CLINICAL THYROIDOLOGY

VOLUME 18 ● ISSUE 2 JULY 2006

A publication of the American Thyroid Association

AMERICAN THYROID ASSOCIATION
FOUNDED 1923

Editor
Robert D. Utiger, M.D.
Thyroid Division
Department of Medicine
Brigham & Women's Hospital
77 Avenue Louis Pasteur
Boston, MA 02115
(617) 525-5171 Telephone
(617) 731-4718 Fax
editorclinthy@thyroid.org

Clinical Thyroidology

Clinical Thyroidology is available on the ATA web site **www.thyroid.org**

CLINICAL THYROIDOLOGY

VOLUME 18 ● ISSUE 2 JULY 2006

Expanding Thyroid Diagnoses

The standard tests for biochemical assessment of thyroid dysfunction are measurements of serum thyrotropin (TSH) and free thyroxine (T_4). As a single test, the former is preferred, because small changes in thyroid secretion and serum free T_4 concentrations result in larger inverse changes in serum TSH concentrations. The proviso, of course, is that the change in serum free T_4 concentration must be caused by an intrinsic thyroid disorder. The value of this approach lies in the fact that thyroid disorders are by far the most common cause of thyroid dysfunction.

Among intrinsic thyroid disorders, those labeled subclinical—the serum TSH concentration is abnormal but the serum free T_4 concentration is within the normal range (but must have changed)—are far more common than those labeled overt—both serum TSH and free T_4 concentrations are abnormal (Figure). That is why, if only one test is done, at least for initial evaluation, measurement of serum TSH is preferred.

There are also disorders extrinsic to the thyroid that cause thyroid dysfunction, namely disorders of the hypothalamus or pituitary that result in TSH deficiency (central hypothyroidism) or TSH excess (central hyperthyroidism). Considering the subclinical-overt terminology from the perspective of thyroid secretion, there aren't any patients with persistently low serum TSH and normal serum free T_4 concentrations (subclinical central hypothyroidism). (This could occur if TSH biologic activity was increased, or TSH receptors were more sensitive to TSH.) Patients with overt central hypothyroidism may have low, normal, or even slightly high serum TSH concentrations. The latter two conditions are a result of secretion of TSH with decreased biologic activity, mainly as a result of thyrotropin-releasing hormone deficiency (see page 40).

A few patients with overt central hyperthyroidism have high serum TSH concentrations, but more have normal serum TSH concentrations; either their TSH has greater than normal biologic activity, or a small persistent increase in TSH secretion within the normal range is sufficient to cause overt hyperthyroidism. Finally, to complete the subclinical-overt analogy, there is subclinical central hyperthyroidism, in which serum TSH concentrations are high but serum free T_4 concentrations are within the normal range. The model for this might be a very small TSH-secreting pituitary adenoma, producing TSH with decreased biologic activity, and perhaps it also occurs in obesity (see page 39).

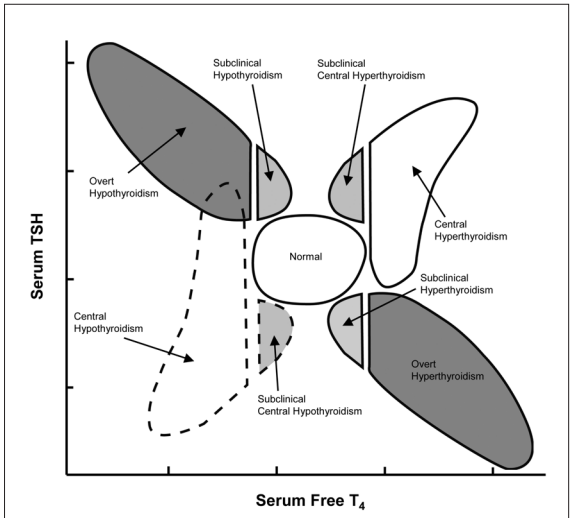

Figure. Serum TSH and Free Thyroxine Concentrations in Hypothalamic, Pituitary, and Thyroid Disorders.

Patients are not much, if at all, benefited by recognition of these subclinical disorders, even the common ones, but their existence, or possible existence, provides a basis for thinking about and investigating the finer aspects of hypothalamic-pituitary-thyroid regulation.

The Editor

Some cardiovascular disorders occur with increased frequency in patients treated for hyperthyroidism or hypothyroidism

Flynn RW, MacDonald TM, Jung RT, Morris AD, Leese GP. Mortality and vascular outcomes in patients treated for thyroid dysfunction. J Clin Endocrinol Metab 2006;91:2159-64.

SUMMARY

Background Both hyperthyroidism and hypothyroidism are associated with cardiovascular and other disorders. Whether treated patients with either thyroid disorder have an increase in cardiovascular morbidity and mortality and all-cause mortality is not known. This study was done to determine the frequency of these outcomes in patients treated for hyperthyroidism or hypothyroidism.

Methods The study subjects were all patients living in Tayside, Scotland, who were treated for hyperthyroidism or hypothyroidism between 1994 and 2001. Prevalent and incident cases were identified from a master list of patients registered with general practitioners; biochemistry, medication, and radioiodine therapy records; the Tayside thyroid registry; hospital records; a diabetes registry; and Scottish morbidity and mortality records.

The primary outcome was all-cause mortality and the secondary outcome was serious vascular events, defined as nonfatal myocardial infarction, nonfatal stroke, or vascular death. Other outcomes were cardiovascular disease, including ischemic heart disease (myocardial infarction, angina), heart failure, and dysrhythmias, and cerebrovascular disease. The frequency of these events in the patients was compared with the frequency in the general population, stratified by sex, age in five-year groups, and presence or absence of diabetes.

Results From 1994 to 2001, 3888 patients were treated for hyperthyroidism and followed for 21,190 patient-years; 772 were incident cases who were followed for 2417 patient-years. For hypothyroidism, there were 15,889 treated patients followed for 79,345 patient-years; 7904 were incident cases followed for 28,616 patient-years. There were 524,152 people in the general population; they were followed for 3,116,719 patient-years. By 2001, the prevalence of hyperthyroidism was 0.7 percent and that of hypothyroidism was 2.9 percent.

There was no increase in all-cause mortality in the treated hyperthyroid patients (standardized mortality ratio [SMR], 1.05; 95 percent confidence interval [CI], 0.96–1.14) or the treated hypothyroid patients (SMR, 1.03; 95 percent CI, 0.99–1.07). There was an increase in serious vascular events in the treated hypothyroid patients (standardized incidence ratio [SIR], 1.10; 95 percent CI, 1.06–1.15), but not in the treated hyperthyroid patients.

Among the incident cases, there was an increase in dysrhythmias in the treated hyperthyroid patients and small increases in death from cardiovascular disease and in serious vascular events, cardiovascular disease, including ischemic heart disease, heart failure, and dysrhythmias, and cerebrovascular disease in the treated hypothyroid patients (Table).

Table. Incident Mortality and Cardiovascular Events in Patients Treated for Hyperthyroidism or Hypothyroidism, 1994-2001.

	Treated Hyperthyroidism		Treated Hypothyroidism	
Cause of death	Obs/Exp*	SMR (95% CI)	Obs/Exp	SMR (95% CI)
All causes	48/48	1.00 (0.74-1.33)	816/779	1.05 (0.98-1.12)
Cardiovascular disease	11/13	0.84 (0.42-1.49)	251/218	1.15 (1.02-1.31)
Event	Obs/Exp	SIR (95% CI)	Obs/Exp	SIR (95% CI)
Serious vascular events	33/32	1.03 (0.71-1.45)	598/516	1.16 (1.07-1.26)
Cardiovascular disease	40/31	1.29 (0.92-1.76)	652/450	1.45 (1.34-1.57)
Ischemic heart disease	17/17	1.01 (0.59-1.61)	349/242	1.44 (1.30-1.60)
Heart failure	6/6	0.92 (0.34-2.01)	127/104	1.22 (1.01-1.45)
Dysrhythmias	19/6	3.22 (1.94-5.03)	133/87	1.53 (1.28-1.82)
Cerebrovascular disease	11/8	1.29 (0.65-2.32)	160/128	1.25 (1.07-1.46)

*Exp/Obs, observed/expected.

Conclusion All-cause mortality is not increased in treated hyperthyroid or hypothyroid patients. The frequency of dysrhythmias is increased in treated hyperthyroid patients, and the frequency of serious vascular events, cardiovascular disease, and cerebrovascular disease is slightly increased in treated hypothyroid patients.

COMMENTARY

This large, population-based study from Scotland found no significant increase in all-cause or cardiovascular mortality in patients treated for hyperthyroidism, in contrast to several previous studies that reported increased mortality in hyperthyroid patients treated with radioiodine. The reasons for this difference are not clear: it may be because in the previous studies radioiodine treatment was given mainly to older patients, whereas this study included younger patients. They are more likely to be treated with antithyroid drugs, and they are less likely to have cardiac complications. In this regard, it would be useful to know to know if the outcomes differed by age group, severity of hyperthyroidism, and type of treatment.

Patients treated for hypothyroidism were at increased risk of cardiovascular events and mortality. Since this group was identified from thyroxine (T_4) prescription records, it probably included patients with subclinical as well as overt hypothyroidism. Taken at face value, the results suggest that hypothyroidism (overt or subclinical) is associated with atherosclerosis, and that T_4 therapy is ineffective or only partly effective at reducing vascular risk.

There are other possible interpretations. People treated for hypothyroidism may be more likely to have heart disease diagnosed and vice versa. It is also possible that the adverse outcomes reflect inadequate or excessive T_4 dosage. Nevertheless, the study raises a disturbing possibility: that if subclinical and overt hypothyroidism are indeed risk factors for cardiovascular disease, T_4 replacement may not return that risk to normal.

John P. Walsh, M.B.B.S., Ph.D.
Sir Charles Gairdner Hospital
Perth, Australia

Subclinical thyroid dysfunction has few deleterious cardiovascular effects

Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, Tracy RP, Ladenson PW. Thyroid status, cardiovascular risk, and mortality in older adults. JAMA 2006;295:1033-41.

SUMMARY

Background Whether subclinical thyroid dysfunction (high or low serum thyrotropin [TSH] and normal serum free thyroxine [T_4] concentrations) increases cardiovascular morbidity and mortality is not clear. In this study, the incidence of several cardiovascular disorders and cardiovascular and all-cause mortality were determined in a cohort of older women and men in whom thyroid function had been assessed at base line.

Methods The study subjects were 3233 subjects (1926 women, 1307 men; 95 percent white) aged ≥65 years (mean age, 73) enrolled in the Cardiovascular Health Study, a population-based study of risk factors for cardiovascular disease, between 1989 and 1993. Subjects taking thyroid hormone or drugs that alter thyroid function were excluded. At base line, serum TSH (normal range, 0.45 to 4.5 mU/L) was measured in all subjects, and serum free T_4 was measured in subjects with serum TSH concentrations <0.10 mU/L or >4.5 mU/L. The subjects were categorized into four groups: subclinical hyperthyroidism, serum TSH 0.10 to 0.44 mU/L or serum TSH <0.10 mU/L and normal serum free T_4; euthyroid; serum TSH 0.45 to 4.5 mU/L; subclinical hypothyroidism, serum TSH >4.5 to <20 mU/L and normal serum free T_4; and overt hypothyroidism, serum TSH >4.5 to 20 mU/L and low serum free T_4 or serum TSH ≥20 mU/L.

Prevalent and incident atrial fibrillation, coronary heart disease (angina, myocardial infarction, coronary angioplasty or bypass surgery), and cerebrovascular disease (stroke, transient ischemic attack) were determined by self-report, electrocardiography, and review of medical records at base line and twice yearly thereafter. Cardiovascular (coronary heart disease, cerebrovascular disease, peripheral vascular disease) death and death from other causes were determined from medical records, autopsy reports, and death certificates.

Results At base line, 2639 subjects (82 percent) were euthyroid, 47 (1 percent) had subclinical hyperthyroidism, 496 (15 percent) subclinical hypothyroidism, and 51 (2 percent) overt hypothyroidism. There were no differences in the prevalence of atrial fibrillation, coronary heart disease, or cerebrovascular disease in the four groups (Table 1).

Table 1. Prevalence of Atrial Fibrillation, Coronary Heart Disease, and Cerebrovascular Disease in 3233 Subjects According to Thyroid Status.

	No.	Atrial Fibrillation	Coronary Heart Disease	Cerebrovascular Disease
Euthyroid	2639	5.2%	18.5%	5.8%
Subclinical hyperthyroidism	47	8.5%	23.4%	4.3%
Subclinical hypothyroidism	496	4.8%	19.8%	5.0%
Overt hypothyroidism	51	3.9%	23.5%	7.8%

During a mean follow-up period of 12.5 years, the incidence of atrial fibrillation was slightly higher in the subjects with subclinical hyperthyroidism than in the euthyroid subjects (Table 2). There were no differences in the incidence of coronary heart disease or cerebrovascular disease or cardiovascular or all-cause mortality in the four groups.

Table 2. Incidence of Atrial Fibrillation According to Thyroid Status.

	No. at Risk	Atrial Fibrillation	
		Incidence/1000 person-years (95% CI)	Hazard Ratio* (95% CI)
Euthyroid	2502	31 (29-33)	1.0
Subclinical hyperthyroidism	43	67 (44-102)	2.2 (1.4-3.3)
Subclinical hypothyroidism	472	34 (28-40)	1.1 (0.9-1.3)
Overt hypothyroidism	49	25 (14-46)	0.9 (0.5-1.6)

*Adjusted for age, sex, cardiovascular disease at base line, and thyroid hormone therapy during follow-up. CI denotes confidence interval.

Conclusion Among older subjects, the risk of coronary heart or cerebrovascular disease or cardiovascular or all-cause mortality is not increased in those with subclinical hyperthyroidism or subclinical or overt hypothyroidism, but the risk of atrial fibrillation is increased in those with subclinical hyperthyroidism.

