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CLINICAL THYROIDOLOGY

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The Taxonomy of Hashimoto

Almost a century ago Hashimoto described four women with goiters that appeared to have become lymphoid organs—hence the name struma lymphomatosa (1). From this beginning, as the eponym for a relatively well-defined clinical and pathological syndrome, Hashimoto's name has been applied to an increasing number of thyroid and other conditions.

The first steps in this process were the discovery that patients with Hashimoto's disease had high serum concentrations of antithyroid antibodies (2), that the concentrations were high in patients with hypothyroidism and a normal-sized or atrophic thyroid gland, and finally that the concentrations were high in patients with no thyroid dysfunction or no change in thyroid size at all. The terms Hashimoto's disease and Hashimoto's thyroiditis have been applied to all these conditions. A better term is chronic autoimmune thyroiditis, retaining the term Hashimoto's disease (thyroiditis) for patients with goiter and high serum antithyroid antibody concentrations. Because definitions vary, anyone using the term Hashimoto's disease must provide theirs.

The name encompasses still more. Many people with various nonthyroid disorders, some thought to be autoimmune disorders, have high serum antithyroid antibody concentrations, prompting the conclusion that there is some association between the particular disorder and chronic autoimmune thyroiditis, or, in colloquial terms, Hashimoto's disease. This issue of *Clinical Thyroidology* contains articles describing associations between high serum antithyroid antibody concentrations and chronic urticaria (p. 36) and the polycystic ovarian syndrome (p. 37). Perhaps the epitome of these associations is Hashimoto's encephalopathy. The strength of these associations has varied, and the studies were often not well-controlled (a critical problem given the high frequency of high serum antithyroid antibody concentrations in healthy people). More important is the lack of biologic plausibility of the associations. The antibodies don't affect the thyroid, so why should they affect any other organ?

Given that so many people have high serum antithyroid antibody concentrations, it is hard to escape the conclusion that tolerance to thyroid tissue is lost more readily than tolerance to any other organ. Hence, the linkage of Hashimoto, rather than Addison or someone else, to encephalopathy (or urticaria or ovariopathy?) doesn't provide much insight into the pathogenesis of the particular disorder(s). These are idiopathic disorders, and at least for now we should leave it at that.

Robert D. Utiger, M.D.

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1. Hashimoto H. Zur Kenntniss der Lymphomatosen Veränderung der Schilddrüse (Struma lymphomatosa). Arch Klin Chir 1912;97:219-48.
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Clinical Thyroidology is available on the ATA web site (www.thyroid.org)

Quality of life is reduced in patients with hypothyroidism, hyperthyroidism, and goiter

Bianchi GP, Zaccheroni V, Solaroli E, Vescini F, Cerutti R, Zoli M, Marchesini G. Health-related quality of life in patients with thyroid disorders. *Qual Life Res* 2004;13:45-54.

SUMMARY

Background Thyroid disorders are common, but relatively few patients have many symptoms, and the extent to which their quality of life is altered has not been studied often. This study assessed the quality of life in patients with several thyroid disorders.

Methods The study subjects were 317 consecutive patients (275 women, 42 men; age range, 18 to 85 years) seen in a specialty clinic in Bologna, Italy, for evaluation of symptoms or abnormal serum hormonal values suggesting the presence of a thyroid disorder. They included 36 patients with overt hypothyroidism, 45 patients with subclinical hypothyroidism, 27 patients with overt hyperthyroidism, 18 patients with subclinical hyperthyroidism, and 191 euthyroid patients with goiter (there were an additional 51 patients with Hashimoto's thyroiditis, not considered further in this summary because both euthyroid and hypothyroid patients were considered together).

At the time of diagnosis, the patients were queried about mood and behavioral problems, sleep problems, and their perception of their health, and they completed the Medical Outcomes Study Short Form-36 (SF-36) and the Nottingham Health Profile (NHP). The SF-36 consists of questions about eight domains of physical and mental health (physical functioning, physical role limitation, emotional role limitation, bodily pain, vitality, mental health, general health, and social functioning). The NHP consists of questions about six domains (energy, emotional reactions, sleep, social isolation, mobility, and pain). The results were compared with those obtained in two large population studies in Italy, after stratification by age and sex, and the differences were expressed as Z scores (difference between patient value and control mean, divided by the standard deviation of the control group).

Results A substantial proportion of the patients in all three groups reported mood and behavioral problems, sleep problems, and changes in perceived health during the previous year (Table 1).

Table 1. Self-Reported Health Effects in Patients with Hypothyroidism, Hyperthyroidism, and Goiter.

	Hypothyroidism	Hyperthyroidism	Goiter
Mood and behavior problems	65%	47%	58%
Sleep problems	63%	44%	57%
Perception of health in past year (worse/no change/better)	41/46/13%	51/42/7%	35/56/9%

The Z score was not lower than -1.00 for any domain of the SF-36 in any of the three patient groups (Table 2). The results of the NHP deviated even less from the control subjects (and in a few instances were >0).

Table 2. Z Scores for Selected Domains of the SF-36 in Patients with Hypothyroidism, Hyperthyroidism, and Goiter.

	Hypothyroidism	Hyperthyroidism	Goiter
Physical functioning	-0.46*	-0.31	-0.23*
Physical role limitation	-0.63*	-0.72*	-0.23*
Emotional role limitation	-0.71*	-0.65*	-0.29*
Vitality	-0.48*	-0.29	-0.36*
General health	-0.60*	-0.50*	-0.38*
Social functioning	-0.60*	-0.41*	-0.30*

*P<0.05, as compared with population values.

The Z scores for the patients with subclinical hypothyroidism and subclinical hyperthyroidism were closer to 0 than the Z scores for those with overt hypothyroidism and overt hyperthyroidism, respectively.

Conclusion Patients with hypothyroidism, hyperthyroidism, or goiter have decreased quality of life.

COMMENTARY

These results seem to indicate that quality of life, at least as measured by the two questionnaires, is not seriously reduced in patients with thyroid dysfunction or goiter (Z scores of -0.80 or lower are considered to represent large deficits). These questionnaires are considered to assess quality of life accurately in patients with many different disorders, but it is possible that thyroid disorders are not among them. In general, the scores in the patients with hypothyroidism and hyper-

thyroidism were lower than those in the euthyroid patients with goiter (not otherwise characterized, but excluding Hashimoto's thyroiditis). Also, there were differences, although not statistically significant, in the scores in patients with overt hypothyroidism and those with subclinical hypothyroidism, and similarly in patients with overt and subclinical hyperthyroidism, indicating that quality of life decreases as thyroid secretion becomes more abnormal and the frequency of symptoms of abnormal thyroid secretion increases. Wider use of

these or similar questionnaires should help to resolve some of the questions regarding the impact of subclinical hypothyroidism and subclinical hyperthyroidism.

Robert D. Utiger, M.D.

Cardiovascular and metabolic responses to triiodothyronine are similar in mice lacking β -adrenergic receptors and normal mice

Bachman ES, Hampton TG, Dhillon H, Amende I, Wang J, Morgan JP, Hollenberg AN. The metabolic and cardiovascular effects of hyperthyroidism are largely independent of β -adrenergic stimulation. *Endocrinology* 2004;145:2767-74.

SUMMARY

Background Thyroid hormones and catecholamines have similar stimulatory cardiovascular and metabolic actions. These actions may be synergistic or additive, and in the case of thyroid hormone may involve adrenergic receptor activation. This study evaluated the cardiovascular and metabolic actions of thyroid hormone in animals lacking β -adrenergic receptors.

Methods The study animals were 12- to 14-week-old normal mice and mice lacking the genes for all three isoforms of the β -adrenergic receptor. The two types of mice had similar body weights and serum thyroxine (T_4) and triiodothyronine (T_3) concentrations. Cardiovascular responsiveness to β -adrenergic activation was determined by measurements of cardiac time intervals by electrocardiography and heart weights after administration of the β -adrenergic agonist isoproterenol for three days. Thyroid hormone responsiveness was determined in a similar manner, and also by measurements of cardiac hemodynamics, cardiac genes, and oxygen consumption (measured as heat production), after intraperitoneal administration of T_3 , 4 μ g daily, or saline for 14 days.

Results As compared with wild-type mice, the mice lacking β -adrenergic receptors had a lower rate of oxygen consumption, a slower heart rate (553 vs. 719 beats per minute),

and prolonged PR and QT intervals. Blood pressure, cardiac contractility (peak left ventricular systolic pressure, left ventricular end-diastolic pressure, maximum rates of pressure rise and fall), and cardiac weight were similar in the two groups. Administration of isoproterenol caused an increase in heart rate, ST segment depression, and heart weight in the normal mice, but not in the mice lacking β -adrenergic receptors.

Administration of T_3 reduced serum T_4 concentrations and increased oxygen consumption to the same extent (approximately 14 percent) in wild-type mice and mice lacking β -adrenergic receptors, but body weight did not change. Heart rate increased from 553 to 636 beats per minute (15 percent) in mice lacking β -adrenergic receptors, and from 719 to 820 beats per minute (14 percent) in wild-type mice. Cardiac contractility increased similarly in response to T_3 in both groups of mice. Cardiac weight also increased in response to T_3 in both groups, but the increase was greater in wild-type mice. The expression of the *HCN2* (pacemaker) gene increased in response to T_3 in both groups.

Conclusion Mice lacking β -adrenergic receptors and normal mice have similar cardiovascular and metabolic responses to T_3 , indicating that these actions of T_3 are not mediated by adrenergic activation.

COMMENTARY

Many of the effects of hyperthyroidism have been attributed to sympathetic activation, but attempts to document activation have for the most part been unsuccessful. Catecholamine production is not increased, and sensitivity to catecholamine infusions is little, if at all, increased. Perhaps the best evidence for such activation is the beneficial effect of β -adrenergic receptor antagonist drugs to decrease cardiac rate and contractility, oxygen consumption, and symptoms such as tremor and anxiety in patients with hyperthyroidism. While the decreases in cardiovascular function are greater in patients with hyperthyroidism than in normal subjects, the fractional decreases are similar in the two groups, evidence

against synergism between thyroid hormone and catecholamines.

These results in mice provide stronger evidence that the effects of thyroid hormone and sympathetic activation are not synergistic. The mice lacking β -adrenergic receptors had a lower heart rate, less cardiac contractility, and a lower rate of oxygen consumption, as compared with wild-type mice, but serum T_4 and T_3 concentrations were similar in both groups. The ability of T_3 , in what looks like a high dose, but which did not cause weight loss, to increase heart rate, cardiac contractility, cardiac weight (hypertrophy), and oxygen consumption also was similar in both groups.

These results do not negate the benefits of β -adrenergic antagonist drug therapy in patients with hyperthyroidism,

but they support studies indicating that it is less beneficial than antithyroid drug therapy (1).

Robert D. Utiger, M.D.

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The outcome of hyperthyroidism caused by Graves' disease can be predicted

Orunesu E, Bagnasco M, Salmaso C, Altrinetti V, Bernasconi D, Del Monte P, Pesce G, Marugo M, Mela GS. Use of an artificial neural network to predict Graves' disease outcome within 2 years of drug withdrawal. *Eur J Clin Invest* 2004;34:210-7.

SUMMARY

Background Patients with hyperthyroidism caused by Graves' disease who are treated with an antithyroid drug may have recurrent hyperthyroidism after the drug is stopped, indicating persistence or recurrence of the disease. Treatment decisions might be facilitated if the course could be predicted reliably. This study was done to determine the importance of different clinical and biochemical variables for predicting outcome after cessation of drug therapy.

