malabsorption of T_4.

Case Report A 79-year-old woman with hypothyroidism after subtotal thyroidectomy was euthyroid and had normal serum thyrotropin (TSH) concentrations for several years while taking 0.15 mg T_4 daily. She was found to have osteopenia, and was treated with raloxifene, 60 mg daily, which she took with the T_4 early in the morning. She then had onset of symptoms of hypothyroidism, and a month later her serum TSH concentration was 14.5 mU/L. The dose of T_4 was increased to 0.2 mg daily, but her symptoms persisted, and four months later her serum TSH concentration was 21.4 mU/L (this and other values given below are not in the paper, but were provided by the authors). The dose of T_4 was raised to 0.3 mg daily. Two months later her serum TSH concentration was 9.4 mU/L. She had pernicious anemia, for which she was treated with parenteral vitamin B_{12}; hypertension, treated with hydrochlorothiazide; and depression, treated with sertraline. She also took iron sulfate and a multivitamin containing calcium. She took these latter medications at least four hours after taking T_4 and raloxifene. She had no symptoms of malabsorption. She was advised to take T_4 and raloxifene 12 hours apart; two months later her serum TSH concentration was 0.6 mU/L. She then took the T_4 and raloxifene at the same time for a month, after which her serum TSH concentration was 13.0 mU/L; it fell to 2.2 mU/L when she again took the T_4 and raloxifene separately.

On two occasions she was given 1 mg of T_4, once without and once with 60 mg of raloxifene, and serum T_4 was measured at frequent intervals for six hours (Table). After ingestion of T_4 alone, her serum T_4 concentration increased from 12.0 μg/dl (155 nmol/L) to a peak of 29.7 μg/dl (383 nmol/L) at 90 minutes. In contrast, her serum T_4 concentration increased from 12.3 μg/dl (159 nmol/L) to a peak of 19.2 μg dl (248 nmol/L) at 300 minutes after ingestion of T_4 plus raloxifene, and the values were lower at all times.

Table. Serum T_4 Concentrations (μg/dl) after Oral Administration of 1 mg of T_4 without and with 60 mg of Raloxifene.

	Time (minutes)								
	0	30	60	90	120	180	240	300	360
T_4 alone	12.0	14.9	23.7	29.7	28.5	21.5	22.3	22.0	19.5
T_4 and raloxifene	12.3	14.8	16.2	18.8	18.8	18.1	18.3	19.2	17.2

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

Conclusion Raloxifene inhibits gastrointestinal absorption of T_4.

COMMENTARY

The results of both the acute T_4 absorption tests and the chronic studies in which T_4 and raloxifene were given simultaneously and separately provide good evidence that raloxifene decreased T_4 absorption in this woman. Possible mechanisms for the decrease include formation of complexes of raloxifene and T_4 in the intestinal lumen, impairment of T_4 absorption across the intestinal mucosa, and increased hepatic uptake of T_4. Of possible relevance is that this woman had pernicious anemia, and therefore atrophic gastritis and achlorhydria, raising the possibility that the absence of hydrogen ions in her gastric secretions contributed to the ability of raloxifene to decrease T_4 absorption. She also was taking iron, a multivitamin containing some calcium, and sertraline, each of which may increase the need for T_4 in patients with hypothyroidism (1-3), but she did not take them at the same time as she took T_4. While raloxifene has estrogen-agonist activity in some tissues, unlike estrogens it raises serum thyroxine-binding globulin concentrations very little (4), and therefore increased serum binding of T_4 did not contribute to the woman's need for more T_4.

Will the increased need for T_4 in this woman prove to be unique, or will other women taking raloxifene and T_4 be affected similarly? For now, it is prudent to add raloxifene to the gradually increasing list of drugs that limit T_4 absorption. And when malabsorption is suspected, an absorption test, with measurements of serum T_4 before and 60 and 120 minutes after administration of 1 mg of T_4, may be useful for distinguishing between T_4 malabsorption and poor compliance (pseudomalabsorption).

Robert D. Utiger, M.D.

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Lower doses of radioiodine can be given to reduce the size of multinodular goiters when iodine uptake is stimulated by pretreatment with thyrotropin

Nieuwlaat WA, Huysmans DA, van den Bosch HC, Sweep CG, Ross HA, Corstens FH, Hermus AR. Pretreatment with a single, low dose of recombinant human thyrotropin allows dose reduction of radioiodine therapy in patients with nodular goiter. J Clin Endocrinol Metab 2003;88:3121-9.

SUMMARY

Background Iodine-131 (I-131) therapy decreases goiter size in patients with a multinodular goiter who are euthyroid. However, high doses are required, because thyroid uptake of I-131 is usually normal or low. Thyrotropin (TSH) can be given to increase uptake, and therefore to reduce the administered dose of I-131, but the extent to which this alters the short- and long-term effects of I-131 therapy in these patients is not known. In this study the effects of I-131 therapy in patients pretreated with TSH to stimulate I-131 uptake was determined.

Methods Twenty-two patients (18 women, 4 men; mean [±SD] age, 60±9 years) with a nontoxic multinodular goiter referred for I-131 therapy to reduce the size of their goiter were studied.

I-131 uptake was measured and I-123 scintigraphy was done 24 hours after oral administration of the isotopes. All of the scans showed a heterogeneous pattern of uptake. Two or more weeks later, the patients were given 0.01 or 0.03 mg of human TSH by intramuscular injection (12 and 10 patients, respectively), followed 24 hours later by administration of I-131. Thyroid I-131 uptake was measured 24 hours after that. Thirteen to 84 days later the patients were given the same dose of TSH, and 24 hours later they were given a therapeutic dose of I-131. The dose was based on the patient's TSH-stimulated 24-hour I-131 uptake, measured previously, and was calculated to deliver 100 μCi (3.7 MBq) of I-131/g of thyroid tissue at 24 hours after administration. Thyroid weight was estimated by planimetry from the base-line scan; it ranged from 70 to 265 g.

The following studies were done before and at varying intervals in the year after I-131 therapy: clinical examinations, measurements of serum thyroid hormones, TSH, and TSH-receptor antibodies; and measurements of thyroid volume and smallest cross-sectional area of the trachea by magnetic resonance imaging.

Results The higher dose of TSH stimulated 24-hour thyroid I-131 uptake slightly more than did the lower dose (Table), allowing a greater reduction in the dose of I-131 needed to deliver the same radiation dose to the thyroid.

Table. Results of Measurements of Thyroid I-131 Uptake before I-131 Therapy and Measurements of Thyroid Volume and Tracheal Area before and One Year after I-131 Therapy According to Dose of TSH.