COMMENTARY

The proportions of subjects with subclinical hyperthyroidism and subclinical and overt hypothyroidism in this study were similar to the proportions found in other cross-sectional studies of older subjects. Very few subjects had overt hyperthyroidism, and they were excluded.

Atrial fibrillation is the one cardiovascular abnormality more or less consistently associated with subclinical hyperthyroidism in older subjects. The risk is small, as in this study, but it increases as serum TSH declines, consistent with the notion that an increase in thyroid hormone production is the cause of the increase in risk (1).

Coronary heart disease is the cardiovascular abnormality most often thought to be associated with overt hypothyroidism and, by extrapolation, subclinical hypothyroidism. The historic reason for suspecting these associations was primarily the presence of high serum total and low-density lipoprotein cholesterol concentrations in subjects with overt hypothyroidism (true in this study) and slightly high concentrations in those with subclinical hypothyroidism (not true in this study, the values were similar to those in the euthyroid group). However, neither the prevalence nor the incidence of coronary heart disease or other cardiovascular diseases or mortality was increased in either group. Furthermore, there was no difference in cardiovascular risk in the subjects with subclinical hypothyroidism at base line who were treated with thyroid hormone at some time during the study.

Robert D. Utiger, M.D.

Reference

1. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med 1994;331:1249-52.

Quality of life is not impaired in patients with chronic subclinical hyperthyroidism

Eustatia-Rutten CF, Corssmit EP, Pereira AM, Frolich M, Bax JJ, Romijn JA, Smit JW. Quality of life in longterm exogenous subclinical hyperthyroidism and the effects of restoration of euthyroidism, a randomized controlled trial. Clin Endocrinol (Oxf) 2006;64:284-91.

SUMMARY

Background Patients with subclinical hyperthyroidism (low serum thyrotropin [TSH] and normal serum thyroid hormone concentrations) may be asymptomatic or have some symptoms that affect their quality of life. In this study, quality of life and neuropsychologic symptoms were evaluated in patients with long-standing subclinical hyperthyroidism before and after the restoration of euthyroidism.

Methods The study subjects were 24 patients (16 women, 8 men; mean age, 50 years) with subclinical hyperthyroidism due to TSH suppressive therapy. All had thyroid carcinoma treated with surgery and radioiodine therapy 10 to 17 (mean, 12) years earlier. They had thereafter been treated with thyroxine (T_4) in doses sufficient to reduce their serum TSH concentrations to below normal (<0.4 mU/L). All were considered cured, as documented by undetectable serum thyroglobulin values and negative radioiodine imaging studies.

The patients were randomly assigned to continue their usual dose of T_4 (low-serum-TSH group) or to take a lower dose, so that their serum TSH concentrations increased to normal (0.4 to 4.8 mU/L) (normal-serum-TSH group). They were given tablets containing 25 μg of T_4 or placebo; the dose of T_4 was adjusted at 6-week intervals to achieve the target serum TSH values. At base line and after six months, the patients completed five questionnaires and serum TSH and free T_4 were measured. The questionnaires were the Short Form-36 (36 questions about physical and mental well-being and limitations), the Multidimensional Fatigue Inventory (20 questions about physical and mental fatigue and motivation), the Hospital Anxiety and Depression Scale (14 questions about anxiety and depression), a hyperthyroidism symptom scale (10 questions), and the Somatoform Disorders Questionnaire (55 questions about symptoms during the preceding week).

Results Eight women and four men were assigned to each group. The duration of T_4 therapy in the two groups was the same, and at base line their daily doses of T_4 and their serum TSH and free T_4 concentrations were similar. The scores on the questionnaires, including the hyperthyroid symptom scale, were normal, and there were no differences between the two groups, with two exceptions. The depression subscore of the Hospital Anxiety and Depression Scale was lower (less depression) in the patients in both groups than in normal subjects, and the score on the Somatoform Disorders Questionnaire was higher (more symptoms).

At six months, the mean daily dose of T_4 had not changed in the high-serum-TSH group (185 vs. 165 μg), whereas it was lower in the normal-serum-TSH group (129 vs. 173 μg). The median base-line and 6-month serum TSH concentrations were 0.06 and 0.04 mU/L, respectively, in the low-serum-TSH group and 0.01 and 2.7 mU/L, respectively, in the normal-serum-TSH group. The mean serum free T_4 concentration was similar at both times in the low-serum-TSH group, but was lower at six months in the normal-serum-TSH group (1.4 vs. 1.8 ng/dl [18 vs. 23 pmol/L]).

There were no changes in the scores for any of the questionnaires in the low-serum-TSH group during the 6-month study period. Thus, they remained more depressed (according to the depression subscale of the Hospital Anxiety and Depression Scale) and still had a higher score on the Somatoform Disorders Questionnaire than normal subjects. In the normal-serum-TSH group, the score for physical role limitations was slightly lower, indicating more limitation, and the score for reduced motivation on the Multidimensional Fatigue Inventory decreased. There was no change in the hyperthyroid symptom score or any of the other scores.

Conclusion Patients who have had subclinical hyperthyroidism due to excess T_4 therapy for many years have no decrease in quality of life and differ little from normal subjects in mood, fatigue, and somatic symptoms, and the findings do not change when the dose of T_4 is reduced and they are euthyroid.

COMMENTARY

Studies of patients with subclinical hyperthyroidism have focused on three areas, symptoms and quality of life, cardiovascular function (and risk of cardiac disorders, mainly atrial fibrillation), and bone density (osteoporosis and fracture). With respect to the studies of symptoms and quality of life, the causes of subclinical hyperthyroidism (endogenous or exogenous) have varied, as have the methods of assessment and the serum TSH concentrations (albeit always low), and in most studies the duration of subclinical hyperthyroidism was not known. It is not surprising, therefore, that the results have varied (the studies are summarized in Table 1 of the article).

Among these studies, this was the most extensive, in terms of questions asked, and the most clearly negative. Subclinical hyperthyroidism was not associated with either symptoms or a decrease in quality of life. It may be argued that it was negative because the patients had been taking T_4 for a long time, and therefore had become either acclimatized or resistant to the effects of excess T_4, other than its ability to inhibit TSH secretion. The lack of change when the dose was reduced for six months supports the conclusion that subclinical hyperthyroidism causes few symptoms and has no deleterious effects on quality of life. That is not to say that it should be ignored, but symptoms should be attributed to it only with caution.

Robert D. Utiger, M.D.

Patients with hyperthyroidism caused by Graves' disease may have thymic hyperplasia mimicking a thymoma

Yamanaka K, Nakayama H, Watanabe K, Kameda Y. Anterior mediastinal mass in a patient with Graves' disease. Ann Thorac Surg 2006;81:1904-6.

SUMMARY

Background Some patients with hyperthyroidism caused by Graves' disease have thymic enlargement, and it is probably being recognized with increasing frequency as an incidental finding in patients with hyperthyroidism who undergo thoracic imaging for other reasons. Awareness of this association is important; otherwise, the patient may be thought to have a thymoma or other mediastinal mass and therefore to need surgery. This article describes a patient with Graves' hyperthyroidism who had a mediastinal mass that proved to be a hyperplastic thymus.

Case Report A 28-year-old woman had a two-month history of weight loss despite an increase in appetite, palpitations, tremor, and thyroid enlargement. Physical examination revealed signs of hyperthyroidism and a diffuse goiter. Her serum free thyroxine concentration was high and her serum thyrotropin (TSH) concentration was low. Computed tomography (CT) of the chest (the indication for the study was not stated) revealed a 3.5-by-3.0 cm anterior mediastinal mass (Figure).

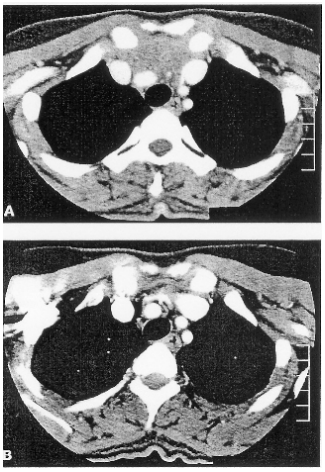

Figure. A. Contrast-enhanced CT of the chest showing an anterior mediastinal mass. B. Contrast-enhanced CT after antithyroid drug therapy for three months. Reproduced with permission of the authors and the American Thoracic Society.

She was treated with 30 mg of methimazole daily, and became clinically euthyroid in several weeks. To exclude the possibility that the mass was a tumor, it was biopsied through a small collar incision. Microscopy revealed normal thymic architecture, including cortex, medulla, Hassall's corpuscles, and fat. Antithyroid drug therapy was continued and she remained euthyroid. Three months later, the mass had disappeared.

Conclusion Patients with hyperthyroidism caused by Graves' disease may have thymic hyperplasia, which can result in thymic enlargement sufficient to be confused with a thymoma. The thymic hyperplasia diminishes with antithyroid therapy.

COMMENTARY

Thymic biopsies and chest CT imaging often reveal thymic hyperplasia in patients with Graves' hyperthyroidism (1,2). In the most extensive study of the thymus in patients with Graves' hyperthyroidism, thymic cross-sectional area was measured in 23 patients and 38 normal subjects (2). On average, the area was three to four times higher in the patients than in age-matched normal subjects (the thymus decreases in size throughout adult life). Thymic area decreased substantially in the 13 patients who were studied during prolonged antithyroid drug therapy. The decrease was associated with a fall in both thyroid secretion and serum concentrations of TSH-receptor antibodies. Normal thymic tissue (nonneoplastic thymic tissue from patients with a thymoma) was found to contain TSH receptor mRNA and protein, and TSH-receptor antibodies bound to thymic membranes in vitro. Thus, reversible thymic hyperplasia may be the rule in patients with Graves' hyperthyroidism.

Thymic hyperplasia can also occur in patients with thyroid carcinoma. In a study of 57 patients who underwent chest CT, the thymus was identified in 24 (42 percent) and 19 (33 percent) had an enlarged thymus, as compared with age-matched normal subjects (3). All the patients had been taking high doses of thyroxine for many months. No patient had thymic uptake of radioiodine.

What is common to these two groups of patients is thyroid hormone excess, more so in the patients with Graves' hyperthyroidism than in those with thyroid carcinoma. That this may be the cause of thymic hyperplasia is supported by the regression that occurs during antithyroid drug therapy in patients with Graves' hyperthyroidism. However, it is more likely that thymic hyperplasia in patients with Graves' hyperthyroidism is caused by TSH-receptor antibodies, particularly because it has not been reported in patients with toxic nodular goiter.

There is no reason to look for thymic hyperplasia in any of these patients. However, it is important to remember that it can occur, should chest CT imaging be done for any reason, so that patients do not undergo unnecessary biopsy or even resection of the thymus.

Jeffrey R. Garber, M.D.
Beth Israel Deaconess Hospital
Boston, MA

References

1. Michie W, Gunn A. The thyroid, the thymus and autoimmunity. Br J Clin Pract 1966;20:9-13.

2. Murakami M, Hosoi Y, Negishi T, et al. Thymic hyperplasia in patients with Graves' disease: identification of thyrotropin receptors in human thymus. J Clin Invest 1996;98:2228-34.

3. Niendorf ER, Parker JA, Yechoor V, et al. Thymic hyperplasia in thyroid cancer patients. J Thorac Imaging 2005;20:1-4.

Pancytopenia may occur in patients with hyperthyroidism

Lima CS, Wittmann DE, Castro V, Tambascia MA, Lorand-Metze I, Saad ST, Costa FF. Pancytopenia in untreated patients with Graves' disease. Thyroid 2006;16:403-9.

SUMMARY

Background Most patients with hyperthyroidism have normal blood counts and normal bone marrow function, although minor degrees of anemia, leukopenia, thrombocytopenia, and lymphocytosis may be present. Rare patients have more severe or combined abnormalities. This report describes four patients with hyperthyroidism caused by Graves' disease who had pancytopenia.

Case Reports Patient 1 was a 71-year-old man who had weakness, pallor, and goiter. In addition to hyperthyroidism, he had anemia, leukopenia, granulocytopenia, and thrombocytopenia (Table). Bone marrow biopsy revealed slight erythroid, granulocytic, and megakaryocytic hypercellularity. He was treated with methimazole and then radioiodine, and his hematologic values improved.

Table. Hematologic Findings and Serum Free Thyroxine (T_4) Concentrations in Four Patients with Pancytopenia and Hyperthyroidism Caused by Graves' Disease.

Patient	Hemoglobin (g/dl)	White Cells ($\times 10^6$/L)	Granulocytes ($\times 10^6$/L)	Platelets ($\times 10^9$/L)	Serum Free T_4 (ng/dl)*
1	7.3	2.5	0.9	23	2.9
2	9.5	2.8	1.6	75	5.9
3	11.9	3.9	-	96	7.8
4	4.0	3.0	0.5	10	2.5
Normal	12.0-18.0	5.0-10.0	2.7-6.2	150-300	0.6-1.8

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

Patient 2 was a 39-year-old woman with weight loss, pallor, and goiter. Bone marrow biopsy revealed erythroid, granulocytic, and megakaryocytic hypercellularity. The hematologic values were normal after treatment with methimazole for four months.

Patient 3 was a 39-year-old man with palpitations, tremor, weight loss, tachycardia, goiter, and proptosis. He improved in response to methimazole, but had a cutaneous reaction to the drug. It was stopped, and he was treated with propylthiouracil. Thereafter, he had intermittent episodes of hyperthyroidism and pancytopenia associated with cessation of the drug. He then was treated with radioiodine, after which his blood-cell counts were normal.