Methods The study subjects were 71 consecutive patients (55 women, 16 men; age range, 17 to 77 years) with hyperthyroidism caused by Graves' disease seen at two clinics in Genoa, Italy. The diagnosis was based on clinical manifestations of hyperthyroidism, serum free thyroxine (T_4) and free triiodothyronine (T_3) concentrations ≥ 2 times the upper limit of normal, a diffuse increase in uptake of technetium-99m, and a high serum antithyroid peroxidase antibody concentration. Serum thyrotropin-receptor antibodies were not measured. The patients were treated with 10 to 40 mg of methimazole daily until they were euthyroid, after which the dose was tapered to maintain normal serum free T_4 and free T_3 concentrations. The mean maintenance dose was 5 mg daily. The total duration of therapy was 18 months. The patients were then followed for two years, or until recurrence of hyperthyroidism.

The analysis was based on 21 variables for which information was collected at base line and 4 variables related to therapy. The former included personal characteristics such as age, sex, smoking, mental changes requiring psychotropic drug therapy, and clinical and biochemical findings such as

weight loss, heart rate, ophthalmopathy, serum free T_4 and free T_3 values, serum antithyroid peroxidase antibody values, and thyroid volume and echogenicity. The latter included time to euthyroidism and occurrence of and time to hypothyroidism, if that occurred. A numerical value was assigned to all variables. The results in the recurrence and remission groups were compared, and combinations of variables were analyzed using an artificial neural network approach (also described as forecasting analysis) to identify the variables that predicted recurrence or remission.

Results During the two-year follow-up period, 27 patients (38 percent) remained euthyroid and 44 (62 percent) had recurrent hyperthyroidism. There were no differences in the individual findings in the two groups, except for smoking (26 percent in the remission group, vs. 54 percent in the recurrence group). Based on analysis of all the variables, several subsets of seven variables had the same predictive value as the set of all variables. Among these subsets, the one composed of findings readily obtained at base line that predicted recurrence of hyperthyroidism consisted of presence of smoking, mental changes requiring psychotropic drug therapy, rapid heart rate, presence of a thyroid bruit, a high serum free T_4 concentration, a high serum antithyroglobulin antibody concentration, and thyroid volume >20 ml with both heterogeneity and hypoechoogenicity. Based on these findings, the outcome was predicted correctly in 77 percent of the 44 patients who had a recurrence and 85 percent of the 27 patients who remained in remission.

Conclusion Among patients with hyperthyroidism caused by Graves' disease, the likelihood of prolonged remission can be predicted reliably based on several clinical, biochemical, and ultrasonographic findings at the time of diagnosis.

COMMENTARY

The clinical and biochemical findings at the time of diagnosis in these patients are not described in detail, but were probably similar to those in most patients with Graves' hyperthyroidism, and the frequency of prolonged remission was similar to that in other studies. The only individual finding at base line associated with recurrence of hyperthyroidism was smoking, a known risk factor for Graves' hyperthyroidism and especially ophthalmopathy. Information about this and the other variables included in the subset that had predictive value are indeed easily obtained. However, with the exception of smoking their frequency in

the recurrence and relapse groups is not given, and the results of the neural network or forecasting analysis indicate only the relative importance of a finding in abstract terms.

While the analytic approach used in this study was novel, many investigators have tried to identify findings at base line that predict recurrence or remission of hyperthyroidism after antithyroid drug therapy is stopped. In one study, base-line findings associated with recurrent hyperthyroidism were young age, large goiter, presence of ophthalmopathy, and a high serum concentration of thyrotropin-receptor antibodies (1).

In sum, some base-line findings do predict recurrence or remission of hyper-

thyroidism, in effect predicting persistence or disappearance of Graves' disease, but even combinations of these findings are not sufficiently predictive to be very helpful in individual patients.

Robert D.Utiger, M.D.

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High serum thyrotropin-receptor antibody levels during antithyroid drug therapy predict recurrent hyperthyroidism in patients with Graves' disease

Schott M, Morgenthaler NG, Fritzen R, Feldkamp J, Willenberg HS, Scherbaum WA, Seissler J. Levels of autoantibodies against human TSH receptor predict relapse of hyperthyroidism in Graves' disease. *Horm Metab Res* 2004;36:92-6.

SUMMARY

Background Hyperthyroidism in patients with Graves' disease is caused by thyrotropin (TSH) receptor-stimulating antibodies (TSHR-Ab). Persistence or disappearance of the antibodies during antithyroid drug therapy would be expected to predict recurrent hyperthyroidism or sustained remission, respectively, but often do not. This study was done to determine the predictive value of measurements of serum TSHR-Ab using a new assay for the antibodies.

Methods The study subjects were 93 patients (73 women, 20 men; age range, 15 to 72 years) with hyperthyroidism caused by Graves' disease. All the patients had symptoms and signs of hyperthyroidism, high serum free thyroxine (T₄) and free triiodothyronine (T₃) and low TSH concentrations, and diffuse uptake of pertechnetate (Tc)-99m on scintigraphy. The patients were treated with methimazole or carbimazole for a median duration of 5 months (range not stated); when stopped, the dose ranged from 2.5 to 20 mg daily (the clinical status at the time therapy was stopped is not described). At that time, serum TSHR-Ab were measured by radioreceptor assay using recombinant human TSH receptors, and serum TSH was measured by chemiluminescence assay. The patients were then followed for a median duration of 22 months.

Results Sixty patients (65 percent) had recurrent hyperthyroidism within 24 months after cessation of antithyroid drug therapy, and 33 patients (35 percent) remained euthyroid during a median follow-up period of 17 months.

At the end of the period of antithyroid drug therapy, all patients had high serum TSHR-Ab values. The median serum TSHR-Ab value was 8.6 U/L (range, 1.1 to 150) in the patients who had recurrent hyperthyroidism, and it was 2.1 U/L (range, 1.1 to 22.3) in the patients who remained euthyroid (P<0.001). Among the 29 patients with a serum TSHR-Ab value ≥10 U/L, 28 had recurrent hyperthyroidism and 1 remained euthyroid (Table).

Table. Serum TSHR-Ab Values in Patients Who Had Recurrent Hyperthyroidism or Who Remained Euthyroid after Cessation of Antithyroid Drug Therapy.

Serum TSHR-Ab Value	Recurrence	Remission
≥10 U/L	28	1
<10 U/L	32	32

The positive predictive value of a serum TSHR-Ab value ≥10 U/L, chosen on the basis of receiver-operating-curve analysis, for recurrent hyperthyroidism was 96 percent. The distribution of values ranging from 1.1 to 9.9 U/L in the two groups was similar.

At the same time, the median serum TSH concentration was 0.008 mU/L in the patients who had recurrent hyperthyroidism and 0.20 mU/L in the patients who remained euthyroid (P=0.06).

Conclusion High serum TSHR-Ab values, measured after antithyroid drug therapy for several months, predict recurrent hyperthyroidism in patients with Graves' disease after cessation of therapy.

COMMENTARY

No one doubts that TSHR-Ab are the cause of hyperthyroidism in patients with Graves' disease, and there is a rough correlation between the severity of hyperthyroidism and serum TSHR-Ab values. The values usually fall during antithyroid drug therapy; whether the fall is due to amelioration of hyperthyroidism, an immunosuppressive effect of antithyroid drugs, or some other reason is debated. If TSHR-Ab production ceases, or falls to very low levels not sufficient to raise serum T₄ and T₃ concentrations above normal, then the patient should remain well after therapy is stopped. Thus, measurements of serum TSHR-Ab during drug therapy might

have more predictive value than measurements before therapy.

The rationale for testing after therapy for 5 months is not stated, but may have been that the patients had been euthyroid for a while and therapy was about to be stopped (although many still had low serum TSH concentrations). At this time a quite high serum TSHR-Ab value (≥10 U/L) clearly predicted recurrent hyperthyroidism. The problem is that only about one third of the patients had such a high value at this time. For them, the appropriate step may well be destructive therapy. For the two thirds of the patients with serum TSHR-Ab values <10 U/L, however, the test had no predictive value. It might have performed better if all the patients had been treated

with more drug, or longer, until they had normal serum TSH concentrations.

Robert D. Utiger, M.D.

Antineutrophil cytoplasmic antibodies are present more often in propylthiouracil- than carbimazole-treated patients with hyperthyroidism caused by Graves' disease

Harper L, Chin L, Daykin J, Allahabadia A, Heward J, Gough SC, Savage CO, Franklyn JA. Propylthiouracil and carbimazole associated-antineutrophil cytoplasmic antibodies (ANCA) in patients with Graves' disease. *Clin Endocrinol (Oxf)* 2004;60:671-5.

SUMMARY

Background Some patients with hyperthyroidism caused by Graves' disease have serum antineutrophil cytoplasmic antibodies (ANCAs) at the time of diagnosis, but the antibodies are present more often during therapy with an antithyroid drug, particularly propylthiouracil. This study was done to determine the frequency of serum ANCAs and antimyeloperoxidase (MPO) antibodies in patients with Graves' hyperthyroidism before and during antithyroid drug therapy and in patients with Hashimoto's thyroiditis.

Methods Single serum samples were analyzed from 407 patients with Graves' disease, 200 patients with Hashimoto's thyroiditis (not further defined), and 649 euthyroid subjects. Most if not all of the patients with Graves' disease must have had hyperthyroidism, but this is not stated explicitly; 252 were being treated with carbimazole, 42 with propylthiouracil, 26 had not received either drug, and 87 had been treated in the past, but not for at least six weeks (stated also as one week, with a mean of 26 weeks). The serum samples were tested for ANCA by indirect immunofluorescence using normal peripheral-blood neutrophils and for anti-MPO antibodies by enzyme-linked immunoassay. None of 30 patients who had high serum antithyroid peroxidase concentrations had high serum anti-MPO values.

Results ANCAs were detected in the serum of 81 of the 407 patients with Graves' hyperthyroidism (20 percent), 16 of the 200 patients with Hashimoto's thyroiditis (8 percent), and 30 of the 649 euthyroid subjects (5 percent) ($P < 0.001$,

compared with the patients with Graves' hyperthyroidism). Serum anti-MPO antibody values were high in 13 patients with Graves' hyperthyroidism (3 percent), no patient with Hashimoto's thyroiditis, and 7 euthyroid subjects (1 percent) ($P < 0.05$). The median serum anti-MPO antibody value in the patients with Graves' hyperthyroidism was 21 (range, 15 to 100; normal, < 7.5) (units not specified). The serum anti-MPO antibody value was 100 in one patient with Graves' hyperthyroidism treated with propylthiouracil who had active vasculitis (the values in 95 patients with active ANCA vasculitis, but no thyroid disease, ranged from 11 to 341).

Among the patients with Graves' hyperthyroidism, serum ANCAs and anti-MPO antibodies were most often present in those treated with propylthiouracil (Table). There was no correlation between the presence of ANCAs and the duration of either propylthiouracil or carbimazole therapy.

Table. Frequency of Serum ANCA and Anti-MPO Antibodies in Patients with Graves' Hyperthyroidism According to Treatment.

	No.	ANCA	Anti-MPO Antibodies
No drug therapy	26	1 (4%)	0 (0%)
Propylthiouracil therapy	42	14 (33%)*	5 (12%)*
Carbimazole therapy	252	40 (16%)	3 (1%)
Previous drug therapy	87	26 (30%)	5 (6%)

* $P < 0.05$, compared with the carbimazole group.

Conclusion Untreated patients with Graves' hyperthyroidism rarely have serum ANCAs or anti-MPO antibodies, but the antibodies are relatively common during therapy, especially in patients treated with propylthiouracil.