Dose of TSH (mg)	24-Hour I-131 Uptake Post-TSH (%)	Therapy Dose (mCi)*	Base-Line Thyroid Volume (ml)	One-Year Thyroid Volume (ml)	Base-Line Smallest Tracheal Area (cm^2)	One-Year Smallest Tracheal Area (cm^2)
0.01	50±11	39±17	143±54	91±41	1.2±0.4	1.4±0.4
0.03	54±9	23±6	103±44	62±35	1.1±0.5	1.4±0.6

Values are means (±SD). To convert to MBq, multiply by 37.

No patient had any symptoms or signs of hyperthyroidism or thyroiditis in the first weeks after therapy. Thyroid volume increased by about 5 percent one week after therapy, but tracheal area did not change.

One year after therapy, thyroid volume was lower by 35±14 percent in the low-dose group and 41±12 percent in the high-dose group, and tracheal area increased similarly in both groups. Three patients had hyperthyroidism with high serum concentrations of TSH-receptor antibodies six months after therapy. Eight patients had high serum TSH concentrations, and were treated with thyroxine in the year after therapy.

Conclusion In patients with a multinodular goiter TSH stimulation of I-131 uptake allows use of relatively low doses of I-131 for reduction in goiter size.

COMMENTARY

Multinodular goiters are composed of three types of thyroid tissue. Some is TSH-independent, some is TSH-dependent, and some is not thyroid tissue at all, but rather fibrous and chronic inflammatory tissue. Furthermore, the thyroid tissue that is functioning is not functioning efficiently, when considered on the basis of thyroid activity per unit of weight or volume. Otherwise, all the patients would have hyperthyroidism.

Given this heterogeneity, and inefficiency, it is not surprising that thyroxine therapy is ineffective, and I-131 is not highly effective. In most studies, I-131, given in a dose to deliver 100 mCi (3.7 MBq) at 24 hours, as was given in this study, reduced thyroid volume by about 40 percent in one year and 50 percent in 2 years (1). The one-year effect is about the same as that when the patients were pretreated with TSH, but the I-131 doses needed to deliver that amount of I-131 were lower by a factor of 1.9 in the patients given 0.01 mg of TSH, and by a factor of 2.4 in those given 0.03 mg of TSH. If the same dose of I-131 is delivered to the thyroid, the effects on not only thyroid size, but also on thyroid function, both short- and long-term, should be similar. These preliminary data suggest that they are. The benefit is in the decrease in radiation to other tissues in the patients and to other people.

Robert D. Utiger, M.D.

Positron emission tomography using ^{18}F-fluorodeoxyglucose occasionally reveals incidental thyroid nodules

Kang KW, Kim SK, Kang HS, Lee ES, Sim JS, Lee IG, Jeong SY, Kim SW. Prevalence and risk of cancer of focal thyroid incidentaloma identified by 18F-fluorodeoxyglucose positron emission tomography for metastasis evaluation and cancer screening in healthy subjects. J Clin Endocrinol Metab 2003;88:4100-4.

SUMMARY

Background ^{18}F-Fluorodeoxglucose (FDG) positron emission tomography is being used increasingly not only to detect metastases in patients with cancer, including thyroid cancer, but also for screening for cancer in asymptomatic patients. Like other imaging procedures, FDG imaging may reveal unsuspected thyroid nodules (incidentalomas). This retrospective study was done to determine the frequency of detection of thyroid nodules and the nature of those nodules in patients undergoing FDG imaging for possible non-thyroid tumors.

Methods The study subjects were all 1330 patients who underwent FDG imaging studies at a single cancer center in South Korea between June 2001 and December 2002. They included 999 patients who had the imaging procedure as part of an evaluation for metastatic cancer and 331 patients who were being screened for cancer. Patients known to have thyroid cancer were excluded. Thyroid incidentaloma was defined as focal or diffuse uptake in the thyroid region; focal uptake was uptake in less than one thyroid lobe, and diffuse uptake was uptake throughout both thyroid lobes.

Results Twenty-nine of the 1330 patients (2 percent) had a thyroid incidentaloma, of whom 21 had focal uptake and eight had diffuse uptake. There were 18 women and 3 men (mean age, 55 years; range, 38 to 71). The findings on physical examination or other imaging studies, if done, and the size of the nodules in these patients are not described.

In 15 of the 21 patients who had focal thyroid uptake of FDG the nodule was biopsied or removed surgically. Four patients proved to have a papillary thyroid carcinoma, four patients had a follicular adenoma, and seven patients had an adenomatous nodule; the remaining six patients were not further evaluated. The intensity of FDG uptake was higher in the carcinomas than in the benign nodules. Three of the thyroid carcinomas were in patients being studied for metastatic cancer, and one was in a patient who was being screened for cancer.

Among the eight patients with diffuse thyroid uptake of FDG, most had chronic thyroiditis, based on clinical, biochemical, and serologic studies; one patient had subacute granulomatous thyroiditis.

Conclusion Thyroid incidentalomas, some of which prove to be carcinomas, may be detected by positron emission tomography using ^{18}F-fluorodeoxyglucose.

COMMENTARY

Positron emission tomography using FDG can be added to the list of techniques that detect incidental thyroid nodules. These techniques extend from physical examination, notoriously insensitive, to ultrasonography, which might be called supersensitive, with the sensitivity of other radiologic techniques, including FDG imaging, being closer to that of physical examination. It seems clear that FDG imaging can detect nodules that are too small to be palpable, but how small is not clear. Nodule size was not described in this paper. In a case study of eight patients found to have an incidental thyroid carcinoma on FDG imaging, the size of the tumor, as determined by ultrasonography, ranged from 8 to 39 mm (1).

None of these techniques, of course, are specific for thyroid cancer, but among them FDG imaging may be more specific than the others (but not enough so to be diagnostically useful). This is because it depends on the ability of the tissue to take up and metabolize glucose, and, in general, the metabolic activity of cancer cells, even papillary thyroid-carcinoma cells, is greater than that of normal thyroid cells and cells from benign thyroid nodules. However, not all thyroid carcinomas take up sufficient FDG to be detected (2).

How should patients with thyroid incidentalomas detected by FDG imaging be evaluated? The options range from doing nothing to biopsy, just as they do in patients with a nodule detected by physical examination or any other imaging technique. Given that FDG imaging is usually done to search for metastases in a patient who has cancer (but not thyroid cancer), the evaluation should depend on the patient's major problem(s) and prognosis.

Robert D. Utiger, M.D.

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Serum thyroglobulin values may vary according to assay method in patients with thyroid carcinoma

Weightman DR, Mallick UK, Fenwick JD, Perros P. Discordant serum thyroglobulin results generated by two classes of assay in patients with thyroid carcinoma: correlation with clinical outcome after 3 years of follow-up. Cancer 2003;98:41-7.

SUMMARY

Background Measurements of serum thyroglobulin are an important component of the follow-up of patients with thyroid carcinoma. This has happened despite the fact that serum thyroglobulin can be measured in different ways and continuing debate about the validity of the measurements in patients who have high serum antithyroglobulin antibody concentrations. In this study serum samples submitted for measurements of serum thyroglobulin were analyzed using two assay methods.