Patient 4 was an 18-year-old woman with a 1-year history of weakness and palpitations who had severe pancytopenia. Bone marrow biopsy revealed mild erythroid, granulocytic, and megakaryocytic hypercellularity. She was treated with methimazole, lithium carbonate, and red-cell transfusions for nine months, but hyperthyroidism and pancytopenia persisted. Therefore, she was treated with radioiodine. Two months later, she was euthyroid, but had persistent pancytopenia (hemoglobin, 5.4 g/dl; leukocytes, 3.3×10^9/L; granulocytes, 0.6×10^9/L; and platelets, 1.0×10^9/L). Bone marrow biopsy now revealed marked erythroid, granulocytic, and megakaryocytic hypocellularity. She was treated with antithymocyte globulin, cyclosporine, prednisone, and granulocyte colony-stimulating factor. She improved, and ultimately had near-normal blood-cell counts while taking T_4 and cyclosporine. The evolution to aplastic pancytopenia in this woman was thought not to be thyroid-related.

Studies at the time of diagnosis of pancytopenia and hyperthyroidism in these patients revealed normal reticuloctye counts, normal serum haptoglobin concentrations, negative Coombs' tests, and no evidence of iron, vitamin B_{12}, or folic acid deficiency. All had a diffuse goiter and high serum antithyroid peroxidase or antithyroglobulin antibody concentrations.

Conclusion Patients with Graves' hyperthyroidism may have pancytopenia that improves in response to antithyroid drug therapy.

COMMENTARY

Hematologic abnormalities are not common in patients with hyperthyroidism. For example, in a group of 200 patients, 17 (8.5 percent) had anemia (usually mild), 22 (11 percent) had lymphocytosis, and 5 (2.5 percent) had granulocytopenia ($<1.75\times10^9$/L) (1). In another study of 63 patients, 17 (27 percent) had granulocytopenia ($<2\times10^9$/L) (2). Occasional patients have thrombocytopenia, in at least some instances thought to reflect an association between autoimmune thrombocytopenic purpura and Graves' disease.

These are not the first cases of pancytopenia that improved in response to antithyroid therapy, but it is rare. The cause of the pancytopenia is not known, but likely involves both increased cell turnover and some limitation of hematopoiesis, even though the bone marrow is hypercellular (and serum erythropoietin and granulocyte colony-stimulating concentrations are high).

Most clinicians order complete blood counts when they encounter patients with hyperthyroidism. They do so not because the results are expected to be abnormal or help explain any of the patients' clinical problems, but rather to identify patients with granulocytopenia or anemia, either to disqualify them from antithyroid drug therapy or at least to have a baseline value with which to compare cell counts should they be measured during antithyroid drug therapy. That is, of course, because agranulocytosis or aplastic anemia are occasional complications of antithyroid drug therapy. The presence of hematologic abnormalities, including pancytopenia, is not a contraindication to antithyroid drug therapy, but surely it will be initiated with more caution and closer follow-up than in their absence.

Robert D. Utiger, M.D.

References

1. Reddy J, Brownlie BE, Heaton DC, et al. The peripheral blood picture in thyrotoxicosis. N Z Med J 1981;93:143-5.

2. Iitaka M, Noh JY, Kitahama S, et al. Elevated serum granulocyte colony-stimulating factor levels in patients with Graves' disease. Clin Endocrinol (Oxf) 1998;48:275-80.

Decreased physical activity contributes to weight gain during treatment of hyperthyroidism

Jacobsen R, Lundsgaard C, Lorenzen J, Toubro S, Perrild H, Krog-Mikkelsen I, Astrup A. Subnormal energy expenditure: a putative causal factor in the weight gain induced by treatment of hyperthyroidism. Diabetes Obes Metab 2006;8:220-7.

SUMMARY

Background Many patients with hyperthyroidism lose weight. Their energy expenditure increases, in part because of an increase in physical activity. When treated, some not only regain the weight that was lost but also gain more weight, so that in time they weigh more than before the onset of hyperthyroidism. This study was done to determine the changes in energy expenditure and the contribution of changes in physical activity to energy expenditure in patients with hyperthyroidism before and after treatment.

Methods The study subjects were 8 patients (6 women, 2 men; mean age, 50 years) with hyperthyroidism caused by Graves' disease or nodular goiter and 8 normal subjects (6 women, 2 men; mean age, 30 years). The patients were studied twice, once before treatment and then again when euthyroid approximately 12 months after treatment, which consisted of an antithyroid drug in 7 patients and radioiodine in 1. The normal subjects were studied once.

Each study consisted of measurements of 24-hour energy expenditure, energy expenditure during sleep, basal metabolic rate, and substrate oxidation by indirect calorimetry in a respiratory chamber, and fat mass and fat-free mass by bioelectrical impedance. The subjects were not allowed to exercise except for pedaling for 30 minutes on a bicycle ergometer while in the chamber. Spontaneous physical activity was monitored by motion detectors in the chamber; 24-hour spontaneous physical activity was calculated as the percentage of time a subject was active. Energy expenditure and nutrient oxidation were calculated from the gas exchange and urinary excretion measurements, and energy balance as energy intake minus energy expenditure.

Results The patients with hyperthyroidism gained weight after treatment (Table), due to an increase in fat mass. Their 24-hour energy expenditure, 24-hour energy expenditure adjusted for fat mass, energy expenditure during sleep, basal metabolic rate, and 24-hour spontaneous physical activity all decreased after treatment.

Table. Body Weight and Composition and Metabolic and Physical Activity in Patients with Hyperthyroidism before and after Treatment

	Before Treatment	After Treatment
Weight (kg)	68.5	72.0*
Body-mass index (kg/m^2)	24.0	25.3**
Fat-free mass (kg)	48.8	48.7
Fat mass (kg)	19.8	23.3**
24-hr energy expenditure (MJ	10.4	8.5**
24-hr energy expenditure (fat-free mass) (MJ)	10.5	8.6**
24-hr energy expenditure (sleep) (MJ)	8.0	6.4**
Basal metabolic rate (MJ)	8.6	6.8**
24-hr energy intake (MJ)	8.3	7.9
24-hr energy balance (MJ)	−2.1	−0.6**
24-hr spontaneous physical activity (%)	7.7	6.1*

*P<0.05, compared with before treatment.
**P<0.01, compared with before treatment.

The oxidation of carbohydrate and protein increased and that of fat decreased in absolute terms, but there were no changes when the results were adjusted for 24-hour energy balance.

As compared with the normal subjects, energy expenditure adjusted for fat-free mass and energy expenditure during sleep were higher, and energy balance was more negative in the patients with hyperthyroidism, but 24-hour spontaneous physical activity was not different. After treatment, energy expenditure and spontaneous activity were lower than in the normal subjects, and the decreases correlated with the decrease in serum thyroid hormone concentrations.

Conclusion Energy expenditure but not physical activity is increased in patients with hyperthyroidism. After treatment, both decrease in proportion to the fall in serum thyroid hormone concentrations, suggesting that overly aggressive treatment may explain the excess weight gain sometimes associated with treatment of hyperthyroidism.

COMMENTARY

Studies of weight change in patients with hyperthyroidism are usually confounded by the lack of knowledge of weight before the onset of the disorder. Nevertheless, it seems clear that some patients, when treated, gain more weight than they had lost. Others gain more weight than they would like, even if they do not exceed their pre-hyperthyroidism weight. Still other patients are pleased that they lost weight, and would prefer not to gain any weight when treated. As a result, an increase in weight may lead some patients to reduce or cease antithyroid drug therapy prematurely.

Why should prehyperthyroidism weight be exceeded? One possibility is that the increase in appetite that is characteristic of hyperthyroidism does not decline as rapidly as does energy expenditure after antithyroid therapy. Another is that hyperthyroidism in some way alters food preferences, leading to ingestion of more calorie-dense food, and that change persists. Yet another is overtreatment, even if it results in only transient hypothyroidism (1) or low normal thyroid secretion, as found in this study.

In practice, patients with hyperthyroidism should be advised that they will gain weight when treated, and therefore they must limit their food intake and maintain a high level of physical activity if they are not to gain excess weight.

Robert D. Utiger, M.D.

Reference

1. Dale J, Deykin J, Holder R, et al. Weight gain following treatment of hyperthyroidism. Clin Endocrinol (Oxf) 2001;55:233-9. (Clinical Thyroidology 2001;13:44.)

Graves' disease can occur in patients with human immunodeficiency virus infection during effective antiretroviral therapy

Knysz B, Bolanowski M, Klimczak M, Gladysz A, Zwolinska K. Graves' disease as an immune reconstitution syndrome in an HIV-1-positive patient commencing effective antiretroviral therapy: case report and literature review. Viral Immunol 2006;19:102-7.

SUMMARY

Background Human immunodeficiency virus type 1 (HIV-1) infection results in destruction of CD4 cells and severely compromised immunologic function. Effective antiretroviral drug therapy results in a rise in CD4 cell counts and, in some patients, is associated with the onset of augmented immunologic responses, collectively referred to as immune restoration syndromes. Among them is Graves' disease. This paper describes a patient with HIV infection who had the onset of hyperthyroidism caused by Graves' disease during antiretroviral drug therapy.

Case Report The patient was a 27-year-old woman with HIV infection, probably acquired 10 years earlier by heterosexual contact. At the time of diagnosis in March 2001, her only finding was thrush. Her CD4 T-cell count was 15 cells/μl, her plasma HIV RNA level was 35,000 copies/ml, and her serum free thyroxine (T_4), thyrotropin (TSH), anti-TSH receptor-antibody (TSHR-Ab), and antithyroid peroxidase (TPO-Ab) antibody concentrations were normal (Table). She was treated with stavudine, lamivudine, amprenavir, and ritonavir. Two months later her CD4 cell count was 95 cells/μl and her plasma HIV RNA level was <50 copies/ml. Her CD4 cell count increased progressively to 387 cells/μl in November 2002, and 862 cells/μl in June 2004, and her plasma HIV RNA level remained <50 copies/ml.

Table. CD4 Cell Counts and Serum Free T_4, TSH, and Antithyroid Antibody Concentrations in a Woman with HIV Infection and Graves' Hyperthyroidism.

	March 2001	April 2004	May 2005
CD4 cell count (cells/μl)	12	618	623
Serum free T_4 (ng/dl)	0.9	2.6	1.8
Serum TSH (mU/L)	1.4	<0.03	0.03
Serum TSHR-Ab (U/ml)	<1	-	11
Serum TPO Ab (U/ml)	10	-	178

Normal values: free T_4, 0.7-1.8 ng/dl; TSH, 0.5-4.7 mU/L, TSHR-Ab, <2 U/ml; TPO-Ab, <50 U/ml. To convert free T_4 values to pmol/L, multiply by 12.9.

In late 2003, she noted the onset of weight loss, palpitations, and tremor. Evaluation in April 2004, revealed thyroid enlargement and eyelid retraction. Her serum free T_4 concentration was high and her serum TSH concentration was low (Table). Her CD4 cell count was 618 cells/μl and her plasma HIV RNA level was <50 copies/ml. She was treated with propylthiouracil, and was euthyroid six weeks later.

In November 2004, hyperthyroidism recurred, and treatment was changed to methimazole. When last studied (May, 2005), while taking methimazole, she was clinically euthyroid and her serum free T_4 concentration was normal, but her serum TSH concentration was low. At this time, serum TSHR-Ab and TPO-Ab concentrations were high.

Conclusion Graves' disease and hyperthyroidism can occur as manifestations of the immune reconstitution syndrome that is associated with effective antiretroviral therapy in patients with HIV infection.

COMMENTARY

This case is representative of the cases of Graves' disease and hyperthyroidism that have been described in patients with HIV infection during effective antiretroviral therapy, usually with multiple drugs. Typically, the patients had very low CD4 cell counts and high plasma HIV RNA levels at the time of initiation of antiretroviral therapy, their responses to therapy were very good, and the onset of Graves' disease was delayed. In this patient the time interval from the start of treatment to the diagnosis of Graves' hyperthyroidism was 38 months and the increment in CD4 cells was 603 cells/μl. In a study of five patients (1) and another of 15 patients (2), the interval ranged from 9 to 33 months and the increment in CD4 cells ranged from 44 to 840 cells/μl. In the latter study, Graves' disease was found in 3 percent of women and 0.2 percent of men with HIV infection followed at four treatment centers in the United Kingdom from 2000 to 2002; these percentages approximate those for the population at large.

There are no reports of Graves' disease in patients with HIV infection in the era before effective therapy, a not unexpected finding for a disease in which T cells play a crucial role. Effective antiretroviral therapy results first in an increase in memory T cells, followed by an increase in naïve T cells, which include autoreactive T cells and also regulatory T cells. The autoreactive T cells may respond to thyroid antigens, and the regulatory T cells may provide the cytokines that allow thyroid cells to present antigens to T cells, promote expansion of T cells sensitized to thyroid antigens, or augment antibody production by B cells. It is noteworthy that autoimmune thyroiditis and hypothyroidism have rarely been reported as manifestations of the immune reconstitution syndrome, suggesting, at least with respect to the thyroid gland, that the syndrome is associated more with antibody-mediated than cell-mediated disease.

Robert D. Utiger, M.D.

References

1. Jubault V, Penfornis A, Schillo F, et al. Sequential occurrence of thyroid autoantibodies and Graves' disease after immune restoration in severely immunocompromised human immunodeficiency virus-1-infected patients. J Clin Endocrinol Metab 2000;85:4254-7.

2. Chen F, Day SL, Metcalfe RA, et al. Characteristics of autoimmune thyroid disease occurring as a late complication of immune reconstitution in patients with advanced human immunodeficiency virus (HIV) disease. Medicine (Baltimore) 2005;84:98-106.

Newborn infants should be screened twice for hypothyroidism

Maniatis AK, Taylor L, Letson GW, Bloch CA, Kappy MS, Zeitler P. Congenital hypothyroidism and the second newborn metabolic screening in Colorado, USA. J Pediatr Endocrinol Metab 2006;19:31-8.