COMMENTARY

The results of measurements of serum ANCA and its components in untreated patients with Graves' hyperthyroidism have varied considerably, from 0 to 67 percent having the antibodies (1,2); in this study it was 4 percent. In this and most other studies the frequency was considerably higher in patients treated with propylthiouracil, and somewhat higher in patients treated with methimazole or carbimazole. This relationship with antithyroid drug therapy suggests that the drugs are taken up by neutrophils and bind to myeloperoxidase or other neutrophil components, making them more immunogenic (the drugs alter myeloperoxidase activity in vitro).

Little is known about the natural history of these antibodies in patients with Graves' hyperthyroidism, except to say that they more often appear than disappear during antithyroid drug therapy. Do they appear after treatment with other drugs, radioiodine, or surgery? That seems unlikely, but has not been studied. Among patients with hyperthyroidism, do they occur only in those with Graves' disease? Probably. More important, are the antibodies important? Probably not, with rare exceptions; only a very few patients, nearly all treated with propylthiouracil, have vasculitis, the usual clinical correlate of high serum levels of ANCA.

Robert D. Utiger, M.D.

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Adipogenesis is increased in retroorbital tissue of patients with Graves' ophthalmopathy

Kumar S, Coenen MJ, Scherer PE, Bahn RS. Evidence for enhanced adipogenesis in the orbits of patients with Graves' ophthalmopathy. *J Clin Endocrinol Metab* 2004;89:930-5.

SUMMARY

Background Graves' ophthalmopathy is characterized by enlargement of both orbital fibroadipose tissue and extraocular muscles. In this study the expression of several genes involved in adipogenesis was measured in retroorbital tissue from patients with Graves' ophthalmopathy and normal subjects.

Methods Retroorbital fibroadipose tissue was obtained during the course of transantral orbital decompression surgery from 22 patients (13 women, 9 men; mean age, 57 years) with Graves' ophthalmopathy, and at autopsy from 18 patients (10 women, 8 men; mean age, 71 years) whose corneas were being harvested for transplantation. The patients with Graves' ophthalmopathy had had hyperthyroidism 56 months before, and they had had ophthalmopathy for 45 months. At the time of surgery, all were euthyroid, 4 had optic neuropathy, 4 were taking glucocorticoids, and 9 were current smokers.

Portions of the tissue from 6 patients with Graves' ophthalmopathy and 3 control patients were cultured for 10 days under conditions that stimulate adipogenesis. Total RNA was isolated from the cultured cells and the fresh tissue samples from all patients in both groups. The levels of mRNA coding for the thyrotropin (TSH) receptor, leptin, adiponectin, peroxisome proliferator activator- γ (PPAR- γ), and preadipocyte factor-1 (PREF-1) were measured by quantitative real-time polymerase chain reactions. (During adipogenesis, the expression of leptin, adiponectin, and PPAR- γ is increased and that of PREF-1 is decreased.)

Results TSH-receptor mRNA was detected in the tissue from all patients with Graves' ophthalmopathy and 14 of the 15 control patients whose tissue was tested. Similarly, leptin, adiponectin, and PPAR- γ mRNA was detected in the tissue from all patients with ophthalmopathy and all control patients. For all four substances, the levels of mRNA were higher in the tissue from the patients with ophthalmopathy. The levels of TSH-receptor mRNA were positively correlated with the levels of leptin, adiponectin, and PPAR- γ mRNA in the tissues from the patients with ophthalmopathy, but not the control patients. There was no correlation between the levels of mRNA for these substances and any clinical characteristics of the patients with ophthalmopathy. There were no differences in the levels of PREF-1 mRNA in the two groups.

The level of TSH-receptor mRNA increased 12-fold in the cell cultures from the patients with ophthalmopathy that were stimulated to differentiate, but only 2-fold in the stimulated cell cultures from the control patients. For leptin mRNA, the increases were 16-fold and 3-fold, respectively, whereas the levels of adiponectin mRNA increased to a similar extent (13- and 9-fold, respectively). In contrast, the levels of mRNA for PPAR- γ and PREF-1 were not higher in the cultures stimulated to differentiate, as compared with the control cultures.

Conclusion Genes involved in adipocyte differentiation and the TSH-receptor gene are activated in retroorbital tissue from patients with Graves' ophthalmopathy.

COMMENTARY

The volume of both retroorbital fibroadipose tissue and extraocular muscles is increased in patients with Graves' ophthalmopathy. The increase in volume of fibroadipose tissue could be due to adipogenesis or adipocyte hypertrophy. The finding of higher levels of the mRNAs for leptin, adiponectin, and PPAR- γ in the tissue suggests the increase is due to adipogenesis, with the proviso that the increases in mRNA result in increases in production of the relevant proteins. The correlation between the increases in mRNA levels for these substances and that for the

TSH-receptor suggests that the receptors are located on the same cells.

What is the stimulus that leads to an increase in adipogenesis in the orbits? A likely candidate is TSH-receptor antibodies, present in the serum of most patients with ophthalmopathy. It would be of interest to determine the effects of the antibodies on retroorbital fibroadipose tissue *in vitro*.

A clinical footnote: PPAR- γ agonist drugs (thiazolidinediones) stimulate adipogenesis, and in one patient with diabetes mellitus and Graves' disease one of these drugs (pioglitazone) exacerbated ophthalmopathy (1).

Reference

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Robert D. Utiger, M.D.

Carotid intima-media thickness is increased in subclinical hypothyroidism

Monzani F, Caraccio N, Kozakowa M, Dardano A, Vittone F, Virdis A, Taddei S, Palombo C, Ferrannini E. Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism: a double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 2004;89:2099-106.

SUMMARY

Background An increase in thickness of the intimal and medial layers of the carotid arteries is a risk factor for arteriosclerotic vascular disease, including myocardial infarction and stroke. Hypothyroidism may also be a risk factor for the disease. In this study the thickness of the intimal and medial layers (intima-media thickness) of the carotid arteries and biochemical risk factors for arteriosclerosis were measured in patients with subclinical hypothyroidism before and during thyroxine (T₄) therapy.

Methods The study subjects were 45 patients (37 women, 8 men; mean [±SD] age, 37±11 years) with subclinical hypothyroidism (high serum thyrotropin [TSH] and normal serum free T₄ concentrations) for at least six months, and 32 normal subjects (27 women, 5 men; mean age, 35±10 years). Among the patients with subclinical hypothyroidism, 36 had Hashimoto's thyroiditis and 9 had been treated with radioiodine for a nodular goiter. Serum TSH, free T₄, lipids and homocysteine were measured in all subjects. The thickness of the intima and media of both common carotid arteries and the carotid bifurcation was determined by ultrasonography, and the results were averaged.

The patients with subclinical hypothyroidism were then randomly assigned to receive 25 µg of T₄ or placebo daily; the dose of T₄ was raised in 25-µg increments until the patients' serum TSH concentration was ≤3.6 mU/L. Treatment was continued for six months (median total treatment period, 10 months), at which time the biochemical and ultrasound measurements were repeated. The investigator who performed the intima-media thickness measurements was not aware of treatment-group assignment.

Results The patients with subclinical hypothyroidism higher serum TSH concentrations (6.3 vs. 1.2 mU/L), lower serum free T₄ concentrations, and higher serum total and low-density lipoprotein (LDL) cholesterol concentrations, as compared with the normal subjects. Serum high-density lipoprotein (HDL) cholesterol, triglyceride, and homocysteine concentrations were similar in the two groups. The mean intima-media thickness of the carotid arteries was 0.75 mm in the patients with subclinical hypothyroidism and 0.63 in the normal subjects (P<0.01).

The mean carotid intima-media thickness decreased in the patients who were treated with T₄, whereas it did not change in the patients in the placebo group (Table).

	T ₄ Therapy (n=23)		Placebo (n=22)	
	Base Line	During Therapy	Base Line	During Therapy
Serum TSH (mU/L)	6.0	1.3*	5.7	6.0
Intima-media thickness (mm)	0.76	0.67*	0.74	0.77

*P<0.001, compared with base line

Serum total and LDL cholesterol concentrations decreased in the T₄-therapy group (P<0.01), but not in the placebo group. Serum HDL cholesterol, triglyceride, and homocysteine concentrations did not change in either group.

Conclusion Carotid intima-media thickness is increased in patients with subclinical hypothyroidism, and it decreases during T₄ therapy.

COMMENTARY

The increase in carotid intima-media thickness and the decrease in response to T₄ therapy in these patients with subclinical hypothyroidism were similar to those in 35 patients with overt hypothyroidism (cause not stated) (1). In that study, the patients' mean intima-media thickness was 0.64 mm, as compared with 0.56 mm in matched normal subjects, and it decreased to 0.55 mm after treatment with T₄ for one year. The similarity of the increase in thickening above normal in the two groups is rather surprising, but may not be real, because the studies were done in different countries using different equipment.

Increases in intima-media thickness of this magnitude had little effect on the risk of myocardial infarction or stroke in a large cohort study (2). Nonetheless, they provide additional evidence that arteriosclerosis may be accelerated in patients with hypothyroidism.

Robert D. Utiger, M.D.

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Severe mental impairment and poor physiologic status are associated with mortality in myxedema coma

Rodriguez I, Fluiters E, Perez-Mendez LF, Luna R, Paramo C, Garcia-Mayor RV. Factors associated with mortality of patients with myxoedema coma: prospective study of 11 cases treated at a single institution. *J Endocrinol* 2004;180: 347-50.

SUMMARY

Background Patients with myxedema coma, by definition, have impaired consciousness, and many have complicating illnesses. Treatment is controversial. This study describes the clinical findings and response to thyroxine (T_4) therapy, given according to two randomly assigned treatment regimens, in patients with myxedema coma.

Methods From 1985 to 2002, eleven patients (10 women, 1 man; mean age, 68 years [range, 20 to 84]) with myxedema coma were treated at a single hospital in Spain. Myxedema coma was defined as impaired mental status, hypothermia ($\leq 35.0^\circ\text{C}$), the presence of a precipitating illness (urinary tract infection, respiratory infection, typhoid fever), and a low serum free T_4 concentration. Eight patients had high serum thyrotropin (TSH) concentrations, and three had low to slightly high serum TSH concentrations and a nonsecreting pituitary tumor. Five patients were seen in the winter, and six at other times. The patients were evaluated using the Glasgow coma and APACHE (Acute Physiology and Chronic Health Evaluation) II scores.

The patients were admitted to the intensive-care unit, and were randomly assigned to receive a single intravenous dose of 500 μg of T_4 followed by daily intravenous doses of 100 μg , or daily intravenous doses of 100 μg , until they were able to take T_4 orally. All patients were given hydrocortisone until adrenal insufficiency was excluded.

Results No patient was known to have hypothyroidism at the time of admission. Seven patients were obtunded, and four were comatose. Their heart rates ranged from 38 to

144 beats per minute, respiratory rates from 10 to 25 per minute, rectal temperature from 33.6 to 35.0 $^\circ\text{C}$, and mean arterial pressure from 68 to 128 mm Hg. Their serum sodium concentrations ranged from 110 to 144 mmol/L (nine had values <130), potassium concentrations from 2.7 to 6.0 mmol/L, and creatinine concentrations from 0.9 to 2.4 mg/dl (80 to 212 $\mu\text{mol/L}$). The Glasgow coma scores ranged from 3 to 14 (low is more abnormal), and the APACHE II scores from 14 to 34 (high is more abnormal). Serum TSH concentrations ranged from 28 to 153 mU/L and serum free T_4 concentrations from 0.15 to 0.46 ng/dl (1.9 to 5.9 pmol/L) in the eight patients with primary hypothyroidism, and from 0.4 to 9.8 mU/L and 0.15 to 0.37 ng/dl (1.9 to 4.8 pmol/L), respectively, in the three patients with central hypothyroidism.