Methods All serum samples from patients with differentiated thyroid carcinoma submitted for measurements of thyroglobulin to a single laboratory serving a large city in the United Kingdom were analyzed using a radioimmunoassy (RIA) and an immunoradiometric assay (IRMA). The results of both assays were expressed in terms of the same thyroglobulin standard (CRM 457). Thyroglobulin recovery was determined by analysis of serum samples before and after addition of 30 μg/L of thyroglobulin in the IRMA. Serum antithyroglobulin antibodies were measured by an immunoradiometric assay in most of the samples in which the serum thyroglobulin values were discordant.

Assay results were considered discordant when the result in one of the assays was undetectable, and the result in the other was >1 μg/L. Patients with detectable serum thyroglobulin values, as measured by RIA or IRMA, were evaluated for persistent or recurrent carcinoma by radioiodine imaging or ultrasonography.

Results During the four-month study period serum thyroglobulin was measured in 82 patients who had been treated for thyroid carcinoma and for whom follow-up data were available. All were taking thyroxine, and all had low or undetectable serum thyrotropin concentrations. The serum thyroglobulin values were concordant in 66 patients (80 percent), of whom 56 had undetectable values and 10 had values >1 μg/L.

Four patients (5 percent) had serum thyroglobulin values <1 μg/L, as measured by IRMA, and values ranging from 7.2 to 45 μg/L, as measured by RIA. Recovery was high, although two of the patients had high serum antithyroglobulin antibody concentrations. One patient had metastatic disease at that time, and it was detected later in another; the other two patients had undetectable serum thyroglobulin concentrations (measured only by IRMA) and no evidence of thyroid carcinoma three years later.

Twelve patients (15 percent) had detectable serum thyroglobulin values (range, 1.4 to 360 μg/L) as measured by IRMA, but values <1 μg/L as measured by RIA. Recovery ranged from 92 to 102 percent, and no patient had a high serum antithyroglobulin antibody concentration. Imaging studies were abnormal in three patients and normal in nine patients. Ten of these patients subsequently had metastatic disease, one had minimal uptake in the thyroid bed and later had a serum thyroglobulin value <1 μg/L (IRMA), and one had no evidence of disease during follow-up.

Conclusion In patients with thyroid carcinoma, serum thyroglobulin concentrations measured by RIA and IRMA are usually concordant, but when discordant, they are more likely to be falsely undetectable when measured by RIA.

COMMENTARY

Clinicians have come to rely increasingly on the results of measurements of serum thyroglobulin, rather than imaging studies, in caring for patients with thyroid carcinoma. This change has simplified follow-up, and there is no evidence that it has had a deleterious effect on outcome.

That said, it is important to note the problems associated with assays for serum thyroglobulin. There is no standard assay for thyroglobulin, both RIAs and IRMAs (and other types of immunometric assays [IMAs]) being in use. The functional sensitivity of the assays varies. Different antibodies are used in the different types of assay and the epitope specificity of the different antibodies undoubtedly varies substantially. Therefore, the results may be different in different assays.

There is also the problem of interference by antithyroglobulin antibodies and heterophil antibodies. Measuring the recovery of thyroglobulin added in vitro in either type of assay is not a reliable way to detect these antibodies or correct for their presence. Addition of animal immunoglobulins in vitro reduces, but does not eliminate, the interference by heterophil antibodies. Given these problems, it is not surprising that measurements of serum thyroglobulin are sometimes discordant, as they were in this study. These factors plus the fact that the functional sensitivity of the RIA used in this study was lower than that of the IRMA explain the discordant results.

Those caring for patients with thyroid carcinoma should know how serum thyroglobulin is measured in their patients, the functional sensitivity of the assay, and whether the assay overestimates or underestimates serum thyroglobulin in the presence of antithyroglobulin antibodies.

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Extensive involvement of cervical lymph nodes and high postoperative plasma calcitonin concentrations predict tumor recurrence in patients with medullary thyroid carcinoma

Pellegriti G, Leboulleux S, Baudin E, Bellon N, Scollo C, Travagli JP, Schlumberger M. Long-term outcome of medullary thyroid carcinoma in patients with normal postoperative medical imaging. Br J Cancer 2003;88:1537-42.

SUMMARY

Background Patients with medullary thyroid carcinoma who are thought to have complete tumor removal, as determined not only at surgery but also by imaging studies soon after surgery, may have either high or undetectable plasma calcitonin concentrations. In this study the outcome of patients with these findings was determined.

Methods From 1988 to 1998, 63 patients (mean age, 42 years; range, 3 to 72) with medullary carcinoma underwent total thyroidectomy and bilateral lymph node resection, with apparently complete tumor removal, and had normal postoperative imaging studies three to six months after surgery. These studies consisted of ultrasonography of the neck, computed tomography [CT] of the chest, ultrasonography or CT of the abdomen, and radionuclide bone scans. Plasma calcitonin, measured between 6 and 12 weeks after surgery, was undetectable in 35 patients (56 percent) and high in 28 patients (44 percent); the values in the latter group ranged from 13 to 1772 pg/ml.

The patients were reevaluated every six months with clinical examinations and measurements of plasma calcitonin. Ultrasonography of the neck and abdomen was done yearly, and CT of the chest and radionuclide bone scans were done in patients with high plasma calcitonin concentrations.

Results Ten patients had TNM stage I tumors (≤1 cm), 13 had stage II tumors (>1 to ≤4 cm), and 40 had stage III tumors (any tumor size, with local extension and positive lymph nodes). The mean duration of follow-up was 7 years (range, 0.4 to 15), during which 45 patients (71 percent) remained free of tumor and 18 patients (29 percent) had recurrent tumor (Table).

Table. Characteristics of 63 Patients with Medullary Thyroid Carcinoma with Normal Imaging after Surgery.

	No Recurrence (n=45)	Recurrence (n=18)
Women/men	28/17	7/11
Mean age - yr (range)	42	42
Sporadic/hereditary tumor*	30/15	14/4
Postoperative plasma calcitonin (undetectable/high)	32/13	3/15
TNM Stage (I/II/III)	10/12/23	0/1/17

*Determined by family history and *ret* protooncogene mutation analysis. Includes patients with familial medullary carcinoma and multiple endocrine adenoma types 2A and 2B.

The five-year recurrence-free survival rate was 79 percent. Eighteen patients (29 percent) had an imaging-detected recurrence. The recurrent tumor was in cervical lymph nodes in eight patients, distant sites (liver, lungs, bone) in eight patients, and lymph nodes and distant sites in two patients. Fifteen of these 18 patients had a high plasma calcitonin concentration postoperatively, and all 18 had high concentrations when the recurrent tumor was detected. The overall five-year survival rate was 97 percent.