SUMMARY

Background Most infants with congenital hypothyroidism appear normal at birth, but have mental retardation by the time hypothyroidism becomes clinically apparent. Screening of newborn infants for hypothyroidism, which is mandated by law in all states in the United States and in many other countries, has proven highly successful for early identification of affected infants, allowing early treatment and therefore preventing the retardation. However, some affected infants are missed by screening. Therefore, some states have mandated that all infants be tested a second time a week or two later. This study evaluated the results of second screening in one of these states.

Methods The results of the first and second screening tests of all infants born in Colorado from 1996 to 2004 were reviewed. The first heel-prick blood sample was collected within three days after birth. Thyroxine (T_4) was measured, and if the T_4 value was <6.0 μg/dl (77 nmol/L) or <10th percentile for the day, thyrotropin (TSH) was measured. TSH values <20 mU/L were considered normal. If the TSH value was 20 to 39 mU/L (borderline), follow-up to ensure second screening was initiated. If the value was >39 mU/L (presumed positive), the infant was recalled for serum testing to confirm the diagnosis. The second screening test, done 8 to 14 days after birth, consisted of the same measurements with the same cut-off values, except that any TSH value >20 mU/L was considered positive, and the infant was recalled for serum testing.

Results During the 8-year period, 494,324 infants were screened soon after birth (mostly on day 2), and 471,877 (95.4 percent) were screened a second time. The first screening identified 185 infants with hypothyroidism (1 in 2672) and the second 42 infants, giving a total of 227 infants (1 in 2178). The infants identified by the second screening test constituted 18.5 percent of the total.

There were 3083 infants with borderline results on the first screening, of whom 2938 (95.3 percent) had a normal second screening and 26 (0.8 percent) had hypothyroidism (Table). There were 463 infants with presumed positive results on the first screening. Among them, 300 (64.8 percent) had normal serum tests and 159 (34.3 percent) had hypothyroidism. The results of the second screening were borderline in 70 infants and presumed positive in 34 infants, of whom 22 (31.4 percent) and 20 (58.8 percent), respectively, had hypothyroidism.

Table. Results of Borderline and Presumed Positive First and Second Screening Tests for Hypothyroidism in Infants in Colorado, 1996-2004.

First screen	No.	2nd Screen Normal	Serum Tests Normal	Hypo-thyroidism	Other Conditions*
Borderline	3083	2938 (95.3%)	NA	26 (0.8%)	119 (3.9%)
Presumed positive	463	NA**	300 (64.8%)	159 (34.3%)	4 (0.9%)
Second screen					
Borderline	70		45 (64.3%)	22 (31.4%)	3 (4.3%)
Presumed positive	34		14 (41.2%)	20 (58.8%)	0

*Death, otherwise not specified. **Not applicable.

There were no differences in gestational age, proportion of infants with gestational age <37 weeks or >42 weeks, or birth weight in the infants with hypothyroidism identified by the first and second screening tests. As compared with all infants, the proportions of infants with hypothyroidism whose gestational age was <37 weeks or >42 weeks were higher, as were the proportions whose birth weight was low (<2500 g) or very low (<1500 g).

The mean blood-spot T_4 value in the infants with hypothyroidism identified by the first screening test was 5.4 μg/dl (70 nmol/L) and their mean blood-spot TSH value was 206 mU/L. The mean first-screen blood-spot T_4 value for the infants identified by the second screening test was 12.4 μg/dl (160 nmol/L); two thirds had T_4 values above the threshold for measurement of blood-spot TSH.

Conclusion Screening of newborn infants for hypothyroidism a second time soon after birth identifies additional cases.

COMMENTARY

The benefit of newborn screening for hypothyroidism is unquestioned. The screening may be done by measurement of T_4 and then, if the T_4 value is below a certain threshold, measurement of TSH; measurement of TSH, with measurement of T_4 if the TSH value is above a certain threshold; or routine measurement of both. No matter how the screening is done, some infants are missed, and, as described by Maniatis et al., that number is not trivial.

Two thirds of the 42 infants identified by second screening in this study initially had T_4 values above the threshold mandating measurement of TSH, and therefore it was not measured. A moderate increase in T_4 threshold would not have led to measurement of TSH in many of these infants, given that their mean T_4 value was 12.4 μg/dl (160 nmol/L), but TSH would have had to be measured a lot more often, and anyway their TSH values may well have been normal then. Other infants who pass initial screening are those with low blood-spot T_4 and normal TSH values. Many prove to be normal, their initial findings being attributed to immaturity of the hypothalamus or pituitary, so that the normal postnatal surge in TSH secretion is reduced or absent, or to glucocorticoid or illness-induced inhibition of TSH secretion. Some, however, prove to have hypothyroidism.

Therefore, some infants who prove to have hypothyroidism caused by thyroid disease may be truly normal at birth, and have acquired hypothyroidism postnatally, and others have hypothyroidism plus inappropriately low TSH secretion due to immaturity or illness at that time. The existence of these two disorders is the basis for second screening. It is logistically more difficult than the first screening, and fewer cases will be detected, and therefore the program will be more costly. But missing approximately 20 percent of cases of hypothyroidism in newborn infants seems unacceptable.

Robert D. Utiger, M.D.

Radioactive iodine therapy for goiter occasionally induces hyperthyroidism due to Graves' disease

Schmidt M, Gorbauch E, Dietlein M, Faust M, Stutzer H, Eschner W, Theissen P, Schicha H. Incidence of postradioiodine immunogenic hyperthyroidism/Graves' disease in relation to a temporary increase in thyrotropin receptor antibodies after radioiodine therapy for autonomous thyroid disease. Thyroid 2006;16:281-8.

SUMMARY

Background Patients with nodular goiter may be treated with radioactive iodine (I-131) to decrease thyroid function or goiter size. However, this treatment may result in immunogenic hyperthyroidism (hyperthyroidism caused by Graves' disease). In this study, the frequency of the appearance of thyrotropin (TSH)-receptor antibodies (TSHR-Ab) and of Graves' hyperthyroidism was determined in a large group of patients with goiter treated with I-131.

Methods The study subjects were 421 patients with uninodular goiter, 494 patients with multinodular goiter, and 84 patients with diffuse (nonimmunogenic but autonomous) goiter who were treated with I-131 because they had overt hyperthyroidism or subclinical hyperthyroidism (serum thyrotropin [TSH] concentration ≤0.1 mU/L). The latter was spontaneously occurring in some patients, but in others it was induced by administration of thyroxine (T_4) given to confirm the presence of TSH-independent thyroid function. Patients with a high serum concentration of TSHR-Ab were excluded. The goal of I-131 therapy was to eliminate hyperthyroidism and the autonomously functioning thyroid tissue. The dose delivered to the thyroid ranged from 110 to 850 Gy.

Serum TSH, free T_4, TSHR-Ab (measured by radioreceptor assay using recombinant human TSH receptors; normal range, ≤2 U/L), and antithyroid peroxidase (TPO) antibodies were measured and thyroid ultrasonography and scinitigraphy were performed before and after I-131 therapy. Post-radioiodine Graves' hyperthyroidism was defined as overt clinical and biochemical hyperthyroidism, a high serum TSHR-Ab concentration, the appearance of hypoechogenicity on ultrasonography, and a homogeneous pattern of radionuclide uptake on scintigraphy.

Results Fifteen of the 999 patients (1.5 percent) had Graves' hyperthyroidism after I-131 therapy. They included 8 of the 421 patients with uninodular goiter (1.9 percent), 6 of the 494 patients with a multinodular goiter (1.2 percent), and 1 of the 84 patients with a diffuse goiter (1.2 percent).

Before I-131 therapy, most had subclinical hyperthyroidism. After I-131 therapy, all 15 patients had overt hyperthyroidism with homogeneous radionuclide uptake on scintigraphy; 1 patient had Graves' ophthalmopathy. The hyperthyroidism occurred an average of 5 months (range, 1 to 13) after I-131 therapy. At that time, in addition to high serum TSHR-Ab concentrations (2.3 to 21.5 U/L), 11 patients had high serum anti-TPO antibody concentrations.

Fifty-seven of the 999 patients (6 percent) had high serum anti-TPO antibody concentrations at the time of I-131 therapy. Six (10 percent) later had hyperthyroidism, and 51 did not.

Thirteen of the 999 patients (1.3 percent) had a transient rise in serum TSHR-Ab concentration, but not hyperthyroidism, after I-131 therapy.

Conclusion Patients with autonomous thyroid function caused by nodular or diffuse goiter have a low risk of Graves' hyperthyroidism after I-131 therapy.

COMMENTARY

Therapeutic doses of I-131 are given to damage or destroy thyroid follicular cells in order to ameliorate hyperthyroidism in patients with Graves' disease or nonimmunogenic hyperthyroidism (toxic nodular goiter) or to reduce thyroid size in patients with nontoxic nodular goiter. In patients with Graves' disease nearly all the follicles are damaged or destroyed, whereas only hyperfunctioning ("hot") follicles are affected in patients with a nodular goiter. The dying thyroid follicular cells may release their constituents, including TSH receptors or components of the receptor, into the extracellular fluid.

I-131 therapy has several undesirable effects on thyroid function. One is hypothyroidism caused directly by I-131-induced destruction of most or all functioning follicles. This is almost the rule in patients with Graves' hyperthyroidism who are treated with I-131, and it occurs in a substantial proportion of those with toxic nodular goiter or nontoxic nodular goiter who are so treated. A second is autoimmune thyroiditis (immunogenic hypothyroidism). A third is immunogenic hyperthyroidism (Graves' disease).

Schmidt et al. focused on the latter, and did not mention hypothyroidism. They found the incidence of Graves' hyperthyroidism after I-131 therapy for nonimmunogenic hyperthyroidism to be low (1.5 percent), but others have found it to be as high as 5 percent (1). Whatever the incidence, the mere existence of the condition is of interest. First, it indicates that radiation-induced release of thyroid-cell constituents may initiate production of the TSHR-Ab that cause Graves' hyperthyroidism. Second, it indicates that a goiter in which most, if not all, of the hyperfunctioning follicles, and probably also many normally functioning follicles, are destroyed still contains enough healthy thyroid follicles to produce excess thyroid hormone in response to the newly produced TSHR-Ab. In the patients with high serum TSHR-Ab concentrations, but no hyperthyroidism, after I-131 therapy, the thyroid follicles may be so badly damaged that they cannot regenerate even when highly stimulated. Alternatively, their serum TSHR-Ab may block rather than activate TSH receptors. These patients would have immunogenic hypothyroidism, the second possible effect of I-131 mentioned above.

Hugo Studer, M.D.
Muri, Switzerland

Reference

1. Nygaard B, Knudsen JH, Hegedus L, et al. Thyrotropin receptor antibodies and Graves' disease, a side-effect of ^{131}I treatment in patients with nontoxic goiter. J Clin Endocrinol Metab 1997;82:2926-30.

The increasing incidence of thyroid cancer is due to an increase in detection of small papillary carcinomas

Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006;295:2164-7.

SUMMARY

Background The incidence of thyroid cancer has increased in the United States and other countries in recent years. This study was done to determine if the increase was due to a true increase in incidence or detection of small, previously unrecognized cancers.

Methods Data on the annual incidence of different types of thyroid cancer and the size of the cancers in the United States were obtained from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. This program collects annual data on cancer incidence from the cancer registries of five states and four metropolitan areas. These areas constitute approximately 10 percent of the United States' population. Incidence data were available for 1973 to 2002 and size data for 1988 to 2002. Data on mortality from thyroid cancer for 1973 to 2002 were obtained from the National Vital Statistics System.

The overall annual incidence and mortality from thyroid cancer were calculated, with age adjustment to the U.S. population in 2000. The annual incidence of papillary carcinoma, follicular carcinoma, and medullary/anaplastic carcinoma was also calculated. These four tumor types constituted 99.5 percent of all cancers of the thyroid listed in the SEER data base.

Results For 2002, approximately 2400 people were found to have thyroid cancer in the nine SEER regions. Their median age was 46 years, as compared with 45 years in 1995, and 73 percent were women. Eighty-eight percent of the cancers were papillary carcinomas, 9 percent follicular carcinomas, and 3 percent medullary/anaplastic carcinomas.

The incidence of thyroid cancer in 1973 was 3.6 per 100,000 people, and it increased to 8.7 per 100,000 in 2002, a 2.4-fold increase (P for trend <0.01) (Table 1). There was a parallel increase in the incidence of papillary carcinoma, from 2.7 per 100,000 in 1973 to 7.7 per 100,000 in 2002, a 2.9-fold increase (P for trend <0.01). There was no change in the incidence of follicular carcinoma or medullary/anaplastic carcinoma during the same period.

Table 1. Incidence of Thyroid Cancer and Papillary Carcinoma and Thyroid-Cancer Mortality, per 100,000 People, 1973-2002.*

	1973	1982	1988	1992	1998	2002
Thyroid Cancer	3.6	4.3	4.7	5.6	6.8	8.7
Papillary carcinoma	2.7	3.3	3.6	4.5	5.7	7.7
Mortality	0.57	0.48	0.44	0.46	0.44	0.47

Most of the increase in incidence of papillary carcinoma was due to an increase in small tumors (Table 2). The increase in tumors ≤1.0 cm accounted for 49 percent and the increase in tumors ≤2.0 cm for 87 percent of the increase in incidence of papillary carcinoma from 1988 to 2002.

Table 2. Incidence of Papillary Carcinoma According to Size, per 100,000 People, 1988-2002.*

	1988	1992	1998	2002
≤1.0 cm	1.5	2.0	2.5	3.5
1.1-2.0 cm	0.6	0.7	1.2	2.1
2.1-5.0 cm	1.2	1.3	1.5	1.6
>5.0 cm	0.2	0.4	0.3	0.3

There was no change in mortality from thyroid cancer from 1973 to 2002.