Four of the 11 patients (36 percent) died 4 to 15 days after admission. One patient died of septic shock, and three of circulatory failure. Age, heart rate, and body temperature on admission were similar in the survivors and nonsurvivors. Three of the four patients who were comatose on admission, but only one of the seven who were obtunded, died. The initial Glasgow coma scores were lower (5 vs. 12, $P < 0.01$) and the APACHE II scores were higher (32 vs. 18, $P < 0.01$) in the patients who died. Among the six patients who received the high initial dose of T_4 , one (17 percent) died, as compared with three of the five patients (60 percent) who received the low dose ($P > 0.05$).

Conclusion Among patients with myxedema coma, the level of consciousness and degree of physiologic impairment are the most important predictors of survival.

COMMENTARY

Definitions of myxedema coma vary. For example, some authors have required the presence of coma or hypothermia, and therefore excluded patients who were arousable or did not have hypothermia. These distinctions seem minor, and should not obscure the fact that patients with myxedema coma, however defined, are very ill. Furthermore, most have other problems, including hypotension, respiratory depression, hyponatremia, and infection.

This study focused on the factors affecting outcome, including the efficacy of two randomly assigned regimens of T_4 therapy. The trend of the results favors the high initial dose of T_4 . No

patient received triiodothyronine (T_3), but it has been advocated on the presumption—almost certainly true—that the patients' concomitant nonthyroidal illness(es) will result in inhibition of the extrathyroidal conversion of any available T_4 to T_3 in most organs, and therefore T_3 should be given to circumvent this inhibition. The counter presumption is that it is better to provide the substrate (T_4), because conversion is tissue-specific and should not be circumvented. In a summary of the results of many regimens of T_4 or T_3 , or both, given intravenously or orally, in 87 patients with myxedema coma, of whom 27 (31 percent) died, the mortality rates were highest in patients given daily doses of ≥ 75 μg of T_3 or ≥ 500 μg of T_4 (the doses

were estimated as the average daily doses during the first three days of therapy)(1). The results of this summary and this new study suggest that moderately high doses of T_4 are best.

Robert D. Utiger, M.D.

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Thyroxine plus triiodothyronine and thyroxine alone have similar effects on mood and cognitive function in patients with hypothyroidism

Siegmund W, Spieker K, Weike AI, Giessmann T, Modess C, Dabers T, Kirsch G, Sanger E, Engel G, Hamm AO, Nauck M, Meng W. Replacement therapy with levothyroxine plus triiodothyronine (bioavailable molar ratio 14:1) is not superior to thyroxine alone to improve well-being and cognitive performance in hypothyroidism. *Clin Endocrinol (Oxf)* 2004; 60:750-7.

SUMMARY

Background Many patients with hypothyroidism who are treated with thyroxine (T₄) do not feel well. Treatment with a combination of T₄ and triiodothyronine (T₃) is little if at all more effective, but in most studies of the combination the patients were given arbitrary doses of T₃. In this study the effects of T₄ alone were compared with a combination of T₄ and T₃ in which the T₄:T₃ ratio was calculated to be the same as that secreted by the thyroid in normal subjects.

Methods The study subjects were 26 patients (21 women, 5 men; age range, 23 to 69 years) with hypothyroidism treated with 100 to 175 µg of T₄ daily. Three patients had autoimmune thyroiditis, six had Graves' hyperthyroidism and had been treated with radioiodine or surgery, and 17 had other, unspecified thyroid disorders for which they had been treated with radioiodine or surgery.

The patients were treated for four weeks with their usual dose of T₄, given once daily in locally prepared capsules. Then they were given, in random order for 12 weeks, capsules containing their usual dose of T₄ or capsules containing 95 percent of that dose as T₄ and 5 percent as T₃. This formulation was designed to provide T₄ and T₃ in a ratio of 14:1, assuming that 90 percent of the T₄ and 100 percent of the T₃ was absorbed. At the end of each 12-week treatment period, heart rate and serum thyrotropin (TSH), free T₄, free T₃, sex hormone-binding globulin, and lipids were measured, and multiple psychological tests were administered. These tests included the Beck Depression Inventory, the State-Trait Anxiety Inventory, the Profile of Mood Scales, and the Symptom Check-List 90. Cognitive function was assessed using the Digit Span Test and the Digit Symbol Test of the Wechsler Adult Intelligence Scale and the Visual

Scanning Test. The results did not vary according to sequence of treatment, and were therefore combined.

Results Twenty-three patients completed the study. There were no differences in heart rate, blood pressure, or biochemical values at the end of the 12-week treatment periods, except that the mean serum TSH concentration was lower and more patients had undetectable serum TSH concentrations at the end of the T₄-plus-T₃ period (table).

	T ₄	T ₄ plus T ₃
Serum TSH (mU/L)	1.5	0.5*
Serum TSH <0.02 mU/L (no.)	2	8
Serum free T ₄ (ng/dl)	1.6	1.6
Serum free T ₃ (ng/dl)	0.3	0.3
Serum cholesterol (mg/dl)	228	216
Serum sex hormone-binding globulin (mg/L)	3.8	4.3

*P<0.05, compared with T₄ alone group. Conversion factors: free T₄, ng/dl × 12.9 = pmol/L; free T₃, ng/dl × 15.4 = pmol/L; and cholesterol, mg/dl × 0.026 = mmol/L.

There were no differences in the results of the tests of mood, anxiety, other psychopathology, well-being, or cognitive function at the end of the two treatment periods. At the end of the T₄-plus-T₃ period, the eight patients with undetectable serum TSH concentrations had more depressive symptoms than the 15 patients who had more normal serum TSH values.

Conclusion Combination T₄ and T₃ therapy does not improve mood, general well-being, or cognitive function more than T₄ alone in patients with hypothyroidism.

COMMENTARY

This is the fourth study in which combination T₄ and T₃ therapy had no benefit, as compared with T₄ alone, in patients with hypothyroidism (see *Clinical Thyroidology* 2004;16:5-7). The daily dose of T₃ (5 to 9 µg) was based on a reasonable physiological proposition, and was the lowest of any of the studies (the dose was 10, 15, and 25 µg daily in the three other negative studies, and 12.5 µg in the one positive study [1]). The T₄ doses also varied, as did the extent to which the dose of T₄ was reduced when T₄ and T₃

were given.

In the earlier studies, the serum TSH concentrations during T₄-plus-T₃ therapy were similar or higher than during T₄ therapy. In this study, the mean serum TSH concentration was lower, and some of the patients had quite low values. The lack of benefit of combined therapy, despite the low serum TSH values, suggests that over treatment with T₄ is not the solution to the problem of continued symptoms and lack of well-being in patients treated with T₄ alone.

Robert D. Utiger, M.D.

Reference

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Sustained-release triiodothyronine results in less variation in serum concentrations than standard triiodothyronine

Hennemann G, Docter R, Visser TJ, Postema PT, Krenning EP. Thyroxine plus low-dose, slow-release triiodothyronine replacement in hypothyroidism: proof of principle. *Thyroid* 2004;14:271-5.

SUMMARY

Background Patients with hypothyroidism are usually treated with thyroxine (T₄) alone, despite the fact that the normal thyroid gland secretes both T₄ and triiodothyronine (T₃). One reason is that T₄ is converted to T₃ outside the thyroid gland. Another is that treatment with T₃ results a transient rise in serum T₃ concentrations. In this study the effects of sustained-release and standard preparations of T₃ were compared in patients with hypothyroidism.

Methods The study subjects were 15 patients (12 women, 3 men; age range, 26 to 79 years) with hypothyroidism. Fourteen had been taking 150 µg of T₄ and one 125 µg of T₄ daily for at least three months. The patients took their usual daily dose of T₄ for six weeks. They then took 125 µg of T₄ plus 6 µg of standard T₃ or sustained-release T₃ daily, each for six weeks, in a random crossover protocol. The composition of the sustained-release preparation of T₃ is not described. On the fifth day of the last week of each 6-week period, serum total T₄, total T₃, and thyrotropin (TSH) were measured before, and 1.5, 3, 6, and 9 hours after ingestion of T₄ or T₄ plus T₃.

Results The median serum T₄ concentrations increased by approximately 20 percent 1.5 to 3 hours after T₄ ingestion at the end of all three 6-week study periods (Table). In contrast, the median serum T₃ concentrations varied; there was little change at the end of the T₄ period, a small sustained rise at the end of the T₄-plus-sustained-release-T₃ period,

and an early rise and fall at the end of the T₄-plus-standard-T₃ period. The median serum TSH concentrations were similar in the two T₃-treatment groups.

Table. Median Serum T₄ and T₃ Concentrations after Ingestion of T₄, T₄ plus Standard T₃, and T₄ plus Sustained-Release T₃.*

	Base Line	1.5 Hours	3 Hours	6 Hours	9 Hours
T₄					
Serum T ₄ (µg/dl)	8.5	9.1	9.7	9.0	8.4
Serum T ₃ (ng/dl)	90	92	86	90	91
T₄ plus standard T₃					
Serum T ₄ (µg/dl)	8.1	8.9	9.1	8.8	9.0
Serum T ₃ (ng/dl)	93	116	118	97	105
T₄ plus sustained-release T₃					
Serum T ₄ (µg/dl)	8.1	9.2	9.1	8.6	8.8
Serum T ₃ (ng/dl)	83	98	103	104	101

*These results were shown in Figure 2 in the paper; the exact values were supplied by the authors.
To convert serum T₄ and T₃ to nmol/L, multiply by 12.9 and 0.0154, respectively.

The mean maximal serum T₃ concentration was 119 ng/dl (1.8 nmol/L) in the T₄-plus-standard-T₃ group and 108 ng/dl (1.7 nmol/L) in the T₄-plus-sustained-release-T₃ group (P=0.04); the respective peak serum T₃ values were at 3.2 and 5.0 hours (P=0.03). The respective areas under the serum T₃ curves were similar, suggesting that total absorption was similar.

Conclusion Ingestion of a sustained-release preparation of T₃ results in less variation in serum T₃ concentrations than ingestion of standard T₃, but overall absorption is similar.

COMMENTARY

Serum T₄ and T₃ concentrations do not vary according to the time of day in normal subjects, indicating that both are constantly produced and cleared. In the case of T₃ production, this means constant production not only by the thyroid but also by many other tissues, because 70 to 80 percent of the T₃ in serum is produced from T₄ in these other tissues.

In patients with hypothyroidism, in whom thyroidal T₃ production is minimal, therapy with T₄ alone does not quite restore serum T₃ concentrations to normal, unless serum T₄ concentrations are raised to the upper part of their normal range. The solution has been to add a little T₃. When this is done, however, serum T₃ concentrations rise and fall in several hours, even after doses as low as 6 µg (Table). After higher doses, for

example, 25 µg, serum T₃ concentrations are transiently supranormal. The solution to the rise and fall response is sustained-release T₃. The preparation used in this study did result in a slower rise in serum T₃ concentrations, and lower peak values, but a rise nonetheless. So it does not quite reproduce normal physiology.

Is combining a little T₃ with T₄ in patients with hypothyroidism important? In most studies in which standard T₃ was added to T₄ there was little benefit of the combination (see page 29, and also *Clinical Thyroidology* 2004;16:5-7). Might some unidentified adverse effects of the small rise and fall in serum T₃ concentrations in these studies obscure the benefits of T₃ given in conjunction with T₄? That seems unlikely. There are no data to suggest that there are hour-to-hour changes in any actions of T₃ after its administration as single doses, but

changes are possible, especially if T₃ has nongenomic actions. The availability of sustained-release preparations of T₃ will allow both this question of hour-to-hour changes in action and the value of combination T₄ and T₃ therapy in patients with hypothyroidism to be reexamined.