The factors that predicted recurrence were tumor stage, percentage of positive lymph nodes, and the postoperative plasma calcitonin value, but not age, type of tumor (sporadic or hereditary), or extent of lymph node dissection. The five-year recurrence-free survival rate was 90 percent in the 35 patients with undetectable postoperative plasma calcitonin values, and it was 61 percent in the 28 patients with high values at that time.

Conclusion Patients with medullary thyroid carcinoma who have extensive cervical lymph node involvement at surgery and high plasma calcitonin concentrations after surgery are likely to have recurrent carcinoma.

COMMENTARY

Medullary thyroid carcinomas are considered to be moderately aggressive tumors. The key factor determining outcome is the extent of the tumor at the time of diagnosis. At that time, the majority of patients have cervical lymph-node involvement. The nodal involvement may be bilateral, even if there is no tumor in the contralateral thyroid lobe (1). This is a strong argument for extensive bilateral neck dissection for all patients with this tumor.

This study of patients with normal postoperative imaging studies indicates two things. One, among patients who have undetectable postoperative plasma calcitonin values, the risk of recurrence is very low. For these patients, especially those with very localized disease, repeated imaging is probably not indicated. Two, among those with high postoperative plasma calcitonin values, nearly as many do not have a recurrence as do. For them, it is difficult not to search for disease repeatedly, but the diligence with which recurrent disease is sought should be tempered by whether the patient has rising plasma calcitonin concentrations, and the lack of evidence that early detection and excision of recurrent tumor improve survival.

To put these results in a broader perspective, another 59 patients who underwent surgery during the same interval at the same center had abnormal postoperative imaging studies. It is likely that most if not all had high plasma calcitonin concentrations then. It is also likely that their recurrence rate was considerably higher, if not 100 percent, and their survival rate considerably lower.

Robert D. Utiger, M.D.

Reference

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Persistent thyroid pain in patients with Hashimoto's thyroiditis may be relieved by thyroidectomy

Kon YC, DeGroot LJ. Painful Hashimoto's thyroiditis as an indication for thyroidectomy: clinical characteristics and outcome in seven patients. J Clin Endocrinol Metab 2003;88:2667-72.

SUMMARY

Background The most common cause of thyroid pain and tenderness is subacute granulomatous thyroiditis, but these symptoms can occur in patients with Hashimoto's thyroiditis. This case series describes the clinical and biochemical findings in a small group of patients with Hashimoto's thyroiditis who had thyroid pain and tenderness and who underwent thyroidectomy to relieve the symptoms.

Summary of Cases During a seven-year period, seven women with Hashimoto's thyroiditis who had prolonged thyroid pain and tenderness were evaluated and ultimately treated by thyroidectomy. Some patients had constant pain, but in others it was intermittent. The pain was sometimes asymmetric, and it radiated to the ears or jaw in several patients. Pain severity, estimated retrospectively on a scale from 0 (no pain) to 10 (severe pain), varied from 2 to 10. The duration of pain varied from 1 month to 3 years. All the patients had a goiter before or when the pain began; at that time six patients were euthyroid (four while taking thyroxine [T_4]) and one patient had mild hypothyroidism. Three patients were known to have Hashimoto's thyroiditis and hypothyroidism and had been treated with T_4 for several years before the onset of pain. One patient was initially thought to have subacute granulomatous thyroiditis.

At initial evaluation, five patients had normal thyroid function, one was overtreated with T_4, and one had subclinical hypothyroidism. Thyroid radioiodine uptake, measured in five patients, ranged from 17 to 28 percent at 24 hours. All the patients had a normal erythrocyte sedimentation rate. Five of the six patients tested had high serum titers of antithyroid microsomal antibodies. Fine-needle-aspiration biopsy, done in five patients, revealed lymphocytic thyroiditis in four (plus occasional giant cells in two), and was inconclusive in one.

All seven patients were treated with T_4 at some time, in some instances with temporary improvement in pain. Four patients were treated with nonsteroidal anti-inflammatory drugs; one had partial pain relief, two did not improve, and one could not tolerate the drug. Five patients were treated with one or more courses of a glucocorticoid; two had no response, and three improved, but relapsed when treatment was reduced or stopped.

All patients underwent subtotal or near-total thyroidectomy 0.5 to 6 years after the onset of pain. From 4.4 to 46 g of thyroid tissue was removed. Histologic examination of the thyroid revealed lymphocytic thyroiditis, sometimes with extensive fibrosis and lymphoid follicles, in all patients. All patients then received T_4. Four patients had complete relief of pain, one had partial relief, and two improved but later relapsed (these two patients were treated with radioiodine, and had pain later).

Conclusion Some patients with Hashimoto's thyroiditis have thyroid pain that persists despite T_4 and antiinflammatory drug therapy, but it may subside after thyroidectomy.

COMMENTARY

Thyroid pain and tenderness are very nearly diagnostic of subacute granulomatous thyroiditis, but can occur in patients with infectious thyroiditis, patients in whom there is hemorrhage into a thyroid nodule, and, as documented here, rare patients with Hashimoto's thyroiditis. Mild thyroid pain—perhaps neck discomfort or fullness is a better term—can occur in any patient in whom the thyroid gland is enlarged, including patients with Hashimoto's thyroiditis and those with Graves' disease, particularly when the enlargement is substantial or its onset is fairly rapid.

How often do patients with Hashimoto's disease have thyroid pain and tenderness? Probably not often; the two largest reported series each described eight patients (1,2). Were the seven patients in this new paper all the patients with the disease with thyroid pain and tenderness encountered by the authors during this interval? Probably not; it seems likely that there were other patients with these symptoms who improved with time, T_4 therapy, or antiinflammatory drug therapy. What distinguishes those few patients who have thyroid pain and tenderness from the many who do not? In three patients in this series, thyroid tissue was adherent to surrounding structures, and in two patients giant cells were seen in the thyroid, suggesting a more intense inflammatory process than usual.

From a clinical perspective, this subtype of Hashimoto's thyroiditis has to be distinguished from subacute granulomatous thyroiditis. Features favoring the former diagnosis include a history of thyroid disease, slow onset of pain, less severe pain, longer duration of pain, lack of response to anti-inflammatory drug therapy, high serum concentrations of antithyroid antibodies, presence of hypothyroidism, and the results of cytology or histology.

Robert D. Utiger, M.D.

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Healthy women from families with autoimmune thyroid disease often have serologic evidence of thyroid autoimmunity

Strieder TG, Prummel MF, Tijssen JG, Endert E, Wiersinga WM. Risk factors for and prevalence of thyroid disorders in a cross-sectional study among healthy female relatives of patients with autoimmune thyroid disease. Clin Endocrinol 2003;59:396-401.