Conclusion The incidence of thyroid cancer increased in the United States from 1973 to 2002, due to an increase in detection of small papillary carcinomas. There was no increase in mortality from thyroid cancer during this interval.

*Some values in Tables 1 and 2 were not given in the published paper and were kindly supplied by the authors.

COMMENTARY

The American Cancer Society has for years published estimates of the number of new cases of thyroid (and other) cancers expected to occur that year, based on SEER data for the previous year. The annual estimates for thyroid cancer have continuously increased, and the estimate for 2006 (30,180 vs. 25,690 for 2005) was no exception (1). These estimates are often the first or second reference in reviews about thyroid cancer, with the inference if not the statement that there is an epidemic of thyroid cancer. It was, therefore, refreshing, and reassuring, to see this paper. The analysis, based on SEER data, puts the so-called epidemic of thyroid cancer in perspective; it is due to the increasing detection of small, often very small, papillary thyroid cancers. This finding is not surprising, given the urgency with which endocrinologists have been advised to find and biopsy small thyroid nodules, as if all were potentially capable of lethal invasion and metastasis. Many people must have small thyroid cancers for years, given the high frequency with which they are detected at autopsy. And there is no epidemic of thyroid-cancer mortality at all.

The results of this study should provide reassurance to the many patients who are being discovered to have small thyroid cancers. They should also lead to less intensive therapy and follow-up, and perhaps even less aggressive case finding.

Ian D. Hay, M.D., Ph.D.
Mayo Clinic
Rochester, MN

Reference

1. Jemal A, Siegel R, Ward E. et al. Cancer statistics, 2006.CA Cancer J Clin 2006;56:106-30.

The frequency of nonthyroid cancer is slightly increased in patients with thyroid cancer

Sandeep TC, Strachan MW, Reynolds RM, Brewster DH, Scelo G, Pukkala E, Hemminki K, Anderson A, Tracey E, Friis S, McBride ML, Kee-Seng C, Pompe-Kirn V, Kliewer EV, Tonita JM, Jonasson JG, Martos C, Boffetta P, Brennan P. Second primary cancers in thyroid cancer patients: a multinational record linkage study. J Clin Endocrinol Metab 2006;91:1819-25.

SUMMARY

Background Patients with one cancer may have an increased risk of another cancer. This study was done to determine the risk of a second primary cancer in patients with thyroid cancer and, conversely, the risk of thyroid cancer in patients with a nonthyroid cancer.

Methods The data for the analyses were obtained from 13 cancer registries in Australia, Canada (three), Denmark, Finland, Iceland, Norway, Singapore, Slovenia, Spain, Sweden, and United Kingdom that had been established at least 25 years ago. Each registry provided data on all primary cancers, including the patient's age and sex, date of diagnosis of the first cancer and follow-up data, and date of diagnosis of the second cancer. To determine if there was an excess of second cancers, the observed number was compared with the expected number calculated from the age-, sex-, and calendar year-specific incidence rate for each registry. Standardized incidence ratios (SIRs) were calculated, and after stratification for age at first cancer diagnosis, sex, follow-up, and date of second cancer diagnosis.

Results There were 39,002 patients with primary thyroid cancer, followed for 356,035 person-years. They included 29,030 women (74 percent) and 9972 men (26 percent); 22,188 (57 percent) were <56 years old. The thyroid cancer was a papillary carcinoma in 15,523 (40 percent), a follicular carcinoma in 5260 (13 percent), a medullary carcinoma in 1170 (3 percent), and unclassified in 17,049 (44 percent).

Among these 39,002 patients, 2821 (7 percent) had a second primary cancer (SIR, 1.31; 95 percent confidence interval, 1.26–1.36). There were more than 100 cases of 8 types of cancer, for 7 of which the frequency was increased (Table). The frequency of cancer of the oral cavity/pharynx, salivary glands, larynx, small intestine, bone, brain, and other endocrine glands, and soft-tissue sarcoma also was statistically significantly increased.

Table 1. SIRs of Second Primary Cancers (>100 Cases) in 39,002 Patients with Thyroid Cancer.

	No.	SIR*
Stomach	119	**1.22**
Colon/rectum	335	**1.27**
Lung	179	0.93
Nonmelanoma skin	140	**1.42**
Breast (women)	552	**1.31**
Prostate	206	**1.52**
Kidney	134	**2.33**
Lymphoma	102	**1.68**
Leukemia	105	**2.26**

*Bold type, lower 95 percent confidence interval >1.00

There were 1990 patients in whom thyroid cancer was the second primary cancer; they differed from the patients in whom the thyroid cancer was the first cancer in age (499 [25 percent] were <56 years old), but not sex or type of thyroid cancer. There were more than 100 cases of thyroid cancer, and a statistically significant increase in frequency of thyroid cancer, in patients with cancer of the colon/rectum, melanoma, non-melanoma skin, breast (women), cervix, and uterus (SIR, 1.29 to 1.84). The risk of thyroid cancer was also increased in patients with other cancers, including cancers of the oral cavity/pharynx, larynx, esophagus, stomach, and liver; brain tumors; lymphoma; and leukemia.

Conclusion The frequency of a second nonthyroid cancer is increased by approximately 30 percent in patients with thyroid cancer. Conversely, the frequency of thyroid cancer is increased in patients with some other cancers.

COMMENTARY

These results complement those of a similar study based on data from the U.S. Surveillance, Epidemiology and End Results (SEER) program (1). Among 29,456 patients with thyroid cancer followed for up to 27 years, 2214 (8 percent) had a second cancer, an 11 percent increase compared with the general population, and the risk of thyroid cancer in 2,036,597 patients with other cancers was increased by 42 percent. In general, the sites of the nonthyroid cancers, whether the first or the second cancer, and the increase in risk associated with cancer at those sites, were similar in the two studies.

These associations may in part be the result of more intensive evaluation and surveillance when a cancer is detected. In the study of Sandeep et al., many of the second cancers, both nonthyroid and thyroid, were detected within one year after diagnosis of the first cancer. Nonetheless, the fact that the same organs tended to be involved, whether as the site of the second cancer in patients with thyroid cancer or the site of the first (nonthyroid) cancer in patients who later had thyroid cancer, suggests some common genetic or environmental predisposition. There are plausible explanations for some of these associations. An increase in cancer of the oral cavity/pharynx, salivary glands, stomach, colon/rectum, breast, and kidney may be linked to radiation from iodine-131 therapy for thyroid cancer. Conversely, radiation therapy for breast cancer, cancer of the larynx, or lymphoma may increase the risk of thyroid cancer.

For those who treat patients with thyroid cancer, these results should serve as a reminder to encourage patients who are treated with iodine-131 to minimize retention of the iodine-131 in the salivary glands, stomach, large intestine, and kidneys and urinary system.

Robert D. Utiger, M.D.

Reference

1. Ronckers CM, McCarron P, Ron E. Thyroid cancer and multiple primary tumors in the SEER cancer registries. Int J Cancer 2005;117:281-8.

Multifocal papillary carcinomas usually arise from the same clone of thyroid cells

McCarthy RP, Wang M, Jones TD, Strate RW, Cheng L. Molecular evidence for the same clonal origin of multifocal papillary thyroid carcinomas. Clin Cancer Res 2006;12:2414-8.

SUMMARY

Background Patients with papillary carcinoma of the thyroid may have one or more small foci of papillary carcinoma in addition to their main tumor. The smaller tumors may be metastases of the main tumor or independent tumors. In this study, the genetic relationships between tumors in the same patient were studied using molecular analysis of polymorphisms of three autosomal genes and X-chromosome inactivation.

Methods Papillary-carcinoma tissue from 23 women (mean age, 44 years) was analyzed. The diameter of the largest tumor in each woman ranged from 0.3 to 4.5 cm (mean, 1.8), and they had from one to five additional, smaller noncontiguous tumors (total, 64). All were confined to the thyroid gland.

Tumor and normal thyroid tissue were identified on archived slides prepared for standard histologic evaluation, and approximately 400 to 1000 cells were removed by laser microdissection of a section on an adjacent unstained slide. DNA was extracted from the cells, and a polymorphic gene on each of three different chromosomes was amplified. They were chromosome 3p25 (D3S1597), chromosome 9p21 (D9S161), and chromosome 18p11.22-p11 (D18S53). The products of these genes are thought to be tumor suppressor genes, and therefore alterations of the genes may contribute to the pathogenesis of papillary carcinoma. The results of these analyses are informative only if the alleles are different in the normal tissue. If the pattern of alleles (both present or one lost [loss of heterozygosity]) is similar in different tumors in a woman, then the tumors are considered to have a common clonal origin, and if the pattern differs the tumors are considered to have independent clonal origins.

The pattern of X-chromosome inactivation was determined by amplification of its constituent androgen-receptor gene and detection of active and inactive alleles. The results, as above, are informative only if both alleles are detected in normal tissue, indicative of random X–chromosome inactivation. The results in tumor tissue are interpreted as described above.

Results The results of the analyses of the polymorphic genes were similar in all the tumors from 20 of the 23 women (87 percent). They included 1 woman with 5 tumors, 1 with 4 tumors, and 7 with 3 tumors. In the 1 woman with 6 tumors, the results were similar in 5. There was loss of one or more alleles in the tumors in 15 women.

The pattern of X-chromosome inactivation was similar in all the tumors in 19 of the 20 women (95 percent) in whom the results were informative. In 6 women, all the tumors had both alleles (e.g., an active and an inactive X chromosome); in 13, all the tumors had only 1 allele, whether activated or inactivated.

Conclusion In most patients with multifocal papillary carcinoma of the thyroid, the clonal composition of each tumor is the same, suggesting common parentage and therefore that tumors can metastasize within the thyroid.

COMMENTARY

Multifocality is a hallmark of papillary thyroid carcinoma. The frequency with which two or more separate foci of tumor have been found has varied widely, from approximately 20 to 80 percent of patients, no doubt depending mostly on the diligence with which both lobes of the thyroid were examined. As an example, in a study of 105 consecutive patients in which both lobes of the thyroid were sectioned at 2- to 3-mm intervals (an average of 19 sections for each lobe), foci of tumor, usually <4 mm, in addition to the primary tumor were found in 82 patients (78 percent), including in the contralateral thyroid lobe in 64 (61 percent) (1).

Are the smaller tumors metastases of the primary tumor, or independent tumors? Probably both. Histologically, they look alike. Genetically, there were within-patient differences in the tumors in most patients in several studies (2,3), whereas in this study, in which more genes were analyzed, within-patient differences were rare.

If the smaller tumors are metastases, they presumably get to the contralateral lobe via lymphatic channels in the isthmus. If they are independent tumors, the lymphatic anatomy doesn't matter. From a therapeutic perspective, what matters at present is whether the patient has multifocal tumors, not whether they are clonally alike or different. Since many are too small to be detected by any imaging test, bilateral thyroidectomy should continue to be the operation of choice for patients with papillary carcinoma.

Robert D. Utiger, M.D.

References

1. Katoh R, Sasaki J, Kurihara H, et al. Multiple thyroid involvement (intraglandular metastasis) in papillary thyroid carcinoma. A clinicopathologic study of 105 consecutive patients. Cancer 1992;70:1585-90.

2. Sugg SL, Ezzat S, Rosen IB, et al. Distinct multiple *RET/PTC* gene rearrangements in multifocal papillary thyroid neoplasia. J Clin Endocrinol Metab 1998;83:4116-22.

3. Shattuck TM, Westra WH, Ladenson PW, Arnold A. Independent clonal origins of distinct tumor foci in multifocal papillary thyroid carcinoma. N Engl J Med 2005;352:2406-12.

Patients with Graves' disease found to have a small thyroid carcinoma at the time of thyroidectomy have an excellent prognosis

Kikuchi S, Noguchi S, Yamashita H, Uchino S, Kawamoto H. Prognosis of small thyroid cancer in patients with Graves' disease. Br J Surg 2006;93:434-9.

SUMMARY

Background Some patients with hyperthyroidism caused by Graves' disease also have thyroid carcinoma. This study was done to determine the prognosis of patients with Graves' hyperthyroidism who had a small incidentally detected thyroid carcinoma, as compared with patients with other thyroid disorders found to have an incidental carcinoma.

Methods The study subjects were 509 patients with Graves' hyperthyroidism and 509 age- and sex-matched patients with other thyroid disorders found to have a ≤1.0 cm carcinoma (microcarcinoma) at the time of thyroidectomy between 1970 and 1996 at a single clinic in Japan. Among the latter, 247 patients had adenomatous nodules, 146 a follicular adenoma, and 73 chronic thyroiditis. There were 476 women and 33 men (mean age, 44 years) in each group, and they were matched for tumor size and year of treatment.

Among the patients with Graves' disease, 502 (99 percent) were treated by subtotal thyroidectomy and 7 (1 percent) by lesser operations. In contrast, among the non–Graves' disease patients, 182 (36 percent) were treated by subtotal thyroidectomy and 324 (64 percent) by lesser operations. No additional treatment was given.

Results The size and types of carcinoma in the two groups were similar, as was the frequency of multifocal tumors (Table). In contrast, lymph-node metastases and invasion of adjacent tissue were more common in the non–Graves' disease group.

Table. Clinical Characteristics of Small Thyroid Carcinomas in Patients with Graves' Hyperthyroidism and Non–Graves' Disease Patients.

	Graves' Disease (n=509)	Non-Graves' Disease (n=509)
Type of carcinoma		
Papillary	432 (85%)	435 (85%)
Follicular	66 (13%)	64 (12%)
Other	11 (2%)	10 (2%)
Maximum diameter (cm)	4.4	4.5
Encapsulated tumor	229 (45%)	282 (55%)
Multifocal	46 (9%)	49 (10%)
Lymph-node metastasis	18 (4%)	76 (13%)*
Recurrence	3 (1%)	17 (3%)*

*P<0.01, compared Graves' disease group.