Robert D. Utiger, M.D

Thyroxine therapy has little effect on the size of thyroid nodules in postmenopausal women

Constante G, Crocetti U, Schifino E, Ludovico O, Capula C, Nicotera M, Arturi F, Filetti S. Slow growth of benign thyroid nodules after menopause: no need for long-term thyroxine suppressive therapy in post-menopausal women. *J Endocrinol Invest* 2004;27:31-6.

SUMMARY

Background Patients with thyroid nodules may be treated with thyroxine (T₄), but its efficacy and safety are debated. This retrospective study evaluated the effects of T₄ in postmenopausal women with thyroid nodules, because these women would be expected to be more sensitive to the deleterious effects of T₄ than younger women and men.

Methods The study subjects were 81 women with a single palpable thyroid nodule known to have been present for less than six months. They ranged in age from 45 to 54 years, and were at least one year postmenopausal. All the women had solid, hypofunctioning nodules, as determined by ultrasonography and scintigraphy, respectively, and all had biopsies consistent with a colloid nodule. Some of the women had additional small (<0.3 ml) nodules. All had normal thyroid function and normal serum antithyroid antibody concentrations; their mean urinary iodine excretion was 54 µg/L. Women with nodules >12 ml and those taking estrogen were excluded.

Forty-three women were treated with T₄, in a dose of 1.3 to 1.8 µg/kg daily; the remaining 38 women declined therapy or were ineligible because they had osteoporosis or cardiovascular disease. Thyroid function was assessed and ultrasonography done yearly. Thyroid volume was estimated as the volume of an ellipsoid; changes in volume of >50 percent were considered clinically important

Results All the women were followed for at least one year, and 29 and 26 women in the T₄ and untreated groups, respectively, were followed for five years (the reasons for dropping out are not fully described, but included noncompliance with T₄ therapy and onset of functional autonomy).

The base-line characteristics of the T₄-treated and untreated women were similar (Table). Thereafter, serum thyrotropin (TSH) concentrations were lower in the former group, but serum free T₄ and free triiodothyronine concentrations were similar in both groups at all times.

	Base Line	1 Year	3 Years	5 Years
T ₄ -treated women				
Serum TSH (mU/L)	1.2	0.4	0.4	0.4
Nodule volume (ml)	2.8	2.6	2.5	2.6
Untreated women				
Serum TSH (mU/L)	1.2	1.2	1.1	1.1
Nodule volume (ml)	2.8	2.9	2.8	2.6

There were no changes in median thyroid volume in either group. After one year, nodule volume decreased by >50 percent in 6 women (14 percent) and increased by >50 percent in 1 woman (2 percent) in the T₄-therapy group, whereas nodule volume decreased in 1 woman (3 percent) and increased in 2 women (5 percent) in the untreated group. At three years, nodule volume had decreased in 1 more T₄-treated woman (2 percent) and increased in 1 more untreated woman (3 percent). There were no changes between years 3 and 5.

Conclusion T₄ therapy in postmenopausal women with a thyroid nodule rarely results in a decrease in nodule size.

COMMENTARY

Benign thyroid nodules tend to grow very slowly. T₄ therapy may slow nodule growth, or even reduce nodule size. However, the evidence for benefit is far from compelling (1), and is hardly strengthened by this study. These women had mild to moderate iodine deficiency, which might increase the likelihood of a decrease in thyroid volume in response to a decrease in TSH secretion. The stated reason for the focus on postmenopausal women is their susceptibility to the deleterious effects of T₄. Some women did stop taking T₄, but why is not clearly described; the fall in serum TSH concen-

trations in the women in this group was so small that they would be unlikely to have any deleterious effects.

Might the lack of nodule growth in the untreated women be due to estrogen deficiency? The data presented hardly allow that conclusion, but one wonders. There is evidence that thyroid tissue contains estrogen receptors, and that estrogen has mitogenic activity in this tissue (2). So perhaps there is a biologic basis for a difference in the rate of growth of benign thyroid nodules, and thyroid carcinomas for that matter, in premenopausal and postmenopausal women.

Robert D. Utiger, M.D.

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Radioiodine doses of 25 to 50 mCi are equally effective for thyroid remnant ablation in patients with thyroid carcinoma

Bal CS, Kumar A, Pant GS. Radioiodine dose for remnant ablation in differentiated thyroid carcinoma: a randomized clinical trial in 509 patients. *J Clin Endocrinol Metab* 2004;89:1666-73.

SUMMARY

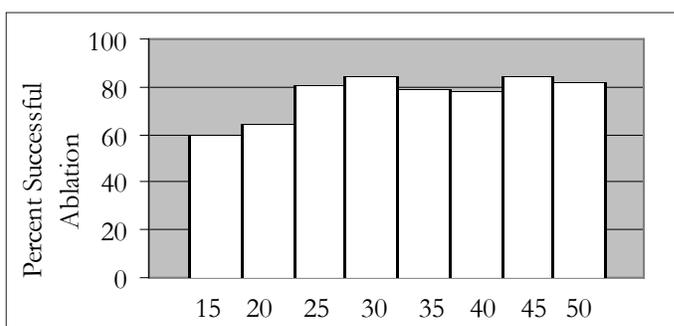
Background Most patients with papillary or follicular thyroid carcinoma are treated with iodine (I)-131 after initial surgery to destroy any remaining normal thyroid tissue. The doses of I-131 given for this purpose have varied widely, and the optimal dose is not known. This study was a randomized trial of the efficacy of different doses of I-131 for thyroid remnant ablation in patients with thyroid carcinoma.

Methods Five hundred sixty-five patients with thyroid carcinoma were randomly assigned to receive 15 to 50 mCi (555 to 1850 MBq) of I-131 in increments of 5 mCi (185 MBq). Fifty-six patients were later excluded because metastases were detected on a posttherapy scan or they were lost to follow-up before the assessment of efficacy. Among the remaining 509 patients, the ratio of females to males was 2.6 to 1, and the mean age was 38 years [range, 7 to 75]; 410 patients (81 percent) had papillary carcinoma and 99 (19 percent) follicular carcinoma. Tumor size varied from 1 to 16 cm (mean, 5).

At a median time of 2 months after surgery, and after cessation of thyroxine (T₄) therapy, 48-hour I-131 uptake was measured (mean uptake, 9 percent), and the patients were given the assigned dose of I-131. A posttherapy scan was done, and T₄ (2 µg/kg/day) was given. Six months later, after cessation of T₄, thyroid uptake was measured and a whole-body scan was done 48 hours after administration of 2 to 3 mCi (74 to 111 MBq) of I-131. (On both occasions the patients were advised to avoid foods rich in iodine, but were not given a low-iodine diet.) Ablation was considered successful if two of the following criteria were met: the scan

was negative, 48-hour I-131 uptake was ≤0.2 percent, and serum thyroglobulin was ≤10 ng/ml. Patients in whom ablation was not successful were given another dose of I-131.

Results The clinical characteristics, tumor type and size, and I-131 uptake at the time of treatment were similar in the patients in each of the eight treatment groups. The I-131 treatment was successful in 395 patients (78 percent) overall. The success rate was approximately 60 percent in the patients who received 15 and 20 mCi (555 and 740 MBq), and approximately 80 percent in those who received the higher doses (Figure).



Factors associated with successful ablation were more extensive surgery, lower initial I-131 uptake, and I-131 dose ≥25 mCi (925 MBq).

Conclusion Doses of I-131 of 25 to 50 mCi (925 to 1850 MBq) are equally effective in destroying the thyroid remnant in patients with thyroid carcinoma.

COMMENTARY

In this study several relatively low doses of I-131 were equally effective in destroying thyroid remnants. The impetus for the study was an earlier study from the same center in which 149 patients were randomly assigned to receive mean doses of I-131 of 30, 51, 87, and 155 mCi [1110, 1887, 3219, and 5735 MBq]; the respective rates of successful ablation were 63, 78, 74, and 77 percent (1).

Others have given 100 mCi (3700 MBq), or even more, with not much more success. However, a meta-analysis of the results in 967 patients revealed that higher doses of I-131 (75 to 100 mCi [2775 to 3700 MBq] vs. 30 mCi [1110 MBq]) were somewhat more effective (69 vs. 54 percent) (2).

It seems that no reasonable dose of I-131 will always destroy the thyroid remnant, and the shallow dose-response argues for lower doses, at least in patients who have small remnants and are unlikely to have to have residual tumor after initial surgery. This not only reduces their radiation exposure, but also that of other people.

Robert D. Utiger, M.D.

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Patients with an incidentally detected medullary thyroid carcinoma have a good prognosis

Raffel A, Cupisti K, Krausch M, Wolf A, Schulte KM, Roher HD. Incidentally found medullary thyroid cancer: treatment rationale for small tumors. *World J Surg* 2004;28:397-401.

SUMMARY

Background Patients with a nodular goiter who are operated on are sometimes found unexpectedly to have a small thyroid carcinoma. These incidental carcinomas are usually papillary or follicular carcinomas, but a few are medullary carcinomas. The study was undertaken to review the clinical findings and course of patients with an incidental medullary carcinoma of the thyroid.

Methods Among 261 patients with medullary carcinoma seen at a single hospital in Germany from 1986 to 2001, the carcinoma was incidental in 15 (12 women, 3 men; age range, 35 to 75 years). The diagnosis was based on histology and immunostaining (positive for calcitonin, chromogranin, and carcinoembryonic antigen, and negative for thyroglobulin). No patient had a family history of medullary carcinoma. After diagnosis, the patients were tested for germline mutations in exons 10, 11, and 13 of the *RET* proto-oncogene. Serum carcinoembryonic antigen and basal and pentagastrin-stimulated serum calcitonin were measured periodically after initial surgery.

Results In 11 patients, the indication for surgery was a multinodular goiter; in one patient, biopsy of a nodule in the thyroid lobe opposite to the lobe that contained the medullary carcinoma was suspicious for papillary carcinoma, but apparently none was found. These 11 patients underwent bilateral partial or subtotal thyroidectomy. Two

of them underwent a second operation soon thereafter to remove remaining thyroid tissue and, in one patient, cervical lymph nodes. In three patients, the indication for surgery was a single hypofunctioning nodule; two of these patients underwent thyroid lobectomy and one bilateral partial thyroidectomy. (The only other patient who had a biopsy was in this group; the biopsy was read as suspicious for carcinoma, type not specified.) One patient who was operated on to resect a hyperfunctioning adenoma was found to have a small medullary carcinoma adjacent to the adenoma. The medullary carcinomas ranged in size from 0.1 to 2.5 cm; 12 were ≤ 0.8 cm. No patient had other foci of carcinoma within the thyroid, but in one patient tumor was found in cervical lymph nodes at the initial operation. Whether any patient also had C-cell hyperplasia is not mentioned. No patient had a *RET* proto-oncogene mutation.

The patients were followed for 0.5 to 10 years (mean, 4.6). One patient (initial tumor size, 0.5 cm) had a recurrence of tumor in the neck, and underwent a second operation. At last follow-up, all the patients were alive, and none had clinical or biochemical evidence of persistent or recurrent medullary carcinoma.

Conclusion Patients found to have an incidental medullary thyroid carcinoma detected during surgery for other thyroid disorders and who have no germline *RET* mutation have a good prognosis.