SUMMARY

Background There are both genetic and environmental risk factors for autoimmune thyroid disease. Their nature and importance are not known, and they may differ according to whether the person has autoimmune hyperthyroidism (Graves' disease) or autoimmune hypothyroidism (Hashimoto's disease). In this study risk factors for the two disorders and thyroid function were assessed in women who had a relative known to have autoimmune thyroid disease.

Methods The study subjects were 803 women who had a first- or second-degree relative with autoimmune thyroid disease and thyroid dysfunction. They were healthy, had no history of thyroid disease, and were 18- to 65-years old. The relatives' records were reviewed; they were considered to have autoimmune thyroid disease if there was documentation of hyper- or hypothyroidism and high serum concentrations of thyrotropin (TSH)-receptor or antithyroid peroxidase (TPO) antibodies.

The women were asked to complete a questionnaire about smoking habits, oral contraceptive and other estrogen therapy, and number of pregnancies. They also underwent a brief physical examination and had measurements of serum TSH, free thyroxine (T_4), and anti-TPO and antithyroglobulin (Tg) antibodies.

Results Among the 803 women, 713 (89 percent) had one or more first-degree relatives with autoimmune thyroid disease, and 90 (11 percent) had one or more second-degree relatives with the disease. There were 440 women from 233 families with more than one member with autoimmune thyroid disease. All affected relatives in 109 families (47 percent) had Graves' disease, all affected relatives in 47 families (20 percent) had Hashimoto's disease, and both disorders were present in the remaining 77 families (33 percent).

A few of the women had hypothyroidism or hypothyroidism (Table). A substantially higher number (212 [26 percent]) had a high serum anti-TPO antibody concentration, but only 66 women (8 percent) had a high serum anti-Tg antibody concentration. In the normal women serum TSH concentrations were positively correlated with serum anti-TPO antibody concentrations.

Table. Characteristics of 803 Women with One or More Relatives with Autoimmune Thyroid Disease.

	All 803	Hypothyroidism* 29 (4%)	Normal 759 (94%)	Hyperthyroidism* 15 (2%)
Age–yr (mean)	36	43	36	44
Serum TSH–mU/L (median)	1.7	8.8	1.7	0.1
Serum anti-TPO antibodies >100 U/ml	216 (27%)	25 (86%)	183 (24%)	8 (53%)
Smoking, ever	463 (58%)	20 (69%)	436 (57%)	7 (47%)
Smoking, current	280 (35%)	12 (42%)	266 (35%)	2 (13%)
Estrogen, ever	726 (90%)	28 (97%)	688 (81%)	10 (67%)
Estrogen, current	360 (45%)	10 (34%)	348 (46%)	2 (13%)
Pregnancy	415 (52%)	18 (62%)	384 (51%)	13 (87%)

*Hypothyroidism, 19 subclinical and 10 overt; hyperthyroidism, 12 subclinical and 3 overt.

Hypothyroidism was associated with older age (odds ratio, 1.1). For hyperthyroidism, ever-estrogen therapy was protective (odds ratio, 0.2), whereas pregnancy was a predictive factor (odds ratio, 6.9). Among the normal women, a high serum anti-TPO antibody concentration was associated with older age (odds ratio, 1.04), and current smoking and ever-estrogen therapy were protective against high concentrations (odds ratios, 0.7 and 0.6, respectively).

Conclusion A substantial fraction of women with relatives who have autoimmune thyroid disease have high serum anti-TPO antibody concentrations, and some have thyroid dysfunction.

COMMENTARY

The frequency of high serum anti-TPO antibody concentrations in these women was rather high (27 percent), but women from families with no autoimmune thyroid disease, or simply normal women, were not studied. In most general surveys of normal women, approximately 10 to 15 percent had high serum anti-TPO antibody concentrations. It seems reasonable to conclude that there is some familial predisposition to production of anti-TPO antibodies, or more likely familial predisposition to autoimmune thyroid disease—either Graves' disease or Hashimoto's disease—for which anti-TPO antibodies are a marker.

The search for nongenetic risk or predictive factors (it seems awkward to call pregnancy or estrogen therapy an environmental factor) for thyroid dysfunction or high serum anti-TPO antibody concentrations was basically negative, notwithstanding a few instances in which the 95 percent confidence interval did not overlap 1.0. Furthermore, these instances were anomalous. Why should ever-estrogen therapy but not current estrogen therapy protect against hyperthyroidism? The search for nongenetic risk or predictive factors should go on, keeping in mind that they may differ in people who have Graves' disease and those who have Hashimoto's disease, but it seems unlikely that there are major undiscovered ones.

Robert D. Utiger, M.D.

Serum antithyroid antibodies disappear after complete thyroid ablation in patients with thyroid cancer

Chiovato L, Latrofa F, Braverman LE, Pacini F, Capezzone M, Masserini L, Grasso L, Pinchera A. Disappearance of humoral thyroid autoimmunity after complete removal of thyroid antigens. Ann Intern Med 2003;139:346-51.

SUMMARY

Background Many people have high serum titers or concentrations of one or more thyroid antibodies, but the extent to which continued production of these antibodies is dependent on the presence of thyroid tissue as a source of antigen is not clear. This study was done to determine the effect of complete elimination of thyroid tissue on the production of thyroid antibodies.

Methods The study subjects were 182 patients (151 women, 31 men; mean [±SD] age, 40±14 years) with differentiated thyroid carcinoma who had high serum titers of thyroid peroxidase (TPO), thyroglobulin (Tg), or thyrotropin (TSH)-receptor antibodies at the time of diagnosis of the carcinoma. Ten patients (5 percent) also had hyperthyroidism caused by Graves' disease, as defined by overt hyperthyroidism, diffuse goiter, and the presence of serum TSH-receptor antibodies, and 34 patients (19 percent) had Hashimoto's disease, as defined by a diffuse, goiter and a high serum titer of TPO or Tg antibodies.

All the patients underwent near-total or total thyroidectomy, followed by iodine-131 (I-131) and thyroxine therapy. Thereafter, thyroid ultrasonography, chest x-rays, whole-body I-131 imaging, and measurements of serum Tg and the three antibodies were done at least yearly. Ninety-three patients (51 percent) received more than one dose of I-131. Complete thyroid destruction was defined as two consecutive negative whole-body I-131 scans and a serum Tg concentration <3 μg/L (in patients with no serum Tg antibodies). Disappearance of serum TPO, Tg, or TSH-receptor antibodies was defined as a negative test for the respective antibody during temporary cessation of thyroxine therapy.

Serum TPO and Tg antibodies were measured by agglutination methods; a serum antibody titer of 1:100 or higher was considered positive. TSH-receptor antibodies were measured by radioreceptor assay or bioassay; the criteria for positive tests are not stated.