The mean duration of follow-up was 13 years in both groups. During that period 3 of the 509 patients with Graves' disease (1 percent) had a recurrence of thyroid carcinoma, as compared with 17 (3 percent) of the non–Graves' disease patients. The recurrences in the Graves' disease group were in cervical lymph nodes in 2 patients and bone in 1 patient, and the recurrences in the non–Graves' disease group were in the thyroid bed, cervical lymph nodes, or both, in 16 patients and bone in 1 patient. The predictors of recurrence were older age and non–Graves' disease, but not the size of the carcinoma, the presence of multiple foci of carcinoma, lymph-node metastasis at the time of surgery, or the extent of surgery.

The 20-year survival rate was 99 percent in the patients with Graves' disease and 93 percent in the non–Graves' disease group (P<0.01).

Conclusion Patients with Graves' hyperthyroidism found to have a microcarcinoma at the time of thyroidectomy have an excellent prognosis, better than that of patients with other thyroid disorders who have a microcarcinoma.

COMMENTARY

In this study, microcarcinomas were found in 23 percent (509 of 2199) of patients treated by thyroidectomy. Whether any of the carcinomas were detected by ultrasonography is not stated, nor are the histologic criteria used to identify them. The overall frequency of carcinoma may well have been higher, if some of the other 1690 patients had a carcinoma >1 cm in size, as is likely. Among patients with Graves' hyperthyroidism with clinically detected nodules, the frequency of carcinoma has ranged from 2 to 46 percent (1). These percentages vary because the patients were evaluated in different ways, the nodules varied in size, the indications for surgery (as opposed to other antithyroid therapy) varied, and not least because there are cytologic similarities between Graves' disease and papillary carcinoma (2).

The practical question is how diligently should one look for a carcinoma in patients with Graves' hyperthyroidism. Patients who have a palpable nodule, whether their thyroid is diffusely enlarged or not, should be evaluated in the same way as any patient with a thyroid nodule. The frequency of carcinoma among nodules may be increased in patients with Graves' hyperthyroidism, and their prognosis may be poorer than that of patients who do not have Graves' hyperthyroidism (1). Among patients with microcarcinomas, however, Kikuchi et al. found that those with Graves' hyperthyroidism have a better prognosis. These results argue against looking for small nodules and therefore for ordering ultrasonography routinely in patients with Graves' hyperthyroidism.

Robert D. Utiger, M.D.

References

1. Belfiore A, Russo D, Vigneri R, Filetti S. Graves' disease, thyroid nodules and thyroid cancer. Clin Endocrinol (Oxf) 2001;55:711-8.

2. Anderson SR, Mandel S, LiVolsi VA, et al. Can cytomorphology differentiate between benign nodules and tumors arising in Graves' disease? Diagn Cytopathol 2004;31:64-7.

Patients with diffuse sclerosing papillary carcinoma have a poorer prognosis than patients with classical papillary carcinoma

Falvo L, Giacomelli L, D'Andrea V, Marzullo A, Guerriero G, de Antoni E. Prognostic importance of sclerosing variant in papillary thyroid carcinoma. Am Surg 2006;72:438-44.

SUMMARY

Background There are several subtypes of papillary carcinoma of the thyroid, including classical, follicular variant, tall-cell, columnar, and diffuse sclerosing carcinomas. The latter three subtypes are considered to be more aggressive, but they are rare and little is known about their behavior. In this study, the clinical characteristics and course of patients with diffuse sclerosing papillary carcinoma were compared with those of patients with classical papillary carcinoma.

Methods From 1992 to 2000, 398 patients with papillary carcinoma were treated and followed at a single center in Italy. They included 83 patients with diffuse sclerosing papillary carcinoma and 168 patients with classical papillary carcinoma (how the latter were selected from the cohort of 398 patients is not stated). The diagnosis of diffuse sclerosing papillary carcinoma was based on the presence of diffuse infiltration of one or both lobes of the thyroid with multiple small islands of cells with the nuclear features of papillary carcinoma, often within lymphatic channels, squamous metaplasia, dense sclerosis, abundant psammoma bodies, and lymphocytic infiltration.

The initial diagnosis in the patients with diffuse sclerosing papillary carcinoma was based on biopsy in 18 patients (22 percent) and operative findings in 65 (78 percent); most of the latter were operated on for a multinodular goiter or chronic thyroiditis. All the patients underwent total thyroidectomy, 40 (48 percent) underwent lymph-node dissection, and 30 (36 percent) were treated with radioiodine. Among the patients with classical papillary carcinoma, the tumor was detected by biopsy in 71 (42 percent) and at surgery in 85 (50 percent); all underwent total thyroidectomy, 27 (16 percent) underwent lymph-node dissection, and 84 (50 percent) were treated with radioiodine.

Demographic, clinical, pathologic, and follow-up information were collected for each patient.

Results The clinical characteristics and pathologic findings at diagnosis in the two groups are shown in the Table. The mean duration of follow-up was 7.6 years (range, 4 to 10).

Table 1. Characteristics of Patients with Diffuse Sclerosing Papillary Carcinoma and Classical Papillary Carcinoma.

	Diffuse Sclerosing (n=83)	Classical (n=168)
Women/men	59/24	123/45
Age (yr)	40	45
Tumor size – cm (range)	0.9 (0.2-4.5)	1.2 (0.1-8.0)
Tumor stage		
Stage 1 (≤2 cm)	33 (40%)	99 (59%)
Stage 2–4	50 (60%)	69 (41%)
Multifocal	18 (22%)	22 (13%)
Bilateral	8 (10%)	11 (6%)
Soft-tissue/vascular invasion	23 (28%)	15 (9%)

During follow-up, 13 patients (16 percent) with diffuse sclerosing papillary carcinoma had a lymph-node recurrence, 6 (7 percent) had distant metastases, and 3 (4 percent) died of tumor-related causes. The respective figures in the patients with classical papillary carcinoma were 6 (4 percent), 2 (1 percent), and 1 (1 percent). The rates of recurrence and mortality were statistically significantly higher in the patients with diffuse sclerosing papillary carcinoma.

Conclusion Patients with diffuse sclerosing papillary carcinoma are more likely to have lymph-node and distant metastases and die of their tumor than are patients with classical papillary carcinoma.

COMMENTARY

Diffuse sclerosing papillary carcinoma is a well-recognized subtype of papillary carcinoma. It is considered rare; the authors of a 2004 review counted only 65 cases (1), and, among 1086 patients with papillary carcinoma seen at a single center in Hong Kong, only 8 (1 percent) had a diffuse sclerosing papillary carcinoma. Yet, Falvo et al. identified 83 patients with this tumor among 398 patients with papillary carcinoma (21 percent). The histologic criteria for the diagnosis of diffuse sclerosing papillary carcinoma in these studies were similar, but it is hard to escape the conclusion that different pathologists have different opinions about the extent of sclerosis or squamous metaplasia needed before assigning this diagnosis.

The available information about the course of these tumors is also conflicting, with some evidence that they are not more aggressive than are classical papillary carcinomas (2), and some evidence that they are more aggressive (1, this study). That is despite the fact that the tumors in the patients with diffuse sclerosing papillary carcinoma were slightly smaller than those in the patients with classical papillary carcinoma (Table).

Given the discrepancy in data about course, most clinicians will probably choose to treat patients with diffuse sclerosing papillary carcinoma slightly more aggressively than similar patients with classical papillary carcinoma. That may include treating more patients with very small tumors with radioiodine and more intensive follow-up. What is really needed, of course, is more precise diagnosis, whether based on histopathologic or molecular analysis.

Robert D. Utiger, M.D.

References

1. Sywak M, Pasieka JL, Ogilvie T. A review of thyroid cancer with intermediate differentiation. J Surg Oncol 2004;86:44-54.

2. Chow SM, Chan JK, Law SC, et al. Diffuse sclerosing variant of papillary thyroid carcinoma—clinical features and outcome. Eur J Surg Oncol 2003; 29:446-9.

Higher iodine intake is associated with higher rate of hypothyroidism and autoimmune thyroiditis

Teng W, Shan Z, Teng X, Guan H, Li Y, Teng D, Jin Y, Yu X, Fan C, Chong W, Yang F, Dai H, Yu Y, Li J, Chen Y, Zhao D, Shi X, Hu F, Mao J, Gu X, Yang R, Tong Y, Wang W, Gao T, Li C. Effect of iodine intake on thyroid diseases in China. N Engl J Med 2006;354:2783-93.

SUMMARY

Background Both iodine deficiency and iodine excess can cause thyroid dysfunction, but the type and frequency of thyroid dysfunction among people chronically ingesting a constant amount of iodine is not known. In this study, thyroid function was assessed in 1999 and 2004 in residents of regions in China in which iodine intake was different and did not change during the study period.

Methods In 1999, 3761 subjects aged 14 years and older living in three regions in China were examined, underwent thyroid ultrasonography, and had measurements of serum thyrotropin (TSH), antithyroid peroxidase (anti-TPO) antibodies, and antithyroglobulin (anti-Tg) antibodies, and urinary iodine. The same studies were done in 3018 of these subjects in 2004. Serum free thyroxine (T_4) and TSH-receptor antibodies (TSHR-Ab) were measured in subjects who had abnormal serum TSH concentrations (<0.3 or >4.8 mU/L). The regions were Panshan, where the people consumed locally produced salt with low iodine content (mild iodine deficiency); Zhangwu, where salt had been iodinated since 1997 (adequate iodine intake); and Huanghua, where the water has a high iodine content (high iodine intake).

Results In Panshan (mild iodine deficiency), 1103 people were studied in 1999 and 884 in 2004. The respective numbers were 1584 and 1270 in Zhangwu (adequate iodine intake) and 1074 and 864 in Huanghua (high iodine intake). The ratio of women to men was approximately 3:1 in each region, and their mean ages ranged from 36 to 39 years in 1999 and 42 to 45 years in 2004. Median urinary iodine excretion in 1999 and 2004 was, respectively, 103 and 97 μg/L in Panshan, 375 and 350 μg/L in Zhangwu, and 615 and 635 μg/L in Huanghua.

The prevalence and cumulative incidence of thyroid dysfunction in Panshan, Zhangwu, and Huanghua are shown in the Table. The prevalence of overt hypothyroidism and subclinical hypothyroidism increased with increasing iodine intake, as did the cumulative incidence of subclinical hypothyroidism. The prevalence and cumulative incidence of autoimmune thyroiditis also increased with increasing iodine intake, especially among subjects with high serum anti-TPO or anti-Tg antibody values at base line. The prevalence and cumulative incidence of diffuse goiter decreased with increasing iodine intake, as did the cumulative incidence of nodular goiter.

Conclusion The prevalence and cumulative incidence of subclinical hypothyroidism and autoimmune thyroiditis increase with increasing iodine intake.

Table. 1999 Prevalence and Cumulative Incidence (1999-2004) in Panshan (Mild Iodine Deficiency), Zhangwu (Adequate Iodine Intake), and Huanghua (High Iodine Intake).

	Panshan		Zhangwu		Huanghua	
Thyroid disorder*	Prevalence	Incidence	Prevalence	Incidence	Prevalence	Incidence
			No. (%)			
Overt hypothyroidism	3 (0.3)	2 (0.2)	15 (0.9)	6 (0.5)	21 (2.0)	3 (0.3)
Subclinical hypothyroidism	10 (0.9)	2 (0.2)	46 (2.9)	33 (2.6)	65 (6.1)	25 (2.9)
Autoimmune thyroiditis	5 (0.5)	2 (0.2)	27 (1.7)	13 (1.0)	30 (2.8)	11 (1.3)
Overt hyperthyroidism	18 (1.6)	12 (1.4)	32 (2.0)	12 (0.9)	13 (1.2)	7 (0.8)
Subclinical hyperthyroidism	41 (3.7)	12 (1.4)	62 (3.9)	25 (2.0)	12 (1.1)	9 (1.0)
Graves' disease	15 (1.4)	7 (0.8)	20 (1.3)	7 (0.6)	12 (1.1)	5 (0.6)
Diffuse goiter	159 (19.5)	48 (7.1)	205 (13.5)	53 (4.4)	54 (5.1)	57 (6.9)
Nodular goiter	30 (3.7)	34 (5.0)	52 (3.4)	29 (2.4)	26 (2.5)	7 (0.8)

*Overt hypothyroidism; serum TSH high, free T_4 low: subclinical hypothyroidism; serum TSH high, free T_4 normal: autoimmune thyroiditis; overt or subclinical hypothyroidism, serum anti-TPO antibody >100 U/ml: overt hyperthyroidism; serum TSH low, free T_4 high: subclinical hyperthyroidism; serum TSH low, free T_4 normal: Graves' disease; overt hyperthyroidism, serum TSHR-Ab or anti-TPO antibodies high: diffuse goiter; thyroid volume >19.4 ml (women) or >25.4 ml (men): nodular goiter; high thyroid volume with nodules >10 mm in longest diameter.

COMMENTARY

What stands out among these data are the increasing frequency of subclinical and overt hypothyroidism and of autoimmune thyroiditis (as a cause of hypothyroidism) as a function of increasing iodine intake. The increase was greatest in subjects who had high base-line serum anti-TPO or anti-Tg concentrations. For example, among subjects with high base-line serum anti-TPO antibody concentrations, the cumulative incidence of hypothyroidism was 1.6 percent in Panshan, 10.6 percent in Zhangwu, and 16.0 percent in Huanghua. However, the frequency (prevalent and incident) of high serum antibody concentrations was similar in all three places. These results suggest that the effect of a higher iodine intake is to cause a decline in thyroid secretion, but not to cause thyroid autoimmunity, and that the antithyroid action of iodine is enhanced in the presence of thyroid autoimmunity.

Robert D. Utiger, M.D.