COMMENTARY

The clinical findings in these patients were, not surprisingly, heterogeneous. Among the three patients with solitary hypofunctioning nodules that were medullary carcinomas, one had a biopsy that was suspicious for carcinoma, but apparently not medullary carcinoma. Since all three underwent surgery to remove the clinically detected nodule, to call the medullary carcinoma unsuspected is reasonable, but to call it incidental seems inappropriate. The one patient with a hyperfunctioning nodule truly had an incidental medullary carcinoma (0.1 cm), as did the 11 patients who had a multinodular goiter. The overall size of the goiter in these patients is not given, nor is the specific indication for surgery. Their carcinomas ranged in size from 0.1 to 2.2 cm, but in a large multinodular goiter one 2.2-cm carcinoma might well be an incidental finding.

Would these incidental medullary carcinomas have been detected preoperatively if serum calcitonin had been measured, as some have recommended for all patients with thyroid nodular disease (1)? It depends on the size of the carcinoma. Patients with small (<1 cm) tumors may not have high basal or stimulated serum calcitonin concentrations (1). Those with bigger tumors usually do, but so do some patients with C-cell hyperplasia but no medullary carcinoma (C-cell hyperplasia is occasionally found in nodular goiters and Hashimoto's thyroiditis).

What should be done in patients found to have an incidental medullary carcinoma? If the diagnosis is made during the operation, for example, on the basis of analysis of frozen sections, the patient should undergo total or near-total thyroidectomy and bilateral lymph node dissection. The patient might have a germline *RET* mutation, and therefore be at risk for multiple tumors, and some

patients with sporadic medullary carcinomas ≤ 1 cm have lymph-node metastases at diagnosis. If the carcinoma is detected after surgery, further treatment should be guided by the results of mutation analysis, the size of the carcinoma, the extent of the operation that was done, and measurements of serum calcitonin.

Robert D. Utiger, M.D.

Reference

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Outcome in patients with poorly differentiated thyroid carcinomas is intermediate between well-differentiated and anaplastic carcinomas

Volante M, Landolfi S, Chiusa L, Palestini N, Motta M, Codegone A, Torchio B, Papotti MG. Poorly differentiated carcinomas of the thyroid with trabecular, insular, and solid patterns: a clinicopathologic study of 183 patients. *Cancer* 2004;100:950-7.

SUMMARY

Background Insular carcinomas, trabecular carcinomas, and solid carcinomas constitute a group of thyroid carcinomas known collectively as poorly differentiated carcinomas. The cells of these carcinomas lack the cytologic features of papillary carcinoma, and the cells are arrayed in islands, trabeculae, or solid masses, not follicles. Other features are high rates of mitotic activity and necrosis. This retrospective study was done to determine the pathologic features of these tumors and the outcome in 183 patients.

Methods Among 2900 patients with thyroid carcinoma seen at two hospitals in Turin, Italy, between 1960 and 2002, 183 (6 percent) had tumors that were considered insular, trabecular, or solid carcinomas. The inclusion criteria were the presence of focal or more extensive masses of follicular-derived (thyroglobulin-positive) cells arranged in nests or islands (insular pattern), or in trabeculae or solid masses (trabecular-solid pattern), with invasion of the capsule or vessels surrounding the tumor. The sections were reviewed by four pathologists, and graded according to the predominant pattern of growth, cell size, mitoses, necrosis, and Hurthle-cell changes. The patients' records were reviewed, and the outcomes compared with those of 68 patients with papillary carcinoma, 71 patients with follicular carcinoma, and 35 patients with anaplastic carcinoma (how these patients were selected is not stated).

Results There were 127 women and 56 men (mean age, 56 years). The mean tumor size was 5.3 cm; 60 percent of the patients had a coexisting nodular goiter. The predominant growth pattern was insular in 50 percent and trabecular-solid in 50 percent. The insular or trabecular-solid pattern was focal (<50 percent) in 10 percent of the tumors, pre-

dominant (50 to 75 percent) in 23 percent, and pure (>75 percent) in 67 percent; the remainder of the tumor was a follicular carcinoma in 87 percent and a papillary carcinoma in 13 percent. Forty-eight percent of the tumors were composed of small uniform cells with little cytoplasm, and 52 percent were composed of large cells with abundant cytoplasm. The mean number of mitoses per 10 high-power fields was 2.2 (range, 0 to 37). Focal or extensive necrosis was seen in 47 percent of the tumors, Hurthle-cell changes in 36 percent, and extensive vascular invasion (invasion of >3 vessels outside the capsule) in 54 percent.

Most patients underwent thyroidectomy and were treated with radioiodine. Seventy-nine patients (43 percent) were considered to have clinically aggressive tumors, as manifested by recurrence, metastasis, or death. At last follow-up, 91 patients (50 percent) had no evidence of disease, 37 (20 percent) were alive with disease, 42 (23 percent) had died of thyroid carcinoma, and 13 (7 percent) had died of other causes. The 5- and 10-year survival rates were 85 and 67 percent, respectively. The survival rates were intermediate between those of the patients with papillary or follicular carcinoma and those with anaplastic carcinoma. Patient and tumor characteristics associated with poor outcome were age >45 years, tumor necrosis, and high frequency of mitoses, but not tumor size, cell size, extent of tumor composed of the poorly differentiated cells, or extent of vascular invasion.

Conclusion Insular, trabecular, or solid thyroid carcinomas are more aggressive than typical papillary or follicular thyroid carcinomas, especially if mitoses and necrosis are prominent within the tumors.

COMMENTARY

These unusual tumors are likely to be classified differently by different pathologists. How little insular or trabecular-solid architecture need be present before the tumor is called a poorly differentiated carcinoma? How clear is the distinction between insular carcinoma and trabecular-solid carcinoma? How important is the presence of mitoses or necrosis? The first two questions were not addressed in this study, but both mitoses and necrosis proved to be important determinants of prognosis.

However defined, it seems clear that as a group these poorly differentiated carcinomas are more aggressive than well-differentiated carcinomas, with mortality rates in other studies comparable to those described above (as summarized in ref. 1). Few molecular studies have been done in these tumors, and as yet no characteristic mutations or gene rearrangements have been identified (2).

Robert D. Utiger, M.D.

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Somatostatin-receptor scans may reveal recurrent or metastatic tumor in patients with thyroid carcinoma

Giammarile F, Houzard C, Bournaud C, Hafdi Z, Sassolas G, Borson-Chazot F. Diagnostic management of suspected metastatic thyroid carcinoma: clinical value of octreotide scintigraphy in patients with negative high-dose radioiodine scans. *Eur J Endocrinol* 2004;150:277-83.

SUMMARY

Background Patients with thyroid carcinoma who are thought to have persistent or recurrent disease on the basis of a high serum thyroglobulin concentration are usually evaluated by whole-body radioiodine scans. In patients in whom this scan is negative, other imaging studies may be done to localize the tumor. This study evaluated the efficacy of somatostatin-receptor scanning in such patients.

Methods Somatostatin-receptor scans using indium (In)-111-octreotide were done in 43 patients with thyroid carcinoma who had high serum thyroglobulin concentrations and negative whole-body iodine (I)-131 scans. There were 25 women and 18 men, ranging in age from 22 to 70 years. Twenty had papillary carcinoma, 9 follicular carcinoma, 8 Hurthle-cell carcinoma, and 6 insular carcinoma. They had been treated by total thyroidectomy and 54 to 108 mCi (2 to 4 GBq) of I-131 1 to 23 years earlier. All had later been treated with I-131 from one to eight times (cumulative dose, 100 to 900 mCi [3.7 to 33.3 GBq]), after which no patient had any foci of I-131 uptake.

The In-111-octreotide scans were done 1 week to 10 years after the last I-131 treatment, at a time when the patients' serum thyroglobulin concentrations ranged from 0.7 to 5850 ng/ml. All but three patients were taking thyroxine and had undetectable serum thyrotropin concentrations. The patients were given an intravenous injection of 3 mCi (110 MBq) of In-111-octreotide, and whole-body scans were done 4, 24, and 48 hours later. Chest radiography and ultrasonography of the neck were done in all patients, and computed tomography (CT) or magnetic resonance (MR) scans of the neck, chest, or abdomen were done in most patients (these tests are referred to as conventional imaging). Twenty-seven patients underwent positron-emission tomography (PET).

Results Thirty-three patients (77 percent) had a local recurrence or one or more distant metastases of their carcinoma, as detected by one or more of the imaging tests and confirmed by pathologic examination of resected tissue or at follow-up. In-111-octreotide scans were positive in 22 patients (51 percent), and they were the only positive scans in 3 patients (7 percent). Two patients had lung uptake of In-111-octreotide that proved to be caused by sarcoidosis in one patient and tuberculosis in the other. Chest radiographs, neck ultrasonography, and CT or MR scans were positive in 30 patients (70 percent). The PET scan was positive in 16 of the 27 patients (59 percent) in whom the test was done; it was the only positive test in one patient.

The carcinoma was in the neck in 15 patients, mediastinum in 18, lungs in 17, bone in 5, and abdomen in 4. The sensitivity of In-111-octreotide scanning was higher than that of the conventional imaging tests for detecting carcinoma in the mediastinum (93 vs. 56 percent), but lower for detecting carcinoma in the neck (43 vs. 93 percent), lungs (65 vs. 94 percent), and bone (25 vs. 100 percent).

Eighteen patients had serum thyroglobulin concentrations ≤ 50 ng/ml, of whom 3 (17 percent) had a positive In-111-octreotide scan. In contrast, among the 25 patients with serum thyroglobulin concentrations > 50 ng/ml, the In-111-octreotide scan was positive in 19 (76 percent).

A positive In-111-octreotide scan led to changes in therapy in four patients (surgery in three and treatment with a high dose of In-111-octreotide in one). The patients in whom In-111-octreotide scans revealed no tumor had no evidence of recurrence during follow-up for 15 to 46 months.

Conclusion In-111-octreotide scans reveal recurrent or metastatic thyroid carcinoma in some patients who have high serum thyroglobulin concentrations and negative whole-body I-131 scans.

COMMENTARY

Several imaging tests can be done in patients with thyroid carcinoma who have evidence of recurrence, which is usually manifested as a high serum thyroglobulin concentration, but a negative whole-body diagnostic I-131 (or I-123) scan and also a negative scan after administration of a high dose of I-131. Ultrasonography of the neck is undoubtedly at the top of the list, if not done immediately after detection of the high serum thyroglobulin value. Many recur-

rences are in the neck, and the sensitivity of ultrasonography for detecting them is high, although specificity is low. The next step is usually CT of the neck and chest. In this study the overall sensitivity of these two tests was 80 percent (as compared with 64 percent for In-111-octreotide scans).

The choice among PET, In-111-octreotide, or technetium (Tc)-99m-sestamibi scans is not clear. In this and most other studies of these scans, there were a few patients in whom one scan revealed carcinoma but other scans were negative.

The important question is not whether one scanning technique is better, but what is to be gained by finding recurrent or metastatic thyroid carcinoma that does not concentrate radioiodine. Carcinoma in the neck, and localized carcinoma elsewhere, can be resected, but, as in this study, therapy is not often altered. These scans that rarely modify therapy should be done only after consultation with the patient about possible benefits.

Robert D. Utiger, M.D.

Chronic urticaria may be associated with autoimmune thyroid disease

Verneuil L, Leconte C, Ballet JJ, Coffin C, Laroche D, Izard JP, Reznik Y, Leroy D. Association between chronic urticaria and thyroid autoimmunity: a prospective study involving 99 patients. *Dermatology* 2004;208:98-103.