Results At base line, 172 patients (94 percent) had a positive test for serum TPO antibodies, and 116 patients (64 percent) had a positive test for serum Tg antibodies; 106 patients (58 percent) had positive tests for both antibodies. Eight patients (4 percent), all of whom had Graves' disease, had a positive test for TSH-receptor antibodies. The tumor was a papillary carcinoma in 156 patients (86 percent) and a follicular carcinoma in 26 (14 percent). The patients with Graves' disease and Hashimoto's disease, as defined clinically, had the appropriate histologic findings. The remaining patients had varying degrees of focal autoimmune thyroiditis; no attempt was made to correlate the extent of thyroiditis with serum antibody titer.

The mean duration of follow-up was 10±4 years; 108 patients (59 percent) were followed for 8 years, and 69 (38 percent) were followed for 12 years; 4 patients (2 percent) died of thyroid carcinoma. Serum TPO and Tg antibody titers decreased gradually in all patients after initial surgical and I-131 therapy. The median time to disappearance (titer <1:100) of serum TPO antibodies was 6.3 years (95 percent confidence interval, 5.3 to 7.2), and the median time to disappearance of serum Tg antibodies was 3.0 years (1.9 to 4.1). Serum TPO or Tg antibodies, or both, disappeared in 59 of the 182 patients (32 percent) in four years, and in 61 of the 108 patients (56 percent) followed for eight years. The median time to disappearance of all thyroid tissue was 2.8 years (2.4 to 3.2). Serum TSH-receptor antibodies disappeared by 6 years in the 8 patients with positive tests at base line. During follow-up, patients in whom normal or abnormal thyroid tissue was present were more likely to have high serum titers of TPO or Tg antibodies. The persistence of serum TPO or Tg antibodies was not correlated with sex, age, or the presence of Graves' disease or Hashimoto's disease.

Conclusion In patients with thyroid carcinoma, complete ablation of thyroid tissue results in disappearance of serum TPO, Tg, and TSH-receptor antibodies.

COMMENTARY

Complete thyroid ablation should remove not only thyroid follicular cells, the source of TPO and Tg, but also intrathyroidal lymphocytes, the likely source of most of the TPO and Tg antibodies detected in serum. Antibody production might persist in the absence of thyroid tissue if there were appropriately sensitized lymphocytes in cervical lymph nodes or other lymphocyte-bearing organs, but based on the results of this study, that does not happen often.

The situation with respect to TSH-receptor antibodies in patients with Graves' disease is a little different. These antibodies disappear spontaneously in a substantial proportion of patients with Graves' hyperthyroidism treated with an antithyroid drug; thyroid ablation is not required. On the other hand, thyroid ablation would not be expected to remove all TSH receptors, because they are present on retroorbital fibroadipose tissue, and maybe fibroadipose tissue elsewhere as well, in patients with Graves' ophthalmopathy and perhaps normal subjects as well. Thus, the disappearance of TSH receptor antibodies is more the result of changes in immune tolerance, whereas the disappearance of TPO and Tg antibodies is more the result of loss of antigen.

Robert D. Utiger, M.D.

Low maternal serum free thyroxine concentrations are a risk factor for delayed infant neurodevelopment

Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol 2003;59:282-8.

SUMMARY

Background The neurodevelopment of infants of mothers with overt hypothyroidism or iodine deficiency is impaired, and so also may be that of infants of mothers who have slightly low serum free thyroxine (T_4) concentrations. In this study the neurodevelopment of infants whose mothers had relatively low serum free T_4 concentrations and those whose mothers had higher concentrations during early pregnancy was assessed at one and two years of age.

Methods The study began with enrollment of 194 healthy women who at 12 weeks of gestation had a serum free T_4 concentration in the lowest 10th percentile (≤0.96 ng/dl [12.4 pmol/L]) or the 50th to 90th percentile (1.2 to 1.5 ng/dl [15.6 to 19.2 pmol/L]). All the mothers had serum TSH concentrations of 0.15 to 2.0 mU/L. As the study progressed, women were excluded because they had obstetrical complications, and infants were excluded because they had a low birth weight or chronic illness. As a result, there were 63 one-year-old and 57 two-year-old infants in the low serum free T_4 group and 62 one-year-old and 58 two-year-old infants in the higher serum free T_4 group. Detailed information about the pregnancy, delivery, and postpartum health was obtained from the mothers. Infant development was assessed at age one and two years using the Bayley Scales of Infant Development, which includes a Mental Scale (coordination, language development) and a Psychomotor Scale (motor development) (mean normal score for each scale, 100).

Results The age, family education and income, gestational age, birth weight, and breastfeeding status of the mothers and infants in both groups were similar. The Mental and Psychomotor Scale scores were lower in the infants in the low serum free T_4 group at both one and two years (Table).

Table. Mean (±SD) Mental and Psychomotor Scores at Age One and Two Years in the Infants in the Lower Serum Free T_4 and Higher Serum Free T_4 Groups.

	Low Serum Free T_4	Higher Serum Free T_4	P Value
One year			
Mental score	95±15	105±14	0.004
Psychomotor score	91±15	99±14	0.02
Two years			
Mental score	98±15	106±14	0.02
Psychomotor score	92±16	102±16	0.005

At age one year, 19 infants had delayed mental function (defined as score <84), 15 of whom (79 percent) were in the low serum free T_4 group; the respective numbers at age two years were 11 and 8 (73 percent). At age one year, 21 infants had delayed motor function, of whom 16 (76 percent) were in the low serum free T_4 group; the respective numbers at age two years were 22 and 17 (77 percent). Both scores were positively correlated with maternal serum free T_4 concentrations at 12 weeks ($P<0.01$).

Among the infants in the low serum free T_4 group, the 37 whose mothers had higher serum free T_4 concentrations at 24 and 32 weeks of gestation had Mental and Psychomotor Scale scores at age two years similar to the scores of the infants in the higher serum free T_4 group. In contrast, both scores were low in the 20 infants in the low serum free T_4 group whose mothers had no increase or lower serum free T_4 concentrations at 24 and 32 weeks of gestation than at 12 weeks of gestation.

Conclusion Neurodevelopment is delayed in infants whose mothers have low serum free T_4 concentrations at 10 weeks of gestation, especially those infants whose mothers have persistently low concentrations.

COMMENTARY

In a previous study by many of the same investigators, infants of mothers who had serum free T_4 concentrations ≤5th and ≤10th percentiles at 12 weeks of gestation had lower Bayley Psychomotor Scale scores than infants whose mothers had higher serum free T_4 concentrations at that time (1). In both that study and this new study, the focus was on hypothyroxinemia, as defined arbitrarily by percentile values for serum free T_4, and not hypothyroidism, as defined by high serum TSH concentrations. One reason to focus on hypothyroxinemia is the need for T_4, whether supplied by mother or fetus, as a substrate for triiodothyronine (T_3) production in the nervous system. This reaction is catalyzed by type 2 deiodinase, which along with T_3-nuclear receptors is detectable in human fetal cerebral cortex in the first trimester. This enzyme is upregulated by T_4 deficiency, attesting to the importance of T_4 for normal neurodevelopment.