Table of Contents

Thyroid size decreases in children and adolescents with chronic autoimmune thyroiditis who are treated with thyroxine

Svensson J, Ericsson UB, Nilsson P, Olsson C, Jonsson B, Lindberg B, Ivarsson SA. Levothyroxine treatment reduces thyroid size in children and adolescents with chronic autoimmune thyroiditis. J Clin Endocrinol Metab 2006;91:1729-34.

SUMMARY

Background Chronic autoimmune thyroiditis is characterized by normal or decreased thyroid function and normal or increased thyroid volume. In this study, the effect of thyroxine (T_4) therapy on thyroid function and volume was evaluated in children and adolescents with chronic autoimmune thyroiditis.

Methods The study subjects were 90 children and adolescents, 73 girls (mean age, 12 years; range, 6 to 18) and 17 boys (mean age, 14 years; range, 9 to 18) with chronic autoimmune thyroiditis, as defined by a high serum concentration of antithyroid peroxidase or antithyroglobulin antibodies and thyroid hypoechogenicity, as determined by ultrasonography.

Serum thyrotropin (TSH), total T_4 or free T_4, and thyroid volume were measured before and during treatment with T_4, given in doses sufficient to reduce serum TSH to low normal values. The primary outcome measure was the change in thyroid volume during treatment, as measured by ultrasonography. The results were corrected for age and body-surface area and expressed as the standard deviation score (SDS). Goiter was defined as SDS >2.0.

Results Before treatment, 61 of the 90 patients (68 percent) had a goiter. Thirty-five patients (39 percent) were euthyroid, 42 (47 percent) had subclinical hypothyroidism, and 13 (14 percent) had overt hypothyroidism. Their median base-line SDS values were 2.5, 2.8, and 3.1, respectively (Table 1).

The mean duration of treatment was 2.8 years (range, 0.5 to 10), during which the median thyroid-volume SDS decreased from 2.8 to 1.5 (P<0.01). The decrease in thyroid volume SDS was correlated with the thyroid-volume SDS at base line, duration of treatment, and base-line serum TSH concentration.

Table 1. Characteristics of Children and Adolescents with Chronic Autoimmune Thyroiditis and Response to T_4 Treatment.

	No.	No. with Goiter (%)	Median Thyroid Volume SDS	
			Base Line	Final
All patients	90	61 (68%)	2.8	1.5*
Euthyroid	35	23 (66%)	2.5	1.8*
Subclinical hypothyroidism**	42	29 (69%)	2.8	1.5*
Overt hypothyroidism**	13	9 (69%)	3.1	0.9*

*P<0.01, compared with base line.
**Subclinical hypothyroidism, serum TSH >4.0 mU/L and serum free T_4>0.7 ng/dl (9 pmol/L); overt hypothyroidism, serum TSH >4.0 mU/L, free T_4 ≤0.7 ng/dl (9 pmol/L).

Among the patients with goiter, the decrease in goiter was greater in those with hypothyroidism (median serum TSH, 16.5 mU/L; range, 4.1 to 270) than in those who were euthyroid (median serum TSH. 2.0 mU/L; range 0.2 to 3.8) (Table 2). Among the patients with no goiter, the median thyroid volume decreased in the patients who had hypothyroidism, but did not change in the patients who were euthyroid (data not shown).

Table 2. Effect of T_4 Treatment in Patients with Goiter.

	No.	Median Thyroid Volume SDS	
		Base Line	Final
Goiter	61	3.7	2.0*
Hypothyroidism	38	3.9	1.5*
Euthyroid	23	3.1	2.1*
No goiter	29	1.2	0.6*
Hypothyroidism	17	1.0	-0.8*

*P<0.01, compared with base line.

Conclusion In children and adolescents with chronic autoimmune thyroiditis who have hypothyroidism, T_4 therapy results in a decrease in thyroid volume, whether or not they have a goiter. In those who are euthyroid, thyroid volume decreases only in those with goiter.

COMMENTARY

During puberty, the thyroid gland grows considerably (1). This can complicate the assessment of disease- or therapy-related changes in thyroid size, and was accounted for in this study by the use of corrections for age and size. The results then were made comparable among different sex and age groups by expression as SDS.

The causes of goiter in patients with chronic autoimmune thyroiditis are hyperplasia and hypertrophy of thyroid follicular cells, lymphocytic infiltration, and fibrosis. T_4 treatment usually results in some decrease in thyroid volume in these patients, whether children, adolescents, or adults. The decrease is gradual, and it is usually greater in patients with overt hypothyroidism than in those with subclinical hypothyroidism or normal thyroid function, as in this study. There is little correlation between change in thyroid volume and change in serum antithyroid antibody concentrations. Lastly, follow-up biopsies are little changed. These findings suggest that T_4 therapy does little to ameliorate the underlying lymphocytic infiltration and fibrosis. It does, of course, inhibit TSH secretion, even when that is not increased, and this inhibition in turn results in reversal of thyroid-follicular-cell hyperplasia and hypertrophy.

Robert D. Utiger, M.D.

Reference

1. Fleury Y, Van Melle G, Woringer V, et al. Sex-dependent variations and timing of thyroid growth during puberty. J Clin Endocrinol Metab 2001;86:750-4.

The course and outcome of pregnancy are normal in women with subclinical hyperthyroidism

Casey BM, Dashe JS, Wells CE, McIntire DD, Leveno KJ, Cunningham FG. Subclinical hyperthyroidism and pregnancy outcomes. Obstet Gynecol 2006;107:337-41.

SUMMARY

Background Hyperthyroidism in pregnant women is associated with an increase in miscarriage, fetal growth retardation, preterm delivery, and increased perinatal morbidity and mortality. In this study, the frequency of disorders of pregnancy and of abnormal fetal outcomes was determined in women found to have subclinical hyperthyroidism during their pregnancy.

Methods Serum thyrotropin (TSH) was measured in 25,765 women who later delivered singleton infants weighing ≥500 g. To identify overt or subclinical hyperthyroidism, serum free thyroxine (T_4) was measured in women who had a serum TSH concentration ≤0.2 mU/L. Women who had a serum free T_4 concentration >1.75 ng/dl (22.7 pmol/L) were considered to have overt hyperthyroidism, and were referred for further evaluation. Women who had serum free T_4 concentrations ≤1.75 ng/dl (22.7 pmol/L) and serum TSH concentrations ≤2.5th percentile for week of gestation (the cutoff values ranged from 0.008 to 0.67 mU/L at different weeks of gestation) were considered to have subclinical hyperthyroidism.

The outcomes of pregnancy in these women were compared with the outcomes in women who had serum TSH concentrations between the 5th and 95th percentiles. The outcomes included gestational hypertension, defined as blood pressure ≥140/90 mm Hg; and severe preeclampsia, defined as blood pressure >160/110 mm Hg, serum creatinine >1.0 mg/dl (88.4 μmol/L), thrombocytopenia, a high serum aspartate aminotransferase concentration, or proteinuria. Major malformations were defined as aneuploidy, an identifiable syndrome, or an anomaly of a major organ system.

Results Among the women, 433 (1.7 percent) had subclinical hyperthyroidism and 23,124 were normal (serum TSH concentration between the 5th and 95th percentiles). The serum TSH concentrations in the women with subclinical hyperthyroidism ranged from 0.002 to 0.67 mU/L, and their serum free T_4 concentrations ranged from 0.68 to 1.75 ng/dl (8.8 to 22.6 pmol/L). The mean age of the women in both groups was 25 years, but those with subclinical hyperthyroidism had a slightly lower body mass index (30 vs. 31 kg/m^2) and fewer were nulliparous (28 vs. 36 percent, P<0.01).

The frequency of gestational hypertension was lower in the women with subclinical hyperthyroidism (Table), and the difference persisted after adjustment for parity and race/ethnicity. There were no differences in the frequency of severe preeclampsia; diabetes mellitus; placental abruption; gestational age at delivery ≤36 weeks, ≤34 weeks, or ≤32 weeks; or cesarean delivery.

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

	Subclinical Hyperthyroidism (n=433)	Normal Women (n=23,124)
Gestational hypertension	26 (6%)*	2046 (9%)*
Severe preeclampsia	15 (4%)	1221 (5%)
Gestational age ≤36 weeks	22 (5%)	1480 (6%)
Birth weight (g)	3340	3354
Admission to intensive care	12 (3%)	512 (2%)
Major malformations	5 (1%)	271 (1%)
Perinatal mortality (per 1000)	1 (2%)	176 (8%)

*P = 0.04.

There were no differences in birth weight; percentage of infants with birth weight ≤1000 g, ≤2500 g, or ≥4000 g; or any other fetal outcome.

Conclusion The course and outcome of pregnancy are normal in women found to have subclinical hyperthyroidism during their pregnancy.

COMMENTARY

That pregnant women with subclinical hyperthyroidism have normal pregnancies and deliveries is reassuring. However, it is important to note that serum TSH was measured only once, and that many women had values that ordinarily would not be considered low — for example, 0.45 or 0.65 mU/L. Whether the results apply to women with persistent subclinical hyperthyroidism is not clear, and the inclusion of women with values in the 0.45 to 0.65 mU/L range, even though low according to the authors' estimates, may result in underestimation of the effects of subclinical hyperthyroidism.

Single serum TSH values may be low because the sample was collected at the nadir between pulses of TSH secretion. The values also may be low for several weeks late in the first trimester, when serum free T_4 concentrations are highest (even if not supranormal). This is when serum chorionic gonadotropin concentrations are highest, and therefore when its thyroid-stimulating action is greatest. This transient gestational subclinical (or overt) hyperthyroidism is particularly likely to occur in women with hyperemesis, because their serum chorionic gonadotropin concentrations are very high. It also could occur as a result of mutations of the TSH receptor that render it more sensitive to activation by chorionic gonadotropin or production of chorionic gonadotropin with greater than usual thyroid-stimulating activity.

Finally, subclinical hyperthyroidism may persist throughout pregnancy in women with thyroid carcinoma being treated with T_4 to suppress TSH secretion to below normal. In these women, the dose of T_4 is usually raised as needed to maintain the suppression. There are no prospective studies of pregnancy in women with thyroid carcinoma, but retrospective studies do not suggest that adverse outcomes of pregnancy are common in these women.

— Robert D. Utiger, M.D.

Table of Contents

Thyroxine absorption is decreased in patients with *Heliocobacter pylori*–related gastritis and atrophic gastritis and by omeprazole therapy

Centanni M, Gargano L, Canettieri G, Viceconti N, Franchi A, Delle Fave G, Annibale B. Thyroxine in goiter, *Helicobacter pylori* infection, and chronic gastritis. N Engl J Med 2006;354:1787-95.

SUMMARY

Background The absorption of orally administered thyroxine (T_4) may be decreased in patients with gastrointestinal disorders and by several drugs. In this study, the effect of *Helicobacter pylori (H. pylori)*–related gastritis, atrophic gastritis, and omeprazole on T_4 absorption was determined.

Methods The study subjects were 248 patients with a multinodular goiter treated with T_4 to reduce the size of their goiter. All initially had normal serum thyrotropin (TSH) and free T_4 concentrations. They were treated with 50 μg of T_4 daily, and the dose was gradually raised until their serum TSH concentrations were low (0.05 to 0.2 mU/L; normal range, 0.2 to 4.0). While taking T_4, 113 had clinical findings suggestive of decreased gastric acid secretion, such as chronic dyspepsia or anemia caused by vitamin B_{12} or iron deficiency. They included 53 patients with *H. pylori* gastritis, as defined by a positive gastric biopsy and C^{13}-urea breath test or a high serum concentration of *H. pylori* antibodies; and 60 patients with atrophic gastritis, as defined by biopsy, 31 of whom had a high serum concentration of *H. pylori* antibodies. The dose of T_4 needed to maintain serum TSH concentrations between 0.05 to 0.2 mU/L (two measurements at least eight months apart) in these 113 patients was compared with the dose needed in 135 patients with no gastrointestinal disorders (reference group). Overall, there were 234 women and 14 men in these groups, and their mean age ranged from 48 to 55 years.

In addition, 11 T_4-treated patients (all women) with goiter were studied before diagnosis, at the time of diagnosis, and after successful therapy of symptomatic *H. pylori* infection, and 10 T_4-treated patients (all women) with goiter were studied before and during long-term treatment with omeprazole for gastroesophageal reflux disease.

Results The median doses of T_4 needed to maintain serum TSH concentrations between 0.05 and 0.2 mU/L in the patients with *H. pylori* gastritis and those with atrophic gastritis with or without concurrent *H. pylori* infection were 22 to 34 percent higher than in the reference group (Table). The mean free T_4 concentrations were similar in all the groups.

Table. T_4 Dose Required to Maintain Low Serum TSH Concentrations in Patients with Multinodular Goiter with and without Gastritis.

	No.	Mean Serum TSH (mU/L)	Median T_4 Dose (μg/day)	Median T_4 Dose (μg/kg/day)
Reference group	135	0.12	100	1.53
Patients with *H. pylori* gastritis	53	0.11	125	1.87*
Patients with atrophic gastritis	60	0.11	125	1.95*
H. pylori infection	31	0.11	150	2.05*
No *H. pylori* infection	29	0.12	125	1.90*

*P<0.01, compared with reference group.

The 11 patients who later had *H. pylori* infection had a median serum TSH concentration of 0.11 mU/L while taking 1.56 μg/kg/day of T_4. The concentration was 1.35 mU/L at the time of diagnosis of the infection, and it was 0.12 mU/L after successful antibiotic and omeprazole therapy; the T_4 dose then was 1.70 μg/kg/day.

The 10 patients who had gastroesophageal reflux had a median serum TSH concentration of 0.10 mU/L while taking 1.58 μg/kg/day of T_4. After treatment with omeprazole, 40 mg/day, for at least six months, their serum TSH concentration increased to 1.70 mU/L. The median concentration decreased to <0.20 mU/L after the T_4 dose was raised to 2.16 μg/kg/day.