SUMMARY

Background Most patients with chronic urticaria are not allergic to any environmental substance, and the urticaria is thought to be a manifestation of an underlying autoimmune disorder, including possibly autoimmune thyroid disease. This study was done to determine the relationship between chronic urticaria and autoimmune thyroid disease.

Methods Four groups of people were studied. One group consisted of 45 patients (35 women, 10 men; mean age, 43 years) with chronic urticaria referred to a dermatology clinic. Chronic urticaria was defined as three or more episodes of urticaria or angioedema weekly for at least six weeks. The second group consisted of 32 patients (30 women, 2 men; mean age, 43 years) with goiter, thyroid nodules, hyperthyroidism, or hypothyroidism who had a high serum concentration of antithyroid peroxidase (TPO), antithyroglobulin (Tg), or thyrotropin (TSH)-receptor antibodies. The third group consisted of 22 patients (18 women, 4 men; mean age, 50 years) with similar thyroid disorders, but normal serum concentrations of all three antibodies. No details are provided about the causes or numbers of patients with goiter or thyroid nodules or the numbers of patients with hyperthyroidism or hypothyroidism in these two groups. The fourth group consisted of 30 normal subjects (20 women, 10 men; mean age, 40 years). The patients with thyroid disorders were questioned about urticaria by a dermatologist (and followed for a year for skin eruptions). Serum free thyroxine, TSH, and antithyroid antibodies were measured in all subjects, and antinuclear, anti-DNA, anti-IgE antibodies against multiple food antigens, rheumatoid factor, and several components of the complement system were measured in the patients with urticaria.

Results The 45 patients with chronic urticaria had three or more episodes of urticaria per week for 3 months to 15 years; most had been treated with an antihistamine drug or glucocorticoids, with varying efficacy. All had normal thyroid function. Twelve patients (27 percent) had a high serum concentration of one or more antithyroid antibodies (anti-TPO, four patients; anti-Tg, four patients; both, four patients) (Table); none had a high serum anti-TSH receptor antibody concentration. Among these 12 patients, four were considered to have Hashimoto's thyroiditis (presumably they had a goiter), three had thyroid nodules, and five had no thyroid disorder. Ten of the 45 patients had high serum concentrations of one or more immunologic factors (antinuclear antibodies, rheumatoid factor) or low complement CH50 concentrations, but none had IgE antibodies to any of the antigens tested. Three of these 10 patients had a high serum antithyroid antibody concentration.

Group	Chronic Urticaria	High Serum Anti-TPO or Anti-Tg Value
Chronic urticaria (n=45)	45 (100%)	12 (27%)*
Thyroid disorders, thyroid autoimmunity (n=32)	4 (12%)	32 (100%)
Thyroid disorders, no thyroid autoimmunity (n=22)	2 (9%)	0 (0%)
Normal subjects (n=30)	0 (0%)	1 (3%)

*P<0.01, compared with normal subjects.

Six patients in the two thyroid-disorder groups had a history of urticaria (Table), and four of them also had urticaria during the one-year follow-up period. None of the normal subjects had a history of urticaria, and one had a high serum anti-TPO antibody concentration.

Conclusion Patients with chronic urticaria are more likely to have high serum concentrations of anti-TPO or anti-Tg antibodies than are normal subjects.

COMMENTARY

This is not the first or the largest study to describe an association between chronic urticaria and high serum anti-TPO or anti-Tg antibody concentrations. However, it may be the first in which urticaria was looked for in patients with thyroid disorders, but this part of the results is not very useful because of the paucity of information about the patients in these two groups.

Considering the patients with chronic urticaria, should patients with this disorder who have high serum concentrations of one or more antithyroid antibodies be said to have Hashimoto's urticaria? This seems no more justifiable

than saying that patients with encephalopathy who have high serum antithyroid antibody concentrations have Hashimoto's encephalopathy. The fact that urticaria was no more frequent in the patients with thyroid disorders who had high serum antithyroid antibody concentrations than in those with normal concentrations argues against any cutaneous effect of the antibodies.

Indeed, there is no biologic reason to implicate anti-TPO or anti-Tg antibodies in the pathogenesis of any disorder, thyroid or otherwise. Urticaria, and encephalopathy, may well have an autoimmune basis, but it is likely that the high serum antithyroid antibody concentrations found in some patients with either

disorder is simply a manifestation of loss of tolerance to self antigens, and is not of any pathogenic importance.

Robert D. Utiger, M.D.

The frequency of autoimmune thyroiditis is increased in women with the polycystic ovarian syndrome

Janssen OE, Mehlmauer N, Hahn S, Offner AH, Gartner R. High prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome. *Eur J Endocrinol* 2004;150:363-9.

SUMMARY

Background The polycystic ovary syndrome is characterized by menstrual disturbances and hyperandrogenemia. Given that autoimmune thyroiditis is less common in men than in women, hyperandrogenemia in women might be expected to reduce the frequency of autoimmune thyroiditis. In this cross-sectional study the frequency of thyroid dysfunction and autoimmune thyroiditis was determined in women with the syndrome.

Methods The study subjects were 175 women with the polycystic ovary syndrome, as defined by amenorrhea or oligomenorrhea and clinical (hirsutism or alopecia) or biochemical (serum testosterone >58 ng/dl [2 nmol/L]) evidence of hyperandrogenism, and 168 age-matched women with normal menses. Twenty-two women (13 percent) with the polycystic ovary syndrome and 3 normal women (2 percent) were known to have autoimmune thyroiditis and were taking thyroxine. Serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), gonadal steroids, thyrotropin (TSH), free thyroxine, antithyroid peroxidase (TPO) and antithyroglobulin (Tg) antibodies, and insulin sensitivity were measured and thyroid ultrasonography was performed in all women. Insulin sensitivity was measured by the homeostasis model assessment (HOMA) method (fasting serum insulin × fasting serum glucose ÷ 22.5).

Results The mean ages of the women with the polycystic ovary syndrome and the normal women were 28 and 30 years, respectively, and their mean body-mass index values were 30 and 26 kg per square meter of body-surface area, respectively (P<0.01). Serum LH, FSH, and testosterone concentrations were higher, serum estradiol concentrations

were similar, and serum progesterone concentrations were lower in the women with the polycystic ovary syndrome, and they were more insulin-resistant (Table).

Serum	Polycystic Ovary Syndrome	Normal Women
LH (IU/L)	12.3*	3.8
FSH (IU/L)	4.9*	4.1
Progesterone (ng/ml)	1.0*	8.5
Testosterone (ng/dl)	75*	29
HOMA (mU × mmol/L)	4.7*	2.4
TSH (mU/L)	2.0*	1.4
Free thyroxine (ng/dl)	1.1	1.2
Anti-TPO antibodies (U/L)	123*	10
Anti-Tg antibodies (U/L)	113*	4

Conversion factors: serum progesterone × 3.2 = nmol/L; testosterone × 0.035 = nmol/L; and × free thyroxine 12.9 = pmol/L.
*P<0.01, as compared with the normal women.

The women with the polycystic ovary syndrome had slightly higher serum TSH concentrations and substantially higher serum anti-TPO and anti-Tg antibody concentrations, as compared with the normal women; 47 (27 percent) of the former, but only 14 (8 percent) of the latter, had high serum antithyroid antibody concentrations. Thyroid volume was similar in both groups (15 vs. 12 ml, P>0.05), but hypoechogenicity was more common in the women with the polycystic ovary syndrome (42 vs. 6 percent, P<0.01).

Conclusion Autoimmune thyroiditis, as manifested by serologic and ultrasonographic abnormalities, is more common in women with the polycystic ovary syndrome than in normal women.

COMMENTARY

Women with the polycystic ovary syndrome have not only the two disorders that define the syndrome, but also insulin insensitivity, dyslipidemia, and type 2 diabetes mellitus. Thyroid disorders have not been on the list.

Thyroid function is routinely assessed in women with menstrual abnormalities and infertility, and, therefore, it is surprising that there have been few studies of thyroid function in these women. In this study, serum TSH concentrations were only slightly higher in the women with the polycystic ovarian syndrome than in the normal women, but few had hypothyroidism (the highest

serum TSH value was 6.2 mU/L). However, there were substantial differences in serum antithyroid antibody concentrations and thyroid hypoechogenicity in the two groups of women, findings that indicate the presence of autoimmune thyroiditis in the women with the polycystic ovary syndrome.

The authors hypothesize that a high serum ratio of estrogen to progesterone is responsible for the increased prevalence of autoimmune thyroiditis in women with the polycystic ovary syndrome. This hypothesis could be pursued by studies of the effects of insulin-sensitizing drugs and oral contraceptives on thyroid function and autoimmunity in these women. Whatever the underlying

pathophysiologic mechanism, these results suggest that autoimmune thyroiditis should be added to the list of disorders associated with the polycystic ovary syndrome (and vice versa).

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Thyroid echogenicity is decreased in patients with Hashimoto's thyroiditis

Loy M, Cianchetti ME, Cardia F, Melis A, Boi F, Mariotti S. Correlation of computerized gray-scale sonographic findings with thyroid function and thyroid autoimmune activity in patients with Hashimoto's thyroiditis. *J Clin Ultrasound* 2004;32:136-40.

SUMMARY

Background Ultrasonography can be used to not only measure thyroid size and identify thyroid nodules, but also to provide information about the pathologic anatomy and the functional activity of thyroid tissue. This retrospective study evaluated the use of computerized gray-scale ultrasonography to quantitate thyroid echogenicity in patients with Hashimoto's thyroiditis.

Methods The study subjects were 77 patients (69 women, 8 men; mean age, 47 years [range, 18 to 76]) with Hashimoto's thyroiditis. The diagnosis was based on unspecified clinical and laboratory findings, and, in 15 patients, on the results of fine-needle aspiration biopsy. Twenty-eight patients were euthyroid, 20 had subclinical hypothyroidism (high serum thyrotropin [TSH] and normal free thyroxine [T₄] values), and 29 had overt hypothyroidism (high serum TSH and low free T₄ values); 23 of the latter were receiving T₄ and had normal serum TSH values. The results in these patients were compared with those in 50 normal subjects (43 women, 7 men; mean age, 42 years [range, 20 to 68]). None of the latter subjects had a high serum antithyroid peroxidase antibody concentration, or any thyroid abnormality as detected by ultrasonography.

Thyroid volume was measured using ultrasonography in all subjects. The echogenicity of the thyroid and strap muscles was measured by computerized gray-scale ultrasonography in transverse sections of each thyroid lobe and an ipsilateral strap muscle. The instrument settings were kept constant, and the results were quantitated as the mean tissue density of both lobes of the thyroid or strap muscles on an arbitrary scale of 0 to 63.

Results The mean thyroid density (echogenicity) in all patients with Hashimoto's thyroiditis was 15.9 units, as compared with 24.3 units in the normal subjects (P<0.05) (Table). Among the patients with Hashimoto's thyroiditis, the thyroid density was highest in those who were euthyroid, intermediate in those with subclinical hypothyroidism, and lowest in those with overt hypothyroidism (P<0.05). The density of the strap muscles was similar (11.0 to 12.5 units) in the five groups shown in the Table.

Group	No.	Serum TSH (mU/L)	Serum Anti-TPO Ab (U/ml)	Thyroid Volume (ml)	Thyroid Density*
Normal subjects	50	1.3	<20	12.0	24.3
Hashimoto's disease					
Euthyroid	28	1.2	1055	12.9	18.9
Subclinical hypothyroidism	20	8.6	883	18.0	14.9
Overt hypothyroidism	6	73.0	1286	9.7	11.1
Treated overt hypothyroidism	23	1.0	570	9.0	14.6

TPO Ab denotes thyroid peroxidase antibodies.
*Arbitrary units.