These and other studies have led to a recommendation that serum free T_4 be measured early in pregnancy, and that T_4 or perhaps iodine be given if the value is low, independent of the serum TSH value. Raising iodine intake by pregnant women in most parts of the world seems reasonable, but this can be done universally and without any biochemical screening. Serum free T_4 screening seems premature, as does serum TSH screening, given the unproven benefit of T_4 treatment and the risks of overtreatment. The finding in this study that it was the persistence of low serum free T_4 values that was most deleterious means repeated testing would be needed.

Robert D. Utiger, M.D.

Reference

1. Pop VJ, Kuijpens JL, van Baar AL, et al. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol 1999;50:149-55.

The combination of high serum free thyroxine and normal or high serum thyrotropin concentrations is rare and has multiple explanations

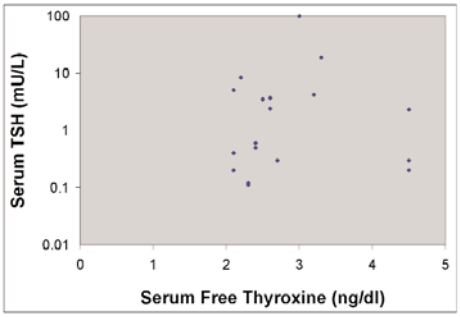
Mitchell DR, Parvin CA, Gronowski AM. Rules-based detection of discrepancies between TSH and free T_4 results. Clin Chim Acta 2003;332:89-94.

SUMMARY

Background Measurements of serum free thyroxine (T_4) and thyrotropin (TSH) together reliably identify patients with overt and subclinical hypothyroidism and overt and subclinical hyperthyroidism. However, a few patients have high serum free T_4 concentrations and serum TSH concentrations that range from just below to above the normal range. These results are consistent with the presence of a TSH-secreting pituitary tumor or generalized thyroid hormone resistance, both of which are very rare. In this study the frequency of these findings was determined and an attempt was made to determine their cause.

Methods During a 30-month period, serum TSH and free T_4 were measured by sensitive immunoasays in 7918 serum samples in the clinical laboratory of a large tertiary-care hospital. The normal range for the serum free T_4 assay was 0.7 to 1.8 ng/dl (9.0 to 23.2 pmol/L), and that for the serum TSH assay was 0.4 to 6.2 mU/L. Samples in which the serum free T_4 concentration was >2.0 ng/dl (25.8 pmol/L) and the serum TSH concentration was >0.1 mU/L were selected for this study. These serum samples were reanalyzed, if possible; if the values were unchanged, serum TSH was measured using a more sensitive assay. The patient's medical records were then reviewed.

Results The serum free T_4 and TSH concentrations were >2 ng/dl (25.8 pmol/L) and >0.1 mU/L, respectively, in 18 of the 7918 serum samples (0.2 percent), from 17 patients (Figure).



There were four explanations for these 18 results. The results in three samples were from analytic errors, of which two were due to heterophil antibodies and one was unexplained. All three patients had hyperthyroidism. The results in four samples were indicative of a thyroid disorder; three patients had thyroid hormone resistance, and one had hypothyroidism and had just begun to take T_4. Three samples were from two newborn infants, in whom serum TSH and free T_4 concentrations are high for several days after birth. The patient with the serum TSH value of 100 mU/L (Figure) was a three-day-old infant whose mother had been taking an antithyroid drug; this infant's values three days later also met the study criteria (serum TSH, 3.8 mU/L; serum free T_4, 2.6 ng/dl [33.5 pmol/L]). The results in the remaining eight samples could not be explained. Most of these samples could not be reanalyzed. Several of the patients had test results indicative of either hypothyroidism or hyperthyroidism at other times, either before or after the index sample was collected.

Conclusion The combination of high serum free T_4 concentrations and serum TSH concentrations >0.1 mU/L can sometimes be explained by analytic error, a thyroid disorder, or infancy, but often they cannot be explained.

COMMENTARY

The criteria used in this study to identify samples in which there were discrepancies between the serum free T_4 and TSH values were based on the assumption that nearly all patients who have high serum free T_4 concentrations have very low serum TSH concentrations. These criteria would certainly result in inclusion of the rare patients with thyroid hormone resistance or a TSH-secreting pituitary adenoma, all of whom would be expected to have serum TSH concentrations well above 0.1 mU/L. Would the criteria have excluded all patients with hyperthyroidism due to other causes? Apparently they did. The paper contains a figure showing the results of measurements in 2007 other patients during six months of the study; all those with serum free T_4 values >2.0 ng/dl (25.8 pmol/L) had serum TSH values ≤0.1 mU/L. Still, there could be patients with a high set point for TSH secretion when healthy, for example, a serum TSH concentration of 3.5 mU/L and a serum free T_4 concentration of 1.6 ng/dl (20.6 pmol/L), in whom the serum TSH concentration fell only to 0.15 mU/L (a 96 percent fall) after onset of hyperthyroidism.

Another known cause of the discrepant results evaluated in this study is the ingestion (or injection) of high doses of T_4 in a patient with hypothyroidism, as occurred in one patient in this study. The T_4 may be given to treat severe hypothyroidism, or a noncompliant patient may take it for a few days before a visit to the physician. This pattern of results can also occur in patients taking amiodarone, which slows T_4 clearance (including T_4 conversion to triiodothyronine). TSH secretion tends to rise slightly, as do serum free T_4 concentrations, due to both increased TSH secretion and slowed T_4 clearance.

As a practical matter, when discrepant results of the type evaluated here are detected, the most appropriate steps are to reevaluate the patient in the light of the results, and ask the laboratory to repeat the tests. If no explanation is forthcoming, a new serum sample should be analyzed, using different assay methods if discrepant results are again obtained.

Robert D. Utiger, M.D.

Critical illness alters the activity of two deiodinases

Peeters RP, Wouters PJ, Kaptein E, van Toor H, Visser TJ, Van den Berghe G. Reduced activation and increased inactivation of thyroid hormone in tissues of critically ill patients. J Clin Endocrinol Metab 2003;88:3202-11.

SUMMARY

Background Patients with severe nonthyroidal illness have multiple abnormalities in pituitary–thyroid function and peripheral thyroid hormone metabolism. The most common changes are a decrease in serum triiodothyronine (T_3) concentrations and an increase in serum reverse triiodothyronine (rT_3) concentrations. These changes are caused by changes in the activity of one or more of the three deiodinases that catalyze the deiodination of thyroxine (T_4), T_3, or rT_3 (Table). In this study, serum T_4, T_3, and rT_3 and the activity of the deiodinases (D1–3) in liver and muscle were measured in patients who died of an acute illness.