Conclusion Patients with a nontoxic nodular goiter who are treated with T_4 to inhibit TSH secretion need higher doses of T_4 if they have *H. pylori* gastritis or atrophic gastritis or are treated with omeprazole. These findings indicate that gastric secretion of acid facilitates the absorption of T_4.

COMMENTARY

The unifying feature in these patients was decreased acid secretion, whether caused by *H. pylori* gastritis, atrophic gastritis, or omeprazole (a so-called proton-pump inihibitor drug) therapy. Although acid secretion was not measured, serum gastrin was. The values were slightly high in the patients with *H. pylori* gastritis and very high in the patients with atrophic gastritis, consistent with mild and marked decreases, respectively, in acid secretion, and omeprazole is a potent inhibitor of acid secretion.

A gastritis-related decrease in the absorption of T_4 is likely to occur in all patients treated with T_4, not just those with a multinodular goiter. In patients with hypothyroidism who are adequately treated, the effect might result in an increase in serum TSH concentration to 10 or 15 mU/L and occasionally in clinically important hypothyroidism, and it could delay the benefit of newly initiated T_4 therapy.

With respect to proton-pump inhibitor drugs, there are conflicting data. In this study, omeprazole increased the need for T_4. In another study, administration of 40 mg of pantoprazole daily for seven days to young adults did not reduce the absorption of a single high (4 μg/kg) dose of T_4 (1). These different effects of omeprazole and pantoprazole could be due to differences in the two drugs, the study subjects, or the dose or duration of T_4 administration.

Gastritis with decreased gastric acid secretion should be added to the list of factors that can increase the need for exogenous T_4, and proton-pump inhibitor drugs may do so as well.

Robert D. Utiger, M.D.

Reference

1. Dietrich JW, Gieselbrecht K, Holl RW, Boehm BO. Absorption kinetics of levothyroxine is not altered by proton-pump inhibitor therapy. Horm Metab Res 2006;38:57-9.

Thyrotropin and thyroid hormone secretion is slightly increased in morbid obesity

Michalaki MA, Vagenakis AG, Leonardou AS, Argentou MN, Habeos IG, Makri MG, Psyrogiannis AI, Kalfarentzos FE, Kyriazopoulou VE. Thyroid function in humans with morbid obesity. Thyroid 2006;16:73-8.

SUMMARY

Background There is evidence for a positive association between thyrotropin (TSH) secretion within the normal range and body-mass index, but the relationships between TSH and thyroid hormone secretion are unclear. Thyroid function was assessed and the relationships between thyroid function, insulin sensitivity, and leptin secretion were evaluated in subjects with morbid obesity in this study.

Methods The study subjects were 144 consecutive subjects (110 women, 34 men; mean age, 36 years) with morbid obesity (body-mass index >40 kg/m^2). Their weight had not changed in the preceding three months. Based on history or measurements of serum TSH, total and free thyroxine (T_4), total and free triiodothyronine (T_3), and antithyroid peroxidase (TPO) antibodies, 66 were found to have some thyroid disorder (including subclinical hypothyroidism in 11 subjects) or were taking an oral contraceptive, and were not studied further.

The remaining 78 subjects (59 women, 19 men; mean age, 34 years) had normal serum TSH, total and free T_4, total and free T_3, and anti-TPO antibody concentrations. They and 77 age- and sex-matched normal-weight subjects had measurements of height, weight, waist circumference, and fat and lean body mass (by bioelectrical impedance). An oral glucose-tolerance test was performed in 49 of the morbidly obese subjects, and their insulin sensitivity was determined by calculation of the Quantitative Insulin Sensitivity Check Index (QUICKI) (1/log fasting serum insulin [μU/ml] + fasting serum glucose [mmol/L]). Serum leptin was measured in 28 morbidly obese subjects who had normal oral glucose tolerance.

Results The 78 subjects with morbid obesity and normal thyroid function had higher serum TSH, total T_4, total T_3, and free T_3, but not free T_4, concentrations, as compared with the normal subjects (Table). There was no correlation between the subjects' serum TSH concentrations and body mass index, fat mass, lean body-mass, or waist circumference.

Table. Mean Serum TSH and Thyroid Hormone Concentrations in Morbidly Obese and Normal-Weight Subjects.

Serum	Morbid Obesity (n=78)	Normal-Weight (n=77)	P Value
TSH (mU/L)	2.0	1.7	<0.05
Total T_4 (μg/dl)	8.7	7.6	<0.01
Free T_4 (ng/dl)	1.2	1.3	>0.05
Total T_3 (ng/dl)	154	110	<0.01
Free T_3 (ng/dl)	0.37	0.33	<0.05

To convert total T_4 to nmol/L and free T_4 to pmol/L, respectively, multiply by 12.9; to convert total T_3 to nmol/L, multiply by 0.0154; and to convert free T_3 to pmol/L, multiply by 15.4

Among the 49 morbidly obese subjects who had glucose-tolerance tests, 35 (71 percent) had normal glucose tolerance and 14 (29 percent) had impaired glucose tolerance. In those subjects with normal glucose tolerance, serum TSH concentrations were positively correlated with fasting serum insulin concentrations and negatively correlated with QUICKI values. In the 28 subjects in whom serum leptin was measured, there was no correlation between serum TSH and leptin concentrations.

Conclusion Serum TSH and thyroid hormone concentrations are slightly higher in morbidly obese subjects than in normal-weight subjects, suggesting pituitary resistance to the inhibitory action of T_4 and T_3 on TSH secretion.

COMMENTARY

Obese subjects, including those who are morbidly obese, have slightly higher serum TSH concentrations than do normal-weight subjects. In general, their serum T_4 and T_3 concentrations are not lower than in normal-weight subjects, as would be expected if obesity caused very mild hypothyroidism. Hence the suggestion that obesity is associated with some decrease in the ability of T_4 and T_3 to inhibit TSH secretion (central hyperthyroidism, albeit very mild). The pulsatile and diurnal pattern of TSH secretion in obese subjects is normal, but the set point is higher. However, a positive correlation between serum TSH and T_4 or T_3 concentrations, as might be expected from an increase in set point, has not been described.

Among the 144 subjects studied by Michalaki et al., 11 had subclinical hypothyroidism, presumably as usually defined (high serum TSH and normal serum T_4 concentrations), but their values are not given. Were their serum T_4 concentrations lower than those in the normal-weight subjects, suggesting that they indeed had mild hypothyroidism, or were they higher, suggesting that they should be considered as part of the main group with mild central hyperthyroidism?

Of note, morbidly obese subjects with what was called subclinical hypothyroidism (high serum TSH and normal serum T_4 concentrations) had normal thyroid function after gastric bypass and weight loss (1). That it could have been called subclinical central hyperthyroidism (also characterized by high serum TSH and normal serum T_4 concentrations) should be apparent from the above discussion. Weight loss is probably as likely to ameliorate hypothalamic–pituitary dysfunction as thyroid dysfunction.

Robert D. Utiger, M.D.

Reference

1. Moulin de Moraes CM, Mancini MC, de Melo ME, et al. Prevalence of subclinical hypothyroidism in a morbidly obese population and improvement after weight loss induced by Roux-en-Y gastric bypass. Obes Surg 2005;15:1287-91.

Lack of thyrotropin-releasing hormone impairs the thyrotropin response to hypothyroidism more than does lack of thyroid hormone receptors

Nikrodhanond AA, Ortiga-Carvalho TM, Shibusawa N, Hashimoto K, Liao XH, Refetoff S, Yamada M, Mori M, Wondisford FE. Dominant role of thyrotropin-releasing hormone in the hypothalamic-pituitary-thyroid axis. J Biol Chem 2006;281:5000-7.

SUMMARY

Background Thyrotropin (TSH) secretion is stimulated by thyrotropin-releasing hormone (TRH) and inhibited by thyroid hormone, the latter acting through the β isoform of the nuclear triiodothyronine (T_3) receptor (TR). In this study, the relative potency of these two regulatory mechanisms was evaluated in mice lacking TRH, the β isoform of the receptor, and both.

Methods and Results Mice lacking the TRH gene and the β isoform of the TR were mated to produce mice that were heterozygous for both loci. These mice were then mated to generate normal (wild-type) mice, TRH-deficient mice (TRH KO), TRβ-deficient mice (TRβ KO), and TRH- and TRβ-deficient mice (TRH+TRβ KO). All the mice were normal at birth and were viable thereafter, and their fertility was normal. TRH messenger RNA (mRNA) was not detected in the hypothalamus of the TRH KO and TRH+TRβ KO mice, and was increased in the TRβ KO mice, indicating lack of T_3 inhibition, as compared with wild-type mice.

The TRH KO mice had slightly high serum immunoreactive TSH concentrations, and their serum T_4, although not T_3, concentrations were low (Table). In the absence of the TR (TRβ KO mice), and therefore loss of inhibition of TSH secretion, serum TSH, T_4, and T_3 concentrations were high. The TRH+TRβ KO mice had slightly high serum TSH, low T_4, and normal T_3 concentrations, like the TRH KO mice. The biologic activity of serum TSH in the two groups lacking TRH was decreased.

Hypothyroidism was induced in mice by feeding a low iodine diet plus propylthiouracil and addition of methimazole to drinking water for 35 days. This resulted in very low serum T_4 concentrations in all groups, and very high serum TSH concentrations in all groups except the TRH+TRβ KO group, in which the concentrations were slightly high. Immunostaining of the pituitary glands of these mice for the β-subunit of TSH revealed many thyrotrophs in the wild-type and TRβ KO mice, fewer in the TRH KO mice, and even fewer in the TSH+TRβ KO mice.

Hypothyroid mice were treated with increasing doses of T_3, 0.2, 0.5, and 1.0 μg/day, each for seven days. Serum TSH concentrations progressively declined in all groups, but, as compared with wild-type mice, more rapidly and to a greater extent in the TRH KO mice. The decline was slower and smaller in magnitude in the TRβ KO and TRH+TRβ KO mice, indicative of resistance to T_3.

Table. Changes in Serum T_4, T_3, and TSH Concentrations in TRH KO, TRβ KO, and TRH+TRβ KO Mice, as Compared with Wild-Type Mice.

	Wild-Type	TRH KO	TRβ KO	TRH+TRβ KO
No intervention				
Serum T_4	N	↓	↑	↓
Serum T_3	N	N	↑	N
Serum TSH	N	↑	↑↑	↑
Hypothyroidism				
Serum T_4	↓↓	↓↓	↓↓	↓↓
Serum TSH	↑↑↑↑↑	↑↑↑↑	↑↑↑↑↑	↑

Conclusion TRH KO mice secrete TSH with decreased biologic activity and have central hypothyroidism, and their TSH secretory response to hypothyroidism is impaired, especially when there is concomitant thyroid hormone resistance.

COMMENTARY

TRH is not needed for development of the thyrotrophs. It is needed to maintain TSH secretion, both quantitatively and qualitatively, both basally and in response to drug-induced thyroid deficiency. In the absence of TRH, TSH biologic activity is reduced but absolute TSH secretion is not, as measured by immunoassay; indeed, the TRH KO mice had supranormal serum immunoreactive TSH concentrations, but their serum T_4 concentrations were low. The effect of TRH deficiency was more pronounced in TRH+TRβ KO mice with drug-induced thyroid deficiency; their serum immunoreractive TSH concentrations were very much lower than in all other groups.

A patient with an inactivating mutation of the TRH-receptor gene (TRH-receptor KO) has been described (1), but not a TRH KO patient. This patient was a 9-year-old boy with hypothyroidism and normal serum immunoreactive TSH concentrations, and no serum TSH (or prolactin) response to TRH. TRH deficiency occurs in some humans with idiopathic hypopituitarism and hypothalamic diseases, as determined by biochemical and imaging studies, and some of them have hypothyroidism with slightly to moderately high serum TSH concentrations, but low serum bioactive TSH concentrations, like the TRH KO mice. In some of these patients, repetitive TRH administration results in increased TSH bioactivity and restoration of normal serum T_4 and T_3 concentrations. Patients with TRH deficiency and thyroid disease or thyroid hormone resistance have not been reported, but in all likelihood their serum TSH concentrations would not be very high, like the TRH+TRβ KO mice.

In short, in mice and probably in people, TRH is needed if TSH secretion is to increase appropriately both quantitatively and qualitatively to compensate for thyroid deficiency.

Robert D. Utiger, M.D.

Reference

1. Collu R, Tang J, Castagne J, et al. A novel mechanism for isolated central hypothyroidism: inactivating mutations in the thyrotropin-releasing hormone receptor gene. J Clin Endocrinol Metab 1997;82:1561-5.

Thyroid Review Articles

Boas M, Feldt-Rasmussen U, Skakkebaek NE, Main KM. Environmental chemicals and thyroid function. Eur J Endocrinol 2006;154:599-611.

Brabant G, Beck-Peccoz P, Jarzab B, Laurberg P, Orgiazzi J, Szabolcs I, Weetman AP, Wiersinga WM. Is there a need to redefine the upper normal limit of TSH? Eur J Endocrinol 2006;154:633-7.

Groussin L, Fagin JA. Significance of *BRAF* mutations in papillary thyroid carcinoma: prognostic and therapeutic implications. Nat Clin Pract Endocrinol Metab 2006;2:180-1.

Mandac JC, Chaudhry S, Sherman KE, Tomer Y. The clinical and physiological spectrum of interferon-alpha induced thyroiditis: toward a new classification. Hepatology 2006;43:661-72.

Watt T, Groenvold M, Rasmussen AK, Bonnema SJ, Hegedus L, Bjorner JB, Feldt-Rasmussen U. Quality of life in patients with benign thyroid disorders: a review. Eur J Endocrinol 2006;154:501-10.

American Thyroid Association
6066 Leesburg Pike, Suite 550
Falls Church, VA 22041

CLINICAL THYROIDOLOGY

A publication of the American Thyroid Association