There was no correlation between thyroid volume and thyroid density, or between thyroid density and serum antithyroid peroxidase antibody concentrations. Thyroid density was lower and serum antithyroid peroxidase antibody concentrations were higher in the untreated patients with overt hypothyroidism, as compared with those who were taking T₄ (duration of therapy not stated, but sufficient to reduce serum TSH values to normal).

Conclusion Thyroid echogenicity, as measured by computerized gray-scale ultrasonography, is reduced in patients with Hashimoto's thyroiditis, in proportion to the severity of hypothyroidism but unrelated to thyroid volume.

COMMENTARY

These results confirm the results of subjective judgments that thyroid echogenicity is decreased in patients with Hashimoto's thyroiditis (1). The change is found in patients who are euthyroid as well as in those who have hypothyroidism, and among patients who are euthyroid the presence of hypoechogenicity is associated with later onset of hypothyroidism. On the other hand, not all patients who have Hashimoto's thyroiditis have hypoechogenicity. Some of the variation may reflect different defini-

tions of Hashimoto's thyroiditis. In this study, the diagnosis seems to have been based simply on a high serum antithyroid peroxidase antibody concentration. Whether that alone is enough can be debated, but it is common practice.

Is thyroid hypoechogenicity in patients with Hashimoto's thyroiditis caused by lymphocytic infiltration, fibrosis, or follicular hypertrophy and hyperplasia, alone or in combination? What is the role of TSH stimulation, or of different antithyroid antibodies? As a study tool, quantitative thyroid ultrasonography may prove quite useful, but as a practical

diagnostic or predictive test its time has not yet come.

Robert D. Utiger, M.D.

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Potential of warfarin heralds the onset of hyperthyroidism in patients taking amiodarone

Kurnik D, Loebstein R, Farfel Z, Ezra D, Halkin H, Olchovsky D. Complex drug-drug-disease interactions between amiodarone, warfarin, and the thyroid gland. *Medicine (Baltimore)* 2004;83:107-13.

SUMMARY

Background Amiodarone and hyperthyroidism both augment the anticoagulant effects of warfarin, the former directly by inhibiting the metabolism of warfarin and the latter indirectly by accelerating the clearance of vitamin K-dependent coagulation factors. This article describes three patients taking amiodarone and warfarin in whom an increase in sensitivity to warfarin was the first manifestation of amiodarone-induced hyperthyroidism.

Patient 1 was a 41-year-old woman treated with warfarin after prosthetic mitral-valve replacement at age 23 years; her dose of warfarin ranged from 100 to 110 mg per week for many years (international normalized ratio [INR], 2.5 to 4.0). After the onset of atrial fibrillation in 2000, she was treated with amiodarone, and a warfarin dose of 75 mg weekly was sufficient to maintain INR values of 2.8 to 3.5. Fifteen months later, her INR was 6.2, and her dose of warfarin was reduced to 55 mg weekly. Several weeks later she noted fatigue, palpitations, and dyspnea, and she was found to have atrial fibrillation and overt hyperthyroidism (serum free thyroxine [T_4], 2.1 ng/dl [27 pmol/L]; thyrotropin [TSH], <0.01 mU/L); her thyroid gland was normal in size. Amiodarone was stopped, and propranolol given, with improvement. Seven weeks later her INR was 1.6, and the warfarin dose was increased, ultimately to 95 mg weekly when she had overt hypothyroidism. She then was treated with T_4 .

Patient 2 was a 57-year-old man with dilated cardiomyopathy and paroxysmal atrial fibrillation treated with amiodarone and warfarin in 1998. During 2001, he had INR values of 2.3 to 2.8 while taking 27.5 mg of warfarin weekly. In 2002, his INR was 5.3, and the dose of warfarin was reduced to 17.5 mg weekly, after which the INR values were 2.2 to 2.5. He then had onset of weight loss and weakness, and was found to have hyperthyroidism (serum free T_4 , 6.0 ng/dl [77 pmol/L]; TSH, <0.01 mU/L) and a small goiter.

Amiodarone was stopped, and he was treated with prednisone. He subsequently had normal thyroid function, at which time he was treated with 37.5 mg of warfarin weekly.

Patient 3 was a 52-year-old man with mitral insufficiency and atrial fibrillation treated by valve replacement, amiodarone, and warfarin. For two years, his INR values ranged from 2.5 to 3.1 while taking 20 mg of warfarin weekly. Then, his INR values increased to 3.5 to 4.3 and later to 6.0, despite reduction of warfarin to 12.5 mg weekly. During this interval he became weak and lost weight, and was found to have hyperthyroidism (serum free T_4 , 7.1 ng/dl [92 pmol/L]; TSH, <0.01 mU/L); his thyroid was not enlarged. Amiodarone was stopped, and prednisone was given. He improved little, and six weeks later was hospitalized because of recurrent atrial fibrillation and congestive heart failure. Warfarin was stopped, and he was treated with methimazole, digoxin, furosemide, and enoxaparin. He subsequently improved, and warfarin was reinstated, initially 25 mg weekly and ultimately 35 mg weekly.

The effect of amiodarone to potentiate the effect of warfarin was most evident in patient 1, in whom the dose of warfarin had to be reduced after amiodarone therapy was begun. Patients 2 and 3 started to take warfarin at the same time or after amiodarone; in them the amiodarone effect became evident only later, after onset of hyperthyroidism and cessation of amiodarone, when they required more warfarin than when taking amiodarone. In all three patients the action of warfarin increased with the onset of hyperthyroidism, and conversely the action of warfarin decreased in patient 1 with the onset of hypothyroidism.

Conclusion In patients with a cardiac arrhythmia treated with amiodarone, hyperthyroidism may be heralded by an increase in the action of warfarin, an effect that is superimposed on the effect of amiodarone itself to increase warfarin action.

COMMENTARY

Amiodarone alters the pharmacokinetics of warfarin by inhibiting the activity of several cytochrome P450 enzymes in the liver that metabolize warfarin. The plasma clearance of warfarin slows, plasma concentrations rise, and the drug's anticoagulant activity increases. This effect of amiodarone begins soon after it is started, and the dose of warfarin usually needs to be reduced by 25 to 50 percent to maintain the same level of anticoagulation.

Hyperthyroidism does not alter the pharmacokinetics of warfarin, nor does it alter the action of warfarin to inhibit the synthesis of several coagulation factors. Instead, the anticoagulant action of warfarin is magnified because the degradation of coagulation factors is increased. Thus, less warfarin is needed to achieve a given INR value.

This change is not unique to patients with amiodarone-induced hyperthyroidism, but they are patients who tend to have few clinical manifestations of hyperthyroidism, because they are eld-

erly, their hyperthyroidism is mild, or they are taking a β -adrenergic antagonist drug. Therefore, an increase in INR values, necessitating a decrease in the need for warfarin, may be an important clue to the onset of hyperthyroidism in them.

Robert D. Utiger, M.D.

Genetic factors are more important than environmental factors in determining the set point of pituitary-thyroid function in normal subjects

Hansen PS, Brix TH, Sorensen TI, Kyvik KO, Hegedus L. Major genetic influence on the regulation of the pituitary-thyroid axis: a study of healthy Danish twins. *J Clin Endocrinol Metab* 2004;89:1181-7.

SUMMARY

Background The results of repeated measurements of serum thyroid hormone and thyrotropin (TSH) concentrations vary less in an individual normal subject than among groups of subjects, suggesting that each subject has a unique set point for TSH and therefore thyroid secretion. In this study pituitary-thyroid function was assessed in monozygotic and dizygotic twin pairs in an attempt to determine the genetic influence on this set point.

Methods The twin pairs were a representative sample of twin pairs in the Danish Twin Registry, stratified by age, sex, and zygosity. All the subjects were in self-reported good health, and most lived in the same part of Denmark. The subjects completed questionnaires about their health and life style, and blood samples were collected in the morning for measurements of serum TSH, free thyroxine (T_4), free triiodothyronine (T_3), antithyroid peroxidase antibodies, and antithyroglobulin antibodies. All the measurements were done in the same laboratory.

Initially, 1512 subjects (756 twin pairs) were examined, but one or both twins of 66 pairs were excluded because of self-reported thyroid disease, medications that might affect pituitary-thyroid function, chronic illness, missing values, overt hyperthyroidism, or overt hypothyroidism. Therefore, the study group consisted of 1380 subjects (690 twin pairs), including 284 monozygotic twin pairs, 286 same-sex dizygotic twin pairs, and 120 opposite-sex twin pairs.

Results There were 692 women and 688 men. The mean age of the monozygotic twins, same-sex dizygotic twins, and opposite-sex dizygotic twins was 37 years. The mean serum TSH concentrations were 1.8 mU/L in the women and 1.6 mU/L in the men ($P < 0.01$). The mean serum TSH concentrations were 2.1 mU/L in the 99 subjects with a high serum antithyroid antibody concentration and 1.7 mU/ml in the 1281 subjects with a normal concentration ($P = 0.01$). Serum TSH and free T_4 or free T_3 concentrations were not linearly related in any of the zygosity classes.

Among the monozygotic twin pairs, the ln serum TSH, free T_4 , and free T_3 concentrations in twins 1 and 2 were correlated ($r = 0.64$, $r = 0.63$, and $r = 0.59$, respectively). For the same-sex dizygotic twin pairs, the r values were lower (ln serum TSH, $r = 0.29$; serum free T_4 , $r = 0.30$, and serum free T_3 , $r = 0.37$).

Based on quantitative genetic modeling, additive genetic components accounted for 64 to 65 percent and environmental effects for 35 to 36 percent of the variation in serum TSH, free T_4 , and free T_3 concentrations.

Conclusion Serum TSH and thyroid hormone concentrations are each more closely correlated in monozygotic than dizygotic twins, indicating that interindividual variations in pituitary-thyroid function are primarily determined by genetic factors.

COMMENTARY

That the values for serum TSH, free T_4 , and free T_3 were more similar in the monozygotic twin pairs, as compared with the dizygotic twin pairs, is easy to understand and is not surprising, given the greater phenotypic similarity of the former. However, the assignment of percentage values to the genetic and environmental contributions to the set point is surprising, and the analysis will be unfathomable to all but a handful of readers. In a related study of many of these twin pairs, genetic factors were calculated to account for 71 percent of individual differences in thyroid volume (1).

The set point of TSH secretion is determined by a host of factors, including the capacity of the thyrotroph cells of the pituitary to synthesize TSH; serum

free T_4 and free T_3 concentrations; the sensitivity of the thyrotroph cells to T_4 , T_3 , and thyrotropin-releasing hormone (TRH); and the secretion of TRH, and therefore the hormonal and neural factors that control TRH secretion. Polymorphisms in the genes for enzymes such as deiodinases and the receptors for TRH or T_3 , among others, may explain some of the variations in serum TSH, free T_4 , and free T_3 concentrations between different subjects.

The set point is remarkably constant in an individual subject, so that the month-to-month variation in serum TSH and thyroid hormone concentrations in that subject is considerably less than the variation in a group of subjects. Whether an individual's set point is relatively fixed for years or longer, and what environmental factors might alter it if it is not

fixed, are not known. But if it is not fixed, then the extent of change in thyroid secretion needed to cause a change in TSH secretion might vary, which might have implications for how hypothyroidism and hyperthyroidism are defined and treated.

Robert D. Utiger, M.D.

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Correction

The rise in serum thyroxine binding during pregnancy in women with hypothyroidism only partly explains their increased need for thyroxine (*March* 2004:14). The correct reference for the original article is *Thyroid* 2003;13:1169-75 (not volume 12 as printed).

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