Table. Catalytic Activity and Tissue Localization of Deiodinases.

	Action	Tissue Localization
Type 1 (D1)	$T_4 \rightarrow T_3$, $rT_3 \rightarrow T_2$*	Liver, kidney, thyroid
Type 2 (D2)	$T_4 \rightarrow T_3$	Brain, pituitary, muscle, thyroid
Type 3 (D3)	$T_4 \rightarrow rT_3$, $T_3 \rightarrow T_2$	Brain, skin, uterus, placenta

*T_2, 3,3′-diiodothyronine.

Methods Serum or biopsies of liver or skeletal muscle were obtained from 80 patients who died of cardiovascular collapse, sepsis, multiple organ failure, or severe brain damage. Serum was obtained from 65 patients, liver from 66, and muscle from 66; samples from all three sites were obtained from 51. Thirty-one patients (39 percent) had been treated with T_4, and 40 patients (50 percent) had acute renal failure and had been treated with hemodialysis or hemofiltration. The mean time from admission to the intensive care unit to death was 24 days.

Serum T_4, T_3, rT_3, and thyrotropin (TSH) were measured by immunoassay. The activity of type 1 deiodinase (D1) was determined by measuring the formation of iodine-125 (^{125}I) in tissue homogenates incubated with ^{125}I-rT_3. Type 2 deiodinase (D2) activity was determined by measuring the formation of ^{125}I from ^{125}I-T_4 in these homogenates. Similarly, type 3 deiodinase (D3) activity was determined by measuring the formation of ^{125}I-T_2 from ^{125}I-T_3.

Results The patients' mean (±SD) serum hormone concentrations were: T_4, 3.6±2.2 μg/dl (46±29 nmol/L); T_3, 80±51 ng/dl (1.2±0.8 nmol/L); rT_3, 120±140 ng/dl (1.8±2.2 nmol/L); and TSH, 0.8±1.6 mU/L. The serum T_3:rT_3 molar ratio was 1.2±1.2. As compared with normal subjects, the patients had low serum T_4, T_3, and TSH concentrations, high serum rT_3 concentrations, and low serum T_3:rT_3 molar ratios.

The patients' hepatic D1 activity was 4.5±3.9 pmol/mg/min (normal subjects, approximately 7 pmoles/mg/min), and hepatic D3 activity (not detectable in normal subjects) was 1.0±1.4 fmol/mg/min. Muscle D3 activity (not detectable in normal subjects) was 0.2±0.3 fmol/mg/min. No D1 activity was detected in muscle, and no D2 activity was detected in either liver or muscle. The results were similar in the patients who had received T_4 and those who had not, except that the former had higher serum T_3 concentrations and lower serum TSH concentrations.

Hepatic D1 activity was negatively correlated with serum rT_3 concentrations, but not serum T_3 concentrations, indicating the importance of D1 in deiodination of rT_3. Hepatic D1 activity was lowest (about 2 pmol/mg/min) in the patients who died of cardiovascular collapse, and highest (and normal) in the patients who died of severe brain damage. Hepatic D1 activity was low in patients with acute renal failure, and was negatively correlated with serum creatinine concentrations in all patients. Hepatic D3 activity was positively correlated with serum rT_3 concentrations.

Conclusion In critically ill patients hepatic D1 activity is decreased and hepatic and muscle D3 activity is increased, suggesting that changes in the activity of multiple deiodinases in multiple organs contribute to the patients' low serum T_3 and high serum rT_3 concentrations.

COMMENTARY

These results provide insight into the causes of the low serum T_3 concentrations and high serum rT_3 concentrations found in patients with nonthyroidal illnesses. Serum T_3 concentrations are low because the extrathyroidal production of T_3 is decreased and deiodination of T_3 is increased. The former is due to decreased hepatic D1 and perhaps muscle D2 activity, and the latter is due to increased hepatic and muscle D3 activity. Serum rT_3 concentrations are high because the extrathyroidal production of rT_3 is increased and its deiodination is decreased. The former is due to increased hepatic and muscle D3 activity, and the latter to decreased hepatic D1 activity.

The relative contributions of these changes in the activities of the different deiodinases in these and other tissues to overall T_3 and rT_3 production are not known. What is known is that the changes in enzyme activity vary in different illnesses, as exemplified by the lower hepatic D1 activity in patients with renal failure, as compared with patients with more normal renal function, and lower hepatic D1 activity in patients who died from cardiovascular collapse, as compared with those who died from other causes. Serum T_3 concentrations reflect the overall balance between T_3 production and clearance, but the key clinical questions are the extent of any decrease in the availability of T_3 within individual tissues, rather than overall production, whether in the tissue most affected by the illness or other tissues, and whether the decrease in T_3 availability promotes or impedes recovery from the effects of the illness. Until more is known about the latter, administration of either T_4 or T_3 to patients with nonthyroidal illness is problematic.

Robert D. Utiger, M.D.

Thyroid Review Articles

Cappola AR, Ladenson PW. Hypothyroidism and atherosclerosis. J Clin Endocrinol Metab 2003;88:2438-44.

Cooper DS. Antithyroid drugs in the management of patients with Graves' disease: an evidence-based approach to therapeutic controversies. J Clin Endocrinol Metab 2003;88:3474-81.

Knobel M, Medeiros-Neto G. An outline of inherited disorders of the thyroid hormone generating system. Thyroid 2003;13:771-801.

Pearce EN, Farwell AP, Braverman LE. Thyroiditis. N Engl J Med 2003;348:2646-55.

Silva JE. The thermogenic effect of thyroid hormone and its clinical implications. Ann Intern Med 2003;139:205-13.

Van Vliet G. Development of the thyroid gland: lessons from congenitally hypothyroid mice and men. Clin Genet 2003;63:445-55.

Correction

Papillary thyroid microcarcinomas grow slowly or not at all (July 2003:30). The second and third lines of the sentence at the top of the right column of the Summary should read "…. increased by ≥2 mm in approximately 25 percent, and it decreased by ≥2 mm in approximately 10 percent (Table)." In both instances the change was erroneously described as ≥2 cm.

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Program outline:

- Description of patients at risk for thyroid dysfunction
- Overview of diagnosis and management of thyroid disorders during pregnancy
- Review of normal thyroid function in healthy women and changes during pregnancy
- Discussion of the prevalence and etiology of thyroid dysfunction during pregnancy
- Review of evidence of adverse effect on pregnancy outcome and fetal and childhood development
- Discussion of the potential role of environmental toxins on thyroid function
- Review of the diagnosis and management of thyroid disorders during pregnancy, including a focus on whether at-risk patients can be identified and the potential benefits of population screening

Further Information and Registration

This activity has been approved for AMA PRA credit.

Program and registration information will be available two months prior to the conference on the Johns Hopkins website at: www.hopkinscme.org/cme

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